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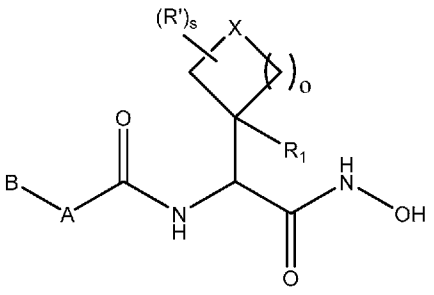

(I)

(57) Abstract: The disclosure relates to antibacterial compounds having the Formula (I), where R1, R', A, B, X, s, and o are described herein, as well as stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, pharmaceutical compositions comprising such compounds, methods of treating bacterial infections by the administration of such compounds, and processes for the preparation of the compounds.

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ANTIBACTERIAL AGENTS

Government Rights

[0001] This invention was made with government support under NIH-NIAID contract HHSN272201500009C awarded by the National Institutes of Health. The government has certain rights in the invention.

Cross Reference To Related Applications

[0002] This application claims the benefit of U.S. Provisional Application No. 62/353,910, filed June 23, 2016, the content of which is incorporated herein by reference in its entirety.

Field of Disclosure

[0003] This disclosure pertains generally to treating infections caused by gram-negative bacteria. More specifically, the present disclosure pertains to treating gram-negative infections by modulating activity of UDP-3-O-(*R*-3-hydroxydecanoyl)-*N*-acetylglucosamine deacetylase (LpxC). The present disclosure provides small molecule inhibitors of LpxC, pharmaceutical formulations containing such inhibitors, methods of treating patients with such pharmaceutical formulations, and methods of preparing such pharmaceutical formulations and inhibitors. The present disclosure pertains to treating gram-negative infections by administering compounds capable of inhibiting activity of LpxC, either alone or in combination with administering a second antibacterial compound.

Background of the Disclosure

[0004] Over the past several decades, the frequency of antimicrobial resistance and its association with serious infectious diseases have increased at alarming rates. The problem of antibacterial resistance is compounded by the existence of bacterial strains resistant to multiple antibacterials. Thus, there is a need for new antibacterials, particularly antibacterials with novel mechanisms of action. A previously unexploited but highly conserved target, LpxC, provides a new opportunity for developing broad-spectrum antibacterial small molecules that comprise a new class of active bactericidal chemical entities that should encounter little, if any, naturally-occurring, target-related resistance. LpxC (the enzyme uridyldiphospho-3-O-(*R*-

hydroxydecanoyl)-*N*-acetylglucosamine deacetylase) is present across all Gram-negative bacterial species of interest and is involved in the first committed step in outer membrane biosynthesis. Thus LpxC is essential for survival and presents an ideal target for antibiotic activity in most Gram-negative bacterial species.

[0005] Researchers have identified some compounds with antibacterial activity that target lipid A biosynthesis. For example, Jackman et al. (*J. Biol. Chem.*, 2000, 275(15), 11002-11009); Wyckoff et al. (*Trends in Microbiology*, 1998, 6(4), 154-159); U.S. Patent Application Publication No. 2001/0053555 (published 20 December 2001, corresponding to International PCT Publication No. WO 98/18754, published 7 May 1998); International PCT Publication No. WO 00/61134 (published 19 October 2000); U.S. Patent Application Publication No. 2004/0229955 (published 18 November 2004); International PCT Publication No. WO 2008/027466 (published 6 March 2008); International PCT Publication No. WO 2008/105515 (published 4 September 2008); International PCT Publication No. WO 2008/154642 (published 18 December 2008); International PCT Publication No. WO 2009/158369 (published 30 December 2009); International PCT Publication No. WO 2010/017060 (published 11 February 2010); International PCT Publication No. WO 2010/024356 (published 4 March 2010); International PCT Publication No. WO 2010/031750 (published 25 March 2010); International PCT Publication No. WO 2010/032147 (published 25 March 2010); International PCT Publication No. WO 2010/100475 (published 10 September 2010); International PCT Publication No. WO 2011/045703 (published 21 April 2011); International PCT Publication No. WO 2011/073845 (published 23 June 2011); International PCT Publication No. WO 2011/005355 (published 13 January 2011); International PCT Publication No. WO 2004/062601 (published 29 July 2004); International PCT Publication No. WO 2012/154204 (published 15 November 2012); International PCT Publication No. WO 2013/039947 (published 21 March 2013); International PCT Publication No. WO 2013/170030 (published 14 November 2013); International PCT Publication No. WO 2013/170165 (published 14 November 2013); International PCT Publication No. WO 2014/165075 (published 9 October 2014); and International PCT Publication No. WO 2011/132712 (published 27 October 2011) all disclose compounds having antibacterial anti-LpxC activity. The commercial development of these LpxC inhibitors has been complicated by toxicity of these compounds in mammalian animals at concentrations at or near those required for antibacterial activity. The compounds presented

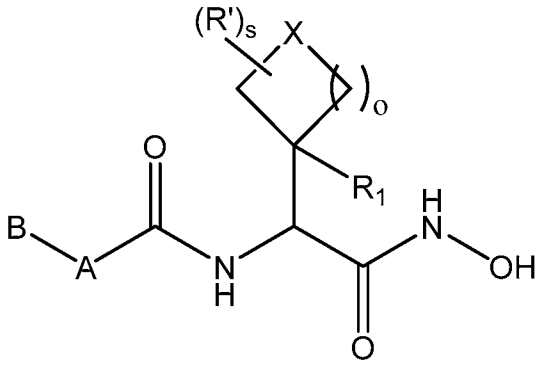
herein are significantly better tolerated, more active, and/or less protein-bound than other closely related compounds having anti-LpxC activity.

[0006] Although there have been advances in the field, there remains a need for LpxC inhibitors that have activity as bactericidal agents against gram-negative bacteria and have improved pharmacokinetic properties. It is, accordingly, an object of this disclosure to provide compounds and combinations of such compounds for use in the preparation of non-toxic antibacterials and other pharmaceuticals capable of inhibiting gram-negative bacterial infections.

Summary of the Disclosure

[0007] The present disclosure provides novel compounds, prodrugs, pharmaceutical formulations including the compounds, methods of inhibiting UDP-3-O-(*R*-3-hydroxydecanoyl)-*N*-acetylglucosamine deacetylase (LpxC), and methods of treating, preventing, and reducing the risk of microbial infections. The present disclosure also provides pharmaceutically acceptable salts, esters, *N*–oxides, and prodrugs of these compounds. The LpxC inhibitors of the present disclosure have unique and unexpected improved pharmacokinetic properties (*i.e.*, lower clearance rates).

[0008] A first aspect of the disclosure relates to compounds of Formula (I):



(I),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof,

wherein:

X is $S(O)_q$ or NR_6;

A is (C_6-C_{10}) aryl, heteroaryl, (C_3-C_7) cycloalkyl, (C_4-C_7) cycloalkenyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, cycloalkenyl, or heterocycloalkyl is optionally substituted with one or more R_7;

B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, -OR_8, -$S(O)_rR_8$, halogen, (C_6-C_{10}) aryl, heteroaryl, or –SF_5, wherein the aryl and heteroaryl are optionally substituted with R_2;

R_1 is H, (C_1-C_4) alkyl, (C_2-C_4) alkenyl, (C_2-C_4) alkynyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$(CH_2)_m$heterocycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$heterocycloalkyl, halogen, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$,-$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino;

R_2 is (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, halogen, -OH, -NH_2, or -CN;

R_3 is H, (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl, heterocycloalkyl, or heteroaryl, wherein the alkyl is optionally substituted with one or more R_4, and wherein the cycloalkyl, heterocycloalkyl, or heteroaryl are optionally substituted with one or more R_5;

each R_4 is independently at each occurrence -OH, -NH_2, (C_1-C_4) alkoxy, (C_1-C_4) alkylamino, or (C_1-C_4) dialkylamino;

each R_5 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, halogen, (C_1-C_4) hydroxyalkyl, –C(O)H, –C(=O)(C_1-C_4) alkyl, -OH, -NH_2, (C_1-C_4) alkylamino, (C_1-C_4) dialkylamino, or -$S(O)_p$(C_1-C_4)alkyl;

R_6 is H, (C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -C(O)H, -C(O)(C_1-C_4) alkyl, -$S(O)_r$(C_1-C_4) alkyl, or -C(O)O(C_1-C_4) alkyl;

each R_7 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or halogen; or two R_7 together on adjacent atoms with the atoms to which they are attached form a (C_6-C_{10}) aryl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a heteroaryl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a (C_4-C_8) cycloalkyl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a heterocycloalkyl ring optionally substituted with one or more R_9;

R_8 is (C_1-C_4) alkyl, (C_2-C_4) alkenyl, (C_2-C_4) alkynyl, (C_1-C_4) haloalkyl, or (C_3-C_6) cycloalkyl, wherein the alkyl, alkenyl, or alkynyl are optionally substituted with one or more substituents selected from (C_3-C_7) cycloalkyl and heterocycloalkyl;

each R_9 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or halogen;

each R' is (C_1-C_4) alkyl;

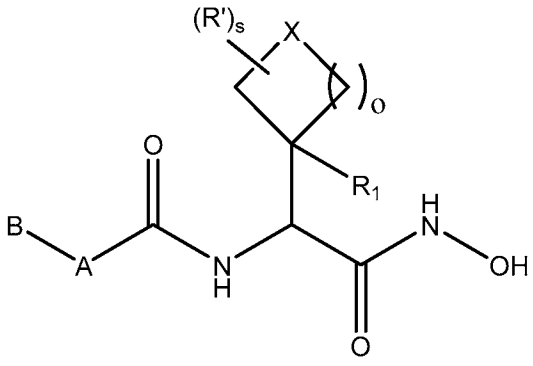
o is 1 or 2;

s is 0, 1, or 2;

each q, p, and r is independently at each occurrence 0, 1, or 2; and

each m and n is independently at each occurrence 0, 1, 2, or 3.

[0009] Another aspect of the disclosure relates to a prodrug of a compound of Formula (I) having a Formula (II):



(II),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof,

wherein:

X is $S(O)_q$ or NR_6;

A is (C_6-C_{10}) aryl, heteroaryl, (C_3-C_7) cycloalkyl, (C_4-C_7) cycloalkenyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, cycloalkenyl, or heterocycloalkyl is optionally substituted with one or more R_7;

B is –C≡C—R_3 or –C≡C–C≡C–R_3;

R_1 is H, (C_1-C_4) alkyl, (C_2-C_4) alkenyl, (C_2-C_4) alkynyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$(CH_2)_m$heterocycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$heterocycloalkyl, halogen, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$,-$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino;

R_3 is (C_1-C_4) alkyl substituted with one or more Q;

R_6 is H, (C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -C(O)H, -C(O)(C_1-C_4) alkyl, -$S(O)_r$(C_1-C_4) alkyl, or -C(O)O(C_1-C_4) alkyl;

each R_7 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or halogen; or

two R_7 together on adjacent atoms with the atoms to which they are attached form a (C_6-C_{10}) aryl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a heteroaryl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a (C_4-C_8) cycloalkyl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a heterocycloalkyl ring optionally substituted with one or more R_9;

each R_9 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or halogen;

each R' is (C_1-C_4) alkyl;

R_a is (C_1-C_{10}) alkyl, (C_3-C_7) cycloalkyl, or heterocycloalkyl, wherein the alkyl, cycloalkyl, or heterocycloalkyl are optionally substituted with one or more substituents selected from -OH, $-NH_2$, $-CO_2H$, $-SO_3H$, $-NHC(NH)NH_2$, and $-OP(=O)(OH)_2$;

o is 1 or 2;

s is 0, 1, or 2;

each q, p, and r is independently at each occurrence 0, 1, or 2;

each m and n is independently at each occurrence 0, 1, 2, or 3; and

each Q is independently at each occurrence $-OP(=O)(OH)_2$, $-OCH_2OP(=O)(OH)_2$, $-OC(=O)R_a$, $-OCH_2OC(=O)\ R_a$, or $-OC(=O)R_a$; and

wherein Q is a cleavable group.

[0010] Another aspect of the disclosure relates to a method of treating a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0011] Another aspect of the disclosure relates to a method of preventing a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0012] Another aspect of the disclosure relates to a method of reducing the risk of a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0013] Another aspect of the disclosure relates to a method of treating a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection an effective amount of a prodrug of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0014] Another aspect of the disclosure relates to a method of preventing a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection an effective amount of a prodrug of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0015] Another aspect of the disclosure relates to a method of reducing the risk of a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection an effective amount of a prodrug of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0016] Another aspect of the disclosure is directed to pharmaceutical compositions comprising a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof and a pharmaceutically acceptable carrier. The pharmaceutical acceptable carrier may further include an excipient, diluent, or surfactant.

[0017] Another aspect of the disclosure is directed to pharmaceutical compositions comprising a prodrug of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof and a pharmaceutically acceptable carrier. The pharmaceutical acceptable carrier may further include an excipient, diluent, or surfactant.

[0018] Another aspect of the present disclosure relates to a method of treating a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection an effective amount of a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[0019] Another aspect of the present disclosure relates to a method of treating a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial

infection an effective amount of a pharmaceutical composition comprising a prodrug of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[0020] Another aspect of the present disclosure relates to a method of preventing a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection an effective amount of a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[0021] Another aspect of the present disclosure relates to a method of preventing a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection an effective amount of a pharmaceutical composition comprising a prodrug of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[0022] Another aspect of the present disclosure relates to a method of reducing the risk of a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection an effective amount of a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[0023] Another aspect of the present disclosure relates to a method of reducing the risk of a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection an effective amount of a pharmaceutical composition comprising a prodrug of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[0024] Another aspect of the present disclosure relates to the use of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the treatment of a bacterial infection.

[0025] Another aspect of the present disclosure relates to the use of a prodrug of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the treatment of a bacterial infection.

[0026] Another aspect of the present disclosure relates to the use of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the prevention of a bacterial infection.

[0027] Another aspect of the present disclosure relates to the use of a prodrug of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the prevention of a bacterial infection.

[0028] Another aspect of the present disclosure relates to the use of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the reduction of the risk of a bacterial infection.

[0029] Another aspect of the present disclosure relates to the use of a prodrug of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the reduction of the risk of a bacterial infection.

[0030] Another aspect of the present disclosure relates to a pharmaceutical composition or formulation comprising an effective amount of an antibacterial compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier or diluent.

[0031] Another aspect of the present disclosure relates to a pharmaceutical composition or formulation comprising an effective amount of an antibacterial compound of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier or diluent.

[0032] Another aspect of the present disclosure relates to a method of inhibiting a deacetylase enzyme in gram-negative bacteria, thereby affecting bacterial growth, comprising administering to a patient in need of such inhibition an LpxC-inhibitory compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0033] Another aspect of the present disclosure relates to a method of inhibiting a deacetylase enzyme in gram-negative bacteria, thereby affecting bacterial growth, comprising administering to a patient in need of such inhibition an LpxC-inhibitory compound of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0034] Another aspect of the present disclosure relates to a method of inhibiting LpxC, thereby modulating the virulence of a bacterial infection, comprising administering to a patient in need of

such inhibition an LpxC-inhibitory compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0035] Another aspect of the present disclosure relates to a method of inhibiting LpxC, thereby modulating the virulence of a bacterial infection, comprising administering to a patient in need of such inhibition an LpxC-inhibitory compound of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0036] Another aspect of the present disclosure relates to a method for treating a patient having a bacterial infection comprising administering to the patient in need thereof an antibacterially effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In a more specific embodiment of the method of treatment, the bacterial infection is a gram-negative bacterial infection. In a further specific embodiment the patient is a mammal and in certain embodiments, a human.

[0037] Another aspect of the present disclosure relates to a method for treating a patient having a bacterial infection comprising administering to the patient in need thereof an antibacterially effective amount of a prodrug of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In a more specific embodiment of the method of treatment, the bacterial infection is a gram-negative bacterial infection. In a further specific embodiment the patient is a mammal and in certain embodiments, a human.

[0038] Another aspect of the present disclosure relates to a method of administering an antibacterially effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, to a patient infected with a fermentative or non-fermentative gram-negative bacteria. Examples of such bacteria include *Pseudomonas aeruginosa*, *Stenotrophomonas maltophila*, *Burkholderia cepacia*, *Alcaligenes xylosoxidans*, *Enterobacteriaceae*, *Haemophilus*, *Franciscellaceae* (e.g., *Franciscella tularensis*) and *Neisseria species*.

[0039] Another aspect of the present disclosure relates to a method of administering an antibacterially effective amount of a prodrug of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, to a patient infected with a fermentative or non-fermentative gram-negative bacteria. Examples of such bacteria include *Pseudomonas aeruginosa*, *Stenotrophomonas maltophila*, *Burkholderia cepacia*, *Alcaligenes*

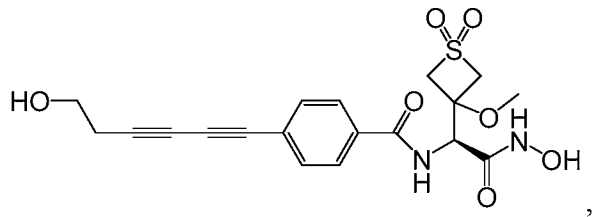
xylosoxidans, *Enterobacteriaceae*, *Haemophilus*, *Franciscellaceae* (e.g., *Franciscella tularensis*) and *Neisseria species*.

[0040] Another aspect of the present disclosure relates to a method of administering an antibacterially effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, to a patient infected with gram-negative bacteria. Examples of such bacteria include *Enterobacteriaceae,* such as *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia* (e.g., *Yersinia pestis*), *Morganella*, *Cedecea*, *Edwardsiella species* and *Escherichia coli*.

[0041] Another aspect of the present disclosure relates to a method of administering an antibacterially effective amount of a prodrug of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, to a patient infected with gram-negative bacteria. Examples of such bacteria include *Enterobacteriaceae,* such as *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia* (e.g., *Yersinia pestis*), *Morganella*, *Cedecea*, *Edwardsiella species* and *Escherichia coli*.

[0042] The present disclosure further provides methods of treating, preventing, or reducing the risk of a bacterial infection associated with modulation of LpxC comprising administering to a subject a compound of the disclosure, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

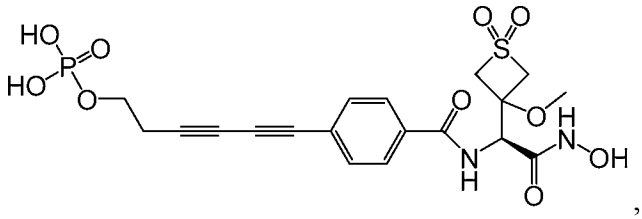
[0043] In some embodiments, the compound of Formula (I) is:



,

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, or tautomer thereof.

[0044] In certain embodiments, the compound of Formula (II) is:



,

or a pharmaceutically acceptable salt, hydrate, solvate, or tautomer thereof.

[0045] The present disclosure provides inhibitors of LpxC that are therapeutic agents in the treatment of bacterial infections, including, but not limited to, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophila*, *Burkholderia cepacia*, *Alcaligenes xylosoxidans*, *Enterobacteriaceae*, *Haemophilus*, *Franciscellaceae* and a *Neisseria* species. Ultimately, the present disclosure provides the medical community with a novel compounds and pharmacological strategy for the treatment of bacterial infections associated with LpxC enzymes.

[0046] The present disclosure further provides a method for treating a bacterial infection in a subject, which include administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. Further provided herein is a method for treating a bacterial infection in a subject, which include administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier. In some variattions, the bacterial infection is caused by a gram-negative bacteria.

[0047] Also provided herein is a method of inhibiting a deacetylase enzyme in gram-negative bacteria, which include contacting the bacteria with a compound as disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0048] In some embodiments of the provided methods, the bacterial infection is an infection of a bacteria selected from the group consisting of *Enterobacteriaceae*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia, Pseudomonas*, *Alcaligenes*, *Haemophilus*, *Franciscellaceae* and *Neisseria* species. In certain varaitions, the gram-negative bacteria is *Enterobacteriaceae* or *Acinetobacter*. In still other embodiments, the *Enterobacteriaceae* is selected from the group consisting of *Serratia, Proteus, Klebsiella, Enterobacter, Citrobacter, Salmonella, Providencia, Yersinia, Morganella, Cedecea, Edwardsiella species,* and *Escherichia coli*. In certain varaitions, the *Burkholderia* is *Burkholderia cepacia, Burkholderia pseudomallei* or *Burkholderia mallei.*

[0049] In still other embodiments of the disclosed methods, the *Acinetobacter* is selected from the group consisting of *Acinetobacter baumannii, Acinetobacter lwoffi, Acinetobacter albensis, Acinetobacter apis, Acinetobacter beijerinckii, Acinetobacter bereziniae, Acinetobacter bohemicus, Acinetobacter boissieri, Acinetobacter bouvetii, Acinetobacter brisouii,*

Acinetobacter calcoaceticus, Acinetobacter courvalinii, Acinetobacter dispersus, Acinetobacter equi, Acinetobacter gandensis, Acinetobacter gerneri, Acinetobacter guangdongensis, Acinetobacter guillouiae, Acinetobacter gyllenbergii, Acinetobacter haemolyticus, Acinetobacter harbinensis, Acinetobacter indicus, Acinetobacter junii, Acinetobacter kookii, Acinetobacter modestus, Acinetobacter nectaris, Acinetobacter nosocomialis, Acinetobacter parvus, Acinetobacter pakistanensis, Acinetobacter populi, Acinetobacter proteolyticus, Acinetobacter pittii, Acinetobacter puyangensis, Acinetobacter qingfengensis, Acinetobacter radioresistens, Acinetobacter rudis, Acinetobacter schindleri, Acinetobacter seifertii, Acinetobacter soli, Acinetobacter tandoii, Acinetobacter tjernbergiae, Acinetobacter towneri, Acinetobacter ursingii, Acinetobacter variabilis, Acinetobacter venetianus, and *Acinetobacter vivianii.*

[0050] Also provided herein is a method of inhibiting LpxC, which include administering to a subject in need thereof a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0051] Provided herein is a compound as disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use as a medicament. Also provided herein is a compound as disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in treating a bacterial infection. Further provided herein is a compound as disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the manufacture of a medicament for treating a bacterial infection. Provided herein are also compounds as disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in inhibiting a deacetylase enzyme in gram-negative bacteria. Provided herein is a compound as disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the manufacture of a medicament for inhibiting a deacetylase enzyme in gram-negative bacteria.

[0052] In certain embodiments of the compound for use provided herein, the bacterial infection is an infection of a bacteria selected from the group consisting of *Enterobacteriaceae*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia, Pseudomonas*, *Alcaligenes*, *Haemophilus*, *Franciscellaceae* and *Neisseria* species. In other variations of the compounds for use provided herein, the gram-negative bacteria is *Enterobacteriaceae* or *Acinetobacter*.

[0053] In some embodiments of the compound for use provided herein, the *Enterobacteriaceae is selected from the group consisting of Serratia, Proteus, Klebsiella, Enterobacter, Citrobacter, Salmonella, Providencia, Yersinia, Morganella, Cedecea, Edwardsiella species,* and *Escherichia coli.* In other embodiments, the *Burkholderia* is *Burkholderia* cepacia, *Burkholderia pseudomallei* or *Burkholderia mallei*. In still further embodiments of the compounds for use provided herein, the *Acinetobacter is selected from the group consisting of Acinetobacter baumannii, Acinetobacter lwoffi, Acinetobacter albensis, Acinetobacter apis, Acinetobacter beijerinckii, Acinetobacter bereziniae, Acinetobacter bohemicus, Acinetobacter boissieri, Acinetobacter bouvetii, Acinetobacter brisouii, Acinetobacter calcoaceticus, Acinetobacter courvalinii, Acinetobacter dispersus, Acinetobacter equi, Acinetobacter gandensis, Acinetobacter gerneri, Acinetobacter guangdongensis, Acinetobacter guillouiae, Acinetobacter gyllenbergii, Acinetobacter haemolyticus, Acinetobacter harbinensis, Acinetobacter indicus, Acinetobacter junii, Acinetobacter kookii, Acinetobacter modestus, Acinetobacter nectaris, Acinetobacter nosocomialis, Acinetobacter parvus, Acinetobacter pakistanensis, Acinetobacter populi, Acinetobacter proteolyticus, Acinetobacter pittii, Acinetobacter puyangensis, Acinetobacter qingfengensis, Acinetobacter radioresistens, Acinetobacter rudis, Acinetobacter schindleri, Acinetobacter seifertii, Acinetobacter soli, Acinetobacter tandoii, Acinetobacter tjernbergiae, Acinetobacter towneri, Acinetobacter ursingii, Acinetobacter variabilis, Acinetobacter venetianus,* and *Acinetobacter vivianii.*

[0054] Further provided herein is a compound as disclosed herein, or pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in inhibiting LpxC. Additionally provided herein is a compound as disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the manufacture of a medicament for inhibiting LpxC.

[0055] In certain embodiments of any of the methods provided herein, after administration of one or more doses of said compound, the subject does not develop vascular irritation. In other embodiments of any of the methods provided herein, after administration of one or more doses of said compound, the subject does not develop phlebitis. In some embodiments, the phlebitis is superficial phlebitis. In other embodiments, the phlebitis is thrombophlebitis. In still other embodiments of any of the methods provided herein, after administration of one or more doses of said compound, the subject does not develop one or more symptoms of phlebitis. In some

embodiments, the one or more symptoms of phlebitis are selected from the group consisting of warmth along the course of a vein, tenderness along the course of a vein, redness along the course of a vein, swelling/bulging along the course of a vein, and drainage of pus.

Description of the Figures

[0056] The present application can be understood by reference to the following description taken in conjunction with the accompanyinf figures.

[0057] FIG. **1.** Hemodynamic parameters and free compound concentrations for anesthetized rats treated with Cmpd A (n=4).

[0058] FIG. **2.** Hemodynamic parameters and free compound concentrations for anesthetized rats treated with Compound I-2 (n=4).

[0059] FIG. **3.** Frequency Distribution (%) of Compound I-4 at Each MIC (μg/mL) for 201 *P. aeruginosa* isolates from RTI Patients and 49 *P. aeruginosa* from CF Patients.

[0060] FIG. **4.** Spontaneous resistance frequencies of five *P. aeruginosa* clinical isolates against Compound I-4, Cmpd B, Cmpd E, and Levofloxacin. Error bars indicate geometric mean +/- geometric SD. Gray shading indicates limit of detection (LOD) range; LOD differs between strains.

[0061] FIG. **5.** Distribution of MIC fold-changes for ninety-eight mutants with spontaneous resistance to Compound I-4, Cmpd B, and Cmpd E before and after passaging on drug-free agar.

[0062] FIG. **6A.** *In vivo* efficacy data for Compound I-4 in the neurotropenic mouse thigh infection model for *Pseudomonas aeruginosa* isolate ATCC27853.

[0063] FIG. **6B.** *In vivo* efficacy data for Compound I-4 in the neurotropenic mouse thigh infection model for *Pseudomonas aeruginosa* isolate LES431.

[0064] FIG. **7A.** *In vivo* efficacy data for Compound I-4 in the neurotropenic mouse lung infection model for *Pseudomonas aeruginosa* isolate ATCC27853.

[0065] FIG. **7B.** *In vivo* efficacy data for Compound I-4 in the neurotropenic mouse lung infection model for *Pseudomonas aeruginosa* isolate LES431.

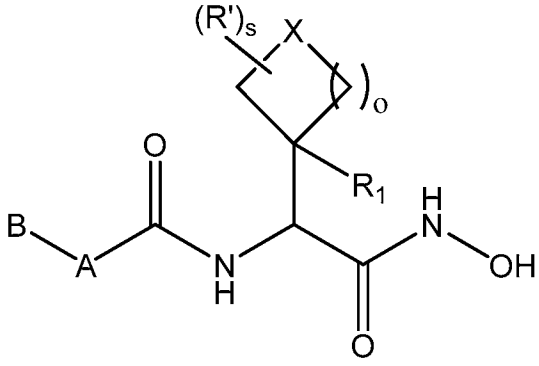
[0066] FIG. **8.** *In vivo* efficacy data for Compound I-4 in the neutropenic mouse lung infection model for three *Pseudomonas aeruginosa* clinical isolates.

Detailed Description of the Disclosure

[0067] The present disclosure relates to compounds, prodrugs, and compositions that are capable of inhibiting the activity LpxC. The disclosure features methods of treating, preventing, or reducing the risk of a bacterial infection in which LpxC plays a role by administering to a patient in need thereof a therapeutically effective amount of a compound of the Formula (I) and/or a prodrug of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. The methods of the present disclosure can be used in the treatment of a variety of bacterial infections including, but not limited to, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophila*, *Burkholderia cepacia*, *Alcaligenes xylosoxidans*, *Enterobacteriaceae*, *Haemophilus*, *Franciscellaceae* and a *Neisseria* species.

[0068] The methods of the present disclosure can be used in the treatment of a variety of bacterial infections including, but not limited to, bacterial infections caused by a bacteria selected from the group consisting of *Enterobacteriaceae*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia, Pseudomonas*, *Alcaligenes*, *Haemophilus*, *Franciscellaceae* and *Neisseria* species. In certain varaitions, the bacterial infection is caused by a gram-negative bacteria, wherein the bacteria is *Enterobacteriaceae* or *Acinetobacter*.

[0069] In a first aspect of the disclosure, the compounds of Formula (I) are described:



(I),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof, wherein R_1, R', A, B, X, o, and s are as described herein above.

[0070] The details of the disclosure are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, illustrative methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms

also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

Definitions

[0071] The articles "a" and "an" are used in this disclosure to refer to one or more than one (*e.g.*, to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0072] The term "and/or" is used in this disclosure to mean either "and" or "or" unless indicated otherwise.

[0073] The term "optionally substituted" is understood to mean that a given chemical moiety (*e.g.*, an alkyl group) can (but is not required to) be bonded other substituents (*e.g.*, heteroatoms). For instance, an alkyl group that is optionally substituted can be a fully saturated alkyl chain (*e.g.*, a pure hydrocarbon). Alternatively, the same optionally substituted alkyl group can have substituents different from hydrogen. For instance, it can, at any point along the chain, be bounded to a halogen atom, a hydroxyl group, or any other substituent described herein. Thus the term "optionally substituted" means that a given chemical moiety has the potential to contain other functional groups, but does not necessarily have any further functional groups. Suitable substituents used in the optional substitution of the described groups include, without limitation, halogen, oxo, -OH, -CN, -COOH, $-CH_2CN$, $-O-(C_1-C_6)$ alkyl, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, $-O-(C_2-C_6)$ alkenyl, $-O-(C_2-C_6)$ alkynyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, -OH, $-OP(O)(OH)_2$, $-OC(O)(C_1-C_6)$ alkyl, $-C(O)(C_1-C_6)$ alkyl, $-OC(O)O(C_1-C_6)$ alkyl, $-NH_2$, $-NH((C_1-C_6)$ alkyl), $-N((C_1-C_6)$ alkyl$)_2$, $-NHC(O)(C_1-C_6)$ alkyl, $-C(O)NH(C_1-C_6)$ alkyl, $-S(O)_2(C_1-C_6)$ alkyl, $-S(O)NH(C_1-C_6)$ alkyl, and $S(O)N((C_1-C_6)$ alkyl$)_2$. The substituents can themselves be optionally substituted. "Optionally substituted" as used herein also refers to substituted or unsubstituted whose meaning is described below.

[0074] As used herein, the term "substituted" means that the specified group or moiety bears one or more suitable substituents wherein the substituents may connect to the specified group or moiety at one or more positions. For example, an aryl substituted with a cycloalkyl may indicate that the cycloalkyl connects to one atom of the aryl with a bond or by fusing with the aryl and sharing two or more common atoms.

[0075] As used herein, the term "unsubstituted" means that the specified group bears no substituents.Unless otherwise specifically defined, the term "aryl" refers to cyclic, aromatic hydrocarbon groups that have 1 to 3 aromatic rings, including monocyclic or bicyclic groups such as phenyl, biphenyl or naphthyl. Where containing two aromatic rings (bicyclic, etc.), the aromatic rings of the aryl group may be joined at a single point (*e.g.*, biphenyl), or fused (*e.g.*, naphthyl). The aryl group may be optionally substituted by one or more substituents, *e.g.*, 1 to 5 substituents, at any point of attachment. Exemplary substituents include, but are not limited to, -H, -halogen, -O-(C_1-C_6) alkyl, (C_1-C_6) alkyl, -O-(C_2-C_6) alkenyl, -O-(C_2-C_6) alkynyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, -OH, -$OP(O)(OH)_2$, -OC(O)(C_1-C_6) alkyl, -C(O)(C_1-C_6) alkyl, -OC(O)O(C_1-C_6) alkyl, -NH_2, -NH((C_1-C_6) alkyl), N((C_1-C_6) alkyl)$_2$, -$S(O)_2$-(C_1-C_6) alkyl, -S(O)NH(C_1-C_6) alkyl, and -S(O)N((C_1-C_6) alkyl)$_2$. The substituents can themselves be optionally substituted. Furthermore when containing two fused rings the aryl groups herein defined may have an unsaturated or partially saturated ring fused with a fully saturated ring. Exemplary ring systems of these aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl, anthracenyl, phenalenyl, phenanthrenyl, indanyl, indenyl, tetrahydronaphthalenyl, tetrahydrobenzoannulenyl, and the like.

[0076] Unless otherwise specifically defined, "heteroaryl" means a monovalent monocyclic aromatic radical of 5 to 24 ring atoms or a polycyclic aromatic radical, containing one or more ring heteroatoms selected from N, O, and S, the remaining ring atoms being C. Heteroaryl as herein defined also means a bicyclic heteroaromatic group wherein the heteroatom is selected from N, O, and S. The aromatic radical is optionally substituted independently with one or more substituents described herein. Examples include, but are not limited to, furyl, thienyl, pyrrolyl, pyridyl, pyrazolyl, pyrimidinyl, imidazolyl, isoxazolyl, oxazolyl, oxadiazolyl, pyrazinyl, indolyl, thiophen-2-yl, quinolyl, benzopyranyl, isothiazolyl, thiazolyl, thiadiazole, indazole, benzimidazolyl, thieno[3,2-b]thiophene, triazolyl, triazinyl, imidazo[1,2-b]pyrazolyl, furo[2,3-c]pyridinyl, imidazo[1,2-a]pyridinyl, indazolyl, pyrrolo[2,3-c]pyridinyl, pyrrolo[3,2-c]pyridinyl, pyrazolo[3,4-c]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-c]pyridinyl, thieno[2,3-b]pyridinyl, benzothiazolyl, indolyl, indolinyl, indolinonyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, benzofuran, chromanyl, thiochromanyl, tetrahydroquinolinyl, dihydrobenzothiazine, dihydrobenzoxanyl, quinolinyl, isoquinolinyl, 1,6-naphthyridinyl, benzo[de]isoquinolinyl, pyrido[4,3-b][1,6]naphthyridinyl, thieno[2,3-b]pyrazinyl, quinazolinyl, tetrazolo[1,5-a]pyridinyl,

[1,2,4]triazolo[4,3-a]pyridinyl, isoindolyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,4-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, imidazo[5,4-b]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, tetrahydro pyrrolo[1,2-a]pyrimidinyl, 3,4-dihydro-2H-1λ^2-pyrrolo[2,1-b]pyrimidine, dibenzo[b,d] thiophene, pyridin-2-one, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1H-pyrido[3,4-b][1,4] thiazinyl, benzooxazolyl, benzoisoxazolyl, furo[2,3-b]pyridinyl, benzothiophenyl, 1,5-naphthyridinyl, furo[3,2-b]pyridine, [1,2,4]triazolo[1,5-a]pyridinyl, benzo [1,2,3]triazolyl, imidazo[1,2-a]pyrimidinyl, [1,2,4]triazolo[4,3-b]pyridazinyl, benzo[c][1,2,5]thiadiazolyl, benzo[c][1,2,5]oxadiazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, 3,4-dihydro-2H-pyrazolo [1,5-b][1,2]oxazinyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridinyl, thiazolo[5,4-d]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, thieno[2,3-b]pyrrolyl, 3H-indolyl, and derivatives thereof. Furthermore when containing two fused rings the heteroaryl groups herein defined may have an unsaturated or partially saturated ring fused with a fully saturated ring. Exemplary ring systems of these heteroaryl groups include indolinyl, indolinonyl, dihydrobenzothiophenyl, dihydrobenzofuran, chromanyl, thiochromanyl, tetrahydroquinolinyl, dihydrobenzothiazine, 3,4-dihydro-1H--isoquinolinyl, 2,3-dihydrobenzofuran, indolinyl, indolyl, and dihydrobenzoxanyl.

[0077] Halogen or "halo" refers to fluorine, chlorine, bromine, or iodine.

[0078] Alkyl refers to a straight or branched chain saturated hydrocarbon containing 1-12 carbon atoms. Examples of a (C_1-C_4) alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, sec-butyl, and *tert*-butyl.

[0079] "Alkoxy" refers to a straight or branched chain saturated hydrocarbon containing 1-12 carbon atoms containing a terminal "O" in the chain, *e.g.,* -O(alkyl). Examples of alkoxy groups include without limitation, methoxy, ethoxy, propoxy, butoxy, t-butoxy, or pentoxy groups.

[0080] "Cycloalkyl" or "carbocyclyl" means monocyclic or polycyclic saturated carbon rings containing 3-18 carbon atoms. Examples of cycloalkyl groups include, without limitations, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptanyl, cyclooctanyl, norboranyl, norborenyl, bicyclo[2.2.2]octanyl, or bicyclo[2.2.2]octenyl and derivatives thereof. A C_3-C_8 cycloalkyl is a cycloalkyl group containing between 3 and 8 carbon atoms. A cycloalkyl group can be fused (*e.g.*, decalin) or bridged (*e.g.*, norbornane).

[0081] The term "cycloalkenyl" means monocyclic, non-aromatic unsaturated carbon rings containing 4-18 carbon atoms. Examples of cycloalkenyl groups include, without limitation,

cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and norborenyl. A C_4-C_8 cycloalkenyl is a cycloalkenyl group containing between 4 and 8 carbon atoms.

[0082] "Heterocyclyl" or "heterocycloalkyl" refer to monocyclic or polycyclic rings containing carbon and heteroatoms taken from oxygen, nitrogen, or sulfur and wherein there are not delocalized π electrons (aromaticity) shared among the ring carbon or heteroatoms. The heterocycloalkyl ring structure may be substituted by one or more substituents. The substituents can themselves be optionally substituted. Examples of heterocyclyl rings include, but are not limited to, oxetanyl, azetadinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, oxazolinyl, oxazolidinyl, thiazolinyl, thiazolidinyl, pyranyl, thiopyranyl, tetrahydropyranyl, dioxalinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S-dioxide, piperazinyl, azepinyl, oxepinyl, diazepinyl, tropanyl, oxazolidinonyl, and homotropanyl.

[0083] The term "hydroxyalkyl" means an alkyl group as defined above, where the alkyl group is substituted with one or more OH groups. Examples of hydroxyalkyl groups include HO-CH_2-, HO-CH_2-CH_2- and CH_3-CH(OH)-.

[0084] The term "haloalkyl" as used herein refers to an alkyl group, as defined herein, which is substituted one or more halogen. Examples of haloalkyl groups include, but are not limited to, trifluoromethyl, difluoromethyl, pentafluoroethyl, trichloromethyl, etc.

[0085] The term "haloalkoxy" as used herein refers to an alkoxy group, as defined herein, which is substituted one or more halogen. Examples of haloalkyl groups include, but are not limited to, trifluoromethoxy, difluoromethoxy, pentafluoroethoxy, trichloromethoxy, etc.

[0086] The term "cyano" as used herein means a substituent having a carbon atom joined to a nitrogen atom by a triple bond, *e.g.*, C≡N.

[0087] The term "alkylamino" as used herein refers to an amino or NH_2 group where one of the hydrogens have been replaced with an alkyl group, as defined herein above, *i.e.*, -NH(alkyl). Example of alkylamino groups include, but are not limited to, methylamino (*i.e.*, -NH(CH_3)), ethylamino, propylamino, iso-propylamino, dn-butylamino, sec-butylamino, tert-butylamino, etc.

[0088] The term "dialkylamino" as used herein refers to an amino or NH_2 group where both of the hydrogens have been replaced with alkyl groups, as defined herein above, *i.e.*, -N(alkyl)$_2$. The alkyl groups on the amino group can be the same or different alkyl groups. Example of alkylamino groups include, but are not limited to, dimethylamino (*i.e.*, -N(CH_3)$_2$), diethylamino,

dipropylamino, diiso-propylamino, di-n-butylamino, di-sec-butylamino, di-tert-butylamino, methyl(ethyl)amino, methyl(butylamino), etc.

[0089] The term "solvate" refers to a complex of variable stoichiometry formed by a solute and solvent. Such solvents for the purpose of the disclosure may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, MeOH, EtOH, and AcOH. Solvates wherein water is the solvent molecule are typically referred to as hydrates. Hydrates include compositions containing stoichiometric amounts of water, as well as compositions containing variable amounts of water.

[0090] The term "isomer" refers to compounds that have the same composition and molecular weight but differ in physical and/or chemical properties. The structural difference may be in constitution (geometric isomers) or in the ability to rotate the plane of polarized light (stereoisomers). With regard to stereoisomers, the compounds of Formula (I) may have one or more asymmetric carbon atom and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers.

[0091] The disclosure also includes pharmaceutical compositions comprising an effective amount of a disclosed compound and a pharmaceutically acceptable carrier. Representative "pharmaceutically acceptable salts" include, *e.g.*, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, dihydrochloride, edetate, edisylate, estolate, esylate, fumerate, fiunarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, magnesium, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

[0092] A "patient" or "subject" is a mammal, *e.g.*, a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, or non-human primate, such as a monkey, chimpanzee, baboon or rhesus.

[0093] An "effective amount" when used in connection with a compound is an amount effective for treating or preventing a disease in a subject as described herein.

[0094] The term "carrier", as used in this disclosure, encompasses carriers, excipients, and diluents and means a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body of a subject.

[0095] The term "treating" with regard to a subject, refers to improving at least one symptom of the subject's disorder. Treating includes curing, improving, or at least partially ameliorating the disorder.

[0096] The term "disorder" is used in this disclosure to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

[0097] The term "administer", "administering", or "administration" as used in this disclosure refers to either directly administering a disclosed compound or pharmaceutically acceptable salt of the disclosed compound or a composition to a subject, or administering a prodrug derivative or analog of the compound or pharmaceutically acceptable salt of the compound or composition to the subject, which can form an equivalent amount of active compound within the subject's body.

[0098] The term "prodrug," as used in this disclosure, means a compound which is convertible in vivo by metabolic means (*e.g.*, by hydrolysis) to a disclosed compound.

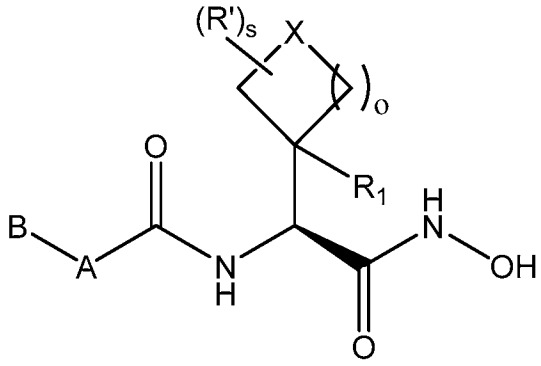
[0099] The term "hydrate," refers to a combination of water with a compound of Formula (I) or (II) wherein the water retains its molecular state as water and is either absorbed, adsorbed, or contained within a crystal lattice of the substrate molecule.

[00100] The term "antibacterial agent" refers to agents that have either bactericidal or bacteriostatic activity. The term "inhibiting the growth" indicates that the rate of increase in the numbers of a population of a particular bacterium is reduced. Thus, the term includes situations in which the bacterial population increases but at a reduced rate, as well as situations where the growth of the population is stopped, as well as situations where the numbers of the bacteria in the population are reduced or the population even eliminated. If an enzyme activity assay is used to screen for inhibitors, one can make modifications in uptake/efflux, solubility, half-life, etc. to compounds in order to correlate enzyme inhibition with growth inhibition. The activity of

antibacterial agents is not necessarily limited to bacteria but may also encompass activity against parasites, virus, and fungi.

[0100] The present disclosure relates to compounds or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, capable of inhibiting LpxC, which are useful for the treatment of bacterial infections. The disclosure further relates to compounds, or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, which are useful for inhibiting LpxC.

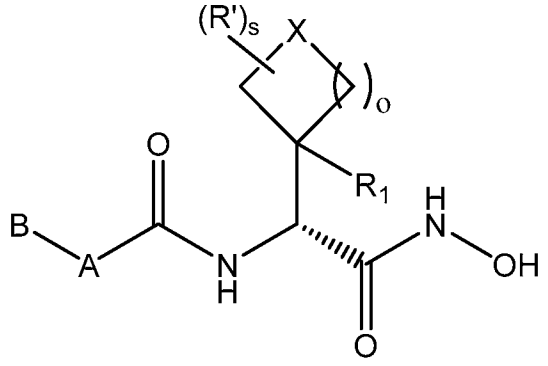
[0101] In one embodiment, the compounds of Formula (I) have the structure of Formula (Ia):



(Ia),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

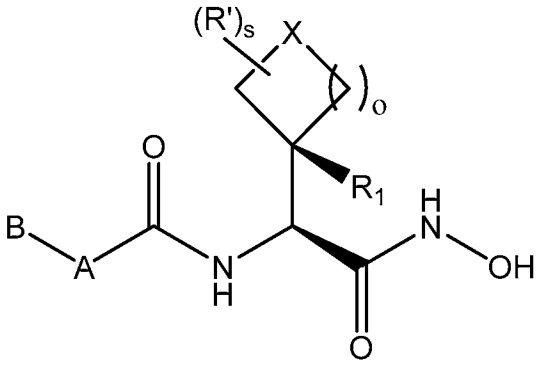
[0102] In another embodiment, the compounds of Formula (I) have the structure of Formula (Ib):



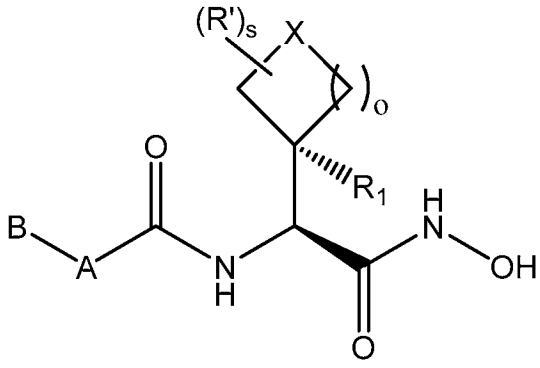
(Ib),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

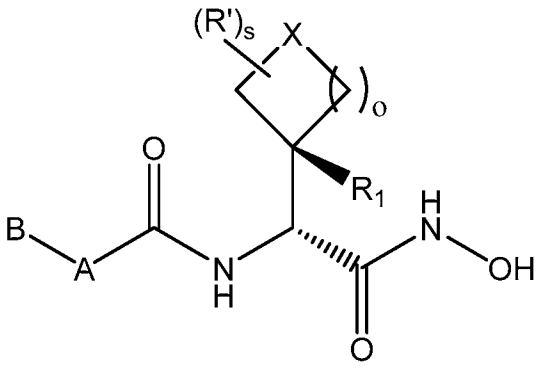
[0103] In one embodiment, the compounds of Formula (I) have the structure of Formula (Ic), Formula (Id), Formula (Ie), or Formula (If):



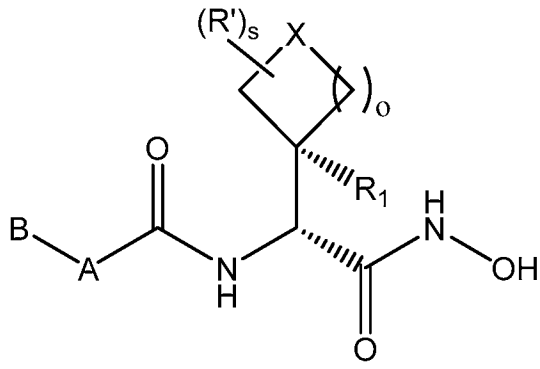
(Ic),



(Id)



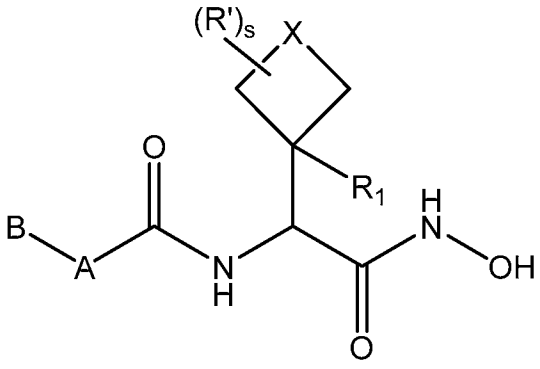
(Ie) or



(If)

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

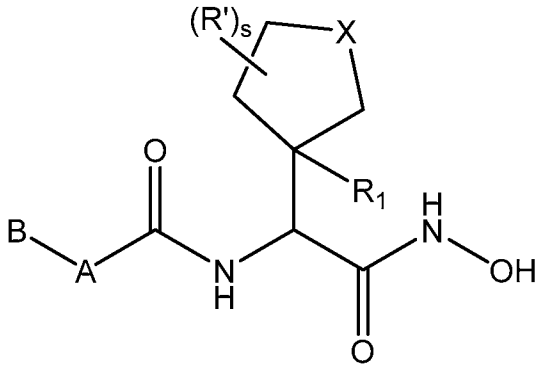
[0104] In another embodiment, the compounds of Formula (I) have the structure of Formula (Ig):



(Ig),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

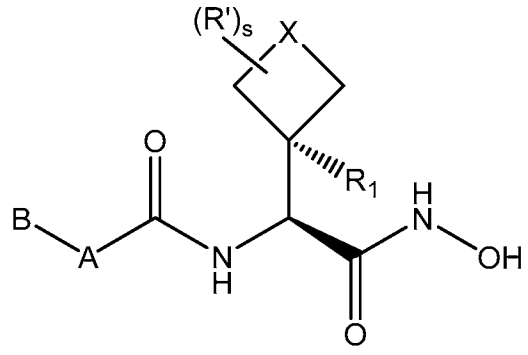
[0105] In another embodiment, the compounds of Formula (I) have the structure of Formula (Ih):



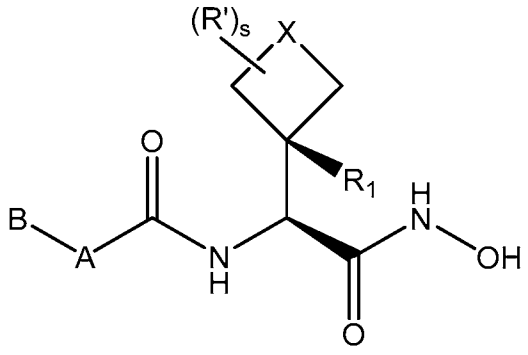
(Ih),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

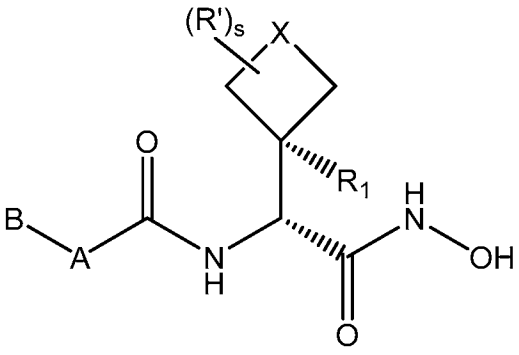
[0106] In another embodiment, the compounds of Formula (I) have the structure of Formula (Ii), Formula (Ij), Formula (Ik), or Formula (Il):



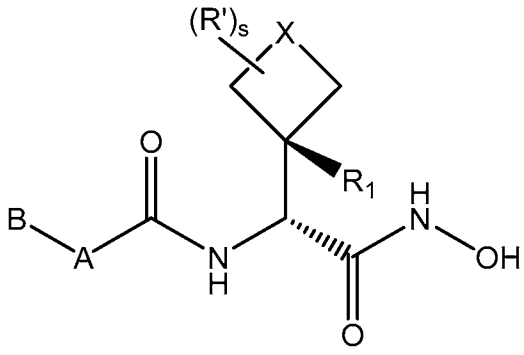
(Ii),



(Ij),



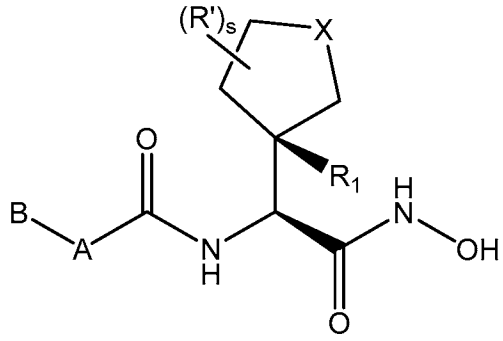
(Ik), or



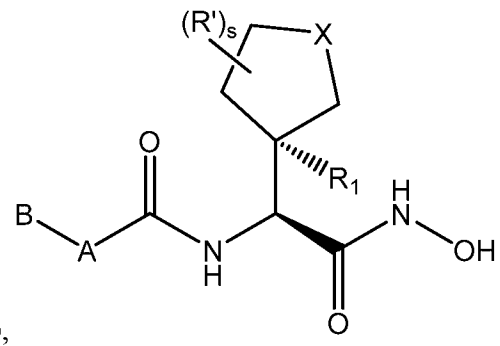
(Il),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

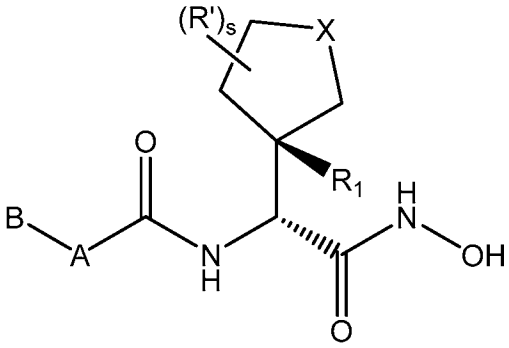
[0107] In another embodiment, the compounds of Formula (I) have the structure of Formula (Im), Formula (Io), Formula (Ip), or Formula (Iq):



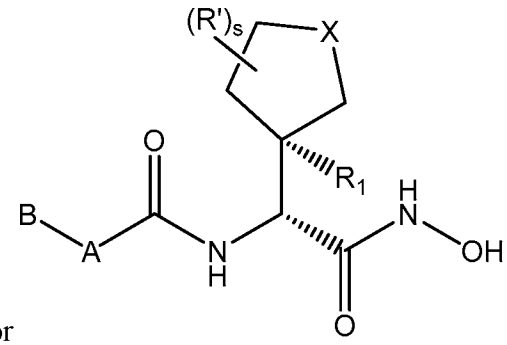
(Im),



(Io),



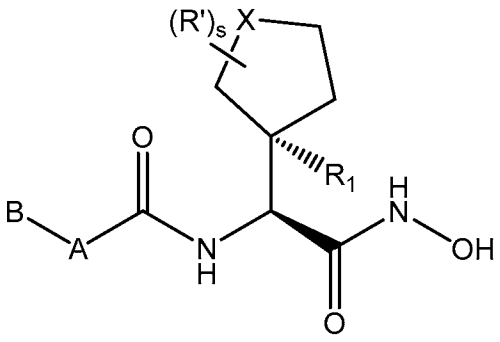
(Ip), or



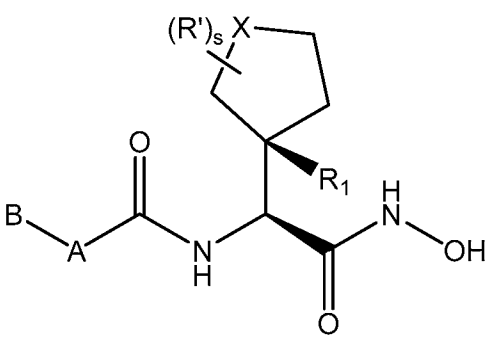
(Iq),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

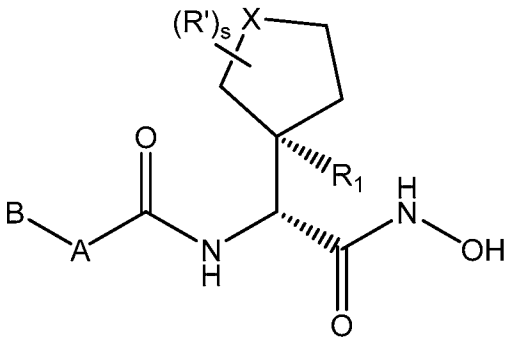
[0108] It should be understood that Formulae (Im), (Io), (Ip), and (Iq) may also be represented as:



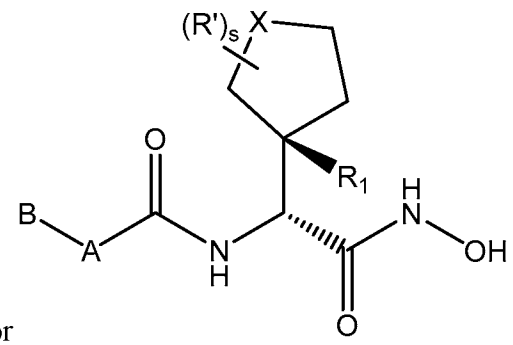
(Im),



(Io),

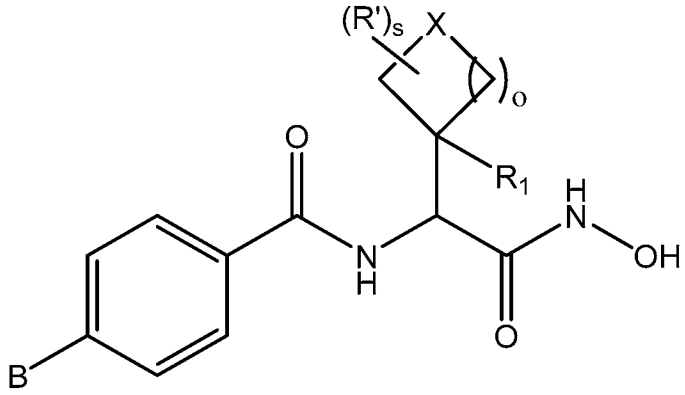


(Ip), or



(Iq),

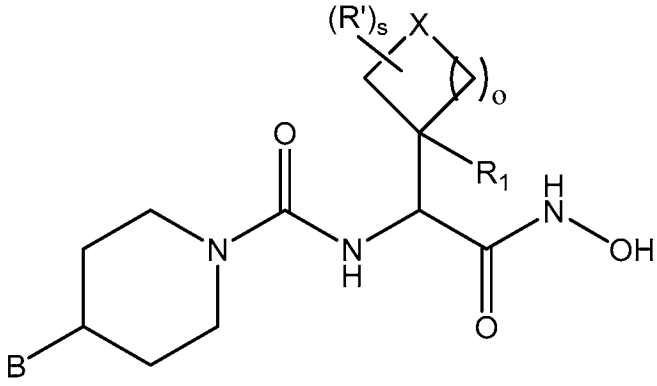
[0109] In another embodiment, the compounds of Formula (I) have the structure of Formula (Ir):



(Ir),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

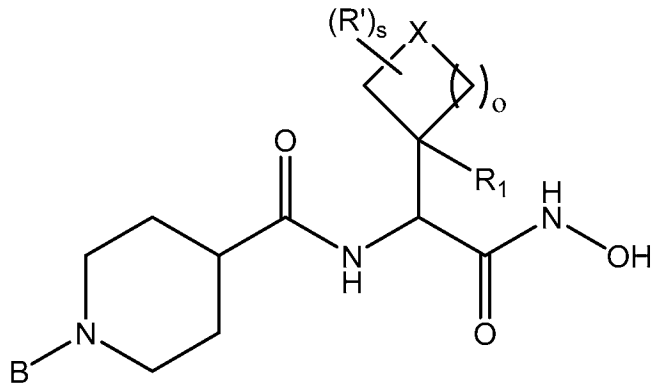
[0110] In another embodiment, the compounds of Formula (I) have the structure of Formula (Iu):



(Iu),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

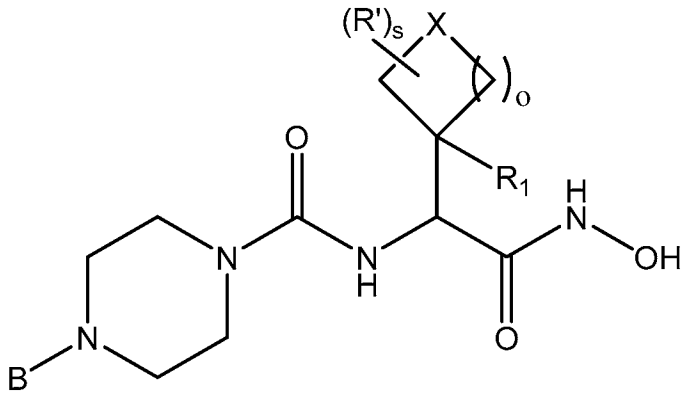
[0111] In another embodiment, the compounds of Formula (I) have the structure of Formula (Iv):



(Iv),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

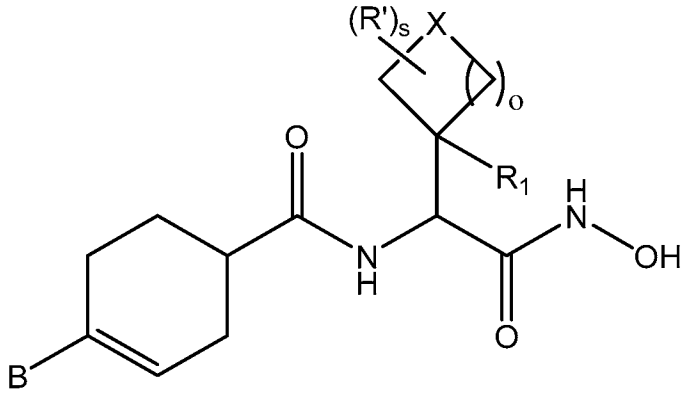
[0112] In another embodiment, the compounds of Formula (I) have the structure of Formula (Ix):



(Ix),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

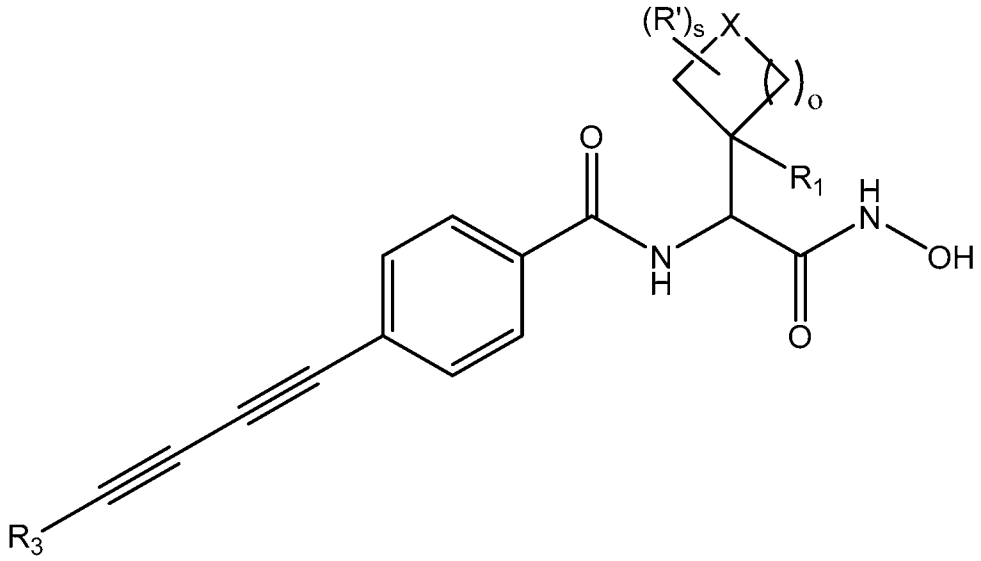
[0113] In another embodiment, the compounds of Formula (I) have the structure of Formula (Iy):



(Iy),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

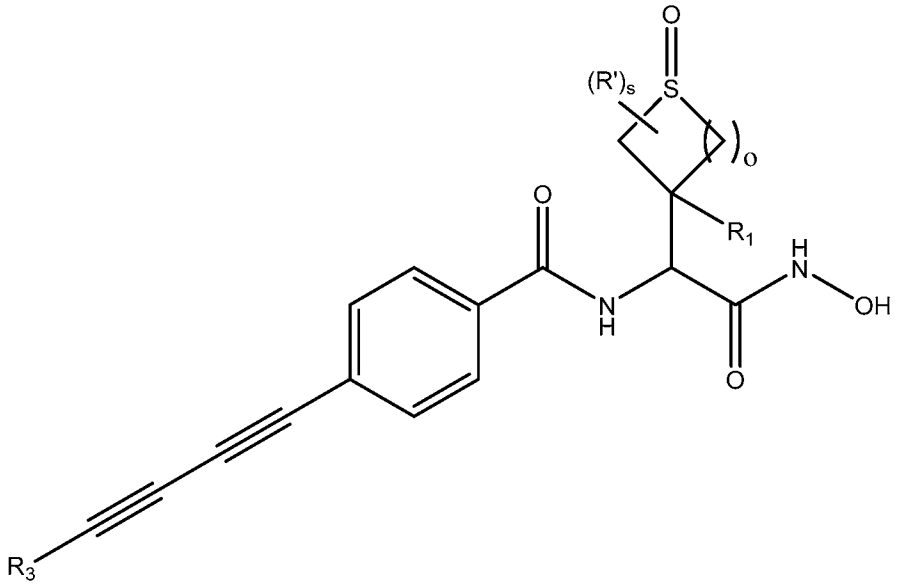
[0114] In another embodiment, the compounds of Formula (I) have the structure of Formula (Iz):



(Iz),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

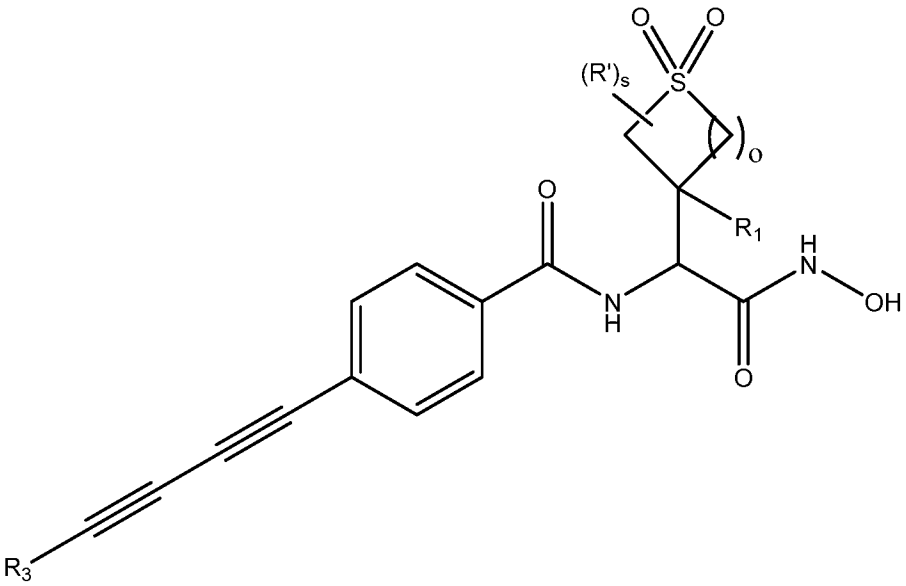
[0115] In another embodiment, the compounds of Formula (I) have the structure of Formula (Iaa):



(Iaa),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

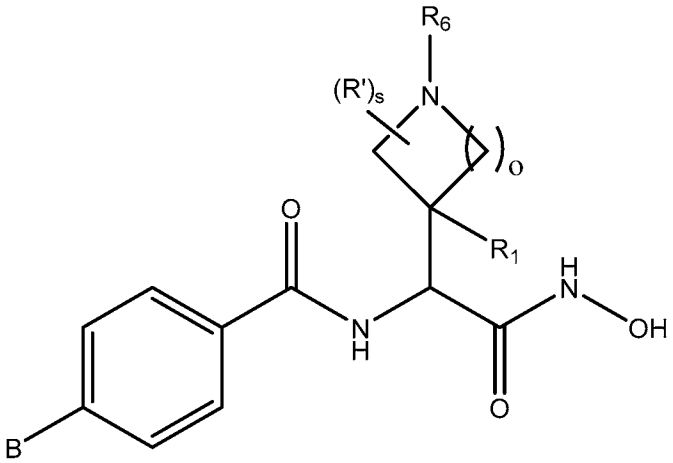
[0116] In another embodiment, the compounds of Formula (I) have the structure of Formula (Ibb):



(Ibb),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

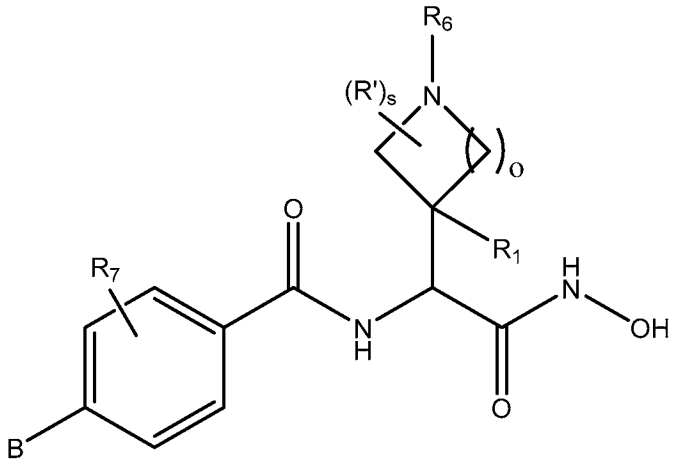
[0117] In another embodiment, the compounds of Formula (I) have the structure of Formula (Icc):



(Icc),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

[0118] In another embodiment, the compounds of Formula (I) have the structure of Formula (Idd):



(Idd),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

[0119] In some embodiments of the Formulae above, X is $S(O)_2$. In another embodiment, X is S(O). In yet another embodiment, X is NR^6.

[0120] In some embodiments of the Formulae above, A is (C_6-C_{10}) aryl, (C_3-C_7) cycloalkyl, (C_4-C_7) cycloalkenyl, or heterocycloalkyl, wherein the aryl, cycloalkyl, cycloalkenyl, or heterocycloalkyl is optionally substituted with one or more R_7. In one embodiment, A is unsubstituted (C_6-C_{10}) aryl, unsubstituted (C_3-C_7) cycloalkyl, unsubstituted (C_4-C_7) cycloalkenyl, or unsubstituted heterocycloalkyl. In another embodiment, A is (C_6-C_{10}) aryl, (C_3-C_7) cycloalkyl, (C_4-C_7) cycloalkenyl, or heterocycloalkyl, wherein the aryl, cycloalkyl, cycloalkenyl, or heterocycloalkyl is substituted with one or more R_7. In another embodiment, A is (C_6-C_{10}) aryl optionally substituted with one or more R_7. In yet another embodiment, A is (C_6-C_{10}) aryl. In one embodiment, A is unsubstituted (C_6-C_{10}) aryl. In another embodiment, A is (C_6-C_{10}) aryl substituted with one or more R_7. In another embodiment, A is phenyl optionally substituted with one or more R_7. In another embodiment, A is phenyl. In one embodiment, A is unsubstituted phenyl. In another embodiment, A is phenyl substituted with one or more R_7. In yet another embodiment, A is (C_4-C_7) cycloalkenyl optionally substituted with one or more R_7. In another embodiment, A is (C_4-C_7) cycloalkenyl. In yet another embodiment, A is cyclopentenyl or cyclohexenyl optionally substituted with one or more R_7. In another embodiment, A is cyclopentenyl or cyclohexenyl. In yet another embodiment, A is cyclohexenyl optionally substituted with one or more R_7. In another embodiment, A is cyclohexenyl. In yet another embodiment, A is heterocycloalkyl optionally substituted with one or more R_7. In another

embodiment, A is heterocycloalkyl. In yet another embodiment, A is piperazinyl, piperidinyl, pyrrolidinyl, or morpholinyl optionally substituted with one or more R_7. In another embodiment, A is piperazinyl, piperidinyl, pyrrolidinyl, or morpholinyl. In yet another embodiment, A is piperazinyl or piperidinyl optionally substituted with one or more R_7. In another embodiment, A is piperazinyl or piperidinyl. In yet another embodiment, A is (C_6-C_{10}) aryl or heterocycloalkyl, wherein the aryl or heterocycloalkyl is optionally substituted with one or more R_7. In another embodiment, A is (C_6-C_{10}) aryl, (C_3-C_7) cycloalkyl, or (C_4-C_7) cycloalkenyl, wherein the aryl, cycloalkyl, or cycloalkenyl, is optionally substituted with one or more R_7. In yet another embodiment, A is (C_6-C_{10}) aryl, (C_3-C_7) cycloalkyl, or heterocycloalkyl, wherein the aryl, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more R_7. In some embodiments of the Formulae above, (C_3-C_7) cycloalkyl, (C_4-C_7) cycloalkenyl, or heterocycloalkyl, wherein the cycloalkyl, cycloalkenyl, or heterocycloalkyl is optionally substituted with one or more R_7.

[0121] In some embodiments of the Formulae above, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, -OR_8, -$S(O)_rR_8$, halogen, or –SF_5. In another embodiment, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –C≡C–CH=CH–R_3. In yet another embodiment, B is –C≡C—R_3 or –C≡C–C≡C–R_3. In another embodiment, B is –C≡C—R_3. In yet another embodiment, B is –C≡C–C≡C–R_3. In another embodiment, B is –C≡C–CH=CH–R_3. In yet another embodiment, B is (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, -OR_8, -$S(O)_rR_8$, halogen, (C_6-C_{10}) aryl, heteroaryl, or –SF_5, wherein the aryl and heteroaryl are optionally substituted with R_2. In one embodiment, B is unsubstituted (C_6-C_{10}) aryl or unsubstituted heteroaryl. In another embodiment, B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl or heteroaryl are substituted with R_2. In another embodiment, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5. In yet another embodiment, B is –C≡C–C≡C–R_3 or –SF_5. In another embodiment, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5. In yet another embodiment, B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, B is (C_1-C_4) haloalkyl, -OR_8, -$S(O)_rR_8$, halogen, or –SF_5.

[0122] In some embodiments of the Formulae above, R_1 is H, (C_1-C_3) alkyl, (C_2-C_3) alkenyl, (C_2-C_3) alkynyl, (C_1-C_3) alkoxy, (C_1-C_3) haloalkyl, (C_1-C_3) haloalkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$(CH_2)_m$heterocycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$heterocycloalkyl, halogen, -$S(O)_p$(C_1-C_3)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_3) alkylamino, or -$(CH_2)_n$(C_1-C_3)

dialkylamino. In another embodiment, R_1 is (C_1-C_3) alkyl, (C_2-C_3) alkenyl, (C_2-C_3) alkynyl, (C_1-C_3) alkoxy, (C_1-C_3) haloalkyl, (C_1-C_3) haloalkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$(CH_2)_m$heterocycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$heterocycloalkyl, halogen, -$S(O)_p$(C_1-C_3)alkyl, -OH, -$(CH_2)_nNH_2$,-$(CH_2)_n$(C_1-C_3) alkylamino, or -$(CH_2)_n$(C_1-C_3) dialkylamino. In yet another embodiment, R_1 is (C_1-C_3) alkoxy or -OH. In another embodiment, R_1 is (C_1-C_3) alkyl, (C_2-C_3) alkenyl, (C_2-C_3) alkynyl, (C_1-C_3) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_3)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_3) alkylamino, or -$(CH_2)_n$(C_1-C_3) dialkylamino. In another embodiment, R_1 is (C_1-C_3) alkyl, (C_2-C_3) alkenyl, (C_2-C_3) alkynyl, (C_1-C_3) alkoxy, or -OH. In one embodiment, R_1 is (C_1-C_3) alkoxy. In another embodiment, R_1 is methoxy.

[0123] In some embodiments of the Formulae above, R_2 is (C_1-C_3) alkyl, (C_1-C_3) alkoxy, (C_1-C_3) haloalkyl, (C_1-C_3) haloalkoxy, halogen, -OH, -NH_2, or –CN. In another embodiment, R_2 is (C_1-C_3) alkyl, (C_1-C_3) alkoxy, (C_1-C_3) haloalkyl, or (C_1-C_3) haloalkoxy. In another embodiment, R_2 is halogen, -OH, -NH_2, or –CN. In another embodiment, R_2 is (C_1-C_3) alkyl, (C_1-C_3) alkoxy, (C_1-C_3) haloalkyl, (C_1-C_3) haloalkoxy, halogen, -OH, or -NH_2. In another embodiment, R_2 is (C_1-C_3) alkyl, (C_1-C_3) alkoxy, (C_1-C_3) haloalkyl, (C_1-C_3) haloalkoxy, or halogen. In another embodiment, R_2 is -OH, -NH_2, or –CN. In certain embodiments, R_2 is absent.

[0124] In some embodiments of the Formulae above, R_3 is H, (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl, heterocycloalkyl, or heteroaryl, wherein the alkyl is optionally substituted with one or more R_4, and wherein the cycloalkyl, heterocycloalkyl, or heteroaryl are optionally substituted with one or more R_5. In one embodiment, R_3 is unsubstituted (C_1-C_4) alkyl, unsubstituted (C_3-C_7) cycloalkyl, unsubsituted heterocycloalkyl, or unsubstituted heteroaryl. In another embodiment, R_3 is (C_1-C_4) alkyl substituted with one or more R_4. In still another embodiment, R_3 is (C_3-C_7) cycloalkyl, heterocycloalkyl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, or heteroaryl is substituted with one or more R_5. In another embodiment, R_3 is H, (C_1-C_4) alkyl, or (C_3-C_7) cycloalkyl, wherein the alkyl is optionally substituted with one or more R_4, and wherein the cycloalkyl is optionally substituted with one or more R_5. In another embodiment, R_3 is H or (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, R_3 is H, (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl, or

heterocycloalkyl, wherein the alkyl is optionally substituted with one or more R_4, and wherein the cycloalkyl or heterocycloalkyl are optionally substituted with one or more R_5. In another embodiment, R_3 is (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl, or heterocycloalkyl, wherein the alkyl is optionally substituted with one or more R_4, and wherein the cycloalkyl or heterocycloalkyl are optionally substituted with one or more R_5. In another embodiment, R_3 is (C_3-C_7) cycloalkyl, or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl are optionally substituted with one or more R_5. In another embodiment, R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, R_3 is azetidinyl optionally substituted with one or more R_5. In another embodiment, R_3 is cyclopropyl optionally substituted with one or more R_5.

[0125] In another embodiment, R_3 is H, (C_1-C_4) alkyl, or (C_3-C_7) cycloalkyl, wherein the alkyl is substituted with one or more R_4, and wherein the cycloalkyl is substituted with one or more R_5. In another embodiment, R_3 is H or (C_1-C_4) alkyl substituted with one or more R_4. In another embodiment, R_3 is (C_1-C_4) alkyl substituted with one or more R_4. In another embodiment, R_3 is (C_1-C_4) alkyl substituted with one or more R_4 or (C_3-C_7) cycloalkyl substituted with one or more R_5. In another embodiment, R_3 is H, (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl, or heterocycloalkyl, wherein the alkyl is substituted with one or more R_4, and wherein the cycloalkyl or heterocycloalkyl are optionally substituted with one or more R_5. In another embodiment, R_3 is (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl, or heterocycloalkyl, wherein the alkyl is substituted with one or more R_4, and wherein the cycloalkyl or heterocycloalkyl are optionally substituted with one or more R_5. In one embodiment, R_3 is (C_1-C_4) alkyl, wherein the (C_1-C_4) alkyl is substituted with one R_4. In a certain embodiment, R_3 is ethyl substituted with one R_4.

[0126] In some embodiments of the Formulae above, each R_4 is independently at each occurrence -OH, -NH_2, (C_1-C_3) alkoxy, (C_1-C_3) alkylamino, or (C_1-C_3) dialkylamino. In another embodiment, each R_4 is independently at each occurrence –OH, -NH_2, or (C_1-C_4) alkoxy. In yet another embodiment, each R_4 is independently at each occurrence –OH or (C_1-C_4) alkoxy. In another embodiment, each R_4 is independently at each occurrence -NH_2, (C_1-C_4) alkylamino, or (C_1-C_4) dialkylamino. In yet another embodiment, each R_4 is independently at each occurrence -OH. In another embodiment, each R_4 is independently at each occurrence –OH or (C_1-C_3) alkoxy. In yet another embodiment, each R_4 is independently at each occurrence (C_1-C_4) alkoxy. In another embodiment, each R_4 is independently at each occurrence –OH, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, or t-butoxy. In yet another embodiment, each R_4 is

independently at each occurrence methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, or t-butoxy. In another embodiment, each R_4 is independently at each occurrence –OH, methoxy, or ethoxy. In yet another embodiment, each R_4 is independently at each occurrence -OH or methoxy. In another embodiment, each R_4 is independently at each occurrence methoxy. In one embodiment, R_3 is (C_1-C_4) alkyl, wherein the (C_1-C_4) alkyl is substituted with one R_4, and wherein the R_4 is –OH. In one embodiment, R_3 is ethyl substituted with one –OH.

[0127] In some embodiments of the Formulae above, each R_5 is independently at each occurrence (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, (C_1-C_3) alkoxy, (C_1-C_3) haloalkoxy, halogen, (C_1-C_3) hydroxyalkyl, –C(O)H, –C(=O)(C_1-C_3) alkyl, -OH, -NH_2, (C_1-C_3) alkylamino, (C_1-C_3) dialkylamino, or -$S(O)_p$(C_1-C_3)alkyl. In another embodiment, each R_5 is independently at each occurrence (C_1-C_3) alkyl, (C_1-C_3) alkoxy, (C_1-C_3) hydroxyalkyl, –C(O)H, –C(=O)(C_1-C_3) alkyl, -OH, -NH_2, (C_1-C_3) alkylamino, (C_1-C_3) dialkylamino, or -$S(O)_p$(C_1-C_3)alkyl. In yet another embodiment, each R_5 is independently at each occurrence R_5 is independently at each occurrence -OH, -NH_2, (C_1-C_3) alkylamino, (C_1-C_3) dialkylamino, or -$S(O)_p$(C_1-C_3)alkyl. In another embodiment, each R_5 is independently at each occurrence R_5 is independently at each occurrence (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, (C_1-C_3) alkoxy, (C_1-C_3) haloalkoxy, halogen, (C_1-C_3) hydroxyalkyl.

[0128] In another embodiment, each R_5 is independently at each occurrence (C_1-C_3) alkyl, (C_1-C_3) alkoxy, (C_1-C_3) hydroxyalkyl, –C(O)H, or –C(=O)(C_1-C_3) alkyl. In yet another embodiment, each R_5 is independently at each occurrence (C_1-C_3) alkyl, (C_1-C_3) alkoxy, or (C_1-C_3) hydroxyalkyl. In another embodiment, each R_5 is independently at each occurrence –C(O)H, -C(=O)(C_1-C_3) alkyl, or -$S(O)_p$(C_1-C_3)alkyl. In yet another embodiment, each R_5 is independently at each occurrence –C(O)H, or –C(=O)(C_1-C_3) alkyl. In another embodiment, each R_5 is independently at each occurrence (C_1-C_3) alkyl or (C_1-C_3) hydroxyalkyl. In yet another embodiment, each R_5 is independently at each occurrence (C_1-C_3) alkyl. In another embodiment, each R_5 is independently at each occurrence (C_1-C_3) hydroxyalkyl. In yet another embodiment, each R_5 is independently at each occurrence (C_1-C_3) alkyl, (C_1-C_3) hydroxyalkyl, -C(O)H, or –C(=O)(C_1-C_3) alkyl. In another embodiment, each R_5 is independently at each occurrence –C(O)H, or –C(=O)methyl.

[0129] In some embodiments of the Formulae above, R_6 is H, (C_1-C_3) alkyl, (C_1-C_3) hydroxyalkyl, -C(O)H, -C(O)(C_1-C_3) alkyl, -$S(O)_r$(C_1-C_3) alkyl, or -C(O)O(C_1-C_4) alkyl. In

another embodiment, R_6 is H, (C_1-C_2) alkyl, (C_1-C_2) hydroxyalkyl, -C(O)H, -C(O)(C_1-C_2) alkyl, -S(O)$_r$(C_1-C_2) alkyl, or -C(O)O(C_1-C_4) alkyl. In yet another embodiment, R_6 is -C(O)H, -C(O)(C_1-C_2) alkyl, -S(O)$_r$(C_1-C_2) alkyl, or -C(O)O(C_1-C_4) alkyl. In another embodiment, R_6 is -C(O)H, -C(O)(C_1-C_2) alkyl, or -C(O)O(C_1-C_4) alkyl. In yet another embodiment, R_6 is H, (C_1-C_2) alkyl, or (C_1-C_2) hydroxyalkyl. In another embodiment, R_6 is H or (C_1-C_3) alkyl. In yet another embodiment, R_6 is H. In another embodiment, R_6 is methyl, ethyl, n-propyl or iso-propyl. In yet another embodiment, R_6 is methyl or ethyl. In another embodiment, R_6 is methyl. In yet another embodiment, R_6 is H or methyl.

[0130] In some embodiments of the Formulae above, each R_7 is independently at each occurrence (C_1-C_3) alkyl, (C_1-C_3) alkoxy, (C_1-C_3) haloalkyl, (C_1-C_3) haloalkoxy, or halogen. In another embodiment, each R_7 is independently at each occurrence (C_1-C_3) haloalkyl, (C_1-C_3) haloalkoxy, or halogen. In yet another embodiment, each R_7 is independently at each occurrence halogen. In another embodiment, each R_7 is independently at each occurrence (C_1-C_3) haloalkoxy. In yet another embodiment, each R_7 is independently at each occurrence (C_1-C_3) haloalkyl. In another embodiment, each R_7 is independently at each occurrence (C_1-C_3) haloalkoxy or halogen. In yet another embodiment, each R_7 is independently at each occurrence (C_1-C_3) haloalkyl or halogen. In another embodiment, each R_7 is independently at each occurrence (C_1-C_3) alkyl or (C_1-C_3) alkoxy. In yet another embodiment, each R_7 is independently at each occurrence (C_1-C_3) alkoxy, (C_1-C_3) haloalkyl, (C_1-C_3) haloalkoxy, or halogen.

[0131] In another embodiment, two R_7 together on adjacent atoms with the atoms to which they are attached form a (C_6-C_{10}) aryl ring optionally substituted with one or more R_9. In yet another embodiment, two R_7 on adjacent atoms together with the atoms to which they are attached form a heteroaryl ring optionally substituted with one or more R_9. In another embodiment, two R_7 on adjacent atoms together with the atoms to which they are attached form a (C_4-C_8) cycloalkyl ring optionally substituted with one or more R_9. In yet another embodiment, two R_7 on adjacent atoms together with the atoms to which they are attached form a heterocycloalkyl ring optionally substituted with one or more R_9. In another embodiment, two R_7 together on adjacent atoms with the atoms to which they are attached form a (C_6-C_{10}) aryl ring optionally substituted with one to three R_9. In yet another embodiment, two R_7 on adjacent atoms together with the atoms to which they are attached form a heteroaryl ring optionally substituted with one to three R_9. In another embodiment, two R_7 on adjacent atoms together with the atoms to which they are attached form

a (C_4-C_8) cycloalkyl ring optionally substituted with one to three R_9. In yet another embodiment, two R_7 on adjacent atoms together with the atoms to which they are attached form a heterocycloalkyl ring optionally substituted with one to three R_9.

[0132] In some embodiments of the Formulae above, R_8 is (C_1-C_3) alkyl, (C_2-C_3) alkenyl, (C_2-C_3) alkynyl, (C_1-C_3) haloalkyl, or (C_3-C_6) cycloalkyl, wherein the alkyl, alkenyl, or alkynyl are optionally substituted with one or more substituents selected from (C_3-C_7) cycloalkyl and heterocycloalkyl. In another embodiment, R_8 is (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, or (C_3-C_6) cycloalkyl, wherein the alkyl is optionally substituted with one or more substituents selected from (C_3-C_7) cycloalkyl and heterocycloalkyl. In yet another embodiment, R_8 is (C_3-C_6) cycloalkyl or (C_1-C_3) alkyl optionally substituted with one or more substituents selected from (C_3-C_7) cycloalkyl and heterocycloalkyl. In another embodiment, R_8 is (C_1-C_3) alkyl, (C_2-C_3) alkenyl, (C_2-C_3) alkynyl, or (C_1-C_3) haloalkyl, wherein the alkyl, alkenyl, or alkynyl are optionally substituted with one or more substituents selected from (C_3-C_7) cycloalkyl and heterocycloalkyl. In yet another embodiment, R_8 is (C_1-C_3) haloalkyl or (C_1-C_3) alkyl optionally substituted with one or more substituents selected from (C_3-C_7) cycloalkyl and heterocycloalkyl. In another embodiment, R_8 is (C_1-C_3) alkyl or (C_1-C_3) haloalkyl.

[0133] In some embodiments of the Formulae above, each R_9 is independently at each occurrence (C_1-C_3) alkyl, (C_1-C_3) alkoxy, (C_1-C_3) haloalkyl, (C_1-C_3) haloalkoxy, or halogen. In another embodiment, each R_9 is independently at each occurrence (C_1-C_3) alkyl, (C_1-C_3) alkoxy, (C_1-C_3) haloalkyl, or (C_1-C_3) haloalkoxy. In yet another embodiment, each R_9 is independently at each occurrence (C_1-C_3) alkyl, (C_1-C_3) alkoxy, or halogen. In another embodiment, each R_9 is independently at each occurrence (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, (C_1-C_3) haloalkoxy, or halogen. In yet another embodiment, each R_9 is independently at each occurrence (C_1-C_3) haloalkyl, (C_1-C_3) haloalkoxy, or halogen. In another embodiment, each R_9 is independently at each occurrence (C_1-C_3) alkyl, (C_1-C_3) alkoxy, (C_1-C_3) haloalkoxy, or halogen.

[0134] In some embodiments of the Formulae above, each R' is (C_1-C_3) alkyl. In another embodiment, R' is (C_1-C_2) alkyl. In another embodiment, R' is (C_2-C_3) alkyl. In yet another embodiment, R' is methyl, ethyl, n-propyl, or iso-propyl. In another embodiment, R' is methyl or ethyl. In yet another embodiment, R' is ethyl, n-propyl, or iso-propyl. In another embodiment, R' is methyl. In yet another embodiment, R' is ethyl. In another embodiment, R' is n-propyl, or iso-propyl.

[0135] In some embodiments of the Formulae above, o is 1. In another embodiment, o is 2.

[0136] In some embodiments of the Formulae above, s is 0, 1, or 2. In some embodiments of the Formulae above, s is 0 or 1. In another embodiment, s is 1 or 2. In yet another embodiment, s is 0. In another embodiment, s is 1. In another embodiment, s is 2.

[0137] In some embodiments of the Formulae above, q is independently at each occurrence 0, 1, or 2. In some embodiments of the Formulae above, q is independently at each occurrence 0 or 1. In another embodiment, q is independently at each occurrence 1 or 2. In yet another embodiment, q is independently at each occurrence 0. In another embodiment, q is independently at each occurrence 1. In yet another embodiment, q is independently at each occurrence 2.

[0138] In some embodiments of the Formulae above, p is independently at each occurrence 0, 1, or 2. In some embodiments of the Formulae above, p is independently at each occurrence 0 or 1. In another embodiment, p is independently at each occurrence 1 or 2. In yet another embodiment, p is independently at each occurrence 0. In another embodiment, p is independently at each occurrence 1. In yet another embodiment, p is independently at each occurrence 2.

[0139] In some embodiments of the Formulae above, r is independently at each occurrence 0, 1, or 2. In some embodiments of the Formulae above, r is independently at each occurrence 0 or 1. In another embodiment, r is independently at each occurrence 1 or 2. In yet another embodiment, r is independently at each occurrence 0. In another embodiment, r is independently at each occurrence 1. In yet another embodiment, r is independently at each occurrence 2.

[0140] In some embodiments of the Formulae above, each m is independently at each occurrence 0, 1, 2, or 3. In some embodiments of the Formulae above, each m is independently at each occurrence 0, 1, or 2. In another embodiment, each m is independently at each occurrence 0 or 1. In yet another embodiment, each m is independently at each occurrence 1 or 2. In another embodiment, each m is independently at each occurrence 2 or 3. In yet another embodiment, each m is independently at each occurrence 1, 2, or 3. In another embodiment, each m is independently at each occurrence 0. In yet another embodiment, each m is independently at each occurrence 1. In another embodiment, each m is independently at each occurrence 2. In yet another embodiment, each m is independently at each occurrence 3.

[0141] In some embodiments of the Formulae above, each n is independently at each occurrence 0, 1, 2, or 3. In some embodiments of the Formulae above, each n is independently at each occurrence 0, 1, or 2. In another embodiment, each n is independently at each occurrence 0 or 1.

In yet another embodiment, each n is independently at each occurrence 1 or 2. In another embodiment, each n is independently at each occurrence 2 or 3. In yet another embodiment, each n is independently at each occurrence 1, 2, or 3. In another embodiment, each n is independently at each occurrence 0. In yet another embodiment, each n is independently at each occurrence 1. In another embodiment, each n is independently at each occurrence 2. In yet another embodiment, each n is independently at each occurrence 3.

[0142] In some embodiments of the Formulae above, X is $S(O)_2$. In another embodiment, X is $S(O)_2$ and A is $(C_6\text{-}C_{10})$ aryl optionally substituted with one to three R_7. In another embodiment, X is $S(O)_2$, A is $(C_6\text{-}C_{10})$ aryl optionally substituted with one to three R_7, and B is –C≡C—R_3, -C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5. In another embodiment, X is $S(O)_2$, A is $(C_6\text{-}C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, and o is 1. In another embodiment, X is $S(O)_2$, A is $(C_6\text{-}C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, and R_1 is H, $(C_1\text{-}C_4)$ alkyl, $(C_1\text{-}C_4)$ alkenyl, $(C_1\text{-}C_4)$ alkynyl, $(C_1\text{-}C_4)$ alkoxy, $-(CH_2)_m(C_3\text{-}C_7)$ cycloalkyl, $-O(CH_2)_m(C_3\text{-}C_7)$ cycloalkyl, $-S(O)_p(C_1\text{-}C_4)$alkyl, -OH, $-(CH_2)_nNH_2$, $-(CH_2)_n(C_1\text{-}C_4)$ alkylamino, or $-(CH_2)_n(C_1\text{-}C_4)$ dialkylamino. In another embodiment, X is $S(O)_2$, A is $(C_6\text{-}C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, -C≡C–CH=CH–R_3, or –SF_5, o is 1, and R_1 is $(C_1\text{-}C_4)$ alkyl, $(C_1\text{-}C_4)$ alkenyl, $(C_1\text{-}C_4)$ alkynyl, $(C_1\text{-}C_4)$ alkoxy, $-(CH_2)_m(C_3\text{-}C_7)$ cycloalkyl, $-O(CH_2)_m(C_3\text{-}C_7)$ cycloalkyl, $-S(O)_p(C_1\text{-}C_4)$alkyl, -OH, $-(CH_2)_nNH_2$, $-(CH_2)_n(C_1\text{-}C_4)$ alkylamino, or $-(CH_2)_n(C_1\text{-}C_4)$ dialkylamino.

[0143] In certain embodiments of the Formulae above, such as in Formulae (I), (Ia), (Ib), or (Ig), X is $S(O)_q$; A is $(C_6\text{-}C_{10})$ aryl, wherein the aryl is unsubstituted or substituted with one or more R_7; B is -C≡C–C≡C–R_3; R_3 is $(C_1\text{-}C_4)$ alkyl substituted with one or more R_4; and R_1 is $(C_1\text{-}C_4)$ alkoxy. In certain embodiments, s is 0. In one embodiment, o is 1. In one embodiment, q is 2. In one embodiment, A is unsubstituted $(C_6\text{-}C_{10})$ aryl. In another embodiment, A is unsubstituted phenyl. In still another embodiment, R_3 is ethyl substituted with one or more R_4. In a certain embodiment, R_3 is ethyl substituted with –OH. In still another embodiment, R_1 is methoxy.

[0144] In one embodiment of Formula (I), X is $S(O)_2$, A is $(C_6\text{-}C_{10})$ aryl wherein the aryl is unsubstituted or substituted with one or more R_7, B is -C≡C–C≡C–R_3, R_3 is $(C_1\text{-}C_4)$ alkyl substituted with one or more R_4, o is 1, R_1 is $(C_1\text{-}C_4)$ alkoxy, and s is 0. In one embodiment, A is unsubstituted $(C_6\text{-}C_{10})$ aryl. In another embodiment, A is unsubstituted phenyl. In still another

embodiment, R_3 is ethyl substituted with one or more R_4. In a certain embodiment, R_3 is ethyl substituted with –OH. In still another embodiment, R_1 is methoxy.

[0145] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is -C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0146] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0147] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4)

alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0148] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0149] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, and o is 2. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is -C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0150] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more

R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is -C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0151] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0152] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0153] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl,

-O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0154] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, and B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or -SF_5, and o is 1. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino.

[0155] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, and o is 1. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3

is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0156] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, and o is 1. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino and R_3 is (C_1-C_4) alkyl optionally substituted with one or more.

[0157] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, and o is 1. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0158] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, and o is 1. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl

optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0159] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, and o is 2. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is -C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0160] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or -SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0161] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$)

dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is -C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0162] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is -C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0163] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is -C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0164] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, and B is –C≡C–C≡C–R_3 or –SF_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, and o is 1. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is -C≡C–C≡C–R_3 or –SF_5, o is 1, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl,

(C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is -C≡C–C≡C–R_3 or –SF_5, o is 1, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0165] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0166] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is -C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0167] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3

is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is -C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0168] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or -SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0169] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, and o is 2. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino.

[0170] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally

substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0171] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is -C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl,-OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0172] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or -SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0173] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is

$S(O)_2$, A is $(C_6\text{-}C_{10})$ aryl optionally substituted with one to three R_7, B is -C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is $(C_1\text{-}C_4)$ alkyl, $(C_1\text{-}C_4)$ alkenyl, $(C_1\text{-}C_4)$ alkynyl, $(C_1\text{-}C_4)$ alkoxy, -$(CH_2)_m(C_3\text{-}C_7)$ cycloalkyl, -$O(CH_2)_m(C_3\text{-}C_7)$ cycloalkyl, -$S(O)_p(C_1\text{-}C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1\text{-}C_4)$ alkylamino, or -$(CH_2)_n(C_1\text{-}C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0174] In another embodiment, X is $S(O)_2$, A is $(C_6\text{-}C_{10})$ aryl optionally substituted with one to three R_7, and B is –C≡C—R_3. In another embodiment, X is $S(O)_2$, A is $(C_6\text{-}C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, and o is 1. In another embodiment, X is $S(O)_2$, A is $(C_6\text{-}C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, and R_1 is H, $(C_1\text{-}C_4)$ alkyl, $(C_1\text{-}C_4)$ alkenyl, $(C_1\text{-}C_4)$ alkynyl, $(C_1\text{-}C_4)$ alkoxy, -$(CH_2)_m(C_3\text{-}C_7)$ cycloalkyl, -$O(CH_2)_m(C_3\text{-}C_7)$ cycloalkyl, -$S(O)_p(C_1\text{-}C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1\text{-}C_4)$ alkylamino, or -$(CH_2)_n(C_1\text{-}C_4)$ dialkylamino. In another embodiment, X is $S(O)_2$, A is $(C_6\text{-}C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, and R_1 is $(C_1\text{-}C_4)$ alkyl, $(C_1\text{-}C_4)$ alkenyl, $(C_1\text{-}C_4)$ alkynyl, $(C_1\text{-}C_4)$ alkoxy, -$(CH_2)_m(C_3\text{-}C_7)$ cycloalkyl, -$O(CH_2)_m(C_3\text{-}C_7)$ cycloalkyl, -$S(O)_p(C_1\text{-}C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1\text{-}C_4)$ alkylamino, or -$(CH_2)_n(C_1\text{-}C_4)$ dialkylamino.

[0175] In another embodiment, X is $S(O)_2$, A is $(C_6\text{-}C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is H, $(C_1\text{-}C_4)$ alkyl, $(C_1\text{-}C_4)$ alkenyl, $(C_1\text{-}C_4)$ alkynyl, $(C_1\text{-}C_4)$ alkoxy, -$(CH_2)_m(C_3\text{-}C_7)$ cycloalkyl, -$O(CH_2)_m(C_3\text{-}C_7)$ cycloalkyl, -$S(O)_p(C_1\text{-}C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1\text{-}C_4)$ alkylamino, or -$(CH_2)_n(C_1\text{-}C_4)$ dialkylamino, and R_3 is $(C_1\text{-}C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3\text{-}C_7)$ cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is $(C_6\text{-}C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is $(C_1\text{-}C_4)$ alkyl, $(C_1\text{-}C_4)$ alkenyl, $(C_1\text{-}C_4)$ alkynyl, $(C_1\text{-}C_4)$ alkoxy, -$(CH_2)_m(C_3\text{-}C_7)$ cycloalkyl, -$O(CH_2)_m(C_3\text{-}C_7)$ cycloalkyl, -$S(O)_p(C_1\text{-}C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1\text{-}C_4)$ alkylamino, or -$(CH_2)_n(C_1\text{-}C_4)$ dialkylamino, and R_3 is $(C_1\text{-}C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3\text{-}C_7)$ cycloalkyl optionally substituted with one or more R_5.

[0176] In another embodiment, X is $S(O)_2$, A is $(C_6\text{-}C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is H, $(C_1\text{-}C_4)$ alkyl, $(C_1\text{-}C_4)$ alkenyl, $(C_1\text{-}C_4)$ alkynyl, $(C_1\text{-}C_4)$ alkoxy, -$(CH_2)_m(C_3\text{-}C_7)$ cycloalkyl, -$O(CH_2)_m(C_3\text{-}C_7)$ cycloalkyl, -$S(O)_p(C_1\text{-}C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1\text{-}C_4)$ alkylamino, or -$(CH_2)_n(C_1\text{-}C_4)$ dialkylamino, and R_3 is $(C_1\text{-}C_4)$ alkyl

optionally substituted with one or more R_4. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0177] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0178] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0179] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, and o is 2. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with

one to three R_7, B is –C≡C—R_3, o is 2, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0180] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0181] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is(C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0182] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino,

or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5.

[0183] In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0184] In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, and B is –C≡C–C≡C–R_3. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, and o is 1. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is -C≡C–C≡C–R_3, o is 1, and R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is -C≡C–C≡C–R_3, o is 1, and R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino.

[0185] In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-

C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0186] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0187] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0188] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino,

or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0189] In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, and o is 2. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, and R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, and R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino.

[0190] In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5.

[0191] In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino,

or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4.

[0192] In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5.

[0193] In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0194] In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, and B is –C≡C–CH=CH–R_3. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, and o is 1. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is -C≡C–CH=CH–R_3, o is 1, and R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is -C≡C–CH=CH–R_3, o is 1, and R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$

alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino.

[0195] In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5.

[0196] In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is -C≡C–CH=CH–R_3, o is 1, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4.

[0197] In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino,

or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5.

[0198] In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0199] In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, and o is 2. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, and R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, and R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino.

[0200] In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3

is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0201] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0202] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0203] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino,

or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0204] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, and B is $-SF_5$. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is $-SF_5$, and o is 1. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is $-SF_5$, o is 1, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is $-SF_5$, o is 1, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino.

[0205] In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is $-SF_5$, and o is 2. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is $-SF_5$, o is 2, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino. In another embodiment, X is $S(O)_2$, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is $-SF_5$, o is 2, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino.

[0206] In some embodiments of the Formulae above, X is S(O). In another embodiment, X is S(O) and A is (C_6-C_{10}) aryl optionally substituted with one to three R_7. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, and B is $-C\equiv C-$—R_3, -$C\equiv C-C\equiv C-R_3$, $-C\equiv C-CH=CH-R_3$, or $-SF_5$. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is $-C\equiv C-R_3$, $-C\equiv C-C\equiv C-R_3$, $-C\equiv C-CH=CH-R_3$, or $-SF_5$, and o is 1. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is $-C\equiv C-R_3$, $-C\equiv C-C\equiv C-R_3$, $-C\equiv C-CH=CH-R_3$, or $-SF_5$, o is 1, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino. In another embodiment, X is S(O), A is (C_6-C_{10})

aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0207] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$,-$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0208] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$,-$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0209] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$,-$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or

more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0210] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$,-$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0211] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, and o is 2. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is -C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0212] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl,

-O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0213] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0214] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0215] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0216] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0217] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino,

or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0218] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0219] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0220] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three

R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0221] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0222] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0223] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, and B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or -SF_5, and o is 1. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, and R_1 is H, (C_1-C_4) alkyl,

(C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0224] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or -SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0225] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0226] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7)

cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is -C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0227] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, and o is 2. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino.

[0228] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0229] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7)

cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0230] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0231] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0232] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, and B is –C≡C–C≡C–R_3 or –SF_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, and o is 1. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is

–C≡C–C≡C–R_3 or –SF_5, o is 1, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0233] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0234] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0235] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-

C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0236] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0237] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, and o is 2. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino.

[0238] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or-$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3

is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0239] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0240] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or-$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0241] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or-$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3

is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0242] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, and B is –C≡C—R_3. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, and o is 1. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0243] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0244] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH,

$-(CH_2)_nNH_2$, $-(CH_2)_n(C_1-C_4)$ alkylamino, or $-(CH_2)_n(C_1-C_4)$ dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, $-(CH_2)_m(C_3-C_7)$ cycloalkyl, $-O(CH_2)_m(C_3-C_7)$ cycloalkyl, $-S(O)_p(C_1-C_4)$alkyl, -OH, $-(CH_2)_nNH_2$, $-(CH_2)_n(C_1-C_4)$ alkylamino, or $-(CH_2)_n(C_1-C_4)$ dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0245] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, $-(CH_2)_m(C_3-C_7)$ cycloalkyl, $-O(CH_2)_m(C_3-C_7)$ cycloalkyl, $-S(O)_p(C_1-C_4)$alkyl, -OH, $-(CH_2)_nNH_2$, $-(CH_2)_n(C_1-C_4)$ alkylamino, or $-(CH_2)_n(C_1-C_4)$ dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, $-(CH_2)_m(C_3-C_7)$ cycloalkyl, $-O(CH_2)_m(C_3-C_7)$ cycloalkyl, $-S(O)_p(C_1-C_4)$alkyl, -OH, $-(CH_2)_nNH_2$, $-(CH_2)_n(C_1-C_4)$ alkylamino, or $-(CH_2)_n(C_1-C_4)$ dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0246] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, $-(CH_2)_m(C_3-C_7)$ cycloalkyl, $-O(CH_2)_m(C_3-C_7)$ cycloalkyl, $-S(O)_p(C_1-C_4)$alkyl, -OH, $-(CH_2)_nNH_2$, $-(CH_2)_n(C_1-C_4)$ alkylamino, or $-(CH_2)_n(C_1-C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, $-(CH_2)_m(C_3-C_7)$ cycloalkyl, $-O(CH_2)_m(C_3-C_7)$ cycloalkyl, $-S(O)_p(C_1-C_4)$alkyl, -OH, $-(CH_2)_nNH_2$, $-(CH_2)_n(C_1-C_4)$ alkylamino, or $-(CH_2)_n(C_1-C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0247] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, and B is –C≡C—R_3. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, and o is 2. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, $-(CH_2)_m(C_3-C_7)$ cycloalkyl,

-O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino.

[0248] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0249] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0250] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is

(C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0251] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0252] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, and B is –C≡C–C≡C–R_3. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, and o is 1. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0253] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with

one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0254] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0255] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0256] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O),

A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0257] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, and o is 2. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0258] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0259] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is S(O), A is (C_6-

C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0260] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0261] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0262] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, and B is –C≡C–CH=CH–R_3. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, and o is 1. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH,

-$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino. In another embodiment, X is S(O), A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, and R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino.

[0263] In another embodiment, X is S(O), A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl,-OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5.

[0264] In another embodiment, X is S(O), A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4. In another embodiment, X is S(O), A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4.

[0265] In another embodiment, X is S(O), A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl,-OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is

(C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0266] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl,-OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0267] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, and o is 2. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0268] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or-$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with

one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0269] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0270] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0271] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1

is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0272] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, and B is –SF_5. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –SF_5, and o is 1. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –SF_5, o is 1, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –SF_5, o is 1, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0273] In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –SF_5, and o is 2. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –SF_5, o is 2, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is S(O), A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –SF_5, o is 2, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0274] In some embodiments of the Formulae above, X is NR^6. In another embodiment, X is NR^6 and A is (C_6-C_{10}) aryl optionally substituted with one to three R_7. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, and B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, and o is 1. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7)

cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino.

[0275] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$,-($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0276] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$,-($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0277] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl,

-O$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -S$(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$,-$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -O$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -S$(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5.

[0278] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -O$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -S$(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$,-$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 1, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -O$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -S$(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0279] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, and o is 2. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, and R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -O$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -S$(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, and R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -O$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -S$(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino.

[0280] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0281] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0282] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino,

or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5.

[0283] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or $–SF_5$, o is 2, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, or $–SF_5$, o is 2, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0284] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, and B is –C≡C—R_3, –C≡C–C≡C–R_3, or $–SF_5$. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or $–SF_5$, and o is 1. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or $–SF_5$, o is 1, and R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or $–SF_5$, o is 1, and R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino.

[0285] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or $–SF_5$, o is 1, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is

(C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0286] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0287] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0288] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is

–C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0289] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, and o is 2. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0290] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0291] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is

–C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0292] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0293] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, –C≡C–C≡C–R_3, or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0294] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, and B is –C≡C–C≡C–R_3 or –SF_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, and o is 1. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another

embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0295] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0296] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy,-$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0297] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5,

o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy,-$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0298] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy,-$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0299] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, and o is 2. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0300] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4)

alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0301] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0302] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0303] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3 or –SF_5, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7)

cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0304] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, and B is –C≡C—R_3. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, and o is 1. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino.

[0305] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0306] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4)

alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0307] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0308] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0309] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, and o is 2. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl,

(C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino.

[0310] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0311] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0312] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino,

or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5.

[0313] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C—R_3, o is 2, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0314] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, and B is –C≡C–C≡C–R_3. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, and o is 1. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, and R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, and R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino.

[0315] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl,

-OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0316] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0317] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0318] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 1, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n$(C_1-C_4) alkylamino,

or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0319] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, and o is 2. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, and R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, and R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino.

[0320] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5.

[0321] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$

cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0322] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0323] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–C≡C–R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0324] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, and B is –C≡C–CH=CH–R_3. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, and o is 1. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl, -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4)

alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino.

[0325] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5.

[0326] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4.

[0327] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino,

or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5.

[0328] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 1, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0329] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, and o is 2. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, and R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, and R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino.

[0330] In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is H, $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is $(C_1$-$C_4)$ alkyl optionally substituted with one or more R_4 or $(C_3$-$C_7)$ cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is $(C_6$-$C_{10})$ aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is $(C_1$-$C_4)$ alkyl, $(C_1$-$C_4)$ alkenyl, $(C_1$-$C_4)$ alkynyl, $(C_1$-$C_4)$ alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3

is (C_1-C_4) alkyl optionally substituted with one or more R_4 or (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0331] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0332] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is (C_3-C_7) cycloalkyl optionally substituted with one or more R_5.

[0333] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is –C≡C–CH=CH–R_3, o is 2, R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -S$(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$, -$(CH_2)_n$($C_1$-$C_4$) alkylamino,

or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino, and R_3 is heterocycloalkyl optionally substituted with one or more R_5.

[0334] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, and B is $-SF_5$. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is $-SF_5$, and o is 1. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is $-SF_5$, o is 1, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is $-SF_5$, o is 1, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino.

[0335] In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is $-SF_5$, and o is 2. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is $-SF_5$, o is 2, and R_1 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino. In another embodiment, X is NR^6, A is (C_6-C_{10}) aryl optionally substituted with one to three R_7, B is $-SF_5$, o is 2, and R_1 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, (C_1-C_4) alkoxy, -$(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$O(CH_2)_m(C_3$-$C_7)$ cycloalkyl, -$S(O)_p(C_1$-$C_4)$alkyl, -OH, -$(CH_2)_nNH_2$, -$(CH_2)_n(C_1$-$C_4)$ alkylamino, or -$(CH_2)_n(C_1$-$C_4)$ dialkylamino.

[0336] In another embodiment, X is $S(O)_2$ and A is (C_4-C_7) cycloalkenyl optionally substituted with one or more R_7. In another embodiment, X is $S(O)_2$ and A is (C_4-C_7) cycloalkenyl. In another embodiment, X is $S(O)_2$, A is (C_4-C_7) cycloalkenyl optionally substituted with one or more R_7, and o is 1. In another embodiment, X is $S(O)_2$, A is (C_4-C_7) cycloalkenyl, and o is 1. In another embodiment, X is $S(O)_2$, A is (C_4-C_7) cycloalkenyl optionally substituted with one or more R_7, and o is 2. In another embodiment, X is $S(O)_2$, A is (C_4-C_7) cycloalkenyl, and o is 2.

[0337] In another embodiment, X is $S(O)_2$, A is (C_4-C_7) cycloalkenyl optionally substituted with one or more R_7, o is 1, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, X is $S(O)_2$, A is (C_4-C_7) cycloalkenyl, o is 1, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally

substituted with R_2. In another embodiment, X is $S(O)_2$, A is (C_4-C_7) cycloalkenyl optionally substituted with one or more R_7, o is 2, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, X is $S(O)_2$, A is (C_4-C_7) cycloalkenyl, o is 2, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2.

[0338] In another embodiment, X is $S(O)_2$ and A is heterocycloalkyl optionally substituted with one or more R_7. In another embodiment, X is $S(O)_2$ and A is heterocycloalkyl. In another embodiment, X is $S(O)_2$, A is heterocycloalkyl optionally substituted with one or more R_7, and o is 1. In another embodiment, X is $S(O)_2$, A is heterocycloalkyl, and o is 1. In another embodiment, X is $S(O)_2$, A is heterocycloalkyl optionally substituted with one or more R_7, and o is 2. In another embodiment, X is $S(O)_2$, A is heterocycloalkyl, and o is 2.

[0339] In another embodiment, X is $S(O)_2$, A is heterocycloalkyl optionally substituted with one or more R_7, o is 1, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, X is $S(O)_2$, A is heterocycloalkyl, o is 1, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, X is $S(O)_2$, A is heterocycloalkyl optionally substituted with one or more R_7, o is 2, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, X is $S(O)_2$, A is heterocycloalkyl, o is 2, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2.

[0340] In another embodiment, X is S(O) and A is (C_4-C_7) cycloalkenyl optionally substituted with one or more R_7. In another embodiment, X is S(O) and A is (C_4-C_7) cycloalkenyl. In another embodiment, X is S(O), A is (C_4-C_7) cycloalkenyl optionally substituted with one or more R_7, and o is 1. In another embodiment, X is S(O), A is (C_4-C_7) cycloalkenyl, and o is 1. In another embodiment, X is S(O), A is (C_4-C_7) cycloalkenyl optionally substituted with one or more R_7, and o is 2. In another embodiment, X is S(O), A is (C_4-C_7) cycloalkenyl, and o is 2.

[0341] In another embodiment, X is S(O), A is (C_4-C_7) cycloalkenyl optionally substituted with one or more R_7, o is 1, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, X is S(O), A is (C_4-C_7) cycloalkenyl, o is 1, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, X is S(O), A is (C_4-C_7) cycloalkenyl optionally substituted with

one or more R_7, o is 2, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, X is S(O), A is (C_4-C_7) cycloalkenyl, o is 2, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2.

[0342] In another embodiment, X is S(O) and A is heterocycloalkyl optionally substituted with one or more R_7. In another embodiment, X is S(O) and A is heterocycloalkyl. In another embodiment, X is S(O), A is heterocycloalkyl optionally substituted with one or more R_7, and o is 1. In another embodiment, X is S(O), A is heterocycloalkyl, and o is 1. In another embodiment, X is S(O), A is heterocycloalkyl optionally substituted with one or more R_7, and o is 2. In another embodiment, X is S(O), A is heterocycloalkyl, and o is 2.

[0343] In another embodiment, X is S(O), A is heterocycloalkyl optionally substituted with one or more R_7, o is 1, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, X is S(O), A is heterocycloalkyl, o is 1, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, X is S(O), A is heterocycloalkyl optionally substituted with one or more R_7, o is 2, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, X is S(O), A is heterocycloalkyl, o is 2, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2.

[0344] In another embodiment, X is NR^6 and A is (C_4-C_7) cycloalkenyl optionally substituted with one or more R_7. In another embodiment, X is NR^6 and A is (C_4-C_7) cycloalkenyl. In another embodiment, X is NR^6, A is (C_4-C_7) cycloalkenyl optionally substituted with one or more R_7, and o is 1. In another embodiment, X is NR^6, A is (C_3-C_7) cycloalkenyl, and o is 1. In another embodiment, X is NR^6, A is (C_4-C_7) cycloalkenyl optionally substituted with one or more R_7, and o is 2. In another embodiment, X is NR^6, A is (C_4-C_7) cycloalkenyl, and o is 2.

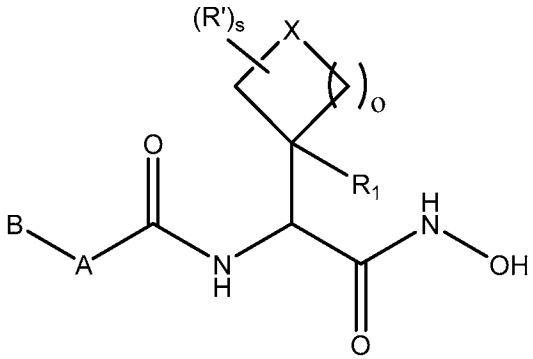
[0345] In another embodiment, X is NR^6, A is (C_4-C_7) cycloalkenyl optionally substituted with one or more R_7, o is 1, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, X is NR^6, A is (C_4-C_7) cycloalkenyl, o is 1, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, X is NR^6, A is (C_4-C_7) cycloalkenyl optionally substituted with one or more R_7, o is 2, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are

optionally substituted with R_2. In another embodiment, X is NR^6, A is (C_4-C_7) cycloalkenyl, o is 2, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2.

[0346] In another embodiment, X is NR^6 and A is heterocycloalkyl optionally substituted with one or more R_7. In another embodiment, X is NR^6 and A is heterocycloalkyl. In another embodiment, X is NR^6, A is heterocycloalkyl optionally substituted with one or more R_7, and o is 1. In another embodiment, X is NR^6, A is heterocycloalkyl, and o is 1. In another embodiment, X is NR^6, A is heterocycloalkyl optionally substituted with one or more R_7, and o is 2. In another embodiment, X is NR^6, A is heterocycloalkyl, and o is 2.

[0347] In another embodiment, X is NR^6, A is heterocycloalkyl optionally substituted with one or more R_7, o is 1, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, X is NR^6, A is heterocycloalkyl, o is 1, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, X is NR^6, A is heterocycloalkyl optionally substituted with one or more R_7, o is 2, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2. In another embodiment, X is NR^6, A is heterocycloalkyl, o is 2, and B is (C_6-C_{10}) aryl or heteroaryl, wherein the aryl and heteroaryl are optionally substituted with R_2.

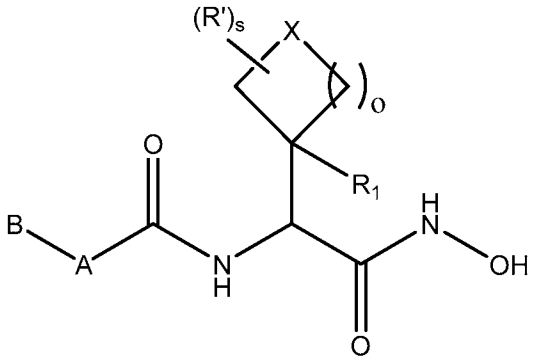
[0348] Another aspect of the disclosure relates to a prodrug of a compound of Formula (I) having a Formula (II):



(II),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof, wherein R_1, R', A, B, X, o, and s are as described herein above.

[0349] Another aspect of the disclosure relates to compounds of Formula (II), wherein the compound of Formula (II) is a prodrug of Formula (I):



(II),

or pharmaceutically acceptable salts, hydrates, solvates, stereoisomers, or tautomers thereof;

wherein:

R_1, R', A, X, o, and s are as described above for Formula (I);

B is –C≡C—R_3 or –C≡C–C≡C–R_3;

R_3 is (C_1-C_4) alkyl substituted with one or more Q; and

each Q is independently at each occurrence -OP(=O)$(OH)_2$, -OCH_2OP(=O)$(OH)_2$, -OC(=O)R_a, or -OCH_2OC(=O).

[0350] In some embodiments of Formula (II), R_3 is (C_1-C_4) alkyl substituted with one to two Q. In another embodiment, R_3 is (C_1-C_4) alkyl substituted with one Q.

[0351] In some embodiments of Formula (II), each Q is independently at each occurrence -OP(=O)$(OH)_2$, -OCH_2OP(=O)$(OH)_2$, -OC(=O)R_a, or -OCH_2OC(=O)R_a, wherein Q is a cleavable group. In another embodiment, each Q is independently at each occurrence -OP(=O)$(OH)_2$ or -OCH_2OP(=O)$(OH)_2$, wherein Q is a cleavable group. In another embodiment, each Q is independently at each occurrence -OC(=O)R_a, or -OCH_2OC(=O)R_a, wherein Q is a cleavable group. In another embodiment, each Q is independently at each occurrence -OP(=O)$(OH)_2$, -OCH_2OP(=O)$(OH)_2$, or -OC(=O)R_a, wherein Q is a cleavable group. In another embodiment, each Q is independently at each occurrence -OP(=O)$(OH)_2$, -OCH_2OP(=O)$(OH)_2$, or -OCH_2OC(=O)R_a, wherein Q is a cleavable group. In another embodiment, each Q is independently at each occurrence OP(=O)$(OH)_2$, -OCH_2OP(=O)$(OH)_2$, or -OC(O)CH$(NH_2)(CH_2)_4$NHC(NH)NH_2. In another embodiment, each Q is -OCH_2OC(=O) R_a or -OC(=O)R_a, wherein Q is a cleavable group. In another embodiment, each Q is -OC(=O)R_a. In another embodiment, each Q is -OC(=O)R_a, -OCH_2OC(=O)R_a,-OCH_2OC(=O) R_a or -OC(=O)R_a, wherein Q is a cleavable group.

[0352] In some embodiments of Formula (II), R_a is (C_1-C_{10}) alkyl optionally substituted with one or more substituents selected from -OH, -NH_2, -CO_2H, -SO_3H, -NHC(NH)NH_2, and -OP(=O)$(OH)_2$. In another embodiment, R_a is (C_1-C_6) alkyl optionally substituted with one or more substituents selected from -OH, -NH_2, -CO_2H, -SO_3H, and -OP(=O)$(OH)_2$. In yet another embodiment, R_a is (C_1-C_6) alkyl optionally substituted with one or more substituents selected from -NH_2, -NHC(NH)NH_2, and -OP(=O)$(OH)_2$. In another embodiment, R_a is (C_3-C_7) cycloalkyl optionally substituted with one or more substituents selected from -OH, -NH_2, -CO_2H, -SO_3H, and -OP(=O)$(OH)_2$. In yet another embodiment, R_a is heterocycloalkyl are optionally substituted with one or more substituents selected from -OH, -NH_2, -CO_2H, -SO_3H, and -OP(=O)$(OH)_2$. In another embodiment, R_a is (C_1-C_{10}) alkyl or (C_3-C_7) cycloalkyl, wherein the alkyl or cycloalkyl, are optionally substituted with one or more substituents selected from -OH, -NH_2, -CO_2H, -SO_3H, and -OP(=O)$(OH)_2$.

[0353] In yet another embodiment, R_a is (C_1-C_{10}) alkyl or heterocycloalkyl, wherein the alkyl or heterocycloalkyl are optionally substituted with one or more substituents selected from -OH, -NH_2, -CO_2H, -SO_3H, and -OP(=O)$(OH)_2$. In another embodiment, R_a is (C_3-C_7) cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl are optionally substituted with one or more substituents selected from -OH, -NH_2, -CO_2H, -SO_3H, and -OP(=O)$(OH)_2$.

[0354] In some embodiments of Formula (II), A is (C_6-C_{10}) aryl wherein the aryl is unsubstituted or substituted with one or more R_7; B is –C≡C—R_3 or –C≡C–C≡C–R_3; R_3 is (C_1-C_4) alkyl substituted with one or more Q; at least one Q is -OP(=O)$(OH)_2$, -OCH_2OP(=O)$(OH)_2$, or -OC(=O)R_a; R_a, if present, is (C_1-C_{10}) alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents selected from the group consisting of -OH, -NH_2, -CO_2H, -SO_3H, -NHC(NH)NH_2, and -OP(=O)$(OH)_2$; and R_1 is (C_1-C_4) alkoxy. In certain embodients, X is $S(O)_q$. In some embodiments, X is $S(O)_q$, wherein q is 2. In some embodiments, A is unsubstituted (C_6-C_{10}) aryl. In one embodiment, A is unsubstituted phenyl. In another embodiment, R_3 is ethyl, and Q is -OP(=O)$(OH)_2$. In another embodiment, R_3 is ethyl, and Q is -OCH_2OP(=O)$(OH)_2$. In still another embodiment, R_3 is ethyl, and Q is -OC(=O)R_a. In certain embodiments, Q is -OC(=O)R_a, wherein R_a is (C_1-C_{10}) alkyl substituted with one or more substituents selected from -NH_2 and -NHC(NH)NH_2. In one embodiment, o is 1, and s is 0.

[0355] In certain embodiments of Formula (II), A is unsubstituted phenyl; B is –C≡C–C≡C–R_3; R_3 is ethyl substituted with one Q; Q is -OP(=O)$(OH)_2$; X is $S(O)_q$, wherein q is 2; o is 1; and s is 0.

[0356] In other embodiments of Formula (II), A is unsubstituted phenyl; B is –C≡C–C≡C–R_3; R_3 is ethyl substituted with one Q; Q is -$OCH_2OP(=O)(OH)_2$; X is $S(O)_q$, wherein q is 2; o is 1; and s is 0.

[0357] In still other embodiments of Formula (II), A is unsubstituted phenyl; B is –C≡C–C≡C–R_3; R_3 is ethyl substituted with one Q; Q is -$OC(=O)R_a$; R_a is n-pentyl substituted with -NH_2 and -$NHC(NH)NH_2$.

[0358] Non-limiting illustrative compounds of the disclosure include:

N-(1-(3-hydroxy-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-1**);

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(((1R,2R)-2-(hydroxymethyl)cyclopropyl)buta-1,3-diyn-1-yl)benzamide (**I-10**);

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide (**I-11**);

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-12**);

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-methoxyhexa-1,3-diyn-1-yl)benzamide (**I-13**);

N-(2-(hydroxyamino)-1-(3-(methylthio)-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-14**);

N-(1-(3-amino-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-15**);

N-(2-(hydroxyamino)-1-(3-(methylamino)-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-16**);

N-(1-(3-(dimethylamino)-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-17**);

cis and trans-N-(2-(hydroxyamino)-1-(3-methoxy-1-oxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-18** and **I-19**);

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-2**);
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-phenylpiperazine-1-carboxamide (**I-20**);
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxamide (**I-21**);
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-phenylpiperidine-1-carboxamide (**I-22**);
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-1-phenylpiperidine-4-carboxamide (**I-23**);
4-((S)-5,6-dihydroxyhexa-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide (**I-24**);
4-((S)-6,7-dihydroxyhepta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide (**I-25**);
4-((R)-6,7-dihydroxyhepta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide (**I-26**);
(S)-N-(1-(1,1-dioxido-3-vinylthietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-27**);
(S)-N-(1-(3-ethyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-28**);
(S)-N-(1-(3-cyclopropyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-29**);
(R)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-3**);
N-(1-(3-ethynyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-30**);
(S)-N-(2-(hydroxyamino)-1-(3-methyl-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-31**);
6-(4-((2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)carbamoyl)phenyl)hexa-3,5-diyn-1-yl dihydrogen phosphate (**I-32**);

N-((S)-2-(hydroxyamino)-1-((S)-3-methoxy-1,1-dioxidotetrahydrothiophen-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-33**);
N-((S)-2-(hydroxyamino)-1-((R)-3-methoxy-1,1-dioxidotetrahydrothiophen-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-34**);
(E)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhex-3-en-1-yn-1-yl)benzamide (**I-35**);
(Z)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhex-3-en-1-yn-1-yl)benzamide (**I-36**);
(S)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-4**);
(S)-N-(2-(hydroxyamino)-2-oxo-1-(3-vinylazetidin-3-yl)ethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-40**);
(S)-N-(1-(3-ethylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-41**);
(S)-N-(1-(3-cyclopropylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-42**);
(S)-N-(1-(3-ethynylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-43**);
N-(1-(3-(cyclopropylmethoxy)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-44**);
N-(2-(hydroxyamino)-2-oxo-1-(3-propoxyazetidin-3-yl)ethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-45**);
N-(1-(3-ethoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-ethynylbenzamide (**I-46**);
N-(1-(3-ethoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-47**);
N-(2-(hydroxyamino)-1-(3-(methylthio)azetidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-48**);
4-(azetidin-3-ylbuta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide (**I-5**);
4-((1-formylazetidin-3-yl)buta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide (**I-6**);

N-(1-(3-ethoxy-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-7**);
4-((1-acetylazetidin-3-yl)buta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide (**I-8**);
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhepta-1,3-diyn-1-yl)benzamide (**I-9**);
N-(1-(3-hydroxy-1-oxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-37**);
4-bromo-N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)benzamide (**I-38**);
N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-39**);
N-(2-(hydroxyamino)-1-(3-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-49**);
4-bromo-N-(2-(hydroxyamino)-1-(3-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)benzamide (**I-50**);
N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-51**);
N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide (**I-52**);
N-(1-(3-hydroxy-1-(2-hydroxyethyl)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-53**);
N-(1-(3-hydroxy-1-(2-hydroxyethyl)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide (**I-54**);
N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(((1R,2R)-2-(hydroxymethyl)cyclopropyl)buta-1,3-diyn-1-yl)benzamide (**I-55**);
N-(2-(hydroxyamino)-1-(1-methyl-3-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-56**);
(S)-N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-57**);
(R)-N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-58**);

N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-59**);
N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-60**);
N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-61**);
N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-62**);
N-(2-(hydroxyamino)-1-(3-methoxy-1-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-63**);
N-(2-(hydroxyamino)-1-(3-methoxy-1-methylazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-64**);
(S)-N-(2-(hydroxyamino)-1-(3-methylazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-65**);
N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(((1R,2R)-2-(hydroxymethyl)cyclopropyl)buta-1,3-diyn-1-yl)benzamide (**I-66**);
N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide (**I-67**);
tert-butyl 3-(2-(hydroxyamino)-2-oxo-1-(4-(pentafluoro-λ^6-sulfanyl)benzamido)ethyl)-3-(methylsulfonyl)azetidine-1-carboxylate (**I-68**);
N-(1-(1-acetyl-3-hydroxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-69**);
N-(1-(3-hydroxy-1-(methylsulfonyl)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-70**);
N-(1-(1-formyl-3-hydroxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-71**);
N-(1-(1-acetyl-3-methoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-72**);
N-(2-(hydroxyamino)-1-(3-methoxy-1-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-73**);

N-(1-(1-formyl-3-methoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-74**);

N-(2-(hydroxyamino)-1-(3-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-75**);

(S)-N-(2-(hydroxyamino)-1-(3-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-76**);

N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(penta-1,3-diyn-1-yl)benzamide (**I-77**);

N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(penta-1,3-diyn-1-yl)benzamide (**I-78**);

N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(penta-1,3-diyn-1-yl)benzamide (**I-79**);

N-(2-(hydroxyamino)-1-(3-methoxy-1-methylazetidin-3-yl)-2-oxoethyl)-4-(penta-1,3-diyn-1-yl)benzamide (**I-80**);

N-(1-(azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-81**);

N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide (**I-82**);

N-(2-(hydroxyamino)-1-(3-(methylamino)azetidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-83**);

N-(2-(hydroxyamino)-1-(3-methoxy-1-methylazetidin-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide (**I-84**);

2-fluoro-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethoxy)benzamide (**I-85**);

N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethoxy)benzamide (**I-86**);

N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethyl)benzamide (**I-87**);

2-fluoro-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethyl)benzamide (**I-88**);

N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-((trifluoromethyl)thio)benzamide (**I-89**);

3-fluoro-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethoxy)benzamide (**I-90**);

3-fluoro-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethyl)benzamide (**I-91**);

N-((R)-1-((2R,3R)-3-hydroxy-2-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro λ^6-sulfanyl)benzamide (**I-92**);

N-((S)-1-((2R,3R)-3-hydroxy-2-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide (**I-93**);

N-((R)-1-((2S,3S)-3-hydroxy-2-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide (**I-94**);

N-((S)-1-((2S,3S)-3-hydroxy-2-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-95**);

(S)-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-96**);

(R)-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-97**);

N-((R)-2-(hydroxyamino)-1-((2S,3S)-3-(metho);xy-2-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-98**);

(S)-N-(2-(hydroxyamino)-1-(3-methylazetidin-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide (**I-99**);

N-(2-(hydroxyamino)-1-((2S,3S)-3-methoxy-2-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-100**);

N-((S)-2-(hydroxyamino)-1-((2R,3S)-3-methoxy-2-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-101**);

(S)-N-(1-(3-((dimethylamino)methyl)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro-λ^6--sulfanyl)benzamide (**I-102**);

N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-((1-methylazetidin-3-yl)buta-1,3-diyn-1-yl)benzamide (**I-103**);

N-((S)-2-(hydroxyamino)-1-((R)-3-hydroxypyrrolidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-104**);
N-((S)-2-(hydroxyamino)-1-((S)-3-hydroxypyrrolidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-105**);
N-((1S)-2-(hydroxyamino)-1-(3-hydroxypyrrolidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-106**);
N-((S)-2-(hydroxyamino)-1-((R)-3-hydroxypyrrolidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-107**);
6-(4-((2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)carbamoyl)phenyl) hexa-3,5-diyn-1-yl dihydrogen phosphate (**I-108**);
((6-(4-((2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)carbamoyl) phenyl)hexa-3,5-diyn-1-yl)oxy)methyl dihydrogen phosphate (**I-109**); and
6-(4-((2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)carbamoyl)phenyl) hexa-3,5-diyn-1-yl N6-carbamimidoyllysinate (**I-110**).

[0359] In another embodiment of the disclosure, the compounds of Formula (I), are enantiomers. In other embodiments of the disclosure, the compounds of Formula (II), or the pharmaceutically acceptable salts, hydrates, solvates, stereoisomers, or tautomers thereof, are enantiomers. In still other embodiments of the disclosure, the compounds of Formula (II), or the pharmaceutically acceptable salts, hydrates, solvates, stereoisomers, or tautomers thereof, are enantiomers. In some embodiments the compounds are the (*S*)-enantiomer. In other embodiments the compounds are the (*R*)-enantiomer. In yet other embodiments, the compounds of Formula (I) may be (+) or (-) enantiomers.

[0360] It should be understood that all isomeric forms are included within the present disclosure, including mixtures thereof. If the compound contains a double bond, the substituent may be in the E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans configuration. All tautomeric forms are also intended to be included.

[0361] Compounds of the disclosure, and pharmaceutically acceptable salts, hydrates, solvates, stereoisomers and prodrugs thereof may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present disclosure.

[0362] The compounds of the disclosure may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the disclosure as well as mixtures thereof, including racemic mixtures, form part of the present disclosure. In addition, the present disclosure embraces all geometric and positional isomers. For example, if a compound of the disclosure incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the disclosure. Each compound herein disclosed includes all the enantiomers that conform to the general structure of the compound. The compounds may be in a racemic or enantiomerically pure form, or any other form in terms of stereochemistry. The assay results may reflect the data collected for the racemic form, the enantiomerically pure form, or any other form in terms of stereochemistry.

[0363] Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of the disclosure may be atropisomers (*e.g.*, substituted biaryls) and are considered as part of this disclosure. Enantiomers can also be separated by use of a chiral HPLC column.

[0364] It is also possible that the compounds of the disclosure may exist in different tautomeric forms, and all such forms are embraced within the scope of the disclosure. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the disclosure.

[0365] All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this disclosure, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). (For example, if a compound of Formula (I)incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced

within the scope of the disclosure. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the disclosure.) Individual stereoisomers of the compounds of the disclosure may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present disclosure can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms "salt", "solvate", "ester," "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

[0366] The compounds of Formula I may form salts which are also within the scope of this disclosure. Reference to a compound of the Formula herein is understood to include reference to salts thereof, unless otherwise indicated.

[0367] The present disclosure relates to compounds which are modulators of LpxC. In one embodiment, the compounds of the present disclosure are inhibitors of LpxC.

[0368] The disclosure is directed to compounds as described herein and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, and pharmaceutical compositions comprising one or more compounds as described herein, or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof.

Method of Synthesizing the Compounds

[0369] The compounds of the present disclosure may be made by a variety of methods, including standard chemistry. Suitable synthetic routes are depicted in the Schemes given below.

[0370] The compounds of Formula (I) may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthetic schemes. In the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles or chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection processes, as well as the reaction conditions and order of their execution, shall be consistent with the preparation of compounds of Formula (I).

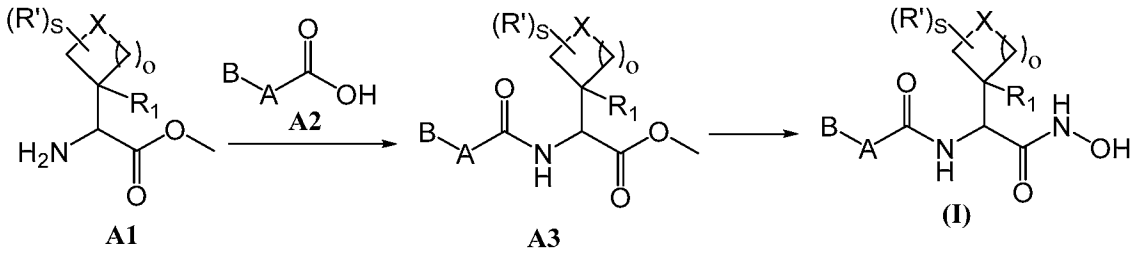
[0371] Those skilled in the art will recognize if a stereocenter exists in the compounds of Formula (I). Accordingly, the present disclosure includes both possible stereoisomers (unless specified in the synthesis) and includes not only racemic compounds but the individual enantiomers and/or diastereomers as well. When a compound is desired as a single enantiomer or diastereomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be affected by any suitable method known in the art. See, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

[0372] The compounds described herein may be made from commercially available starting materials or synthesized using known organic, inorganic, and/or enzymatic processes.

Preparation of compounds

[0373] The compounds of the present disclosure can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, compounds of the present disclosure can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art. Preferred methods include but are not limited to those methods described below. Compounds of the present disclosure can be synthesized by following the steps outlined in General Scheme 1 which comprises an example of sequence of assembling intermediates **A1**, **A2**, and **A3**. Starting materials are either commercially available or made by known procedures in the reported literature or as illustrated.

General Scheme 1



wherein R_1, R' A, B, X, s, and o are defined as in Formula (I).

[0374] The general manner of preparing target compounds of Formula **(I)** by using intermediates **A1**, **A2**, and **A3** is outlined above in General Scheme **1**. Coupling of carboxylic acid **A2** with amine **A1** under standard amide forming conditions using a coupling agent, *e.g.*, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide with 1-hydroxybenzotriazole (EDCI/HOBt), (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), O-benzotriazole-N,N,N,N'-tetramethyl-uronium-hexafluoro-phosphate (HBTU) or [bis (dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU), and a base, *e.g.*, triethylamine (TEA), N,N-diisopropylethylamine (DIEA), or 4-dimethylaminopyridine (DMAP), in a solvent (*i.e.* DCM or DMF, etc.) provides intermediate **A3**. Treatment of **A3** with hydroxyl amine (NH_2OH) in a solvent (*i.e.*, isopropanol) provides the desired product of Formula **(I)**.

[0375] Compounds of Formula **(I)** can exist as enantiomeric or diastereomeric stereoisomers. Enantiomerically pure compounds of Formula **(I)** can be prepared using enantiomerically pure chiral building blocks. Alternatively, racemic mixtures of the final compounds or a racemic mixture of an advanced intermediate can be subjected to chiral purification as described herein below to deliver the desired enantiomerically pure intermediates or final compounds. In the instances where an advanced intermediate is purified into its individual enantiomers, each individual enantiomer can be carried on separately to deliver the final enantiomerically pure compounds of Formula **(I)**.

[0376] It should be understood that in the description and formula shown above, the various groups R_1, $R_{s'}$, A, B, X, o, and other variables are as defined above, except where otherwise indicated. Furthermore, for synthetic purposes, the compounds of General Scheme 1 are mere representatives with elected radicals to illustrate the general synthetic methodology of the compounds of Formula (I) as defined herein.

Methods of Using the Disclosed Compounds

[0377] Another aspect of the disclosure relates to a method of treating a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection an effective amount of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0378] Another aspect of the disclosure relates to a method of preventing a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection

an effective amount of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0379] Another aspect of the disclosure relates to a method of reducing the risk of a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection an effective amount of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0380] Another aspect of the present disclosure relates to a method of treating a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection an effective amount of a pharmaceutical composition comprising an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[0381] Another aspect of the present disclosure relates to a method of preventing a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection an effective amount of a pharmaceutical composition comprising an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[0382] Another aspect of the present disclosure relates to a method of reducing the risk of a bacterial infection. The method comprises administering to a patient in need of a treatment for a bacterial infection an effective amount of a pharmaceutical composition comprising an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[0383] The present disclosure also relates to the use of an inhibitor of LpxC for the preparation of a medicament used in the treatment of a bacterial infection, wherein the medicament comprises an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0384] The present disclosure also relates to the use of an inhibitor of LpxC for the preparation of a medicament used in the reduction of the risk of a bacterial infection, wherein the medicament comprises an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0385] Another aspect of the present disclosure relates to the use of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the treatment of a bacterial infection.

[0386] Another aspect of the present disclosure relates to the use of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the prevention of a bacterial infection.

[0387] Another aspect of the present disclosure relates to the use of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the reduction of the risk of a bacterial infection.

[0388] In another aspect, the present disclosure relates to the use of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating a bacterial infection.

[0389] In another aspect, the present disclosure relates to the use of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for preventing a bacterial infection.

[0390] In another aspect, the present disclosure relates to the use of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for reducing the risk of a bacterial infection.

[0391] Another aspect of the present disclosure relates to a method of inhibiting a deacetylase enzyme in gram-negative bacteria, thereby affecting bacterial growth, comprising administering to a patient in need of such inhibition an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0392] Another aspect of the present disclosure relates to a method of inhibiting LpxC, thereby modulating the virulence of a bacterial infection, comprising administering to a patient in need of such inhibition an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0393] Another aspect of the present disclosure relates to a method for treating a patient having a bacterial infection comprising administering to the patient in need thereof an antibacterially

effective amount of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In a more specific embodiment of the method of treatment, the bacterial infection is a gram-negative bacterial infection. In a further specific embodiment the patient is a mammal and in certain embodiments, a human.

[0394] Another aspect of the present disclosure relates to a method of administering an antibacterially effective amount of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, to a patient infected with a fermentative or non-fermentative gram-negative bacteria. Examples of such bacteria include *Pseudomonas aeruginosa*, *Stenotrophomonas maltophila*, *Burkholderia cepacia*, *Alcaligenes xylosoxidans*, *Enterobacteriaceae*, *Haemophilus*, *Franciscellaceae* (*i.e.*, *Franciscella tularensis*) and *Neisseria species*. In some aspects, provided herein is a method of administering an antibacterially effective amount of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, to a patient infected with a fermentative or non-fermentative gram-negative bacteria, wherein the bacteria is selected from the group consisting of *Pseudomonas*, *Stenotrophomonas*, *Burkholderia*, *Alcaligenes*, *Enterobacteriaceae*, *Haemophilus*, *Franciscellaceae* and *Neisseria species*. In certain embodiments, the *Pseudomonas* is *Pseudomonas aeruginosa*. In another embodiment, the *Stenotrophomonas* is *Stenotrophomonas maltophila*. In still another embodiment, the *Burkholderia* is *Burkholderia cepacia*. In yet another embodiment, the *Alcaligenes* is *Alcaligenes xylosoxidans*. In some embodiments, the *Franciscellaceae* is *Franciscella tularensis*. In some embodiments, the *Enterobacteriaceae* is selected from the group consisting of *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia*, *Morganella*, *Cedecea*, *Edwardsiella* species, and *Escherichia coli*. In other embodiments, the *Yersinia* is *Yersinia pestis*.

[0395] Another aspect of the present disclosure relates to a method of administering an antibacterially effective amount of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, to a patient infected with gram-negative bacteria. Examples of such bacteria include *Enterobacteriaceae,* such as *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia* (e.g., *Yersinia pestis*), *Morganella*, *Cedecea*, *Edwardsiella*

species and *Escherichia coli*. Thus, in some embodiments, the gram-negative bacteria is *Yersenai pestis*.

[0396] The present disclosure further provides methods of treating, preventing, or reducing the risk of a bacterial infection associated with inhibition of LpxC comprising administering to a subject an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0397] The present disclosure provides inhibitors of LpxC that are therapeutic agents in the treatment of bacterial infections, including, but not limited to, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophila*, *Burkholderia cepacia*, *Alcaligenes xylosoxidans*, *Enterobacteriaceae*, *Haemophilus*, *Franciscellaceae* and a *Neisseria species*. Ultimately, the present disclosure provides the medical community with a novel compounds and pharmacological strategy for the treatment of bacterial infections associated with LpxC enzymes.

[0398] The present disclosure also provides inhibitors of LpxC that are therapeutic agents in the treatment of a bacterial infection, wherein the bacterial infection is an infection from the bacteria *Enterobacteriaceae*. In some embodiments, the *Enterobacteriaceae* is selected from the group consisting of *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia*, *Morganella*, Cedecea, *Edwardsiella* species, and *Escherichia* coli. In one embodiment, the *Yersinia* is *Yersinia pestis*. The present disclosure also provides inhibitors of LpxC that are therapeutic agents in the treatment of a bacterial infection, wherein the bacterial infection is an infection from a bacteria selected from the group consisting of *Pseudomonas*, *Stenotrophomonas*, *Burkholderia*, *Alcaligenes*, *Enterobacteriaceae*, *Haemophilus*, *Franciscellaceae* and a *Neisseria* species. In a certain embodiments, the *Pseudomonas* is *Pseudomonas aeruginosa*. In another embodiment, the *Stenotrophomonas* is *Stenotrophomonas maltophila*. In still another embodiment, the *Burkholderia* is *Burkholderia cepacia*. In yet another embodiment, the *Alcaligenes* is *Alcaligenes xylosoxidans*. In some embodiments, the *Franciscellaceae* is *Franciscella tularensis*.

[0399] Also provided herein are inhibitors of LpxC that are therapeutic agents in the treatment of a bacterial infection, wherein the bacterial infection is an infection of a bacteria selected from the group consisting of *Enterobacteriaceae*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia,* and *Pseudomonas*. In one embodiment, the *Enterobacteriaceae* is selected from the group consisting of *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia*,

Morganella, *Cedecea*, *Edwardsiella* species, and *Escherichia coli*. In one embodiment, the *Yersinia* is *Yersinia pestis*. In one embodiment, the bacteria is *Burkholderia*. In one embodiments, the *Burkholderia* is *Burkholderia pseudomallei* or *Burkholderia mallei*. In one embodiment, the bacteria is *Acinetobacter*. In certain embodiments, the *Acinetobacter* is selected from the group consisting of *Acinetobacter baumannii*, *Acinetobacter lwoffi, Acinetobacter albensis, Acinetobacter apis, Acinetobacter beijerinckii, Acinetobacter bereziniae, Acinetobacter bohemicus, Acinetobacter boissieri, Acinetobacter bouvetii, Acinetobacter brisouii, Acinetobacter calcoaceticus, Acinetobacter courvalinii*, *Acinetobacter dispersus*, *Acinetobacter equi*, *Acinetobacter gandensis, Acinetobacter gerneri, Acinetobacter guangdongensis, Acinetobacter guillouiae, Acinetobacter gyllenbergii, Acinetobacter haemolyticus, Acinetobacter harbinensis, Acinetobacter indicus, Acinetobacter junii, Acinetobacter kookii, Acinetobacter modestus*, *Acinetobacter nectaris, Acinetobacter nosocomialis, Acinetobacter parvus, Acinetobacter pakistanensis*, *Acinetobacter populi*, *Acinetobacter proteolyticus*, *Acinetobacter pittii, Acinetobacter puyangensis, Acinetobacter qingfengensis, Acinetobacter radioresistens, Acinetobacter rudis, Acinetobacter schindleri, Acinetobacter seifertii, Acinetobacter soli, Acinetobacter tandoii, Acinetobacter tjernbergiae, Acinetobacter towneri, Acinetobacter ursingii, Acinetobacter variabilis, Acinetobacter venetianus,* and *Acinetobacter vivianii*. In one embodiment, the *Acinetobacter* is *Acinetobacter baumannii* or *Acinetobacter lwoffi.*

[0400] Provided herein are inhibitors of LpxC that are therapeutic agents in the treatment of a bacterial infection, wherein the bacterial infection is an infection of a bacteria selected from the group consisting of *Enterobacteriaceae*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia, Pseudomonas*, *Alcaligenes*, *Haemophilus*, *Franciscellaceae* and a *Neisseria* species. In some embodiments, the *Enterobacteriaceae* is selected from the group consisting of *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia*, *Morganella*, *Cedecea*, *Edwardsiella* species, and *Escherichia coli*. In certain embodiments, the *Yersinia* is *Yersinia pestis*. In certain embodiments, the *Bulkholderia* is *Burkholderia pseudomallei*, *Burkholderia mallei,* or *Burkholderia cepacia*. In some embodiments, the *Pseudomonas* is *Pseudomonas aeruginosa.* In another embodiment, the *Stenotrophomonas* is *Stenotrophomonas maltophila.* In yet another embodiment, the *Alcaligenes* is *Alcaligenes xylosoxidans*. In some embodiments, the *Franciscellaceae* is *Franciscella tularensis.* In one embodiment, the bacteria is *Acinetobacter*.

In certain embodiments, the *Acinetobacter* is an *Acinetobacter* species as previously described above.

[0401] In another aspect, the present disclosure provides a method of inhibiting a deacetylase enzyme in a gram-negative bacteria, thereby affecting bacterial growth, comprising administering to a patient in need of such inhibition an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0402] In another aspect, the present disclosure provides a method of inhibiting LpxC, thereby modulating the virulence of a bacterial infection, comprising administering to a patient in need of such inhibition an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In certain embodiments of the method of inhibiting LpxC using a compound of the present disclosure, the IC_{50} value of the compound is less than or equal to 10 μM with respect to LpxC. In other embodiments, the IC_{50} value is less than or equal to 1 μM, is less than or equal to 0.1 μM, is less than or equal to 0.050 μM, is less than or equal to 0.030 μM, is less than or equal to 0.025 μM, or is less than or equal to 0.010 μM.

[0403] In another aspect, the present disclosure provides a method for treating a patient having a gram-negative bacterial infection comprising administering to the patient in need thereof an antibacterially effective amount of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0404] In another aspect, the present disclosure provides a method of administering a therapeutically effective amount of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, to a patient infected with a fermentative or non-fermentative gram-negative bacteria. Examples of fermentative or non-fermentative gram-negative bacteria include *Pseudomonas aeruginosa*, *Stenotrophomonas maltophila*, *Burkholderia cepacia*, *Alcaligenes xylosoxidans*, *Enterobacteriaceae*, *Haemophilus*, *Franciscellaceae* (e.g., *Franciscella tularensis*) and *Neisseria species*.

[0405] In some aspects, provided herein is a method of administering a therapeutically effective amount of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, to a patient infected with a

fermentative or non-fermentative gram-negative bacteria, wherein the bacteria is selected from the group consisting of *Pseudomonas*, *Stenotrophomonas*, *Burkholderia*, *Alcaligenes*, *Enterobacteriaceae*, *Haemophilus*, *Franciscellaceae* and *Neisseria species*. In certain embodiments, the *Pseudomonas* is *Pseudomonas aeruginosa.* In another embodiment, the *Stenotrophomonas* is *Stenotrophomonas maltophila.* In still another embodiment, the *Burkholderia* is *Burkholderia cepacia*. In yet another embodiment, the *Alcaligenes* is *Alcaligenes xylosoxidans*. In some embodiments, the *Franciscellaceae* is *Franciscella tularensis.* In some embodiments, the *Enterobacteriaceae* is selected from the group consisting of *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia*, *Morganella*, *Cedecea*, *Edwardsiella* species, and *Escherichia coli*. In other embodiments, the *Yersinia* is *Yersinia pestis*.

[0406] In some embodiments the compound is a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In some embodiments, the compound is a compound of Formulae (Ia), (Ib), (Ig), (Ir), (Iz), or (Ibb), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In certain embodiments the compound is a compound of Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof.

[0407] In another aspect, the present disclosure provides a method of administering an inhibitory amount of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, to gram-negative bacteria, such as *Enterobacteriaceae* which is selected from the group consisting of organisms such as *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia* (e.g., *Yersinia pestis*), *Morganella*, *Cedecea*, *Edwardsiella species* and *Escherichia coli*. In some embodiments, the *Enterobacteriaceae* is *Yersinia*. In certain embodiments, the *Yersinia* is *Yersinia pestis*.

[0408] Provided herein is a method of treating a bacterial infection in a subject, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I) or Formula (II) as disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer or tautomer thereof, wherein the bacterial infection is an infection of a bacteria selected from the group consisting of *Enterobacteriaceae*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia,* and *Pseudomonas*. In one embodiment, the

Enterobacteriaceae is selected from the group consisting of *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia*, *Morganella*, *Cedecea*, *Edwardsiella* species, and *Escherichia coli*. In one embodiment, the *Yersinia* is *Yersinia pestis*. In one embodiment, the bacteria is *Burkholderia*. In one embodiments, the *Burkholderia* is *Burkholderia pseudomallei* or *Burkholderia mallei*. In one embodiment, the bacteria is *Acinetobacter*. In certain embodiments, the *Acinetobacter* is an *Acinetobacter* species as previously described above.

[0409] Provided herein is a method of treating a bacterial infection in a subject, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I) or Formula (II) as disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer or tautomer thereof, wherein the bacterial infection is an infection of a bacteria selected from the group consisting of *Enterobacteriaceae*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia, Pseudomonas*, *Alcaligenes*, *Haemophilus*, *Franciscellaceae* and a *Neisseria* species. In some embodiments, the *Enterobacteriaceae* is selected from the group consisting of *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia*, *Morganella*, *Cedecea*, *Edwardsiella* species, and *Escherichia coli*. In certain embodiments, the *Yersinia* is *Yersinia pestis*. In certain embodiments, the *Bulkholderia* is *Burkholderia pseudomallei*, *Burkholderia mallei,* or *Burkholderia cepacia*. In some embodiments, the *Pseudomonas* is *Pseudomonas aeruginosa.* In another embodiment, the *Stenotrophomonas* is *Stenotrophomonas maltophila.* In yet another embodiment, the *Alcaligenes* is *Alcaligenes xylosoxidans*. In some embodiments, the *Franciscellaceae* is *Franciscella tularensis.* In one embodiment, the bacteria is *Acinetobacter*. In certain embodiments, the *Acinetobacter* is an *Acinetobacter* species as previously described above.

[0410] In certain embodiments, the patient may be a mammal, and in some embodiments, a human.

[0411] In certain embodiments of any of the methods disclosed herein, after administration of one or more doses of said compound, the subject does not develop vascular irritation. In other embodiments of any of the methods disclosed herein, after administration of one or more doses of said compound, the subject does not develop phlebitis. In some embodiments, the phlebitis is superficial phlebitis. In other embodiments, the phlebitis is thrombophlebitis. In still other embodiments of any of the methods disclosed herein, after administration of one or more doses

of said compound, the subject does not develop one or more symptoms of phlebitis. In some embodiments, the one or more symptoms of phlebitis are selected from the group consisting of warmth along the course of a vein, tenderness along the course of a vein, redness along the course of a vein, swelling/bulging along the course of a vein, and drainage of pus. In some embodiments, the method is a method of treating a bacterial infection, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I) or Formula (II) as disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer or tautomer thereof.

[0412] Symptoms of phlebitis include warmth along the course of a vein, tenderness along the course of a vein, redness along the course of a vein, swelling/bulging along the course of a vein, and drainage of pus.

[0413] Bacterial infections susceptible to treatment according to the present disclosure include primary infections and co-infections caused by a species of bacteria and one or more additional infectious agents such as, for example, bacteria, virus, parasite and fungus.

[0414] Compounds of the disclosure can be used for treating conditions caused by the bacterial production of endotoxin and, in particular, by gram-negative bacteria and bacteria that use LpxC in the biosynthesis of lipopolysaccharide (LPS) or endotoxin.

[0415] Compounds of the disclosure also are useful in treating conditions that are caused or exacerbated by the bacterial production of lipid A and LPS or endotoxin, such as sepsis, septic shock, systemic inflammation, localized inflammation, chronic obstructive pulmonary disease (COPD) and acute exacerbations of chronic bronchitis (AECB). For these conditions, treatment includes the administration of a compound of the disclosure, or a combination of compounds of the disclosure, optionally with a second agent wherein the second agent is a second antibacterial agent or a non-antibacterial agent.

[0416] The compounds of the disclosure provided herein may also be used as a medicament. The compounds of the disclosure may be used in treating a bacterial infection. Compounds of the disclosure may be used in the manufacture of a medicament for treating a bacterial infection. The bacterial infection may be an infection of any of the bacteria as described herein.

[0417] The compounds disclosed here in may used in inhibiting a deacetylase enzyme in gram-negative bacteria. Compounds of the disclosure may also be used in the manufacture of a

medicament for inhibiting a deacetylase enzyme in gram-negative bacteria. The gram-negative bacteria may be any of the gram-negative bacteria as described herein.

[0418] In some embodiments, the compounds described herein may be used in inhibiting LpxC. Compounds disclosed herein may also be used in the manufacture of a medicament for inhibiting LpxC.

[0419] For sepsis, septic shock, systemic inflammation, localized inflammation, chronic obstructive pulmonary disease (COPD) and acute exacerbations of chronic bronchitis (AECB), representative non-antibacterial agents include antiendotoxins including endotoxin receptor-binding antibodies, endotoxin-binding antibodies, anti-CD14-binding protein antibodies, antilipopolysaccharide-binding protein antibodies and tyrosine kinase inhibitors.

[0420] In treatment of serious or chronic respiratory tract infections, compounds of the present disclosure may also be used with non-antibacterial agents administered via inhalation. Representative non-antibacterial agents used in this treatment include anti-inflammatory steroids, non-steroidal anti-inflammatory agents, bronchiodilators, mucolytics, anti-asthma therapeutics and lung fluid surfactants. In particular, the non-antibacterial agent may be albuterol, salbuterol, budesonide, beclomethasone, dexamethasone, nedocromil, beclomethasone, fluticasone, flunisolide, triamcinolone, ibuprofin, rofecoxib, naproxen, celecoxib, nedocromil, ipratropium, metaproterenol, pirbuterol, salmeterol, formoterol, indacaterol, bronchiodilators, mucolytics, calfactant, beractant, poractant alfa, surfaxin or pulmozyme (also called domase alfa).

[0421] Compounds of the disclosure can be used alone or in combination with a second antibacterial agent for the treatment of a serious or chronic respiratory tract infection including serious lung and nosocomial infections such as those caused by *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus mirabilis*, *Serratia marcescens*, *Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Alcaligenes xylosoxidans*, *Flavobacterium meningosepticum*, *Providencia stuartii* and *Citrobacter freundi*, community lung infections such as those caused by *Haemophilus Influenzae*, *Legionella* species, *Moraxella catarrhalis*, *Branhamella catarrhalis*, *Enterobacter* species, *Klebsiella* species, and *Proteus* species, infections caused by other bacterial species such as *Neisseria* species, *Shigella* species, *Salmonella* species, *Helicobacter pylori*, *Vibrionaceae* and *Bordetella* species, as well as infections caused by a *Brucella* species, *Francisella tularensis* and/or *Yersinia Pestis*.

[0422] Compounds of the present disclosure can be used alone or in combination with a second antibacterial agent for the treatment of a bacterial infection, wherein the bacterial infection is caused by a bacteria selected from the group consisting of *Enterobacter*, *Legionella*, *Klebsiella*, *Proteus*, *Neisseria*, *Shigella*, *Salmonella*, *Brucella*, *Vibrionaceae* and *Bordetella*. In some embodiments, the *Enterobacter* is *Enterobacter aerogenes* or *Enterobacter cloacae*. Compounds of the present disclosure can be used alone or in combination with a second antibacterial agent for the treatment of a bacterial infection, wherein the bacterial infection is cased by a bacteria selected from the group consisting of *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Proteus mirabilis, Serratia marcescens, Stenotrophomonas maltophilia, Pseudomonas aeruginosa, Burkholderia cepacia, Alcaligenes xylosoxidans, Flavobacterium meningosepticum, Providencia stuartii and Citrobacter freundi, Haemophilus Influenzae, Moraxella catarrhalis, Branhamella catarrhalis, Helicobacter pylori, Francisella tularensis* and *Yersinia Pestis*.

[0423] Compounds of the disclosure can be used alone or in combination with a second antibacterial agent for the treatment of a bacterial infection, wherein the infection is an infection of a bacteria selected from the group consisting of *Enterobacteriaceae*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia,* and *Pseudomonas*. In one embodiment, the *Enterobacteriaceae* is selected from the group consisting of *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia*, *Morganella*, *Cedecea*, *Edwardsiella* species, and *Escherichia coli*. In one embodiment, the *Yersinia* is *Yersinia pestis*. In one embodiment, the bacteria is *Burkholderia*. In one embodiments, the *Burkholderia* is *Burkholderia pseudomallei* or *Burkholderia mallei*. In one embodiment, the bacteria is *Acinetobacter*. In certain embodiments, the *Acinetobacter* is an *Acinetobacter* species as previously described above.

[0424] Compounds of the disclosure can be used alone or in combination with a second antibacterial agent for the treatment of a bacterial infection, wherein the bacterial infection is caused by a bacteria selected from the group consisting of *Enterobacteriaceae*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia, Pseudomonas*, *Legionella*, *Klebsiella*, *Proteus*, *Neisseria*, *Shigella*, *Salmonella*, *Brucella*, *Vibrionaceae* and *Bordetella*. In one embodiment, the *Enterobacteriaceae* is selected from the group consisting of *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia*, *Morganella*, *Cedecea*, *Edwardsiella* species, and *Escherichia coli*. In some embodiments, the *Enterobacter* is

Enterobacter aerogenes or *Enterobacter cloacae*. In one embodiment, the *Yersinia* is *Yersinia pestis*. In one embodiment, the bacteria is *Burkholderia*. In one embodiments, the *Burkholderia* is *Burkholderia pseudomallei* or *Burkholderia mallei*. In one embodiment, the bacteria is *Acinetobacter*. In certain embodiments, the *Acinetobacter* is an *Acinetobacter* species as previously described above.

[0425] When used for treating patients infected with gram-negative bacterial infections, compounds of the present disclosure can be used to sensitize gram-negative bacteria to the effects of a second agent.

[0426] The present disclosure provides novel combinations of compounds including an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, as well as methods for treating patients infected with gram-negative bacteria. The novel combinations provided herein can be formulated into pharmaceutical formulations and medicaments that are useful in the methods of the disclosure. The disclosure also provides for the use of the novel combinations in preparing medicaments and pharmaceutical formulations, for use of the combinations in treating bacterial infections in a patient.

[0427] In one embodiment, a second antibacterial agent is used in combination with an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. Examples of suitable second antibacterial agents include, but are not limited to, vancomycin, linezolid, azithromycin, imipenem, teicoplanin, daptomycin, clindamycin, rifampin, cefotaxime, gentamicin, novobiocin or telavancin. In one such embodiment, the antibacterial agent is vancomycin, teicoplanin, rifampin, azithromycin, telavancin or novobiocin. Most preferably, the antibacterial agent is vancomycin or rifampin. In some embodiments of the disclosure, the antibacterial agent and/or LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, is administered at a sub-therapeutic dose, wherein a subtherapeutic dose is a dose that would be insufficient to treat bacterial infections, if administered alone.

[0428] One therapeutic use of the compounds or compositions of the present disclosure which inhibit LpxC is to provide treatment to patients or subjects suffering from a bacterial infection.

[0429] The disclosed compounds of the disclosure can be administered in effective amounts to treat or prevent a disorder and/or prevent the development thereof in subjects.

[0430] Another aspect of the disclosure is directed to pharmaceutical compositions or formulations comprising an effective amount of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof and a pharmaceutically acceptable carrier. The pharmaceutical acceptable carrier may further include an excipient, diluent, or surfactant.

[0431] Administration of the disclosed compounds can be accomplished via any mode of administration for therapeutic agents. These modes include systemic or local administration such as oral, nasal, parenteral, transdermal, subcutaneous, vaginal, buccal, rectal or topical administration modes.

[0432] Depending on the intended mode of administration, the disclosed compositions can be in solid, semi-solid or liquid dosage form, such as, for example, injectables, tablets, suppositories, pills, time-release capsules, elixirs, tinctures, emulsions, syrups, powders, liquids, suspensions, or the like, sometimes in unit dosages and consistent with conventional pharmaceutical practices. Likewise, they can also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, and all using forms well known to those skilled in the pharmaceutical arts.

[0433] The disclosed compounds can be also formulated as a suppository that can be prepared from fatty emulsions or suspensions; using polyalkylene glycols such as propylene glycol, as the carrier.

[0434] Pharmaceutical compositions of the present disclosure comprise a therapeutically effective amount of an LpxC-inhibitory compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, formulated together with one or more pharmaceutically acceptable carriers or diluents. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials that can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as

magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0435] The pharmaceutical compositions of this disclosure can be administered to humans and other animals orally, rectally, parenterally (as by intravenous, intramuscular or subcutaneous injection), intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, or as an oral or nasal spray, or a liquid aerosol or dry powder formulation for inhalation.

[0436] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0437] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, 1% lidocaine, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0438] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0439] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form may be accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations may also be prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissues.

[0440] Compositions for rectal or vaginal administration are preferably suppositories that can be prepared by mixing the compounds of this disclosure with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0441] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) a diluent, *e.g.*, purified water, triglyceride oils, such as hydrogenated or partially hydrogenated vegetable oil, or mixtures thereof, corn oil, olive oil, sunflower oil, safflower oil, fish oils, such as EPA or DHA, or their esters or triglycerides or mixtures thereof, omega-3 fatty acids or derivatives thereof, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, sodium, saccharin, glucose and/or glycine; b) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, c) binders such as, for example, carboxymethylcellulose, alginates, magnesium aluminum silicate, starch paste, gelatin, sucrose, acacia, tragacanth,

methylcellulose, sodium carboxymethylcellulose, magnesium carbonate, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, waxes and/or polyvinylpyrrolidone, if desired; d) humectants such as glycerol, e) disintegrating agents such as starches, agar, cellulose and its derivatives such as sodium carboxymethyl cellulose, methyl cellulose, ethyl cellulose and cellulose acetate, calcium carbonate, sodium carbonate, potato or tapioca starch, certain silicates, bentonite, xanthan gum, algic acid or its sodium salt, or effervescent mixtures; f) solution retarding agents such as paraffin, g) absorption accelerators such as quaternary ammonium compounds, h) wetting agents such as, for example, acetyl alcohol and glycerol monostearate, i) absorbents such as kaolin and bentonite clay; j) lubricants such as silica, talcum, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, sodium lauryl sulfate, and mixtures thereof; k) an emulsifier or dispersing agent, such as Tween 80, Labrasol, HPMC, DOSS, caproyl 909, labrafac, labrafil, peceol, transcutol, capmul MCM, capmul PG-12, captex 355, gelucire, vitamin E TGPS or other acceptable emulsifier; and/or l) an agent that enhances absorption of the compound such as cyclodextrin, hydroxypropyl-cyclodextrin, PEG400, PEG200. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0442] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0443] The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0444] The antibacterial compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as

sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0445] Dosage forms for topical or transdermal administration of a compound of this disclosure include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulations, ear drops, and the like are also contemplated as being within the scope of this disclosure.

[0446] The ointments, pastes, creams and gels may contain, in addition to an active compound of this disclosure, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0447] Compositions of the disclosure may also be formulated for delivery as a liquid aerosol or inhalable dry powder. Liquid aerosol formulations may be nebulized predominantly into particle sizes that can be delivered to the terminal and respiratory bronchioles where bacteria reside in patients with bronchial infections, such as chronic bronchitis and pneumonia. Pathogenic bacteria are commonly present throughout airways down to bronchi, bronchioli and lung parenchema, particularly in terminal and respiratory bronchioles. During exacerbation of infection, bacteria can also be present in alveoli. Liquid aerosol and inhalable dry powder formulations are preferably delivered throughout the endobronchial tree to the terminal bronchioles and eventually to the parenchymal tissue.

[0448] Aerosolized formulations of the disclosure may be delivered using an aerosol forming device, such as a jet, vibrating porous plate or ultrasonic nebulizer, preferably selected to allow the formation of an aerosol particles having with a mass medium average diameter predominantly between 1 to 5 μm. Further, the formulation preferably has balanced osmolarity ionic strength and chloride concentration, and the smallest aerosolizable volume able to deliver effective dose of the compounds of the disclosure to the site of the infection. Additionally, the

aerosolized formulation preferably does not impair negatively the functionality of the airways and does not cause undesirable side effects.

[0449] Aerosolization devices suitable for administration of aerosol formulations of the disclosure include, for example, jet, vibrating porous plate, ultrasonic nebulizers and energized dry powder inhalers, that are able to nebulize the formulation of the disclosure into aerosol particle size predominantly in the size range from 1-5 pm. Predominantly in this application means that at least 70% but preferably more than 90% of all generated aerosol particles are 1 to 5 μm range. A jet nebulizer works by air pressure to break a liquid solution into aerosol droplets. Vibrating porous plate nebulizers work by using a sonic vacuum produced by a rapidly vibrating porous plate to extrude a solvent droplet through a porous plate. An ultrasonic nebulizer works by a piezoelectric crystal that shears a liquid into small aerosol droplets. A variety of suitable devices are available, including, for example, AeroNeb and AeroDose vibrating porous plate nebulizers (AeroGen, Inc., Sunnyvale, Calif.), Sidestream7 nebulizers (Medic-Aid Ltd., West Sussex, England), Pari LC7 and Pari LC Star7 jet nebulizers (Pari Respiratory Equipment, Inc., Richmond, Va.), and Aerosonic (DeVilbiss Medizinische Produkte (Deutschland) GmbH, Heiden, Germany) and μLtraAire7 (Omron Healthcare, Inc., Vernon Hills, Ill.) ultrasonic nebulizers.

[0450] Compounds of the disclosure may also be formulated for use as topical powders and sprays that can contain, in addition to the compounds of this disclosure, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

[0451] Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0452] According to the methods of treatment of the present disclosure, bacterial infections are treated or prevented in a patient such as a human or lower mammal by administering to the patient a therapeutically effective amount of a compound of Formula I, or a stereoisomer or pharmaceutically acceptable salt thereof, in such amounts and for such time as is necessary to

achieve the desired result. By a "therapeutically effective amount" of a compound of the disclosure is meant a sufficient amount of the compound to treat bacterial infections, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present disclosure will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts. A physician or veterinarian of ordinary skill in the art can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

[0453] Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present pharmaceutical compositions can contain from about 0.1% to about 99%, from about 5% to about 90%, or from about 1% to about 20% of the disclosed compound by weight or volume.

[0454] Effective dosage amounts of the disclosed compounds, when used for the indicated effects, range from about 0.5 mg to about 5000 mg of the disclosed compound as needed to treat the condition. Compositions for in vivo or in vitro use can contain about 0.5, 5, 20, 50, 75, 100, 150, 250, 500, 750, 1000, 1250, 2500, 3500, or 5000 mg of the disclosed compound, or, in a range of from one amount to another amount in the list of doses. In one embodiment, the compositions are in the form of a tablet that can be scored.

[0455] Methods of formulation are well known in the art and are disclosed, for example, in Remington: The Science and Practice of Pharmacy, Mack Publishing Company, Easton, Pa., 19th Edition (1995). Pharmaceutical compositions for use in the present disclosure can be in the form of sterile, non-pyrogenic liquid solutions or suspensions, coated capsules, suppositories, lyophilized powders, transdermal patches or other forms known in the art.

[0456] A "kit" as used in the instant application includes a container for containing the pharmaceutical compositions and may also include divided containers such as a divided bottle or

a divided foil packet. The container can be in any conventional shape or form as known in the art that is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a resealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle that is in turn contained within a box.

[0457] An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of individual tablets or capsules to be packed or may have the size and shape to accommodate multiple tablets and/or capsules to be packed. Next, the tablets or capsules are placed in the recesses accordingly and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil that is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are individually sealed or collectively sealed, as desired, in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[0458] Another specific embodiment of a kit is a dispenser designed to dispense the daily doses one at a time in the order of their intended use. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter, that indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal that, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

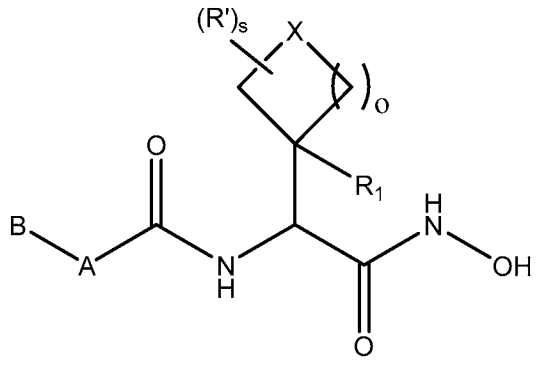
[0459] The kits of the present disclosure may also include, in addition to a compound of the present disclosure, one or more additional pharmaceutically active compounds. For example, the additional compound second antibacterial. The additional compounds may be administered in the same dosage form as the compound of the present disclosure or in a different dosage form. Likewise, the additional compounds can be administered at the same time as the compound of the present disclosure or at different times.

[0460] Compositions of the present compounds may also be used in combination with other known antibacterial agents of similar spectrum to (1) enhance treatment of severe gram-negative infections covered by the spectrum of this compound or (2) add coverage in severe infections in which multiple organisms are suspected in which another agent of a different spectrum may be required in addition to this compound. Potential agents include members of the aminoglycosides, penicillins, cephalosporins, fluoroquinolones, macrolides, glycopeptides, lipopeptides and oxazolidinones. The treatment can involve administering a composition having both a compound of the present disclosure and a second antibacterial compound or administration of a compound of the present inventive compounds followed by or preceded by administration of a second antibacterial agent.

[0461] The foregoing may be better understood by reference to the following examples, that are presented for illustration and not to limit the scope of the inventive concepts.

Exemplary Embodiments

[0462] Embodiment I-1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, and tautomer thereof,

wherein:

X is $S(O)_q$ or NR_6;

A is (C_6-C_{10}) aryl, heteroaryl, (C_3-C_7) cycloalkyl, (C_4-C_7) cycloalkenyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, cycloalkenyl, or heterocycloalkyl is optionally substituted with one or more R_7;

B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, -OR_8, -$S(O)_rR_8$, halogen, (C_6-C_{10}) aryl, heteroaryl, or –SF_5, wherein the aryl and heteroaryl are optionally substituted with R_2;

R_1 is H, (C_1-C_4) alkyl, (C_2-C_4) alkenyl, (C_2-C_4) alkynyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$(CH_2)_m$heterocycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$heterocycloalkyl, halogen, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$,-$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino;

R_2 is (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, halogen, -OH, -NH_2, or -CN;

R_3 is H, (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl, heterocycloalkyl, or heteroaryl, wherein the alkyl is optionally substituted with one or more R_4, and wherein the cycloalkyl, heterocycloalkyl, or heteroaryl are optionally substituted with one or more R_5;

each R_4 is independently at each occurrence -OH, -NH_2, (C_1-C_4) alkoxy, (C_1-C_4) alkylamino, or (C_1-C_4) dialkylamino;

each R_5 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, halogen, (C_1-C_4) hydroxyalkyl, –C(O)H, –C(=O)(C_1-C_4) alkyl, -OH, -NH_2, (C_1-C_4) alkylamino, (C_1-C_4) dialkylamino, or -$S(O)_p$(C_1-C_4)alkyl;

R_6 is H, (C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -C(O)H, -C(O)(C_1-C_4) alkyl, -$S(O)_r$(C_1-C_4) alkyl, or -C(O)O(C_1-C_4) alkyl;

each R_7 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or halogen; or

two R_7 together on adjacent atoms with the atoms to which they are attached form a (C_6-C_{10}) aryl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a heteroaryl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a (C_4-C_8) cycloalkyl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a heterocycloalkyl ring optionally substituted with one or more R_9;

R_8 is (C_1-C_4) alkyl, (C_2-C_4) alkenyl, (C_2-C_4) alkynyl, (C_1-C_4) haloalkyl, or (C_3-C_6) cycloalkyl, wherein the alkyl, alkenyl, or alkynyl are optionally substituted with one or more substituents selected from (C_3-C_7) cycloalkyl and heterocycloalkyl;

each R_9 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or halogen;

each R' is (C_1-C_4) alkyl;

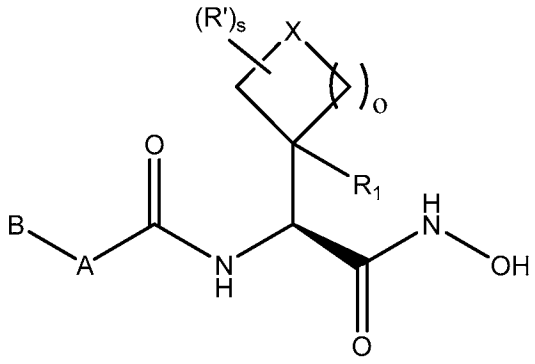
o is 1 or 2;

s is 0, 1, or 2;

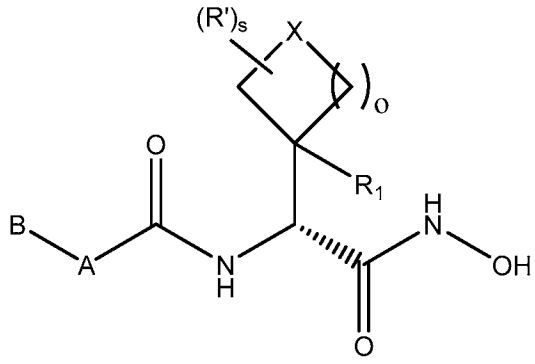
each q, p, and r is independently at each occurrence 0, 1, or 2; and

each m and n is independently at each occurrence 0, 1, 2, or 3.

[0463] Embodiment I-2. The compound of Embodiment I-1, having Formula (Ia) or Formula (Ib):



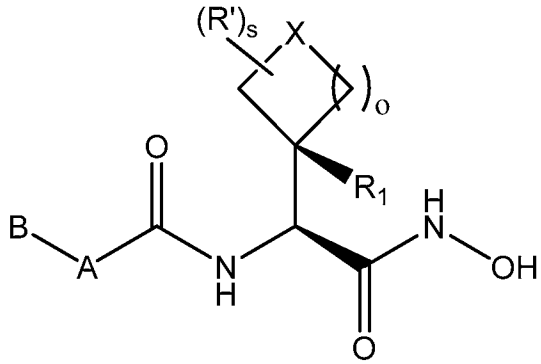
(Ia), or



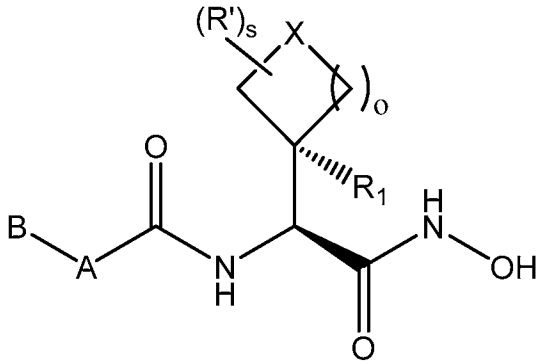
(Ib),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, and tautomer thereof.

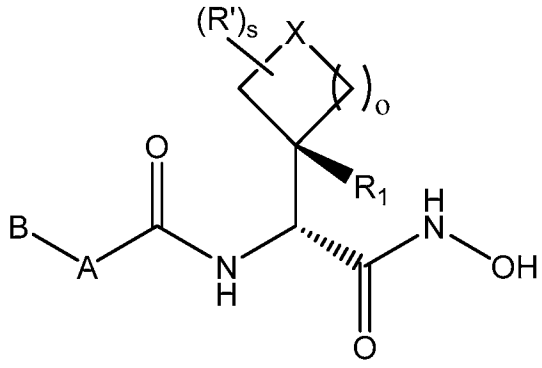
[0464] Embodiment I-3. The compound of Embodiment I-1, having Formula (Ic), Formula (Id), Formula (Ie), or Formula (If):



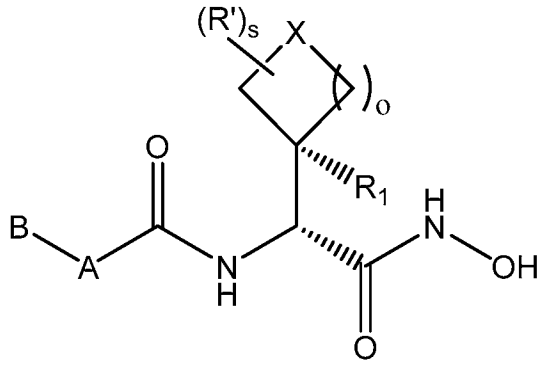
(Ic),



(Id)



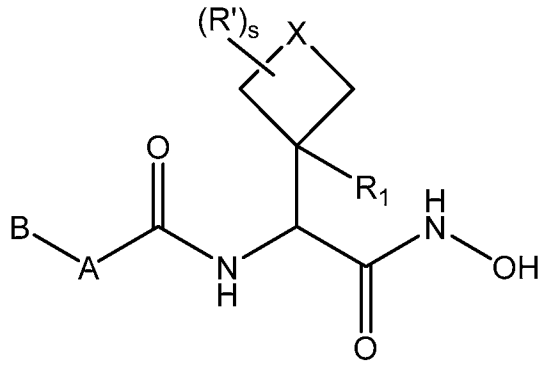
(Ie) or



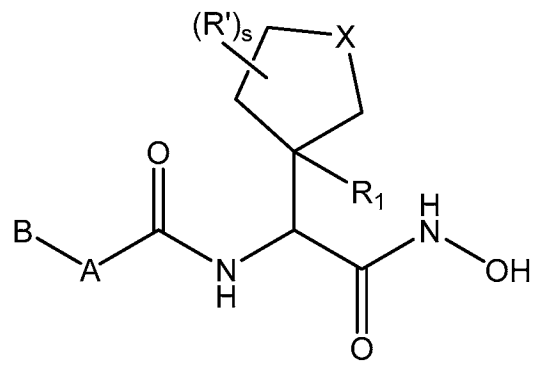
(If)

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, and tautomer thereof.

[0465] Embodiment I-4. The compound of Embodiment I-1, having Formula (Ig) or Formula (Ih):



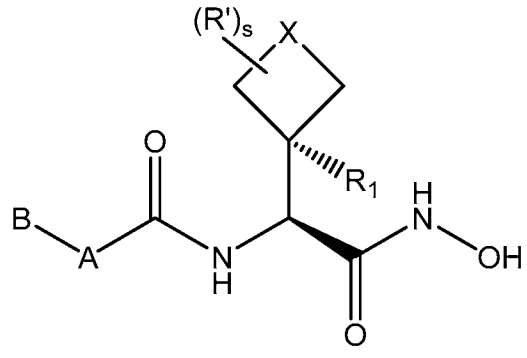
(Ig), or



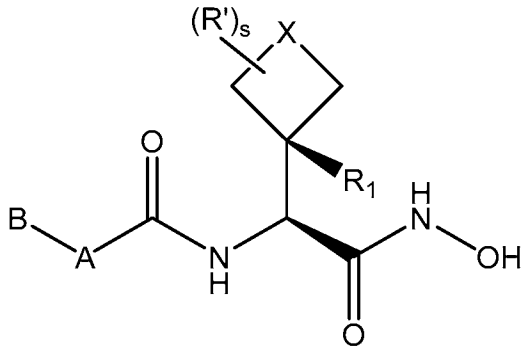
(Ih),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, and tautomer thereof.

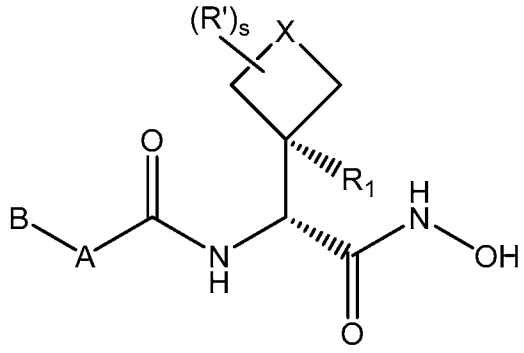
[0466] Embodiment I-5. The compound of Embodiment I-1, having Formula (Ii), Formula (Ij), Formula (Ik), or Formula (Il):



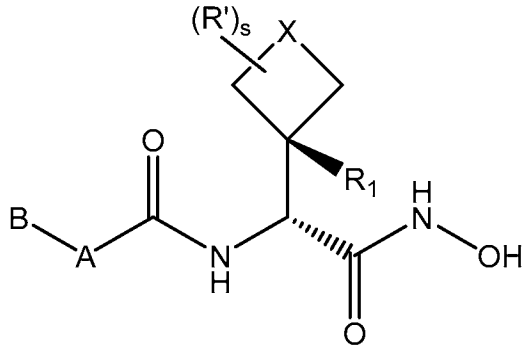
(Ii),



(Ij),



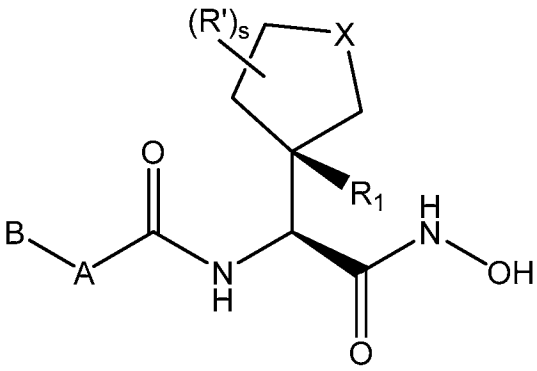
(Ik), or



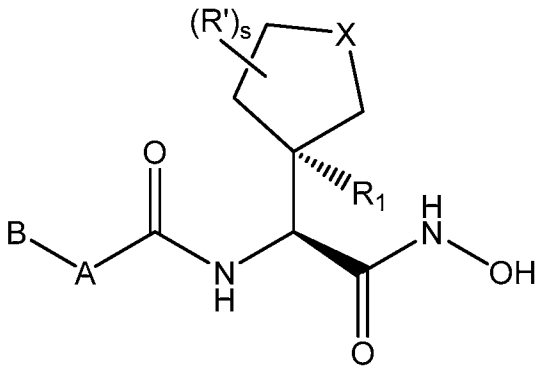
(Il),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, and tautomer thereof.

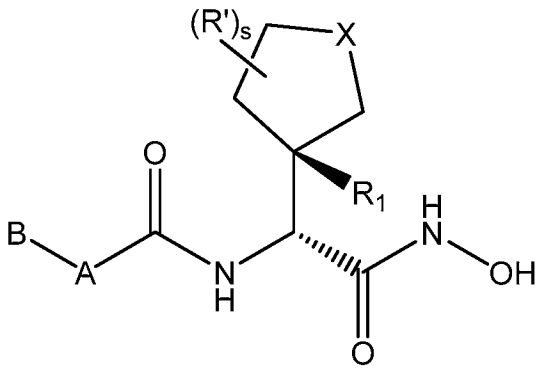
[0467] Embodiment I-6. The compound of Embodiment I-1, having Formula (Im), Formula (Io), Formula (Ip), or Formula (Iq):



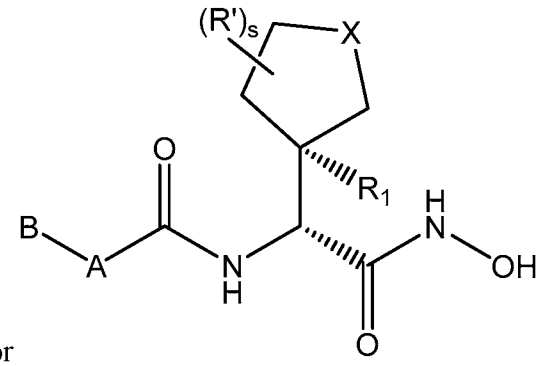
(Im),



(Io),



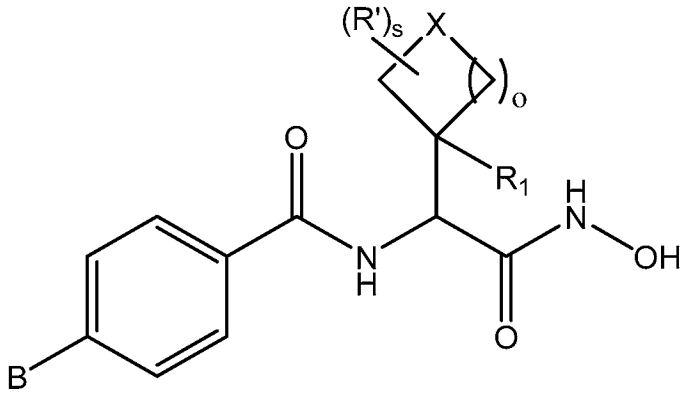
(Ip), or



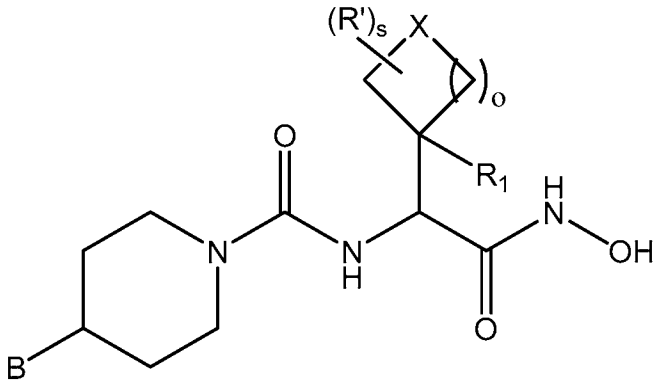
(Iq),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, and tautomer thereof.

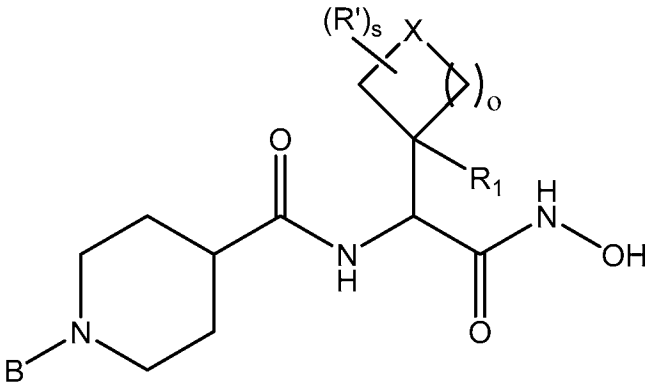
[0468] Embodiment I-7. The compound of Embodiment I-1, having Formula (Ir), Formula (Iu), Formula (Iv), Formula (Ix), or Formula (Iy):



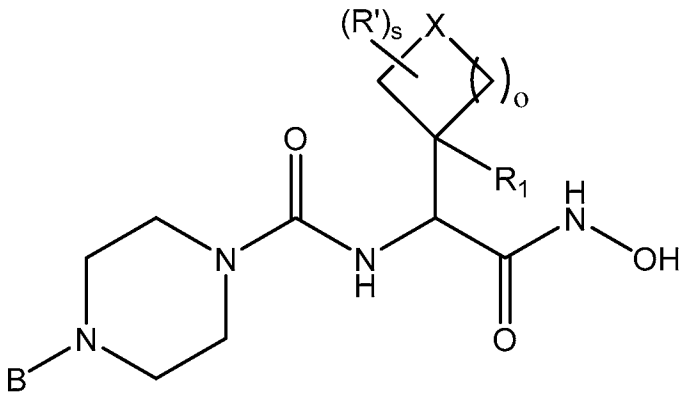
(Ir),



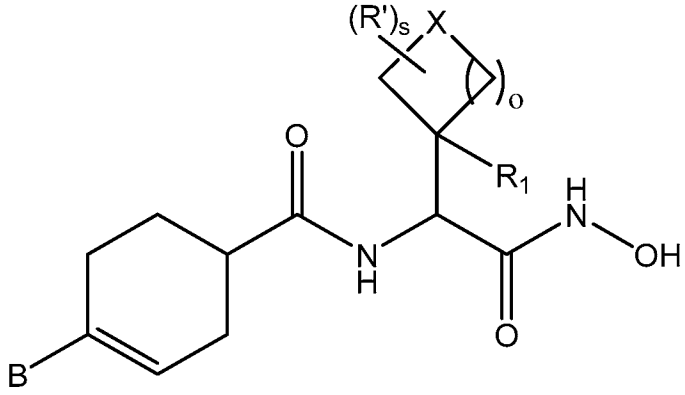
(Iu),



(Iv),



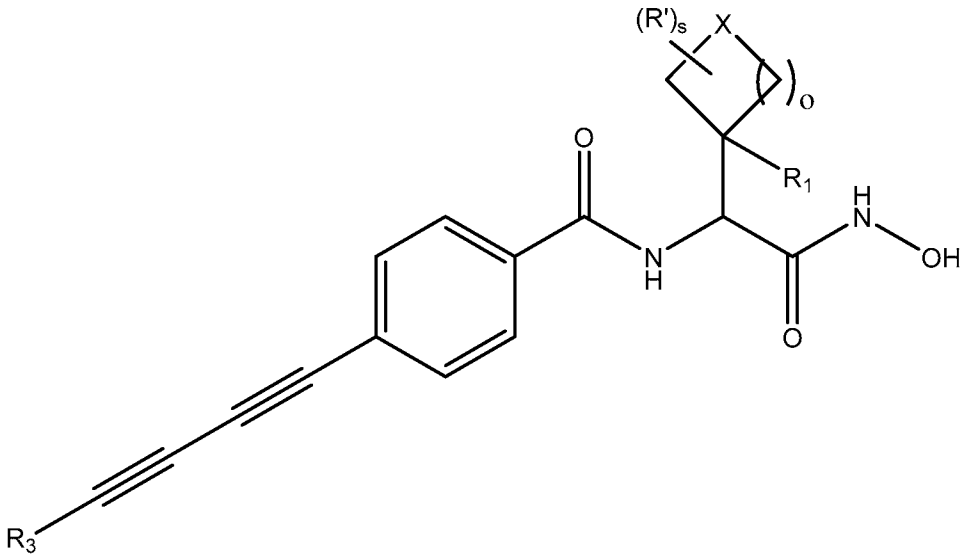
(Ix), or



(Iy),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, and tautomer thereof.

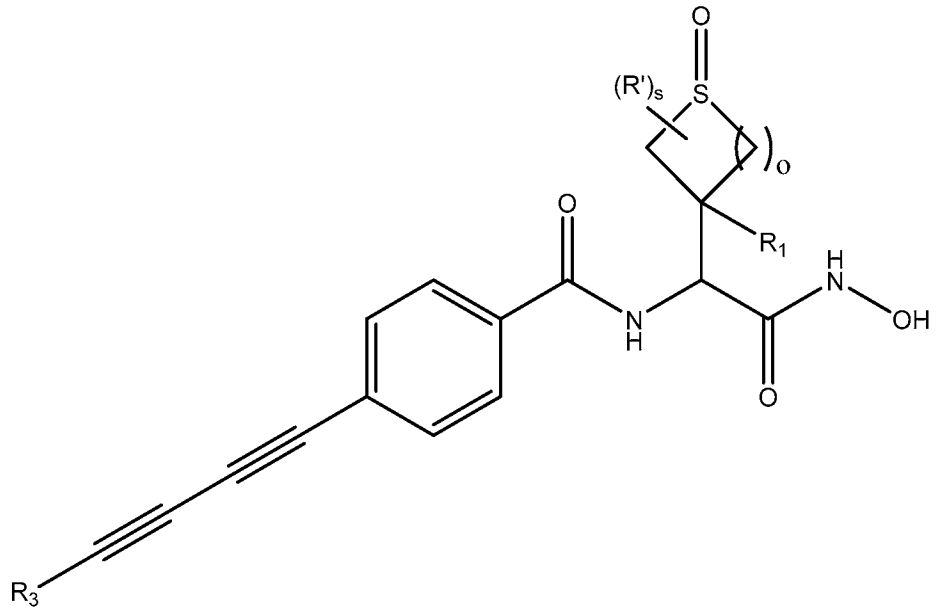
[0469] Embodiment I-8. The compound of Embodiment I-1, having Formula (Iz):



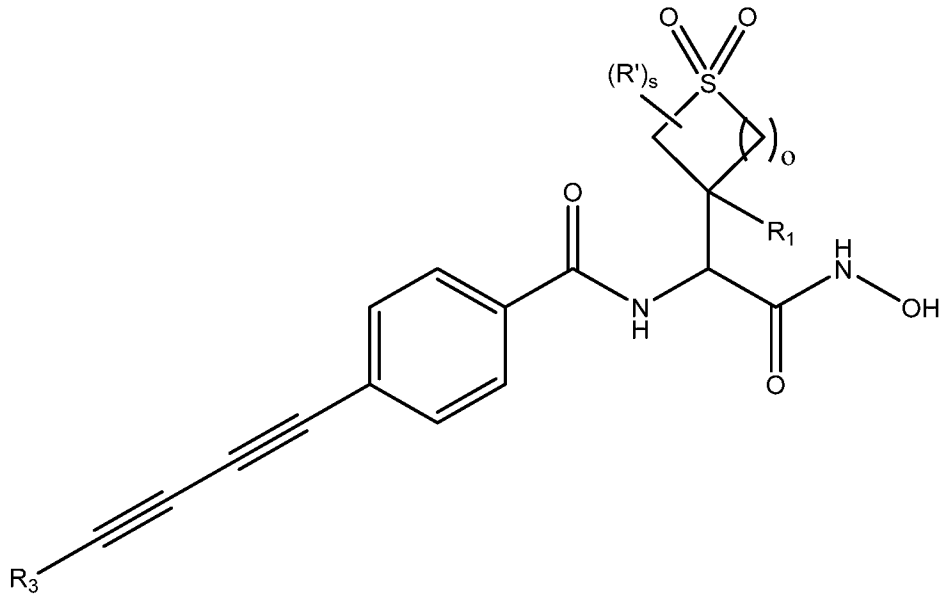
(Iz),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, and tautomer thereof.

[0470] Embodiment I-9. The compound of Embodiment I-1, having Formula (Iaa) or Formula (Ibb):



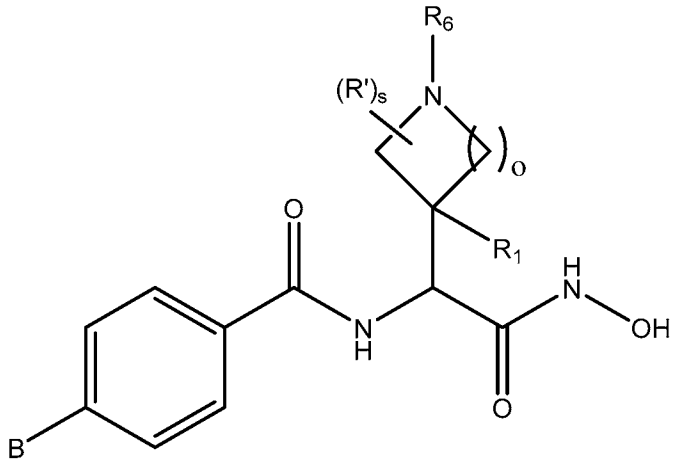
(Iaa),



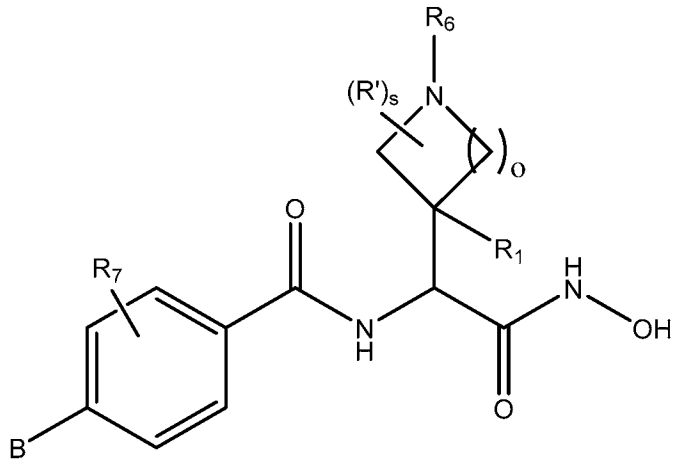
(Ibb),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, and tautomer thereof.

[0471] Embodiment I-10. The compound of Embodiment I-1, having Formula (Icc) or Formula (Idd):



(Icc), or



(Idd),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, and tautomer thereof.

[0472] Embodiment I-11. The compound of any one of Embodiments I-1 to I-6, wherein A is (C_6-C_{10}) aryl, (C_4-C_7) cycloalkenyl, or heterocycloalkyl.

[0473] Embodiment I-12. The compound of any one of Embodiments I-1 to I-6, wherein A is phenyl, cyclohexenyl, piperazinyl, or piperidinyl.

[0474] Embodiment I-13. The compound of any one of Embodiments I-1 to I-7 or I-10, wherein B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, (C_6-C_{10}) aryl, or –SF_5.

[0475] Embodiment I-14. The compound of any one of Embodiments I-1 to I-7 or I-10, wherein B is phenyl or –C≡C–C≡C–R_3.

[0476] Embodiment I-15. The compound of any one of Embodiments I-1 to I-14, wherein R_3 is (C_1-C_4) alkyl substituted with one or more R_4.

[0477] Embodiment I-16. The compound of any one of Embodiments I-1 to I-15, wherein R_3 is methyl, ethyl, or propyl each of which is substituted with one or more R_4.

[0478] Embodiment I-17. The compound of any one of Embodiments I-1 to I-16, wherein R_4 is -OH, or (C_1-C_4) alkoxy.

[0479] Embodiment I-18. The compound of any one of Embodiments I-1 to I-14, wherein R_3 is (C_3-C_7) cycloalkyl or heterocycloalkyl, wherein the cycloalkyl and heterocycloalkyl are optionally substituted with one or more R_5.

[0480] Embodiment I-19. The compound of Embodiment I-18, wherein R_5 is (C_1-C_4) hydroxyalkyl, –C(O)H, or –C(=O)(C_1-C_4) alkyl.

[0481] Embodiment I-20. The compound of any one of Embodiments I-1 to I-8 or I-11 to I-19, wherein X is S(O).

[0482] Embodiment I-21. The compound of any one of Embodiments I-1 to I-8 or I-11 to I-19, wherein X is $S(O)_2$.

[0483] Embodiment I-22. The compound of any one of Embodiments I-1 to I-8 or I-11 to I-19, wherein X is NR_6.

[0484] Embodiment I-23. The compound of Embodiment I-1 selected from the group consisting of:

N-(1-(3-hydroxy-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

(R)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

(S)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

4-(azetidin-3-ylbuta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;

4-((1-formylazetidin-3-yl)buta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;

N-(1-(3-ethoxy-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

4-((1-acetylazetidin-3-yl)buta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhepta-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(((1R,2R)-2-(hydroxymethyl)cyclopropyl)buta-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-methoxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-(methylthio)-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(1-(3-amino-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-(methylamino)-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(1-(3-(dimethylamino)-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(1-(3-hydroxy-1-oxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1-oxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-phenylpiperazine-1-carboxamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-phenylpiperidine-1-carboxamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-1-phenylpiperidine-4-carboxamide;

4-((S)-5,6-dihydroxyhexa-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;
4-((S)-6,7-dihydroxyhepta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;
4-((R)-6,7-dihydroxyhepta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;
N-(1-(1,1-dioxido-3-vinylthietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
(S)-N-(1-(3-ethyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
(S)-N-(1-(3-cyclopropyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(1-(3-ethynyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
(S)-N-(2-(hydroxyamino)-1-(3-methyl-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-((S)-2-(hydroxyamino)-1-((R)-3-methoxy-1,1-dioxidotetrahydrothiophen-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-((S)-2-(hydroxyamino)-1-((S)-3-methoxy-1,1-dioxidotetrahydrothiophen-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
(Z)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhex-3-en-1-yn-1-yl)benzamide;
(E)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhex-3-en-1-yn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-((1-methylazetidin-3-yl)buta-1,3-diyn-1-yl)benzamide;
(S)-N-(1-(3-((dimethylamino)methyl)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-(2-(hydroxyamino)-2-oxo-1-(3-propoxyazetidin-3-yl)ethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(1-(3-(cyclopropylmethoxy)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(S)-N-(1-(3-ethynylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-((S)-2-(hydroxyamino)-1-((2R,3S)-3-methoxy-2-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(2-(hydroxyamino)-1-((2S,3S)-3-methoxy-2-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(S)-N-(2-(hydroxyamino)-1-(3-methylazetidin-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;

N-((R)-2-(hydroxyamino)-1-((2S,3S)-3-methoxy-2-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(S)-N-(2-(hydroxyamino)-2-oxo-1-(3-vinylazetidin-3-yl)ethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(R)-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(S)-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-((S)-1-((2S,3S)-3-hydroxy-2-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-((R)-1-((2S,3S)-3-hydroxy-2-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(S)-N-(1-(3-cyclopropylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(S)-N-(1-(3-ethylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-((S)-1-((2R,3R)-3-hydroxy-2-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(2-(hydroxyamino)-1-(3-(methylthio)azetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-((R)-1-((2R,3R)-3-hydroxy-2-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
3-fluoro-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethyl)benzamide;
3-fluoro-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethoxy)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-((trifluoromethyl)thio)benzamide;
2-fluoro-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethyl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethyl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethoxy)benzamide;
2-fluoro-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethoxy)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1-methylazetidin-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-(methylamino)azetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-(1-(3-ethoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-ethynylbenzamide;
N-(1-(3-ethoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;
N-(1-(azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1-methylazetidin-3-yl)-2-oxoethyl)-4-(penta-1,3-diyn-1-yl)benzamide;
N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(penta-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(penta-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(penta-1,3-diyn-1-yl)benzamide;

(S)-N-(2-(hydroxyamino)-1-(3-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(2-(hydroxyamino)-1-(3-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(1-(1-formyl-3-methoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(1-(1-acetyl-3-methoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(1-(1-formyl-3-hydroxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(1-(3-hydroxy-1-(methylsulfonyl)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(1-(1-acetyl-3-hydroxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

tert-butyl 3-(2-(hydroxyamino)-2-oxo-1-(4-(pentafluoro- λ^6-sulfanyl)benzamido)ethyl)-3-(methylsulfonyl)azetidine-1-carboxylate;

N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;

N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(((1R,2R)-2-(hydroxymethyl)cyclopropyl)buta-1,3-diyn-1-yl)benzamide;

(S)-N-(2-(hydroxyamino)-1-(3-methylazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1-methylazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

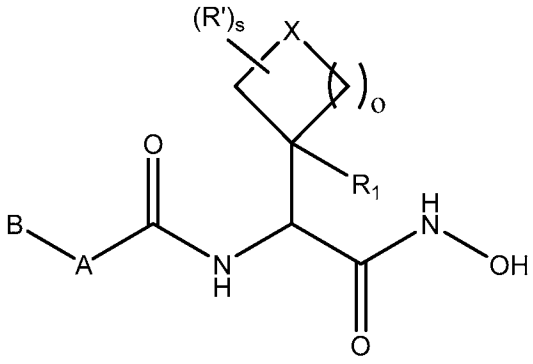
N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
(R)-N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
(S)-N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(1-methyl-3-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(((1R,2R)-2-(hydroxymethyl)cyclopropyl)buta-1,3-diyn-1-yl)benzamide;
N-(1-(3-hydroxy-1-(2-hydroxyethyl)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;
N-(1-(3-hydroxy-1-(2-hydroxyethyl)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;
N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
4-bromo-N-(2-(hydroxyamino)-1-(3-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)benzamide;
N-(2-(hydroxyamino)-1-(3-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide; and
4-bromo-N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)benzamide;

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, and tautomer thereof.

[0485] Embodiment I-24. A prodrug of a compound of Formula (I) having a Formula (II):



(II)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, and tautomer thereof.

wherein:

X is $S(O)_q$ or NR_6;

A is (C_6-C_{10}) aryl, heteroaryl, (C_3-C_7) cycloalkyl, (C_4-C_7) cycloalkenyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, cycloalkenyl, or heterocycloalkyl is optionally substituted with one or more R_7;

B is –C≡C—R_3 or –C≡C–C≡C–R_3;

R_1 is H, (C_1-C_4) alkyl, (C_2-C_4) alkenyl, (C_2-C_4) alkynyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$(CH_2)_m$heterocycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -O$(CH_2)_m$heterocycloalkyl, halogen, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$,-$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino;

R_3 is (C_1-C_4) alkyl substituted with one or more Q;

R_6 is H, (C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -C(O)H, -C(O)(C_1-C_4) alkyl, -$S(O)_n$(C_1-C_4) alkyl, or -C(O)O(C_1-C_4) alkyl;

each R_7 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or halogen; or

two R_7 together on adjacent atoms with the atoms to which they are attached form a (C_6-C_{10}) aryl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a heteroaryl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a (C_4-C_8) cycloalkyl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a heterocycloalkyl ring optionally substituted with one or more R_9;

each R_9 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or halogen;

each R' is (C_1-C_4) alkyl;

R_a is (C_1-C_{10}) alkyl, (C_3-C_7) cycloalkyl, or heterocycloalkyl, wherein the alkyl, cycloalkyl, or heterocycloalkyl are optionally substituted with one or more substituents selected from -OH, $-NH_2$, $-CO_2H$, $-SO_3H$, $-NHC(NH)NH_2$, and $-OP(=O)(OH)_2$;

o is 1 or 2;

s is 0, 1, or 2;

each q, p, and r is independently at each occurrence 0, 1, or 2;

each m and n is independently at each occurrence 0, 1, 2, or 3; and

each Q is independently at each occurrence $-OP(=O)(OH)_2$, $-OCH_2OP(=O)(OH)_2$, $-OC(=O)R_a$, $-OCH_2OC(=O)$ R_a, or $-OC(=O)R_a$ or ; and

wherein Q is a cleavable group.

[0486] Embodiment I-25. The compound of Embodiment I-24, wherein the compound is 6-(4-((2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)carbamoyl)phenyl)hexa-3,5-diyn-1-yl dihydrogen phosphate.

[0487] Embodiment I-26. A pharmaceutical composition comprising, a compound of any one of Embodiments I-1 to I-25, and a pharmaceutically acceptable carrier.

[0488] Embodiment I-27. A method for treating a bacterial infection in a subject comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of Embodiments I-1 to I-25.

[0489] Embodiment I-28. The method according to Embodiment I-27, wherein said bacterial infection is a gram-negative bacterial infection.

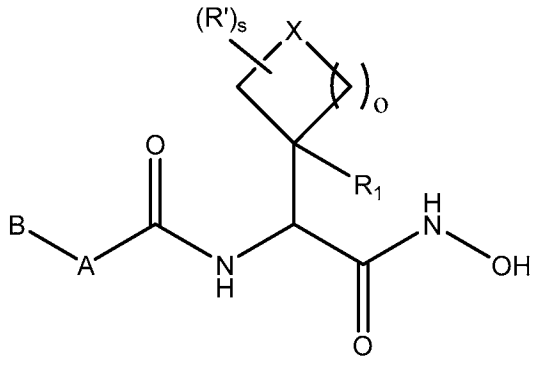
[0490] Embodiment I-29. The method according to Embodiment I-28, wherein said gram-negative bacterial infection is Pseudomonas aeruginosa, Stenotrophomonas maltophila, Burkholderia cepacia, Alcaligenes xylosoxidans, Enterobacteriaceae, Haemophilus, Franciscellaceae or a Neisseria species.

[0491] Embodiment I-30. A method for treating a bacterial infection in a subject comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition according to Embodiment I-26.

[0492] Embodiment I-31. The method according to Embodiment I-30, wherein said bacterial infection is a gram-negative bacterial infection.

[0493] Embodiment I-32. The method according to Embodiment I-31, wherein said gram-negative bacterial infection is Pseudomonas aeruginosa, Stenotrophomonas maltophila, Burkholderia cepacia, Alcaligenes xylosoxidans, Enterobacteriaceae, Haemophilus, Franciscellaceae or a Neisseria species.

[0494] Embodiment II-1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,

wherein:

X is $S(O)_q$ or NR_6;

A is (C_6-C_{10}) aryl, heteroaryl, (C_3-C_7) cycloalkyl, (C_4-C_7) cycloalkenyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, cycloalkenyl, or heterocycloalkyl is optionally substituted with one or more R_7;

B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, -OR_8, -$S(O)_rR_8$, halogen, (C_6-C_{10}) aryl, heteroaryl, or –SF_5, wherein the aryl or heteroaryl is optionally substituted with R_2;

R_1 is H, (C_1-C_4) alkyl, (C_2-C_4) alkenyl, (C_2-C_4) alkynyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$(CH_2)_m$heterocycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$heterocycloalkyl, halogen, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$,-$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino;

R_2 is (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, halogen, -OH, -NH_2, or -CN;

R_3 is H, (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl, heterocycloalkyl, or heteroaryl, wherein the alkyl is optionally substituted with one or more R_4, and wherein the cycloalkyl, heterocycloalkyl, or heteroaryl is optionally substituted with one or more R_5;

each R_4 is independently at each occurrence -OH, -NH_2, (C_1-C_4) alkoxy, (C_1-C_4) alkylamino, or (C_1-C_4) dialkylamino;

each R_5 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, halogen, (C_1-C_4) hydroxyalkyl, –C(O)H, –C(=O)(C_1-C_4) alkyl, -OH, -NH_2, (C_1-C_4) alkylamino, (C_1-C_4) dialkylamino, or -$S(O)_p$(C_1-C_4)alkyl;

R_6 is H, (C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -C(O)H, -C(O)(C_1-C_4) alkyl, -$S(O)_r$(C_1-C_4) alkyl, or -C(O)O(C_1-C_4) alkyl;

each R_7 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or halogen; or

two R_7 on adjacent atoms together with the atoms to which they are attached form a (C_6-C_{10}) aryl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a heteroaryl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a (C_4-C_8) cycloalkyl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a heterocycloalkyl ring optionally substituted with one or more R_9;

R_8 is (C_1-C_4) alkyl, (C_2-C_4) alkenyl, (C_2-C_4) alkynyl, (C_1-C_4) haloalkyl, or (C_3-C_6) cycloalkyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more substituents selected from the group consisting of (C_3-C_7) cycloalkyl and heterocycloalkyl;

each R_9 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or halogen;

each R' is (C_1-C_4) alkyl;

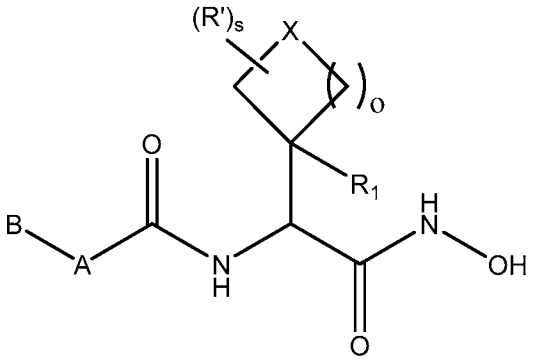
o is 1 or 2;

s is 0, 1, or 2;

each q, p, and r is independently at each occurrence 0, 1, or 2; and

each m and n is independently at each occurrence 0, 1, 2, or 3.

[0495] Embodiment II-2. A compound of Formula (II), wherein the compound is a prodrug of a compound of Formula (I) as claimed in Embodiment II-1:



(II),

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, wherein:

X is $S(O)_q$ or NR_6;

A is (C_6-C_{10}) aryl, heteroaryl, (C_3-C_7) cycloalkyl, (C_4-C_7) cycloalkenyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, cycloalkenyl, or heterocycloalkyl is optionally substituted with one or more R_7;

B is –C≡C—R_3 or –C≡C–C≡C–R_3;

R_1 is H, (C_1-C_4) alkyl, (C_2-C_4) alkenyl, (C_2-C_4) alkynyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$(CH_2)_m$heterocycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -O(CH_2)mheterocycloalkyl, halogen, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$,-$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino;

R_3 is (C_1-C_4) alkyl substituted with one or more Q;

R_6 is H, (C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -C(O)H, -C(O)(C_1-C_4) alkyl, -$S(O)_r$(C_1-C_4) alkyl, or -C(O)O(C_1-C_4) alkyl;

each R_7 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or halogen; or

two R_7 on adjacent atoms together with the atoms to which they are attached form a (C_6-C_{10}) aryl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a heteroaryl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a (C_4-C_8) cycloalkyl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a heterocycloalkyl ring optionally substituted with one or more R_9;

each R_9 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or halogen;

each R' is (C_1-C_4) alkyl;

o is 1 or 2;

s is 0, 1, or 2;

each q, p, and r is independently at each occurrence 0, 1, or 2;

each m and n is independently at each occurrence 0, 1, 2, or 3;

each Q is independently at each occurrence $-OP(=O)(OH)_2$, $-OCH_2OP(=O)(OH)_2$, $-OC(=O)R_a$, or $-OCH_2OC(=O)R_a$;

R_a is (C_1-C_{10}) alkyl, (C_3-C_7) cycloalkyl, or heterocycloalkyl, wherein the alkyl, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, $-CO_2H$, $-SO_3H$, $-NHC(NH)NH_2$, and $-OP(=O)(OH)_2$; and

wherein Q is a cleavable group.

[0496] Embodiment II-3. The compound of Embodiment II-2, wherein Q is $-OP(=O)(OH)_2$ or $-OCH_2OP(=O)(OH)_2$.

[0497] Embodiment II-4. The compound of Embodiment II-2 or II-3, wherein Q is $-OP(=O)(OH)_2$.

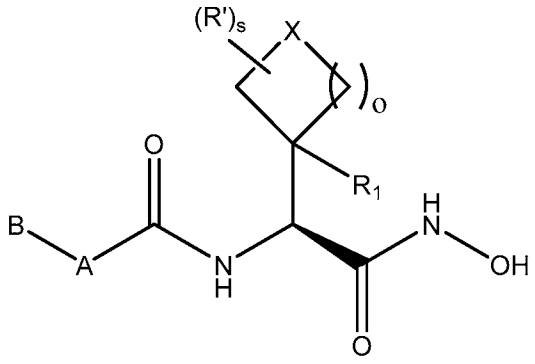
[0498] Embodiment II-5. The compound of Embodiment II-2, wherein Q is $-OC(=O)R_a$ or $-OCH_2OC(=O)R_a$.

[0499] Embodiment II-6. The compound of Embodiment II-2 or II-5, wherein R_a is (C_1-C_{10}) alkyl optionally substituted with one or more substituents independently selected from the group consisting of -OH, $-NH_2$, $-CO_2H$, $-SO_3H$, $-NHC(NH)NH_2$, and $-OP(=O)(OH)_2$.

[0500] Embodiment II-7. The compound of Embodiment II-2, II-5, or II-6, wherein R_a is (C_1-C_{10}) alkyl optionally substituted with one or more substituents independently selected from the group consisting of $-NHC(NH)NH_2$ and $-NH_2$.

[0501] Embodiment II-8. The compound of Embodiment II-2 or II-5, wherein R_a is (C_3-C_7) cycloalkyl or heterocycloalkyl, wherein the (C_3-C_7) cycloalkyl or heterocycloalkyl is optionally substituted with one or more substituents independently selected from the group consisting of -OH, $-NH_2$, $-CO_2H$, $-SO_3H$, $-NHC(NH)NH_2$, and $-OP(=O)(OH)_2$.

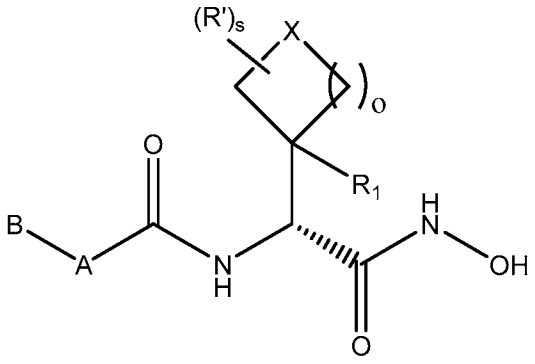
[0502] Embodiment II-9. The compound of any one of Embodiments II-1 to II-8, having Formula (Ia):



(Ia),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

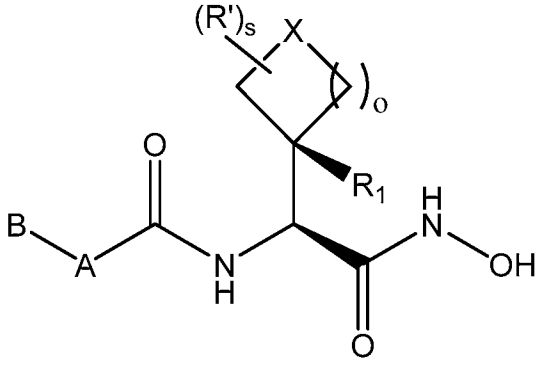
[0503] Embodiment II-10. The compound of any one of Embodiments II-1 to II-8, having Formula (Ib):



(Ib),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

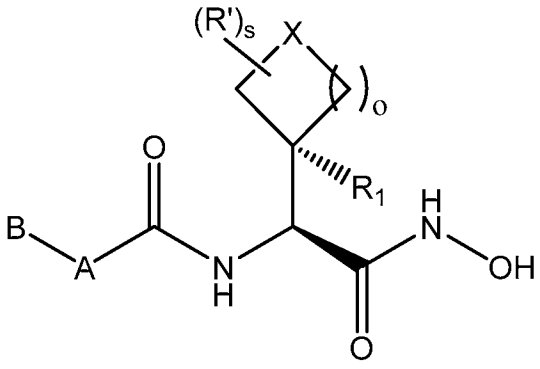
[0504] Embodiment II-11. The compound of any one of Embodiments II-1 to II-9, having Formula (Ic):



(Ic),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

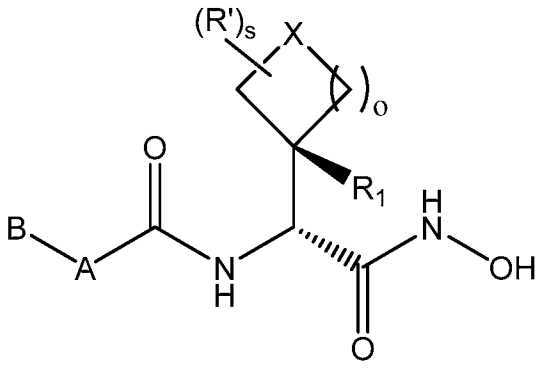
[0505] Embodiment II-12. The compound of any one of Embodiments II-1 to II-9, having Formula (Id):



(Id),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

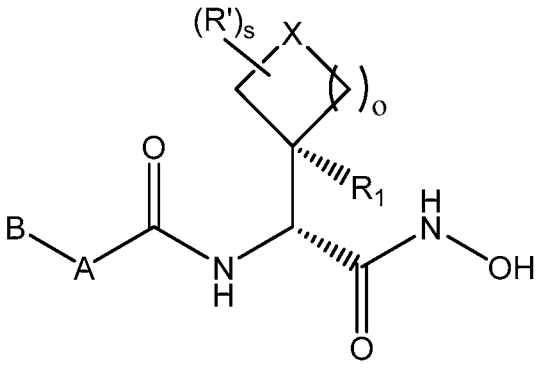
[0506] Embodiment II-13. The compound of any one of Embodiments II-1 to II-8, or II-10, having Formula (Ie):



(Ie),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

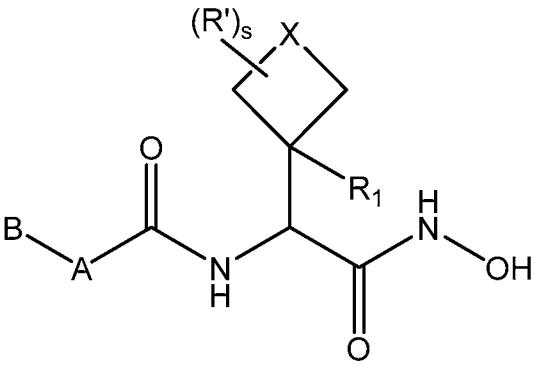
[0507] Embodiment II-14. The compound of any one of Embodiments II-1 to II-8, or II-10, having Formula (If):



(If),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

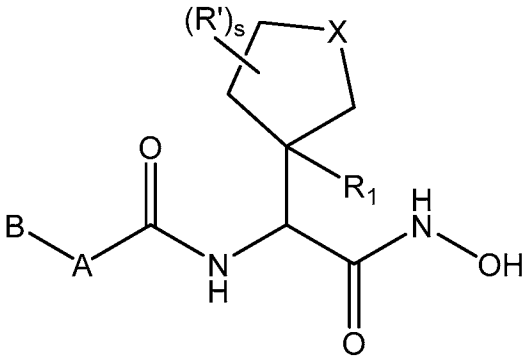
[0508] Embodiment II-15. The compound of any one of Embodiments II-1 to II-8, or II-10, having Formula (Ig):



(Ig),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

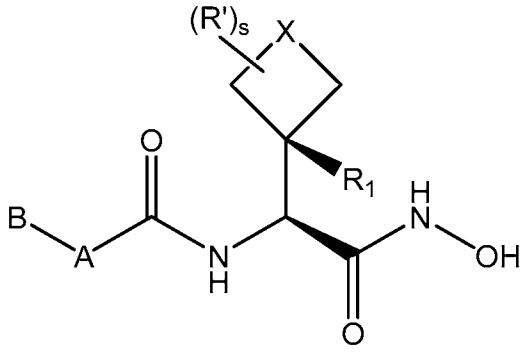
[0509] Embodiment II-16. The compound of any one of Embodiments II-1 to II-8, having Formula (Ih):



(Ih),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

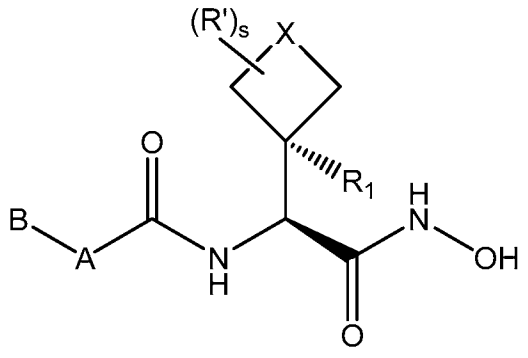
[0510] Embodiment II-17. The compound of any one of Embodiments II-1 to II-9, II-11, or II-15, having Formula (Ij):



(Ij),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

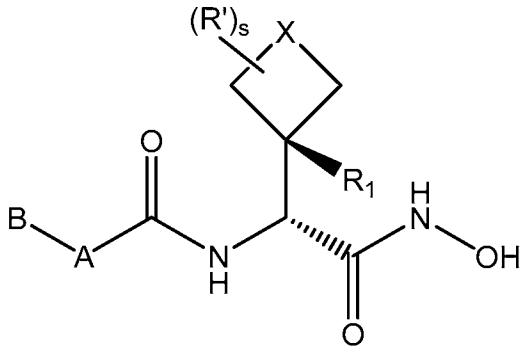
[0511] Embodiment II-18. The compound of any one of Embodiments II-1 to II-9, II-12, or II-15, having Formula (Ii):



(Ii),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

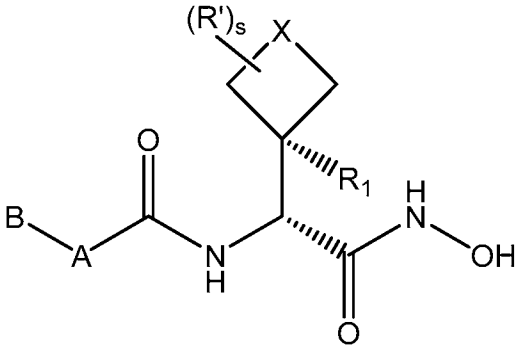
[0512] Embodiment II-19. The compound of any one of Embodiments II-1 to II-8, II-10, II-13, or II-15, having Formula (Il):



(Il),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

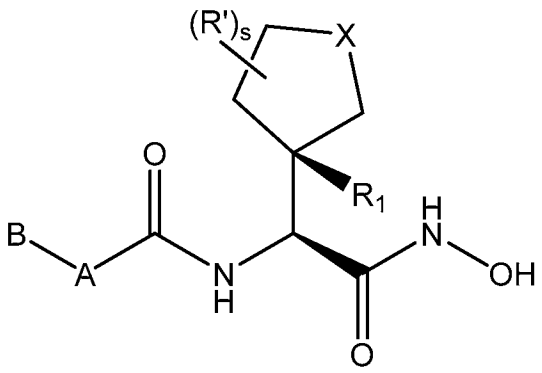
[0513] Embodiment II-20. The compound of any one of Embodiments II-1 to II-8, II-10, II-14, or II-15, having Formula (Ik):



(Ik),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

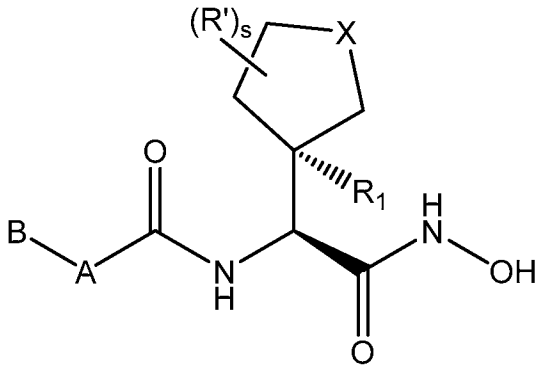
[0514] Embodiment II-21. The compound of any one of Embodiments II-1 to II-9, II-12, or II-16, having Formula (Im):



(Im),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

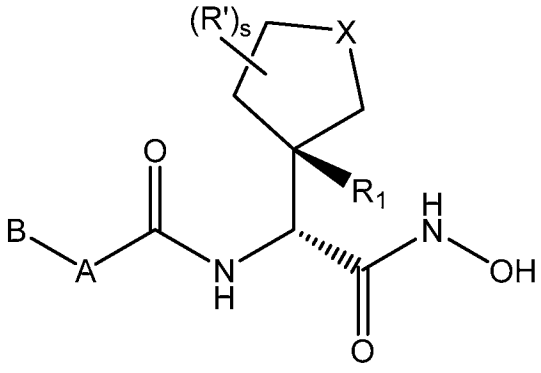
[0515] Embodiment II-22. The compound of any one of Embodiments II-1 to II-9, II-11, or II-16, having Formula (Io):



(Io),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

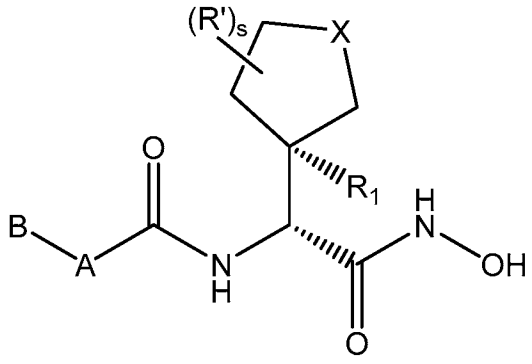
[0516] Embodiment II-23. The compound of any one of Embodiments II-1 to II-8, II-10, or II-16, having Formula (Ip):



(Ip),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

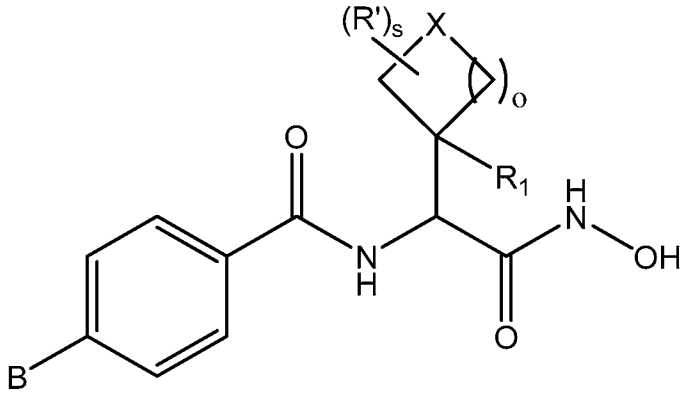
[0517] Embodiment II-24. The compound of any one of Embodiments II-1 to II-8, II-10, or II-16, having Formula (Iq):



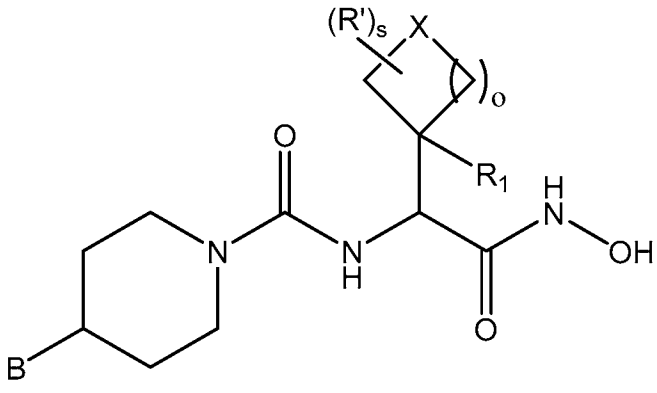
(Iq),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

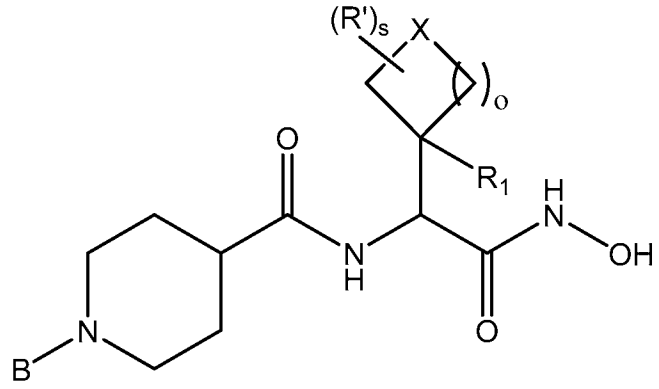
[0518] Embodiment II-25. The compound of any one of Embodiments II-1 to II-8, having Formula (Ir), Formula (Iu), Formula (Iv), Formula (Ix), or Formula (Iy):



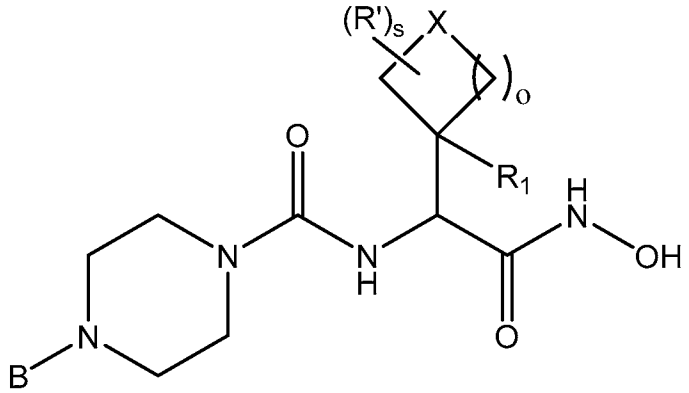
(Ir),



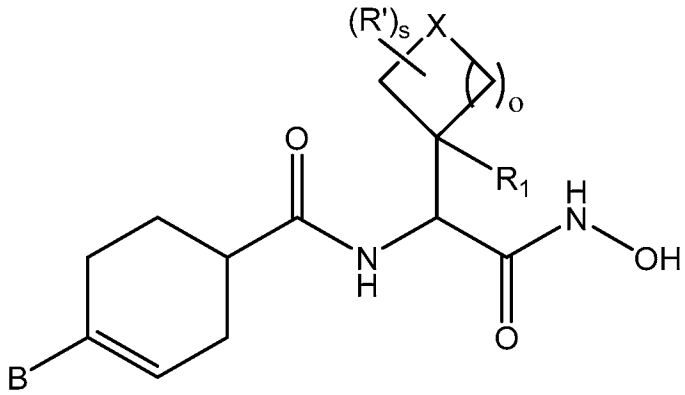
(Iu),



(Iv),



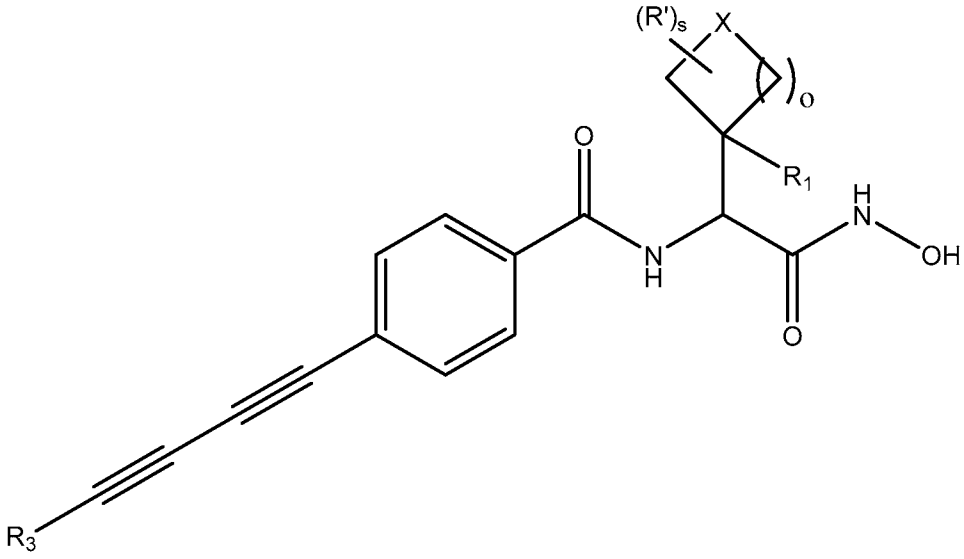
(Ix), or



(Iy),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

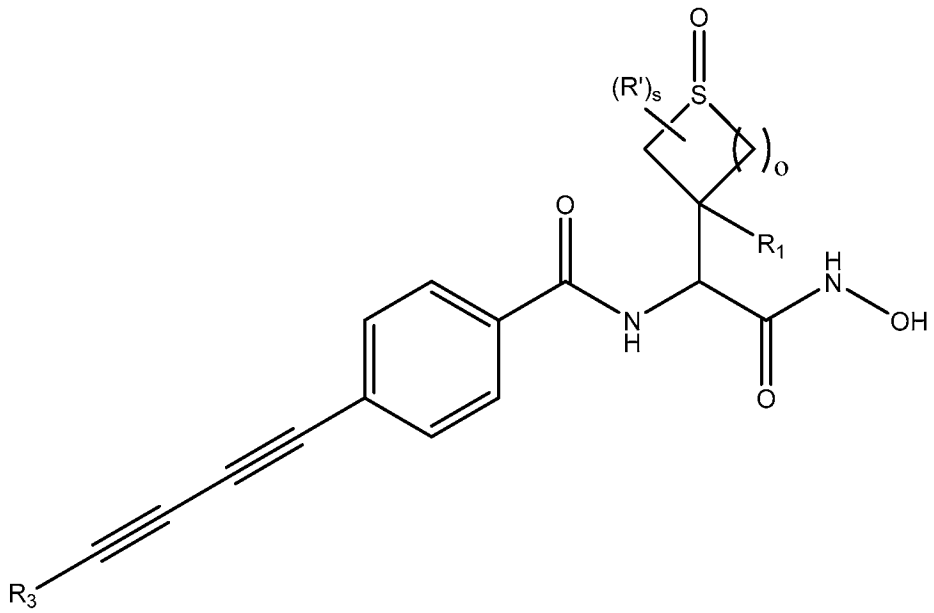
[0519] Embodiment II-26. The compound of any one of Embodiments II-1 to II-8, or II-25, having Formula (Iz):



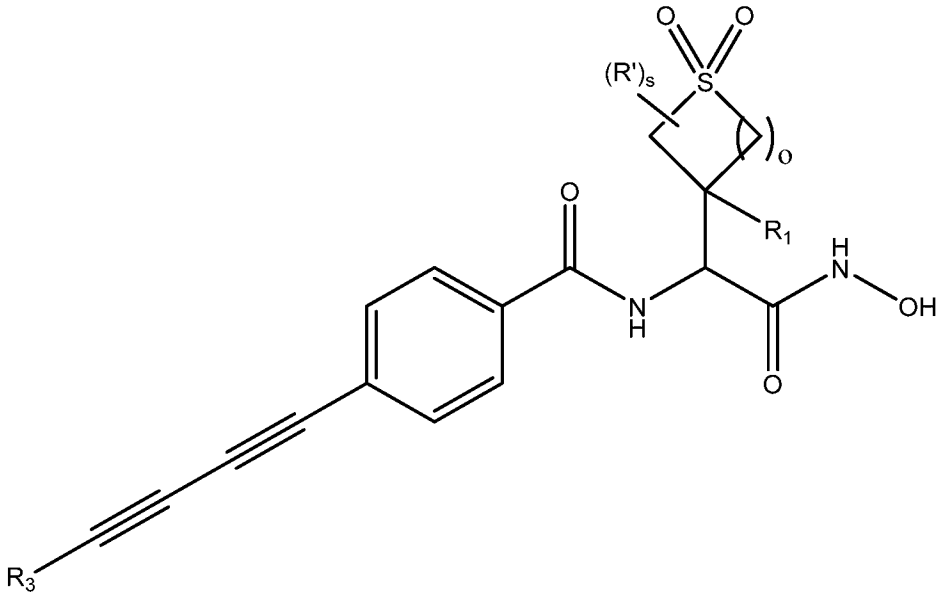
(Iz),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0520] Embodiment II-27. The compound of any one of Embodiments II-1 to II-8, II-25, or II-26, having Formula (Iaa) or Formula (Ibb):



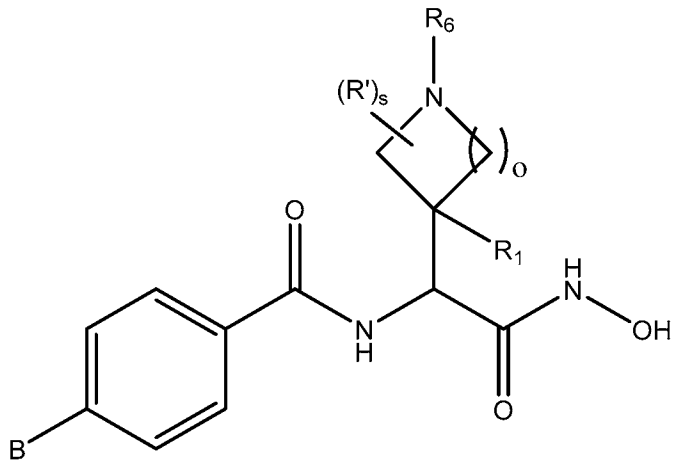
(Iaa),



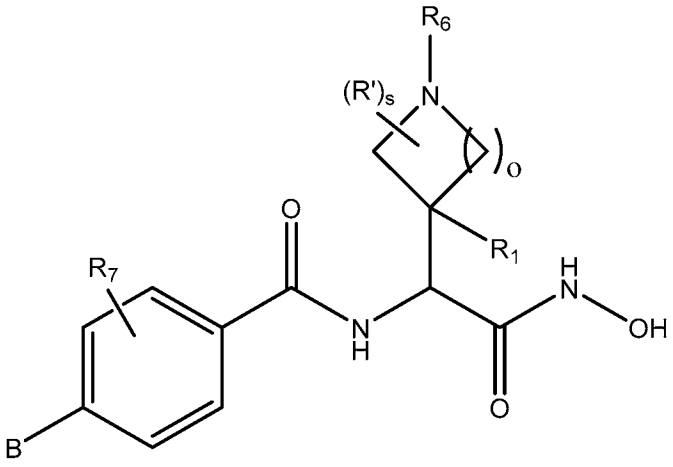
(Ibb),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0521] Embodiment II-28. The compound of any one of Embodiments II-1 to II-8, or II-25, having Formula (Icc) or Formula (Idd):



(Icc), or



(Idd),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0522] Embodiment II-29. The compound of any one of Embodiments II-1 to II-24, wherein A is (C_6-C_{10}) aryl, (C_4-C_7) cycloalkenyl, or heterocycloalkyl, wherein the aryl, cycloalkenyl, or heterocycloalkyl is optionally substituted with one or more R_7.

[0523] Embodiment II-30. The compound of any one of Embodiments II-1 to II-24, or II-29, wherein A is (C_6-C_{10}) aryl, wherein the aryl is optionally substituted with one or more R_7.

[0524] Embodiment II-31. The compound of any one of Embodiments II-1 to II-24, II-29, or II-30, wherein A is phenyl, cyclohexenyl, piperazinyl, or piperidinyl, wherein the phenyl, cyclohexenyl, piperazinyl, or piperadinyl is optionally substituted with one or more R_7.

[0525] Embodiment II-32. The compound of any one of Embodiments II-1 to II-25, or II-28 to 31, wherein B is –C≡C–R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, (C_1-C_4) haloalkyl, -OR_8, -S(O)$_r$$R_8$, halogen, ($C_6$-$C_{10}$) aryl, or –$SF_5$, wherein the aryl or heteroaryl is optionally substituted with R_2.

[0526] Embodiment II-33. The compound of any one of Embodiments II-1, II-9 to II-25, or II-28 to II-32, wherein r is 0 or 2.

[0527] Embodiment II-34. The compound of any one of Embodiments II-1, II-9 to II-25, or II-28 to 32, wherein B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, (C_6-C_{10}) aryl, or –SF_5, wherein the aryl is optionally substituted with R_2.

[0528] Embodiment II-35. The compound of any one of Embodiments II-1, II-9 to II-25, or II-28 to II-32, wherein B is phenyl or –C≡C–C≡C–R_3, wherein the phenyl is optionally substituted with R_2.

[0529] Embodiment II-36. The compound of any one of Embodiments II-1 or II-9 to II-35, wherein R_3 is H, (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl, or heterocycloalkyl, wherein the alkyl is optionally substituted with one or more R_4, and the cycloalkyl or heterocycloalkyl is optionally substituted with one or more R_5.

[0530] Embodiment II-37. The compound of any one of Embodiments II-1 or II-9 to II-36, wherein R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

[0531] Embodiment II-38. The compound of any one of Embodiments II-1 or II-9 to II-37, wherein R_3 is methyl, ethyl, or propyl, wherein the methyl, ethyl, or propyl is optionally substituted with one or more R_4.

[0532] Embodiment II-39. The compound of any one of Embodiments II-1 or II-9 to II-38, wherein R_4 is independently at each occurence -OH, or (C_1-C_4) alkoxy.

[0533] Embodiment II-40. The compound of any one of Embodiments II-1 or II-9 to II-36, wherein R_3 is (C_3-C_7) cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is optionally substituted with one or more R_5.

[0534] Embodiment II-41. The compound of any one of Embodiments II-1 or II-9 to II-40, wherein R_5 is independently at each occurence (C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, –C(O)H, or –C(=O)(C_1-C_4) alkyl.

[0535] Embodiment II-42. The compound of any one of Embodiments II-1 or II-9 to II-41, wherein R_5 is independently at each occurence (C_1-C_4) hydroxyalkyl, –C(O)H, or –C(=O)(C_1-C_4) alkyl.

[0536] Embodiment II-43. The compound of any one of Embodiments II-1, II-9 to II-25, II-28 to II-32, II-34, or II-35, wherein R_2 is halogen.

[0537] Embodiment II-44. The compound of any one of Embodiments II-1, II-9 to II-25, or II-28 to II33, wherein R_8 is (C_1-C_4) alkyl or (C_1-C_4) haloalkyl.

[0538] Embodiment II-45. The compound of any one of Embodiments II-1 to II-26, or II-29 to II-44, wherein X is S(O).

[0539] Embodiment II-46. The compound of any one of Embodiments II-1 to II-26, or II-29 to II-44, wherein X is $S(O)_2$.

[0540] Embodiment II-47. The compound of any one of Embodiments II-1 to II-26, or II-29 to II-44, wherein X is NR_6.

[0541] Embodiment II-48. The compound of Embodiment II-47, wherein R_6 is H, (C_1-C_4) alkyl, or (C_1-C_4) hydroxyalkyl.

[0542] Embodiment II-49. The compound of Embodiment II-47, wherein R_6 is -C(O)H, -C(O)(C_1-C_4) alkyl, -S(O)$_r$(C_1-C_4) alkyl, or -C(O)O(C_1-C_4) alkyl.

[0543] Embodiment II-50. The compound of any one of Embodiments II-1 to II-14 or II-25 to II-49, wherein o is 1.

[0544] Embodiment II-51. The compound of any one of Embodiments II-1 to II-14 or II-25 to II-49, wherein o is 2.

[0545] Embodiment II-52. The compound of any one of Embodiments II-1 to II-51, wherein R_1 is H, (C_1-C_4) alkyl, (C_2-C_4) alkenyl, (C_2-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl or -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino.

[0546] Embodiment II-53. The compound of any one of Embodiments II-1 to II-52, wherein p is 0 or 2.

[0547] Embodiment II-54. The compound of any one of Embodiments II-1 to II-52, wherein n is 0 or 1.

[0548] Embodiment II-55. The compound of any one of Embodiments II-1 to II-52, wherein m is 0 or 1.

[0549] Embodiment II-56. The compound of any one of Embodiments II-1 to II-52, wherein R_1 is (C_1-C_4) alkyl, (C_2-C_4) alkenyl, or (C_2-C_4) alkynyl.

[0550] Embodiment II-57. The compound of any one of Embodiments II-1 to II-52, wherein R_1 is (C_1-C_4) alkoxy.

[0551] Embodiment II-58. The compound of any one of Embodiments II-1 to II-57, wherein s is 1 or 2.

[0552] Embodiment II-59. The compound of any one of Embodiments II-1 to II-58, wherein each R' is independently (C_1-C_2) alkyl.

[0553] Embodiment II-60. The compound of any one of Embodiments II-1 to II-57, wherein s is 0.

[0554] Embodiment II-61.The compound of Embodiment II-1, selected from the group consisting of:

N-(1-(3-hydroxy-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
(R)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
(S)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
4-(azetidin-3-ylbuta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;
4-((1-formylazetidin-3-yl)buta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;
N-(1-(3-ethoxy-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
4-((1-acetylazetidin-3-yl)buta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhepta-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(((1R,2R)-2-(hydroxymethyl)cyclopropyl)buta-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-methoxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-(methylthio)-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(1-(3-amino-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-(methylamino)-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(1-(3-(dimethylamino)-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(1-(3-hydroxy-1-oxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1-oxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-phenylpiperazine-1-carboxamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-phenylpiperidine-1-carboxamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-1-phenylpiperidine-4-carboxamide;
4-((S)-5,6-dihydroxyhexa-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;
4-((S)-6,7-dihydroxyhepta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;
4-((R)-6,7-dihydroxyhepta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;
N-(1-(1,1-dioxido-3-vinylthietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
(S)-N-(1-(3-ethyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
(S)-N-(1-(3-cyclopropyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(1-(3-ethynyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

(S)-N-(2-(hydroxyamino)-1-(3-methyl-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-((S)-2-(hydroxyamino)-1-((R)-3-methoxy-1,1-dioxidotetrahydrothiophen-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-((S)-2-(hydroxyamino)-1-((S)-3-methoxy-1,1-dioxidotetrahydrothiophen-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

(Z)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhex-3-en-1-yn-1-yl)benzamide;

(E)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhex-3-en-1-yn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-((1-methylazetidin-3-yl)buta-1,3-diyn-1-yl)benzamide;

(S)-N-(1-(3-((dimethylamino)methyl)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(2-(hydroxyamino)-2-oxo-1-(3-propoxyazetidin-3-yl)ethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(1-(3-(cyclopropylmethoxy)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(S)-N-(1-(3-ethynylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-((S)-2-(hydroxyamino)-1-((2R,3S)-3-methoxy-2-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(2-(hydroxyamino)-1-((2S,3S)-3-methoxy-2-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(S)-N-(2-(hydroxyamino)-1-(3-methylazetidin-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;

N-((R)-2-(hydroxyamino)-1-((2S,3S)-3-methoxy-2-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(S)-N-(2-(hydroxyamino)-2-oxo-1-(3-vinylazetidin-3-yl)ethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(R)-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(S)-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-((S)-1-((2S,3S)-3-hydroxy-2-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-((R)-1-((2S,3S)-3-hydroxy-2-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
(S)-N-(1-(3-cyclopropylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
(S)-N-(1-(3-ethylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-((S)-1-((2R,3R)-3-hydroxy-2-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-(2-(hydroxyamino)-1-(3-(methylthio)azetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-((R)-1-((2R,3R)-3-hydroxy-2-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
3-fluoro-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethyl)benzamide;
3-fluoro-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethoxy)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-((trifluoromethyl)thio)benzamide;
2-fluoro-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethyl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethyl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethoxy)benzamide;
2-fluoro-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethoxy)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1-methylazetidin-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-(methylamino)azetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-(1-(3-ethoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-ethynylbenzamide;
N-(1-(3-ethoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;
N-(1-(azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1-methylazetidin-3-yl)-2-oxoethyl)-4-(penta-1,3-diyn-1-yl)benzamide;
N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(penta-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(penta-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(penta-1,3-diyn-1-yl)benzamide;
(S)-N-(2-(hydroxyamino)-1-(3-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-(2-(hydroxyamino)-1-(3-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-(1-(1-formyl-3-methoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(1-(1-acetyl-3-methoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(1-(1-formyl-3-hydroxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(1-(3-hydroxy-1-(methylsulfonyl)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(1-(1-acetyl-3-hydroxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

tert-butyl 3-(2-(hydroxyamino)-2-oxo-1-(4-(pentafluoro- λ^6-sulfanyl)benzamido)ethyl)-3-(methylsulfonyl)azetidine-1-carboxylate;
N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;
N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(((1R,2R)-2-(hydroxymethyl)cyclopropyl)buta-1,3-diyn-1-yl)benzamide;
(S)-N-(2-(hydroxyamino)-1-(3-methylazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1-methylazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxy-1-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;
(R)-N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
(S)-N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(1-methyl-3-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(((1R,2R)-2-(hydroxymethyl)cyclopropyl)buta-1,3-diyn-1-yl)benzamide;
N-(1-(3-hydroxy-1-(2-hydroxyethyl)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;
N-(1-(3-hydroxy-1-(2-hydroxyethyl)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;
N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
4-bromo-N-(2-(hydroxyamino)-1-(3-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)benzamide;
N-(2-(hydroxyamino)-1-(3-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;
N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide; and
4-bromo-N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)benzamide;

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

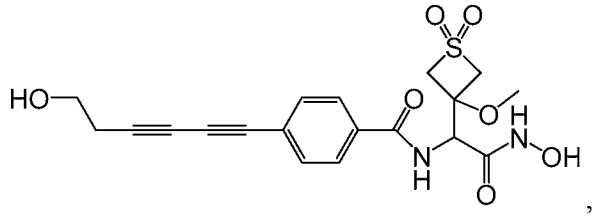
[0555] Embodiment II-62. The compound of Embodiment II-1, wherein the compound is N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0556] Embodiment II-63. The compound of Embodiment II-1, wherein the compound is (S)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0557] Embodiment II-64. The compound of Embodiment II-1, wherein the compound is (R)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

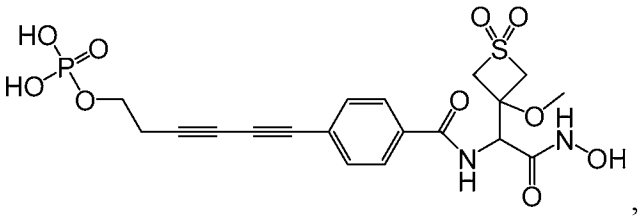
[0558] Embodiment II-65. The compound of Embodiment II-2, wherein the compound is 6-(4-((2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)carbamoyl)phenyl)hexa-3,5-diyn-1-yl dihydrogen phosphate, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof.

[0559] Embodiment II-66. The compound of Embodiment II-1, wherein the compound is:



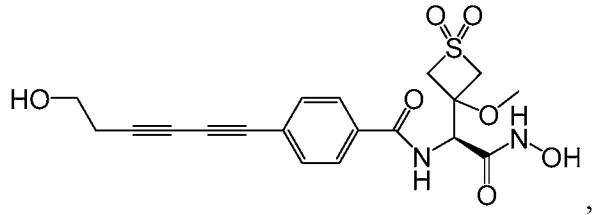
or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0560] Embodiment II-67. The compound of Embodiment II-2, wherein the compound is:



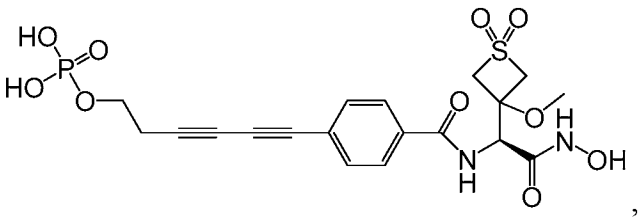
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof.

[0561] Embodiment II-68. The compound of Embodiment II-1, wherein the compound is:



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, or tautomer thereof.

[0562] Embodiment II-69. The compound of Embodiment II-2, wherein the compound is:



or a pharmaceutically acceptable salt, hydrate, solvate, or tautomer thereof.

[0563] Embodiment II-70. A pharmaceutical composition comprising a compound of any one of Embodiments II-1 to II-69, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[0564] Embodiment II-71. A method for treating a bacterial infection in a subject comprising administering to a subject in need thereof a therapeutically effective amount of a compound

according to any one of Embodiments II-1 to II-69, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0565] Embodiment II-72. A method for treating a bacterial infection in a subject, comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition according to Embodiment II-70.

[0566] Embodiment II-73. The method according to Embodiment II-71 or II-72, wherein said bacterial infection is caused by a gram-negative bacteria.

[0567] Embodiment II-74. A method of inhibiting a deacetylase enzyme in gram-negative bacteria, comprising contacting the bacteria with a compound according to any one of Embodiments II-1 to II-69, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0568] Embodiment II-75. The method of Embodiment II-71 or II-72, wherein the bacterial infection is an infection of a bacteria selected from the group consisting of *Pseudomonas aeruginosa*, *Stenotrophomonas maltophila*, *Burkholderia cepacia*, *Alcaligenes xylosoxidans*, *Enterobacteriaceae*, *Haemophilus*, *Franciscellaceae* and *Neisseria* species.

[0569] Embodiment II-76. The method of Embodiment II-71 or II-72, wherein the bacterial infection is an infection of a bacteria selected from the group consisting of *Pseudomonas*, *Stenotrophomonas*, *Burkholderia*, *Alcaligenes*, *Enterobacteriaceae*, *Haemophilus*, *Franciscellaceae* and *Neisseria* species.

[0570] Embodiment II-77. The method of Embodiment II-71 or II-72, wherein the bacterial infection is an infection of a bacteria selected from the group consisting of *Enterobacteriaceae*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia,* and *Pseudomonas*.

[0571] Embodiment II-78. The method of Embodiment II-71 or II-72, wherein the bacterial infection is an infection of a bacteria selected from the group consisting of *Enterobacteriaceae*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia, Pseudomonas*, *Alcaligenes*, *Haemophilus*, *Franciscellaceae* and *Neisseria* species.

[0572] Embodiment II-79. The method of Embodiment II-73 or II-74, wherein the gram-negative bacteria is *Enterobacteriaceae*.

[0573] Embodiment II-80. The method of Embodiment II-73 or II-74, wherein the gram-negative bacteria is *Enterobacteriaceae* or *Acinetobacter*.

[0574] Embodiment II-81. The method of any one of Embodiments II-75 to II-80, wherein the *Enterobacteriaceae* is selected from the group consisting of *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia*, *Morganella*, *Cedecea*, *Edwardsiella* species, and *Escherichia coli*.

[0575] Embodiment II-82. The method of Embodiment II-81, wherein the *Yersinia* is *Yersinia pestis*.

[0576] Embodiment II-83. The method of any one of Embodiments II-76 to II-78, wherein the *Burkholderia* is *Burkholderia cepacia*.

[0577] Embodiment II-84. The method of any one of Embodiments II-76 to II-78, wherein the *Burkholderia* is *Burkholderia pseudomallei* or *Burkholderia mallei*.

[0578] Embodiment II-85. The method of any one of Embodiments II-76 to II-78, wherein the *Burkholderia* is *Burkholderia pseudomallei*, *Burkholderia mallei*, or *Burkholderia cepacia*.

[0579] Embodiment II-86. The method of any one of Embodiments II-77, II-78, or II-80, wherein the *Acinetobacter* is selected from the group consisting of *Acinetobacter baumannii*, *Acinetobacter lwoffi, Acinetobacter albensis, Acinetobacter apis, Acinetobacter beijerinckii, Acinetobacter bereziniae, Acinetobacter bohemicus, Acinetobacter boissieri, Acinetobacter bouvetii, Acinetobacter brisouii, Acinetobacter calcoaceticus, Acinetobacter courvalinii, Acinetobacter dispersus*, *Acinetobacter equi*, *Acinetobacter gandensis, Acinetobacter gerneri, Acinetobacter guangdongensis, Acinetobacter guillouiae, Acinetobacter gyllenbergii, Acinetobacter haemolyticus, Acinetobacter harbinensis, Acinetobacter indicus, Acinetobacter junii, Acinetobacter kookii, Acinetobacter modestus*, *Acinetobacter nectaris, Acinetobacter nosocomialis, Acinetobacter parvus, Acinetobacter pakistanensis*, *Acinetobacter populi*, *Acinetobacter proteolyticus*, *Acinetobacter pittii, Acinetobacter puyangensis, Acinetobacter qingfengensis, Acinetobacter radioresistens, Acinetobacter rudis, Acinetobacter schindleri, Acinetobacter seifertii, Acinetobacter soli, Acinetobacter tandoii, Acinetobacter tjernbergiae, Acinetobacter towneri, Acinetobacter ursingii, Acinetobacter variabilis, Acinetobacter venetianus,* and *Acinetobacter vivianii*.

[0580] Embodiment II-87. A method of inhibiting LpxC, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of Embodiments II-1 to II-69, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0581] Embodiment II-88. The compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, of any one of Embodiments II-1 to II-69 for use as a medicament.

[0582] Embodiment II-89. The compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, of any one of Embodiment II-1 to II-69 for use in treating a bacterial infection.

[0583] Embodiment II-90. The compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, of any one of Embodiments II-1 to II-69 for use in the manufacture of a medicament for treating a bacterial infection.

[0584] Embodiment II-91. The compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, of any one of Embodiments II-1 to II-69 for use in inhibiting a deacetylase enzyme in gram-negative bacteria.

[0585] Embodiment II-92. The compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, of any one of Embodiments II-1 to II-69 for use in the manufacture of a medicament for inhibiting a deacetylase enzyme in gram-negative bacteria.

[0586] Embodiment II-93. The compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, of any one of Embodiments II-1 to II-69 for use in inhibiting LpxC.

[0587] Embodiment II-94. The compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, of any one of Embodiments II-1 to II-69 for use in the manufacture of a medicament for inhibiting LpxC.

[0588] Embodiment II-95. The compound for use of Embodiment II-89 or II-90, wherein the bacterial infection is an infection of a bacteria selected from the group consisting of *Pseudomonas aeruginosa*, *Stenotrophomonas maltophila*, *Burkholderia cepacia*, *Alcaligenes xylosoxidans*, *Enterobacteriaceae*, *Haemophilus*, *Franciscellaceae* and *Neisseria* species.

[0589] Embodiment II-96. The compound for use of Embodiment II-89 or II-90, wherein the bacterial infection is an infection of a bacteria selected from the group consisting of *Pseudomonas*, *Stenotrophomonas*, *Burkholderia*, *Alcaligenes*, *Enterobacteriaceae*, *Haemophilus*, *Franciscellaceae* and *Neisseria* species.

[0590] Embodiment II-97. The compound for use of Embodiment II-89 or II-90, wherein the bacterial infection is an infection of a bacteria selected from the group consisting of *Enterobacteriaceae*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia,* and *Pseudomonas*.

[0591] Embodiment II-98. The compound for use of Embodiment II-89 or II-90, wherein the bacterial infection is an infection of a bacteria selected from the group consisting of *Enterobacteriaceae*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia, Pseudomonas*, *Alcaligenes*, *Haemophilus*, *Franciscellaceae* and *Neisseria* species.

[0592] Embodiment II-99. The compound for use of Embodiment II-91 or II-92, wherein the gram-negative bacteria is *Enterobacteriaceae.*

[0593] Embodiment II-100. The compound for use of Embodiment II-91 or II-92, wherein the gram-negative bacteria is *Enterobacteriaceae* or *Acinetobacter*.

[0594] Embodiment II-101. The compound for use of any one of Embodiments II-95 to II-100, wherein the *Enterobacteriaceae* is selected from the group consisting of *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia*, *Morganella*, *Cedecea*, *Edwardsiella* species, and *Escherichia coli*.

[0595] Embodiment II-102. The compound for use of Embodiment II-101, wherein the *Yersinia* is *Yersinia pestis.*

[0596] Embodiment II-103. The compound for use of any one of Embodiments II-96 to II-98, wherein the *Burkholderia* is *Burkholderia cepacia*.

[0597] Embodiment II-104. The compound for use of any one of Embodiments II-96 to II-98, wherein the *Burkholderia* is *Burkholderia pseudomallei* or *Burkholderia mallei*.

[0598] Embodiment II-105. The compound for use of any one of Embodiments II-96 to II-98, wherein the *Burkholderia* is *Burkholderia pseudomallei*, *Burkholderia mallei*, or *Burkholderia cepacia*.

[0599] Embodiment II-106. The compound for use of any one of Embodiments II-97, II-98, or II-100, wherein the *Acinetobacter* is selected from the group consisting of *Acinetobacter baumannii*, *Acinetobacter lwoffi, Acinetobacter albensis, Acinetobacter apis, Acinetobacter beijerinckii, Acinetobacter bereziniae, Acinetobacter bohemicus, Acinetobacter boissieri, Acinetobacter bouvetii, Acinetobacter brisouii, Acinetobacter calcoaceticus, Acinetobacter courvalinii*, *Acinetobacter dispersus*, *Acinetobacter equi*, *Acinetobacter gandensis, Acinetobacter gerneri, Acinetobacter guangdongensis, Acinetobacter guillouiae, Acinetobacter*

gyllenbergii, Acinetobacter haemolyticus, Acinetobacter harbinensis, Acinetobacter indicus, Acinetobacter junii, Acinetobacter kookii, Acinetobacter modestus, Acinetobacter nectaris, Acinetobacter nosocomialis, Acinetobacter parvus, Acinetobacter pakistanensis, Acinetobacter populi, Acinetobacter proteolyticus, Acinetobacter pittii, Acinetobacter puyangensis, Acinetobacter qingfengensis, Acinetobacter radioresistens, Acinetobacter rudis, Acinetobacter schindleri, Acinetobacter seifertii, Acinetobacter soli, Acinetobacter tandoii, Acinetobacter tjernbergiae, Acinetobacter towneri, Acinetobacter ursingii, Acinetobacter variabilis, Acinetobacter venetianus, and *Acinetobacter vivianii*.

[0600] Embodiment II-107. The method of any one of Embodiments II-71 to II-73, or II-75 to II-87, wherein after administration of one or more doses of said compound, the subject does not develop vascular irritation.

[0601] Embodiment II-108. The method of any one of Embodiments II-71 to II-73, or II-75 to II-87, wherein after administration of one or more doses of said compound, the subject does not develop phlebitis.

[0602] Embodiment II-109. The method of Embodiment II-108, wherein the phlebitis is superficial phlebitis.

[0603] Embodiment II-110. The method of Embodiment II-108, wherein the phlebitis is thrombophlebitis.

[0604] Embodiment II-111. The method of any one of Embodiments II-71 to II-73, or II-75 to II-87, wherein after administration of one or more doses of said compound, the subject does not develop one or more symptoms of phlebitis.

[0605] Embodiment II-112. The method of Embodiment II-111, wherein the one or more symptoms of phlebitis are selected from the group consisting of warmth along the course of a vein, tenderness along the course of a vein, redness along the course of a vein, swelling/bulging along the course of a vein, and drainage of pus.

Examples

[0606] The disclosure is further illustrated by the following examples and synthesis schemes, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is

to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

Analytical Methods, Materials, and Instrumentation

[0607] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance (NMR) spectra were obtained on either Bruker or Varian spectrometers at 250, 300, or 400 MHz. Spectra are given in ppm (δ) and coupling constants, J, are reported in Hertz. Mass spectra were collected using a Waters ZQ Single Quad Mass Spectrometer (ion trap electrospray ionization (ESI)). Purity and low resolution mass spectral data were measured using Waters Acquity i-class ultra-performance liquid chromatography (UPLC) system with Acquity Photo Diode Array Detector, Acquity Evaporative Light Scattering Detector (ELSD) and Waters ZQ Mass Spectrometer. Data was acquired using Waters MassLynx 4.1 software and purity characterized by UV wavelength 220 nm, evaporative light scattering detection (ELSD) and electrospray positive ion (ESI). (Column: Acquity UPLC BEH C18 1.7μm 2.1 X 50 mm; Flow rate 0.6mL/min; Solvent A (95/5/0.1%: 10mM Ammonium Formate/Acetonitrile/Formic Acid), Solvent B (95/5/0.09%: Acetonitrile/Water/Formic Acid); gradient: 5-100% B from 0 to 2 mins, hold 100% B to 2.2 mins and 5% B at 2.21 mins. The absolute configuration of the separated enantiomers of the compounds in the examples described herein were not determined. As such, the configuration of the resolved materials were arbitrarily assigned as R or S in each case.

Bacterial Screens and Cultures

[0608] To test for antimicrobial activity, bacterial screens can be carried out in accordance with the following procedure. Minimum Inhibitory Concentrations (MICs) can be determined by the broth microdilution method in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines. In brief, organism suspensions are adjusted to a 0.5 McFarland standard to yield a final inoculum between 3×10^5 and 7×10^5 colony-forming units (CFU)/mL. Compound dilutions and inocula are made in sterile, cation adjusted Mueller-Hinton Broth (Beckton Dickinson). An inoculum volume of 100 μL is added to wells containing 100 μL of broth with 2-fold serial dilutions of the compound. All inoculated microdilution trays are incubated in ambient air at 35° C. for 18-24 hours. Following incubation, the lowest concentration of the

compound that prevents visible growth (OD600 nm < 0.05) is recorded as the MIC. Performance of the assay is monitored by the use of laboratory quality-control strains and a compound with a defined MIC spectrum (such as levofloxacin), in accordance with CLSI guidelines. Bacterial strains for testing may include, for example, Escherichia Coli ATCC 25922, Klebsiella pneumoniae ATCC 43816, and Pseudomonas aeruginosa PAM1020.

Pharmacokinetic Profile

[0609] The clearance rate of LpxC inhibitors of the present disclosure may be evaluated according to the following procedure: Sprague-Dawley rats are intravenously dosed with compounds of the present invention and known LpxC inhibitors formulated at 10 mg/kg in 10% hydroxypropyl-cyclodextrine in water (pH 8). At 2, 5, 15, and 30 min, 1, 2, 4, 6 and 8 h, 200 μL of blood is collected in tubes containing K_2EDTA. Blood samples are put on ice and, within 15 minutes, centrifuged to generate plasma. An aliquot of 30 μL of each plasma sample is mixed with 100 μl of acetonitrile containing propranolol (at 40 ng/mL used as an internal standard). For samples requiring prior 20X dilution, 3 μL of plasma are mixed with 57 μL of blank plasma, and the resulting dilutions are processed as indicated above. Samples are vortexed for 10 min at 750 rpm and centrifuged at 6,000 rpm for 10 min. Supernatants are subjected to analysis by LC-MS/MS.

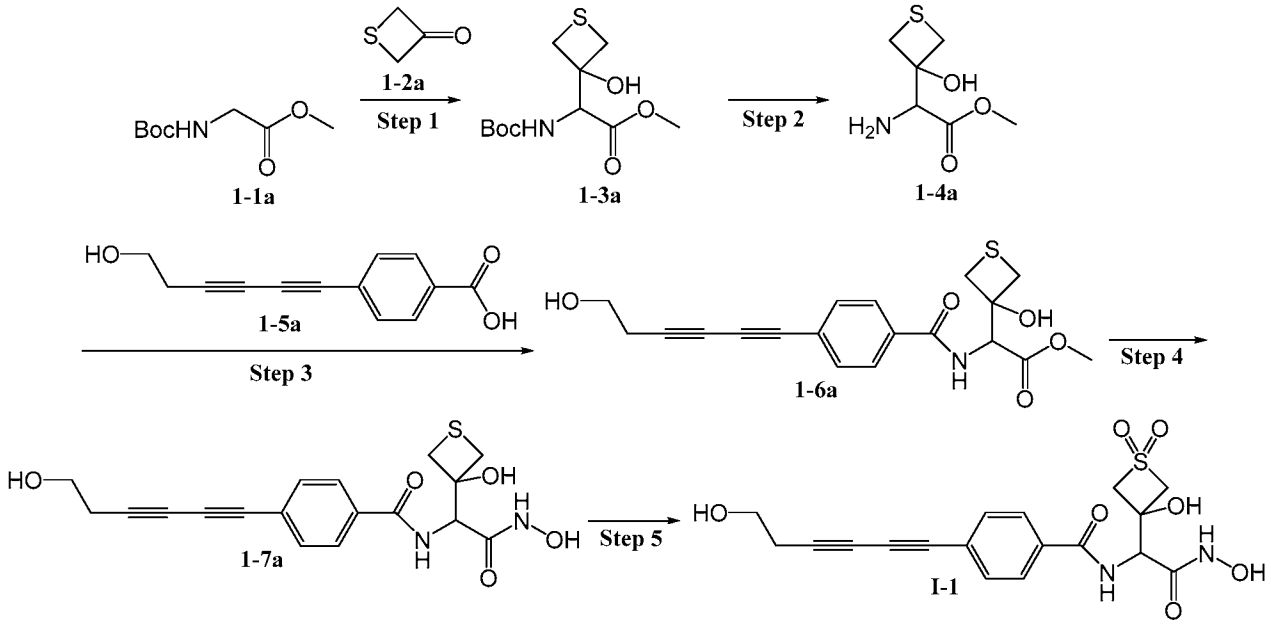
[0610] Abbreviations used in the following examples and elsewhere herein are:

ACN	acetonitrile
AcOH	acetic acid
atm	atmosphere
$BF_3{\cdot}Et_2O$	boron trifluoride diethyl etherate
br	broad
d	doublet
DCM	dichloromethane
DEA	diethylamine
DIBAL-H	diisobutylaluminum hydride
DIEA	*N*,*N*-diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide

Et_2O	diethyl ether
EtOAc	ethyl acetate
ESI	electrospray ionization
h	hour(s)
HATU	[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate
HPLC	high-performance liquid chromatography
IPA	*i*-propyl alcohol or isopropanol
iPrOH	*i*-propyl alcohol or isopropanol
l	liquid
LC/MS	liquid chromatography–mass spectrometry
LiHMDS	lithium hexamethyldisilazide
m	multiplet
*m*CPBA	meta-chloroperoxybenzoic acid
MeCN	acetonitrile
MeLi	methyl lithium
MeOH	methanol
MHz	megahertz
min	minutes
μW	microwave
NMR	nuclear magnetic resonance
PCy_3	tricyclohexylphosphine
$Pd(OAc)_2$	palladium (II) acetate
ppm	parts per million
q	quartet
RT	room temperature
s	singlet
t	triplet
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TLC	thin layer chromatography
TMS-diazomethane	(trimethylsilyl)diazomethane
$TMSCHN_2$	(trimethylsilyl)diazomethane
UV	ultraviolet

Example 1: N-(1-(3-hydroxy-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-1)



Step 1. **Methyl 2-((tert-butoxycarbonyl)amino)-2-(3-hydroxythietan-3-yl)acetate (1-3a).**

[0611] A solution of LiHMDS (120 mL, 4.00 equiv) in THF was added to a 500 mL 3-necked flask purged and maintained with an inert atmosphere of nitrogen and cooled to -78 °C. A solution of methyl 2-[[(tert-butoxy)carbonyl]amino]acetate (**1-1a**, 5.6 g, 29.60 mmol, 1.0 eq.) in tetrahydrofuran (100 mL) was then added dropwise and the resulting mixture was stirred for 2 h at -78 °C. A solution of $BF_3{\cdot}Et_2O$ (3.8 mL, 29.6 mmol) and thietan-3-one (**1-2a**, 2.6 g, 29.5 mmol, 1.0 equiv) in THF (100 mL) was added dropwise at –78 °C and the resulting solution was stirred for 1 h at –78 °C and 2 h at –50 °C. The reaction was then quenched by the addition of 100 mL of saturated aqueous NH_4Cl and extracted with 2 x 150 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography eluting with dichloromethane/ethyl acetate (10:1). This resulted in 4 g (49%) of methyl 2-[[(tert-

butoxy)carbonyl]amino]-2-(3-hydroxythietan-3-yl)acetate (**1-3a**) as a light yellow oil. LCMS (ESI): $[M+H]^+ = 278.1$.

Step 2. **Methyl 2-amino-2-(3-hydroxythietan-3-yl)acetate (1-4a).**

[0612] A solution of methyl 2-((tert-butoxycarbonyl)amino)-2-(3-hydroxythietan-3-yl)acetate (**1-3a**, 0.17 g, 0.613 mmol) in 30% TFA/DCM (3 mL) was stirred at 0 °C (ice bath) for 1h. The reaction mixture was then concentrated to dryness and triturated with Et_2O/hexanes to give 180 mg of product **1-4a** as a TFA salt (quant).

Step 3: **Methyl 2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)-2-(3-hydroxythietan-3-yl)acetate (1-6a).**

[0613] A solution of methyl 2-amino-2-(3-hydroxythietan-3-yl)acetate (**1-4**, TFA salt, 0.17 g, 0.63 mmol), 4-(6-hydroxyhexa-1,3-diyn-1-yl)benzoic acid (**1-5a**) (0.14 g, 0.67 mmol, 1.1 equiv) and DIEA (0.42 mL, 2.45 mmol, 4.0 equiv) in DMF (0.6 mL) was cooled to 0 °C in an ice bath and HATU (0.25 g, 0.65 mmol) was added in one portion. After 15 min, the reaction mixture was quenched by the addition of cold saturated aqueous NH_4Cl. Solid precipitates were quickly collected by filtration and dissolved in EtOAc. The EtOAc solution containing product was dried with anhydrous Na_2SO_4, filtered, and concentrated to give pure product **1-6a** (0.11 g, 55% yield).

Step 4: **N-(2-(hydroxyamino)-1-(3-hydroxythietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (1-7a).**

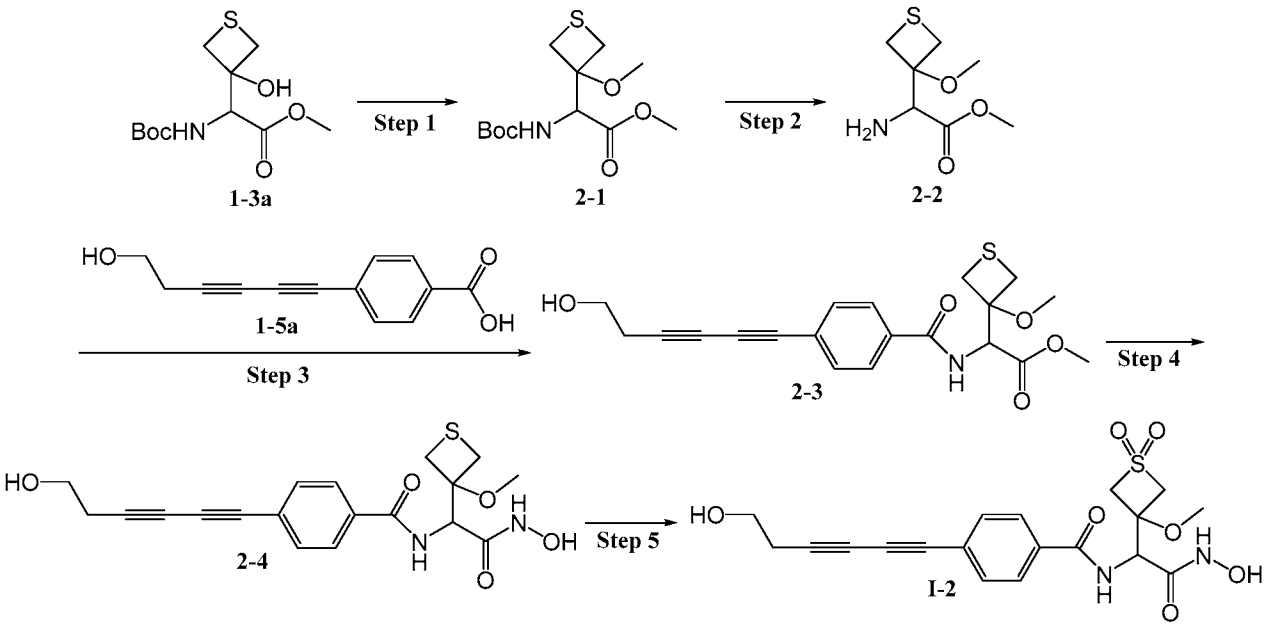
[0614] To a solution of methyl 2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)-2-(3-hydroxy-thietan-3-yl)acetate (**1-6a**) (0.14 g, 0.36 mmol) in 0.4 ml IPA was added 0.4 mL NH_2OH at 0 °C. The resulting suspension was stirred at room temperature overnight. The crude solution was purified by reverse-phase HPLC to afford 30 mg pure compound **1-7a**.

Step 5: **N-(1-(3-hydroxy-1,1-*dioxidothietan*-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-1).**

[0615] To a solution of N-(2-(hydroxyamino)-1-(3-hydroxythietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide **(1-7a)** (0.138 g, 0.35 mmol) in acetonitrile/water (1:1, 0.4 mL) at 0 °C (ice bath) was added 30% peracetic acid (2 mL). After 2 h, additional peracetic acid (0.4 mL) was added and the reaction was stirred until complete conversion to product was observed. The reaction mixture was purified by RP-HPLC and lyophilized to give 13 mg of **I-1**.

^{1}H NMR (250 MHz, DMSO-d_6): 10.88 (s, 1H), 9.05 (s, 1H), 8.70 (d, J = 9.3 Hz, 1H), 7.89 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H), 6.52 (s, 1H), 4.98 (t, J = 5.5 Hz, 1H), 4.79 (d, J = 9.0 Hz, 1H), 4.69 (d, J = 13.5 Hz, 1H), 4.44 (d, J = 13.0 Hz, 1H), 3.96 (dt, J = 3.3, 14.3 Hz, 2H), 3.53 (q, J = 6.3 Hz, 2H), 2.54 (t, J = 6.5 Hz, 2H). LCMS (ESI): $[M+H]^+$ = 407.2.

Example 2: N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-2)



Step 1. **Methyl 2-((tert-butoxycarbonyl)amino)-2-(3-methoxythietan-3-yl)acetate (2-1).**

[0616] To a solution of methyl 2-((*tert*-butoxycarbonyl)amino)-2-(3-hydroxythietan-3-yl)acetate (**1-3a**, 1.05 g, 3.79 mmol) in acetonitrile (12 mL) was added methyl iodide (6 mL) followed by Ag_2O (2.16 g, 9.45 mmol, 2.5 equiv.). The resulting mixture was stirred at 37 °C for 2.5 h, then diluted with EtOAc and filtered through Celite. The filtrate was concentrated to dryness to give crude product, which was purified by silica gel chromatography (eluting with EtOAc in hexanes, 0-30%) to provide 450 mg pure methyl 2-((*tert*-butoxycarbonyl)amino)-2-(3-methoxythietan-3-yl)acetate (**2-1**) (40% yield).

Step 2: **Methyl 2-amino-2-(3-methoxythietan-3-yl)acetate (2-2).**

[0617] A solution of methyl 2-((*tert*-butoxycarbonyl)amino)-2-(3-methoxythietan-3-yl)acetate (0.39 g, 1.34 mmol) in 30% TFA/DCM (3 mL) was stirred at 0 °C (ice bath) for 1 h. The reaction

mixture was then concentrated to dryness and triturated with Et_2O/hexanes to give 400 mg of methyl 2-amino-2-(3-methoxythietan-3-yl)acetate (**2-2**) as the TFA salt (quant).

Step 3: **Methyl 2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)-2-(3-methoxythietan-3-yl)acetate (2-3).**

[0618] A solution of methyl 2-amino-2-(3-methoxythietan-3-yl)acetate (TFA salt, 0.2 g, 0.69 mmol), 4-(6-hydroxyhexa-1,3-diyn-1-yl)benzoic acid (**1-5a**, 0.14 g, 0.65 mmol, 0.95 equiv) and DIEA (0.3 mL, 1.7 mmol, 2.5 equiv) in DMF (1 mL) was cooled to 0 °C in an ice bath and HATU (0.25 g, 0.65 mmol) was added in one portion. After 15 min, the reaction mixture was quenched by the addition of cold saturated aqueous NH_4Cl. Solid precipitates were quickly collected by filtration and dissolved in EtOAc. The EtOAc solution containing product was dried with anhydrous Na_2SO_4, filtered, and concentrated to give pure methyl 2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)¬benzamido)-2-(3-methoxythietan-3-yl)acetate (**2-3**, 0.14 g, 55% yield).

Step 4: **N-(2-(hydroxyamino)-1-(3-methoxythietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (2-4).**

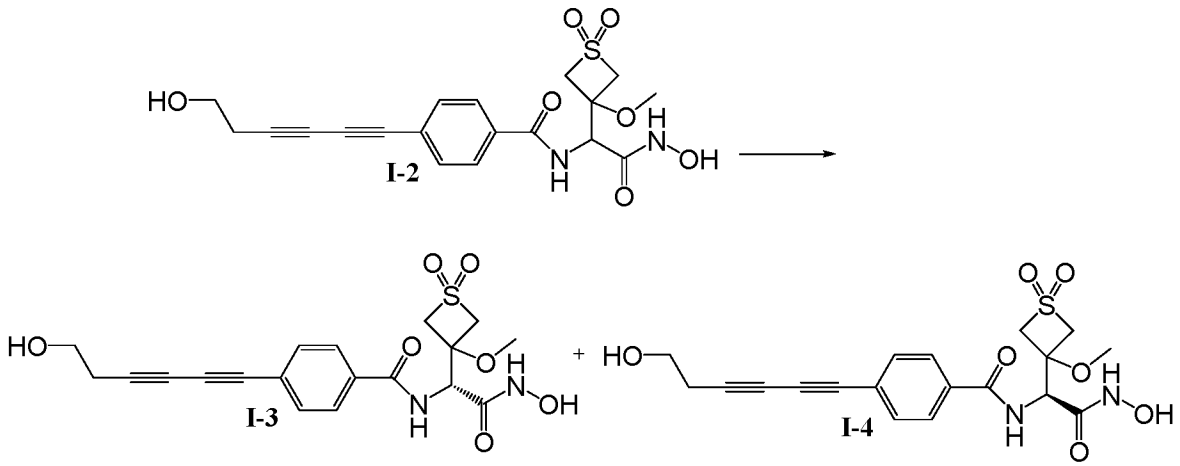
[0619] To a solution of methyl 2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)¬benzamido)-2-(3-methoxythietan-3-yl)acetate (**2-3**, 0.14 g, 0.36 mmol) in THF/MeOH (1:1, 1.8 mL) was added $NH_2OH.HCl$ (0.36 g, 5.17 mmol, 14 equiv) under an atmosphere of nitrogen and the resulting suspension was cooled to -35 °C. After 15 min, a 25% solution of NaOMe in MeOH (1.27 mL, 5.91 mmol, 16 equiv) was added slowly and the resulting mixture was stirred at -20 °C for 20 min and then at 0 °C for 1 h. The reaction mixture was poured into a cold saturated aqueous NH_4Cl solution and extracted with $CHCl_3$ containing 20% IPA. The combined organic layers were concentrated and dried *in vacuo* to give pure N-(2-(hydroxyamino)-1-(3-methoxythietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**2-4**, 0.138 g, 95% yield).

Step 5: **N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-2).**

[0620] To a solution of N-(2-(hydroxyamino)-1-(3-methoxythietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (0.138 g, 0.35 mmol) in acetonitrile / water (1:1, 1.5 mL) at 0 °C (ice bath) was added 30% peracetic acid (2 mL). After 2 h, additional peracetic acid (1.5 mL) was added and the reaction was stirred for an additional 1 h. The reaction mixture was

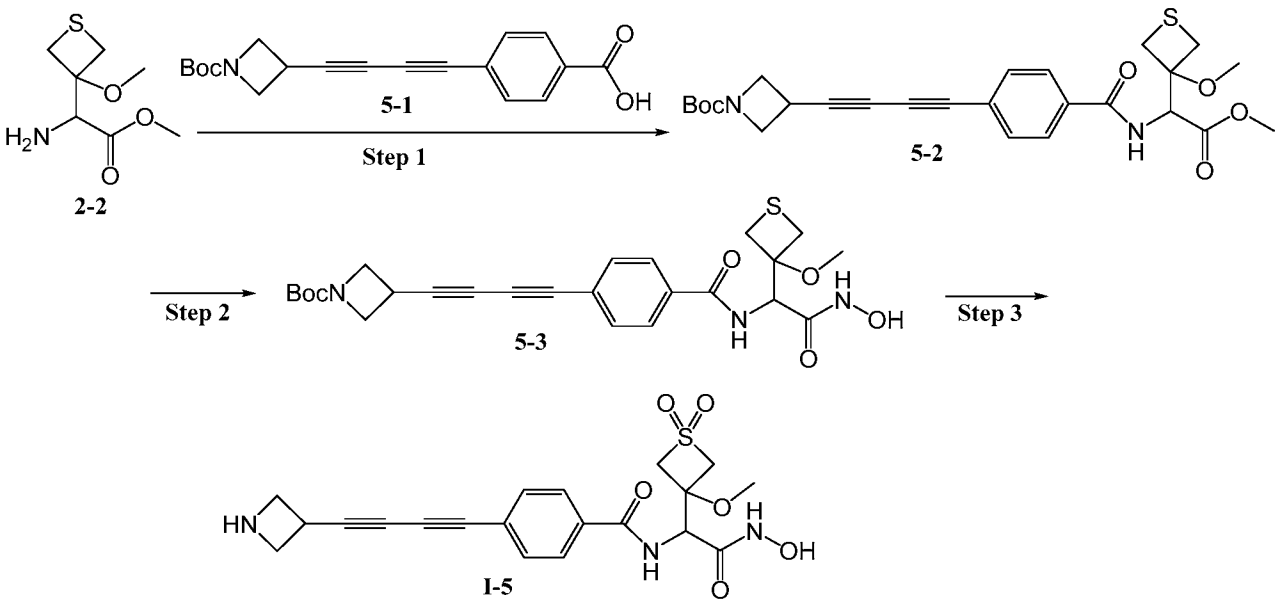
concentrated to near dryness and triturated with hexanes three times. The resulting crude product was carefully dissolved in 10% TEA/DMSO and purified by RP-HPLC to provide pure N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxido¬thietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)¬benzamide **I-2** (45 mg, 30%). ^{1}H NMR (250 MHz, DMSO-d_6): 11.10 (s, 1H), 9.0 (d, J = 9.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 5.05 (d, J = 9.3 Hz, 1H), 4.96 (d, J = 14.5 Hz, 1H), 4.36 (dd, J = 3.0, 14.5 Hz, 1H), 4.18 (d, J = 14.5 Hz, 1H), 4.11 (dd, J = 4.0, 15.0 Hz, 1H), 3.54 (q, J = 6.3 Hz, 2H), 3.35 (s, 3H), 2.54 (t, J = 6.3 Hz, 2H). LCMS (ESI): $[M+H]^+$ = 421.3.

Example 3: (R)- N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-3) and (S)- N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-4)



[0621] Racemic **I-2** was separated on a Chiracel®–AD-H column using IPA with 0.1% TFA in CO_2(l).

Example 4: 4-(Azetidin-3-ylbuta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide trifluoroacetic acid salt (I-5)



Step 1. **tert-butyl 3-((4-((2-methoxy-1-(3-methoxythietan-3-yl)-2-oxoethyl)carbamoyl) phenyl)buta-1,3-diyn-1-yl)azetidine-1-carboxylate (5-2)**.

[0622] A solution of methyl 2-amino-2-(3-methoxythietan-3-yl)acetate (**2-2**) (TFA salt, 0.24 g, 0.75 mmol), 4-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)buta-1,3-diyn-1-yl)benzoic acid (**5-1**) (0.24 g, 0.95 mmol, 0.95 equiv) and DIEA (0.36 mL, 2.1 mmol, 2.8 equiv) in DMF (1.5 mL) was cooled to 0 °C in an ice bath and HATU (0.29 g, 0.79 mmol) was added in one portion. After 15 min, the reaction mixture was quenched by the addition of cold saturated aqueous NH_4Cl. Solid precipitates were quickly collected by filtration and dissolved in EtOAc. The EtOAc solution containing product was dried with anhydrous Na_2SO_4, filtered, and concentrated to give crude product (0.45 g). The crude product was purified by silica gel chromatography to afford 290 mg of product **5-2**.

Step 2: **tert-butyl 3-((4-((2-(hydroxyamino)-1-(3-methoxythietan-3-yl)-2-oxoethyl) carbamoyl)phenyl)buta-1,3-diyn-1-yl)azetidine-1-carboxylate (5-3).**

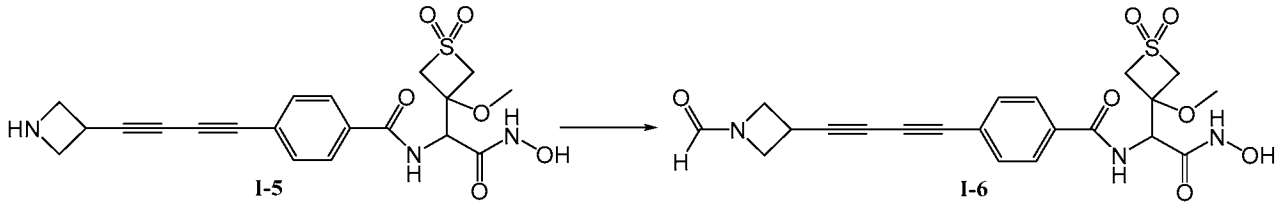
[0623] To a solution of *tert*-butyl 3-((4-((2-methoxy-1-(3-methoxythietan-3-yl)-2-oxoethyl) carbamoyl)phenyl)buta-1,3-diyn-1-yl)azetidine-1-carboxylate (**5-2**, 0.29 g, 0.58 mmol) in THF/MeOH (1:1, 6.0 mL) was added $NH_2OH \cdot HCl$ (0.56 g, 8.15 mmol, 14 equiv) under an

atmosphere of nitrogen. The resulting suspension was cooled to –35 °C. After 15 min, a 25% solution of NaOMe in MeOH (2.0 mL, 9.28 mmol, 16 equiv) was added slowly and the resulting mixture was stirred at –20 °C for 20 min and then at 0 °C for 1 h. The reaction mixture was quenched with 1.1 equiv of 1N HCl/dioxane at –10 °C. After allowing the mixture to warm to room temperature, it was poured into a saturated aqueous NH_4Cl solution and extracted with $CHCl_3$ containing 20% IPA. The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give 220 mg of crude product **5-3** (75% yield).

Step 3: **4-(Azetidin-3-ylbuta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide trifluoroacetic acid salt (I-5)**.

[0624] *tert*-Butyl 3-((4-((2-(hydroxyamino)-1-(3-methoxythietan-3-yl)-2-oxoethyl) carbamoyl)-phenyl)buta-1,3-diyn-1-yl)azetidine-1-carboxylate (**5-3**, 85 mg 0.17 mmol, 1.0 equiv) was suspended in 2.0 mL dichloromethane and cooled to 0 °C (ice bath). *m*CBPA (0.096 g, 0.56 mmol, 3.3eq) was then added in one portion. After 2 h, 2.0 mL of TFA/DCM was added and the mixture was stirred for an additional 20 minutes at 0 °C. The reaction mixture was concentrated to dryness and the resulting residue was triturated with ether/hexane to give 100 mg of crude TFA salt **I-5**. The crude product was purified by RP-HPLC and lyophilized to give 58 mg of TFA salt **I-5**. (61% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88 – 7.78 (m, 2H), 7.68 – 7.58 (m, 2H), 5.01 (s, 1H), 4.89 – 4.77 (m, 1H), 4.41 – 4.11 (m, 5H), 4.02 (s, 1H), 3.99 – 3.85 (m, 2H), 3.30 (s, 3H). LCMS (ESI): $[M+H]^+$ = 432.1.

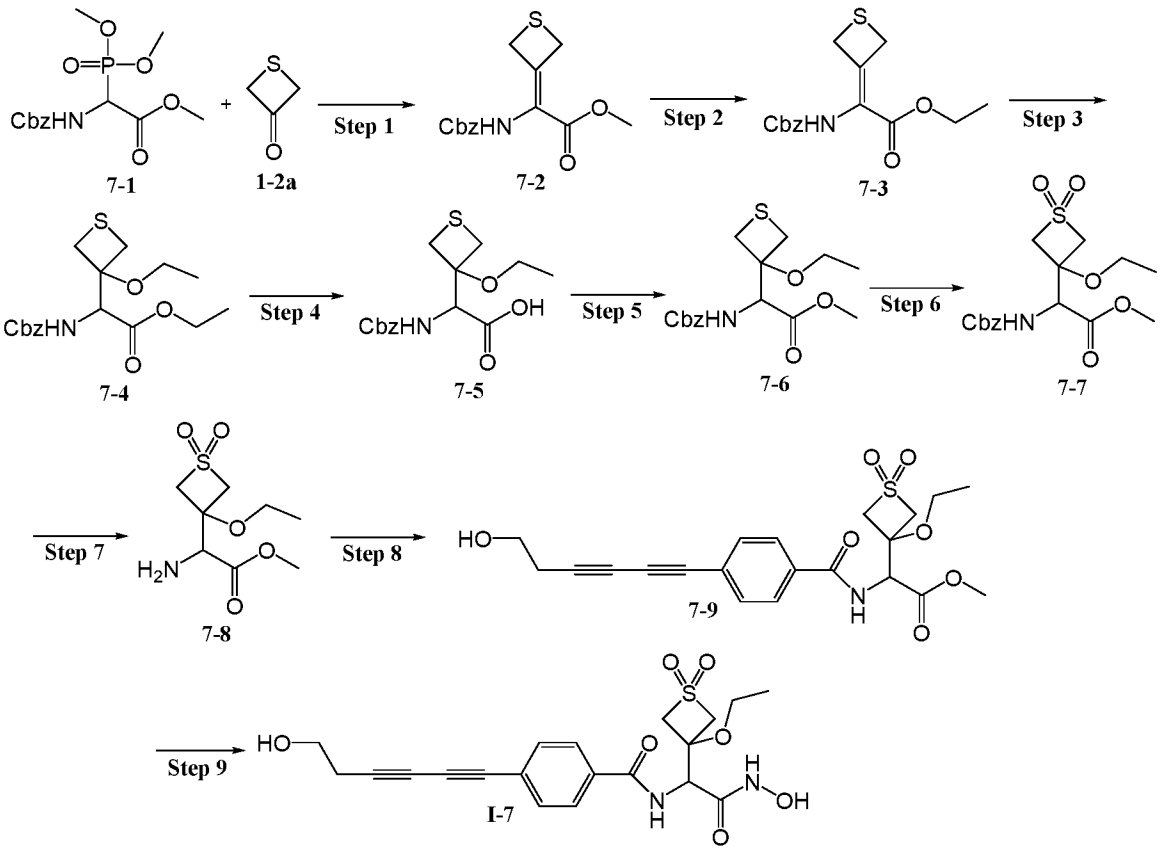
Example 5: 4-((1-formylazetidin-3-yl)buta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide (I-6).



[0625] 4-(Azetidin-3-ylbuta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide TFA salt (**I-5**, 95 mg, 0.174 mmol) was dissolved in 1.1 mL DMF. DIEA (0.272 mmol, 0.047 mL, 1.5 equiv) was added and the resulting solution was cooled to 0 °C (ice bath). 2,2,2-Trifluoroethylformate (1.1 equiv, 0.19 mmol, 0.019 mL)

was added dropwise. After 2 h, the reaction was quenched with acetic acid (0.435 mmol, 0.025 mL, 2.5 equiv) and purified by RP- HPLC. to give 49 mg of **I-6**. ^{1}H NMR (250 MHz, DMSO-*d*$_6$): 11.10 (s, 1H), 9.17 (s, 1H), 9.03 (d, *J* = 9.0 Hz, 1H), 7.95 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 5.05 (d, *J* = 9.0 Hz, 1H), 4.97 (d, *J* = 14.5 Hz, 1H), 4.36 – 4.47 (m, 2H), 4.12 – 4.24 (m, 4H), 3.77 – 3.92 (m, 2H), 3.35 (s, 3H). LCMS (ESI): $[M+H]^+$ = 459.7.

Example 6: 2-(3-ethoxy-1,1-dioxo-λ^6-thietan-3-yl)-N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]acetamide trifluoroacetic acid salt (I-7)



Step 1. **Methyl 2-[[(benzyloxy)carbonyl]amino]-2-(thietan-3-ylidene)acetate (7-2).**

[0626] 1,1,3,3-Tetramethylguanidine (0.631 mL) was added dropwise to a solution of methyl 2-[[(benzyloxy)carbonyl]amino]-2-(dimethoxyphosphoryl)acetate (**7-1**, 1.5 g, 4.53 mmol, 1.00 equiv) in oxolane (10 mL) at -20 °C and the resulting mixture was stirred for 1 h at -20 °C. Thietan-3-one (**1-2a**, 438 mg, 4.97 mmol, 1.1 equiv) in THF (20 mL) was then added at –20 °C and the resulting solution was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 100 mL of 0.1N aqueous HCl and extracted with 2 x 100 mL of ethyl acetate. The organic layers were combined, washed with 100 mL of saturated aqueous

$NaHCO_3$ and 100 mL of brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (1:4). The product containing fractions were combined and concentrated giving 500 mg (38%) of methyl 2-[[(benzyloxy)carbonyl]amino]-2-(thietan-3-ylidene)acetate **7-2** as a white solid. LCMS (ESI): $[M+H]^+ = 294.1$.

Step 2. **Ethyl 2-[[(benzyloxy)carbonyl]amino]-2-(thietan-3-ylidene)acetate (7-3).**

[0627] To a solution of methyl 2-[[(benzyloxy)carbonyl]amino]-2-(thietan-3-ylidene)acetate (**7-2**, 400 mg, 1.36 mmol, 1.00 equiv) in ethanol (5 mL) was added sodium ethoxide (93 mg, 1.37 mmol, 1.0 equiv) at 0 °C and the resulting solution was then stirred for 1 h at room temperature. The reaction was quenched by the addition of 100 mL of water and AcOH (1 mL). The resulting solution was extracted with 2 x 100 mL of ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (1:4). The product containing fractions were combined and concentrated resulting in 350 mg (84%) of ethyl 2-[[(benzyloxy)carbonyl]amino]-2-(thietan-3-ylidene)acetate (**7-3**) as a white solid. LCMS (ESI): $[M+H]^+ = 308.1$.

Step 3. **Ethyl 2-[[(benzyloxy)carbonyl]amino]-2-(3-ethoxythietan-3-yl)acetate (7-4).**

[0628] To a solution of ethyl 2-[[(benzyloxy)carbonyl]amino]-2-(thietan-3-ylidene)acetate (**7-3**, 250 mg, 0.81 mmol, 1.00 equiv) in ethanol (5 mL) was added sodium ethoxide (83 mg, 1.22 mmol, 1.5 equiv) at 0 °C. The resulting mixture was stirred for 24 h at room temperature then quenched by the addition of 50 mL of water with AcOH (1 mL). The resulting solution was extracted with 3 x 50 mL of ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 200 mg (70%) of crude ethyl 2-[[(benzyloxy)carbonyl]amino]-2-(3-ethoxythietan-3-yl)acetate (**7-4**) as a brown oil. LCMS (ESI): $[M+H]^+ = 354.1$.

Step 4. **2-[[(benzyloxy)carbonyl]amino]-2-(3-ethoxythietan-3-yl)acetic acid (7-5).**

[0629] To a solution of ethyl 2-[[(benzyloxy)carbonyl]amino]-2-(3-ethoxythietan-3-yl)acetate (**7-4**, 200 mg, 0.57 mmol, 1.0 equiv) in tetrahydrofuran (1 mL), methanol (1 mL) and water (1 mL) was added NaOH (80 mg, 2.0 mmol, 3.5 equiv) and the resulting solution was stirred for 1 h

at room temperature. The reaction was then quenched by the addition of 50 mL of water with AcOH (1 mL). The resulting solution was extracted with 3 x 50 mL of ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide 150 mg (81%) of crude 2-[[(benzyloxy)carbonyl]amino]-2-(3-ethoxythietan-3-yl)acetic acid (**7-5**) as a brown oil.

Step 5. **Methyl 2-[[(benzyloxy)carbonyl]amino]-2-(3-ethoxythietan-3-yl)acetate (7-6).**

[0630] To a solution of 2-[[(benzyloxy)carbonyl]amino]-2-(3-ethoxythietan-3-yl)acetic acid (**7-5**, 150 mg, 0.46 mmol, 1.0 equiv), methanol (0.1 mL) in dichloromethane (0.9 mL) was added $TMSCHN_2$ (0.5 mL, 2N in hexane, 2.0 equiv). The resulting solution was stirred for 5 min at room temperature, then concentrated under vacuum. The residue was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (1:7). The product containing fractions were combined and concentrated affording 100 mg (64%) of methyl 2-[[(benzyloxy)carbonyl]amino]-2-(3-ethoxythietan-3-yl)acetate (**7-6**) as a colorless oil. LCMS (ESI): $[M+H]^+ = 340.1$.

Step 6. **Methyl 2-(((benzyloxy)carbonyl)amino)-2-(3-ethoxy-1,1-dioxidothietan-3-yl)acetate (7-7).**

[0631] To a solution of methyl 2-[[(benzyloxy)carbonyl]amino]-2-(3-ethoxythietan-3-yl)acetate (**7-6**, 100 mg, 0.29 mmol, 1.00 equiv) in methanol/tetrahydrofuran/water (6 mL, 1:1:1) was added Oxone (365 mg, 2.0 equiv) and the resulting solution was stirred for 3 h at room temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum, resulting in 80 mg (73%) of methyl 2-(((benzyloxy)carbonyl)amino)-2-(3-ethoxy-1,1-dioxidothietan-3-yl)acetate (**7-7**) as a colorless oil which was used in the next step without further purification. LCMS (ESI): $[M+H]^+ = 372.1$.

Step 7. **Methyl 2-amino-2-(3-ethoxy-1,1-dioxidothietan-3-yl)acetate (7-8).**

[0632] To a solution of methyl 2-(((benzyloxy)carbonyl)amino)-2-(3-ethoxy-1,1-dioxidothietan-3-yl)acetate (**7-7**, 80 mg, 0.22 mmol, 1.0 equiv) in methanol (10 mL) was added 10% palladium on carbon (20 mg). The resulting solution was purged with H_2 three times and stirred for 1 h at room temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum, resulting in 50 mg (98%) of methyl 2-amino-2-(3-ethoxy-1,1-dioxidothietan-3-

yl)acetate (**7-8**) as a light brown oil which was used in the next step without further purification. LCMS (ESI): $[M+H]^+ = 238.0$.

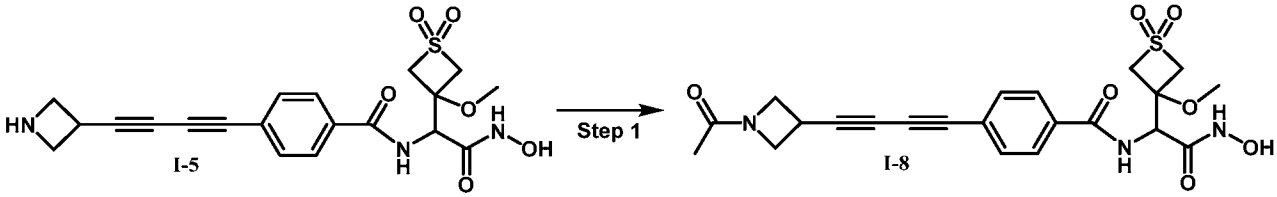
Step 8. **Methyl 2-(3-ethoxy-1,1-dioxidothietan-3-yl)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)acetate (7-9).**

[0633] To a solution of 4-(6-hydroxyhexa-1,3-diyn-1-yl)benzoic acid (**1-5a**, 50 mg, 0.23 mmol, 1.0 equiv) in N,N-dimethylformamide (3 mL) was added HATU (76 mg, 0.20 mmol, 1.0 equiv), DIEA (77 mg, 0.60 mmol, 1.0 equiv) and methyl 2-amino-2-(3-ethoxy-1,1-dioxidothietan-3-yl)acetate (50 mg, 0.21 mmol, 1.0 equiv). The resulting solution was stirred for 1 h at room temperature. The reaction was then quenched by the addition of 20 mL of water and extracted with 2 x 30 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified using a silica gel column eluting with ethyl acetate/petroleum ether (1:1) to provide 20 mg (20%) of methyl 2-(3-ethoxy-1,1-dioxidothietan-3-yl)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido) acetate (**7-9**) as a light yellow crude oil. LCMS (ESI): $[M+H]^+ = 434.1$

Step 9. **N-(1-(3-ethoxy-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide trifluoroacetic acid salt (I-7).**

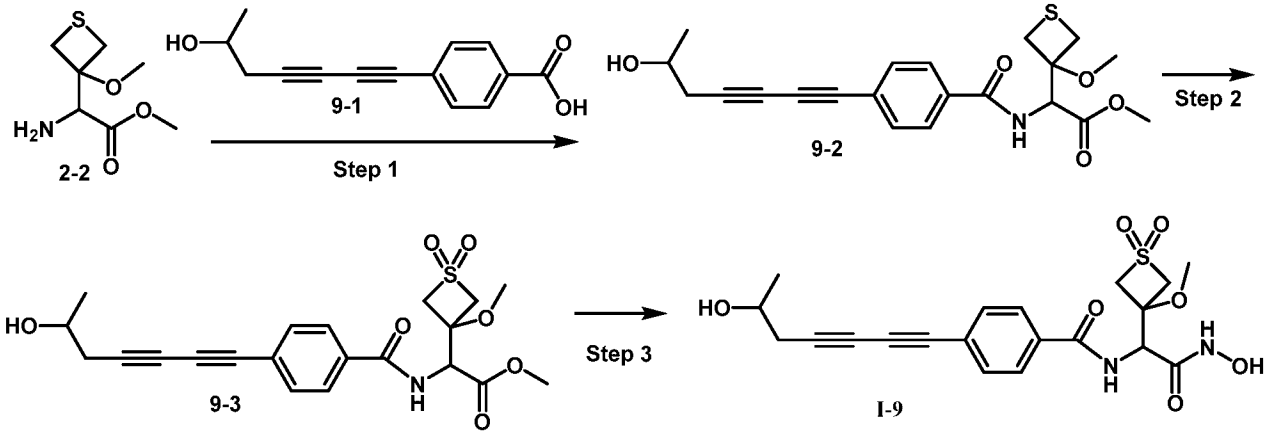
[0634] To a solution of methyl 2-(3-ethoxy-1,1-dioxidothietan-3-yl)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)acetate (**7-9**, 20 mg, 0.05 mmol, 1.00 equiv) in IPA (3 mL) was added hydroxylamine (2 mL, 50%). The resulting solution was stirred for 16 h at room temperature, then concentrated under vacuum. The residue was purified by Prep-HPLC using the following conditions: Type, Xbridge CSH Prep C18 OBD; Column, 19*150mm, 5um; Mobile phase, Water (0.05%TFA) and ACN (10.0% ACN up to 50.0% in 10 min); Detector, UV 254nm to afford 5.7 mg (23%) of N-(1-(3-ethoxy-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide trifluoroacetic acid salt (**I-7**) as a white solid. LCMS (ESI): $[M+H]^+ = 435.1$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.08 (s, 1H), 9.16 (s, 1H), 9.01 (d, J = 9.0 Hz, 1H), 7.90 – 7.87 (m, 2H), 7.66 – 7.63 (m, 2H), 5.07 – 4.97 (m, 3H), 4.47 – 4.35 (m, 1H), 4.22 – 4.13 (m, 1H), 4.11 – 4.06 (m, 1H), 3.65 – 3.52 (m, 4H), 2.58 – 2.54 (m, 2H).

Example 7: 2-([4-[4-(1-acetylazetidin-3-yl)buta-1,3-diyn-1-yl]phenyl]formamido)-N-hydroxy-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetamide (I-8)



[0635] To a solution of 2-([4-[4-(azetidin-3-yl)buta-1,3-diyn-1-yl]phenyl]formamido)-N-hydroxy-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetamide (**I-5**, 80 mg, 0.19 mmol, 1.0 equiv) in tetrahydrofuran (5 mL) was added sodium bicarbonate (47 mg, 0.56 mmol, 3.0 equiv) and acetyl chloride (17 mg, 0.22 mmol, 1.2 equiv). The resulting solution was stirred for 1 h at 0-5 °C. The crude product (70 mg) was purified by Prep-HPLC with the following conditions (2#-AnalyseHPLC-SHIMADZU(HPLC-10)): Column, XSelect CSH Prep C18 OBD Column, 5 um, 19*150mm; mobile phase, Waters (0.05% HCl) and ACN (10.0% ACN up to 35.0% in 10 min); Detector, UV 254/220 nm to afford 25.8 mg (29%) of 2-([4-[4-(1-acetylazetidin-3-yl)buta-1,3-diyn-1-yl]phenyl]formamido)-N-hydroxy-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetamide (**I-8**) as a white solid. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.13 – 11.05 (m, 1H), 9.16 (d, *J* = 1.2 Hz, 1H), 9.02 (d, *J* = 9.1 Hz, 1H), 7.96 – 7.85 (m, 2H), 7.72 – 7.61 (m, 2H), 5.11 – 4.92 (m, 2H), 4.45 – 4.32 (m, 2H), 4.27 – 4.06 (m, 4H), 3.85 – 3.63 (m, 2H), 3.34 (s, 3H), 1.75 (s, 3H). LCMS (ESI): $[M+H]^+$ = 474.1.

Example 8: N-hydroxy-2-[[4-(6-hydroxyhepta-1,3-diyn-1-yl)phenyl]formamido]-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetamide hydrochloride (I-9)



Step 1. **Methyl 2-[[4-(6-hydroxyhepta-1,3-diyn-1-yl)phenyl]formamido]-2-(3-methoxythietan-3-yl)acetate (9-2).**

[0636] To a solution of 4-(6-hydroxyhepta-1,3-diyn-1-yl)benzoic acid (**9-1**, 116 mg, 0.51 mmol, 1.0 equiv) in N,N-dimethylformamide (4 mL) was added HATU (215 mg, 0.57 mmol, 3.0 equiv), DIEA (197 mg, 1.52 mmol, 1.1 equiv) and methyl 2-amino-2-(3-methoxythietan-3-yl)acetate (**2-2**, 97 mg, 0.51 mmol, 1.0 equiv). The resulting solution was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 30 mL of saturated aqueous NH_4Cl and extracted with 3 x 50 mL of ethyl acetate. The combined organic layers were washed with 3 x 50 mL of brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography eluting with dichloromethane/ethyl acetate (5:1), resulting in 150 mg (74%) of methyl 2-[[4-(6-hydroxyhepta-1,3-diyn-1-yl)phenyl]formamido]-2-(3-methoxythietan-3-yl)acetate (**9-2**) as a light yellow oil. LCMS (ESI): $[M+H]^+ = 402.2$.

Step 2. **Methyl 2-[[4-(6-hydroxyhepta-1,3-diyn-1-yl)phenyl]formamido]-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetate (9-3).**

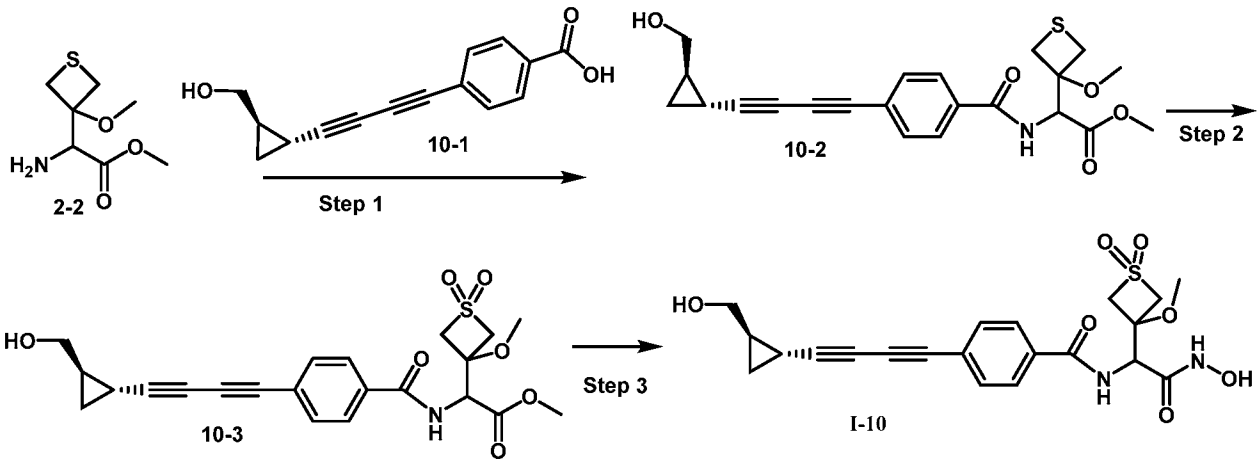
[0637] To a solution of methyl 2-[[4-(6-hydroxyhepta-1,3-diyn-1-yl)phenyl]formamido]-2-(3-methoxythietan-3-yl)acetate (**9-2**, 150 mg, 0.37 mmol, 1.0 equiv) in dichloromethane (4 mL) was added *m*CPBA (80%) (322 mg, 1.87 mmol, 4.0 equiv) at 0 °C and the resulting solution was stirred for 2 h at room temperature. The reaction mixture was diluted with 50 mL of DCM and washed with 3 x 50 mL of $Na_2S_2O_3$ (aq). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue **9-3** was used in the next step without further purification. LCMS (ESI): $[M+H]^+ = 434.1$.

Step 3. **N-hydroxy-2-[[4-(6-hydroxyhepta-1,3-diyn-1-yl)phenyl]formamido]-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetamide hydrochloride (I-9).**

[0638] To a solution of methyl 2-[[4-(6-hydroxyhepta-1,3-diyn-1-yl)phenyl]formamido]-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetate (**9-3**, 160 mg, 0.37 mmol, 1.0 equiv) in IPA (2 mL), was added hydroxylamine (2 mL, 50%). The resulting solution was stirred for 16 h at room temperature and then concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (2#-AnalyseHPLC-SHIMADZU(HPLC-10)): Column,

XSelect CSH Prep C18 OBD Column, 5 um,19*150 mm; mobile phase, Waters (0.05% HCl) and ACN (11.0% ACN up to 44.0% in 6 min); Detector, UV 254/220 nm to afford 46.5 mg (27%) of N-hydroxy-2-[[4-(6-hydroxyhepta-1,3-diyn-1-yl)phenyl]formamido]-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetamide hydrochloride as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.09 (s, 1H), 9.16 (s, 1H), 9.02 (d, J = 9.1 Hz, 1H), 7.94 – 7.84 (m, 2H), 7.70 – 7.59 (m, 2H), 5.11 – 4.93 (m, 2H), 4.45 – 4.32 (m, 1H), 4.31 – 4.07 (m, 2H), 3.83 (m, 1H), 3.34 (s, 3H), 1.14 (d, J = 6.1 Hz, 3H). LCMS (ESI): $[M+H]^+$ = 435.1.

Example 9: N-hydroxy-2-[(4-[4-[(1R,2R)-2-(hydroxymethyl)cyclopropyl]buta-1,3-diyn-1-yl]phenyl)formamido]-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetamide hydrochloride (I-10)



Step 1. **Methyl 2-[(4-[4-[(1R,2R)-2-(hydroxymethyl)cyclopropyl]buta-1,3-diyn-1-yl]phenyl)formamido]-2-(3-methoxythietan-3-yl)acetate (10-2)**.

[0639] To a solution of 4-4-[(1R,2R)-2-(hydroxymethyl)cyclopropyl]buta-1,3-diyn-1-ylbenzoic acid (**10-1**, 138 mg, 0.57 mmol, 1.1 equiv) in N,N-dimethylformamide (5 mL) was added HATU (239 mg, 0.63 mmol, 1.2 equiv), DIEA (202 mg, 1.56 mmol, 3.0 equiv) and methyl 2-amino-2-(3-methoxythietan-3-yl)acetate (**2-2**, 100 mg, 0.52 mmol, 1.00 equiv)and the resulting solution was stirred for 1 h at room temperature. The reaction mixture was then quenched by the addition of 10 mL of saturated aqueous NH_4Cl and extracted with 3 x 30 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (1:2), resulting in 100 mg (46%) of methyl 2-[(4-[4-[(1R,2R)-2-

(hydroxymethyl)cyclopropyl]buta-1,3-diyn-1-yl]phenyl)formamido]-2-(3-methoxythietan-3-yl)acetate (**10-2**) as a yellow oil. LCMS (ESI): $[M+H]^+$=414.1.

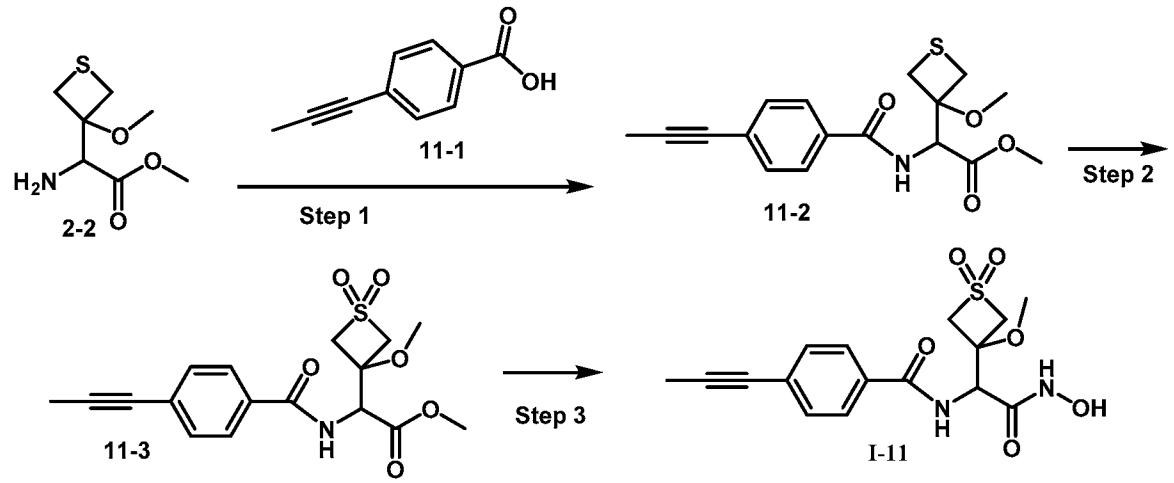
Step 2. **Methyl 2-[(4-[4-[(1R,2R)-2-(hydroxymethyl)cyclopropyl]buta-1,3-diyn-1-yl]phenyl) formamido]-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetate (10-3).**

[0640] To a solution of methyl 2-[(4-[4-[(1R,2R)-2-(hydroxymethyl)cyclopropyl]buta-1,3-diyn-1-yl]phenyl)formamido]-2-(3-methoxythietan-3-yl)acetate (**10-2**, 150 mg, 0.36 mmol, 1.0 equiv) in dichloromethane (3 mL) was added *m*CPBA (200 mg, 1.16 mmol, 3.0 equiv) and the resulting solution was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 30 mL of $Na_2S_2O_3$(aq) and extracted with 3 x 50 mL of ethyl acetate. The combined organic layers dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum resulting in 100 mg (62%) of methyl 2-[(4-[4-[(1R,2R)-2-(hydroxymethyl)cyclopropyl]buta-1,3-diyn-1-yl]phenyl)formamido]-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetate (**10-3**) as a white solid. LCMS (ESI): $[M+H]^+$=446.1.

Step 3. **Synthesis of N-hydroxy-2-[(4-[4-[(1R,2R)-2-(hydroxymethyl)cyclopropyl]buta-1,3-diyn-1-yl]phenyl)formamido]-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetamide hydrochloride (I-10).**

[0641] To a solution of methyl 2-[(4-[4-[(1R,2R)-2-(hydroxymethyl)cyclopropyl]buta-1,3-diyn-1-yl]phenyl)formamido]-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetate (**10-3**, 100 mg, 0.22 mmol, 1.0 equiv) in IPA (2 mL) was added hydroxylamine (1 mL, 50%) and the resulting solution was stirred for 16 h at room temperature. The crude product (70 mg) was purified by Prep-HPLC using the following conditions: Column, XSelect CSH Prep C18 OBD Column, 5 um, 19*150mm; mobile phase, Waters (0.05% HCl) and ACN (10.0% ACN up to 35.0% in 10 min); Detector, UV 254/220 nm to afford 28 mg (26%) of N-hydroxy-2-[(4-[4-[(1R,2R)-2-(hydroxymethyl)cyclopropyl]buta-1,3-diyn-1-yl]phenyl)formamido]-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetamide hydrochloride (**I-10**) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.11 (s, 1H), 9.02 (d, J = 9.1 Hz, 1H), 7.90 (d, J = 8.2, 2.2 Hz, 2H), 7.64 (m, 2H), 5.13 – 4.94 (m, 2H), 4.45 – 4.11 (m, 3H), 3.45 (m,1H), 3.36 (d, J = 2.2 Hz, 3H), 3.27 (m, 1H), 1.54 – 1.37 (m, 2H), 1.03 – 0.84 (m, 2H). LCMS (ESI): $[M+H]^+$ = 447.1.

Example 10: N-hydroxy-2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)-2-[[4-(prop-1-yn-1-yl)phenyl] formamido] acetamide (I-11)



Step 1. **Synthesis of Methyl 2-(3-methoxythietan-3-yl)-2-[[4-(prop-1-yn-1-yl)phenyl]formamido]acetate (11-2).**

[0642] To a solution of 4-(prop-1-yn-1-yl)benzoic acid (**11-1**, 82 mg, 0.51 mmol, 1.00 equiv) in N,N-dimethylformamide (3 mL) at 0 °C was added HATU (213 mg, 0.56 mmol, 1.1 equiv), DIEA (197 mg, 1.52 mmol, 3.0 equiv) and methyl 2-amino-2-(3-methoxythietan-3-yl)acetate (**2-2**, 99 mg, 0.52 mmol, 1.0 equiv). The resulting solution was stirred for 2 h at room temperature then quenched by the addition of 30 mL of saturated aqueous NH_4Cl and extracted with 3 x 50 mL of ethyl acetate. The combined organic layers were washed with 3 x 50 mL of brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (1:3). This resulted in 100 mg (58%) of methyl 2-(3-methoxythietan-3-yl)-2-[[4-(prop-1-yn-1-yl)phenyl]formamido]acetate (**11-2**) as a yellow oil. LCMS (ESI): $[M+Na]^+$=356.1.

Step 2. **Methyl 2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)-2-[[4-(prop-1-yn-1-yl)phenyl] formamido]acetate (11-3).**

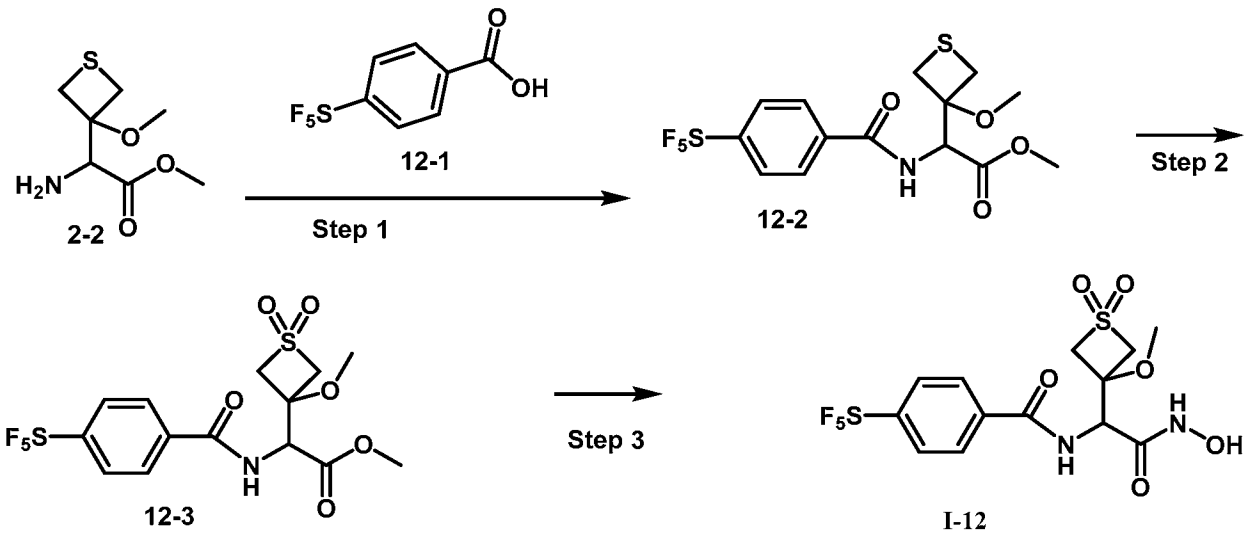
[0643] To a solution of methyl 2-(3-methoxythietan-3-yl)-2-[[4-(prop-1-yn-1-yl)phenyl] formamido]acetate (**11-2**, 100 mg, 0.30 mmol, 1.0 equiv) in dichloromethane (4 mL) at 0 °C was added *m*CPBA (80%) (258 mg, 1.50 mmol, 4.0 equiv). The resulting solution was stirred for 3 h

at room temperature then diluted with 50 mL of DCM and washed with 3 x 50 mL of $Na_2S_2O_3$ (aq). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The resulting residue (**11-3**) was used in next step without further purification. LCMS (ESI): $[M+H]^+ = 366.2$.

Step 3. **N-hydroxy-2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)-2-[[4-(prop-1-yn-1-yl)phenyl] formamido] acetamide (I-11).**

[0644] To a solution of methyl 2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)-2-[[4-(prop-1-yn-1-yl)phenyl]formamido]acetate (**11-3**, 109 mg, 0.30 mmol, 1.0 equiv) in IPA (2 mL) was added hydroxylamine (2 mL, 50%). The resulting solution was stirred for 16 h at room temperature and then concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: Column, XSelect CSH Prep C18 OBD Column, 5 um, 19*150 mm; mobile phase, Waters (0.05% HCl) and ACN (11.0% ACN up to 49.0% in 6 min); Detector, UV 220 nm to afford 58 mg (53%) of N-hydroxy-2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)-2-[[4-(prop-1-yn-1-yl)phenyl]formamido]acetamide (**I-11**) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.08 (d, J = 1.5 Hz, 1H), 9.15 (d, J = 1.4 Hz, 1H), 8.93 (d, J = 9.1 Hz, 1H), 7.90 – 7.80 (m, 2H), 7.52 – 7.42 (m, 2H), 5.11 – 4.93 (m, 2H), 4.38 (m, 1H), 4.26 – 4.06 (m, 2H), 3.32 (s, 1H), 2.07 (s, 3H). LCMS (ESI): $[M+H]^+$ =367.1.

Example 11: N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(pentafluoro-λ⁶-sulfanyl)benzamide (I-12)



Step 1. **Methyl 2-(3-methoxythietan-3-yl)-2-[[4-(pentafluoro-λ^6-sulfanyl)phenyl] formamido]acetate (12-2).**

[0645] To a solution of 4-(pentafluoro-λ^6-sulfanyl)benzoic acid (**12-1**, 127 mg, 0.51 mmol, 1.00 equiv) in N,N-dimethylformamide (4 mL) at 0 °C was added HATU (213 mg, 0.56 mmol, 1.1 equiv), DIEA (197 mg, 1.52 mmol, 3.0 equiv) and methyl 2-amino-2-(3-methoxythietan-3-yl)acetate (**2-2**, 99 mg, 0.52 mmol, 1.0 equiv). The resulting solution was stirred for 2 h at room temperature then quenched by the addition of 30 mL of saturated aqueous NH_4Cl and extracted with 3 x 50 mL of ethyl acetate. The combined organic layers were washed with 3 x 50 mL of brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified using silica gel chromatography eluting with ethyl acetate/petroleum ether (1:3). This provided in 74 mg (34%) of methyl 2-(3-methoxythietan-3-yl)-2-[[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido]acetate (**12-2**) as a yellow oil. LCMS (ESI): $[M+H]^+ = 422.2$.

Step 2. **Methyl 2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[4-(pentafluoro-λ^6-sulfanyl) phenyl]formamido]acetate (12-3).**

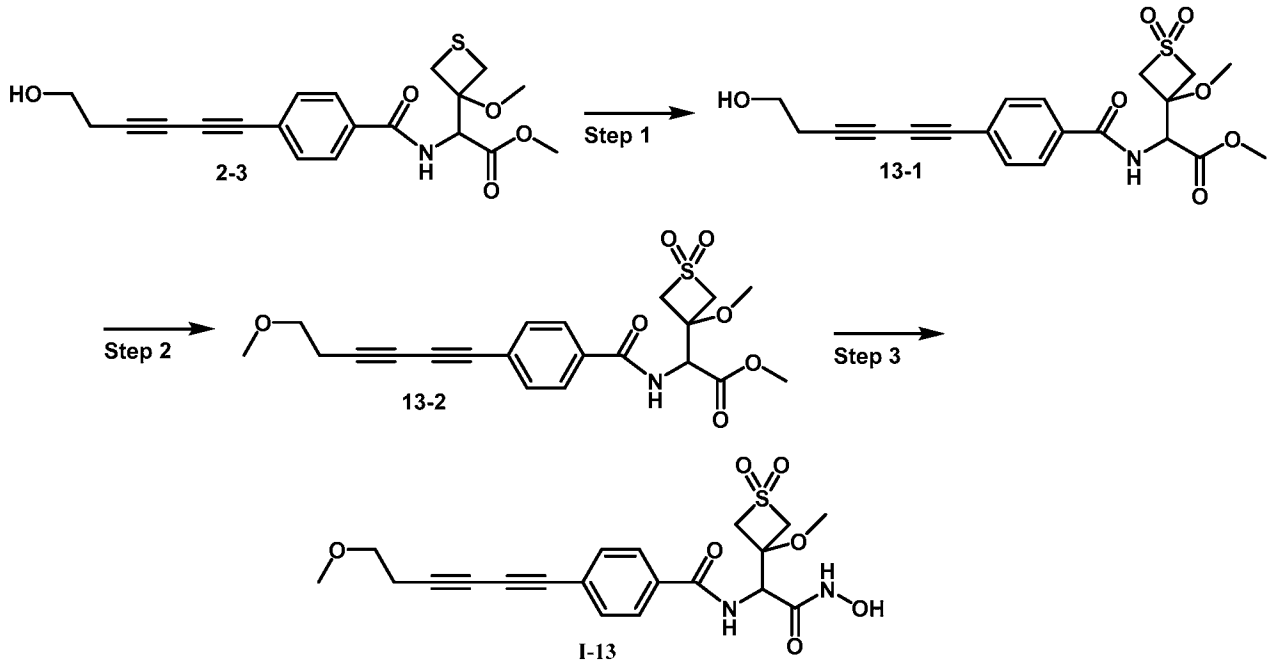
[0646] To a solution of methyl 2-(3-methoxythietan-3-yl)-2-[[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido]acetate (**12-2**, 74 mg, 0.18 mmol, 1.0 equiv) in dichloromethane (3 mL) was added *m*CPBA (80%) (151 mg, 0.88 mmol, 4.0 equiv) and the resulting solution was stirred for 3 h at room temperature. The reaction solution was diluted with 50 mL of DCM and washed with 3 x 50 mL of $Na_2S_2O_3$ (aq). The mixture was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue (**12-3**) was used in next step without further purification. LCMS (ESI): $[M+H]^+ = 454.2$.

Step 3. **N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (I-12).**

[0647] To a solution of methyl 2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido]acetate (**12-3**, 77 mg, 0.17 mmol, 1.0 equiv) in IPA (1 mL) was added hydroxylamine (1 mL, 50%). The resulting solution was stirred for 16 h at room temperature and then concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: Column, XBridge Prep C18 OBD Column, 5 um, 19*150

mm; mobile phase, Waters (0.05% $NH_3.H_2O$) and ACN (10.0% ACN up to 40.0% in 7 min); Detector, UV 220/254 nm to afford 37.5 mg (49%) of N-hydroxy-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido] acetamide (**I-12**) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.12 (s, 1H), 9.29 – 9.16 (m, 2H), 8.05 (br s, 4H), 5.07 (d, J = 9.0 Hz, 1H), 5.02 – 4.90 (m, 1H), 4.40 (m, 1H), 4.30 – 4.09 (m, 2H), 3.32 (s, 1H). LCMS (ESI): $[M+H]^+$ = 455.2.

Example 12: N-hydroxy-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[4-(6-methoxyhexa-1,3-diyn-1-yl)phenyl] formamido]acetamide (I-13)



Step 1. **Methyl 2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetate (13-1).**

[0648] To a solution of methyl 2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-(3-methoxythietan-3-yl)acetate (**2-3**, 150 mg, 0.39 mmol, 1.0 equiv) in dichloromethane (5 mL) was added *m*CPBA (190 mg, 2.0 equiv). The resulting solution was stirred for 3 h at room temperature, then quenched by the addition of 50 mL of 5% aqueous $NaHSO_3$ and extracted with 2 x 50 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography eluting with dichloromethane/ethyl acetate (4:1) resulting in 120 mg (74%) of

methyl 2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetate (**13-1**) as light yellow oil. LCMS (ESI): $[M+H]^+ = 420.1$.

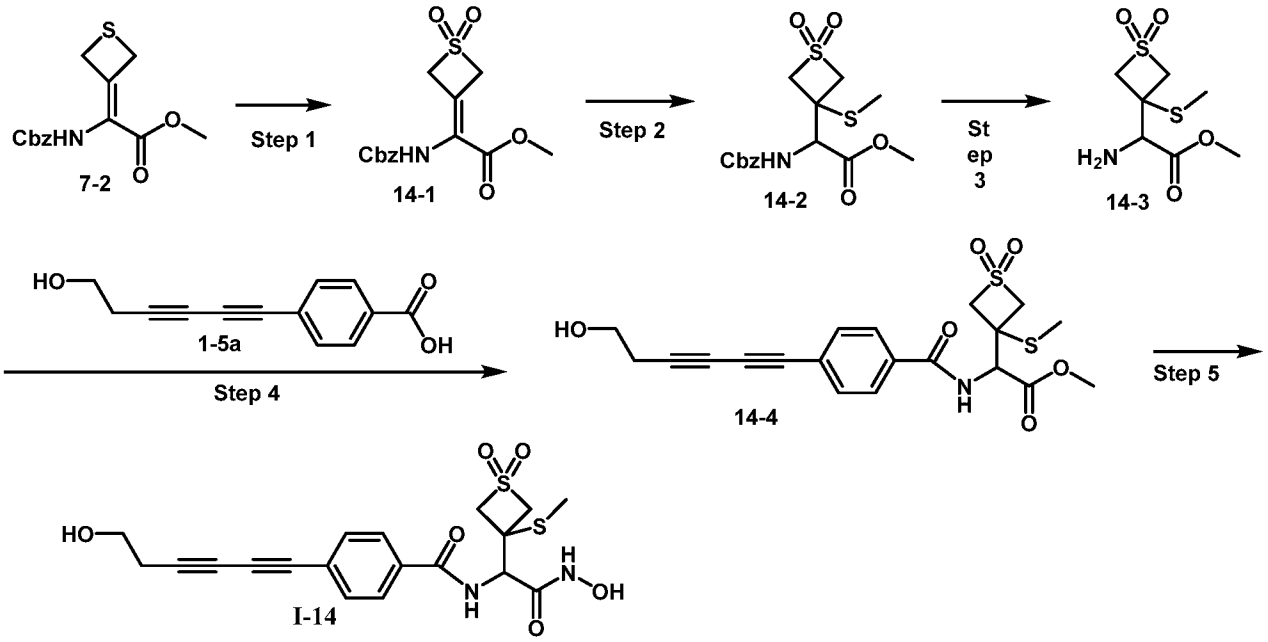
Step 2. **Methyl 2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[4-(6-methoxyhexa-1,3-diyn-1-yl)phenyl] formamido]acetate (13-2).**

[0649] To a solution of methyl 2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetate (**13-1**, 150 mg, 0.36 mmol, 1.0 equiv) in ACN (5 mL) was added Ag_2O (165 mg, 0.72 mmol, 2.0 equiv) and MeI (252 mg, 1.79 mmol, 5.00 equiv). The resulting solution was stirred for 24 h at 50 °C then cooled to room temperature and concentrated under vacuum. The residue was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (36:100) resulting in 80 mg (52%) of methyl 2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[4-(6-methoxyhexa-1,3-diyn-1-yl)phenyl]formamido]acetate (**13-2**) as a colorless solid. LCMS (ESI): $[M+H]^+ = 434.1$.

Step 3. **N-hydroxy-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[4-(6-methoxyhexa-1,3-diyn-1-yl)phenyl] formamido]acetamide (I-13).**

[0650] To a solution of methyl 2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[4-(6-methoxyhexa-1,3-diyn-1-yl)phenyl]formamido]acetate (**13-2**, 80 mg, 0.18 mmol, 1.0 equiv) in IPA (2 mL) was added NH_2OH (1 mL, 50%). The resulting solution was stirred for 16 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column, XBridge Shield RP18 OBD Column, 5 um, 19*150 mm; mobile phase, Waters (0.05%NH_3H_2O) and ACN (5.0% ACN up to 30.0% in 7 min); Detector, uv 220 nm to afford 47 mg (59%) of N-hydroxy-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[4-(6-methoxyhexa-1,3-diyn-1-yl)phenyl]formamido]acetamide (**I-13**) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.92 (d, J = 9.1 Hz, 1H), 7.94 – 7.83 (m, 2H), 7.69 – 7.59 (m, 2H), 5.07 – 4.91 (m, 2H), 4.41 – 4.20 (m, 2H), 4.13 (m, 1H), 3.48 (t, J = 6.3 Hz, 2H), 3.30-3.28 (m, 3H), 3.27 (s, 3H), 2.69 (m, 2H). LCMS (ESI): $[M+H]^+ = 435.1$.

Example 13: N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[3-(methylsulfanyl)-1,1-dioxo-λ⁶-thietan-3-yl]acetamide (I-14)



Step 1. **Methyl 2-[[(benzyloxy)carbonyl]amino]-2-(1,1-dioxo-λ⁶-thietan-3-ylidene)acetate (14-1) .**

[0651] *m*CPBA (2.1 g, 12.21 mmol, 4.0 equiv) was added to a solution of methyl 2-[[(benzyloxy)carbonyl]amino]-2-(thietan-3-ylidene)acetate (**7-2**, 1.0 g, 3.41 mmol, 1.0 equiv) in dichloromethane (20 mL). The resulting solution was stirred for 3 h at room temperature then quenched by the addition of 50 mL of $Na_2S_2O_3$(aq) and extracted with 4 x 100 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography eluting using ethyl acetate/petroleum ether (1:2) resulting in 800 mg (72%) of methyl 2-[[(benzyloxy) carbonyl]amino]-2-(1,1-dioxo-λ⁶-thietan-3-ylidene)acetate (**14-1**) as a yellow solid. LCMS (ESI): $[M+H]^+ = 326.1$.

Step 2. **Methyl 2-[[(benzyloxy)carbonyl]amino]-2-[3-(methylsulfanyl)-1,1-dioxo-λ⁶-hietan-3-yl]acetate (14-2).**

[0652] To a solution of methyl 2-[[(benzyloxy)carbonyl]amino]-2-(1,1-dioxo-λ⁶-thietan-3-ylidene)acetate (**14-1**, 800 mg, 2.46 mmol, 1.0 equiv) in water (10 mL) and tetrahydrofuran (5

mL) was added (methylsulfanyl)methanimidamide sulfuric acid (925 mg, 4.91 mmol, 2.0 equiv) and potassium carbonate (1019 mg, 7.37 mmol, 3.0 equiv). The resulting solution was stirred for 30 min at 55 °C then quenched by the addition of 10 mL of citric acid and extracted with 3 x 50 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography eluting using ethyl acetate/petroleum ether (1:2) resulting in 400 mg (44%) of methyl 2-[[(benzyloxy)carbonyl]amino]-2-[3-(methylsulfanyl)-1,1-dioxo-λ^6-thietan-3-yl]acetate (**14-2**) as a yellow solid. LCMS (ESI): $[M+H]^+ = 374.1$.

Step 3. **Synthesis of Methyl 2-amino-2-[3-(methylsulfanyl)-1,1-dioxo-λ^6-thietan-3-yl]acetate (14-3).**

[0653] To a solution of methyl 2-[[(benzyloxy)carbonyl]amino]-2-[3-(methylsulfanyl)-1,1-dioxo-λ^6-thietan-3-yl]acetate (**14-2**, 800 mg, 2.14 mmol, 1.0 equiv) in methanol (8 mL) and ethyl acetate (16 mL) was added 20% $Pd(OH)_2$ on carbon (800 mg) and 10% Palladium on carbon (400 mg). The resulting solution was purged with H_2 three times and stirred for 4 h at room temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum resulting in 400 mg (78%) of methyl 2-amino-2-[3-(methylsulfanyl)-1,1-dioxo-λ^6-thietan-3-yl]acetate (**14-3**) as a light yellow crude oil. LCMS (ESI): $[M+H]^+ = 240.0$.

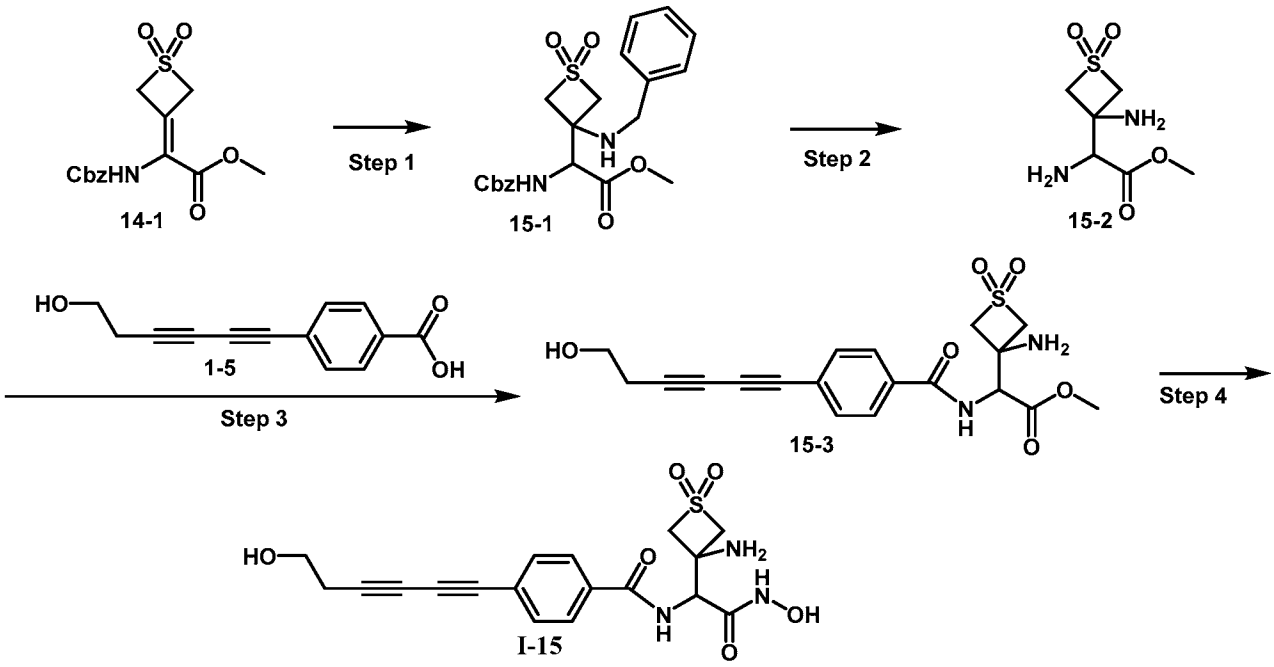
Step 4. **Methyl 2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[3-(methylsulfanyl)-1,1-dioxo-λ^6-thietan-3-yl]acetate (14-4).**

[0654] To a solution of 4-(6-hydroxyhexa-1,3-diyn-1-yl)benzoic acid (**1-5a**, 400 mg, 1.87 mmol, 1.1 equiv) in N,N-dimethylformamide (10 mL) was added HATU (763 mg, 2.01 mmol, 1.2 equiv), DIEA (648 mg, 5.01 mmol, 3.0 equiv) and methyl 2-amino-2-[3-(methylsulfanyl)-1,1-dioxo-λ^6-thietan-3-yl]acetate (**14-3**, 400 mg, 1.67 mmol, 1.0 equiv). The resulting solution was stirred for 2 h at room temperature then quenched by the addition of 20 mL of saturated aqueous NH_4Cl and extracted with 3 x 50 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (1:3) resulting in 300 mg (41%) of methyl 2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl] formamido]-2-[3-(methylsulfanyl)-1,1-dioxo-λ^6-thietan-3-yl]acetate (**14-4**) as a white solid. LCMS (ESI): $[M+H]^+ = 436.1$.

Step 5. **N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[3-(methylsulfanyl)-1,1-dioxo-λ⁶-thietan-3-yl]acetamide (I-14).**

[0655] To a solution of methyl 2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl] formamido]-2-[3-(methylsulfanyl)-1,1-dioxo-λ⁶-thietan-3-yl]acetate (**14-4**, 100 mg, 0.23 mmol, 1.0 equiv) in IPA (2 mL) was added hydroxylamine (1 mL, 50%) and the resulting solution was stirred for 16 h at room temperature. The residue was purified on a C18 column eluting with ACN:H_2O (1:1) resulting in 80 mg (80%) of N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[3-(methylsulfanyl)-1,1-dioxo-λ⁶-thietan-3-yl]acetamide (**I-14**) as a white solid. ^{1}H NMR: (300 MHz, DMSO-*d*$_6$) δ 11.16 (s, 1H), 9.23 (d, *J* = 9.2 Hz, 1H), 9.15 (s, 1H), 7.94 – 7.84 (m, 2H), 7.69 – 7.59 (m, 2H), 5.23 (m, 1H), 5.04 – 4.88 (m, 2H), 4.39-4.20 (m, 1H), 4.05 – 3.94 (m, 1H), 3.55 (m, 2H), 2.56 (t, *J* = 6.5 Hz, 2H), 2.21 (s, 3H). LCMS (ESI): $[M+H]^+$ = 437.1.

Example 14: 2-(3-amino-1,1-dioxo-λ⁶-thietan-3-yl)-N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl] formamido]acetamide (I-15)



Step 1. **Methyl 2-[3-(benzylamino)-1,1-dioxo-λ⁶-thietan-3-yl]-2-[[(benzyloxy) carbonyl] amino]acetate (15-1).**

[0656] To a solution of methyl 2-[[(benzyloxy)carbonyl]amino]-2-(1,1-dioxo-λ⁶-thietan-3-ylidene)acetate (**14-1**, 200 mg, 0.61 mmol, 1.0 equiv) in methanol (3 mL) and tetrahydrofuran (3

mL) was added phenylmethanamine (740 mg, 6.91 mmol, 10 equiv) and the resulting solution was stirred for 2 h at 70 °C in an oil bath and then concentrated under vacuum. The residue was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (1:2) resulting in 200 mg (75%) of methyl 2-[3-(benzylamino)-1,1-dioxo-λ^6-thietan-3-yl]-2-[[(benzyloxy) carbonyl]amino]acetate (**15-1**) as a colorless oil. LCMS (ESI): $[M+H]^+$ = 433.1.

Step 2. **Methyl 2-amino-2-(3-amino-1,1-dioxo-λ^6-thietan-3-yl)acetate (15-2).**

[0657] To a solution of methyl 2-[3-(benzylamino)-1,1-dioxo-λ^6-thietan-3-yl]-2-[[(benzyloxy)carbonyl]amino]acetate (**15-1**, 250 mg, 0.58 mmol, 1.0 equiv) in oxolane (5 mL) was added hydrochloric acid (2M) (0.6 mL, 2.0 equiv) and 20% $Pd(OH)_2$ on carbon (30 mg). The resulting solution was stirred for 1 h at room temperature under an atmosphere of H_2 gas. The solids were removed by filtration and the filtrate was concentrated under vacuum. The resulting residue (**15-2**) was used in the next step without further purification. LCMS (ESI): $[M+H]^+$ = 209.0.

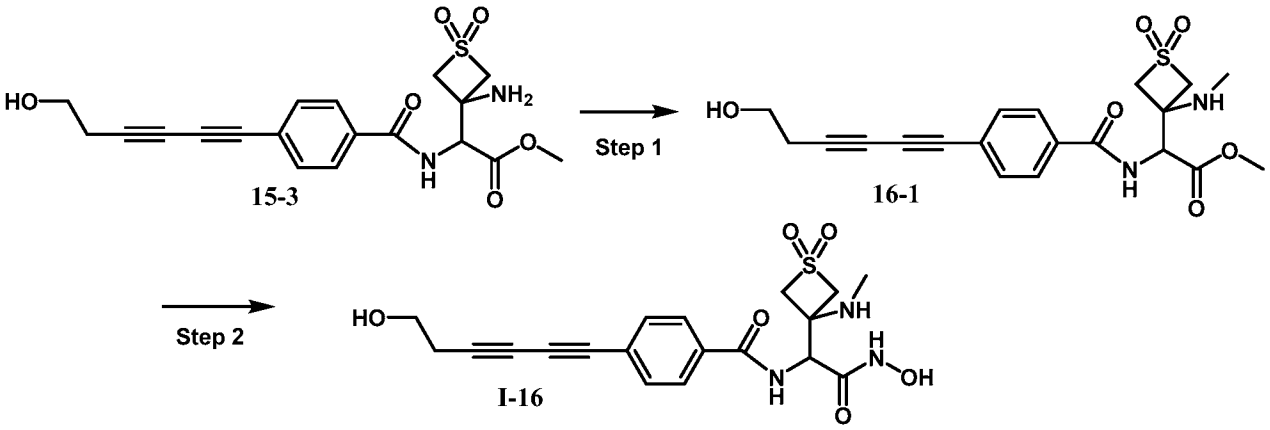
Step 3. **Methyl 2-(3-amino-1,1-dioxo-λ^6-thietan-3-yl)-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]acetate (15-3).**

[0658] To a solution of 4-(6-hydroxyhexa-1,3-diyn-1-yl)benzoic acid (**1-5a**, 130 mg, 0.61 mmol, 1.0 equiv) in N,N-dimethylformamide (5 mL) was added HATU (250 mg, 0.66 mmol, 1.1 equiv), DIEA (240 mg, 1.86 mmol, 3.0 equiv), and methyl 2-amino-2-(3-amino-1,1-dioxo-λ^6-thietan-3-yl)acetate (**15-2**, 125 mg, 0.60 mmol, 1.0 equiv). The resulting solution was stirred for 1 h at room temperature then quenched by the addition of 30 mL of saturated aqueous NH_4Cl and extracted with 3 x 100 mL of ethyl acetate. The combined organic layers were washed with 3 x 50 mL of brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography eluting with dichloromethane/methanol (20:1) resulting in 150 mg (61%) of methyl 2-(3-amino-1,1-dioxo-λ^6-thietan-3-yl)-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]acetate (**15-3**) as a yellow oil. LCMS (ESI): $[M+H]^+$ = 405.1.

Step 4. **2-(3-amino-1,1-dioxo-λ^6-thietan-3-yl)-N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl] formamido]acetamide (I-15).**

[0659] To a solution of methyl 2-(3-amino-1,1-dioxo-λ^6-thietan-3-yl)-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]acetate (**15-3**, 50 mg, 0.12 mmol, 1.0 equiv) in IPA (1 mL) was added hydroxylamine (1 mL, 50%). The resulting solution was stirred for 16 h at room temperature and then concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions : Column, XBridge Shield RP18 OBD column, 5 um, 19*150 mm; mobile phase, Waters (0.05% ammonia) and ACN (5.0% ACN up to 15.0% ACN in 7 min); Detector, UV 254/220 nm to afford 20.8 mg (41%) of 2-(3-amino-1,1-dioxo-λ^6-thietan-3-yl)-N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]acetamide (**I-15**) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.70 (d, J = 9.0 Hz, 1H), 7.95 – 7.83 (m, 2H), 7.69 – 7.60 (m, 2H), 4.98 (m, 1H), 4.78 (d, J = 8.8 Hz, 1H), 4.46 – 4.29 (m, 2H), 3.95 – 3.76 (m, 2H), 3.56 (m, 2H), 2.56 (m, 2H). LCMS (ESI): $[M+H]^+$ = 406.1.

Example 15: N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[3-(methylamino)-1,1-dioxo-λ^6-thietan-3-yl]acetamide (I-16)



Step 1. **Methyl 2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[3-(methylamino)-1,1-dioxo-λ^6-thietan-3-yl]acetate. (16-1)**

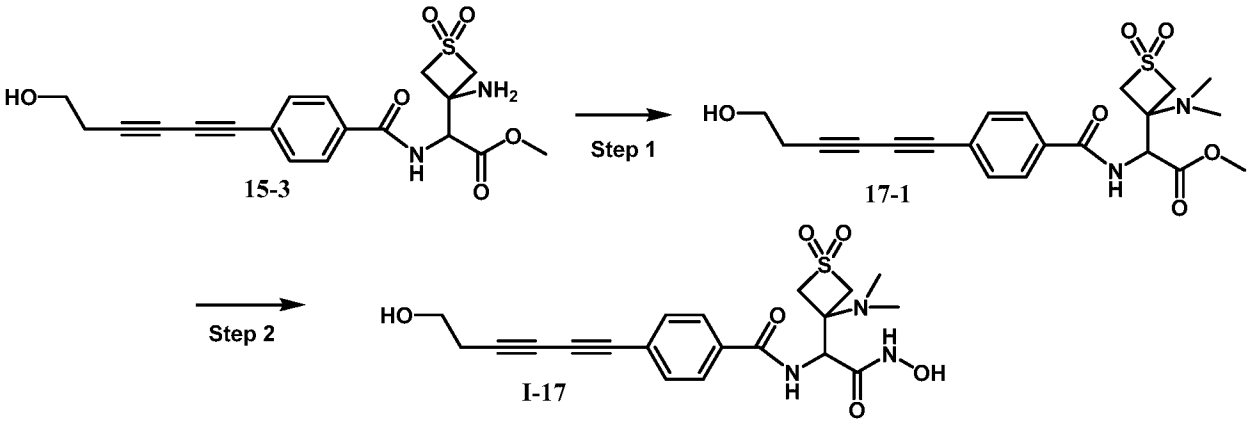
[0660] To a solution of methyl 2-(3-amino-1,1-dioxo-λ^6-thietan-3-yl)-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]acetate (**15-3**, 100 mg, 0.25 mmol, 1.0 equiv) in methanol (2 mL) cooled to 0 °C, was added 37% HCHO (15 mg, 0.80 equiv), $NaBH_3CN$ (44 mg, 0.70 mmol, 3.0 equiv) and acetic acid (0.1 mL). The resulting solution was stirred for 3 h at 0 °C in a water/ice bath and then concentrated under vacuum. The residue was purified by silica gel chromatography

eluting with dichloromethane/ethyl acetate (2:1) resulting in 20 mg (19%) of methyl 2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[3-(methylamino)-1,1-dioxo-λ^6-thietan-3-yl]acetate (**16-1**) as a yellow oil. LCMS (ESI): $[M+H]^+$ = 419.1.

Step 2. **N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[3-(methylamino)-1,1-dioxo-λ^6-thietan-3-yl]acetamide (I-16).**

[0661] To a solution of methyl 2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[3-(methylamino)-1,1-dioxo-λ^6-thietan-3-yl]acetate (**16-1**, 20 mg, 0.05 mmol, 1.0 equiv) in IPA (0.5 mL) was added hydroxylamine (0.5 mL, 50%). The resulting solution was stirred for 16 h at room temperature and then concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: Column, XBridge Shield RP18 OBD Column, 5 um, 19*150 mm; mobile phase, Waters (0.05% ammonia) and ACN (6.0% ACN up to 15.0% in 7 min); Detector, UV 254/220 nm to afford 7.2 mg (36%) of N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[3-(methylamino)-1,1-dioxo-λ^6-thietan-3-yl]acetamide (**I-16**) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 8.3 Hz, 2H), 5.03 – 4.84 (m, 2H), 4.68 (m, 1H), 4.19 (m, 1H), 4.04 (m, 1H), 3.99 – 3.87 (m, 1H), 3.56 (m, 2H), 2.55 (m, 2H), 2.30 (s, 3H). LCMS (ESI): $[M+H]^+$ = 420.0.

Example 16: 2-[3-(dimethylamino)-1,1-dioxo-λ^6-thietan-3-yl]-N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]acetamide (I-17)



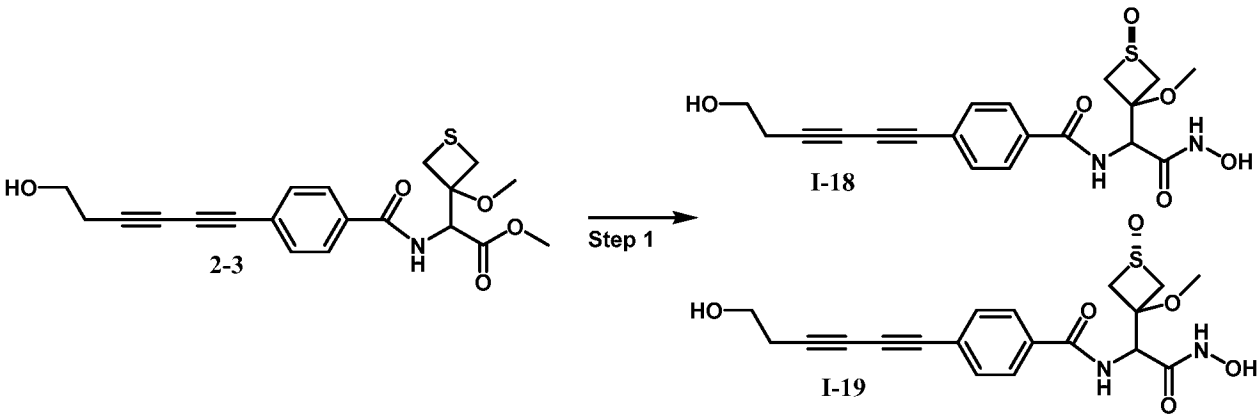
Step 1. **Methyl 2-[3-(dimethylamino)-1,1-dioxo-λ^6-thietan-3-yl]-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]acetate (17-1).**

[0662] To a solution of methyl 2-(3-amino-1,1-dioxo-λ^6-thietan-3-yl)-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]acetate (**15-3**, 50 mg, 0.12 mmol, 1.0 equiv) in methanol (2 mL) was added 37% HCHO (20 mg, 2.0 equiv), $NaBH_3CN$ (24 mg, 0.38 mmol, 3.0 equiv) and acetic acid (0.1 mL). The resulting solution was stirred for 2 h at room temperature then concentrated under vacuum. The resulting residue (**17-1**) was used in next step without further purification. LCMS (ESI): $[M+H]^+ = 433.2$.

Step 2. **2-[3-(dimethylamino)-1,1-dioxo-λ^6-thietan-3-yl]-N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]acetamide (I-17).**

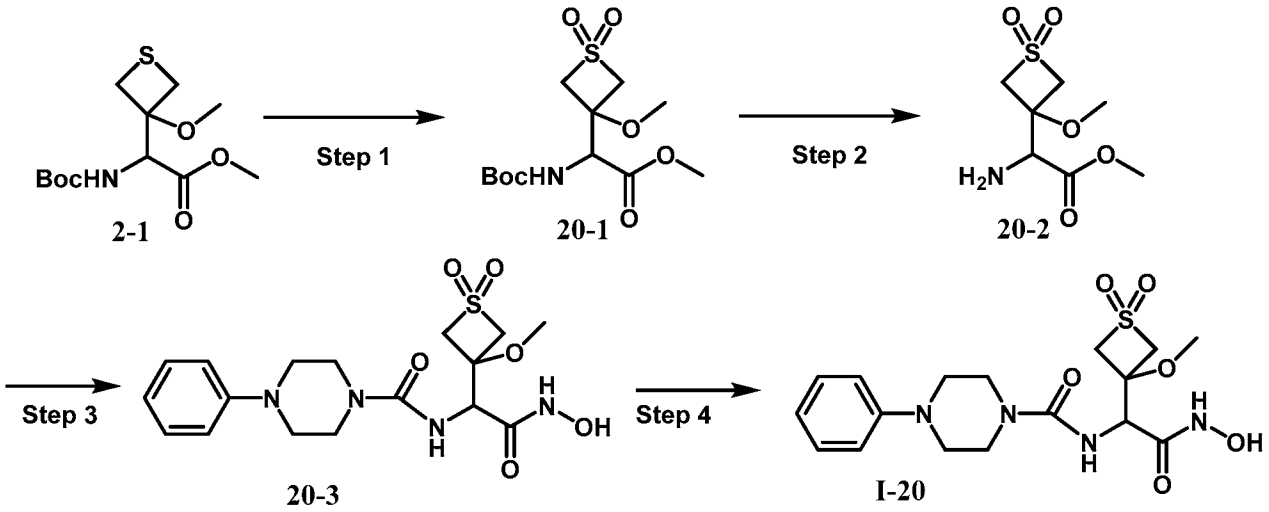
[0663] To a solution of methyl 2-[3-(dimethylamino)-1,1-dioxo-λ^6-thietan-3-yl]-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]acetate (**17-1**, 40 mg, 0.09 mmol, 1.0 equiv) in IPA (1 mL) was added hydroxylamine (1 mL, 50%). The resulting solution was stirred for 16 h at room temperature and then concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (2#-AnalyseHPLC-SHIMADZU(HPLC-10)): Column, XBridge Shield RP18 OBD Column, 5 um, 19*150 mm; mobile phase, Waters (0.05% NH_3. H_2O) and ACN (6.0% ACN up to 15.0% in 7 min); Detector, UV 254/220 nm to afford 4.8 mg (12%) of 2-[3-(dimethylamino)-1,1-dioxo-λ^6-thietan-3-yl]-N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl] formamido]acetamide (**I-17**) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.02 – 8.88 (m, 1H), 7.96 – 7.84 (m, 2H), 7.62 (m, 2H), 5.00 (m, 2H), 4.31 – 4.04 (m, 3H), 3.55 (m, 2H), 2.56 (m, 1H), 2.35 (s, 6H). LCMS (ESI): $[M+H]^+ = 434.0$.

Example 17: cis– and trans– N-(2-(hydroxyamino)-1-(3-methoxy-1-oxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-18 and I-19)



[0664] To a solution of N-(2-(hydroxyamino)-1-(3-methoxythietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**2-3**, 0.20 g, 0.51 mmol) in hexafluoroisopropanol (5 mL) at 0 °C was added hydrogen peroxide (0.3 mL, 30% aqueous, 2.67 mmol, 5 equiv) in a dropwise fashion. After stirring at the same temperature for 15 minutes, LC/MS analysis showed the presence of the desired sulfoxide. The solvents were removed under reduced pressure and the residue was purified by preparative HPLC, to afford 0.049 g of N-(2-(hydroxyamino)-1-(3-methoxy-1-oxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-19**). ^{1}H NMR (250 MHz, DMSO-*d*$_6$): 10.99 (s, 1H), 8.66 (d, *J* = 9.3 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 4.77 (d, *J* = 9.3 Hz, 1H), 4.57 (dd, *J* = 5.3, 13.8 Hz, 1H), 3.89 (dd, *J* = 5.3, 12.8 Hz, 1H), 3.54 (t, J = 6.5 Hz, 2H), 3.32 (s, 3H), 3.23 – 3.35 (m, 2H), 2.54 (t, *J* = 6.3 Hz, 2H). And 0.019 g of **I-18** ^{1}H NMR (250 MHz, DMSO-d$_6$): 10.99 (s, 1H), 8.88 (d, *J* = 8.75 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 4.81 (d, *J* = 8.75 Hz, 1H), 3.89 (dd, *J* = 6.8, 12.5 Hz, 1H), 3.75 (dd, *J* = 6.8, 12.5 Hz, 1H), 3.59 (m, 2H), 3.24 (s, 3H), 3.13 – 3.32 (m, 2H), 2.54 (t, *J* = 6.3 Hz, 2H). LCMS (ESI): $[M+H]^+$ = 405.1.

Example 18: N-hydroxy-2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)-2-[[(4-phenylpiperazin-1-yl)carbonyl]amino] acetamide (I-20)



Step 1. **Methyl 2-[[(tert-butoxy)carbonyl]amino]-2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)acetate (20-1).**

[0665] To a solution of methyl 2-[[(tert-butoxy)carbonyl]amino]-2-(3-methoxythietan-3-yl)acetate (**2-1**, 700 mg, 2.40 mmol, 1.0 equiv) in THF (10 mL), water (1 mL) and methanol (1 mL) was added oxone (2.96 g, 2.0 equiv). The resulting solution was stirred for 12 h at 0 °C in a water/ice bath and then quenched by the addition of 30 mL of DCM. The solids were removed by filtration and the filtrate was concentrated under vacuum resulting in 800 mg (100%) of methyl 2-[[(tert-butoxy)carbonyl]amino]-2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)acetate (**20-1**) as a yellow oil. LCMS (ESI): $[M+H]^+ = 324.4$.

Step 2. **Methyl 2-amino-2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)acetate TFA salt (20-2).**

[0666] To a solution of 2-[[(tert-butoxy)carbonyl]amino]-2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)acetate (**20-1**, 800 mg, 2.47 mmol, 1.0 equiv) in DCM (10 mL) was added trifluoroacetic acid (2 mL). The resulting solution was stirred for 2 h at 0 °C in a water/ice bath and then concentrated under vacuum to provide 0.85 g (154%) of methyl 2-amino-2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)acetate TFA salt (**20-2**) as a yellow oil. LCMS (ESI): $[M+H]^+ = 224.3$.

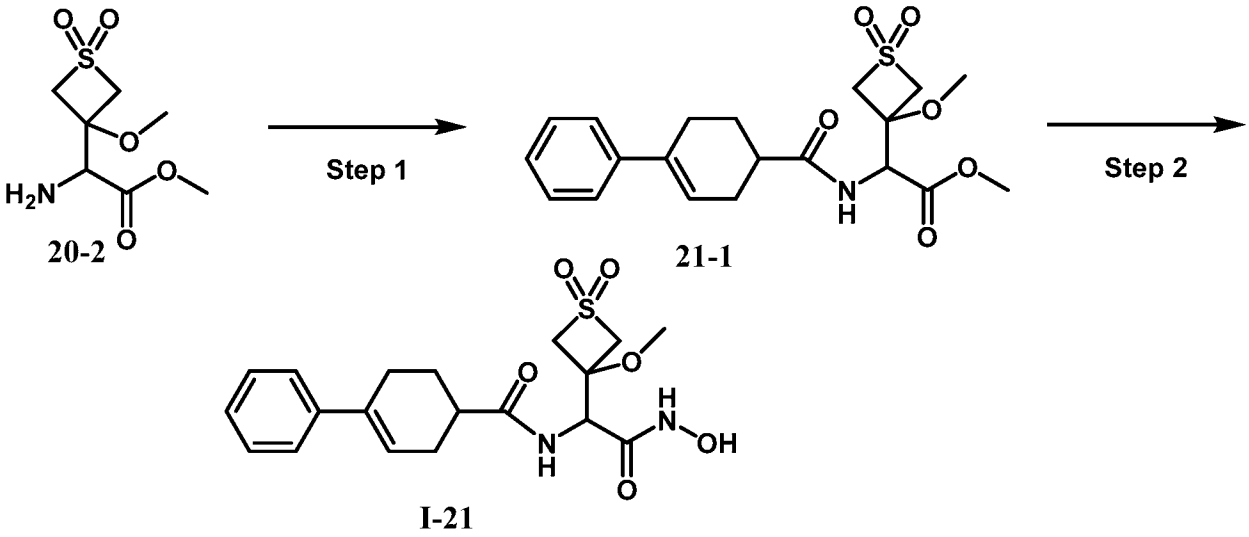
Step 3. **Methyl 2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[(4-phenylpiperazin-1-yl)carbonyl]amino] acetate (20-3).**

[0667] To a solution of methyl 2-amino-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetate TFA salt (**20-2**, 200 mg, 0.90 mmol, 1.0 equiv) in tetrahydrofuran (5 mL) was added DIEA (403 mg, 3.12 mmol, 3.0 equiv) and 4-nitrophenyl chloroformate (230 mg, 1.14 mmol, 1.1 equiv). The resulting solution was stirred for 1 h at 0 ºC – 5 ºC and then 1-phenylpiperazine (185 mg, 1.14 mmol, 1.1 equiv) was added. The resulting solution was stirred for 2 h at room temperature and then quenched by the addition of 20 mL of saturated aqueous NH_4Cl and extracted with 3 x 50 mL of ethyl acetate. The combined organic layers were washed with 2 x 50 mL of brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (1:1) resulting in 80 mg (22%) of methyl 2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[(4-phenylpiperazin-1-yl)carbonyl]amino]acetate (**20-3**) as a light yellow solid. LCMS (ESI): $[M+H]^+ = 412.1$.

Step 4. **N-hydroxy-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[(4-phenylpiperazin-1-yl)carbonyl]amino] acetamide (I-20).**

[0668] To a solution of methyl 2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[(4-phenylpiperazin-1-yl)carbonyl]amino]acetate (**20-3**, 100 mg, 0.24 mmol, 1.0 equiv) in IPA (2 mL) was added hydroxylamine (1 mL, 50%) and the resulting solution was stirred for 16 h at room temperature. The resulting residue was purified by reverse-phase HPLC and the product containing fractions were combined and concentrated under vacuum to provide 57.8 mg (58%) of N-hydroxy-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[(4-phenylpiperazin-1-yl)carbonyl] amino]acetamide as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.95 (br s, 1H), 9.06 (br s, 1H), 7.30 – 7.15 (m, 2H), 7.01 – 6.85 (m, 3H), 6.84 – 6.73 (m, 1H), 4.93 (m, 1H), 4.72 (d, J = 8.8 Hz, 1H), 4.32 (m, 1H), 4.18 (m , 1H), 4.02 (m, 1H), 3.53 (m, 4H), 3.08 (m, 4H). LCMS (ESI): $[M+H]^+ = 413.1$

Example 19: N-hydroxy-2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)-2-[(4-phenylcyclohex-3-en-1-yl)formamido]acetamide (I-21)



Step 1. **Synthesis of Methyl 2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)-2-[(4-phenylcyclohex-3-en-1-yl)formamido] acetate (21-1)**.

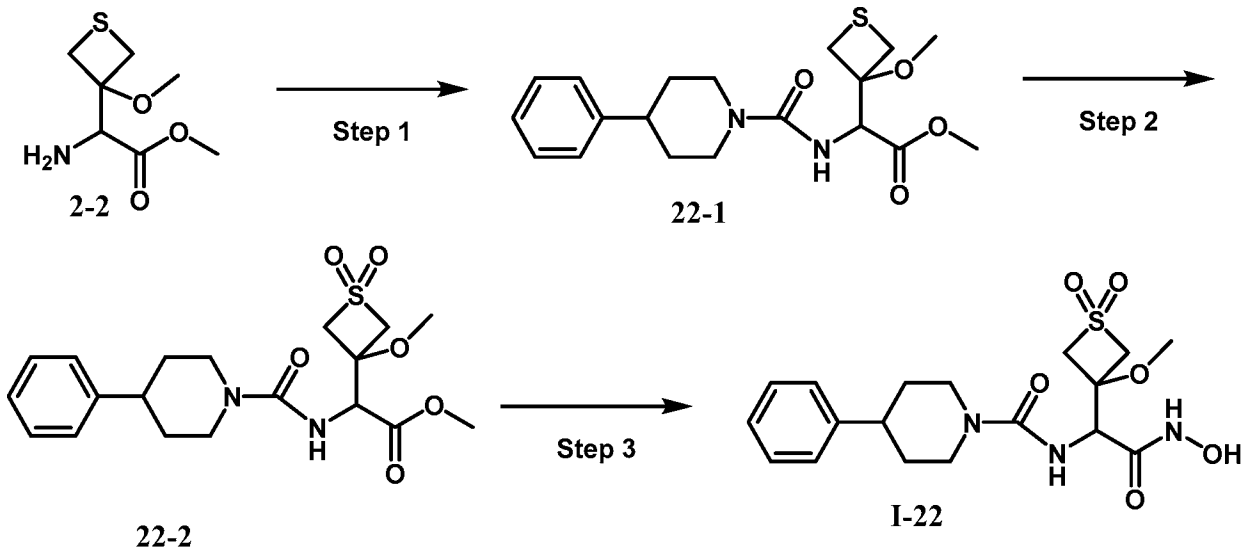
[0669] To a solution of 4-phenylcyclohex-3-ene-1-carboxylic acid (50 mg, 0.25 mmol, 1.0 equiv) in N,N-dimethylformamide (2 mL) was added HATU (95 mg, 0.25 mmol, 1.0 equiv), DIEA (97 mg, 0.75 mmol, 3.0 equiv) and methyl 2-amino-2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)acetate (**20-2**, 55 mg, 0.25 mmol, 1.0 equiv). The resulting solution was stirred for 1 h at room temperature, then quenched by the addition of 30 mL of water, and extracted with 2 x 30 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (1:3) to provide 50 mg (50%) of methyl 2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)-2-[(4-phenylcyclohex-3-en-1-yl)formamido]acetate (**21-1**) as a colorless oil. LCMS (ESI): $[M+H]^+ = 408.1$.

Step 2. **N-hydroxy-2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)-2-[(4-phenylcyclohex-3-en-1-yl)formamido]acetamide (I-21).**

[0670] To a solution of methyl 2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)-2-[(4-phenylcyclohex-3-en-1-yl)formamido]acetate (**21-1**, 50 mg, 0.12 mmol, 1.0 equiv) in IPA (3 mL) was added hydroxylamine (2 mL, 50%). The resulting solution was stirred for 16 h at room temperature and

then concentrated under vacuum. The residue was dissolved in 2 mL of methanol and purified by Flash-Prep-HPLC with the following conditions: Column, C18 silica gel; mobile phase, MeCN/H_2O=1:19 increasing to MeCN/H_2O=1:1 within 20 min; Detector, UV 254 nm to afford 24.3 mg (48%) of N-hydroxy-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[(4-phenylcyclohex-3-en-1-yl)formamido]acetamide (**I-21**) as a white solid. ^{1}H NMR (300 MHz, Methanol-d_4) δ 7.40 – 7.37 (m, 2H), 7.32 – 7.27 (m, 2H), 7.23 – 7.18 (m, 1 H), 6.13 (s, 1H), 4.94 (s, 1H), 4.84 – 4.79 (m, 1H), 4.32 – 4.29 (m, 2H), 4.20 – 4.13 (m,1H), 3.45 – 3.43 (m, 3H), 2.69 -2.65 (m, 1H), 2.64 – 2.44 (m, 4H), 2.39 – 2.15 (m, 1H), 2.15 (s, 1H). LCMS (ESI): $[M+H]^+$ = 409.1.

Example 20: N-hydroxy-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[(4-phenylpiperidin-1-yl)carbonyl]amino]-acetamide (I-22)



Step 1. **Methyl 2-(3-methoxythietan-3-yl)-2-[[(4-phenylpiperidin-1-yl)carbonyl]amino] acetate (22-1):**

[0671] To a solution of methyl 2-amino-2-(3-methoxythietan-3-yl)acetate (**2-2**, 200 mg, 1.05 mmol, 1.0 equiv) in tetrahydrofuran (10 mL) was added 4-nitrophenyl chloroformate (190 mg, 0.94 mmol, 1.0 equiv), DIEA (365 mg, 2.82 mmol, 3.0 equiv) and 4-phenylpiperidine (106 mg, 0.66 mmol, 1.0 equiv), The resulting solution was stirred for 3 h at 0 °C (water/ice bath) and then quenched by the addition of 10 mL of water. The resulting solution was extracted with 3 x 20 mL of ethyl acetate and the combined organic layers were concentrated under vacuum. The resulting residue was purified by silica gel chromatography eluting with ethyl acetate/petroleum

ether (1:5) to provide 80 mg (20%) of methyl 2-(3-methoxythietan-3-yl)-2-[[(4-phenylpiperidin-1-yl)carbonyl]amino]acetate (**22-1**) as a yellow oil. LCMS (ESI): $[M+H]^+ = 379.5$.

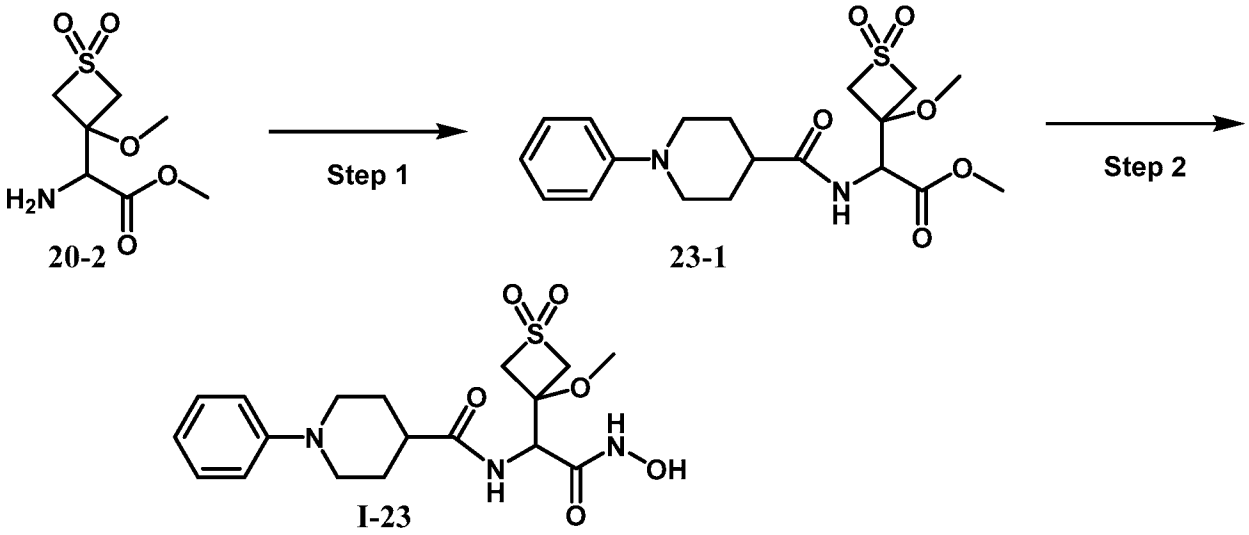
Step 2. **Methyl 2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[(4-phenylpiperidin-1-yl)carbonyl]amino]-acetate (22-2).**

[0672] To a solution of methyl 2-(3-methoxythietan-3-yl)-2-[[(4-phenylpiperidin-1-yl)carbonyl]amino]acetate (**22-1**, 80 mg, 0.21 mmol, 1.0 equiv) in DCM (10 mL) was added *m*-CPBA (146 mg, 0.85 mmol, 4.0 equiv). The resulting solution was stirred for 2 h at 0 °C (water/ice bath) and then quenched by the addition of 20 mL of aqueous $Na_2S_2O_3$. The resulting mixture was extracted with 3 x 20 mL of ethyl acetate and the combined organic layers were concentrated under vacuum to provide 100 mg of methyl 2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[(4-phenylpiperidin-1-yl)carbonyl]amino]acetate (**22-2**) as a crude yellow oil. LCMS (ESI): $[M+H]^+ = 411.5$.

Step 3. **N-hydroxy-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[(4-phenylpiperidin-1-yl)carbonyl]amino]-acetamide (I-22).**

[0673] To a solution of methyl 2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[(4-phenylpiperidin-1-yl)carbonyl]amino]acetate (**22-2**, 100 mg, 0.24 mmol, 1.0 equiv) in IPA (3 mL) was added hydroxylamine (3 mL, 50%). The resulting solution was stirred for 16 h at 25 °C and then concentrated under vacuum. The crude product was purified by Prep-HPLC using the following conditions (2#-AnalyseHPLC-SHIMADZU(HPLC-10)): Column, XBridge Shield RP18 OBD Column, 5 um, 19*150 mm; mobile phase, water (0.05% $NH_3 \cdot H_2O$) and ACN (19% ACN up to 29% in 7 min); to afford 6.5 mg (6%) of N-hydroxy-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[[(4-phenylpiperidin-1-yl)carbonyl]amino]acetamide (**I-22**) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.89 (br s, 1H), 9.00 (br s, 1H), 7.32-7.18 (m, 5H), 6.72 (d, J = 8.9 Hz, 1H), 4.94 (m, 1H), 4.73 (d, J = 8.7 Hz, 1H), 4.36 – 4.16 (m, 4H), 4.23 – 4.19 (m, 1H), 3.31 (s, 3H), 2.82 – 2.73 (m, 3H), 1.76-1.71 (m, 2H), 1.60-1.41 (m, 2H). LCMS (ESI): $[M+H]^+ = 412.5$.

Example 21: N-hydroxy-2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)-2-[(1-phenylpiperidin-4-yl)formamido]acetamide (I-23)



Step 1. **Methyl 2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)-2-[(1-phenylpiperidin-4-yl) formamido]acetate (23-1).**

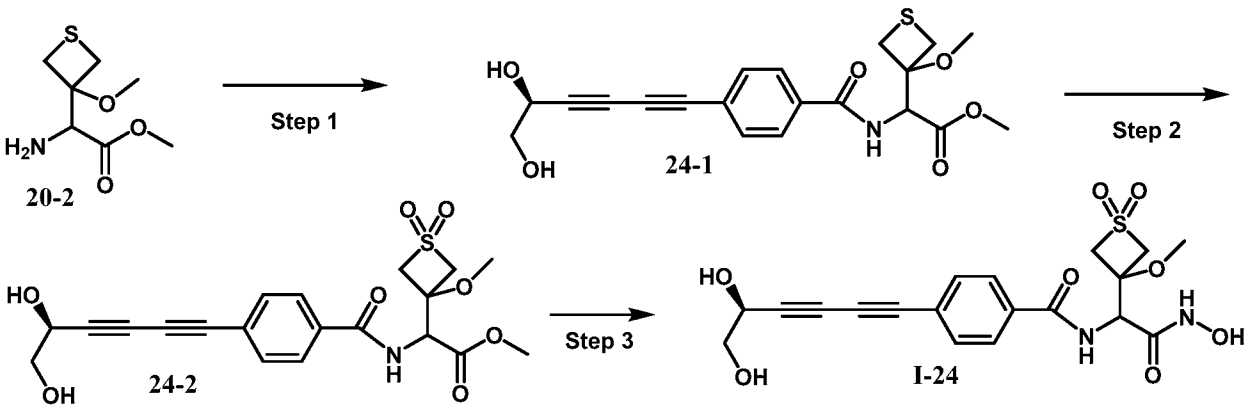
[0674] To a solution of methyl 2-amino-2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)acetate (**20-2**, 300 mg, 1.34 mmol, 1.0 equiv) in DMF (20 mL) was added HATU (511 mg, 1.34 mmol, 1.0 equiv), DIEA (521 mg, 4.03 mmol, 3.0 equiv) and 1-phenylpiperidine-4-carboxylic acid (276 mg, 1.34 mmol, 1.0 equiv). The resulting solution was stirred for 2 h at 25 °C and then concentrated under vacuum to provide 500 mg (91%) of methyl 2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)-2-[(1-phenylpiperidin-4-yl)formamido]acetate (**23-1**) as a yellow oil. LCMS (ESI): $[M+H]^+ = 411.5$.

Step 2. **N-hydroxy-2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)-2-[(1-phenylpiperidin-4-yl) formamido]acetamide (I-23).**

[0675] To a solution of methyl 2-(3-methoxy-1,1-dioxo-λ⁶-thietan-3-yl)-2-[(1-phenylpiperidin-4-yl)formamido]acetate (**23-1**, 200 mg, 0.49 mmol, 1.0 equiv) in IPA (3 mL) was added hydroxylamine (3 mL). The resulting solution was stirred for 16 h at 25 °C and then concentrated under vacuum. The crude product was purified by Prep-HPLC using the following conditions (1#-Pre-HPLC-005(Waters)): Column, Atlantis Prep OBD T3 Column, 19*150 mm, 5 um, mobile phase, water with 0.05% TFA and CH_3CN (up to 3.0% in 10 min, up to 100% in 1 min,

hold 100% in 1 min); Detector, UV 254 nm, to provide 40.7 mg (16%) of N-hydroxy-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)-2-[(1-phenylpiperidin-4-yl)formamido]acetamide trifluoroacetic acid (**I-23**) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.04 (s, 1H), 8.78 (d, J = 9.2 Hz, 1H), 7.41 – 7.19 (m, 4H), 7.05 (s, 1H), 4.88 – 4.75 (m, 2H), 4.40-4.34 (m, 1H), 4.10-4.01 (m, 2H), 3.73 – 3.69 (m, 2H), 3.32 (s, 3H), 3.00 (s, 2H), 2.69-2.60 (m, 2H), 1.98-1.82 (m, 4H). LCMS (ESI): M+H$^+$ = 412.5.

Example 22: 4-(6-hydroxy-5(S)-hydroxyhexa-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide (I-24)



Step 1. **Methyl 2-(4-(6-hydroxy-5(S)hydroxyhexa-1,3-diyn-1-yl)benzamido)-2-(3-methoxythietan-3-yl)acetate (24-1).**

[0676] To a solution of (S)-4-(5,6-dihydroxyhexa-1,3-diyn-1-yl)benzoic acid (0.040 g, 0.17 mmol, 1 equiv), methyl 2-amino-2-(3-methoxy-1,1-dioxo-λ^6-thietan-3-yl)acetate TFA salt (**20-2**, 0.070 g, 0.23 mmol, 1.37 equiv) and HATU (72 mg, 0.19 mmol, 1.1 equiv) in DMF (1 mL) was added DIEA (0.1 mL, 0.6 mmol, 3.5 equiv) at 0 °C, and the resulting mixture was stirred at ambient temperature for 20 min. The reaction mixture was then poured into ice-water (40 mL), and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give crude methyl 2-(4-(6-hydroxy-5(S)-hydroxyhexa-1,3-diyn-1-yl)benzamido)-2-(3-methoxythietan-3-yl)acetate (**24-1**) (0.070 g), which was used in the next step without further purification. MS: [M+H]$^+$ = 404.4.

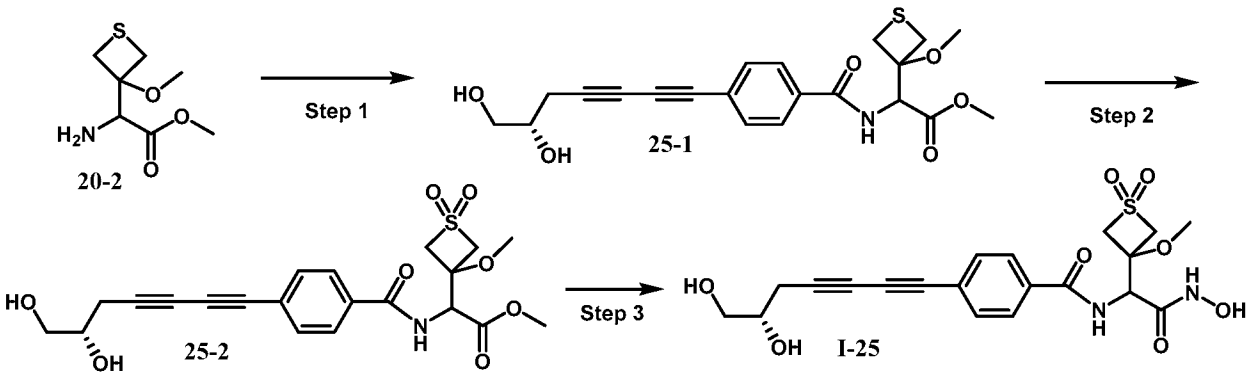
Step 2. **Methyl 2-(4-(6-hydroxy-5(S)-hydroxyhexa-1,3-diyn-1-yl)benzamido)-2-(3-methoxy-1,1-dioxidothietan-3-yl)acetate (24-2).**

[0677] Methyl 2-(4-(6-hydroxy-5(S)-hydroxyhexa-1,3-diyn-1-yl)benzamido)-2-(3-methoxythietan-3-yl)acetate (**24-1**, 0.070 g, 0.17 mmol) in THF-water solution (2 mL, 1.5:1) was treated with 39% peracetic acid (0.18 mL, 2.55 mmol, 15 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 4 h then quenched with saturated aqueous sodium bicarbonate (20 mL), extracted with ethyl acetate (20 mL x 3), washed with brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum to afford methyl 2-(4-(6-hydroxy-5(S)-hydroxyhexa-1,3-diyn-1-yl)benzamido)-2-(3-methoxy-1,1-dioxidothietan-3-yl)acetate (**24-2**, 0.072 g, 97% yield) as an off-white solid. MS: $[M+H]^+ = 436.4$.

Step 3. **4-(6-hydroxy-5(S)-hydroxyhexa-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide (I-24).**

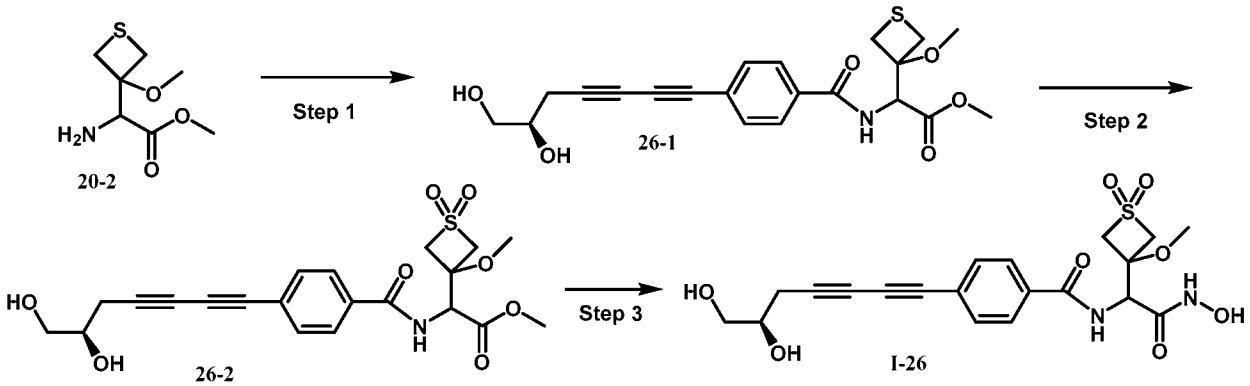
[0678] Isopropyl alcohol (0.7 mL) was added to methyl 2-(4-(6-hydroxy-5(S)hydroxyhexa-1,3-diyn-1-yl)benzamido)-2-(3-methoxy-1,1-dioxidothietan-3-yl)acetate (**24-2**, 0.072 g, 0.17 mmol, 1.0 equiv) and the mixture was cooled in an ice/water bath for 5 min. NH_2OH (50% aq) (0.7 mL) was added and after 5 min the reaction mixture was warmed to room temperature and stirred for 17 hours. The reaction was quenched by adding water then extracting with CH_2Cl_2 / iPrOH (3:1, 2 x 30 mL). The organic phase was evaporated to dryness *in vacuo*. The residue (0.070 g) was dissolved in DMF (0.6 mL) and purified by HPLC (0.01% aq HCl/MeCN). The fractions containing the pure material were collected and dried by lyophilization to provide pure 4-(6-hydroxy-5(S)hydroxyhexa-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide (**I-24**, 0.015 g, 21% yield) as a white solid. ^{1}H NMR (250 MHz, DMSO-d_6): 11.11 (s, 1H), 9.03 (d, J = 9.3 Hz, 1H), 7.89 (d, J = 7.8 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H), 5.05 (d, J = 9.0 Hz, 1H), 4.97 (d, J = 14.8 Hz, 1H), 4.11 – 4.43 (m, 4H), 3.76 (br d. s, 1H), 3.46 (d, J = 6.0 Hz, 2H), 3.35 (s, 3H). MS: $[M+H]^+ = 437.3$.

Example 23: 4-(7-hydroxy-6(S)-hydroxyhepta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide (I-25)



[0679] Following the procedure outlined in Example 22, (S)-4-(6,7-dihydroxyhepta-1,3-diyn-1-yl)benzoic acid (0.019 g, 0.08 mmol) provided (S)-4-(6,7-dihydroxyhepta-1,3-diyn-1-yl)benzoic acid (0.019 g, 0.08 mmol) provided 4-(7-hydroxy-6(S)hydroxyhepta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide (0.008 g) as a white solid. ^{1}H NMR (250 MHz, DMSO-d_6): 11.11 (s, 1H), 9.18 (br d. s, 1H), 9.01 (d, J = 9.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.3 Hz, 2H), 5.05 (d, J = 9.0 Hz, 1H), 4.97 (d, J = 14.3 Hz, 1H), 4.36 (dd, J = 4.0, 14.8 Hz, 1H), 4.19 (d, J = 14.5 Hz, 1H), 4.11 (dd, J = 4.0, 14.8 Hz, 1H), 3.59 – 3.69 (m, 1H), 3.35 – 3.42 (m, 5H), 2.42 – 2.67 (m 2H). MS: $[M+H]^+$ = 451.4.

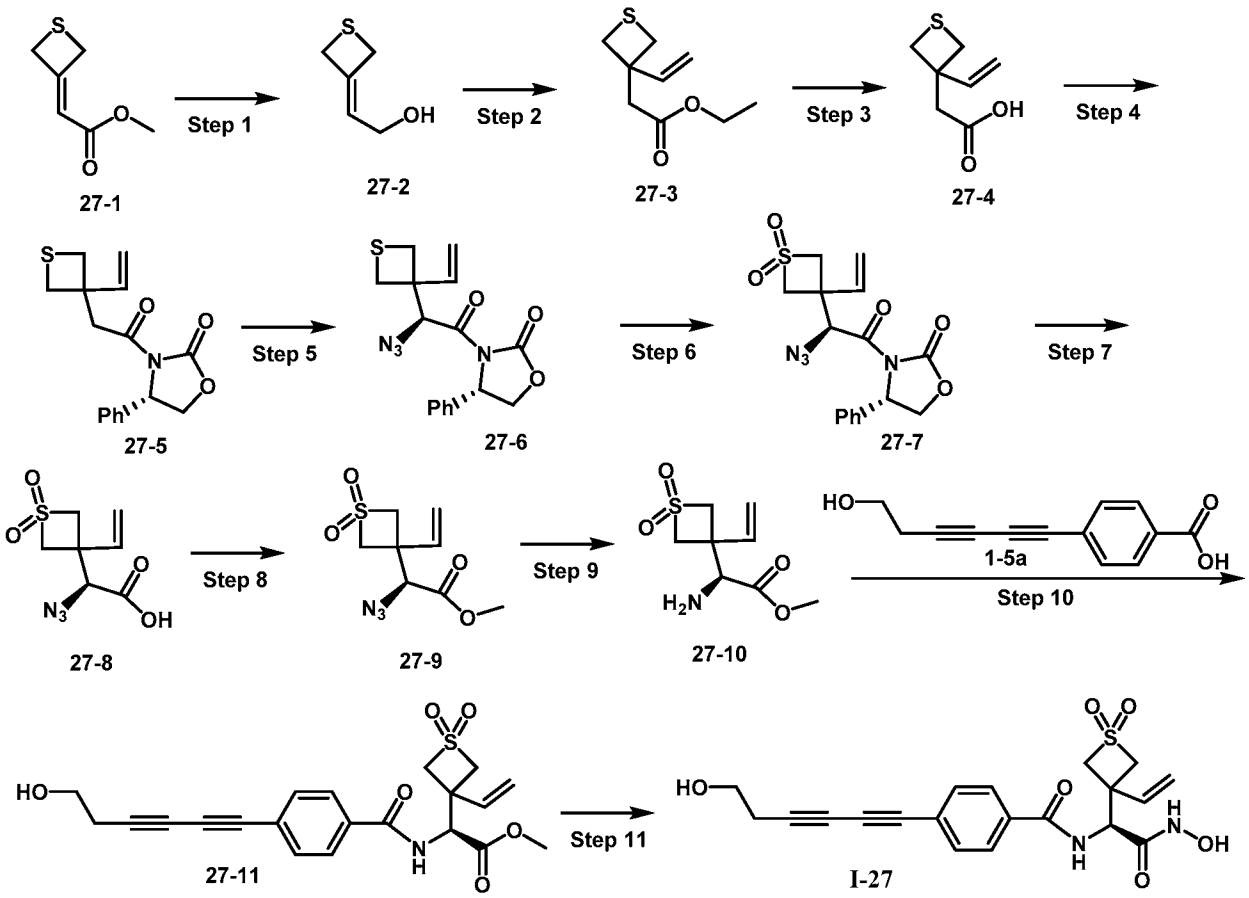
Example 24: 4-(7-hydroxy-6(R)-hydroxyhepta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide (I-26)



[0680] Following the procedure outlined in Example 22, (R)-4-(6,7-dihydroxyhepta-1,3-diyn-1-yl)benzoic acid (0.019 g, 0.08 mmol) provided 4-(7-hydroxy-6(R)hydroxyhepta-1,3-diyn-1-yl)-

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide (0.0065 g) as a white solid. MS: [M+H]+ = 451.4.

Example 25: (S)-N-(1-(1,1-dioxido-3-vinylthietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-27)



Step 1. **2-(thietan-3-ylidene)ethan-1-ol (27-2).**

[0681] DIBAL-H (1 M in toluene, 82.4 mL, 82.4 mmol, 2.5 equiv) was added dropwise over 30 minute to a solution of thietan-3-ylidene-acetic acid methyl ester (**27-1**, 4.75 g, 32.94 mmol) in toluene (60 mL) at –78 °C. The reaction was stirred for 30 minutes and then quenched by the slow addition of methanol (8 mL). The reaction mixture was diluted with ethyl acetate (100 mL) and water (50 mL), the solid was filtered through a pad of Celite, and the filter cake was washed consecutively with ethyl acetate and methanol. The filtrate was washed with brine (2 x 150 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by CombiFlash column chromatography on silica gel (0-40% EtOAc in hexane, over 30 min) and

the fractions containing product were collected and evaporated *in vacuo* to afford 2-(thietan-3-ylidene)ethan-1-ol (**27-2**, 3.64 g, 95.2% yield) as a yellow liquid. ^{1}H NMR (250 MHz, $CDCl_3$), δ 1.66 (bs, 1H), 3.94 (d, 2H, J = 12.25 Hz), 3.97 (d, 2H, J = 6.75 Hz), 4.01 (d, 2H, J = 6.75 Hz), 5.27 (m, 1H). TLC system: a: 5% EtOAc/Hexane for starting material; b. 40% EtOAc/Hexane for product.

Step 2. **Ethyl 2-(3-vinylthietan-3-yl)acetate (27-3).**

[0682] To a solution of 2-(thietan-3-ylidene)ethan-1-ol (**27-2**, 3.6 g, 31 mmol) in toluene (12 mL) was added triethyl orthoacetate (22.6 mL, 124 mmol, 4 equiv) and propionic acid (catalytic amount, 0.086 mL, 1.24 mmol, 0.04 equiv), and the resulting solution was heated in a microwave reactor at 175-180 °C for 1.2 h. After cooling to room temperature, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (100 mL), extracted with ethyl acetate (150 mL), and the organic layer was washed with brine (2 x 70 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by CombiFlash column chromatography on silica gel (eluting with 0-5% EtOAc in hexane, over 30 min) to provide ethyl 2-(3-vinylthietan-3-yl)acetate (**27-3**, 4.5 g, 78% yield) as a pale yellow liquid. ^{1}H NMR (250 MHz, $CDCl_3$), δ 1.24 (t, 3H, J = 7.25 Hz, 4.25 Hz), 2.85 (s, 2H), 3.17 (d, 2H, J = 9.5 Hz), 3.34 (d, 2H, J = 9.5 Hz), 4.12 (q, 2H, J = 7.0 Hz), 5.16 (m, 2H), 6.02 (m, 1H). TLC system: a: 40% EtOAc/Hexane for starting material; b: 5% EtOAc/Hexane for product.

Step 3. **2-(3-Vinylthietan-3-yl)acetic acid (27-4).**

[0683] To the solution of ethyl 2-(3-vinylthietan-3-yl)acetate (**27-3**, 7.5 g, 40.26 mmol) in 120 mL of THF / MeOH (3:1) was added 1 M NaOH (70 mL) and the resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated and washed with diethyl ether (2 x 300 mL). The aqueous layer was acidified to pH 1 with 3 N aqueous HCl, extracted with ethyl acetate (2 x 500 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 2-(3-vinylthietan-3-yl)acetic acid (**27-4**, 6.2 g, 97%) as a pale yellow oil, which was used for the next step of synthesis without further purification. ^{1}H NMR (250 MHz, $CDCl_3$), δ 2.92 (s, 2H), 3.15 (d, 2H, CH_2, J = 9.5 Hz), 3.36 (d, 2H, J = 9.5 Hz), 5.18 (m, 2H), 6.04 (m, 1H). TLC system: a: 5% EtOAc/Hexane for starting material; b: 40% EtOAc/Hexane for product.

Step 4. **(*S*)-4-Phenyl-3-(2-(3-vinylthietan-3-yl)acetyl)oxazolidin-2-one (27-5).**

[0684] In a 500 mL flask the crude 2-(3-vinylthietan-3-yl)acetic acid (**27-4**, 6.28 g, 39.7 mmol, 1 equiv) was dissolved in anhydrous THF (120 mL) and cooled to –15 °C and triethylamine (6.5 mL, 45.65 mmol, 1.15 equiv) was added, followed by dropwise addition of pivaloyl chloride (5.13 mL, 41.68 mmol, 1.05 equiv). The heterogeneous mixture was stirred for 0.5 h at 0 °C, then cooled to –78 °C and stirred for an additional 15 minutes. In a separate 1 L flask, (S)-(+)-4-phenyl-2-oxazolidinone (6.48 g, 39.7 mmol, 1 equiv) was dissolved in anhydrous THF (120 mL) and cooled to –78 °C. A solution of *n*-butyl lithium (2.5 M in hexane, 15.9 mL, 39.7 mmol, 1 equiv) was added dropwise and the resulting mixture was added to the mixed anhydride solution of **27-4** rapidly *via* cannula at -78 °C. The resulting mixture was warmed to 0 °C and stirred for 1 h. The reaction was quenched with 100 mL of 1N citric acid at low temperature, extracted with ethyl acetate (2 x 220 mL), washed with brine (3 x 150 mL), dried over Na_2SO_4, filtered, and concentrated under high vacuum. The residue (~20 g) was purified by CombiFlash column chromatography on silica gel (0–40% EtOAc in hexane, over 40 min, 120 g column) and the fractions containing product and unreacted starting material were collected and concentrated under vacuum. The product was crystallized from a mixture of CH_2Cl_2/hexane (1:4) to afford (S)-4-phenyl-3-(2-(3-vinylthietan-3-yl)acetyl)oxazolidin-2-one (**27-5**, 8.15 g, 67% yield) as a white solid. ^{1}H NMR (250 MHz, $CDCl_3$), δ 3.14 (m, 2H), 3.31 (m, 2H), 3.58 (s, 2H), 4.27 (dd, 1H, J = 3.5 Hz), 4.68 (t, 1H, J = 9.0 Hz, J = 17.5 Hz), 5.05 (m, 2H), 5.38 (dd, 1H, J = 3.5 Hz), 6.02 (m, 1H, CH), 7.28 (m, 5H). MS: $[M+H]^+$ = 304. TLC system: a: 5% EtOAc/Hexane for starting material; b: 40% EtOAc/Hexane for product.

Step 5. **(*S*)-3-((*S*)-2-Azido-2-(3-vinylthietan-3-yl)acetyl)-4-phenyloxazolidin-2-one (27-6).**

[0685] (*S*)-4-Phenyl-3-(2-(3-vinylthietan-3-yl)acetyl)oxazolidin-2-one (**27-5**, 8.1 g, 26.7 mmol) was dissolved in anhydrous THF (120 mL) and cooled in a dry ice/acetone bath to –78 °C. [Bis(trimethylsilyl)amino]sodium (1 M in THF, 29.37 mL, 29.37 mmol, 1.1 equiv) was added dropwise *via* syringe and the mixture was stirred for 1 h at –78 °C before the addition of 2,4,6-triisopropylbenzenesulfonyl azide (10.74 g, 34.71 mmol, 1.3 equiv) in two portions. The reaction mixture was stirred for 20 minutes then quenched with glacial acetic acid (9.16 mL, 160.2 mmol, 6 equiv) followed by the addition of tetramethylammonium acetate (14.22 g, 106.8 mmol, 4 equiv). The mixture was allowed to warm to room temperature and stirred for 2 h. The solution

was partitioned between ethyl acetate (300 mL) and brine (300 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude material (20 g) was purified by CombiFlash silica gel chromatography (0-40% EtOAc / hexanes, 220 g column, over 60 min). The fractions containing product and by-product were collected and evaporated *in vacuo*. The residue (10 g) was re-purified by CombiFlash column chromatography on silica gel (10-70% CH_2Cl_2/hexanes, 120 g column, over 30 min) to afford (S)-3-((S)-2-azido-2-(3-vinylthietan-3-yl)acetyl)-4-phenyloxazolidin-2-one (**27-6**, 7.36 g, 80% yield) as colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$), δ 3.03 (m, 2H), 3.58 (m, 2H), 4.33 (dd, 1H, J = 3.5 Hz), 4.73 (t, 1H, J = 9.0 Hz, J = 17.5 Hz), 5.35 (m, 4H), 6.03 (m, 1H, CH), 7.35 (m, 5H). MS: $[M+H]^+$ = 345.1.

Step 6. **(*S*)-3-((S)-2-azido-2-(1,1-dioxido-3-vinylthietan-3-yl)acetyl)-4-phenyloxazolidin-2-one (27-7).**

[0686] (*S*)-3-((*S*)-2-azido-2-(3-vinylthietan-3-yl)acetyl)-4-phenyloxazolidin-2-one (**27-6**, 6.64 g, 19.28 mmol) in THF-water solution (120 ml, 70 : 50) was treated with 39% peracetic acid (21 mL, 289.2 mmol, 15 equiv) at 0 °C and the resulting mixture was stirred at room temperature for 4 hours and then concentrated under vacuum. The mixture was quenched with saturated aqueous sodium bicarbonate (250 mL), extracted with ethyl acetate (250 mL x 3), washed with brine (300 mL), dried over sodium sulfate, filtered, and evaporated under vacuum to afford (S)-3-((S)-2-azido-2-(1,1-dioxido-3-vinylthietan-3-yl)acetyl)-4-phenyloxazolidin-2-one (**27-7**, 6.84 g, 94% yield) as a white solid, which was used in the next step without any further purification. ^{1}H NMR (250 MHz, $CDCl_3$), δ 4.05 (m, 2H), 4.40 (m, 3H), 4.78 (t, 1H, J = 9.0 Hz, J = 17.5 Hz), 5.42 (m, 3H), 5.71 (s, 1H), 5.99 (m, 1H, CH), 7.35 (m, 5H). MS: $[M+H]^+$ = 377.3.

Step 7. **(*S*)-2-azido-2-(1,1-dioxido-3-vinylthietan-3-yl)acetic acid (27-8).**

[0687] A stirred solution of (*S*)-3-((*S*)-2-azido-2-(1,1-dioxido-3-vinylthietan-3-yl)acetyl)-4-phenyloxazolidin-2-one (**27-7**, 6.83 g, 18.15 mmol) in THF (330 mL) and H_2O (100 mL) cooled to -5 °C, was treated with a solution of LiOOH (1.66 g, 36.3 mmol, 2 equiv) in H_2O (30 mL). After stirring at –5 °C for 10-20 minutes, the reaction was treated with a 10% sodium thiosulfate (70 mL) in H_2O followed by saturated aqueous $NaHCO_3$. Following removal of the THF *in vacuo*, the residue was diluted with water and extracted with CH_2Cl_2 (3 x 100 mL). The aqueous phase was acidified to pH 1 with 3 N HCl and extracted with ethyl acetate (3 x 150 mL). The

combined organics were washed with brine (2 x 200 mL), dried (Na_2SO_4), filtered, and evaporated *in vacuo* to yield (S)-2-azido-2-(1,1-dioxido-3-vinylthietan-3-yl)acetic acid (**27-8**, 2.19 g, 52% yield) as a colorless oil, which was use in the next step without further purification. MS: $[M+78+H]^+ = 310.1$.

Step 8. **methyl (*S*)-2-azido-2-(1,1-dioxido-3-vinylthietan-3-yl)acetate (27-9).**

[0688] A stirred solution (S)-2-azido-2-(1,1-dioxido-3-vinylthietan-3-yl)acetic acid (**27-8**, 2.19 g, 9.47 mmol) in 30 mL of DCM and 3 mL of MeOH was treated with a 2M hexane solution of TMS-diazomethane (5.21 mL, 10.4 mmol, 1.1 equiv) at room temperature and the resulting mixture was allowed to stir for another 15 minutes and then concentrated to yield methyl (S)-2-azido-2-(1,1-dioxido-3-vinylthietan-3-yl)acetate (**27-9**, 2.32 g, 100%), which was used in the next step without further purification. ^1H NMR (250 MHz, $CDCl_3$), δ 3.38 (s, 3H), 4.13 (m, 2H), 4.63 (m, 3H), 5.43 (m, 2H), 6.01 (m, 1H). MS: $[M+H]^+ = 246.1$.

Step 9. **(*S*)-2-amino-2-(1,1-dioxido-3-vinylthietan-3-yl)acetate trifluoroacetic acid salt (27-10).**

[0689] To a solution of methyl (*S*)-2-azido-2-(1,1-dioxido-3-vinylthietan-3-yl)acetate (**27-9**, 0.80 g, 3.26 mmol) in tetrahydrofuran (17 mL) was added triphenylphosphine (0.917 g, 3.49 mmol, 1.07 equiv) under an argon atmosphere. The mixture was stirred at room temperature for 2 h then water (0.234 mL, 13.04 mmol, 4 equiv) was added and the resulting solution was stirred at 52-62 °C for 48 hours. The solvent was then removed under reduced pressure, the residue was re-dissolved in dioxane and di-*tert*-butyl dicarbonate (0.890 g, 4 mmol, 1.2 equiv) was added followed by TEA (0.58 mL, 4.2 mmol, 1.28 equiv). The resulting mixture was stirred at room temperature for 3 hours then concentrated to a residue, which was purified by CombiFlash column chromatography on silica gel (0-50% EtOAc/hexane) to afford methyl (S)-2-((tert-butoxycarbonyl)amino)-2-(1,1-dioxido-3-vinylthietan-3-yl)acetate (0.520 g, 50% yield) as a colorless oil. ^1H NMR (250 MHz, $CDCl_3$), δ 1.46 (s, 9H), 3.76 (s, 3H), 4.06 (m, 2H), 4.48 (m, 2H), 4.77 (d, 1H, J = 9.0 Hz), 5.29 (d, 1H, J = 9.0 Hz), 5.4 (m, 2H), 5.86 (m, 1H). MS: $[M+H]^+ = 320.2$.

[0690] To a solution of methyl (*S*)-2-((tert-butoxycarbonyl)amino)-2-(1,1-dioxido-3-vinylthietan-3-yl)acetate (0.070 g, 0.22 mmol) in DCM (1.5 mL) was added TFA (0.5 mL) at 0 °C and the resulting mixture was allowed to warm to room temperature and stirred for 30-50

minutes. The reaction mixture was concentrated to dryness and triturated with Et_2O/hexanes to give methyl (S)-2-amino-2-(1,1-dioxido-3-vinylthietan-3-yl)acetate (**27-10**, 0.074 g, 100% yield) as the TFA salt. MS: $[M+H]^+$ = 220.2.

Step 10. **(S)-2-(1,1-dioxido-3-vinylthietan-3-yl)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl) benzamido)acetate (27-11).**

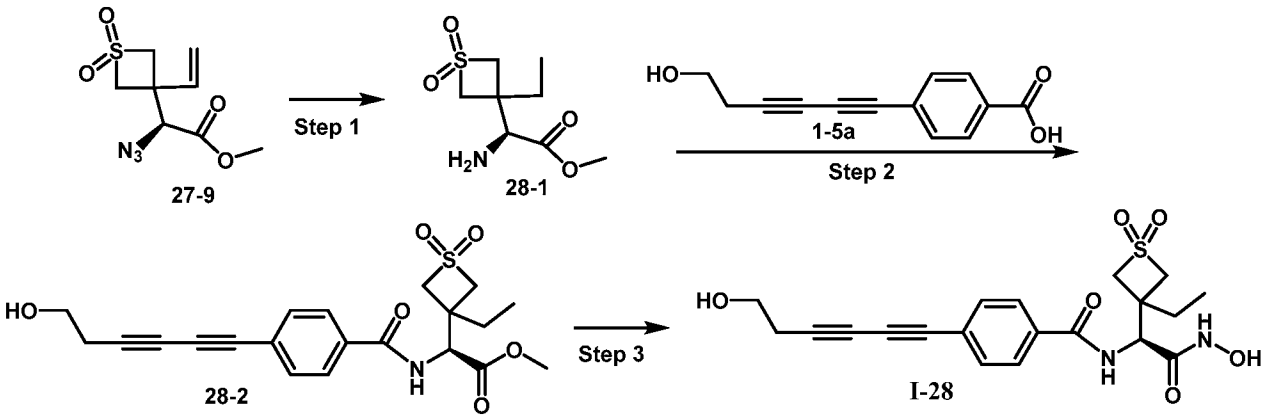
[0691] To a solution of 4-(6-hydroxyhexa-1,3-diyn-1-yl)benzoic acid (**1-5a**, 0.042 g, 0.2 mmol, 1 equiv), (S)-amino-(3-vinyl-1,1-dioxo-thietan-3-yl)-acetic acid methyl ester TFA salt (**27-10**, 0.074 g, 0.22 mmol, 1.1 equiv) and DIEA (0.1 mL, 0.6 mmol, 3 equiv) in DMF (1 mL) was added HATU (83 mg, 0.22 mmol, 1.1 equiv) at 0 °C, and the mixture was stirred at ambient temperature for 20 minutes. The reaction mixture was poured into ice-water (40 mL), and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (60 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give crude methyl (S)-2-(1,1-dioxido-3-vinylthietan-3-yl)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)acetate, **(27-11**, 0.085 g, >100%) as colorless oil, which was used in the next step of synthesis without further purification. MS: $[M+H]^+$ = 416.4

Step 11. **(S)-N-(1-(1,1-dioxido-3-vinylthietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-27).**

[0692] To a stirred suspension of methyl (S)-2-(1,1-dioxido-3-vinylthietan-3-yl)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)acetate (**27-11**, 0.085 g, 0.21 mmol) and $NH_2OH \cdot HCl$ (0.171 g, 2.46 mmol, 12 equiv) in anhydrous MeOH (1.2 mL) and anhydrous THF (1 mL) and cooled to -20 °C in a dry ice/MeOH bath, was added 25% NaOMe/MeOH (0.61 mL, 2.66 mmol, 13 equiv) dropwise under a nitrogen atmosphere. The reaction mixture was stirred at –10 °C for an additional 5 minutes, and then allowed to warm to ambient temperature and stirred for an additional 40 minutes. The reaction mixture was re-cooled to 0 °C in a dry ice/MeOH bath and a solution of 4 M HCl in dioxane (0.7 mL) was then added dropwise. The product was extracted with CH_2Cl_2 / iPrOH (3:1, 2 x 80 mL), and the organic phase was evaporated to dryness *in vacuo*. The resulting residue (80 mg) was dissolved in DMF (0.6 mL) and subjected to HPLC purification [Phenomenex Gemini C-18 column, 110Å (30 x 100 mm); flow rate = 30 mL/min; mobile phase A: 100% water, 0.01 % HCl; mobile phase B: 100% MeCN, 0.01% HCl; gradient elution from 10% B to 40% B in 30 min., detection 254 nm]. Fractions containing the desired

product were dried by lyophilization to provide (S)-N-(1-(1,1-dioxido-3-vinylthietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-27**, 0.026 g, 30.5% yield)) as an off-white solid. ^{1}H NMR (250 MHz, DMSO-d_6): 10.97 (s, 1H), 9.06 (br d. s, 1H), 8.96 (d, J = 9.0 Hz, 1H), 7.89 (d, J = 7.3 Hz, 2H), 7.64 (d, J = 7.3 Hz, 2H), 5.99 (dd, J = 10.8, 17.0 Hz, 1H), 5.41 (d, J = 17.3 Hz, 1H), 5.35 (d, J = 10.5 Hz, 1H), 4.78 – 4.85 (m, 2H), 4.13 – 4.28 (m, 3H), 3.54 (t, J = 6.5 Hz, 2H), 2.55 (t, J = 6.8 Hz, 2H). MS: $[M+H]^+$ = 417.3.

Example 26: (S)-N-(1-(3-ethyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-28)



Step 1. **Methyl (S)-2-amino-2-(3-ethyl-1,1-dioxidothietan-3-yl)acetate (28-1).**

[0693] To a solution of methyl (S)-2-azido-2-(1,1-dioxido-3-vinylthietan-3-yl)acetate (**27-9**, 0.085 g, 0.35 mmol) dissolved in the mixture of MeOH / EtOAc (3 mL, 1:1) was added 10% Pd/C (34 mg, 40%) followed by 20% $Pd(OH)_2$ (25 mg, 30%). The mixture was degassed, placed under a hydrogen atmosphere (1 atm, balloon), and stirred for 2 h. Upon completion, the catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure to give methyl (S)-2-amino-2-(3-ethyl-1,1-dioxidothietan-3-yl)acetate (**28-1**, 0.073 g, 96% yield) as colorless oil. The product was used directly in the next step without further purification. MS: $[M+H]^+$ = 222.2

Step 2. **Methyl (S)-2-(3-ethyl-1,1-dioxidothietan-3-yl)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl) benzamido)acetate (28-2).**

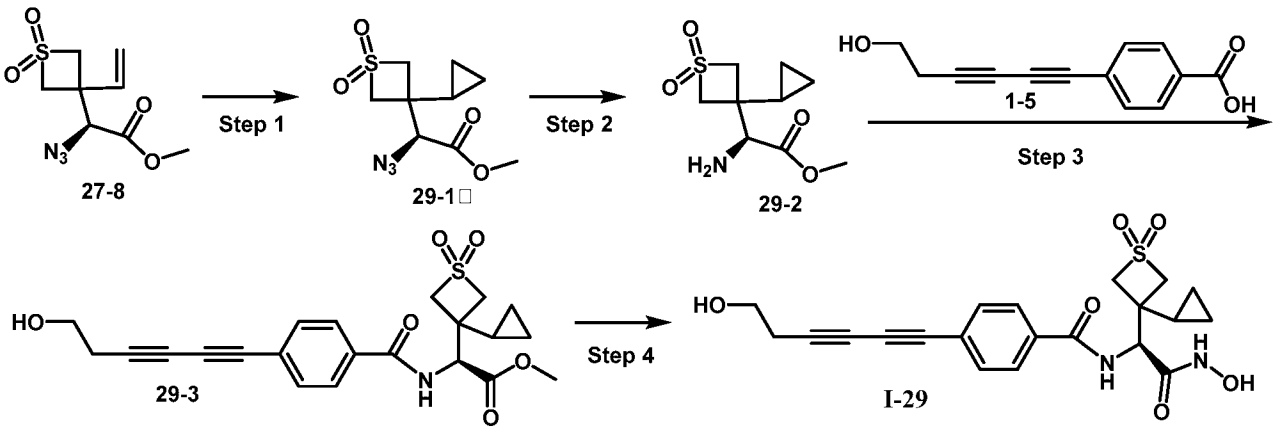
[0694] To a solution of 4-(6-hydroxyhexa-1,3-diyn-1-yl)benzoic acid (**1-5a**, 0.064 g, 0.3 mmol, 1 equiv), methyl (S)-2-amino-2-(3-ethyl-1,1-dioxidothietan-3-yl)acetate (**28-1**, 0.070 g, 0.33 mmol, 1.1 equiv) and DIEA (0.145 mL, 0.9 mmol, 3 equiv) in DMF (1 mL) was added HATU

(0.125 g, 0.33 mmol, 1.1 equiv) at 0 °C, and the resulting mixture was stirred at ambient temperature for 20 minutes. The reaction mixture was poured into ice-water (80 mL), acidified to pH 5 with 1 N HCl, and extracted with ethyl acetate (2 x 60 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give methyl (S)-2-(3-ethyl-1,1-dioxidothietan-3-yl)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido) acetate (**28-2**, 0.120 g, 96% yield) as colorless oil. The crude product used in the next step of synthesis without further purification. MS: $[M+H]^+ = 418.2$.

Step 3. **(S)-N-(1-(3-ethyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-28).**

[0695] Isopropyl alcohol (1 mL) was added to methyl (S)-2-(3-ethyl-1,1-dioxidothietan-3-yl)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)acetate (**28-2**, 0.120 g, 0.29 mmol) and the reaction mixture was cooled in an ice/water bath for 10 minutes. NH_2OH (50% aq, 1 mL) was then added dropwise to the mixture and the resulting mixture was stirred until it was determined to be complete by LC/MS analysis. The reaction mixture was diluted with water and the product was extracted with a mixture of CH_2Cl_2 / iPrOH (3:1, 2 x 80 mL). The combined organic phases were evaporated to dryness. The resulting residue was dissolved in DMF (0.8 mL) and subjected to HPLC purification (0.01% aq HCl / MeCN). Fractions containing the desired product were combined, evaporated, and dried by lyophilization to provide pure (S)-N-(1-(3-ethyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-28**, 0.040 g, 33% yield) as an off-white solid. ^1H NMR (250 MHz, DMSO-d_6): 11.13 (s, 1H), 9.09 (brd. s, 1H), 8.99 (d, J = 9.0 Hz, 1H), 7.89 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 4.77 – 4.86 (m, 2H), 3.81 – 4.12 (m, 3H), 3.54 (t, J = 6.5 Hz, 2H), 2.54 (t, J = 6.5 Hz, 2H), 1.65 – 1.89 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). MS: $[M+H]^+ = 419.3$.

Example 27: (S)-N-(1-(3-cyclopropyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-29)



Step 1. **Methyl (S)-2-azido-2-(3-cyclopropyl-1,1-dioxidothietan-3-yl)acetate (29-1).**

[0696] To a solution of methyl (S)-2-azido-2-(1,1-dioxido-3-vinylthietan-3-yl)acetate (**27-8**, 0.300 g, 1.22 mmol) in Et_2O (2 mL) was added 1N ether solution of diazomethane (6.1 mL, 5 equiv) in one portion at 0 °C. While stirring vigorously and keeping the reaction open to the air, $Pd(OAc)_2$ (41 mg, 0.18 mmol) was added in one portion to the reaction at 0 °C. The reaction was allowed to stir for an additional 15 min, and an additional portion of a 1N ether solution of diazomethane (2 mL) was added followed by $Pd(OAc)_2$ (12 mg, 0.05 mmol) until the starting material was consumed as determined by LC/MS. The excess diazomethane was removed using a stream of nitrogen. The resulting solution was concentrated by rotary evaporation, and the crude material was purified by CombiFlash column chromatography on silica gel (0-45% EtOAc/hexanes, 12 g column, over 15 min) to give methyl (S)-2-azido-2-(3-cyclopropyl-1,1-dioxidothietan-3-yl)acetate (**29-1**, 0.280 g, 88.6% yield) as a colorless oil. MS: $[M+H]^+$= 260.2.

Step 2. **Methyl (S)-2-amino-2-(3-cyclopropyl-1,1-dioxidothietan-3-yl)acetate (29-2).**

[0697] To a solution of methyl (S)-2-azido-2-(3-cyclopropyl-1,1-dioxidothietan-3-yl)acetate (**29-1**, 0.280 g, 1.08 mmol) in a mixture of MeOH / EtOAc (4 mL, 1:1) was added 10% Pd/C (84 mg, 30%) followed by 20% $Pd(OH)_2$ (84 mg, 30%). The mixture was degassed and stirred under a hydrogen atmosphere (1 atm, balloon) for 1 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure to give methyl (S)-2-amino-2-(3-cyclopropyl-1,1-dioxidothietan-3-yl)acetate (**29-2**, 0.242 g, 96% yield) as colorless oil. MS: $[M+H]^+$ = 234.2.

Step 3. **Methyl (S)-2-(3-cyclopropyl-1,1-dioxidothietan-3-yl)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)acetate (29-3).**

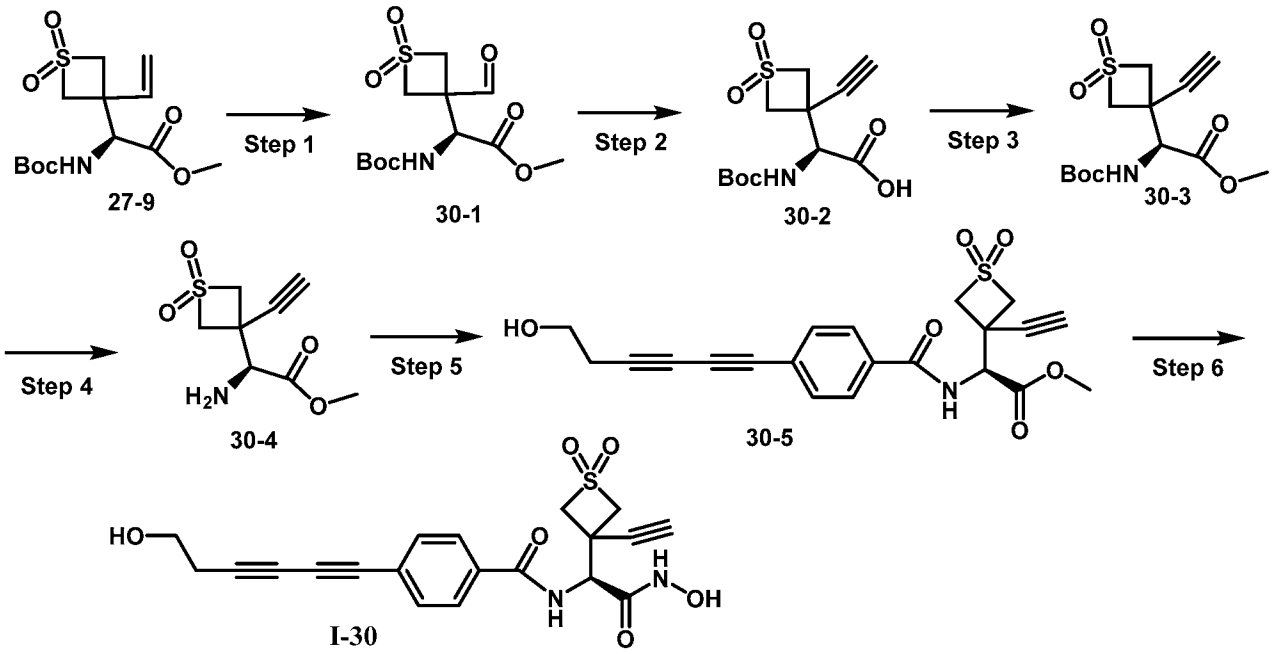
[0698] To a solution of 4-(6-hydroxyhexa-1,3-diyn-1-yl)benzoic acid (**1-5a**, 0.098 g, 0.46 mmol, 1 equiv), methyl (S)-2-amino-2-(3-cyclopropyl-1,1-dioxidothietan-3-yl)acetate (**29-2**, 0.119 g, 0.51 mmol, 1.1 equiv), and DIEA (0.226 mL, 1.38 mmol, 3 equiv) in DMF (3 mL) was added HATU (194 mg, 0.51 mmol, 1.1 equiv) at 0 °C, and the mixture was stirred at ambient temperature overnight. The reaction mixture was poured into ice-water (60 mL), and extracted with EtOAc (2 x 60 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give methyl (S)-2-(3-cyclopropyl-1,1-dioxidothietan-3-yl)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)acetate (**29-3**, 0.20 g,) as colorless oil, which was used in the next step of synthesis without further purification. MS: $[M+H]^+ = 430.4$.

Step 4. **(S)-N-(1-(3-cyclopropyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-29).**

[0699] A mixture of isopropyl alcohol / MeOH (5:1, 2 mL) was added to crude methyl (S)-2-(3-cyclopropyl-1,1-dioxidothietan-3-yl)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)acetate (**29-3**, 0.200 g, 0.46 mmol) and the mixture was cooled in an ice/water bath for 5 min. NH_2OH (50% aq) (2 mL) was added dropwise to the mixture. The resulting mixture was allowed to stir in an ice bath for 5 minutes, then allowed to rise to ambient temperature and stirred for 2 days. After the reaction was complete, water was added and the product was extracted with CH_2Cl_2/iPrOH (3:1, 2 x 80 mL). The combined organic layers were evaporated to dryness *in vacuo* and the resulting residue (0.150 g) was dissolved in DMF (0.6 mL) and subjected to HPLC purification [Phenomenex Gemini C-18 column, 110Å (30 x 100 mm); flow rate = 30 mL/min; mobile phase A: 100% water, 0.01 % HCl; mobile phase B: 100% MeCN, 0.01% HCl; gradient elution from 10% B to 40% B in 30 min., detection 254 nm]. Fractions containing the desired product were combined, acetonitrile was concentrated *in vacuo* and the product was dried by lyophilization to provide (S)-N-(1-(3-cyclopropyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-29**, 0.063 g, 32% yield) as an off-white solid. ^{1}H NMR (250 MHz, DMSO-d_6): 11.06 (s, 1H), 9.0 (d, J = 9.0 Hz, 1H), 7.90 (d, J = 7.3 Hz, 2H), 7.63 (d, J = 7.3 Hz, 2H), 4.77 – 4.83 (m, 2H), 3.98 (d, J = 14.0 Hz, 1H), 3.72 (d, J = 14.3 Hz, 1H), 3.62

(d, J = 15.3 Hz, 1H), 3.54 (dt, J = 1.3, 6.5 Hz, 2H), 2.55 (t, J = 6.0 Hz, 2H), 1.14 (m, 1H), 0.53 (d, J = 7.5 Hz, 2H), 0.39 (d, J = 4.5 Hz, 2H). MS: $[M+H]^+$ = 431.4.

Example 28: (S)-N-(1-(3-ethynyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-30)



Step 1. **Methyl (S)-2-((tert-butoxycarbonyl)amino)-2-(3-formyl-1,1-dioxidothietan-3-yl)acetate (30-1).**

[0700] Osmium tetraoxide (4% in H_2O, 0.5 mL, 0.08 mmol, 0.05 equiv) followed by sodium periodate (1.03 g, 4.8 mmol, 3 equiv) in water (4.5 mL) were added to a solution of (S)-N-Boc-amino-(1,1-dioxo-3-vinyl-thietan-3-yl)-acetic acid methyl ester (**27-9**, 0.512 g, 1.6 mmol) in MeCN (9 mL). The mixture was stirred at room temperature overnight and then diluted with water and ethyl acetate. The resulting solid was filtered through a pad of Celite and the filtrate was extracted with ethyl acetate (2 x 150 mL). The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by CombiFlash column chromatography on silica gel (20%-50% EtOAc in hexanes) to yield methyl (S)-2-((tert-

butoxycarbonyl)amino)-2-(3-formyl-1,1-dioxidothietan-3-yl)acetate (**30-1**, 0.31 g, 60% yield) as a glassy solid. MS: $[M+H]^+$ = 322.2.

Step 2. **(S)-2-((tert-butoxycarbonyl)amino)-2-(3-ethynyl-1,1-dioxidothietan-3-yl)acetic acid (30-2).**

[0701] To a stirring solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-2-(3-formyl-1,1-dioxidothietan-3-yl)acetate (**30-1**, 0.135 g, 0.42 mmol) in MeOH (2 mL) at 0 °C was added dimethyl (1-diazo-2-oxopropyl)phosphonate (0.096 g, 0.5 mmol, 1.2 equiv), followed by potassium carbonate (232 mg, 1.68 mmol, 4 equiv) and the resulting mixture was stirred for 1 h at which time LC/MS analysis showed complete reaction. The reaction mixture was concentrated under reduced pressure, diluted with water (50 mL), and extracted with ethyl acetate (2 x 30 mL). The aqueous phase was adjusted to pH 2 with 1 N hydrochloric acid and extracted with ethyl acetate (2 x 40 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the crude (S)-2-((tert-butoxycarbonyl)amino)-2-(3-ethynyl-1,1-dioxidothietan-3-yl)acetic acid (**30-2**, 0.082 g, 64% yield). The material was used in the next step without further purification. MS: $[M+78+H]^+$ = 382.3.

Step 3. **Methyl (S)-2-((tert-butoxycarbonyl)amino)-2-(3-ethynyl-1,1-dioxidothietan-3-yl)acetate (30-3).**

[0702] A stirred solution of (S)-2-((tert-butoxycarbonyl)amino)-2-(3-ethynyl-1,1-dioxidothietan-3-yl)acetic acid (**30-2**, 0.082 g, 0.27 mmol) in 1 mL of DCM and 0.1 mL of MeOH was treated with a 2M hexane solution of TMS-diazomethane (0.15 mL, 0.3 mmol, 1.1 equiv) at room temperature and the reaction was allowed to stir for 30 minutes. The reaction mixture was concentrated under reduced pressure to yield the desired methyl ester (**30-3**, 0.085 g, 100% yield), which was used in the next step without further purification. MS: $[M+H]^+$ = 318.1.

Step 4. **Methyl (S)-2-amino-2-(3-ethynyl-1,1-dioxidothietan-3-yl)acetate trifluoroacetic acid salt (30-4).**

[0703] To a solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-2-(3-ethynyl-1,1-dioxidothietan-3-yl)acetate (**30-3**, 0.085 g, 0.27 mmol, 1.0 equiv) in DCM (1.5 mL) was added TFA (0.5 mL) at 0 °C. The mixture was allowed to warm to ambient temperature and stirred for

1 hour or until complete as determined by LC/MS analysis. Volatiles were removed *in vacuo* to give methyl (S)-2-amino-2-(3-ethynyl-1,1-dioxidothietan-3-yl)acetate TFA salt (**30-4**, 0.090 g, 100% yield) as the TFA salt. MS: $[M+H]^+ = 218.2$.

Step 5. **Methyl (S)-2-(3-ethynyl-1,1-dioxidothietan-3-yl)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)acetate (30-5).**

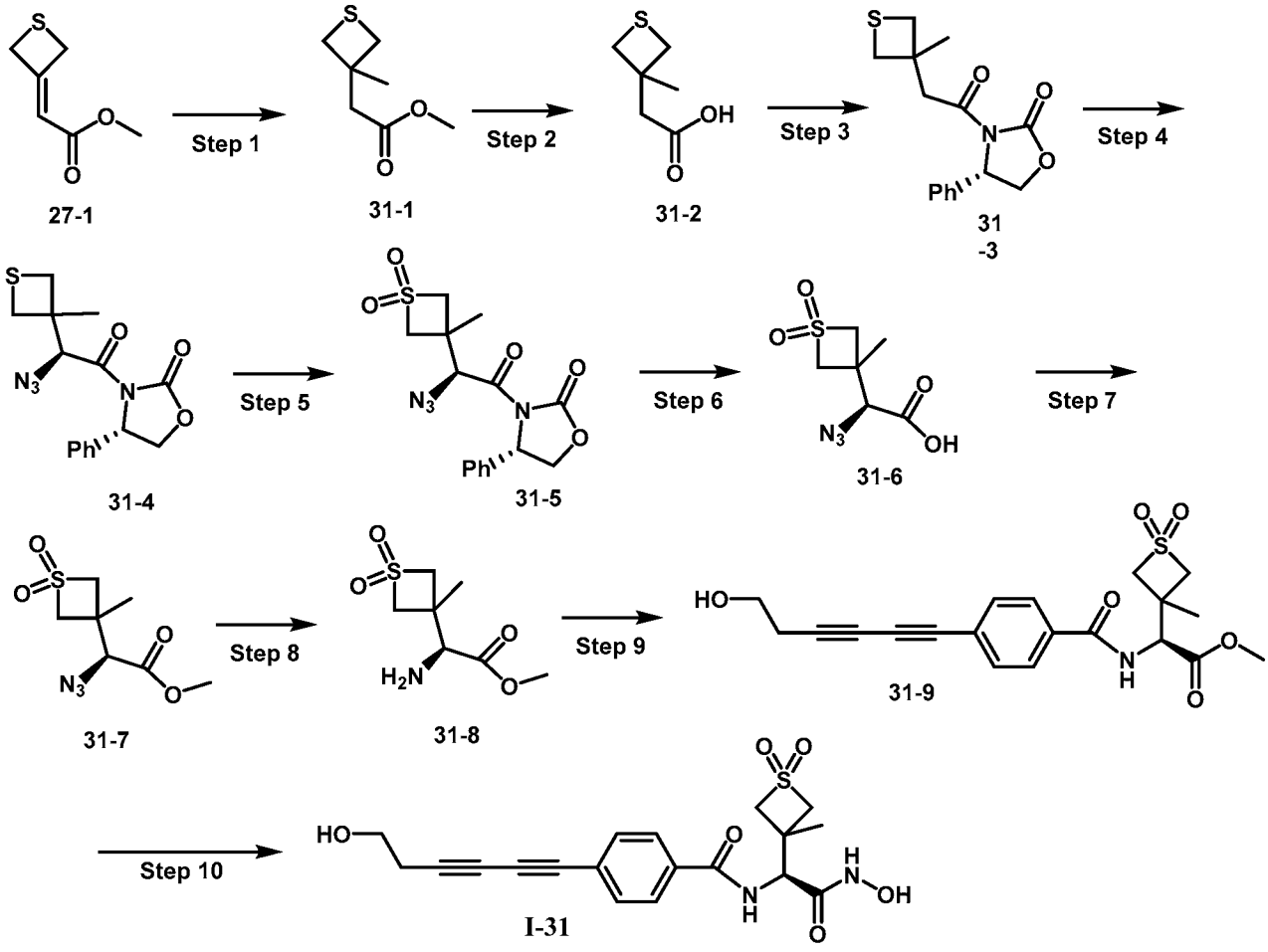
[0704] To a solution of 4-(6-hydroxyhexa-1,3-diyn-1-yl)benzoic acid (**1-5a**, 0.047 g, 0.22 mmol, 1 equiv), methyl (S)-2-amino-2-(3-ethynyl-1,1-dioxidothietan-3-yl)acetate TFA salt (**30-4**, 0.086 g, 0.26 mmol, 1.2 equiv) and DIEA (0.127 mL, 0.77 mmol, 3.5 equiv) in DMF (1 mL) was added HATU (92 mg, 0.24 mmol, 1.1 equiv) at 0 °C, and the mixture was stirred at ambient temperature for 20 minutes. The reaction mixture was poured into ice-water (40 mL), and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (60 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The resulting residue was purified by CombiFlash column chromatography on silica gel (0-70% EtOAc in hexane) to give methyl (S)-2-(3-ethynyl-1,1-dioxidothietan-3-yl)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)acetate (**30-5**, 0.065 g, 71% yield) as an off-white solid. MS: $[M+H]^+ = 414.4$.

Step 6. **(S)-N-(1-(3-ethynyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-30).**

[0705] To a stirred suspension of methyl (S)-2-(3-ethynyl-1,1-dioxidothietan-3-yl)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)acetate (**30-5**, 0.065 g, 0.157 mmol) and $NH_2OH \cdot HCl$ (0.130 g, 1.88 mmol, 12 equiv) in anhydrous MeOH (1 mL) and anhydrous THF (0.8 mL), cooled at –20 °C in a dry ice/MeOH bath and under a nitrogen atmosphere, was added dropwise 25% NaOMe/MeOH (0.47 mL, 2.0 mmol, 13 equiv). The reaction mixture was stirred at –10 °C for an additional 5 minutes. The reaction mixture was allowed to rise to ambient temperature and then stirred for 1 hour. Upon reaction completion, the reaction mixture was cooled to 0 °C in a dry ice/MeOH bath and a solution of 4 M HCl in dioxane (0.63 mL) was added dropwise. The resulting mixture was extracted with CH_2Cl_2 / iPrOH (3:1, 2 x 50 mL), and the combined organic layers were concentrated *in vacuo*. The resulting residue was dissolved in DMF (0.6 mL) and subjected to HPLC purification [Phenomenex Gemini C-18 column, 110Å (30 x 100 mm); flow rate = 30 mL/min; mobile phase A: 100% water, 0.01 % HCl; mobile phase B: 100% MeCN, 0.01% HCl; gradient elution from 10% B to 40% B over 30 min., detection 254 nm]. Fractions

containing the desired product were combined and dried by lyophilization to provide (S)-N-(1-(3-ethynyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-30**, 0.010 g, 15% yield) as an off-white solid. ^{1}H NMR (250 MHz, DMSO-*d*$_6$): 11.11 (s, 1H), 9.14 (m, 2H), 7.90 (d, *J* = 6.8 Hz, 2H), 7.65 (d, *J* = 7.0 Hz, 2H), 4.93 – 5.11 (m, 3H), 4.23 – 4.38 (m, 3H), 3.50 – 3.59 (m, 2H), 2.55 (t, *J* = 7.0 Hz, 2H). MS: $[M+H]^+$ = 415.4.

Example 29: (S)-N-(2-(hydroxyamino)-1-(3-methyl-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-31)



Step 1. **Methyl 2-(3-methylthietan-3-yl)acetate (31-1).**

[0706] To a suspension of CuI (2.9 g, 3.0 equiv) in diethyl ether (25 mL) cooled to 0 °C and under a nitrogen atmosphere was added 1.6 M MeLi (1.6 M in Et_2O, 19.0 mL, 6.0 equiv) was added dropwise via syringe to give a clear solution. After 1 h, the solution was concentrated

quickly under reduced pressure while cooling in an ice bath to remove the ether which was then replaced with cold dichloromethane (17 mL). The resulting solution was cooled to –78°C, $BF_3 \cdot Et_2O$ (2.25 mL, 3.5 equiv) was added and then added to a solution of methyl 2-(thietan-3-ylidene)acetate (**27-1**, 0.750 g, 5.2 mmol) in dichloromethane (17 mL) at –78°C. The resulting mixture was stirred at –78°C for 30 minutes, at –60° C for 1 h, and then at 0 °C for 1 h. The reaction progress was monitored by LCMS, TLC, and NMR. Additional $BF_3 \cdot Et_2O$ (0.64 mL, 1.0 equiv) was added until reaction completion was observed and then the resulting mixture was stirred for 2 h and then stored overnight in a –20 °C freezer. NMR analysis the next day still showed incomplete reaction. The reaction was then quenched by the addition of a cold solution of NH_4Cl / NH_4OH. The resulting mixture was extracted with ethyl acetate and then washed with brine. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford crude methyl 2-(3-methylthietan-3-yl)acetate (**31-1**, 0.730 g, 88% yield). The crude material was used directly in the next reaction.

Step 2. **2-(3-methylthietan-3-yl)acetic acid (31-2).**

[0707] Crude methyl 2-(3-methylthietan-3-yl)acetate (**31-1**, 0.730 g, 4.56 mmol) was dissolved in a mixture of THF/methanol/water (10 mL/2 mL/2 mL) and cooled in an ice bath. Lithium hydroxide (9.5 mL, 2N, 3.5 equiv) was added and the resulting mixture was stirred at room temperature for 1 h. Reaction was monitored by TLC analysis. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed twice with water and the combined aqueous layers were acidified to pH 1 with 5% dilute HCl and extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate, filtered, concentrated and dried under high vacuum to afford 2-(3-methylthietan-3-yl)acetic acid (**31-2**, 0.530 g, 80% yield).

Step 3. **(S)-3-(2-(3-methylthietan-3-yl)acetyl)-4-phenyloxazolidin-2-one (31-3).**

[0708] The crude 2-(3-methylthietan-3-yl)acetic acid (**31-2**, 0.530 g, 3.6 mmol) was dissolved in dry THF (10.0 mL) and cooled to -78 °C under a nitrogen atmosphere. Triethylamine (0.60 mL, 1.15 equiv) was added followed by pivaloyl chloride (0.476 mL, 1.05 equiv), dropwise via syringe. The solution was cooled to 0 °C and the resulting solution (suspension) was stirred for 1 h. Reaction was monitored by TLC analysis until complete consumption of starting material was observed. In a separate flask, (S)-4-phenyloxazolidin-2-one (0.591 g, 3.6 mmol 1.0 equiv) was

dissolved in THF (10 mL) and then cooled to -78 °C under a nitrogen atmosphere. N-butyl lithium solution (1.45 mL, 2.5N, 1.0 equiv) was added dropwise followed by the solution containing the mixed anhydride of **31-2** via cannula. Progress of the reaction was monitored by LCMS and TLC. Once LCMS showed the desired product and a side product. The reaction was allowed to warm to 0 °C over 45 minutes and then quenched with cold 10% citric acid solution. The resulting mixture was extracted twice with ethyl acetate and the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to give 1.5 g crude product. The crude product was purified by flash chromatography using a gradient from 100% hexane to 30% ethyl acetate / hexane to afford pure (S)-3-(2-(3-methylthietan-3-yl)acetyl)-4-phenyloxazolidin-2-one (**31-3**, 0.50 g, 48% yield) (TLC 30% ethyl acetate / hexane).

Step 4. **(S)-3-((S)-2-azido-2-(3-methylthietan-3-yl)acetyl)-4-phenyloxazolidin-2-one (31-4).**

[0709] To a solution of (S)-3-(2-(3-methylthietan-3-yl)acetyl)-4-phenyloxazolidin-2-one (**31-3**, 0.500 g, 1.72 mmol) in dry THF (5 mL) under a nitrogen atmosphere and cooled to –78°C was added NaHMDS (1.8 mL, 1M THF, 1.1 equiv) dropwise via syringe. After stirring for 1 h, trisyl azide (0.615 g, 1.99 mmol, 1.3 equiv) in THF (5.0 mL) was added to the solution –78°C. After 20 minutes, acetic acid (0.61 mL, 6.0 equiv) was added followed by 4.0 equiv of tetramethylammonium acetate (0.909 g) in one portion. The mixture was then allowed to warm room temperature and stirred for an additional 3 h, at which time the reaction was judged to be complete. The reaction mixture was partitioned between ethyl acetate and brine. The aqueous layer was washed twice with ethyl acetate. The combined organic layers were washed once again with brine, dried over sodium sulfate, filtered, and concentrated under vacuum to afford 1.2 g crude product **31-4**. (TLC system 30% Ethyl acetate / hexane). Purification by flash chromatography using a gradient from 100% hexane to 30% ethyl acetate / hexane afforded pure (S)-3-((S)-2-azido-2-(3-methylthietan-3-yl)acetyl)-4-phenyloxazolidin-2-one (**31-4,** 0.695 g).

Step 5. **(S)-3-((S)-2-azido-2-(3-methyl-1,1-dioxidothietan-3-yl)acetyl)-4-phenyloxazolidin-2-one (31-5).**

[0710] To a solution of (S)-3-((S)-2-azido-2-(3-methylthietan-3-yl)acetyl)-4-phenyloxazolidin-2-one (**31-4**, 0.695 g) in dichloromethane (14.0 mL) and cooled in an ice bath was added *m*CPBA (0.790 g, 2 equiv) in one portion. The reaction was allowed to stir for 1 h and monitored by LCMS. An additional *m*CPBA was added with stirring continued until complete consumption of

starting material was observed. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with cold saturated $NaHCO_3$ twice. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give (S)-3-((S)-2-azido-2-(3-methyl-1,1-dioxidothietan-3-yl)acetyl)-4-phenyloxazolidin-2-one (**31-5**, 0.700 g).

Step 6. **(S)-2-azido-2-(3-methyl-1,1-dioxidothietan-3-yl)acetic acid (31-6).**

[0711] To a solution of (S)-3-((S)-2-azido-2-(3-methyl-1,1-dioxidothietan-3-yl)acetyl)-4-phenyloxazolidin-2-one (**31-5**, 0.700 g) in a mixture of THF/water (10 mL/3 mL) cooled in an ice bath was added hydrogen peroxide (1.39 mL, 30%, 6.6 equiv) dropwise and the resulting mixture was stirred for 15 minutes. A solution of LiOH (0.101 g, 2.2 equiv) in water (3.0 mL) was then added dropwise. After 15 minutes, LCMS showed complete hydrolysis. The reaction mixture was quenched with 3.0 mL of saturated $Na_2S_2O_3$ and extracted with ethyl acetate (30 mL) (pH ~ 11) to remove organic impurities. The aqueous layer was acidified with 5% HCl to pH ~ 1 and the aqueous layer extracted with ethyl acetate to give (S)-2-azido-2-(3-methyl-1,1-dioxidothietan-3-yl)acetic acid (**31-6**, 0.440 g).

Step 7. **Methyl (S)-2-Azido-2-(3-methyl-1,1-dioxidothietan-3-yl)acetate (31-7).**

[0712] To a solution of (S)-2-azido-2-(3-methyl-1,1-dioxidothietan-3-yl)acetic acid (**31-6**, 0.440 g) in 10:1 DCM:MeOH (7.0 mL, 0.7 mL) was added TMS-diazomethane (1.13 mL, 1.1 equiv) dropwise at ice bath temperature. After some bubbling occurred, the reaction was stirred for 30 minutes. The mixture was concentrated to dryness, the crude product was triturated with ether, and the resulting solid filtered to afford pure methyl (S)-2-azido-2-(3-methyl-1,1-dioxidothietan-3-yl)acetate (**31-7**, 0.270 g).

Step 8. **Methyl (S)-2-Amino-2-(3-methyl-1,1-dioxidothietan-3-yl)acetate (31-8).**

[0713] To a solution of methyl (S)-2-azido-2-(3-methyl-1,1-dioxidothietan-3-yl)acetate (**31-7**, 0.270 g) n a mixture of ethyl acetate and methanol (4.0 mL / 4.0mL) under a nitrogen atmosphere was added 40 mg of 10% Pd/C and 20% $Pd(OH)_2$ in one portion. Using a hydrogen-filled balloon, the mixture was stirred un an atmosphere of hydrogen for 1 h. LCMS analysis was used to monitor reaction completion. Upon complete consumption of starting material, the catalyst was removed by filtering the reaction mixture through Celite and the filtrate was

concentrated under reduced pressure and dried overnight to afford methyl (S)-2-amino-2-(3-methyl-1,1-dioxidothietan-3-yl)acetate (**31-8**, 0.230 g).

Step 9. **Methyl (S)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)-2-(3-methyl-1,1-dioxidothietan-3-yl)acetate (31-9)**.

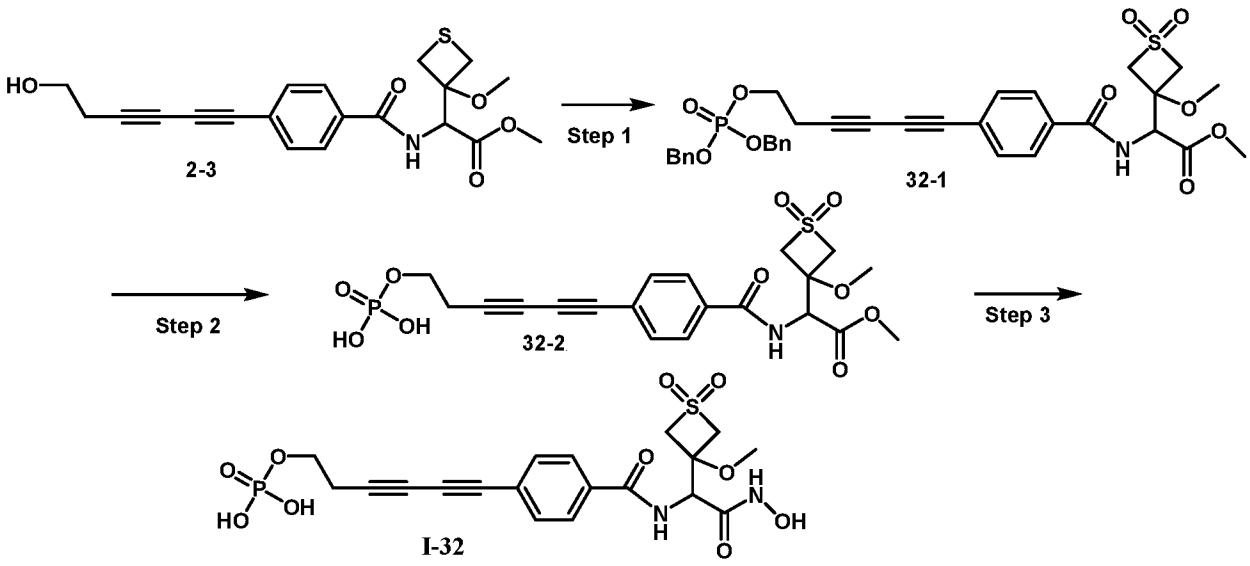
[0714] Methyl (S)-2-amino-2-(3-methyl-1,1-dioxidothietan-3-yl)acetate (**31-8**, 0.110 g, 0.53 mmol) was dissolved in DMF (2.6 mL) and 4-(6-hydroxyhexa-1,3-diyn-1-yl)benzoic acid (0.108 g, 0.50 mmol, 0.95 equiv) was added in one portion. The mixture was cooled in an ice bath, and diisopropylethylamine (0.23 mL, 2.5 equiv) was added followed by HATU (0.211 g, 0.56 mmol, 1.05 equiv) in one portion. The reaction was stirred for 10 minutes at which time, LCMS showed a major product. The reaction was quenched with cold NH_4Cl solution, extracted with ethyl acetate (50 mL), and the organic layer washed with water (20 mL). The aqueous layers were re-extracted with ethyl acetate. The combined organic layers were washed twice with brine, dried over sodium sulfate, filtered, and concentrate to dryness to give methyl (S)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)-2-(3-methyl-1,1-dioxidothietan-3-yl)acetate (**31-9**, 0.30 g).

Step 10. **(S)-N-(2-(hydroxyamino)-1-(3-methyl-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (I-31).**

[0715] Methyl (S)-2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)-2-(3-methyl-1,1-dioxidothietan-3-yl)acetate (**31-9**, 0.260 g, 0.64 mmol) and hydroxylamine hydrochloride (0.618mg, 8.89 mmol, 13.0 equiv) was suspended in a mixture of THF / methanol (3.0 mL / 2.0 mL). The reaction mixture was cooled to -30 °C using a dry ice / methanol bath, after which sodium methoxide (2.2 mL, 25% methanolic solution, 15.0 equiv) was added dropwise via syringe. The mixture was then stirred at -20 °C for 30 minutes, at which time LCMS analysis indicated that the reaction was complete. 1N HCl/dioxane (0.76 mL, 1.1 equiv) was then added dropwise at -10 °C,. After stirring the mixture for a few minutes, the reaction mixture was poured into dilute citric acid / ethyl acetate. The organic layer was washed three times with water followed by brine, dried over sodium sulfate, filtered, and concentrated to give the crude product (0.250 g). HPLC purification followed by lyophilization afforded the pure (S)-N-(2-(hydroxyamino)-1-(3-methyl-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide (**I-31**, 0.079 g). ^{1}H NMR (250 MHz, DMSO-d_6): 11.03 (s, 1H), 8.92 (d, J = 9.0 Hz, 1H), 7.89 (d, J = 7.8 Hz, 2H), 7.63 (d, J = 7.5 Hz, 2H), 4.75 (d, J = 9.0 Hz, 1H), 4.66 (d, J =

14.0 Hz, 1H), 4.19 (d, *J* = 13.5 Hz, 1H), 3.84 (d, *J* = 13.8 Hz, 1H), 3.75 (d, *J* = 14.0 Hz, 1H), 3.54 (t, *J* = 6.5 Hz, 2H), 2.55 (t, J = 6.5 Hz, 2H), 1.47 (s, 3H). MS: $[M+H]^+ = 405.1$.

Example 30: 6-(4-((2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl) carbamoyl)phenyl)hexa-3,5-diyn-1-yl dihydrogen phosphate (I-32)



Step 1. **Methyl 2-(4-(6-((bis(benzyloxy)phosphoryl)oxy)hexa-1,3-diyn-1-yl)benzamido)-2-(3-methoxy-1,1-dioxidothietan-3-yl)acetate (32-1)**.

[0716] A suspension of methyl 2-(4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamido)-2-(3-methoxythietan-3-yl)acetate (**2-3**, 0.220 g, 0.6 mmol, 1 equiv) in CH_2Cl_2 (3 mL) was sequentially treated with a solution of tetrazole in MeCN (0.45 M; 2.7 mL, 0.96 mmol, 1.6 equiv) and dibenzyl N,N-diisopropylphosphoramidite (0.292 mL, 0.87 mmol, 1.45 equiv). After stirring for 2 hours, another portion of dibenzyl N,N-diisopropylphosphoramidite (0.2 ml, 0.6 mmol, 1 equiv) was added followed by a solution of tetrazole in acetonitrile (0.45 M; 2 mL, 0.72 mmol, 1.2 equiv) and the resulting mixture was stirred at room temperature for an additional 17 hours. The reaction mixture was then diluted with ethyl acetate (70 mL). The organic layer was washed with water (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 (5 mL) and *m*-CPBA (75%, 648 mg, 3 mmol, 5 equiv) was added in one portion at 0° C with vigorous stirring which was continued for 2-3 hours or until the reaction was complete. The solvent was evaporated *in vacuo* and the resulting residue was diluted with ethyl acetate, washed with a saturated aqueous solution of

$NaHCO_3$ (2 x 40 mL) and brine, dried over Na_2SO_4, filtered and concentrated. The crude residue (0.70 g) was purified by CombiFlash column chromatography on silica gel (eluting with 0-80% EtOAc in hexane, 1.2 g column, over 30 min) to afford methyl 2-(4-(6-((bis(benzyloxy)-phosphoryl)oxy)hexa-1,3-diyn-1-yl)benzamido)-2-(3-methoxy-1,1-dioxidothietan-3-yl)acetate (**32-1**, 0.22 g, 54% yield) as a colorless oil. MS: $[M+H]^+$ = 680.5.

Step 2. **Methyl 2-(3-methoxy-1,1-dioxidothietan-3-yl)-2-(4-(6-(phosphonooxy)hexa-1,3-diyn-1-yl)benzamido)acetate (32-2).**

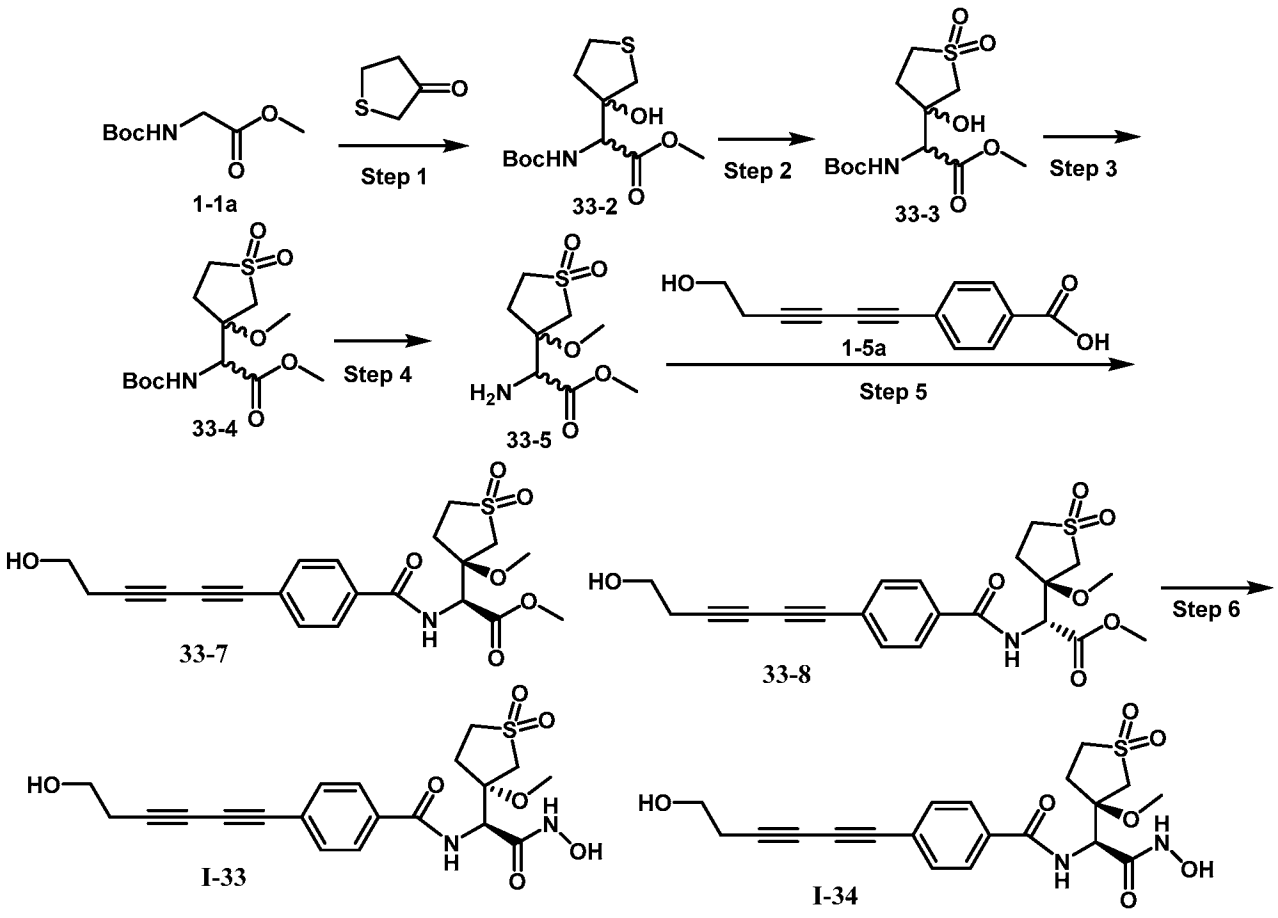
[0717] A solution of methyl 2-(4-(6-((bis(benzyloxy)phosphoryl)oxy)hexa-1,3-diyn-1-yl)benzamido)-2-(3-methoxy-1,1-dioxidothietan-3-yl)acetate (**32-1**, 0.22 g, 0.32 mmol) in TFA/CH_2Cl_2 (3 mL, 1:1) was stirred at room temperature for 20 hours. Volatiles were removed *in vacuo* and the resulting residue was dried under high vacuum to give the crude methyl 2-(3-methoxy-1,1-dioxidothietan-3-yl)-2-(4-(6-(phosphonooxy)hexa-1,3-diyn-1-yl)benzamido)acetate (**32-2**, 0.220 g), which was used in the next step without further purification. MS: $[M+H]^+$ = 500.4

Step 3. **6-(4-((2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl) carbamoyl)phenyl)hexa-3,5-diyn-1-yl dihydrogen phosphate (I-32).**

[0718] To a solution of crude methyl 2-(3-methoxy-1,1-dioxidothietan-3-yl)-2-(4-(6-(phosphonooxy)hexa-1,3-diyn-1-yl)benzamido)acetate (**32-2**, 0.220 g, 0.32 mmol) in isopropyl alcohol (2 mL) and cooled in an ice/water bath (for 5 min) was added NH_2OH (50% aq, 2 mL) dropwise. The resulting mixture was allowed to stir at the same temperature for 5 min, and then allowed to warm to ambient temperature and stir for additional 17 hours. After the reaction was complete, the mixture was diluted with CH_2Cl_2 / iPrOH (3:1, 80 mL and the organic phase was washed with water (2 x 50 mL). The pH of the aqueous phase containing the desired product was adjusted to pH 2 with 1 N hydrochloric acid and the resulting solution was extracted with CH_2Cl_2 / iPrOH (3:1, 6 x 40 mL) keeping the solution's pH at about 2. The solution was concentrated *in vacuo*. The residue (0.140 g) was dissolved in DMF (0.6 mL) and subjected to HPLC purification [Phenomenex Gemini C-18 column, 110Å (30 x 100 mm); flow rate = 30 mL/min; mobile phase A: 100% water, 0.01 % HCl; mobile phase B: 100% MeCN, 0.01% HCl; gradient elution from 10% B to 50% B in 30 min., detection 254 nm]. Fractions containing the desired product were dried to provide 6-(4-((2-(hydroxyamino)-1-(3-methoxy-1,1-

dioxidothietan-3-yl)-2-oxoethyl)carbamoyl) phenyl)hexa-3,5-diyn-1-yl dihydrogen phosphate (**I-32**, 0.052 g, 32% yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): 11.07 (s, 1H), 9.13 (s, 1H), 8.97 (d, J = 4.5 Hz, 1H), 7.88 (d, J = 4.0 Hz, 2H), 7.65 (d, J = 4.5 Hz, 2H), 5.05 (d, J = 4.5 Hz, 1H), 4.95 (d, J = 7.3 Hz, 1H), 4.35 (dd, J = 2.5, 7.8 Hz, 1H), 4.21 (d, J = 7.0 Hz, 1H), 4.12 (dd, J = 2.0, 7.5 Hz, 1H), 3.91 (q, J = 3.3 Hz, 2H), 3.34 (s, 3H), 2.76 (t, J = 3.0 Hz, 2H). MS: $[M+H]^+$ = 501.3.

Example 31: (2S)-N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[(3S)-3-methoxy-1,1-dioxo-λ^6-thiolan-3-yl]acetamide (I-33) and (2S)-N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[(3R)-3-methoxy-1,1-dioxo-λ^6-thiolan-3-yl]acetamide (I-34)



Step 1. **Methyl 2-[[(tert-butoxy)carbonyl]amino]-2-(3-hydroxythiolan-3-yl)acetate (33-2):**

[0719] Into a 2-L 3-necked round-bottom flask purged and maintained under an inert atmosphere of nitrogen and cooled to –78 °C, was placed methyl 2-[[(tert-butoxy)carbonyl] amino]acetate (**1-**

1a, 20 g, 105.7 mmol, 1.0 equiv) and tetrahydrofuran (200 mL). LiHMDS (500 mL, 5.00 equiv) was then added dropwise at -78 °C the resulting mixture was stirred for 1.5 h at -78 °C using a liquid nitrogen bath. $BF_3{\cdot}Et_2O$ (10 mL, 1.50 equiv) in a solution of thiolan-3-one (**33-1**, 21.6 g, 211.3 mmol, 2.0 equiv) in THF (200 mL) was added dropwise at –78 °C. The resulting solution was stirred for 1 h at –78 °C and 2 h at –50 °C. The reaction was then quenched by the addition of 100 mL of NH_4Cl and the resulting solids were removed by filtration. The resulting solution was extracted with 3 x 500 mL of ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude residue was purified by silica gel column eluting with ethyl acetate/petroleum ether (1:3). To provide 13 g (42%) of methyl 2-[[(tert-butoxy)carbonyl]amino]-2-(3-hydroxythiolan-3-yl)acetate (**33-2**) as a yellow oil. LCMS (ESI): $[M+H]^+ = 292.1$.

Step 2. **Methyl 2-[[(tert-butoxy)carbonyl]amino]-2-(3-hydroxy-1,1-dioxo-λ^6-thiolan-3-yl)acetate (33-3).**

[0720] To a solution of methyl 2-[[(tert-butoxy)carbonyl]amino]-2-(3-hydroxythiolan-3-yl)acetate (**33-2**, 3.0 g, 10.3 mmol, 1.0 equiv) in dichloromethane (100 mL) was added *m*CPBA (7.0 g, 4.0 equiv) at 0 °C and the resulting solution was stirred for 2 h at 0 °C. The reaction solution was diluted with 100 mL of DCM and washed with 3 x 100 mL of 5% $NaHSO_3$ (aq.). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude residue was purified by silica gel column eluting with ethyl acetate/petroleum ether (1:2) to provide 1.3 g (39%) of methyl 2-[[(tert-butoxy)carbonyl]amino]-2-(3-hydroxy-1,1-dioxo-λ^6-thiolan-3-yl)acetate (**33-3**) as a white solid. LCMS (ESI): $[M+H]^+ = 324.1$.

Step 3. **Methyl 2-[[(tert-butoxy)carbonyl]amino]-2-(3-methoxy-1,1-dioxo-λ^6-thiolan-3-yl)acetate (33-4).**

[0721] To a solution of methyl 2-[[(tert-butoxy)carbonyl]amino]-2-(3-hydroxy-1,1-dioxo λ^6-thiolan-3-yl)acetate (**33-3**, 1.3 g, 4.02 mmol, 1.0 equiv) in MeI (10 mL) was added Ag_2O (1.8 g) and the resulting solution was stirred for 24 h at 50 °C. The solids were removed by filtration and the filtrate was concentrated under vacuum to provide 1.2 g (88%) of methyl 2-[[(tert-butoxy)carbonyl]amino]-2-(3-methoxy-1,1-dioxo-λ^6-thiolan-3-yl)acetate (**33-4**) as a brown crude oil which was used in the next step without further purification. LCMS (ESI): $[M+H]^+ = 338.1$.

Step 4. **Methyl 2-amino-2-(3-methoxy-1,1-dioxo-λ^6-thiolan-3-yl)acetate (33-5).**

[0722] To a solution of methyl 2-[[(tert-butoxy)carbonyl]amino]-2-(3-methoxy-1,1-dioxo λ^6-thiolan-3-yl)acetate (1.2 g, 3.56 mmol, 1.0 equiv) in dichloromethane (12 mL) was added trifluoroacetic acid (4 mL) dropwise at 0 °C. The resulting solution was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 800 mg (95%) of methyl 2-amino-2-(3-methoxy-1,1-dioxo-λ^6-thiolan-3-yl)acetate as a brown crude oil. LCMS (ESI): $[M+H]^+ = 238.1$.

Step 5. **Methyl 2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-(3-methoxy-1,1-dioxo-λ^6-thiolan-3-yl)acetate (33-6).**

[0723] To a solution of 4-(6-hydroxyhexa-1,3-diyn-1-yl)benzoic acid (**1-5a**, 642 mg, 3.00 mmol, 1.00 equiv) in N,N-dimethylformamide (10 g, 136.82 mmol, 45.65 equiv) was added HATU (1.14 g, 1.00 equiv), DIEA (1.16 g, 8.98 mmol, 3.00 equiv), and methyl 2-amino-2-(3-methoxy-1,1-dioxo-λ^6-thiolan-3-yl)acetate (681 mg, 2.87 mmol, 1.00 equiv) and the resulting solution was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 100 mL of water and extracted with 3 x 100 mL of ethyl acetate. The combined organic layers were washed with 1 x 100 mL of brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude residue was purified by a silica gel column eluting with ethyl acetate/petroleum ether (1:1) to provide 300 mg (23%) of methyl 2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-(3-methoxy-1,1-dioxo-λ^6-thiolan-3-yl)acetate (**33-6**) as a white solid. LCMS (ESI): $[M+H]^+ = 434.1$. The isomers were separated by chiral-stationary phase HPLC to afford (2S)-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[(3S)-3-methoxy-1,1-diox-λ^6-thiolan-3-yl]acetate (**33-7**) and (2S)-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[(3R)-3-methoxy-1,1-dioxo-λ^6-thiolan-3-yl]acetate (**33-8**).

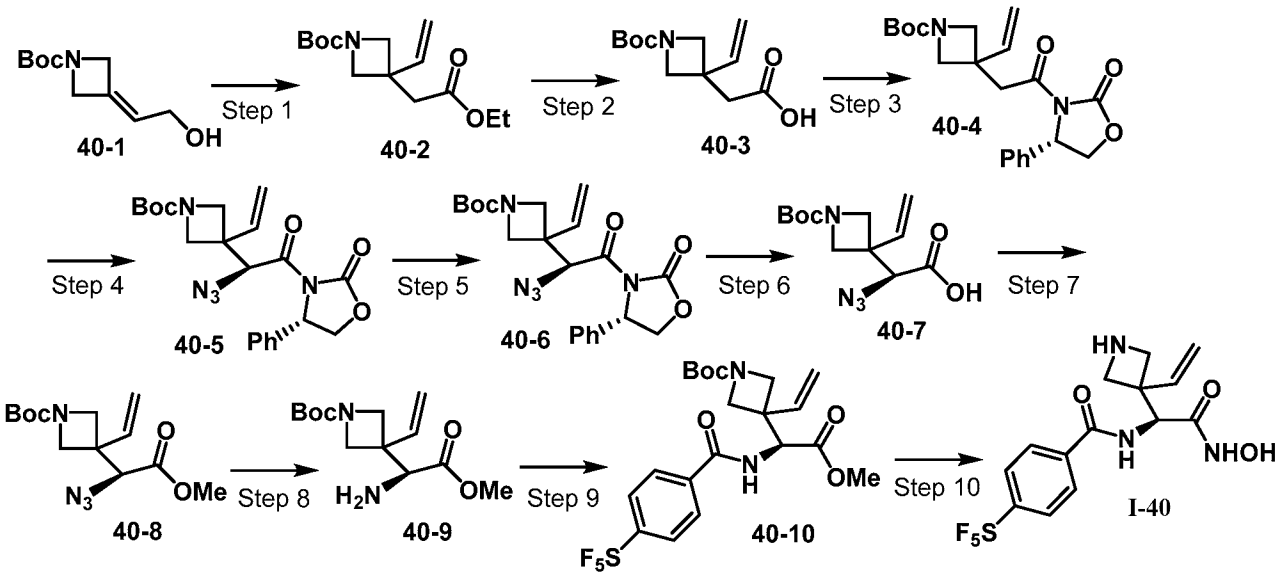
Step 6. **(2S)-N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[(3S)-3-methoxy-1,1-dioxo-λ^6-thiolan-3-yl]acetamide (I-33) and (2S)-N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[(3R)-3-methoxy-1,1-dioxo-λ^6-hiolan-3-yl]acetamide (I-34).**

[0724] To a solution of methyl (2S)-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl] formamido]-2-[(3S)-3-methoxy-1,1-dioxo-λ^6-thiolan-3-yl]acetate (**33-7**, 30 mg, 0.07 mmol, 1.00 equiv) in IPA

(3 mL) was added NH_2OH (2 mL, 50%) and the resulting solution was stirred for 4 h at room temperature and then concentrated under vacuum. The crude residue was purified by Flash-Prep-HPLC using the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, MeCN/H_2O = 5/95 increasing to MeCN/H_2O = 1/4 within 10 min; Detector, UV 254 nm to afford 7.8 mg (26%) of (2S)-N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[(3S)-3-methoxy-1,1-dioxo-λ^6-thiolan-3-yl]acetamide (**I-33**) as a white solid: ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.06 (s, 1H), 9.14 (s, 1H), 8.78 (d, *J* = 9.2 Hz, 1H), 7.89 – 7.86 (m, 2H), 7.66 – 7.63 (m, 2H), 5.03 – 4.98 (m, 2H), 3.80 – 3.75 (m, 1H), 3.59 – 3.52 (m, 2H), 3.27(s, 3H), 3.24 – 3.14 (m, 2H), 3.06 – 2.95(m, 1H), 2.58 – 2.51 (m, 3H), 2.17 – 2.05 (m, 1H). LCMS (ESI): $[M+H]^+$ = 435.1.

[0725] Following the procedure for Step 6 above, intermediate **33-8** was converted to (2S)-N-hydroxy-2-[[4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl]formamido]-2-[(3R)-3-methoxy-1,1-dioxo-λ^6-thiolan-3-yl]acetamide (**I-34**) in 43% yield. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.13 (s, 1H), 9.21 (s, 1H), 8.57 (d, *J* = 9.0 Hz, 1H), 7.89 – 7.86 (m, 2H), 7.64 – 7.62 (m, 2H), 5.05 – 4.98 (m, 2H), 3.59 – 3.53 (m, 3H), 3.45 – 3.40 (m, 1H), 3.31 – 3.20 (m, 4H), 3.14 – 3.03 (m, 1H), 2.59 – 2.54 (m, 3H), 2.22 – 2.10 (m, 1H). LCMS (ESI): $[M+H]^+$ = 435.1.

Example 32: (2S)-2-(3-ethenylazetidin-3-yl)-N-hydroxy-2-{[4-(pentafluoro-λ^6-sulfanyl) phenyl]formamido}acetamide (I-40)



Step 1. **Tert-butyl 3-((ethoxycarbonyl)methyl)-3-vinylazetidine-1-carboxylate (40-2)**.

[0726] A solution of tert-butyl 3-(2-hydroxyethylidene)azetidine-1-carboxylate (**40-1**, 1.4 g, 7.0 mmol), triethyl orthoacetate (4.5 g, 28.0 mmol) and propionic acid (0.017 g, 0.24 mmol) in DMF (4 mL) was irradiated in a microwave reactor at 180 °C for 1 h. The reaction mixture was diluted with H_2O (80 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were concentrated *in vacuo,* and the crude product was purified by flash chromatography (0 – 50% EtOAc in hexanes) to obtain pure tert-butyl 3-((ethoxycarbonyl)methyl)-3-vinylazetidine-1-carboxylate (**40-2**, 1.2 g, 64% yield). ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm 1.24 (t, J = 7.14 Hz, 3 H), 1.44 (s, 9 H) 2.73 (s, 2 H), 3.90 (s, 4 H), 4.12 (q, J = 7.14 Hz, 2 H), 5.06 - 5.23 (m, 2 H), 6.05 (dd, J = 17.36, 10.77 Hz, 1 H). MS: $[M+H]^+$ = 270.1.

Step 2. **2-(1-(tert-butoxycarbonyl)-3-vinylazetidin-3-yl)acetic acid (40-3).**

[0727] To a solution of tert-butyl 3-((ethoxycarbonyl)methyl)-3-vinylazetidine-1-carboxylate (**40-2**, 2.3 g, 8.55 mmol) in THF/MeOH/H_2O (13/4/11 mL) was added LiOH (0.61 g, 25.65 mmol) at room temperature. The mixture was concentrated *in vacuo* after 1 h and the resulting residue was acidified with 5% aqueous HCl (~25 ml) to pH 2 and extracted with EtOAc (100 mL x 2). The combined organic layers were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the crude product which was purified by flash chromatography on silica gel (10-50% EtOAc in hexanes) to afford 2-(1-(tert-butoxycarbonyl)-3-vinylazetidin-3-yl)acetic acid as white solid (**40-3**, 1.9 g, 95% yield). ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm 1.44 (s, 9 H), 2.80 (s, 2 H), 3.90 (d, J = 3.74 Hz, 4 H), 5.08 - 5.25 (m, 2 H), 6.07 (dd, J = 17.41, 10.71 Hz, 1 H). MS: $[M+H]^+$ = 242.1.

Step 3. **Synthesis of (*S*)-4-phenyl-3-(2-(1-(tert-butoxycarbonyl)-3-vinylazetidine-3-yl)acetyl)oxazolidin-2-one (40-4).**

[0728] To a solution of 2-(1-(tert-butoxycarbonyl)-3-vinylazetidin-3-yl)acetic acid (**40-3**, 1.9 g, 8.12 mmol) in anhydrous THF (30 mL) and cooled to -15 °C was added triethylamine (1.2 mL, 8.93 mmol), followed by dropwise addition of pivaloyl chloride (1.04 mL, 8.52 mmol). The heterogeneous mixture was stirred for 20 min at 0 °C, then re-cooled to -78 °C and stirred for 15 min (solution 1). In a separate flask, (S)-(+)-4-phenyl-2-oxazolidinone (1.32 g, 8.12 mmol) was dissolved in anhydrous THF (30 mL) and cooled to -78 °C. A solution of n-butyl lithium (2.5 M in hexane, 3.2 mL, 8.12 mmol) was added dropwise followed by dropwise addition (15 min) of the mixed anhydride solution (solution 1). The resulting mixture was further stirred for 10 min at

–78 °C at which time it was warmed to 0 °C and stirred for 40 min. The reaction mixture was quenched with 10% citric acid (13 mL) and extracted with ethyl acetate (120 mL x 2). The combined organic layers were washed with brine (50 mL x 3), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by CombiFlash column chromatography on silica gel (0 – 40% EtOAc in hexane) to afford (*S*)-4-phenyl-3-(2-(1-(tert-butoxycarbonyl)-3-vinylazetidine-3-yl)acetyl)oxazolidin-2-one (**40-4**, 2.7 g, 87% yield) as white solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm 1.41 (s, 9 H), 3.45 (s, 2 H), 3.77 (t, *J* = 10.71 Hz, 1 H), 3.82 - 3.93 (m, 2 H), 4.29 (dd, *J* = 8.90, 3.74 Hz, 1 H), 4.70 (t, *J* = 8.84 Hz, 1 H), 4.95 - 5.12 (m, 2 H), 5.40 (dd, *J* = 8.62, 3.57 Hz, 1 H), 6.03 (dd, *J* = 17.41, 10.71 Hz, 1 H), 7.24 - 7.44 (m, 5 H). MS: $[M+H]^+$ = 386.6.

Step 4. **(*S*)-3-((*S*) 2-azido-2-(1-(tert-butoxycarbonyl)-3-vinylazetidine-3-yl)acetyl)-4-phenyloxazolidin-2-one (40-5).**

[0729] (*S*)-4-phenyl-3-(2-(1-(tert-butoxycarbonyl)-3-vinylazetidine-3-yl)acetyl)oxazolidin-2-one (2.4 g, 6.21 mmol) was dissolved in anhydrous THF (40 mL) and cooled in a dry ice / acetone bath to –78 °C. [Bis(trimethylsilyl)amino]sodium (1 M in THF, 6.83 mL, 6.83 mmol) was added dropwise *via* syringe and the mixture was stirred for 1 h at -78 °C before the addition of 2,4,6-triisopropylbenzenesulfonyl azide (2.49 g, 8.06 mmol) in two portions. The reaction mixture was stirred for 20 min and then quenched with glacial acetic acid (2.12 mL, 37.2 mmol) followed by the addition of tetramethylammonium acetate (3.3 g, 24.8 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h. The solution was partitioned between ethyl acetate (100 mL x 3) and brine (50 mL). The combined ethyl acetate extract was washed with brine (200 mL), then dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. The crude material was purified by CombiFlash silica gel chromatography (0 – 35% EtOAc / hexanes, 40 g column, over 40 min). The fractions containing product were combined and evaporated *in vacuo* to afford (*S*)-3-((*S*) 2-azido-2-(1-(tert-butoxycarbonyl)-3-vinylazetidine-3-yl)acetyl)-4-phenyloxazolidin-2-one (2.3 g, 87% yield). MS: $[M+H]^+$ = 428.0.

Step 5. **(*S*)-2-(1-(tert-butoxycarbonyl)-3-vinylazetidin-3-yl)-2-azidoacetic acid (40-7).**

[0730] To a stirred solution of (*S*)-3-((*S*) 2-azido-2-(1-(tert-butoxycarbonyl)-3-vinylazetidine-3-yl)acetyl)-4-phenyloxazolidin-2-one (**40-5**, 2.4 g, 5.62 mmol) in THF (25 mL) and H_2O (6 mL) was added 30% H_2O_2 (3.8 mL, 37.1 mmol) dropwise at 0 °C. After 10 min, a solution of LiOH

(0.3 g, 12.4 mmol, 2.2 equiv) in H_2O (8 mL) was added dropwise at 0 °C, and the resulting mixture was stirred for 1 h. The reaction mixture was quenched with a saturated solution of sodium sulfite (100 mL) followed by water (200 mL). The aqueous phase was acidified to pH~3 with 5% HCl and extracted with EtOAc (150 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide (*S*)-2-(1-(tert-butoxycarbonyl)-3-vinylazetidin-3-yl)-2-azidoacetic acid (**40-7**, 1.42 g, 90%) as thick oil which was used in the next step without purification.

Step 6. **tert-butyl 3-((*S*)-(methoxycarbonyl)azidomethyl)-3-vinylazetidine-1-carboxylate (40-8).**

[0731] To a stirred solution (*S*)-2-(1-(tert-butoxycarbonyl)-3-vinylazetidin-3-yl)-2-azidoacetic acid (**40-7**, 1.42 g, 5.03 mmol) in DCM (50 mL) and MeOH (5 mL) was added a 2M hexane solution of TMS-diazomethane (5.1 mL, 10.2 mmol) at 0 °C. The low temperature bath was removed and the reaction mixture was allowed to stir at room temperature for 0.5 h. After the reaction was complete, the volatiles were removed under reduced pressure to yield tert-butyl 3-((*S*)-(methoxycarbonyl)azidomethyl)-3-vinylazetidine-1-carboxylate (**40-8**, 1.27 g, 85%), which was used in the next step without further purification. MS: $[M+H]^+ = 297.3$.

Step 7. **Tert-butyl 3-((*S*)-(methoxycarbonyl)(amino)methyl)-3-vinylazetidine-1-carboxylate (40-9).**

[0732] To a solution of tert-butyl 3-((*S*)-(methoxycarbonyl)azidomethyl)-3-vinylazetidine-1-carboxylate (**40-8**, 1.0 g, 3.3 mmol) in THF (10 mL) was added triphenylphosphine (0.88 g, 3.3 mmol), and the resulting mixture was stirred for 4 h. Water (0.6 mL, 33 mmol) was added, and the resulting mixture was stirred for 12 h at 50 °C. The reaction mixture was concentrated *in vacuo*, 60% EtOAc in hexanes (100 mL) was added, and the solids were filtered off. The residue was rinsed with 60% EtOAc in hexanes (6 mL), and the combined filtrate was concentrated *in vacuo* to provide tert-butyl 3-((*S*)-(methoxycarbonyl)(amino)methyl)-3-vinylazetidine-1-carboxylate (**40-9**, 0.86 g, 95%) which was used without further purification in the next step. MS: $[M+H]^+ = 271.3$.

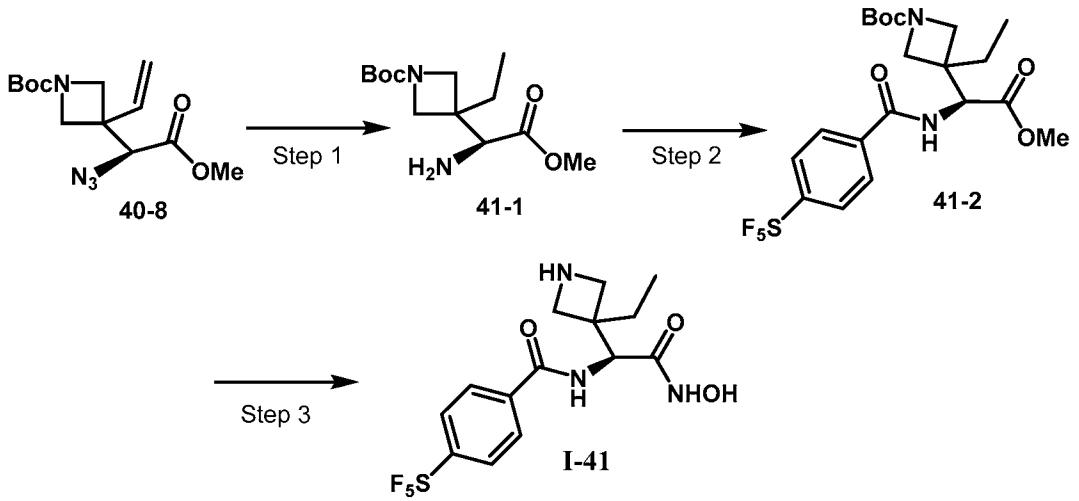
Step 8. **Tert-butyl 3-ethenyl-3-[(1*S*)-2-methoxy-2-oxo-1-{[4-(pentafluoro-λ^6-sulfanyl)phenyl] formamido}ethyl]azetidine-1-carboxylate (40-10).**

[0733] To a solution of tert-butyl 3-((*S*)-(methoxycarbonyl)(amino)methyl)-3-vinylazetidine-1-carboxylate (**40-9**, 0.97 g, 3.6 mmol), 4-(pentafluoro-λ^6-sulfanyl)benzoic acid (0.835 g, 3.37 mmol) and HATU (1.28 g, 3.37 mmol) in DMF (15 mL) cooled to 0 °C in an ice bath was added DIEA (1.8 mL 10.36 mmol), and the resulting mixture was stirred for 30 min. The reaction was quenched by the addition of water (30 mL) and subsequently extracted with EtOAc (60 mL x 2). The combined organic layers were concentrated under reduced pressure and purified by CombiFlash chromatography on silica gel (20 – 40% EtOAc in hexane) to afford tert-butyl 3-ethenyl-3-[(1*S*)-2-methoxy-2-oxo-1-{[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido}-ethyl]azetidine-1-carboxylate as white solid (**40-10**, 1.54 g, 92% yield). ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm 1.44 (s, 9 H), 3.78 (s, 3 H), 3.84 - 3.98 (m, 2 H), 3.99 - 4.09 (m, 1 H), 4.20 - 4.32 (m, 1 H), 5.23 - 5.38 (m, 2 H), 5.44 (dd, *J* = 10.16, 2.47 Hz, 1 H), 5.74 - 6.05 (m, 1 H), 6.46 - 6.64 (m, 1 H), 7.86 (s, 4 H). MS: $[M+H]^+$ = 501.4,

Step 9. **(2S)-2-(3-ethenylazetidin-3-yl)-N-hydroxy-2-{[4-(pentafluoro- λ^6-sulfanyl)phenyl] formamido}acetamide (I-40).**

[0734] To a stirred suspension of tert-butyl 3-ethenyl-3-[(1*S*)-2-methoxy-2-oxo-1-{[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido}ethyl]azetidine-1-carboxylate (**40-10**, 0.1 g, 0.2 mmol) and $NH_2OH \cdot HCl$ (0.138 g, 2.0 mmol) in anhydrous MeOH (0.5 mL) and anhydrous THF (0.5 mL) cooled to -10 °C in a dry ice / MeOH bath and under a nitrogen atmosphere was added 25% NaOMe/MeOH (0.92 mL, 4.0 mmol) dropwise. The reaction mixture was stirred at -10 °C for an additional 30 min at which time it was quenched with 1N HCl (3.5 mL) and concentrated under reduced pressure to dryness. The crude residue was dissolved in DCM (1 mL). TFA (0.4 mL) was added at room temperature and the resulting mixture was stirred for 12 h. The reaction mixture was concentrated *in vacuo* and the product was purified by HPLC to obtain (2*S*)-2-(3-ethenylazetidin-3-yl)-N-hydroxy-2-{[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido}acetamide (**I-40**) (0.047g, 47.5 %) as TFA salt. LCMS (ESI): $[M+H]^+$ = 402.4.

Example 33: (2*S*)-2-(3-ethylazetidin-3-yl)-N-hydroxy-2-{[4-(pentafluoro- λ^6-sulfanyl)phenyl] formamido}acetamide trifluoroacetic acid salt (I-41)



Step 1. **Tert-butyl 3-((S)-(methoxycarbonyl)(amino)methyl)-3-ethylazetidine-1-carboxylate (41-1).**

[0735] To a solution of tert-butyl 3-((S)-(methoxycarbonyl)azidomethyl)-3-vinylazetidine-1-carboxylate (**40-8**, 0.112 g, 0.38 mmol) in MeOH (1 mL) was added 10% Pd/C (22 mg, 20%). The mixture was degassed and placed under a hydrogen atmosphere (1 atm, balloon) and stirred for 4 h. Upon reaction completion, the catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated under reduced pressure to give tert-butyl 3-((S)-(methoxycarbonyl)(amino)methyl)-3-ethylazetidine-1-carboxylate (**41-1**, 0.1 g, quant). The product was used directly in the next step without further purification. MS: $[M+H]^+ = 273.0$.

Step 2. **Tert-butyl 3-ethyl-3-[(1S)-2-methoxy-2-oxo-1-{[4-(pentafluoro- λ^6-sulfanyl)phenyl] formamido}ethyl]azetidine-1-carboxylate (41-2).**

[0736] A solution of tert-butyl 3-((S)-(methoxycarbonyl)(amino)methyl)-3-ethylazetidine-1-carboxylate (**41-1**, 0.1 g, 0.36 mmol), 4-(pentafluoro-λ^6-sulfanyl)benzoic acid (0.08 g, 0.33 mmol) and HATU (0.14 g, 0.36 mmol) in DMF (1.5 mL) was cooled to 0 °C in an ice bath. DIEA (0.23 mL 1.33 mmol) was added, and the resulting mixture was stirred for 30 min at 0 °C. The reaction was quenched by the addition of water (2 mL) and subsequently extracted with EtOAc (5 mL x 2). The combined organic layers were concentrated under reduced pressure and the resulting residue was purified by CombiFlash chromatography on silica gel (20 – 40%

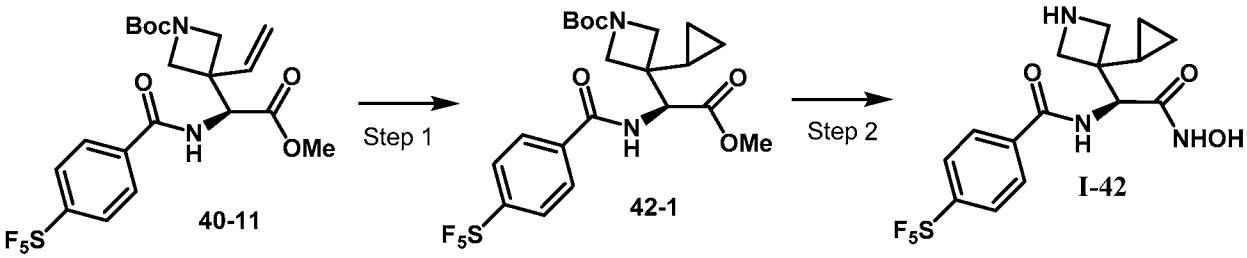
EtOAc in hexane) to afford tert-butyl 3-ethyl-3-[(1S)-2-methoxy-2-oxo-1-{[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido}ethyl]azetidine-1-carboxylate as white solid (**41-2**, 0.15 g, 93% yield). MS: $[M+H]^+$ = 503.4.

Step 3. **(2S)-2-(3-ethylazetidin-3-yl)-N-hydroxy-2-{[4-(pentafluoro-λ^6-sulfanyl)phenyl] formamido}acetamide trifluoroacetic acid salt (I-41).**

[0737] A solution of tert-butyl 3-ethyl-3-[(1S)-2-methoxy-2-oxo-1-{[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido}ethyl]azetidine-1-carboxylate (**41-2**, 0.16 g, 0.33 mmol) in DCM (1.5 mL) was cooled in an ice bath to 0 °C. TFA (0.5 mL) was added, and the resulting mixture was stirred for 30 min at which time it was concentrated *in vacuo*. Water (5 mL) was added to the residue, basified with saturated $NaHCO_3$ (aq) solution and extracted with EtOAc (10 mL x 2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated.

[0738] The resulting residue was re-dissolved in isopropyl alcohol (1.2 mL) and the mixture was cooled in an ice/water bath for 10 min. NH_2OH (50% aq,1.2 mL) was added dropwise, and the reaction mixture was stirred overnight at room temperature. Once the reaction was determined to be complete by LC/MS analysis, the reaction mixture was concentrated *in vacuo* and the product was purified by HPLC to obtain (2S)-2-(3-ethylazetidin-3-yl)-N-hydroxy-2-{[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido}acetamide (**I-41**, 0.050 g, 31.4 % yield) as the TFA salt. LCMS (ESI): $[M+H]^+$ = 404.5.

Example 34: (2S)-2-(3-cyclopropylazetidin-3-yl)-N-hydroxy-2-{[4-(pentafluoro- λ^6-sulfanyl) phenyl]formamido}acetamide trifluoroacetic acid salt (I-42)



Step 1. **Tert-butyl 3-cyclopropyl-3-[(1S)-2-methoxy-2-oxo-1-{[4-(pentafluoro- λ^6-sulfanyl) phenyl]formamido}ethyl]azetidine-1-carboxylate (42-1).**

[0739] 1-Methyl-3-nitro-1-nitrosoguanidine (0.39 g, 2.7 mmol) was added in five portions to a 0 °C pre cooled solution of KOH (1.5 g, 27 mmol) in H_2O (2.8 mL) and Et_2O (10 mL). This

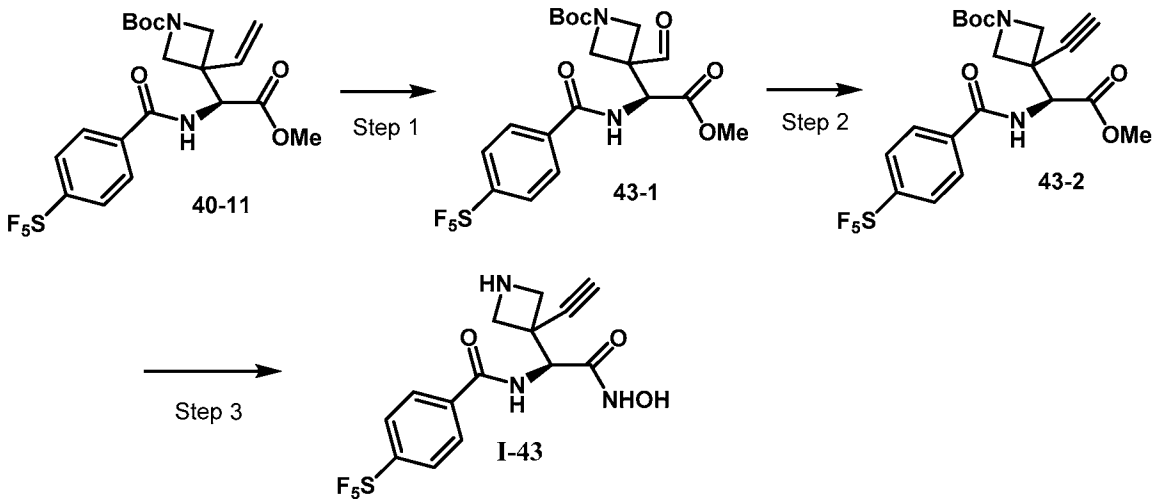
solution was then added to a solution of tert-butyl 3-ethenyl-3-[(1S)-2-methoxy-2-oxo-1-{[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido}ethyl]azetidine-1-carboxylate (**40-11**, 0.15 g, 0.29 mmol) and $Pd(OAc)_2$ (0.007 g, 0.03 mmol) in Et_2O (5 mL) at 0 °C. After 30 min, the reaction mixture was quenched by the addition of AcOH (0.2 mL) and washed with saturated $NaHCO_3$ (aq) solution and brine. The organic layer was concentrated under reduced pressure, and the product was purified by CombiFlash chromatography on silica gel (0 – 40% EtOAc in hexanes) to afford tert-butyl 3-cyclopropyl-3-[(1S)-2-methoxy-2-oxo-1-{[4-(pentafluoro-λ^6-sulfanyl) phenyl]formamido}ethyl]azetidine-1-carboxylate as white solid (**42-1**, 0.1 g, 65% yield). MS: $[M+H]^+ = 515.4$.

Step 2. **(2S)-2-(3-cyclopropylazetidin-3-yl)-N-hydroxy-2-{[4-(pentafluoro- λ^6-sulfanyl) phenyl]formamido}acetamide trifluoroacetic acid salt (I-42).**

[0740] To a stirred suspension of tert-butyl 3-cyclopropyl-3-[(1S)-2-methoxy-2-oxo-1-{[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido}ethyl]azetidine-1-carboxylate (**42-1**, 0.1 g, 0.19 mmol) and $NH_2OH \cdot HCl$ (0.135 g, 1.95 mmol) in anhydrous MeOH (0.5 mL) and anhydrous THF (0.5 mL) cooled to –10 °C in a dry ice / MeOH bath and under a nitrogen atmosphere was added 25% NaOMe/MeOH (0.89 mL, 3.89 mmol) dropwise. The reaction mixture was stirred at –10 °C for 30 min at which time it was quenched with 1N HCl (3.5 mL) and concentrated under reduced pressure to dryness.

[0741] The resulting residue was dissolved in DCM (1 mL). TFA (0.4 mL) was added at room temperature and the resulting mixture was stirred for 12 h. The reaction mixture was concentrated *in vacuo*, and the product was purified by HPLC to obtain (2S)-2-(3-cyclopropylazetidin-3-yl)-N-hydroxy-2-{[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido} acetamide (**I-42**) (0.040 g, 40.2 %) as the TFA salt. LCMS (ESI): $[M+H]^+ = 416.5$.

Example 35: (2S)-2-(3-ethynylazetidin-3-yl)-N-hydroxy-2-{[4-(pentafluoro-λ⁶-sulfanyl) phenyl] formamido}acetamide trifluoroacetic acid salt (I-43)



Step 1. **Tert-butyl 3-formyl-3-[(1S)-2-methoxy-2-oxo-1-{[4-(pentafluoro-λ⁶-sulfanyl) phenyl]formamido}ethyl]azetidine-1-carboxylate (43-1).**

[0742] To a solution of tert-butyl 3-ethenyl-3-[(1S)-2-methoxy-2-oxo-1-{[4-(pentafluoro-λ⁶-sulfanyl)phenyl]formamido}ethyl]azetidine-1-carboxylate (**40-11**, 0.5 g, 1 mmol) in acetonitrile (5 mL) and water (5 mL) was added $NaIO_4$ (0.64 g, 3 mmol) and $K_2OsO_4 \cdot 2H_2O$ (0.045 g, 0.1 mmol) and the resulting mixture was stirred overnight at room temperature. Water (5 mL) and EtOAc (15 mL) were then added and the mixture was filtered through a pad of Celite. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to provide the crude product. Purification by CombiFlash chromatography on silica gel (0 – 40% EtOAc in hexane) provided tert-butyl 3-formyl-3-[(1S)-2-methoxy-2-oxo-1-{[4-(pentafluoro-λ⁶-sulfanyl)phenyl]formamido}ethyl]azetidine-1-carboxylate (**43-1**, 0.1 g, 25% yield). MS: $[M+H]^+ = 503.3$.

Step 2. **Tert-butyl 3-ethynyl-3-[(1S)-2-methoxy-2-oxo-1-{[4-(pentafluoro-λ⁶-sulfanyl) phenyl]formamido}ethyl]azetidine-1-carboxylate (43-2).**

[0743] To a solution of tert-butyl 3-formyl-3-[(1S)-2-methoxy-2-oxo-1-{[4-(pentafluoro-λ⁶-sulfanyl)phenyl]formamido}ethyl]azetidine-1-carboxylate (**43-1**, 0.1 g, 0.2 mmol) in acetonitrile (5 mL) and methanol (1 mL) was added potassium carbonate (0.06 g, 0.4 mmol), followed by the dropwise addition of methyl (1-diazo-2-oxopropyl)phosphonate (0.046 g, 0.25 mmol). The

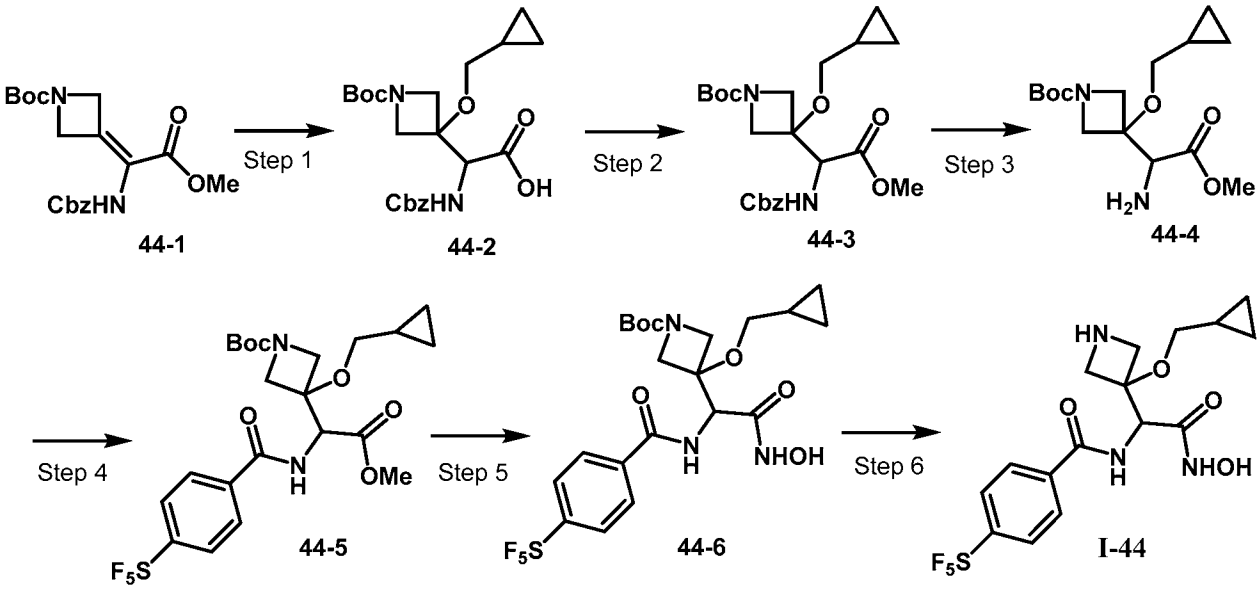
resulting suspension was stirred at room temperature for 16 h and then concentrated under reduced pressure. To the resulting residue was added 5% aqueous solution of $NaHCO_3$ (5 mL), and the mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by CombiFlash chromatography on silica gel (0 – 30% EtOAc in hexane) to afford tert-butyl 3-ethynyl-3-[(1S)-2-methoxy-2-oxo-1-{[4-(pentafluoro-λ^6-sulfanyl)phenyl] formamido}ethyl]azetidine-1-carboxylate (**43-2**, 0.023 g, 22% yield). MS: $[M+H]^+$ = 499.5.

Step 3. **(2S)-2-(3-ethynylazetidin-3-yl)-N-hydroxy-2-{[4-(pentafluoro-λ^6-sulfanyl) phenyl] formamido}acetamide trifluoroacetic acid salt (I-43).**

[0744] To a stirred suspension of tert-butyl 3-ethynyl-3-[(1S)-2-methoxy-2-oxo-1-{[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido}ethyl]azetidine-1-carboxylate (43-2, 0.02 g, 0.04 mmol) and $NH_2OH \cdot HCl$ (0.014 g, 0.2 mmol) in anhydrous MeOH (0.25 mL) and anhydrous THF (0.25 mL) cooled to -10 °C in a dry ice / MeOH bath and under a nitrogen atmosphere was added 25% NaOMe/MeOH (0.09 mL, 0.40 mmol). The reaction mixture was stirred at -10 °C for 30 min at which time it was quenched with 1N HCl (0.3 mL) and concentrated under reduced pressure to dryness.

[0745] The resulting residue was dissolved in DCM (0.5 mL). TFA (0.2 mL) was added at room temperature, and the resulting mixture was stirred for 12 h. The reaction mixture was concentrated *in vacuo*, and the product was purified by HPLC to obtain (2S)-2-(3-ethynylazetidin-3-yl)-N-hydroxy-2-{[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido}acetamide (I-43, 0.003 g, 15 %) as the TFA salt. LCMS (ESI): $[M+H]^+$ = 400.0.

Example 36: 2-[3-(cyclopropylmethoxy)azetidin-3-yl]-N-hydroxy-2-[[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido]acetamide trifluoroacetic acid salt (I-44)



Step 1. **2-[[(benzyloxy)carbonyl]amino]-2-[1-[(tert-butoxy)carbonyl]-3-(cyclopropylmethoxy)azetidin-3-yl]acetic acid: (44-2)**.

[0746] To a solution of tert-butyl 3-(1-[[(benzyloxy)carbonyl]amino]-2-methoxy-2-oxoethylidene)azetidine-1-carboxylate (**44-1**, 1 g, 2.66 mmol, 1.00 equiv) in cyclopropylmethanol (10 mL) was added (cyclopropylmethoxy)sodium (1.6 mL) dropwise at 0 °C. The resulting solution was stirred for 1 h at room temperature, then cooled to 0 °C and (cyclopropylmethoxy)sodium (2.0 mL) was added dropwise. The resulting solution was stirred for 3 h at room temperature. The reaction was then quenched by the addition of 50 mL of water and AcOH (1 mL) and extracted with 2 x 50 mL of ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to provide 500 mg (45%) of tert-butyl 3-(1-[[(benzyloxy)carbonyl]amino]-2-(cyclopropylmethoxy)-2-oxoethylidene)azetidine-1-carboxylate as a yellow crude oil which was used in the next step without further purification. LCMS (ESI): $[M+H]^+ = 417.2$.

[0747] To a solution of tert-butyl 3-(1-[[(benzyloxy)carbonyl]amino]-2-(cyclopropylmethoxy)-2-oxoethylidene)azetidine-1-carboxylate (500 mg, 1.20 mmol, 1.00 equiv) in cyclopropylmethanol (5 mL) was added (cyclopropylmethoxy)sodium (0.9 mL) dropwise at 0 °C and the resulting solution was stirred for 3 h at room temperature. The reaction was then

quenched by the addition of 50 mL of water and AcOH (1 mL) and extracted with 2 x 50 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. This resulted in 400 mg (77%) of 2-[[(benzyloxy)carbonyl]amino]-2-[1-[(tert-butoxy)carbonyl]-3-(cyclopropylmethoxy)azetidin-3-yl]acetic acid (**44-2**) as a light brown crude oil which was used in the next step without further purification.

Step 2. **Tert-butyl 3-(1-[[(benzyloxy)carbonyl]amino]-2-methoxy-2-oxoethyl)-3-(cyclopropylmethoxy)azetidine-1-carboxylate (44-3).**

[0748] To a solution of 2-[[(benzyloxy)carbonyl]amino]-2-[1-[(tert-butoxy)carbonyl]-3-(cyclopropylmethoxy)azetidin-3-yl]acetic acid (**44-2**, 400 mg, 0.92 mmol, 1.00 equiv) in methanol (0.5 mL) and dichloromethane (4.5 mL) was added $TMSCHN_2$ (0.55 mL, 1.20 equiv) and the resulting solution was stirred for 5 min at room temperature. The reaction mixture was concentrated under vacuum and the resulting residue was purified by silica gel column with ethyl acetate/petroleum ether (1:3) to provide 300 mg (73%) of tert-butyl 3-(1-[[(benzyloxy)carbonyl] amino]-2-methoxy-2-oxoethyl)-3-(cyclopropylmethoxy) azetidine-1-carboxylate (**44-3**) as a light yellow oil. LCMS (ESI): $[M+H]^+ = 449.2$,

Step 3. **Tert-butyl 3-(1-amino-2-methoxy-2-oxoethyl)-3-(cyclopropylmethoxy)azetidine-1-carboxylate (44-4).**

[0749] To a solution of tert-butyl 3-(1-[[(benzyloxy)carbonyl]amino]-2-methoxy-2-oxoethyl)-3-(cyclopropylmethoxy) azetidine-1-carboxylate (**44-3**, 300 mg, 0.67 mmol, 1.00 equiv) in methanol (5 mL) was added 10% Pd/C (100 mg) and the resulting solution was purged with H_2 three times and stirred for 2 h at room temperature. The solids were filtered off and the filtrate was concentrated under vacuum to provide 200 mg (95%) of tert-butyl 3-(1-amino-2-methoxy-2-oxoethyl)-3-(cyclopropylmethoxy)azetidine-1-carboxylate (**44-4**) as a light yellow syrup which was used in the next step without further purification. LCMS (ESI): $[M+H]^+ = 315.2$.

Step 4. **Tert-butyl 3-(cyclopropylmethoxy)-3-(2-methoxy-2-oxo-1-[[4-(pentafluoro-λ^6-sulfanyl)phenyl] formamido]ethyl)azetidine-1-carboxylate (44-5).**

[0750] To a solution of 4-(pentafluoro-λ^6-sulfanyl)benzoic acid (100 mg, 0.40 mmol, 1.00 equiv) in dichloromethane (2 mL) was added HATU (152 mg, 0.40 mmol, 1.00 equiv), DIEA (155 mg,

1.20 mmol, 3.00 equiv) and tert-butyl 3-(1-amino-2-methoxy-2-oxoethyl)-3-(cyclopropylmethoxy)azetidine-1-carboxylate (**44-4**, 152 mg, 0.48 mmol, 1.20 equiv) and the resulting solution was stirred for 2 h at room temperature and then concentrated under vacuum. The resulting residue was purified by silica gel column with ethyl acetate/petroleum ether (1:3) to provide 100 mg (46%) of tert-butyl 3-(cyclopropylmethoxy)-3-(2-methoxy-2-oxo-1-[[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido]ethyl)azetidine-1-carboxylate (**44-5**) as a light yellow oil. LCMS (ESI): $[M+H]^+ = 545.2$.

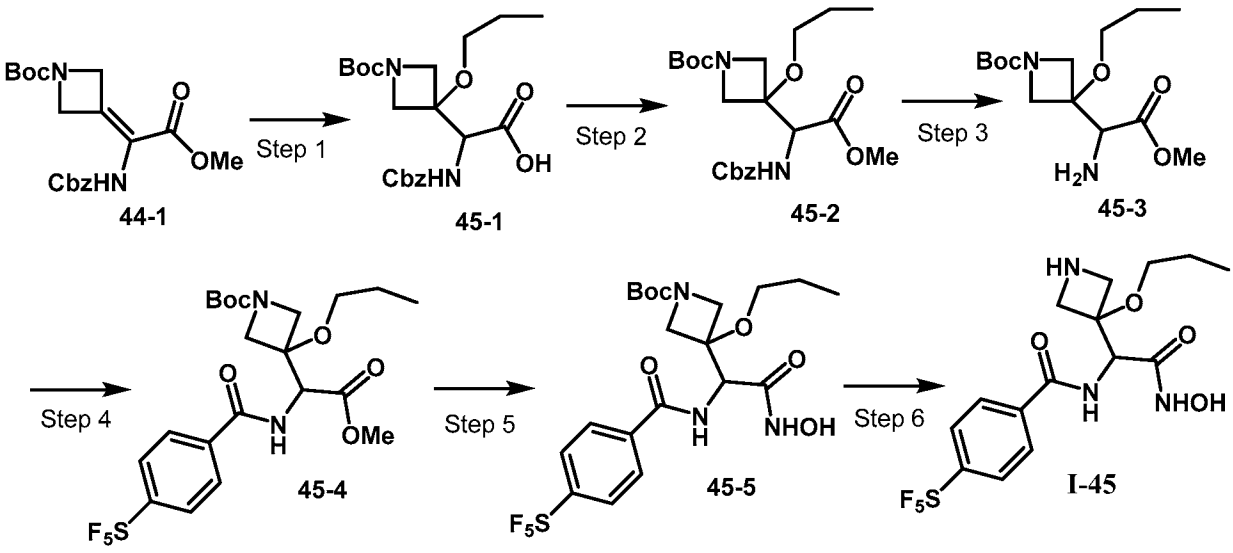
Step 5. **Tert-butyl 3-(cyclopropylmethoxy)-3-[(hydroxycarbamoyl)([[4-(pentafluoro-λ^6-sulfanyl)phenyl] formamido])methyl]azetidine-1-carboxylate (44-6).**

[0751] To a solution of tert-butyl 3-(cyclopropylmethoxy)-3-(2-methoxy-2-oxo-1-[[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido]ethyl)azetidine-1-carboxylate (**44-5**, 100 mg, 0.18 mmol, 1.00 equiv) in IPA (3 mL) was added NH_2OH (2 mL, 50% in H_2O). The resulting solution was stirred for 36 h at room temperature and then concentrated under vacuum to provide 100 mg (100%) of tert-butyl 3-(cyclopropylmethoxy)-3-[(hydroxycarbamoyl)([[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido])methyl]azetidine-1-carboxylate (**44-6**) as a light yellow oil. LCMS (ESI): $[M+H]^+ = 546.2$.

Step 6. **2-[3-(cyclopropylmethoxy)azetidin-3-yl]-N-hydroxy-2-[[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido]acetamide trifluoroacetic acid salt (I-44).**

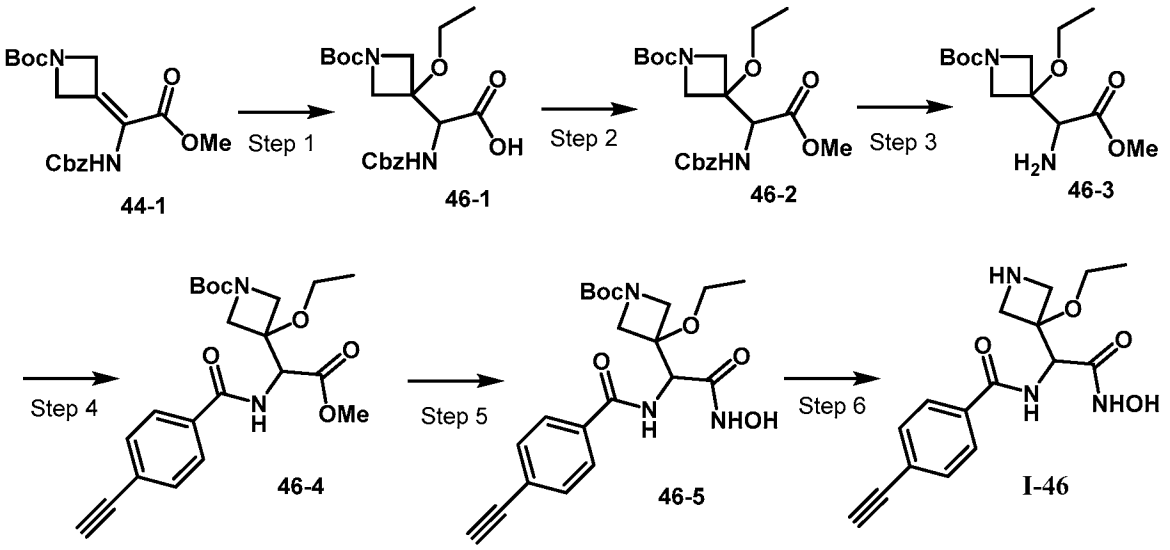
[0752] To a solution of tert-butyl 3-(cyclopropylmethoxy)-3-[(hydroxycarbamoyl)([[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido])methyl]azetidine-1-carboxylate (**44-6**, 100 mg, 0.18 mmol, 1.00 equiv) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL) dropwise at 0 °C. The resulting solution was stirred for 30 min at room temperature and then concentrated under vacuum. The resulting residue was purified by Prep-HPLC with the following conditions: Column, XSelect CSH Prep C18 OBD Column, 5 um, 19*150 mm; mobile phase, water (0.05% TFA) and ACN (5.0% ACN up to 25.0% in 6 min); Detector, uv 254 nm to afford 29.4 mg (36%) of 2-[3-(cyclopropylmethoxy)azetidin-3-yl]-N-hydroxy-2-[[4-(pentafluoro-λ^6-sulfanyl) phenyl]formamido] acetamide trifluoroacetic acid salt (**I-44**) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.15 – 8.12 (m, 2H), 8.06 – 8.03 (m, 2H), 4.92 (s, 1H), 4.50 (m, 1H), 4.14 (m, 1H), 3.98 – 3.89 (m, 2H), 3.51 – 3.45 (m, 1H), 3.39 – 3.34 (m, 1H), 1.05 – 0.98 (m, 1H), 0.47 – 0.40 (m, 2H), 0.22 – 0.15 (m, 2H). LCMS (ESI): $[M+H]^+ = 446.1$.

Example 37: N-hydroxy-2-[[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido]-2-(3-propoxyazetidin-3-yl)acetamide trifluoroacetic acid (I-45)



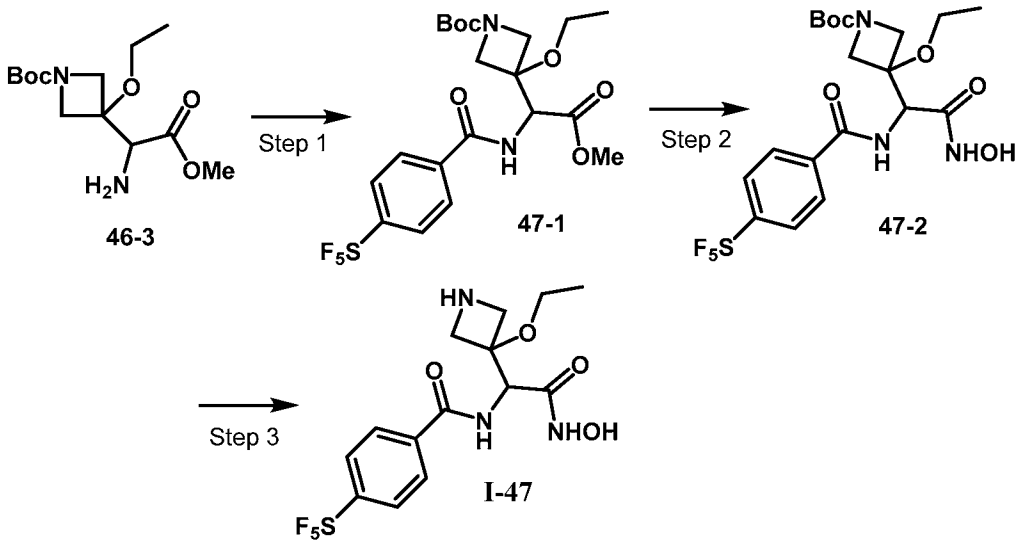
[0753] N-hydroxy-2-[[4-(pentafluoro-λ^6-sulfanyl)phenyl]formamido]-2-(3-propoxyazetidin-3-yl)acetamide trifluoroacetic acid (**I-45**) was synthesized according to the procedure outlined herein above in Example 36. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.04 (s, 1H), 9.14 (m, 2H), 8.98 (m, 1H), 8.65 (m, 1H), 8.09 (m, 4H), 4.94 (d, *J* = 8.5 Hz, 1H), 4.51 (m, 1H), 4.12 (m, 1H), 3.93 (m, 2H), 3.52 (m, 2H), 1.56-1.54 (m, 2H), 0.92 – 0.88 (m, 3H). LCMS (ESI): $[M+H]^+$ = 434.1.

Example 38: N-(1-(3-ethoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-ethynyl-benzamide trifluoroacetic acid (I-46)



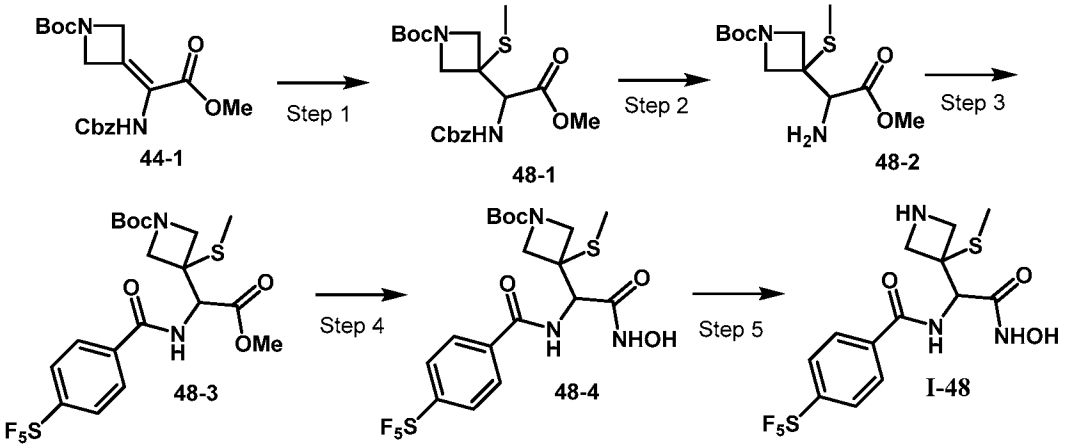
[0754] N-(1-(3-ethoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-ethynylbenzamide trifluoroacetic acid (**I-46**) was synthesized according to the procedure outlined herein above in Example 36.

Example 39: N-(1-(3-ethoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (I-47)



[0755] N-(1-(3-ethoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide (**I-47**) was synthesized according to the procedure outlined herein above in Example 36.

Example 40: N-(2-(hydroxyamino)-1-(3-(methylthio)azetidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide trifluoroacetic acid salt (I-48)



Step 1. **Tert-butyl 3-(1-[[(benzyloxy)carbonyl]amino]-2-methoxy-2-oxoethyl)-3-(methylsulfanyl)azetidine-1-carboxylate (48-1).**

[0756] To a solution of tert-butyl 3-(1-[[(benzyloxy)carbonyl]amino]-2-methoxy-2-oxoethylidene)azetidine-1-carboxylate (**44-1**, 1.1 g, 2.92 mmol, 1.00 equiv) in water (20 mL) and tetrahydrofuran (10 mL) was added 2-methyl-2-thiopseudourea sulfate (1.55 g, 5.58 mmol, 1.90 equiv) and NaOH (350 mg, 8.75 mmol, 3.00 equiv) and the resulting solution was stirred for 1 h at 55 °C in an oil bath. The reaction mixture was then cooled to room temperature and quenched by the addition of 100 mL of 10% citric acid. The resulting solution was extracted with 2 x 150 mL of ethyl acetate and the combined organic layers were washed with 1 x 150 mL of brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue purified by silica gel column eluting with ethyl acetate/petroleum ether (1:3) to provide 1.0 g (81%) of tert-butyl 3-(1-[[(benzyloxy)carbonyl]amino]-2-methoxy-2-oxoethyl)-3-(methylsulfanyl)azetidine-1-carboxylate (**48-1**) as a white solid. LCMS (ESI): $[M+H]^+ = 425.2$.

Step 2. **Tert-butyl 3-(1-amino-2-methoxy-2-oxoethyl)-3-(methylsulfanyl)azetidine-1-carboxylate (48-2):**

[0757] Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of H_2, was placed tert-butyl 3-(1-[[(benzyloxy)carbonyl]amino]-2-methoxy-2-oxoethyl)-3-(methylsulfanyl)azetidine-1-carboxylate (1 g, 2.36 mmol, 1.00 equiv), methanol (20 mL), ethyl acetate (30 mL), 10 % Pd/C (400 mg), and 20% $Pd(OH)_2/C$ (280 mg, 1.99 mmol, 0.85 equiv). The resulting solution was stirred for 4 h at room temperature. The solids were filtered off and the filtrate was concentrated under vacuum. This provided 600 mg (88%) of tert-butyl 3-(1-amino-2-methoxy-2-oxoethyl)-3-(methylsulfanyl)azetidine-1-carboxylate (**48-2**) as a colorless oil. LCMS (ESI): $[M+H]^+ = 291.1$.

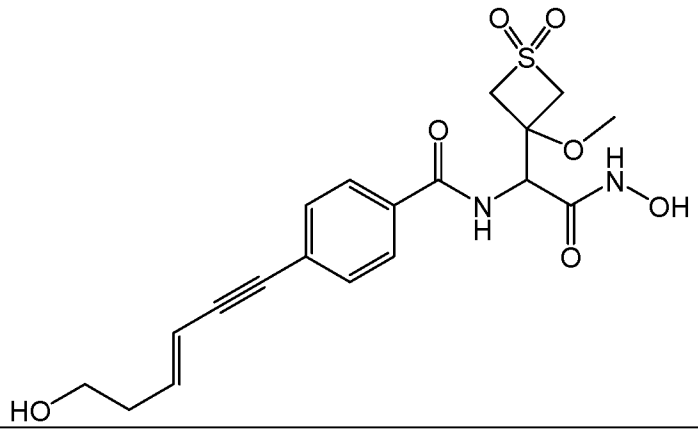
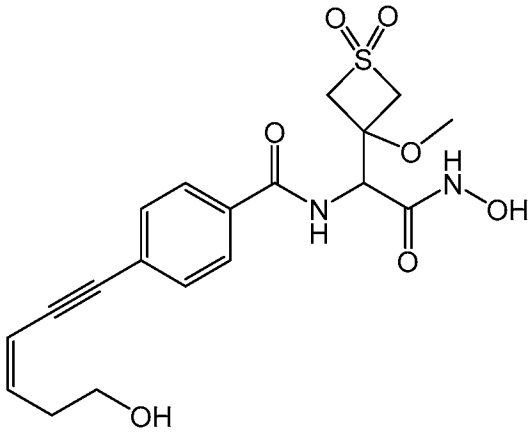
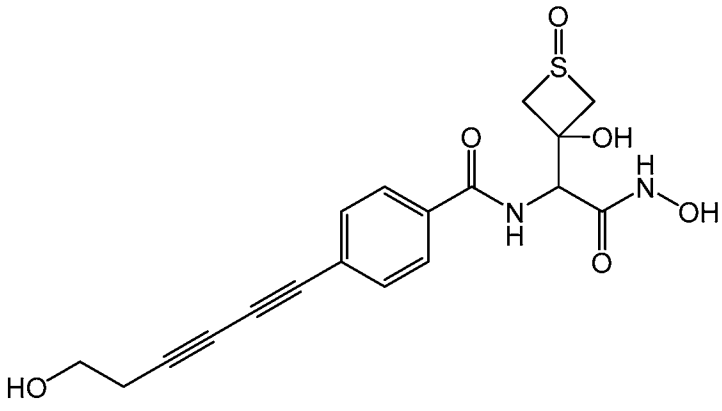
Step 3. **N-(2-(hydroxyamino)-1-(3-(methylthio)azetidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide trifluoroacetic acid salt (I-48)**

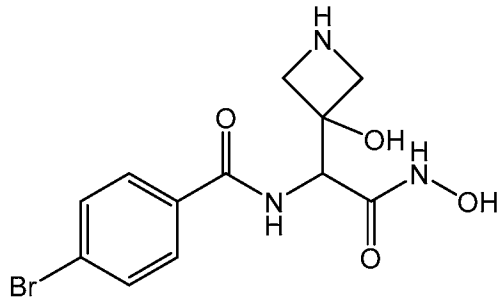
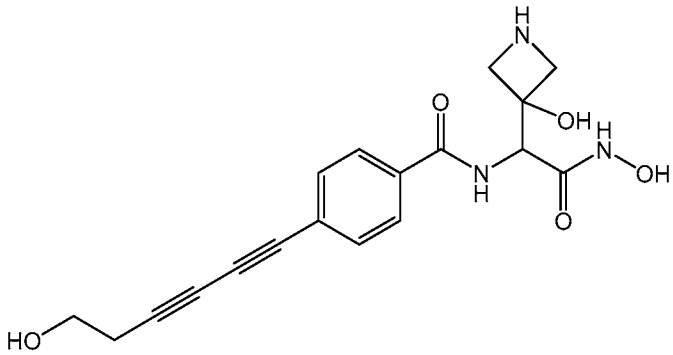
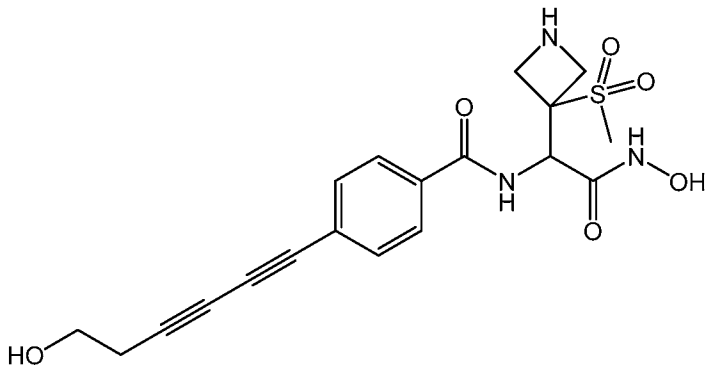
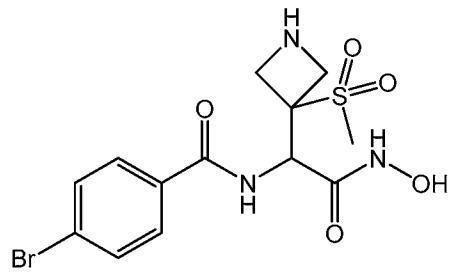
[0758] N-(2-(hydroxyamino)-1-(3-(methylthio)azetidin-3-yl)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide trifluoroacetic acid salt was synthesized according to the procedure outlined herein above in Example 36**.** LCMS (ESI): $[M+H]^+ = 422.1$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.15 (s, 1H), 9.47 (d, $J = 8.7$ Hz, 1H), 9.37 (m, 1H), 9.17 (s, 1H), 8.79 (br s, 1H), 8.14-8.05 (m,

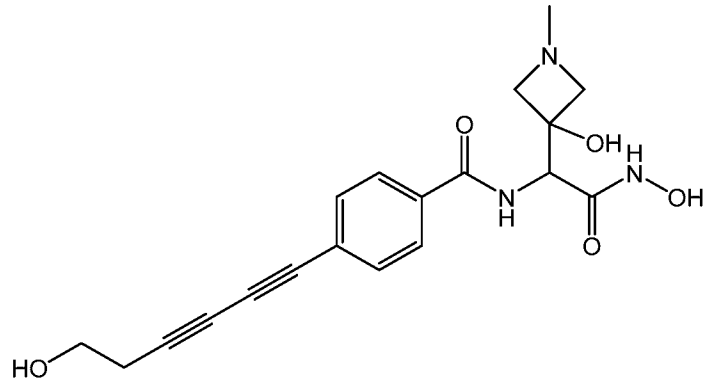
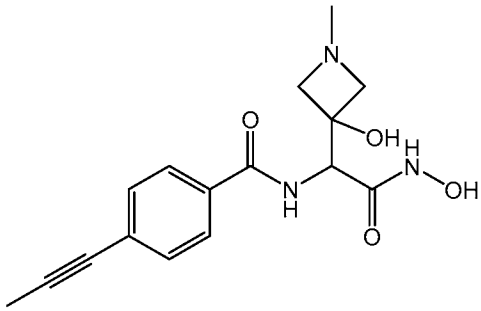
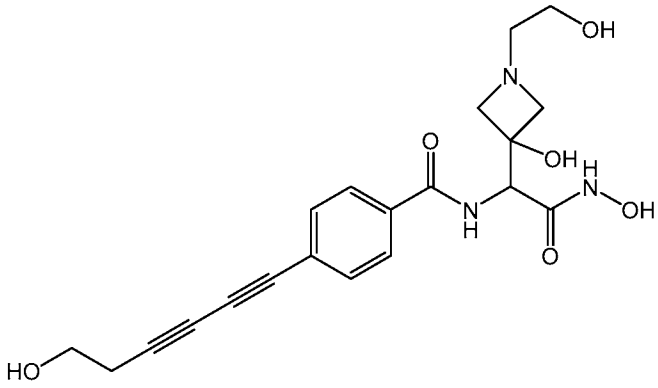
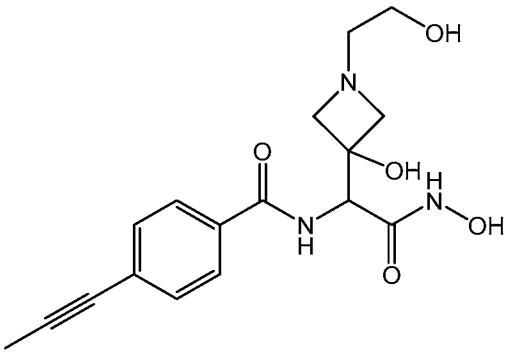
4H), 4.80-4.73 (m, 2H), 4.11-4.05 (m, 1H), 3.80 (m, 1H), 3.69-3.64 (m, 1H), 2.21 (s, 3H). LCMS (ESI): $[M+H]^+ = 422.1$.

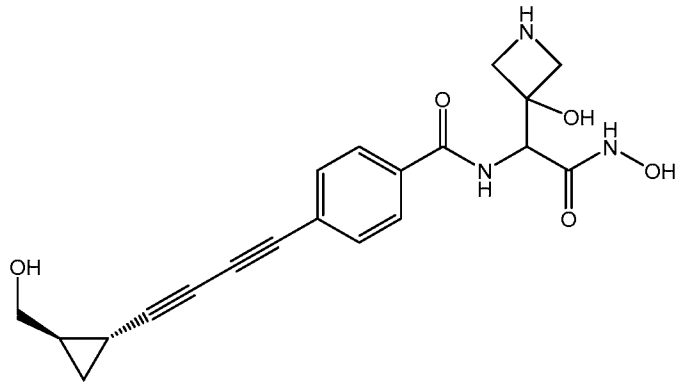
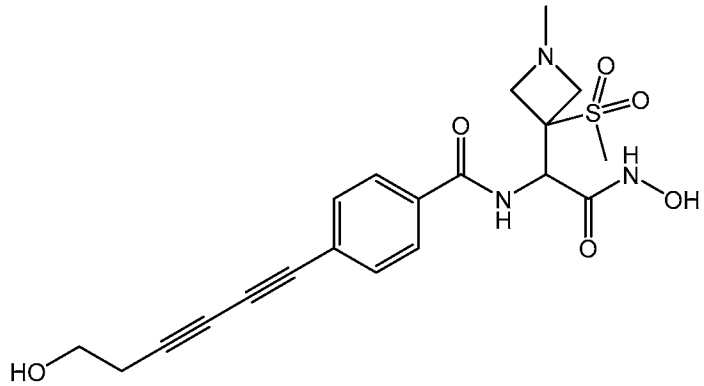
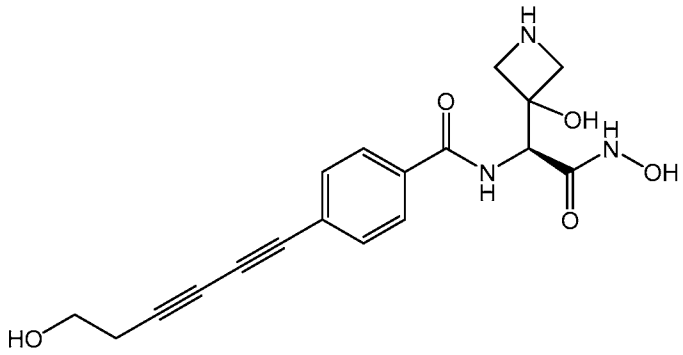
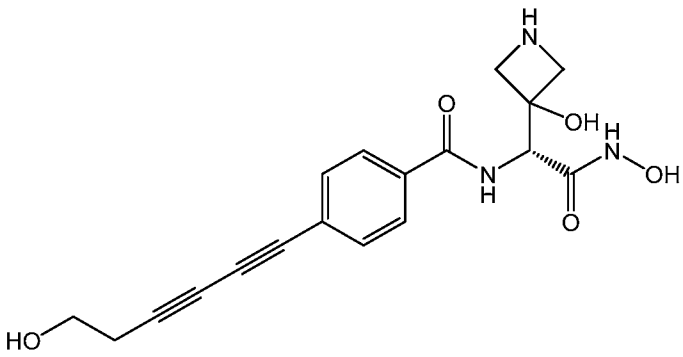
[0759] The Examples in Table 1 below were synthesized according to the procedures outlined above using the appropriate synthetic precursors.

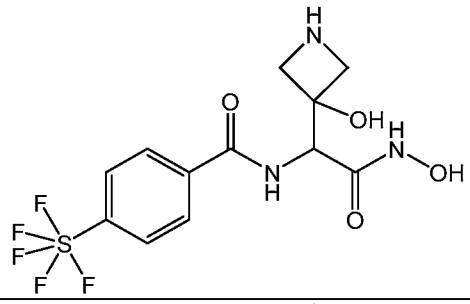
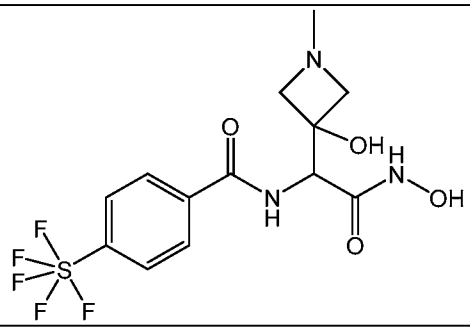
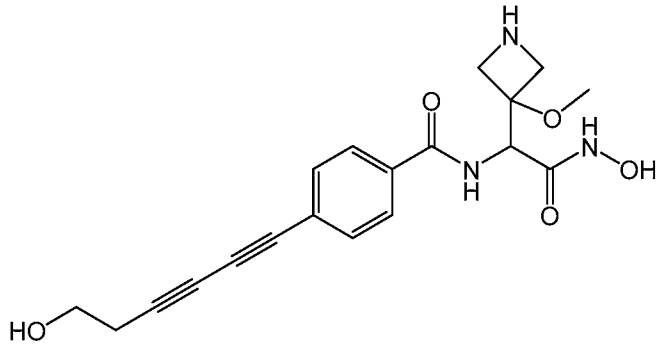
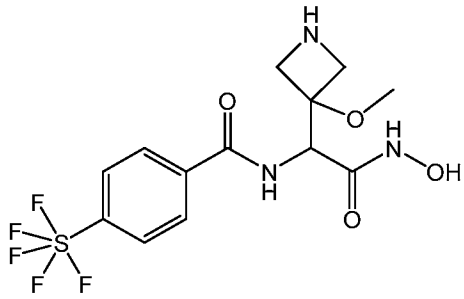
Table 1:

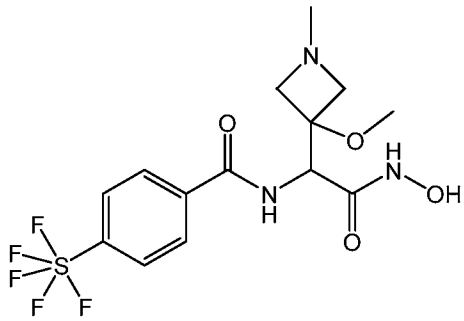
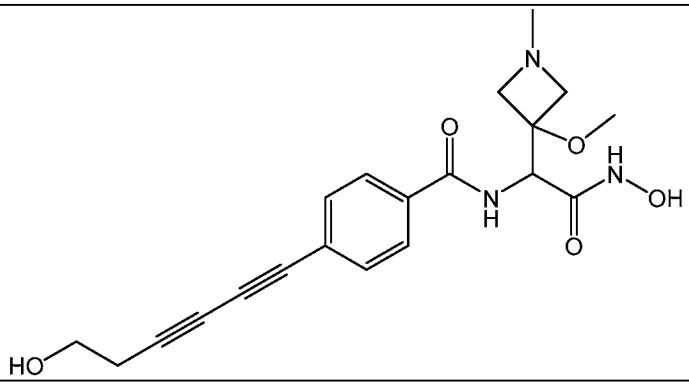
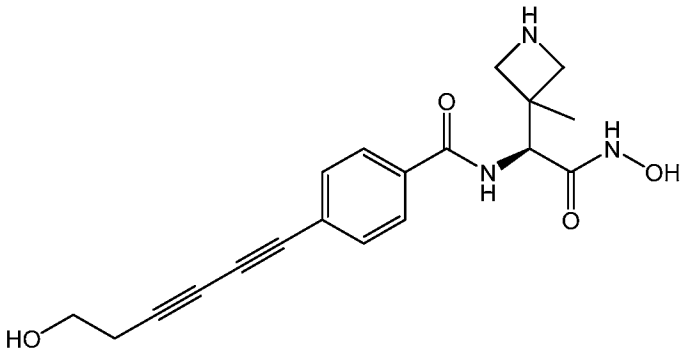
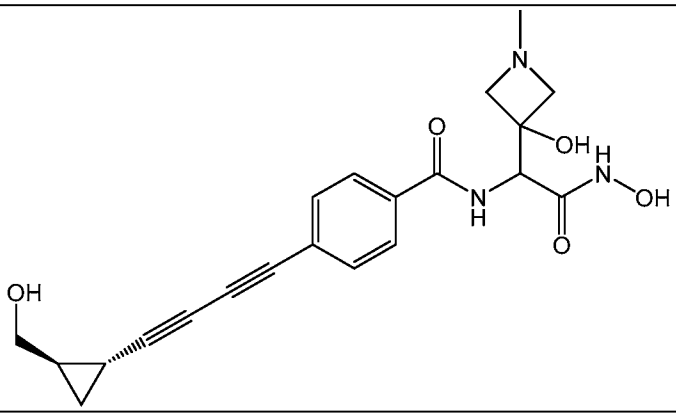
Example (Cmpd no.)	Structure
I-35	
I-36	
I-37	

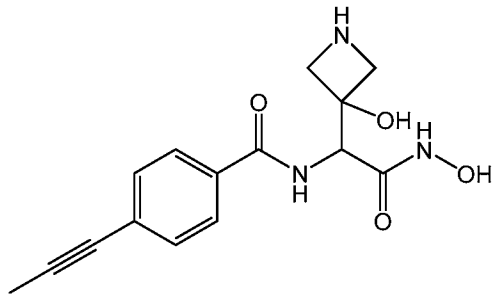
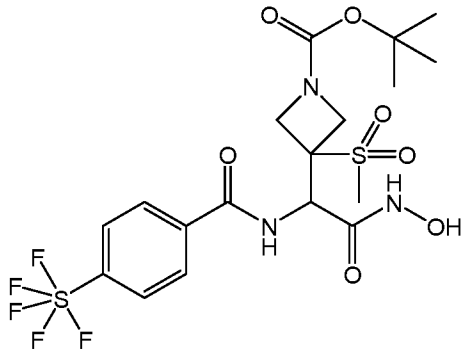
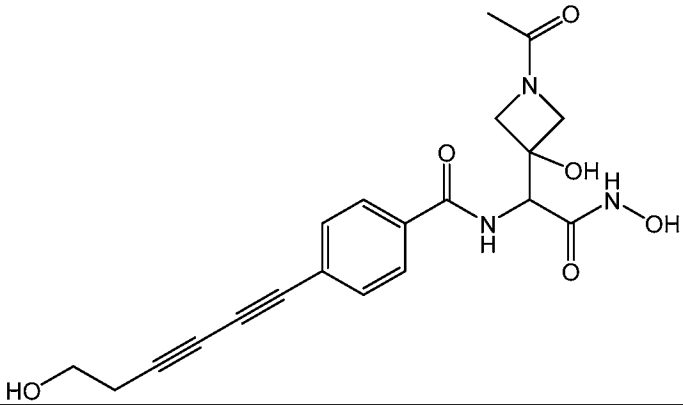
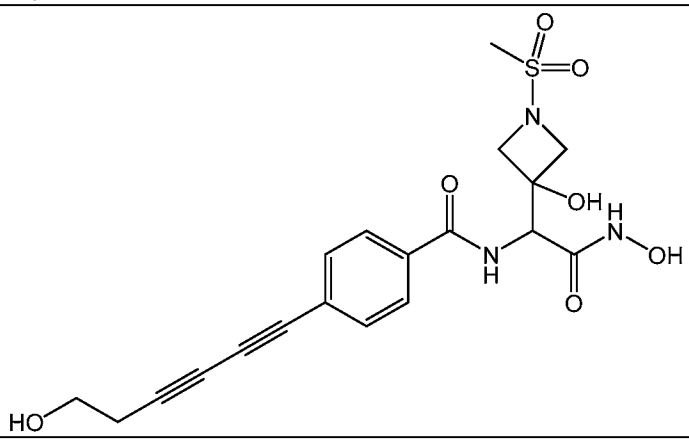
Example (Cmpd no.)	Structure
I-38	
I-39	
I-49	
I-50	

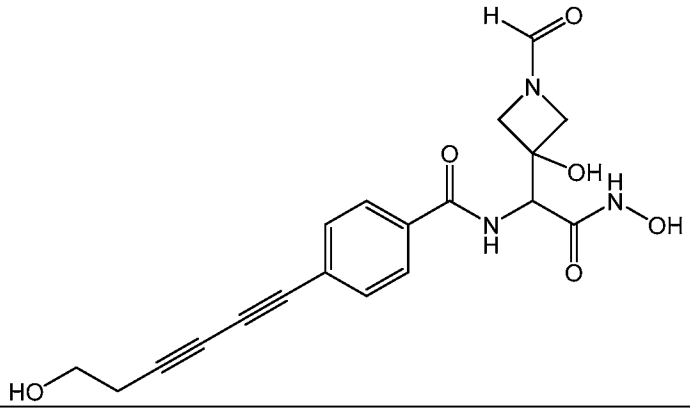
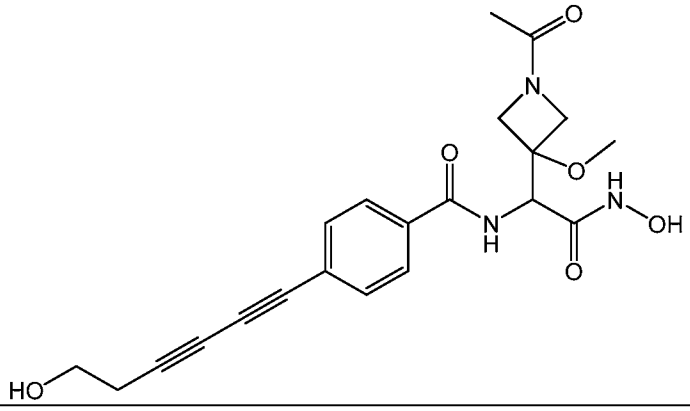
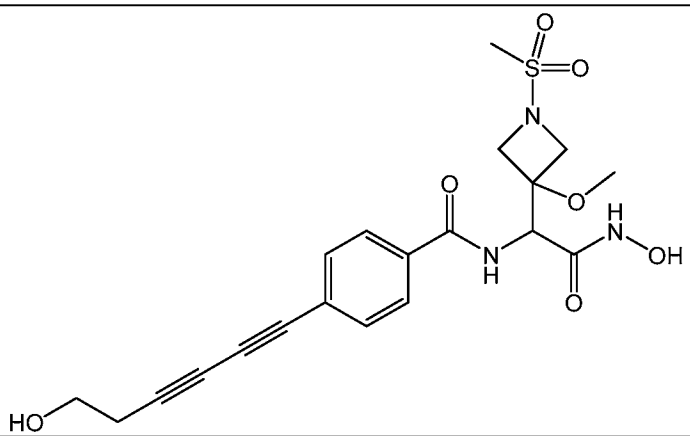
Example (Cmpd no.)	Structure
I-51	
I-52	
I-53	
I-54	

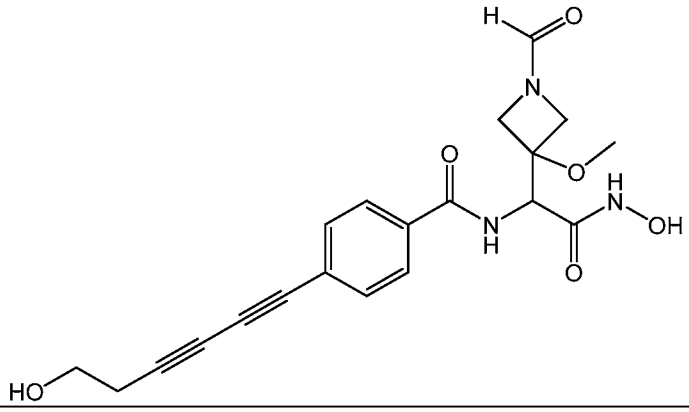
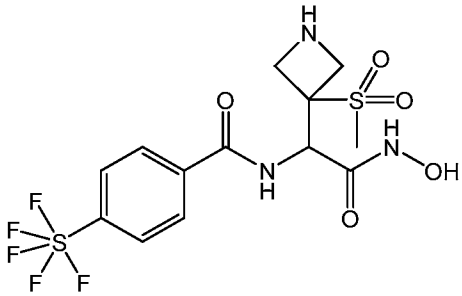
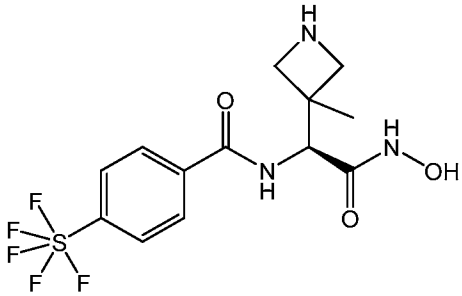
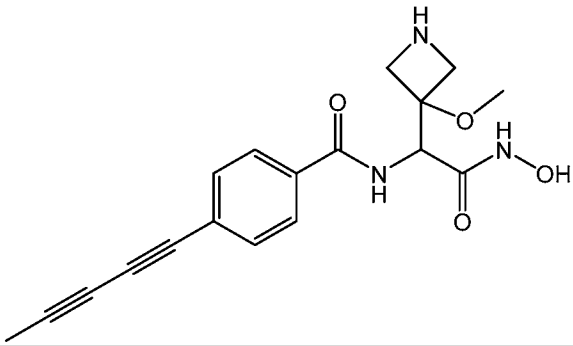
Example (Cmpd no.)	Structure
I-55	
I-56	
I-57	
I-58	

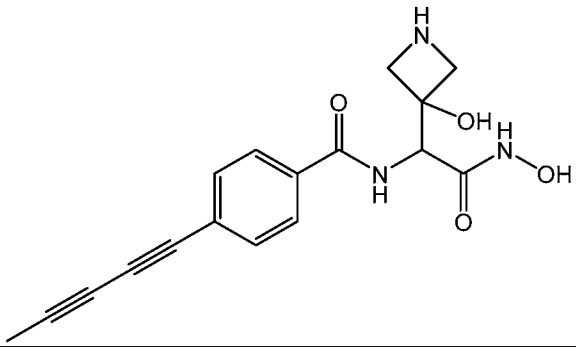
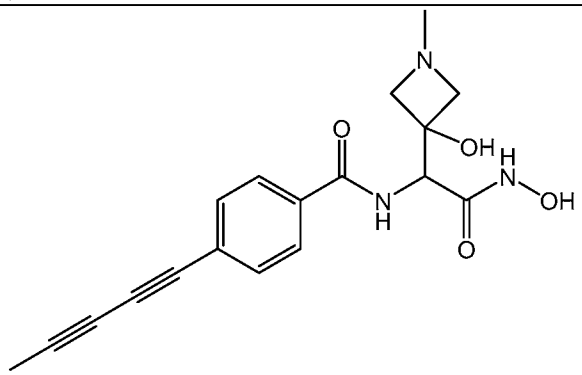
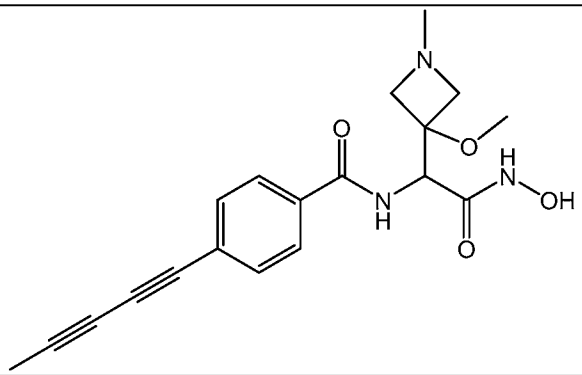
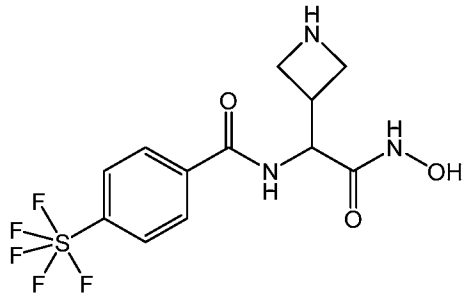
Example (Cmpd no.)	Structure
I-59	
I-60	
I-61	
I-62	

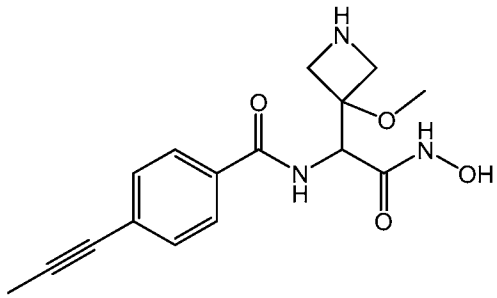
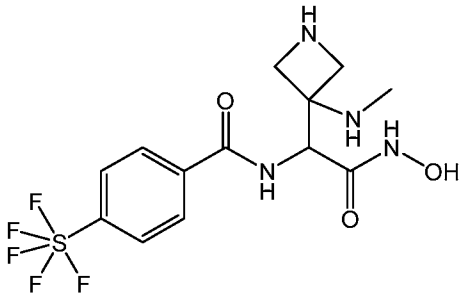
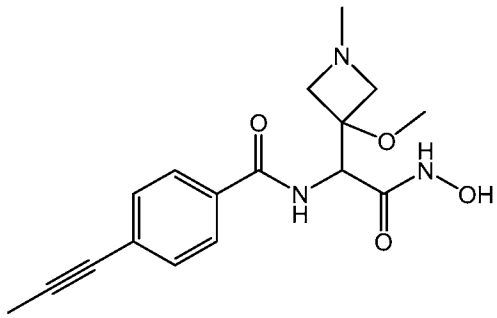
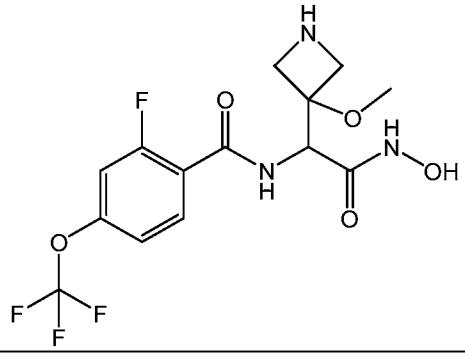
Example (Cmpd no.)	Structure
I-63	
I-64	
I-65	
I-66	

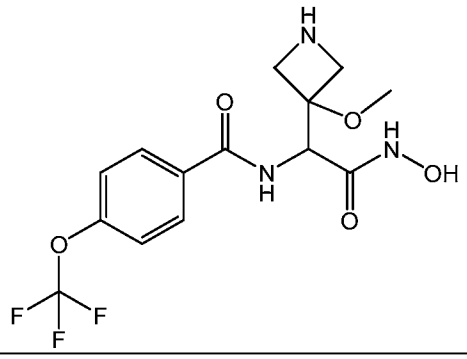
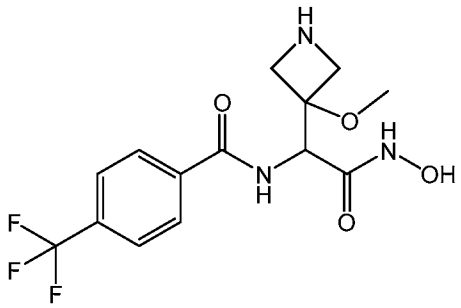
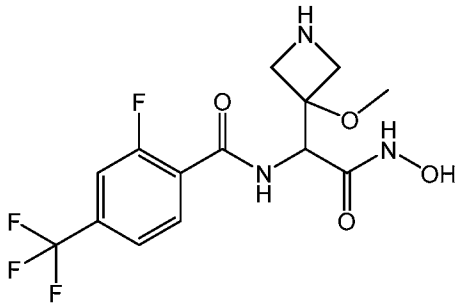
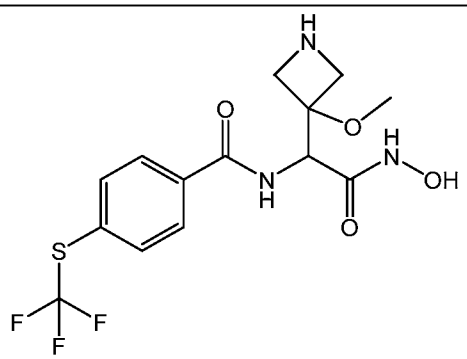
Example (Cmpd no.)	Structure
I-67	
I-68	
I-69	
I-70	

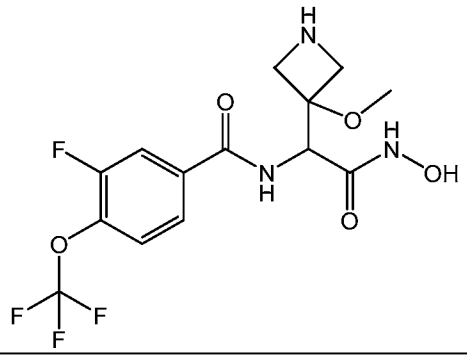
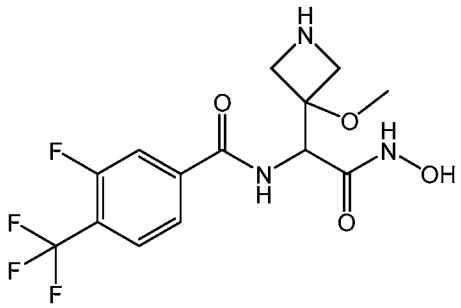
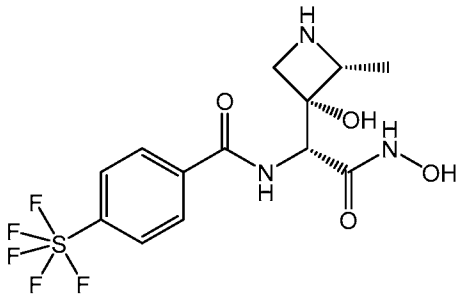
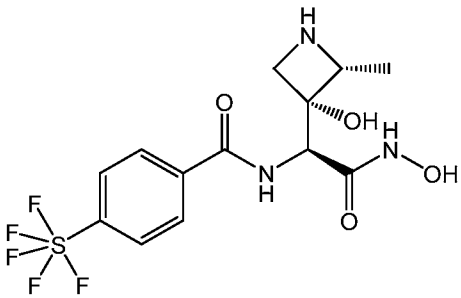
Example (Cmpd no.)	Structure
I-71	
I-72	
I-73	

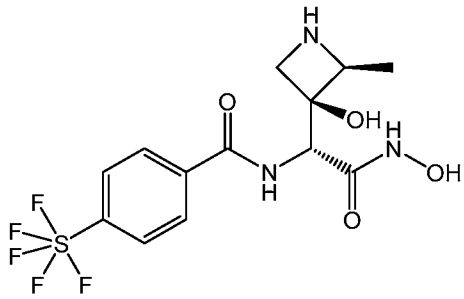
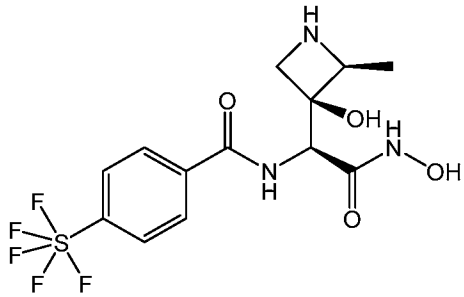
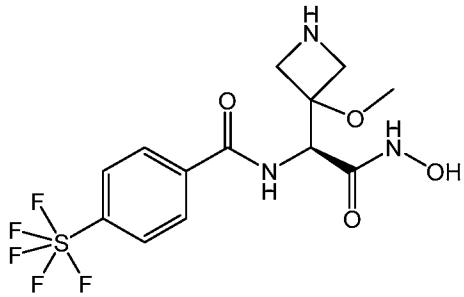
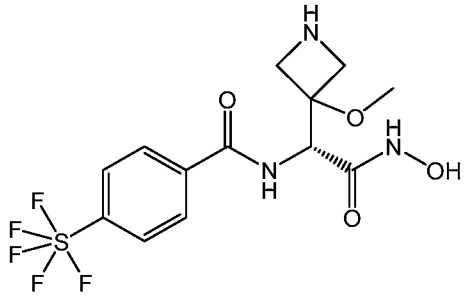
Example (Cmpd no.)	Structure
I-74	
I-75	
I-76	
I-77	

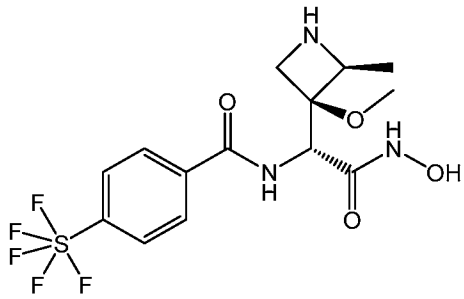
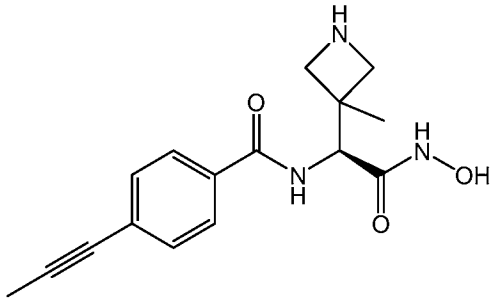
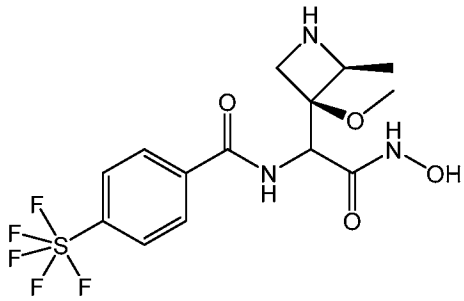
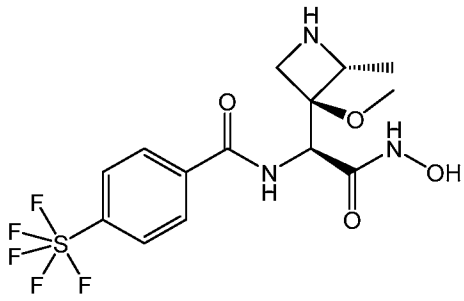
Example (Cmpd no.)	Structure
I-78	
I-79	
I-80	
I-81	

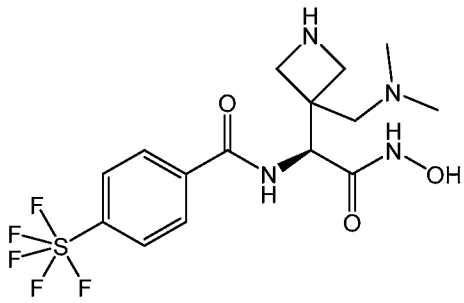
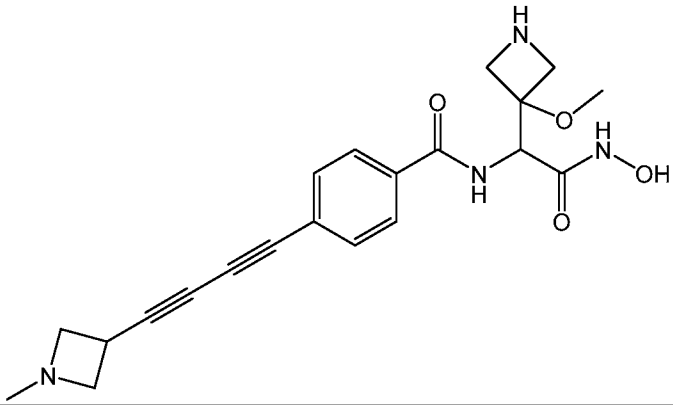
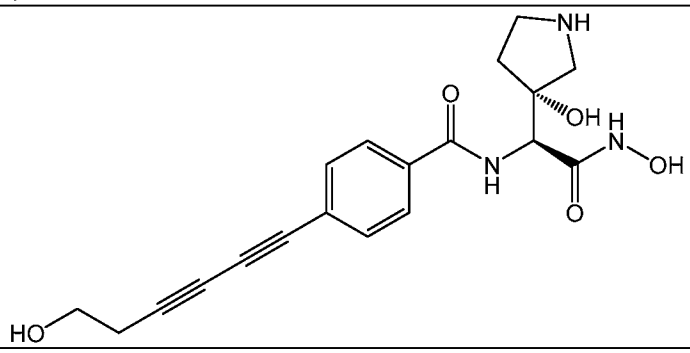
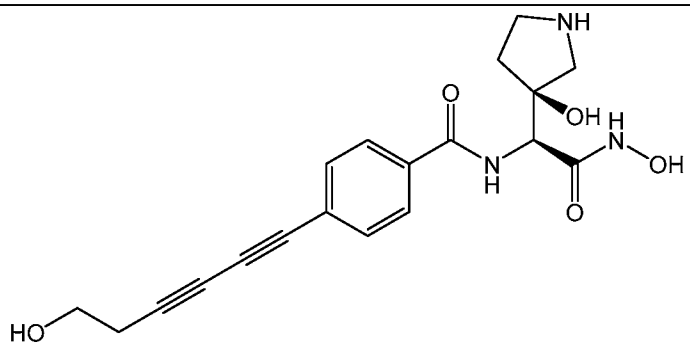
Example (Cmpd no.)	Structure
I-82	
I-83	
I-84	
I-85	

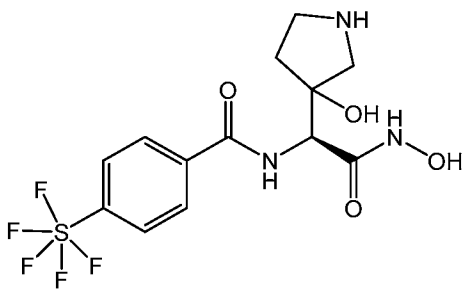
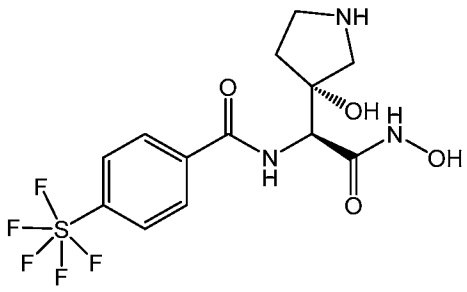
Example (Cmpd no.)	Structure
I-86	
I-87	
I-88	
I-89	

Example (Cmpd no.)	Structure
I-90	
I-91	
I-92	
I-93	

Example (Cmpd no.)	Structure
I-94	
I-95	
I-96	
I-97	

Example (Cmpd no.)	Structure
I-98	
I-99	
I-100	
I-101	

Example (Cmpd no.)	Structure
I-102	
I-103	
I-104	
I-105	

Example (Cmpd no.)	Structure
I-106	
I-107	

Example 42: Biochemical Assay: LpxC Enzymatic Assay for LpxC Activity.

Expression and purification of P. aeruginosa LpxC

[0760] A plasmid encoding *P. aeruginosa* (PAO1) LpxC (residues 1-299 with a C40S mutation) with an N-terminal histidine repeat tag for purification was transformed into Rosetta(DE3)/pLysS *E. coli* cells (Novagen). Cells were grown to an $OD_{600\ nm}$ of 0.5 AU whereupon 0.5 mM of isopropyl β-D-1-thiogalacto pyranoside and 10 μM zinc acetate were added to induce protein overexpression for the next 2.5 hours at 30 °C. The cell culture was pelleted by centrifugation at 10,500 rpm using a JA10.5 rotor (Beckman) for 15 minutes at 4 °C. The supernatant was discarded and the pellet was resuspended in 40 mL of ice cold 25 mM Tris HCl, 100 mM NaCl, 100 μM zinc acetate, 5 mM imidazole at pH 8.0 with trace amounts of benzonase and lysozyme added. The suspension was lysed by shearing the cells using a microfluidizer (Microfluidics, Model LM10). The lysed cells were centrifuged at 18,500 rpm in a JA25.5 rotor (Beckman) for 45 minutes at 4 °C and the resulting supernatant was passed through a 0.45 μm filter and gravity flowed over a His-Cobalt resin (Thermo-Fisher). After the column was washed with multiple column volumes of ice cold 25 mM Tris HCl, 100 mM NaCl, 100 μM zinc acetate, 5 mM imidazole at pH 8.0, the His-tagged LpxC was eluted by adding

approximately 3 column volumes of ice cold 25 mM Tris HCl, 100 mM NaCl, 100 μM zinc acetate, 150 mM imidazole, pH 8.0. The elutant was dialyzed overnight at 4 °C against 25 mM imidazole, pH 7.0, 100 mM KCl, 2 mM DTT, and 20% glycerol. The dialysate was filtered through a 0.2 μm filter and stored in small aliquots at -80 °C. Purity was estimated to be >95% by SDS-PAGE. The final concentration of stored LpxC enzyme was determined using a Bradford Assay (Thermo-Fisher). Typical yield of purified LpxC was approximately 2 mg of protein per 1 L of culture.

[0761] LpxC enzyme assays were conducted in 10 mM sodium phosphate, pH 7.5, 1 mM tris(2-carboxyethyl)phosphine, 0.005% Triton X-100, and <1% DMSO. Compound dilutions of compounds of the present disclosure were preincubated with approximately 0.2 nM *P. aeruginosa* LpxC for 10 minutes in the assay buffer above. Reactions were initiated by the addition of 10X substrate (UDP-3-O-(R-3-hydroxydecanoyl)-N-acetylglucosamine, Honghui Meditech Co.) to a final concentration of 40 μM. Reactions proceeded for 7 hours prior to quenching with 10X HCl to a final concentration of 116 mM. For LC/MS analysis, 20 μL of the quenched reaction solution was injected onto an Agilent Technologies 1290 Infinity UPLC system interfaced to a Agilent Technologies 6120 quadrupole mass spectrometer operating in single ion mode. The LpxC reaction product, UDP-3-O-(R-3-hydroxyacyl)-glucosamine, was separated from the LpxC substrate using a Kinetex 2.6 μm XB-C18 50 x 2.1 mm column. Reaction product and unreacted substrate were eluted into the mass spectrometer with a 1.75 minute gradient starting at 16% acetonitrile, 84% 10 mM ammonium acetate to 95% acetonitrile, 5% 10 mM ammonium acetate. The reaction product was quantified by monitoring the abundance of the parent ion m/z 734. The unreacted substrate was quantified by monitoring the abundance of the parent ion m/z 776. Total activity (0% inhibition control) is obtained from reactions with no compound present and 100% inhibition is defined as the background observed with no LpxC present. For IC_{50} determinations, peak areas of the substrate and product were compared to compute the proportion of substrate reacted by the LpxC enzyme at each compound concentration. The fractional activity is plotted versus the compound concentration in GraphPad Prism and fit to a three-parameter (hill slope fixed at 1) logistic equation using non-linear regression to yield the IC_{50} values.

[0762] Table 2: LpxC activity of compounds of the disclosure in LpxC enzymatic assay.

TABLE 2: LpxC Assay

Compound No.	LpxC Enzyme IC_{50} (nM) PA
I-1	1.3
I-10	0.77
I-11	3
I-12	1.8
I-13	0.56
I-14	3.6
I-15	1.7
I-16	1.9
I-17	7.7
I-18 and I-19	1.5
I-2	0.85
I-20	270
I-21	16
I-22	250
I-23	1100
I-24	4.7
I-25	2.3
I-26	2.1
I-27	0.74
I-28	4.3
I-29	1.8
I-3	8.1
I-30	1.8
I-31	3.5

Compound No.	LpxC Enzyme IC_{50} (nM) PA
I-32	NA
I-33	2.2
I-34	1.4
I-35	1.7
I-36	2.7
I-4	0.71
I-40	41
I-41	210
I-42	32
I-43	55
I-44	160
I-45	260
I-46	1600
I-47	130
I-48	210
I-5	25
I-6	0.45
I-7	0.67
I-8	0.9
I-9	1.9
I-37	1.4
I-38	3700
I-39	53
I-49	3.8

Compound No.	LpxC Enzyme IC_{50} (nM) PA
I-50	340
I-51	160
I-52	2000
I-53	17
I-54	250
I-55	7.5
I-56	30
I-59	340
I-60	440
I-61	56
I-62	140
I-63	680
I-64	150
I-65	19
I-66	4.4
I-67	560
I-69	12
I-70	26
I-71	4.6
I-72	1.4
I-73	2.5
I-74	7
I-75	30
I-76	180

Compound No.	LpxC Enzyme IC_{50} (nM) PA
I-77	30
I-78	18
I-80	76
I-81	2200
I-83	160
I-84	1700
I-85	7000
I-86	1400

Compound No.	LpxC Enzyme IC_{50} (nM) PA
I-89	650
I-90	1200
I-91	1600
I-93	130
I-95	270
I-96	68
I-97	450
I-98	15000

Compound No.	LpxC Enzyme IC_{50} (nM) PA
I-99	270
I-100	37.23
I-101	350
I-102	1000
I-103	1300
I-106	900
I-107	49

Example 43: Antimicrobial Activity in various Bacterial Strains.

[0763] The compounds of the present disclosure were tested for antimicrobial activity. These data are presented in Table 3. The compounds were run against Escherichia Coli ATCC 25922, Klebsiella pneumoniae ATCC 43816, and Pseudomonas aeruginosa PAM1020.

[0764] Minimum Inhibitory Concentrations (MICs) were determined by the broth microdilution method in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines. In brief, organism suspensions were adjusted to a 0.5 McFarland standard to yield a final inoculum between 3×10^5 and 7×10^5 colony-forming units (CFU)/mL. Compound dilutions and inocula were made in sterile, cation adjusted Mueller-Hinton Broth (Beckton Dickinson). An inoculum volume of 100 μL was added to wells containing 100 μL of broth with 2-fold serial dilutions of the compound. All inoculated microdilution trays were incubated in ambient air. Following incubation, the lowest concentration of the compound that prevented visible growth (OD600 nm < 0.05) was recorded as the MIC. Performance of the assay was monitored using laboratory quality-control strains and a compound with a defined MIC spectrum, in accordance with CLSI guidelines.

[0765] Table 3: MIC data of compounds of the disclosure against Escherichia Coli ATCC 25922 (E. Coli), Klebsiella pneumoniae ATCC 43816 (K. Pneum), and Pseudomonas aeruginosa PAM1020 (P.aerug). +++ indicates an MIC of less than 16 micrograms/ml, ++ indicates an MIC

between about 16 micrograms/ml and about 64 micrograms/ml, and + indicates an MIC greater than about 64 micrograms/ml.

TABLE 3: MIC activity

Cmpd No.	K. pneum (mg/L)	E. Coli (mg/L)	P. aerug (mg/L)
I-1	++	+++	+++
I-10	+++	+++	+++
I-11	+	++	+++
I-12	+	+	+++
I-13	+++	+++	+++
I-14	++	+++	+++
I-15	++	+++	+++
I-16	+++	+++	+++
I-17	++	+++	+++
I-18 and I-19	++	+++	+++
I-2	+++	+++	+++
I-20	+	+	++
I-21	+	++	+++
I-22	+	+	++
I-23	+	+	+
I-24	++	++	+++
I-25	++	++	+++

Cmpd No.	K. pneum (mg/L)	E. Coli (mg/L)	P. aerug (mg/L)
I-26	++	+++	+++
I-27	+++	+++	+++
I-28	+++	+++	+++
I-29	++	+++	+++
I-3	++	+++	+++
I-30	++	+++	+++
I-31	+++	+++	+++
I-32	NA	NA	NA
I-33	++	+++	+++
I-34	++	+++	+++
I-35	+++	+++	+++
I-36	++	+++	+++
I-4	+++	+++	+++
I-40	+	+	+++
I-41	+	+	+++
I-42	+	+	+++
I-43	+	++	+++
I-44	+	+	+++

Cmpd No.	K. pneum (mg/L)	E. Coli (mg/L)	P. aerug (mg/L)
I-45	+	+	+++
I-46	+	+	++
I-47	+	+	+++
I-48	+	+	+++
I-5	++	++	+++
I-6	+++	+++	+++
I-7	+++	+++	+++
I-8	+++	+++	+++
I-9	+++	+++	+++
I-37	N/A	N/A	N/A
I-38	+	+	+++
I-39	+	++	+++
I-49	+	+	+++
I-50	+	+	++
I-51	+	++	+++
I-52	+	+	+++
I-53	+	+	++
I-54	+	+	+++
I-55	++	++	+++
I-56	+	+	+++

Cmpd No.	K. pneum (mg/L)	E. Coli (mg/L)	P. aerug (mg/L)
I-57	+	++	+++
I-58	+	+	+
I-59	+	+	+++
I-60	+	+	+++
I-61	+	++	+++
I-62	+	+	+++
I-63	+	+	+++
I-64	+	++	+++
I-65	+	++	+++
I-66	++	+++	+++
I-67	+	+	+++
I-68	+	+	++
I-69	+	+	++
I-70	+	+	++
I-71	+	++	++
I-72	+	++	++
I-73	+	++	+++
I-74	+	++	+++
I-75	+	+	+++
I-76	+	+	+++

Cmpd No.	K. pneum (mg/L)	E. Coli (mg/L)	P. aerug (mg/L)
I-77	++	++	+++
I-78	++	+++	+++
I-79	++	++	+++
I-80	++	++	+++
I-81	+	+	+++
I-82	+	+	+++
I-83	+	+	+++
I-84	+	+	++
I-85	+	+	++
I-86	+	+	+++
I-87	++	++	+++
I-88	+	+	+++
I-89	+	+	+++
I-90	+	+	+++
I-91	+	+	+++
I-92	+	+	+

Cmpd No.	K. pneum (mg/L)	E. Coli (mg/L)	P. aerug (mg/L)
I-93	+	+	+++
I-94	+	+	++
I-95	+	+	+++
I-96	+	+	+++
I-97	+	+	+++
I-98	+	+	++
I-99	+	+	+++
I-100	+	+	+++
I-101	+	+	+++
I-102	+	+	+++
I-103	++	++	++
I-104	+	++	+++
I-105	+	+	+++
I-106	+	+	+++
I-107	+	+	+++

Example 44: Pharmacokinetic Assay: *In Vivo* Clearance in Rat Models.

[0766] The clearance rate of LpxC inhibitors of the present disclosure were tested in an *in vivo* rat model. Compounds of the present invention and known LpxC inhibitors (*i.e.*, compounds A-D) were dosed at 10 mg/kg in male Sprague-Dawley rats intravenously. The data is shown Table **4**.

[0767] Sprague-Dawley rats were intravenously dosed with a compound formulated at 10 mg/kg in 10% hydroxypropyl-cyclodextrine in water (pH 8). At 2, 5, 15, and 30 min, 1, 2, 4, 6 and 8 h, blood was collected in tubes containing K_2EDTA. Blood samples were put on ice and, within 15 minutes, centrifuged to generate plasma. For samples requiring prior 20X dilution, 3 µL of plasma were mixed with 57 µL of blank plasma, and the resulting dilutions were processed as indicated above. Samples were vortexed, then centrifuged. Supernatants were subjected to analysis by LC-MS/MS.

TABLE 4: Clearance (CL) data

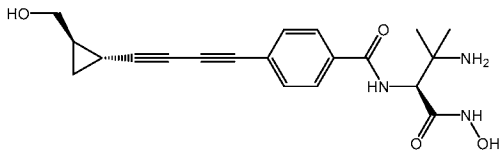
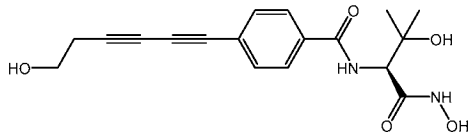
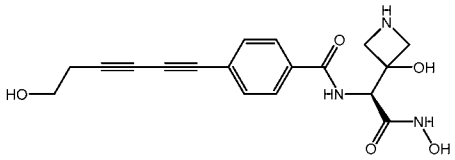
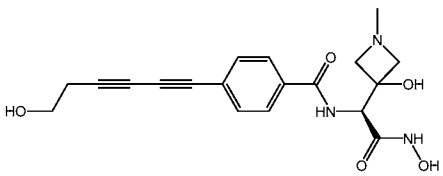
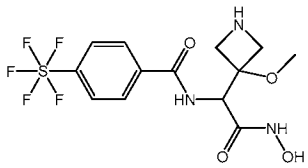
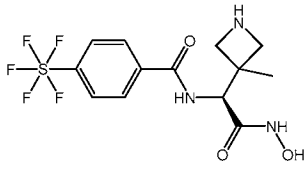
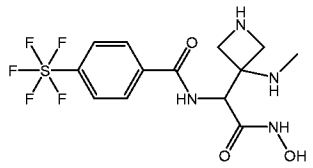
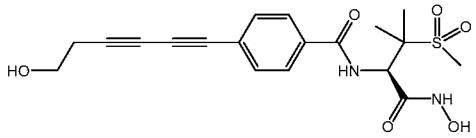
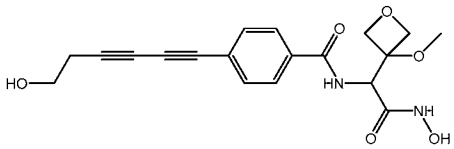
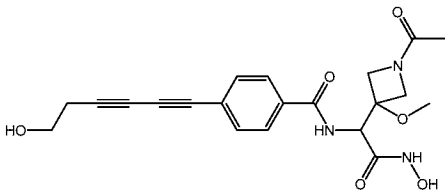
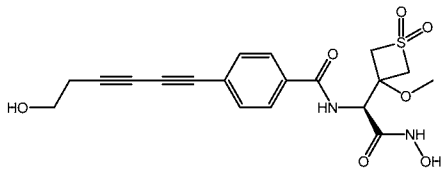
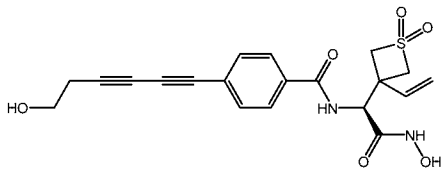
Table 1 Compound	Mean Free CL (L/hr/kg)
Cmpd A 	7.5
Cmpd B 	9.9
I-57 	1.6
I-51 	2.8
I-62 	2.3
I-76 	2.3

Table 1 Compound	Mean Free CL (L/hr/kg)
I-83 	3.1
Cmpd C 	6.5
Cmpd D 	9.1
I-72 	6.4
I-4 	4.4
I-27 	4.7

[0768] As shown in Table **4**, Compounds I-51 and I-57 have lower clearance rates when administered intravenously in rats compared to Cmpd A or Cmpd B which contain a non-cyclic substituent at the carbon alpha to both the amide and the hydroxamate group. The data also demonstrate that improved clearance is maintained in either long tailed (*i.e.*, I-57) or short-tailed compounds (*i.e.*, I-62). Furthermore, the improved clearance is observed with compounds of Formula (I) containing a variety of groups at the R_1 position (*i.e.*, I-62, I-76 and I-83).

[0769] The observed improved PK properties also depend on the identity of the X substituent in Formula (I). As the data show, compounds in which X is sulfur or nitrogen (*i.e.*, I-4 and I-27) show improved clearance data over compounds in which X is an oxygen, *i.e.*, Cmpd D.

Moreover, the conformation of the sulfone can also affect the clearance of the LpxC inhibitor compounds. For example, Cmpd C which contains a non-cyclic sulfone has higher clearance than Compounds I-4 and I-27 in which the sulfone is constrained in a ring.

Example 45: *In vivo* Cardiovascular Study

[0770] The effect of Cmpd A and Compound I-2 (the racemic mixture of Compound I-3 and Compound I-4) on cardiovascular parameters was evaluated in rats.

[0771] Four male Sprague-Dawley rats were anesthetized with isoflurane and transferred to a nosecone rebreathing circuit for spontaneous ventilation on 2.0% isoflurane provided by 100% O_2 carrier gas. Rectal temperature probes interfaced with an individual servo-controlled heating pad to regulate core body temperature. A cannula was introduced to the abdominal aorta of each rat via the right femoral artery for the direct determination of systemic hemodynamics. Each cannula was interfaced with a pre-calibrated pressure transducer connected to a computerized A/D converter and physiological data acquisition system (DSI Ponemah Physiology Platform). The right femoral vein of each rat was also cannulated for infusion of vehicle or test article. Each animal's left jugular vein was cannulated for collection of blood samples during and/or following compound infusion and subsequent determination of plasma compound concentrations.

[0772] Following surgery, the isoflurane dose was reduced to 1.5% and maintained at that concentration for the duration of study. All animals were stabilized before beginning experimental procedures (minimally 10 minutes of post-operative stabilization and 5 minutes of steady-state data defined as physiologically normal (37.0 ±0.2 °C) core temperature and consistent heart rate and mean arterial pressure). These baseline values were recorded and used as reference points for infusion cessation criteria.

[0773] After this equilibration period all animals received intravenous vehicle (20% HPCD, 250 mM Tris, in sterile water for injection, pH 9) for 30 minutes, followed by sequential 30 minute infusions of 3 increasing concentrations of test compound dissolved in vehicle to achieve the desired dosages. Each animal was infused at a prescribed rate (10 mL/kg/h) via a programmable infusion pump (Harvard PHD 2200) for up to two consecutive hours. Blood samples were collected from the jugular venous catheter every 30 minutes during the infusion.

[0774] Infusion cessation criteria were as follows: if, at any time in the experiment, mean arterial pressure or heart rate fell by 30 mm Hg or 30%, respectively, below initial baseline values for 2

contiguous minutes, a blood sample was immediately collected while the infusion was maintained, and the infusion was subsequently terminated. If infusion cessation criteria were achieved, the animal(s) continued to have systemic hemodynamic data collected for 30 minutes following termination of infusion. Blood samples were collected at 2, 6, 12 and 30 minutes following the cessation of the infusion. Rats were euthanized at the completion of the study.

[0775] Whole blood (200 µL) was collected at all timepoints described above into tubes containing K_2EDTA (and 4 µl of hydroxylamine 25 mM in the case of Cmpd A), then maintained on ice and processed within one hour of collection for plasma and stored at -80°C until subsequent bioanalysis.

[0776] *Cmpd A Bioanalysis:* Aliquots of plasma were diluted 50 fold with blank plasma containing 0.5 mM hydroxylamine, and then mixed with an internal standard. Protein precipitation was achieved by the addition of 4 volumes of methanol followed by vigorous shaking. Samples were centrifuged for 10 minutes at 6,000 x g. Supernatants were collected, diluted with 3 volumes of water and subjected to analysis by LC/MSMS on a Shimadzu LC 20 HPLC system connected to an AB Sciex 4000 Qtrap (ESI, positive ion mode), using a Zorbax SB-C3 column (Agilent, dimensions: 50 x 2.1 mm, 5 µm) at a flow rate of 0.8 ml/min. Mobile phase A: 0.1% formic acid in water, mobile phase B: 0.1% formic acid in acetonitrile. Initial conditions 10% B, held for 0.1', followed by a linear gradient to 30% B by over the next 3.9', followed by a linear gradient to 95% B by over the next 0.5' and an isocratic hold at 95% B for 0.5'.

[0777] *Compound I-2 Bioanalysis:* Aliquots of plasma were diluted 50 fold with blank plasma and mixed with an internal standard. Protein precipitation was achieved by the addition of 2 volumes of methanol followed by vigorous shaking. Samples were centrifuged for 10 minutes at 3,250 x g. Supernatants were collected, diluted with 9 volumes of water and subjected to analysis by LC/MSMS on a Shimadzu LC 20 HPLC system connected to an AB Sciex 4000 Qtrap (ESI, positive ion mode), using a Essensil C18 column (Cmion, dimensions: 30 x 3 mm, 5 µm) at a flow rate of 0.7 ml/min. Mobile phase A: 0.1% formic acid in water, mobile phase B: 0.1% formic acid in acetonitrile. Initial conditions 15% B, held for 0.5', followed by a linear gradient to 75% B by over the next 3.5', followed by a linear gradient to 95% B by over the next 0.25' and an isocratic hold at 95% B for 0.5'.

[0778] Free drug concentrations for Cmpd A of up to 8 μg/mL were achieved in the anaesthetized rat study without any significant changes in cardiovascular parameters (heart rate and systolic, diastolic and mean blood pressures) or animal lethality. However, when free drug concentrations (approximately 12% of total drug) of Cmpd A exceeded 8 μg/mL, a significant drop in blood pressure was observed, which resolved following the cessation of the infusion and clearance of the drug. Data are summarized in FIG. **1**.

[0779] One of four rats treated with Compound I-2 showed >80% lower plasma levels of drug compared to other rats and was not included in the data analysis. Free drug concentrations for Compound I-2 of up to 81 μg/mL were achieved in the anaesthetized rat study without any significant changes in cardiovascular parameters (heart rate and systolic, diastolic and mean blood pressures) or animal lethality during the infusion or recovery periods. Data are summarized in FIG. **2**. While these data pertain to the racemic mixture of Compound I-4 and its opposite enantiomer Compound I-3, data from structurally related pairs of enantiomers on the same scaffold indicate that the orientation of the LpxC inhibitors disclosed herein at this stereocenter does not impact cardiovascular toxicity (data not shown). Therefore, these data are expected to apply equally to enantiopure Compound I-4.

Example 46: Phlebitis Toxicology

[0780] Seven groups of 3 New Zealand white male rabbits, 3-3.4 kg body weight received a 20 mL intravenous infusion, as outlined in Table **5**, over 1 hour via a 24-gauge catheter inserted into the distal end of the marginal ear vein.

TABLE 5. Summary design of the rabbit phlebitis study for Cmpd A and Compound I-32.

Group	No. of Animals	Infusate	Dose Concentration (mg/mL)	Diluent Used	Acetate Buffer
1	3	NaCl for Injection	0	-	None
2	3	38mM Acetate Buffer (pH 4.5)	0	Saline	38 mM
3	3	Cmpd A - Low (pH 4.5)	2	Saline	38 mM
4	3	Cmpd A - High (pH 4.5)	8	Saline	38 mM
5	3	Compound I-32 - Low (pH 6.9)*	10	Saline	None

Group	No. of Animals	Infusate	Dose Concentration (mg/mL)	Diluent Used	Acetate Buffer
6	3	Compound I-32 – Mid (pH 6.8)*	30	Saline	None
7	3	Compound I-32 - High (pH 6.5)*	80	Sterile Water	None

*312-335 mOsmol/L

[0781] Fifteen minutes and 1 hour after the end of the 1-hour infusion period, approximately 0.5 ml blood was collected from the marginal ear vein of the untreated ear of animals in groups 5, 6 and 7 (*i.e.*, those who received Compound I-32). Twenty-four hours after the end of the 1-hour infusion period, all rabbits were anesthetized with intramuscular Ketamine/Xylazine and euthanized with an excess dose of isoflurane via inhalation. Between anesthesia and euthanasia, approximately 0.5 ml blood each was collected by cardiac puncture from animals in groups 3, 4, 5, 6 and 7, and approximately 4 ml each from animals in group 1 to serve as blank matrix for bioanalytical procedures (the control samples were not analyzed). Blood samples were collected into EDTA-coated vials (K_2EDTA), covered with aluminum foil to protect from light, gently inverted 10 times, and placed on ice immediately after collection until centrifugation. Samples were centrifuged at 5000 rpm for 3 minutes at 4°C and within 5 minutes of centrifugation, plasma was separated and aliquoted into Eppendorf tubes (covered with aluminum foil) and stored at -20 °C until analysis.

[0782] After euthanasia, the treated vein was flushed with 10 mL of 0.9% NaCl followed by 5 mL of 10% neutral-buffered formalin using a 24-gauge needle and syringe at 1-2 cm distal to the treatment site (away from the tissue being harvested). A 5 cm sample of marginal ear vein tissue was harvested beginning at 1 cm beyond the infusion site and ending at 4 cm distal to this point. Upon harvesting, the marginal ear vein tissue samples were stored at room temperature in 10% neutral-buffered formalin until shipment to Vet Path Services Inc. (Mason, OH) for histopathology evaluation. The samples were processed and stained with hematoxylin and eosin for microscopic examination at Vet Path Services, Inc. Histologic grading including individual grading for endothelial loss, perivascular inflammation, and vascular thrombosis was performed using a 5-point score as described in Table **6**.

TABLE 6. Five-point grading scale and score descriptors for microscopic findings.

Grade	Microscopic Findings		
	Endothelial Loss (E)	**Perivascular Inflammation (I)**	**Vascular Thrombosis (T)**
0	None	None	None
1	Less than 20%.	A few perivascular leukocytes, minimal or barely discernable.	Strands of fibrin extending into lumen of blood vessel, minimal or barely discernable.
2	20 to 40% loss.	Scattered perivascular leukocytes.	Small thrombotic tags, less than 10%.
3	40 to 60% loss.	Aggregations of perivascular leukocytes.	Thrombus with some but limited obstruction, 10 to 40%.
4	60 to 80% loss.	Extensive perivascular leukocytes with limited extension into adjacent tissues.	Thrombus with obstruction 40 to 80%.
5	Greater than 80% loss.	Broad bands of perivascular leukocytes with prominent infiltration of adjacent tissues.	Thrombus with complete or almost complete obstruction, more than 80%.

[0783] Results from the microscopic evaluation of endothelial loss, perivascular inflammation, and vascular thrombosis are shown in Table 7. The saline control animals (Group 1) had no vascular irritation, and the endothelium of the ear vein was intact with no reactive changes. The acetate buffer control animals (Group 2) showed no vascular irritation. One of the animals in Group 2 had less than 20% loss of endothelium of the vein surface, and the basement membrane was seen under the microscope. There were no fibrinous tag adhesions or a leukocyte reaction. The effect for this one animal was attributed to the low pH of the solution and the buffering to that pH which caused endothelial cell injury.

[0784] The cumulative microscopic evaluation scores for endothelial loss, perivascular inflammation, and vascular thrombosis were 1, 8 and 22 for the acetate buffer-vehicle control animals (Group 2), Cmpd A 2 mg/mL animals (Group 3), Cmpd A 8 mg/mL animals (Group 4), respectively using the 5-Point Grading Scale. The principal effect of Cmpd A was loss of a segment of the venous endothelium. The highest dose of the Cmpd A formulation (8 mg/mL) resulted in a loss of approximately half the endothelial lining with an associated leukocytic reaction and thrombus formation that only partially obstructed the vessel.

[0785] In contrast, test article Compound I-32, does not appear to cause any vascular irritation at the low (10 mg/ml) and middle (30 mg/mL) concentrations. At the highest concentration (80 mg/mL), Compound I-32 was found to cause mild vascular irritation that was comparable to that shown by Cmpd A at 2 mg/ml. The animals infused with 80 mg/mL Compound I-32 showed varying loss of venous endothelium. One of them showed less than 20% loss in one of them with barely discernable strands of fibrin extending into lumen of blood vessel. The other two showed a loss of 20%-40% of venous endothelium with small thrombotic tags, less than 10%.

TABLE 7. Microscopic evaluation scores using the 5-Point Grading Scale for endothelial loss, perivascular inflammation and vascular thrombosis.

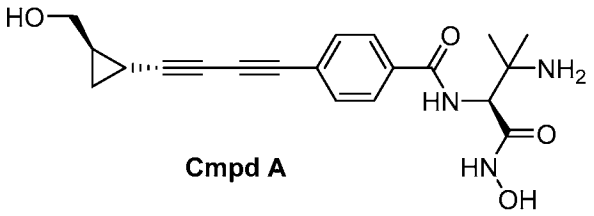
Group	**Rabbit #**	**Histopathology Findings score (5-Point Grading Scale)**			**Total Score**
		Endothelial Loss (E)	**Perivascular Inflammation (I)**	**Vascular Thrombosis (T)**	
Group 1 Saline	1	0	0	0	**0**
	2	0	0	0	
	3	0	0	0	
Group 2 Acetate buffer 38 mM	4	0	0	0	**1**
	5	1	0	0	
	6	0	0	0	
Group 3 Cmpd A 2 mg/ml	7	1	0	1	**8**
	8	2	0	1	
	9	2	0	1	
Group 4 Cmpd A 8 mg/ml	10	3	2	3	**22**
	11	3	2	3	
	12	2	2	2	
Group 5 Compound I-32 10 mg/ml	13	0*	0	0	**0**
	14	0	0	0	
	15	0	0	0	
Group 6 Compound I-32 30 mg/ml	16	0	0	0	**0**
	17	0*	0	0	
	18	0	0	0	
Group 7 Compound I-32 80 mg/ml	19	1*	0	1	**11**
	23	2	0	2	
	21	2	1	2	

* = vein dilated with red cells and plasma, poorly flushed

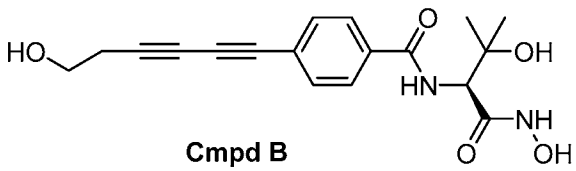
[0786] In summary, under the conditions of this study, the Compound I-32 formulations did not appear to cause any vascular irritation at the low (10 mg/mL) or middle (30 mg/mL) doses and are similar to the saline procedural control. At the highest concentration (80 mg/mL), Compound I-32 was found to cause mild vascular irritation comparable to that shown by Cmpd A at 2 mg/mL, corresponding to a ~40x improvement in safety margin for phlebitis. Bioanalysis of the post-infusion samples confirmed drug exposures and conversion of the Compound I-32 prodrug to Compound I-2.

Example 47. Activity against *P. aeruginosa*

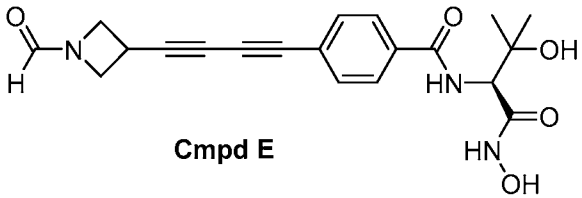
[0787] This example evaluates the antimicrobial susceptibility profiling of Cmpd A, Cmpd B, Compd E, and Compound I-4 against *Pseudomonas aeruginosa* from respiratory tract infections.



Cmpd A



Cmpd B



Cmpd E

[0788] This study evaluated 250 *Pseudomonas aeruginosa* from the IHMA stock culture collection from respiratory tract infections (RTIs), including 49 isolates from cystic fibrosis (CF) patients. Minimum inhibitory concentrations (MICs) using broth microdilution testing was performed following current (2016) CLSI guidelines. A total of 250 isolates were chosen from the IHMA culture collection of recent clinical isolates based on source of isolate (respiratory), year of collection (n): 2010 (49), 2015 (136) and 2016 (65), and region of origin (n; % of total): North America (99; 39.6%), Europe (51; 20.4%), and rest of the world (100; 40%). All CF isolates (n=49; 19.6%) were collected in North America in 2010.

[0789] MIC_{90} values for Compound I-4 were the same for non-CF and CF isolates (2 μg/mL) (Table **8**). The mode for non-CF isolates was 1 μg/mL, whereas the mode for CF isolates was

four-fold lower at 0.25 µg/mL (FIG. **3**). These data indicate that Compound I-4 is active against *P. aeruginosa* from RTI sources including isolates from CF patients.

TABLE 8: *In vitro* activity of Compound I-4 against 250 *P. aeruginosa* isolates.

Organism (n)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	Range (µg/mL)
All *P. aeruginosa* (250)	1	2	≤0.03 - 16
P. aeruginosa, CF (49)	0.5	2	0.12 - 2
P. aeruginosa, non-CF (201)	1	2	≤0.03 - 16

Example 48. Activity against a *Enterobacteriaceae* clinical isolates

[0790] This study evaluates the activity of Compound I-4, Cmpd A, Cmpd B, Cmpd E and four comparator agents was against 20 *Escherichia coli* isolates, 19 *Klebsiella pneumoniae* isolates and 1 *Klebsiella oxytoca* isolate. Included in the panel were isolates encoding genes conferring resistance to beta lactam, fluoroquinolone and aminoglycoside antibiotics. Minimum inhibitory concentrations (MICs) were determined using standard broth microdilution testing methods, such as those described in the 2016 CLSI guidelines.

[0791] Compound I-4, Cmpd E, and Cmpd B were active against *E. coli* clinical isolates with all compounds having an MIC_{90} of 2 µg/mL. In contrast, reduced susceptibility to ceftazidime, ciprofloxacin and gentamicin were observed for isolates in the panel. As compared to *E. coli*, Compound I-4, Cmpd E, and Cmpd B were less active against *Klebsiella* spp. isolates with MIC_{90}s of 8, 8 and 16 µg/mL, respectively. *Klebsiella* spp. isolates had reduced susceptibility to ceftazidime, ciprofloxacin, gentamicin and doripenem. These data indicate that the LpxC inhibitors described herein are active against *Enterobacteriaceae* clinical isolates not susceptible to other antibiotics. Results of the study are shown in Table **9**.

TABLE 9: Activity of LpxC Inhibitors Against *Escherichia coli* and *Klebsiella* spp. clinical isolates

		Compound I-4	Cmpd E	Cmpd B	Cmpd A	CAZ	CIP	GEN	DOR
E. coli clinical isolates (*n* = 20)	**MIC_{90}**	2	2	2	0.25	>32	>4	>64	0.13
	MIC_{50}	1	2	1	0.25	32	>4	4	0.03
	Range	0.12 - 4	0.25 - 4	0.25 - 8	0.06 - 0.5	0.06 - >32	≤0.004 - >4	0.5 – >64	0.03 - >8
	% susceptible[a]	n/a	n/a	n/a	n/a	20%	25%	50%	90%

		Compound I-4	Cmpd E	Cmpd B	Cmpd A	CAZ	CIP	GEN	DOR
Klebsiella spp. clinical isolates (n = 20)	**MIC_{90}**	8	8	16	1	>32	>4	>64	>8
	MIC_{50}	2	4	4	0.5	>32	2	1	0.06
	Range	1 - 32	1 - 16	2 - 16	0.12 - 1	0.25 - >32	≤0.004 - >4	0.25 - >64	0.03 - >8
	% susceptible[a]	n/a	n/a	n/a	n/a	25%	40%	58%	55%

[a] As defined by CLSI 2017 breakpoints.
CAZ=ceftazidime, CIP=ciprofloxacin, GEN=gentamicin, DOR=doripenem

Example 49. Evaluation of Resistance to LpxC Inhibitors in Spontaneous Mutation Frequency Assays Against *Pseudomonas aeruginosa*

[0792] Five *P. aeruginosa* clinical isolates were assessed in a spontaneous resistance frequency study at Micromyx. The strains were selected such that a range of LpxC inhibitor MICs were represented. Spontaneous mutants were selected for each strain on agar plates containing Compound I-4, Cmpd B, Cmpd E, or the comparator levofloxacin, each at 2x, 4x, 8x, or 16x the agar MIC. In addition to frequency, the magnitude of MIC shift conferred by each resistance mutation was determined. To assess this, colonies from each resistance selection plate were archived, passaged on drug-free plates to test for stability of the mutation, and characterized by MIC assay. A total of 98 resistant mutants were collected across all strains and selection conditions, with bias towards colonies selected with higher inhibitor concentrations. The mutants were assayed against the Compound I-4, Cmpd B, Cmpd E, plus a range of comparator antibiotics.

[0793] The wide range of resistance frequencies observed across the 5 strains for all compounds was roughly comparable to that for levofloxacin. Compound I-4 had lower overall resistance frequencies compared to the other compounds (Table **10**, FIG. **4**). At 4x the MIC, the resistance frequencies of Compound I-4 for all 5 strains were within or below the quantifiable range, while for Cmpd B, Cmpd E, and levofloxacin, 1 to 3 strains remained above the upper limit of quantitation. Similarly, at 8x the MIC for Compound I-4, 3 strains had resistance frequencies below the lower limit of quantitation, and the 2 quantifiable strains had relatively low frequencies of 7.1×10^{-9} and 3.3×10^{-10}. Levofloxacin had a similar profile at 8x the MIC, with 3 strains below the limit of quantitation and the other strains had mutation frequencies of and 5.2×10^{-8} and 3.1×10^{-9}. In contrast, only 2 strains had below the limit of quantitation at 8x the MIC,

and the frequencies for the quantifiable strains were generally higher than for Compound I-4 (~10^{-8} for 5 of 6 data points).

TABLE 10: Spontaneous Resistance Frequencies of Five *P. aeruginosa* Clinical Isolates against Compound I-4, Cmpd B, Cmpd E and Levofloxacin

Compound	Selection (fold over MIC)	Frequency of spontaneous resistance				
		Strain MMX 6469	Strain MMX 7752	Strain MMX 7763	Strain MMX 7871	Strain MMX 7880
Compound I-4	2X	6.7×10^{-8}	$>9.0 \times 10^{-8}$	$>8.33 \times 10^{-8}$	4.9×10^{-9}	1.2×10^{-8}
	4X	9.6×10^{-9}	4.0×10^{-8}	4.9×10^{-8}	$<2.6 \times 10^{-10}$	$<1.2 \times 10^{-10}$
	8X	$<1.8 \times 10^{-10}$	7.1×10^{-9}	3.3×10^{-10}	$<2.6 \times 10^{-10}$	$<1.2 \times 10^{-10}$
	16X	$<1.8 \times 10^{-10}$	$<1.8 \times 10^{-10}$	$<1.7 \times 10^{-10}$	$<2.6 \times 10^{-10}$	$<1.2 \times 10^{-10}$
Cmpd B	2X	$>9.0 \times 10^{-8}$	$>9.0 \times 10^{-8}$	$>8.3 \times 10^{-8}$	3.0×10^{-8}	6.2×10^{-9}
	4X	$>9.0 \times 10^{-8}$	$>9.0 \times 10^{-8}$	$>8.3 \times 10^{-8}$	$<2.6 \times 10^{-10}$	2.5×10^{-10}
	8X	1.7×10^{-8}	1.9×10^{-8}	5.0×10^{-8}	$<2.6 \times 10^{-10}$	$<1.2 \times 10^{-10}$
	16X	$<1.8 \times 10^{-10}$	$<1.8 \times 10^{-10}$	$<1.7 \times 10^{-10}$	$<2.6 \times 10^{-10}$	$<1.2 \times 10^{-10}$
Cmpd E	2X	$>6.9 \times 10^{-8}$	$>9.0 \times 10^{-8}$	$>6.7 \times 10^{-8}$	3.6×10^{-8}	5.3×10^{-9}
	4X	6.4×10^{-8}	7.1×10^{-8}	$>6.7 \times 10^{-8}$	$<2.6 \times 10^{-10}$	1.2×10^{-10}
	8X	4.2×10^{-10}	2.9×10^{-8}	3.2×10^{-8}	$<2.6 \times 10^{-10}$	$<1.2 \times 10^{-10}$
	16X	6.9×10^{-10}	$<1.8 \times 10^{-10}$	1.5×10^{-9}	$<2.6 \times 10^{-10}$	$<1.2 \times 10^{-10}$
Levofloxacin	2X	7.6×10^{-8}	$>9.1 \times 10^{-8}$	$>8.3 \times 10^{-8}$	5.1×10^{-10}	2.5×10^{-10}
	4X	3.6×10^{-10}	3.4×10^{-8}	$>8.3 \times 10^{-8}$	$<2.6 \times 10^{-10}$	$<1.2 \times 10^{-10}$
	8X	$<1.8 \times 10^{-10}$	3.1×10^{-9}	5.2×10^{-8}	$<2.6 \times 10^{-10}$	$<1.2 \times 10^{-10}$
	16X	$<1.8 \times 10^{-10}$	$<1.8 \times 10^{-10}$	$<1.7 \times 10^{-10}$	$<2.6 \times 10^{-10}$	$<1.2 \times 10^{-10}$

[0794] An overview of the MIC shifts for the compounds is presented in FIG. **5**. For the majority of mutants, MIC shifts were low to moderate (≤16-fold) for all Compound I-4, Cmpd B, and Cmpd E. The overall distribution of MIC shifts is lower for Compound I-4 (histogram peaks at 2- to 4-fold shifts) compared to Cmpd B and Cmpd E (peaks at 8- to 16-fold shifts). A few mutants showed MIC shifts of 32- to 64-fold for all leads. The phenotype of all but 1 of these mutants matches the profile of a known resistance mutation upstream of the LpxC coding region,

which results in overexpression of the LpxC enzyme. The remaining mutant has a novel phenotype which includes cross-resistance to ceftazidime and levofloxacin and warrants further investigation.

[0795] One mutant showed extremely high MIC shifts of >128-fold against all LpxC inhibitors, plus cross-resistance to aztreonam and ceftazidime, but appeared to be unstable, because resistance was lost after passaging on drug-free plates.

[0796] The overall spontaneous resistance profiles for Compound I-4, Cmpd B, and Cmpd E are promising, with no mutants displaying sustained, high-level resistance. The resistance profile of Compound I-4 is particularly notable, showing the lowest overall resistance frequency, plus a trend toward lower MIC shifts, compared to Cmpd B and Cmpd E.

Example 50. Activity of Cmpd E, Cmpd B, and Compound I-4 against *Yersinia pestis, Francisella tularensis, Burkholderia mallei* and *Burkholderia pseudomallei*

[0797] The *in vitro* activity of compounds was assessed using broth microdilution testing against four BSL3 pathogens in the laboratory of Dr. Hank Heine at the University of Florida. Minimal inhibitory concentration (MIC) values for Compound I-4, Cmpd E, and Cmpd B were determined using standard broth microdilution methods against *Yersinia pestis* (CO92 strain), *Francisella tularensis* (ShuS4 strain), *Burkholderia mallei* (China7 strain), and *Burkholderia pseudomallei* (1026b strain).

[0798] Compound I-4 was active against all four tested pathogens with MICs ranging from 0.5–8 μg/mL. By comparison, Cmpd E and Cmpd B each had MICs ≤ 16 μg/mL against 3 of 4 BSL3 pathogens tested. Cmpd E had an MIC of 4 μg/mL against *Y. pestis*, *B. mallei* and *B. pseudomallei*. Cmpd B had MICs of 1, 2 and 8 μg/mL against *B. mallei*, *B. pseudomallei* and *Y. pestis*, respectively. The results are shown in Table **11**.

TABLE 11: Activity of compounds against BSL3 pathogens

Compound	MIC (μg/mL)			
	***Y. pestis* (CO92)**	***F. tularensis* (ShuS4)**	***B. mallei* (China7)**	***B. pseudomallei* (1026b)**
Compound I-4	2	8	0.5	1
Cmpd B	8	32	1	2
Cmpd E	4	32, >32*	4	4

* Duplicates provided two different values.

Example 51. Efficacy of Compounds in Mice

[0799] *In vivo* efficacy of Compound I-4 was assessed in neutropenic mouse thigh infection and neutropenic mouse lung infection models using two *P. aeruginosa* isolates: the laboratory strain ATCC 27853 and the multi-drug resistant isolate originating from a cystic fibrosis (CF) patient, LES 431. Compound I-4 was dosed QID and QD. Dosing was started 2 hours after inoculation; mice were sacrificed and tissue was collected for CFU counts 24h after initiation of dosing. Seven dose levels were evaluated in the study (1.2-300 mg/kg/day for ATCC27853 and 0.49-120 mg/kg/day for LES 431). Gentamicin 30 mg/kg intravenous BID (thigh) and 10 mg/kg subcutaneous BID (lung) was used as a positive control for ATCC 27853. Colistin 5 mg/kg subcutaneous BID (thigh) and 5 and 10 mg/kg subcutaneous BID (lung) was used as a positive control for LES 431.

[0800] In a follow-up set of studies, 3 *P. aeruginosa* clinical isolates were evaluated in the neutropenic mouse lung model to confirm the *in vivo* efficacy of Compound I-4. One multi-drug resistant isolate originating from a CF patient (ACH-02) and two isolates originating from non-CF patients (ACH-04 and ACH-02) were tested. Seven different QD IV doses of Compound I-4 were assessed (0.45-450 mg/kg/day). As in the initial study dosing was started 2 hours after inoculation; lungs tissue was harvested and homogenized for CFU counts 24h after initiation of dosing. Colistin 10 mg/kg dosed subcutaneously BID was used as a positive control.

[0801] Non-linear four-parameter curve fitting was used to determine the doses needed to achieve stasis, 1-$\log_{10}$ kill and 2-$\log_{10}$ kill for all isolates tested in the neutropenic mouse lung infection model.

[0802] *In vivo* efficacy data for Compound I-4 is summarized in FIG. **6A-6B** (thigh model) and FIG. **7A-7B** (lung model). Dose-dependent decreases in bacterial load were observed against both isolates in the thigh and lung efficacy models. QD dosing of Compound I-4 resulted in greater efficacy compared to QID dosing as determined by the dose (mg/kg/day) necessary to achieve stasis, 1-log kill, and 2-log kill in both infection models. The *in vivo* clinical isolate efficacy data is summarized in FIG. **8**. Stasis, 1-log kill and 2-log kill were achieved for the *P. aeruginosa* clinical isolates ACH-02 and ACH-06 for the assessed dose ranges.

[0803] Non-linear four-parameter curve fitting was used to determine the doses needed to achieve stasis, 1-$\log_{10}$ kill and 2-$\log_{10}$ kill for all isolates tested in the neutropenic mouse lung infection model. Data is summarized in Table **12**. Within the respective Compound I-4 dose

ranges tested, 1-$\log_{10}$ kill was achievable for 5 of 6 isolates at the doses tested and 2-$\log_{10}$ kill was achievable for 4 of 6 isolates. These data indicate that Compound I-4 can achieve a 2-$\log_{10}$ kill *in vivo* against *P. aeruginosa.*

TABLE 12: Compound I-4 dose to achieve stasis, 1-$\log_{10}$ kill and 2-$\log_{10}$ kill against *Pseudomonas aeruginosa* isolates in a neutropenic mouse lung infection efficacy model

Isolate	Origin	Compound I-4 MIC (μg/mL)	Stasis Dose (mg/kg/day)	1-$\log_{10}$ Kill Dose (mg/kg/day)	2-$\log_{10}$ Kill Dose (mg/kg/day)
ACH-02	CF	0.5	4	12	35
LES 431	CF	0.125	2	2	3
ACH-04	Non-CF	1	62	118	>450*
ACH-06	Non-CF	2	55	86	159
ATCC 27853	Non-CF	2	~200*	~250*	~300*

* Insufficient dose range tested to accurately determine value.
Abbreviation: CF, cystic fibrosis; MIC, minimal inhibitory concentration

Example 52. PK/PD analysis of Compounds against *Pseudomonas aeruginosa* in murine infection models

[0804] Compound I-4 PK/PD analyses were conducted for data obtained from the neutropenic mouse thigh and lung models using *P. aeruginosa* isolates ATCC 27853 and LES 431. Efficacy data was obtained using both QD and QID dosing and *f*AUC:MIC, *f*C_{max}:MIC, and *f*T>MIC values were calculated for each regimen. The relationships between PK/PD indices and PD responses at 24h (change of CFU from the baselines) were described by an inhibitory sigmoid E_{max} model (GraphPad Prism 7, [Inhibitor] vs. response -- Variable slope, as shown below). Compound I-4 was the only compound studied using a dose fractionation design, so data for that compound was used to determine the best PK/PD index for LpxC inhibitors. In addition, the PK/PD magnitudes of all compounds were assessed based on the determined PK/PD index (stasis, 1-$\log_{10}$ kill or 2-$\log_{10}$ kill).

[0805] The r^2 values obtained for each index are shown in Table **13** and Table **14**. Higher r^2 values were obtained using *f*AUC:MIC and *f*C_{max}:MIC as compared to *f*T>MIC. The r^2 values for *f*AUC:MIC and *f*C_{max}:MIC were comparable for each model indicating that *f*AUC:MIC and *f*C_{max}:MIC are both potential drivers of the Compound I-4 PK/PD relationship.

TABLE 13: Compound I-4 r^2 Values for PK/PD Indices in the Neutropenic Mouse Lung Infection Model

Mouse Lung Data Set	**r^2 Value**		
	***f*AUC:MIC**	***f*C_{max}:MIC**	***f*T>MIC**
ATCC 27853 and LES 431 Combined	0.72	0.76	0.61
LES 431	0.89	0.76	0.65

TABLE 14: Compound I-4 r^2 Values for PK/PD Indices in the Neutropenic Mouse thigh Infection Model

Mouse Thigh Data Set	**r^2 Value**		
	***f*AUC:MIC**	***f*C_{max}:MIC**	***f*T>MIC**
ATCC 27853 and LES 431 Combined	0.87	0.87	0.77
LES 431	0.88	0.94	0.77

[0806] The Compound I-4 exposures required for stasis, 1-log_{10} kill and 2-log_{10} kill were calculated for both *f*C_{max}:MIC and *f*AUC:MIC. Data are summarized in Table **15** and Table **16**. Similar values were obtained for each data set using the lung and thigh models. Slightly lower values were calculated using only the LES 431 efficacy data versus the combined ATCC 27853/LES 431 data set.

TABLE 15: Calculated *f*C_{max}:MIC values for Compound I-4 in mouse efficacy models using *Pseudomonas aeruginosa*

Model	**Data Set**	***f*C_{max}:MIC**		
		Stasis	**1-log kill**	**2-log kill**
Thigh	Combined	9.6	13.1	18.8
	LES 431	6.5	9.0	12.9
Lung	Combined	10.2	15.9	25.1
	LES 431	6.5	8.1	10.0

TABLE 16: Calculated *f*AUC:MIC values for Compound I-4 in mouse efficacy models using *Pseudomonas aeruginosa*

Model	**Data Set**	***f*AUC:MIC**		
		Stasis	**1-log kill**	**2-log kill**
Thigh	Combined	8.4	11.9	17.7
	LES 431	5.2	8.2	13.5
Lung	Combined	8.7	14.6	23.8
	LES 431	3.8	7.1	12.4

[0807] The results of the PK/PD analysis for Compound I-4 suggest that both fC$_{max}$/MIC and fAUC/MIC need to be considered as drivers of the PK/PD response.

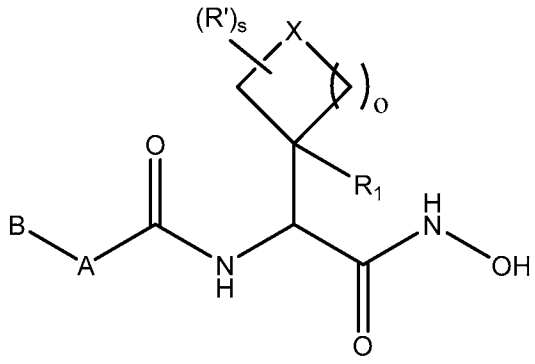
Equivalents

[0808] Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific embodiments described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,

wherein:

X is $S(O)_q$ or NR_6;

A is (C_6-C_{10}) aryl, heteroaryl, (C_3-C_7) cycloalkyl, (C_4-C_7) cycloalkenyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, cycloalkenyl, or heterocycloalkyl is optionally substituted with one or more R_7;

B is –C≡C—R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, -OR_8, -$S(O)_rR_8$, halogen, (C_6-C_{10}) aryl, heteroaryl, or –SF_5, wherein the aryl or heteroaryl is optionally substituted with R_2;

R_1 is H, (C_1-C_4) alkyl, (C_2-C_4) alkenyl, (C_2-C_4) alkynyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$(CH_2)_m$heterocycloalkyl, -$O(CH_2)_m$(C_3-C_7) cycloalkyl, -$O(CH_2)_m$heterocycloalkyl, halogen, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_nNH_2$,-$(CH_2)_n$(C_1-C_4) alkylamino, or -$(CH_2)_n$(C_1-C_4) dialkylamino;

R_2 is (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, halogen, -OH, -NH_2, or -CN;

R_3 is H, (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl, heterocycloalkyl, or heteroaryl, wherein the alkyl is optionally substituted with one or more R_4, and wherein the cycloalkyl, heterocycloalkyl, or heteroaryl is optionally substituted with one or more R_5;

each R_4 is independently at each occurrence -OH, -NH_2, (C_1-C_4) alkoxy, (C_1-C_4) alkylamino, or (C_1-C_4) dialkylamino;

each R_5 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, halogen, (C_1-C_4) hydroxyalkyl, –C(O)H, –C(=O)(C_1-C_4) alkyl, -OH, -NH_2, (C_1-C_4) alkylamino, (C_1-C_4) dialkylamino, or -$S(O)_p$(C_1-C_4)alkyl;

R_6 is H, (C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -C(O)H, -C(O)(C_1-C_4) alkyl, -$S(O)_r$(C_1-C_4) alkyl, or -C(O)O(C_1-C_4) alkyl;

each R_7 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or halogen; or

two R_7 on adjacent atoms together with the atoms to which they are attached form a (C_6-C_{10}) aryl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a heteroaryl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a (C_4-C_8) cycloalkyl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a heterocycloalkyl ring optionally substituted with one or more R_9;

R_8 is (C_1-C_4) alkyl, (C_2-C_4) alkenyl, (C_2-C_4) alkynyl, (C_1-C_4) haloalkyl, or (C_3-C_6) cycloalkyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more substituents selected from the group consisting of (C_3-C_7) cycloalkyl and heterocycloalkyl;

each R_9 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or halogen;

each R' is (C_1-C_4) alkyl;

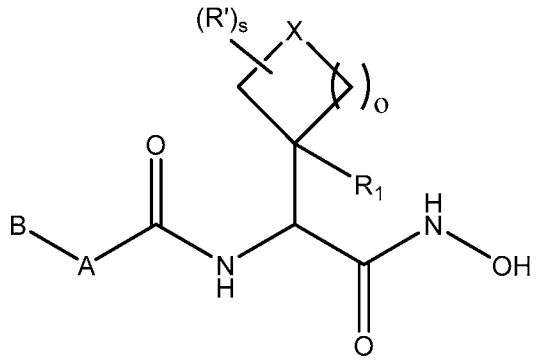
o is 1 or 2;

s is 0, 1, or 2;

each q, p, and r is independently at each occurrence 0, 1, or 2; and

each m and n is independently at each occurrence 0, 1, 2, or 3.

2. A compound of Formula (II), wherein the compound is a prodrug of a compound of Formula (I) as claimed in claim 1:



(II),

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, wherein:

X is $S(O)_q$ or NR_6;

A is (C_6-C_{10}) aryl, heteroaryl, (C_3-C_7) cycloalkyl, (C_4-C_7) cycloalkenyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, cycloalkenyl, or heterocycloalkyl is optionally substituted with one or more R_7;

B is –C≡C—R_3 or –C≡C–C≡C–R_3;

R_1 is H, (C_1-C_4) alkyl, (C_2-C_4) alkenyl, (C_2-C_4) alkynyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, -$(CH_2)_m$(C_3-C_7) cycloalkyl, -$(CH_2)_m$heterocycloalkyl, -O$(CH_2)_m$(C_3-C_7) cycloalkyl, -O(CH_2)mheterocycloalkyl, halogen, -$S(O)_p$(C_1-C_4)alkyl, -OH, -$(CH_2)_n$$NH_2$,-$(CH_2)_n$($C_1$-$C_4$) alkylamino, or -$(CH_2)_n$($C_1$-$C_4$) dialkylamino;

R_3 is (C_1-C_4) alkyl substituted with one or more Q;

R_6 is H, (C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -C(O)H, -C(O)(C_1-C_4) alkyl, -$S(O)_r$(C_1-C_4) alkyl, or -C(O)O(C_1-C_4) alkyl;

each R_7 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or halogen; or

two R_7 on adjacent atoms together with the atoms to which they are attached form a (C_6-C_{10}) aryl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together

with the atoms to which they are attached form a heteroaryl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a (C_4-C_8) cycloalkyl ring optionally substituted with one or more R_9; or two R_7 on adjacent atoms together with the atoms to which they are attached form a heterocycloalkyl ring optionally substituted with one or more R_9;

each R_9 is independently at each occurrence (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or halogen;

each R' is (C_1-C_4) alkyl;

o is 1 or 2;

s is 0, 1, or 2;

each q, p, and r is independently at each occurrence 0, 1, or 2;

each m and n is independently at each occurrence 0, 1, 2, or 3;

each Q is independently at each occurrence $-OP(=O)(OH)_2$, $-OCH_2OP(=O)(OH)_2$, $-OC(=O)R_a$, or $-OCH_2OC(=O)R_a$;

R_a is (C_1-C_{10}) alkyl, (C_3-C_7) cycloalkyl, or heterocycloalkyl, wherein the alkyl, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, $-CO_2H$, $-SO_3H$, $-NHC(NH)NH_2$, and $-OP(=O)(OH)_2$; and

wherein Q is a cleavable group.

3. The compound of claim 2, wherein Q is $-OP(=O)(OH)_2$ or $-OCH_2OP(=O)(OH)_2$.

4. The compound of claim 2 or 3, wherein Q is $-OP(=O)(OH)_2$.

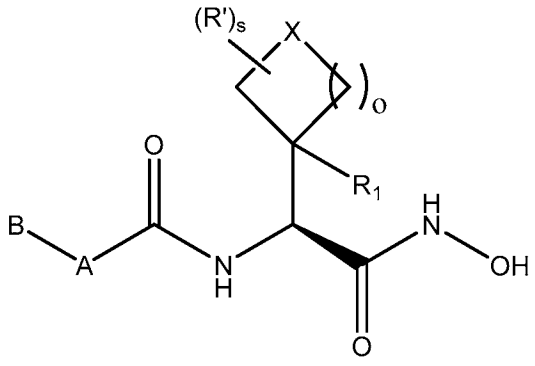
5. The compound of claim 2, wherein Q is $-OC(=O)R_a$ or $-OCH_2OC(=O)R_a$.

6. The compound of claim 2 or 5, wherein R_a is (C_1-C_{10}) alkyl optionally substituted with one or more substituents independently selected from the group consisting of -OH, $-NH_2$, $-CO_2H$, $-SO_3H$, $-NHC(NH)NH_2$, and $-OP(=O)(OH)_2$.

7. The compound of claim 2, 5, or 6, wherein R_a is (C_1-C_{10}) alkyl optionally substituted with one or more substituents independently selected from the group consisting of -NHC(NH)NH_2 and –NH_2.

8. The compound of claim 2 or 5, wherein R_a is (C_3-C_7) cycloalkyl or heterocycloalkyl, wherein the (C_3-C_7) cycloalkyl or heterocycloalkyl is optionally substituted with one or more substituents independently selected from the group consisting of -OH, -NH_2, -CO_2H, -SO_3H, -NHC(NH)NH_2, and -OP(=O)$(OH)_2$.

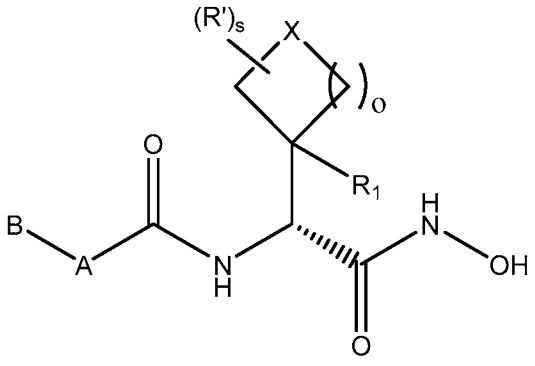
9. The compound of any one of claims 1 to 8, having Formula (Ia):



(Ia),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

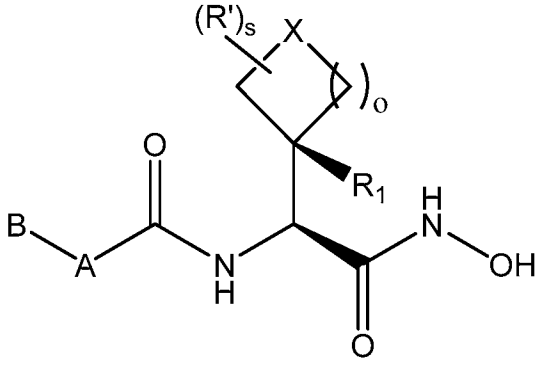
10. The compound of any one of claims 1 to 8, having Formula (Ib):



(Ib),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

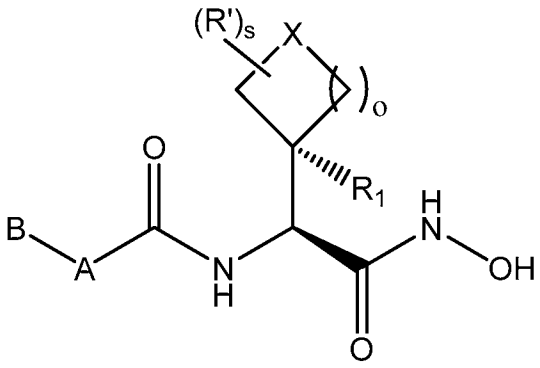
11. The compound of any one of claims 1 to 9, having Formula (Ic):



(Ic),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

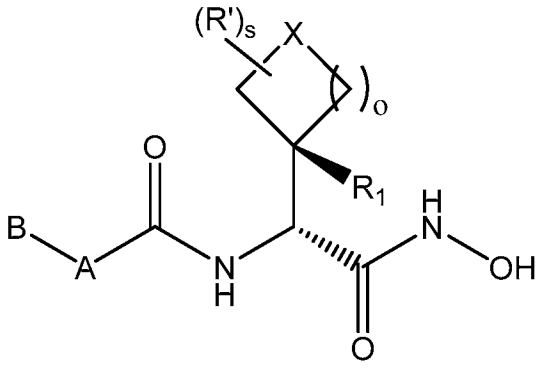
12. The compound of any one of claims 1 to 9, having Formula (Id):



(Id),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

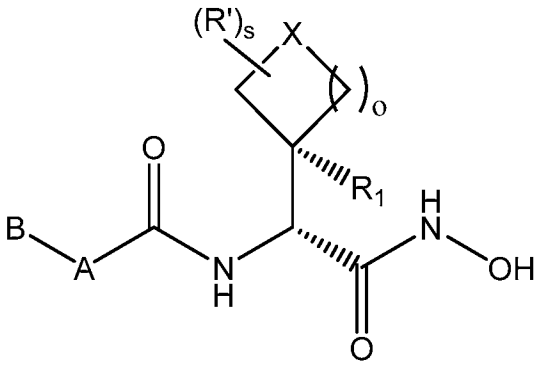
13. The compound of any one of claims 1 to 8, or 10, having Formula (Ie):



(Ie),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

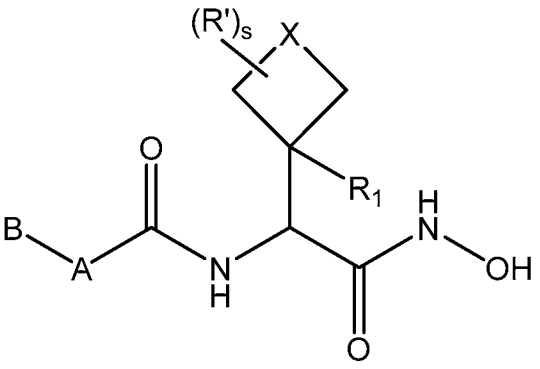
14. The compound of any one of claims 1 to 8, or 10, having Formula (If):



(If),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

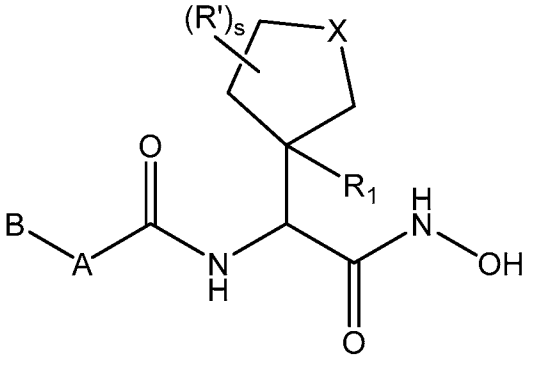
15. The compound of any one of claims 1 to 8, or 10, having Formula (Ig):



(Ig),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

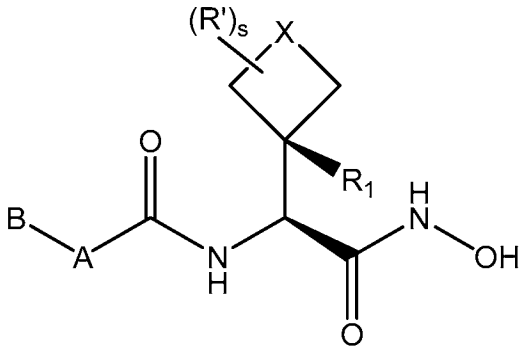
16. The compound of any one of claims 1 to 8, having Formula (Ih):



(Ih),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

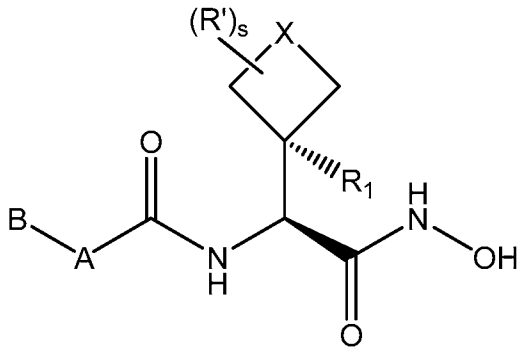
17. The compound of any one of claims 1 to 9, 11, or 15, having Formula (Ij):



(Ij),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

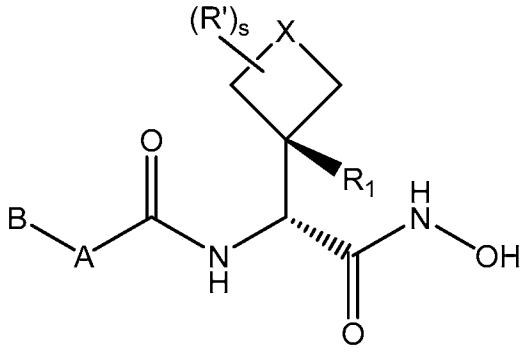
18. The compound of any one of claims 1 to 9, 12, or 15, having Formula (Ii):



(Ii),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

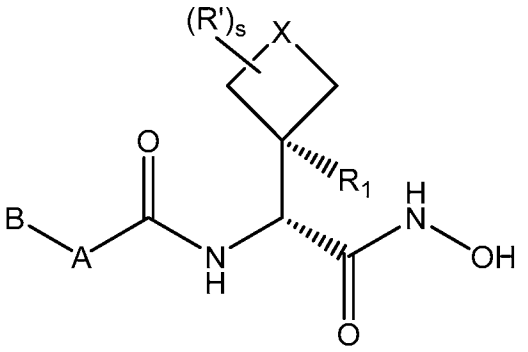
19. The compound of any one of claims 1 to 8, 10, 13, or 15, having Formula (Il):



(Il),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

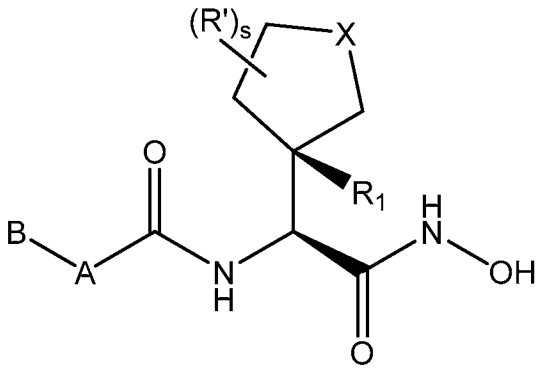
20. The compound of any one of claims 1 to 8, 10, 14, or 15, having Formula (Ik):



(Ik),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

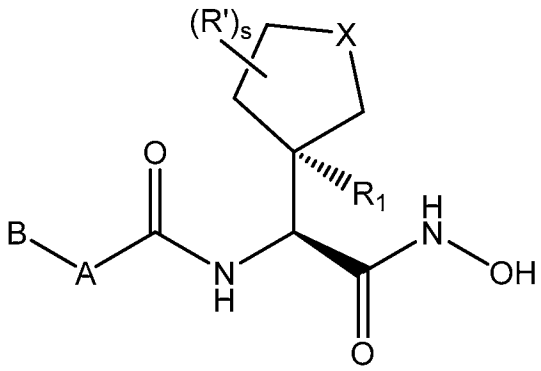
21. The compound of any one of claims 1 to 9, 12, or 16, having Formula (Im):



(Im),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

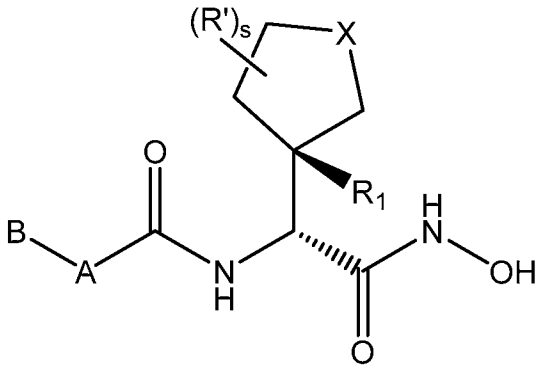
22. The compound of any one of claims 1 to 9, 11, or 16, having Formula (Io):



(Io),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

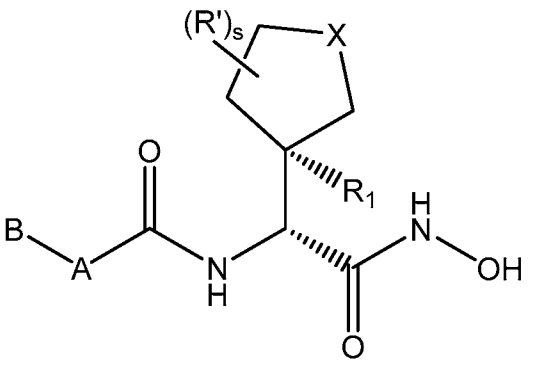
23. The compound of any one of claims 1 to 8, 10, or 16, having Formula (Ip):



(Ip),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

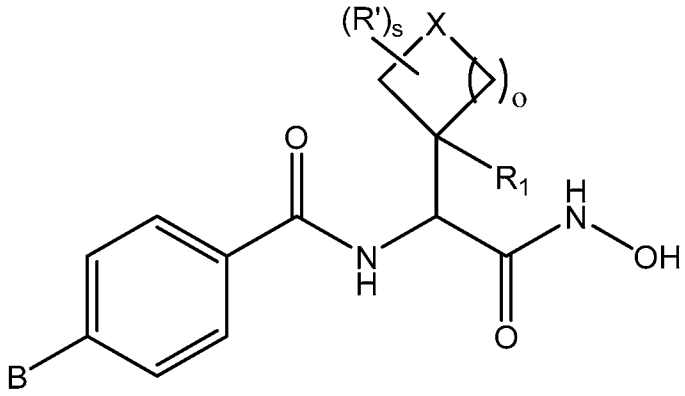
24. The compound of any one of claims 1 to 8, 10, or 16, having Formula (Iq):



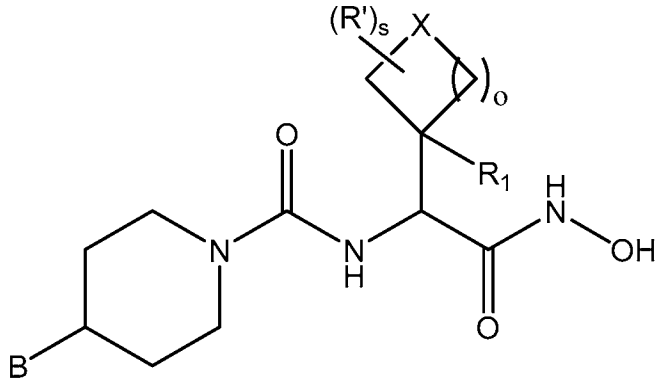
(Iq),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

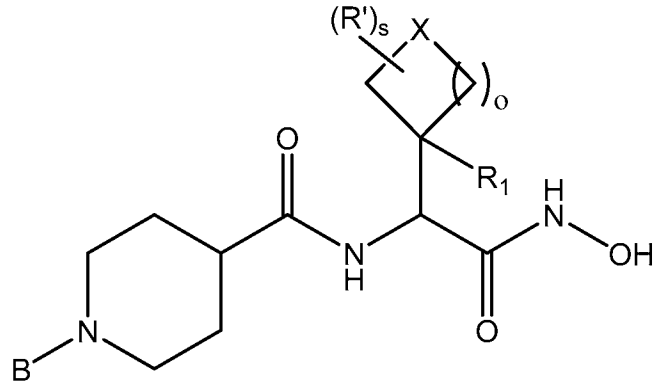
25. The compound of any one of claims 1 to 8, having Formula (Ir), Formula (Iu), Formula (Iv), Formula (Ix), or Formula (Iy):



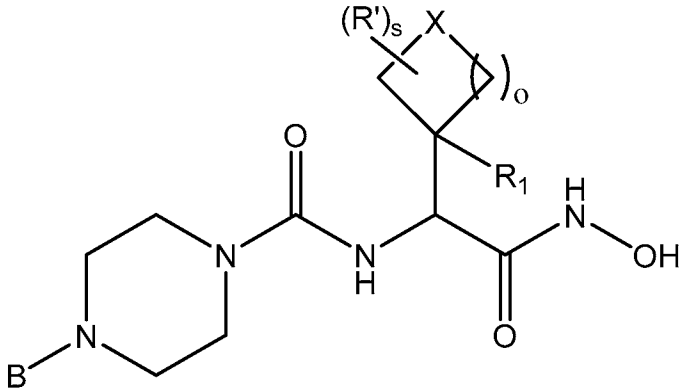
(Ir),



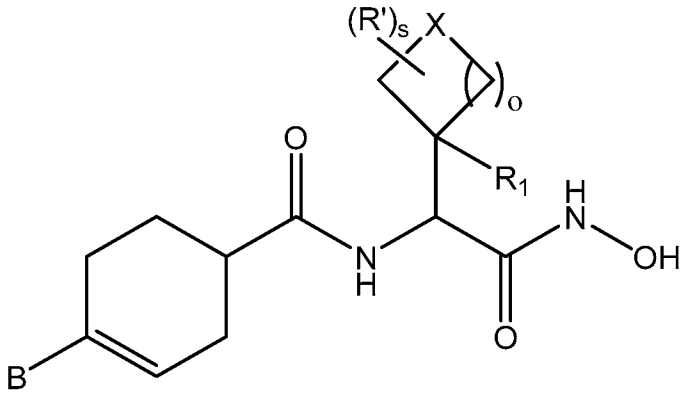
(Iu),



(Iv),



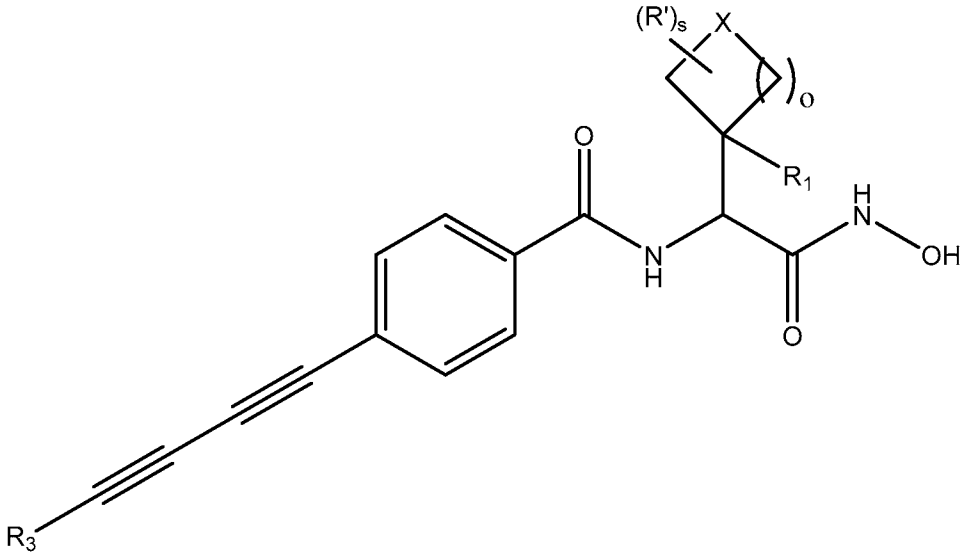
(Ix), or



(Iy),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

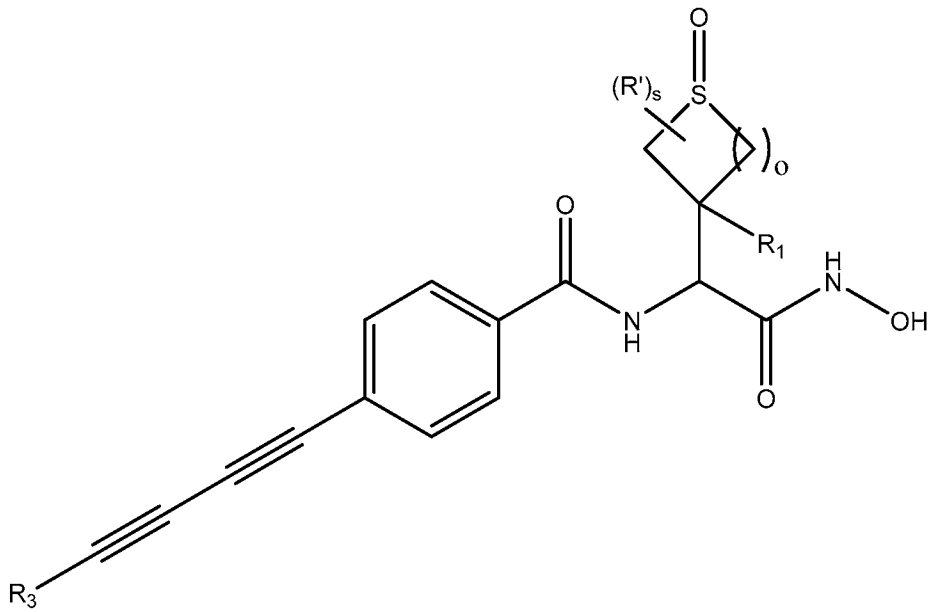
26. The compound of any one of claims 1 to 8, or 25, having Formula (Iz):



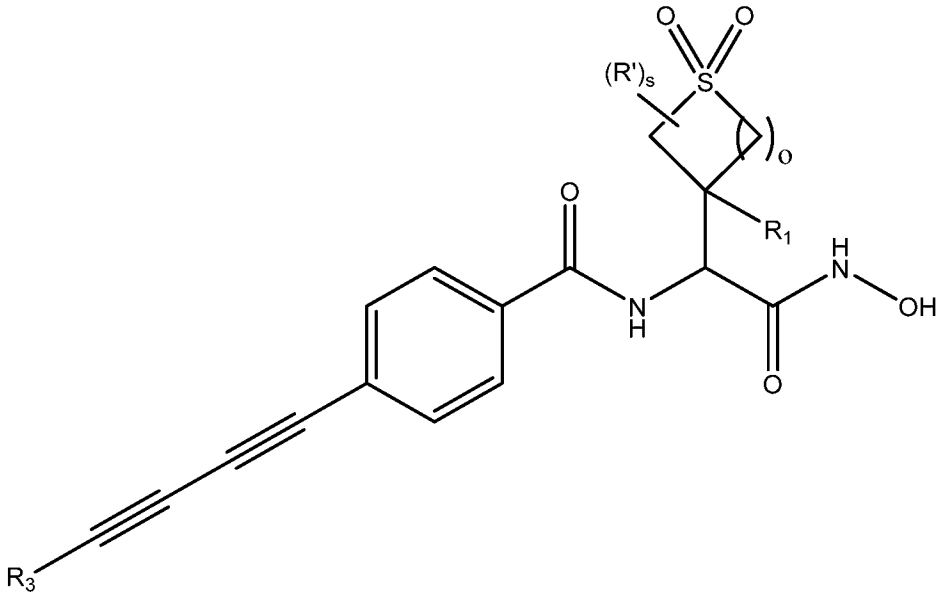
(Iz),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

27. The compound of any one of claims 1 to 8, 25, or 26, having Formula (Iaa) or Formula (Ibb):



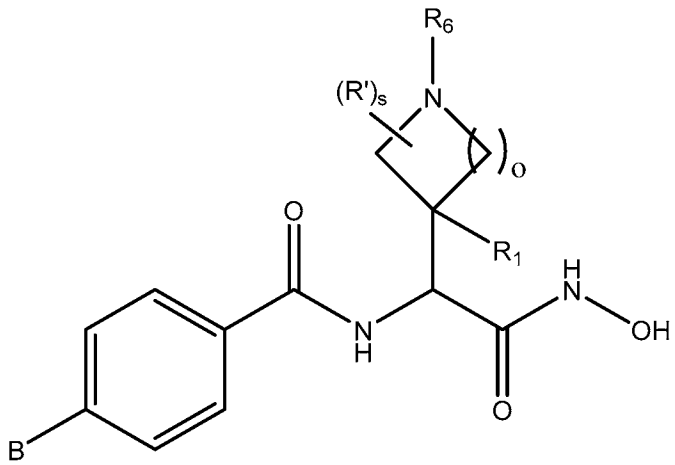
(Iaa),



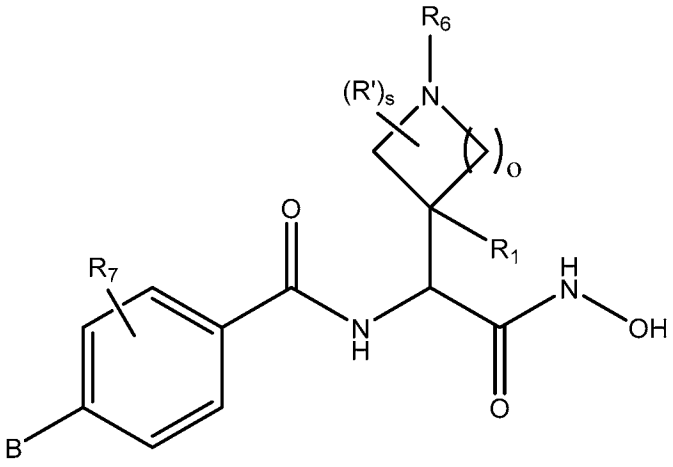
(Ibb),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

28. The compound of any one of claims 1 to 8, or 25, having Formula (Icc) or Formula (Idd):



(Icc), or



(Idd),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

29. The compound of any one of claims 1 to 24, wherein A is (C_6-C_{10}) aryl, (C_4-C_7) cycloalkenyl, or heterocycloalkyl, wherein the aryl, cycloalkenyl, or heterocycloalkyl is optionally substituted with one or more R_7.

30. The compound of any one of claims 1 to 24, or 29, wherein A is (C_6-C_{10}) aryl, wherein the aryl is optionally substituted with one or more R_7.

31. The compound of any one of claims 1 to 24, 29, or 30, wherein A is phenyl, cyclohexenyl, piperazinyl, or piperidinyl, wherein the phenyl, cyclohexenyl, piperazinyl, or piperadinyl is optionally substituted with one or more R_7.

32. The compound of any one of claims 1 to 25, or 28 to 31, wherein B is –C≡C–R_3, –C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, (C_1-C_4) haloalkyl, -OR_8, -S(O)$_r$$R_8$, halogen, ($C_6$-$C_{10}$) aryl, or –$SF_5$, wherein the aryl or heteroaryl is optionally substituted with R_2.

33. The compound of any one of claims 1, 9 to 25, or 28 to 32, wherein r is 0 or 2.

34. The compound of any one of claims 1, 9 to 25, or 28 to 32, wherein B is –C≡C—R_3, -C≡C–C≡C–R_3, –C≡C–CH=CH–R_3, (C_6-C_{10}) aryl, or –SF_5, wherein the aryl is optionally substituted with R_2.

35. The compound of any one of claims 1, 9 to 25, or 28 to 32, wherein B is phenyl or –C≡C–C≡C–R_3, wherein the phenyl is optionally substituted with R_2.

36. The compound of any one of claims 1 or 9 to 35, wherein R_3 is H, (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl, or heterocycloalkyl, wherein the alkyl is optionally substituted with one or more R_4, and the cycloalkyl or heterocycloalkyl is optionally substituted with one or more R_5.

37. The compound of any one of claims 1 or 9 to 36, wherein R_3 is (C_1-C_4) alkyl optionally substituted with one or more R_4.

38. The compound of any one of claims 1 or 9 to 37, wherein R_3 is methyl, ethyl, or propyl, wherein the methyl, ethyl, or propyl is optionally substituted with one or more R_4.

39. The compound of any one of claims 1 or 9 to 38, wherein R_4 is independently at each occurence -OH, or (C_1-C_4) alkoxy.

40. The compound of any one of claims 1 or 9 to 36, wherein R_3 is (C_3-C_7) cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is optionally substituted with one or more R_5.

41. The compound of any one of claims 1 or 9 to 40, wherein R_5 is independently at each occurence (C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, –C(O)H, or –C(=O)(C_1-C_4) alkyl.

42. The compound of any one of claims 1 or 9 to 41, wherein R_5 is independently at each occurence (C_1-C_4) hydroxyalkyl, –C(O)H, or –C(=O)(C_1-C_4) alkyl.

43. The compound of any one of claims 1, 9 to 25, 28 to 32, 34, or 35, wherein R_2 is halogen.

44. The compound of any one of claims 1, 9 to 25, or 28 to 33, wherein R_8 is (C_1-C_4) alkyl or (C_1-C_4) haloalkyl.

45. The compound of any one of claims 1 to 26, or 29 to 44, wherein X is S(O).

46. The compound of any one of claims 1 to 26, or 29 to 44, wherein X is $S(O)_2$.

47. The compound of any one of claims 1 to 26, or 29 to 44, wherein X is NR_6.

48. The compound of claim 47, wherein R_6 is H, (C_1-C_4) alkyl, or (C_1-C_4) hydroxyalkyl.

49. The compound of claim 47, wherein R_6 is -C(O)H, -C(O)(C_1-C_4) alkyl, -S(O)$_r$(C_1-C_4) alkyl, or -C(O)O(C_1-C_4) alkyl.

50. The compound of any one of claims 1 to 14 or 25 to 49, wherein o is 1.

51. The compound of any one of claims 1 to 14 or 25 to 49, wherein o is 2.

52. The compound of any one of claims 1 to 51, wherein R_1 is H, (C_1-C_4) alkyl, (C_2-C_4) alkenyl, (C_2-C_4) alkynyl, (C_1-C_4) alkoxy, -(CH_2)$_m$(C_3-C_7) cycloalkyl or -O(CH_2)$_m$(C_3-C_7) cycloalkyl, -S(O)$_p$(C_1-C_4)alkyl, -OH, -(CH_2)$_n$$NH_2$, -($CH_2$)$_n$($C_1$-$C_4$) alkylamino, or -($CH_2$)$_n$($C_1$-$C_4$) dialkylamino.

53. The compound of any one of claims 1 to 52, wherein p is 0 or 2.

54. The compound of any one of claims 1 to 52, wherein n is 0 or 1.

55. The compound of any one of claims 1 to 52, wherein m is 0 or 1.

56. The compound of any one of claims 1 to 52, wherein R_1 is (C_1-C_4) alkyl, (C_2-C_4) alkenyl, or (C_2-C_4) alkynyl.

57. The compound of any one of claims 1 to 52, wherein R_1 is (C_1-C_4) alkoxy.

58. The compound of any one of claims 1 to 57, wherein s is 1 or 2.

59. The compound of any one of claims 1 to 58, wherein each R' is independently (C_1-C_2) alkyl.

60. The compound of any one of claims 1 to 57, wherein s is 0.

61. The compound of claim 1, selected from the group consisting of:

N-(1-(3-hydroxy-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

(R)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

(S)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

4-(azetidin-3-ylbuta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;

4-((1-formylazetidin-3-yl)buta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;

N-(1-(3-ethoxy-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

4-((1-acetylazetidin-3-yl)buta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhepta-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(((1R,2R)-2-(hydroxymethyl)cyclopropyl)buta-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-methoxyhexa-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-(methylthio)-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(1-(3-amino-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-(methylamino)-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(1-(3-(dimethylamino)-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(1-(3-hydroxy-1-oxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1-oxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-phenylpiperazine-1-carboxamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-phenylpiperidine-1-carboxamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-1-phenylpiperidine-4-carboxamide;

4-((S)-5,6-dihydroxyhexa-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;

4-((S)-6,7-dihydroxyhepta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;

4-((R)-6,7-dihydroxyhepta-1,3-diyn-1-yl)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)benzamide;

N-(1-(1,1-dioxido-3-vinylthietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

(S)-N-(1-(3-ethyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

(S)-N-(1-(3-cyclopropyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(1-(3-ethynyl-1,1-dioxidothietan-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

(S)-N-(2-(hydroxyamino)-1-(3-methyl-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-((S)-2-(hydroxyamino)-1-((R)-3-methoxy-1,1-dioxidotetrahydrothiophen-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-((S)-2-(hydroxyamino)-1-((S)-3-methoxy-1,1-dioxidotetrahydrothiophen-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

(Z)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhex-3-en-1-yn-1-yl)benzamide;

(E)-N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhex-3-en-1-yn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-((1-methylazetidin-3-yl)buta-1,3-diyn-1-yl)benzamide;

(S)-N-(1-(3-((dimethylamino)methyl)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(2-(hydroxyamino)-2-oxo-1-(3-propoxyazetidin-3-yl)ethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(1-(3-(cyclopropylmethoxy)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(S)-N-(1-(3-ethynylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-((S)-2-(hydroxyamino)-1-((2R,3S)-3-methoxy-2-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(2-(hydroxyamino)-1-((2S,3S)-3-methoxy-2-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(S)-N-(2-(hydroxyamino)-1-(3-methylazetidin-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;

N-((R)-2-(hydroxyamino)-1-((2S,3S)-3-methoxy-2-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(S)-N-(2-(hydroxyamino)-2-oxo-1-(3-vinylazetidin-3-yl)ethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(R)-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(S)-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-((S)-1-((2S,3S)-3-hydroxy-2-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-((R)-1-((2S,3S)-3-hydroxy-2-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(S)-N-(1-(3-cyclopropylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(S)-N-(1-(3-ethylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-((S)-1-((2R,3R)-3-hydroxy-2-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(2-(hydroxyamino)-1-(3-(methylthio)azetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-((R)-1-((2R,3R)-3-hydroxy-2-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

3-fluoro-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethyl)benzamide;

3-fluoro-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethoxy)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-((trifluoromethyl)thio)benzamide;

2-fluoro-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethyl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethyl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethoxy)benzamide;

2-fluoro-N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(trifluoromethoxy)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1-methylazetidin-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-(methylamino)azetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(1-(3-ethoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-ethynylbenzamide;

N-(1-(3-ethoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro-λ^6-sulfanyl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;

N-(1-(azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1-methylazetidin-3-yl)-2-oxoethyl)-4-(penta-1,3-diyn-1-yl)benzamide;

N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(penta-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(penta-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(penta-1,3-diyn-1-yl)benzamide;

(S)-N-(2-(hydroxyamino)-1-(3-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(2-(hydroxyamino)-1-(3-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(1-(1-formyl-3-methoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(1-(1-acetyl-3-methoxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(1-(1-formyl-3-hydroxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(1-(3-hydroxy-1-(methylsulfonyl)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(1-(1-acetyl-3-hydroxyazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

tert-butyl 3-(2-(hydroxyamino)-2-oxo-1-(4-(pentafluoro- λ^6-sulfanyl)benzamido)ethyl)-3-(methylsulfonyl)azetidine-1-carboxylate;

N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;

N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(((1R,2R)-2-(hydroxymethyl)cyclopropyl)buta-1,3-diyn-1-yl)benzamide;

(S)-N-(2-(hydroxyamino)-1-(3-methylazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1-methylazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxy-1-methylazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(2-(hydroxyamino)-1-(3-methoxyazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(pentafluoro- λ^6-sulfanyl)benzamide;

(R)-N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

(S)-N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(1-methyl-3-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(((1R,2R)-2-(hydroxymethyl)cyclopropyl)buta-1,3-diyn-1-yl)benzamide;

N-(1-(3-hydroxy-1-(2-hydroxyethyl)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;

N-(1-(3-hydroxy-1-(2-hydroxyethyl)azetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(prop-1-yn-1-yl)benzamide;

N-(1-(3-hydroxy-1-methylazetidin-3-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

4-bromo-N-(2-(hydroxyamino)-1-(3-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)benzamide;

N-(2-(hydroxyamino)-1-(3-(methylsulfonyl)azetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide;

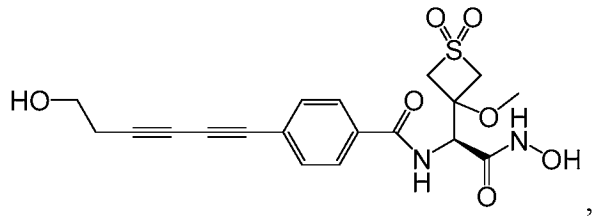
N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide; and

4-bromo-N-(2-(hydroxyamino)-1-(3-hydroxyazetidin-3-yl)-2-oxoethyl)benzamide;

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

62. The compound of claim 1, wherein the compound is N-(2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)-4-(6-hydroxyhexa-1,3-diyn-1-yl)benzamide, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

63. The compound of claim 1, wherein the compound is:

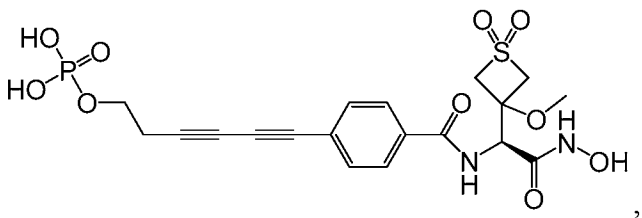


,

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, or tautomer thereof.

64. The compound of claim 2, wherein the compound is 6-(4-((2-(hydroxyamino)-1-(3-methoxy-1,1-dioxidothietan-3-yl)-2-oxoethyl)carbamoyl)phenyl)hexa-3,5-diyn-1-yl dihydrogen phosphate, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof.

65. The compound of claim 2, wherein the compound is:



,

or a pharmaceutically acceptable salt, hydrate, solvate, or tautomer thereof.

66. A pharmaceutical composition comprising a compound of any one of claims 1 to 65, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

67. A method for treating a bacterial infection in a subject comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 65, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

68. A method for treating a bacterial infection in a subject, comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 66.

69. The method according to claim 67 or 68, wherein said bacterial infection is caused by a gram-negative bacteria.

70. A method of inhibiting a deacetylase enzyme in gram-negative bacteria, comprising contacting the bacteria with a compound according to any one of claims 1 to 65, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

71. The method according to claim 67 or 68, wherein the bacterial infection is an infection of a bacteria selected from the group consisting of *Enterobacteriaceae*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia, Pseudomonas*, *Alcaligenes*, *Haemophilus*, *Franciscellaceae* and *Neisseria* species.

72. The method according to claim 69 or 70, wherein the gram-negative bacteria is *Enterobacteriaceae* or *Acinetobacter*.

73. The method according to claim 71 or 72, wherein the *Enterobacteriaceae* is selected from the group consisting of *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia, Morganella*, *Cedecea*, *Edwardsiella species*, and *Escherichia coli.*

74. The method according to claim 71, wherein the *Burkholderia* is *Burkholderia cepacia*,

Burkholderia pseudomallei or *Burkholderia mallei*.

75. The method according to claim 71 or 72, wherein the *Acinetobacter* is selected from the group consisting of *Acinetobacter baumannii*, *Acinetobacter lwoffi*, *Acinetobacter albensis*, *Acinetobacter apis*, *Acinetobacter beijerinckii*, *Acinetobacter bereziniae*, *Acinetobacter bohemicus*, *Acinetobacter boissieri*, *Acinetobacter bouvetii*, *Acinetobacter brisouii*, *Acinetobacter calcoaceticus*, *Acinetobacter courvalinii*, *Acinetobacter dispersus*, *Acinetobacter equi*, *Acinetobacter gandensis*, *Acinetobacter gerneri*, *Acinetobacter guangdongensis*, *Acinetobacter guillouiae*, *Acinetobacter gyllenbergii*, *Acinetobacter haemolyticus*, *Acinetobacter harbinensis*, *Acinetobacter indicus*, *Acinetobacter junii*, *Acinetobacter kookii*, *Acinetobacter modestus*, *Acinetobacter nectaris*, *Acinetobacter nosocomialis*, *Acinetobacter parvus*, *Acinetobacter pakistanensis*, *Acinetobacter populi*, *Acinetobacter proteolyticus*, *Acinetobacter pittii*, *Acinetobacter puyangensis*, *Acinetobacter qingfengensis*, *Acinetobacter radioresistens*, *Acinetobacter rudis*, *Acinetobacter schindleri*, *Acinetobacter seifertii*, *Acinetobacter soli*, *Acinetobacter tandoii*, *Acinetobacter tjernbergiae*, *Acinetobacter towneri*, *Acinetobacter ursingii*, *Acinetobacter variabilis*, *Acinetobacter venetianus*, and *Acinetobacter vivianii*.

76. A method of inhibiting LpxC, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 65, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

77. The compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, of any one of claims 1 to 65 for use as a medicament.

78. The compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, of any one of claims 1 to 65 for use in treating a bacterial infection.

79. The compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, of any one of claims 1 to 65 for use in the manufacture of a medicament for treating a bacterial infection.

80. The compound for use according to claim 78 or 79, wherein the bacterial infection is an infection of a bacteria selected from the group consisting of *Enterobacteriaceae*, *Acinetobacter*,

Stenotrophomonas, *Burkholderia*, *Pseudomonas*, *Alcaligenes*, *Haemophilus*, *Franciscellaceae* and *Neisseria* species.

81. The compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, of any one of claims 1 to 65 for use in inhibiting a deacetylase enzyme in gram-negative bacteria.

82. The compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, of any one of claims 1 to 65 for use in the manufacture of a medicament for inhibiting a deacetylase enzyme in gram-negative bacteria.

83. The compound for use according to claim 81 or 82, wherein the gram-negative bacteria is *Enterobacteriaceae* or *Acinetobacter*.

84. The compound for use according to claim 80 or 83, wherein the *Enterobacteriaceae* is selected from the group consisting of *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Yersinia*, *Morganella*, *Cedecea*, *Edwardsiella species*, and *Escherichia coli*.

85. The compound for use according to claim 80, wherein the *Burkholderia* is *Burkholderia* cepacia, *Burkholderia pseudomallei* or *Burkholderia mallei*.

86. The compound for use according to claim 80 or 83, wherein the *Acinetobacter* is selected from the group consisting of *Acinetobacter baumannii*, *Acinetobacter lwoffi*, *Acinetobacter albensis*, *Acinetobacter apis*, *Acinetobacter beijerinckii*, *Acinetobacter bereziniae*, *Acinetobacter bohemicus*, *Acinetobacter boissieri*, *Acinetobacter bouvetii*, *Acinetobacter brisouii*, *Acinetobacter calcoaceticus*, *Acinetobacter courvalinii*, *Acinetobacter dispersus*, *Acinetobacter equi*, *Acinetobacter gandensis*, *Acinetobacter gerneri*, *Acinetobacter guangdongensis*, *Acinetobacter guillouiae*, *Acinetobacter gyllenbergii*, *Acinetobacter haemolyticus*, *Acinetobacter harbinensis*, *Acinetobacter indicus*, *Acinetobacter junii*, *Acinetobacter kookii*, *Acinetobacter modestus*, *Acinetobacter nectaris*, *Acinetobacter nosocomialis*, *Acinetobacter parvus*, *Acinetobacter pakistanensis*, *Acinetobacter populi*, *Acinetobacter proteolyticus*, *Acinetobacter pittii*, *Acinetobacter puyangensis*, *Acinetobacter qingfengensis*, *Acinetobacter radioresistens*, *Acinetobacter rudis*, *Acinetobacter schindleri*, *Acinetobacter seifertii*, *Acinetobacter soli*,

Acinetobacter tandoii, Acinetobacter tjernbergiae, Acinetobacter towneri, Acinetobacter ursingii, Acinetobacter variabilis, Acinetobacter venetianus, and *Acinetobacter vivianii*.

87. The compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, of any one of claims 1 to 65 for use in inhibiting LpxC.

88. The compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, of any one of claims 1 to 65 for use in the manufacture of a medicament for inhibiting LpxC.

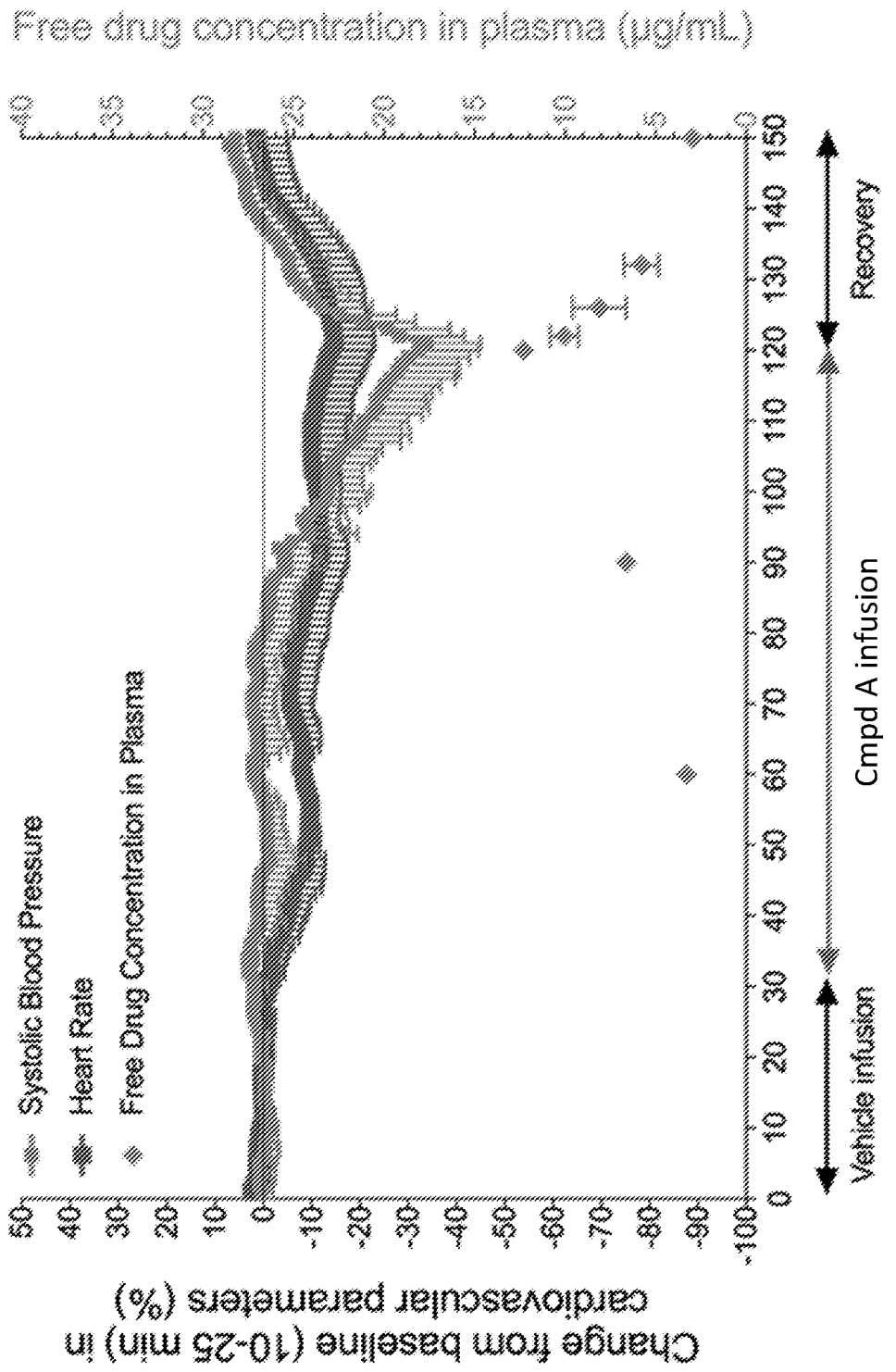

Free drug concentration in plasma (µg/mL)
40
35
30
25
20
15
10
5
0
Systolic Blood Pressure
Heart Rate
Free Drug Concentration in Plasma
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
Change from baseline (10-25 min) in cardiovascular parameters (%)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
Vehicle infusion
Cmpd A infusion
Recovery
Time (minutes)

FIG. 1

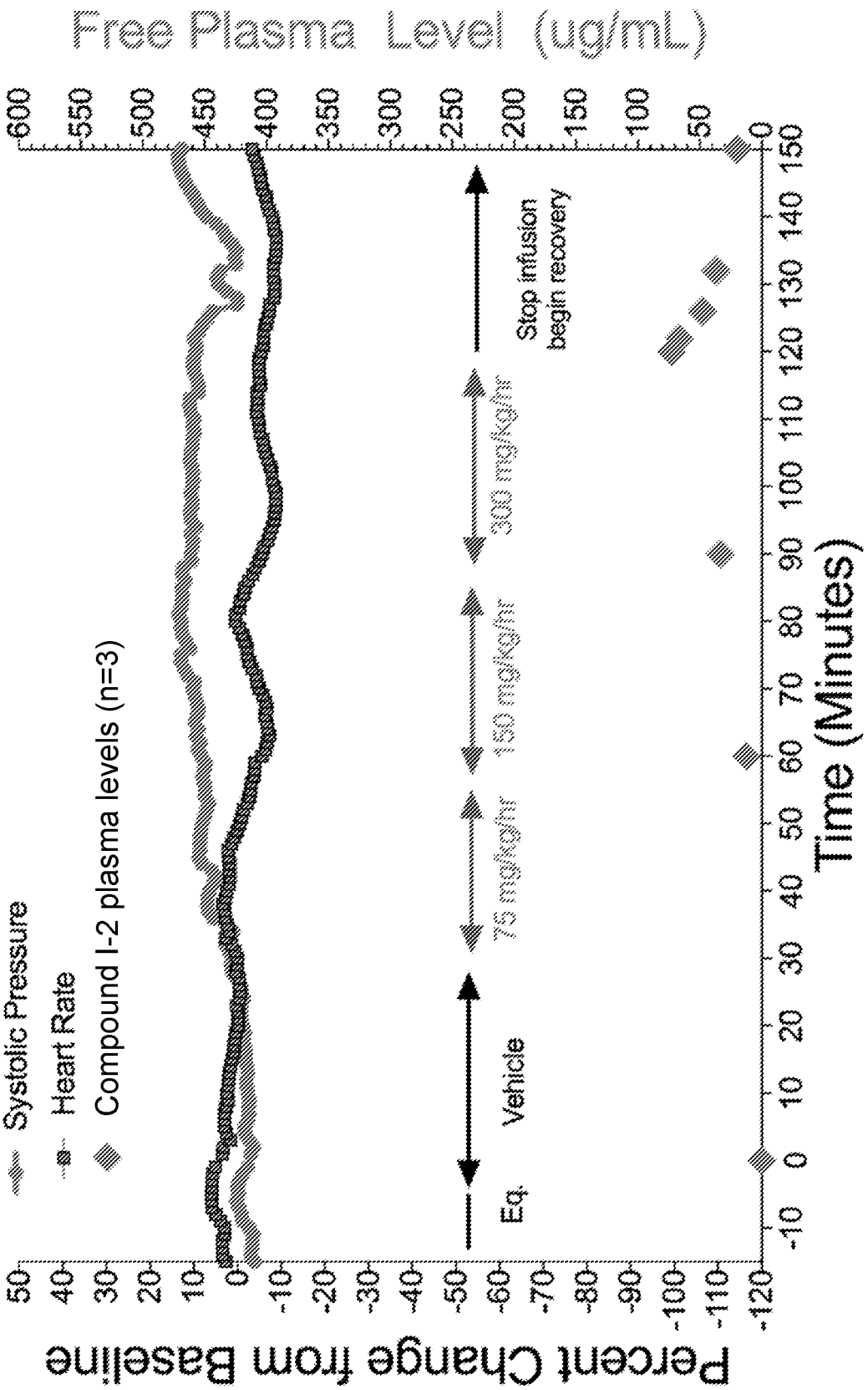

Free Plasma Level (ug/mL)
Percent Change from Baseline
Time (Minutes)
Systolic Pressure
Heart Rate
Compound I-2 plasma levels (n=3)
Eq.
Vehicle
75 mg/kg/hr
150 mg/kg/hr
300 mg/kg/hr
Stop infusion
begin recovery

FIG. 2

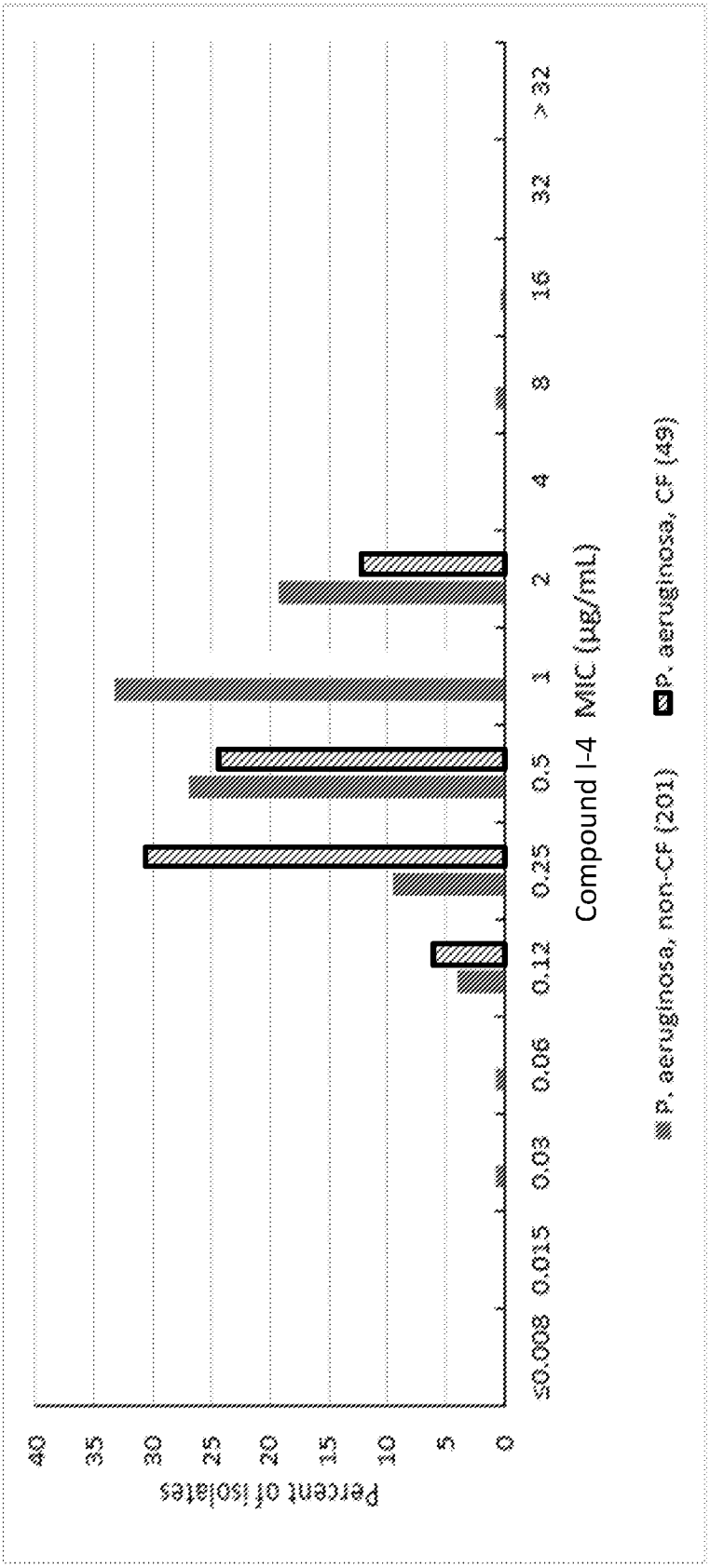

Percent of isolates
40
35
30
25
20
15
10
5
0
≤0.008
0.015
0.03
0.06
0.12
0.25
0.5
1
2
4
8
16
32
>32
Compound I-4 MIC (µg/mL)
P. aeruginosa, non-CF (201)
P. aeruginosa, CF (49)

FIG. 3

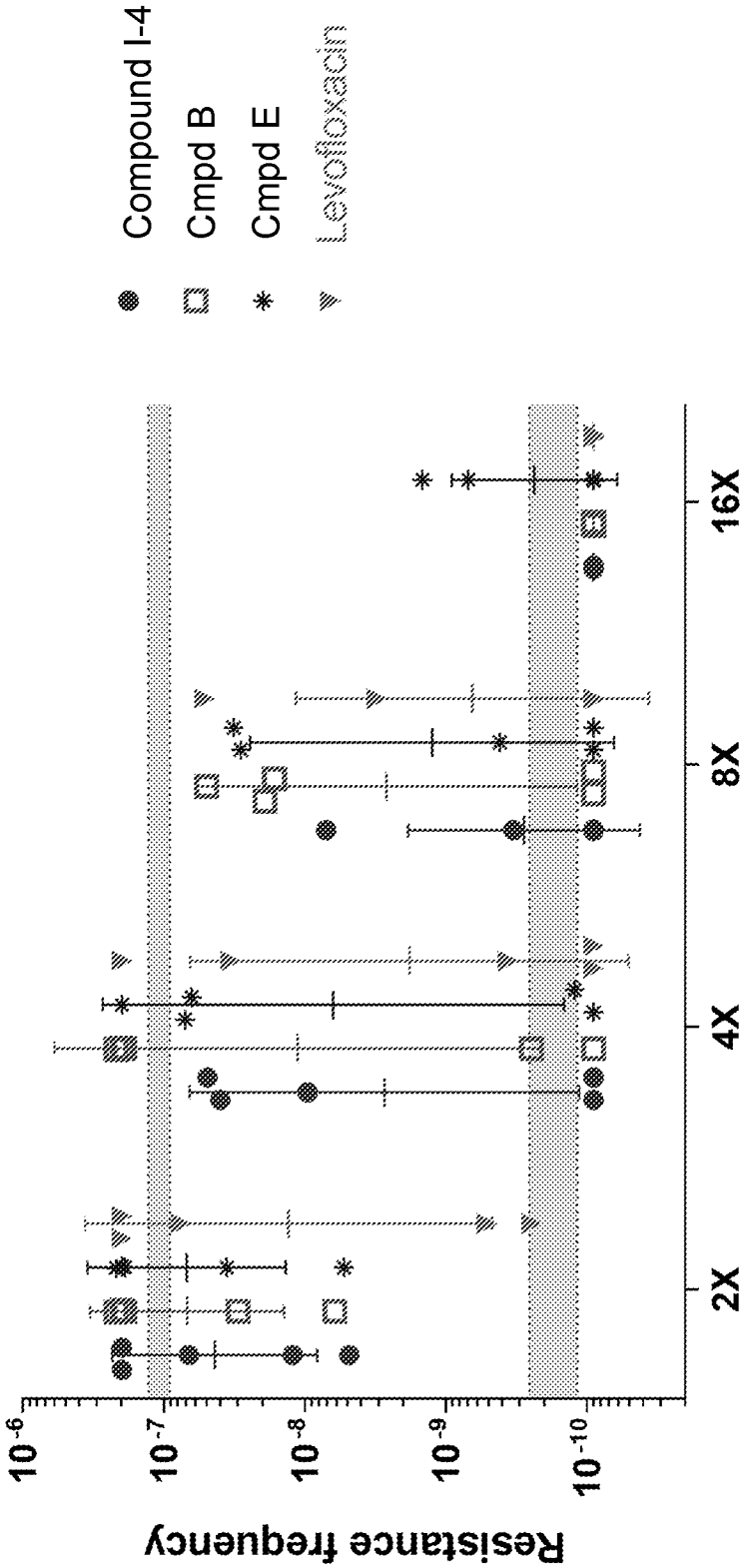

Compound I-4
Cmpd B
Cmpd E
Levofloxacin
Resistance frequency
10-6
10-7
10-8
10-9
10-10
2X
4X
8X
16X
Fold over MIC

FIG. 4

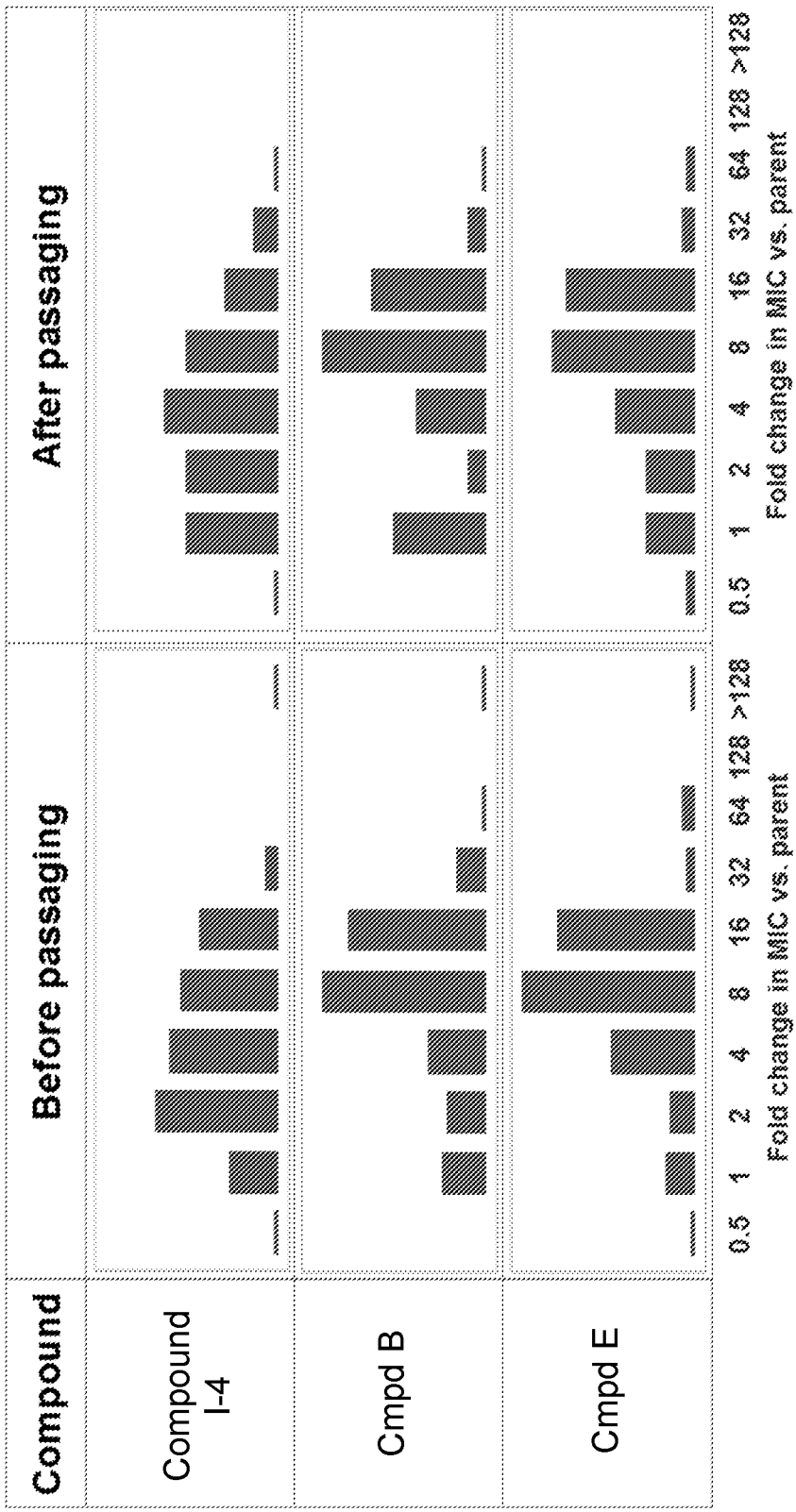

Compound
Before passaging
After passaging
Compound I-4
Cmpd B
Cmpd E
0.5 1 2 4 8 16 32 64 128 >128
Fold change in MIC vs. parent
0.5 1 2 4 8 16 32 64 128 >128
Fold change in MIC vs. parent

FIG. 5

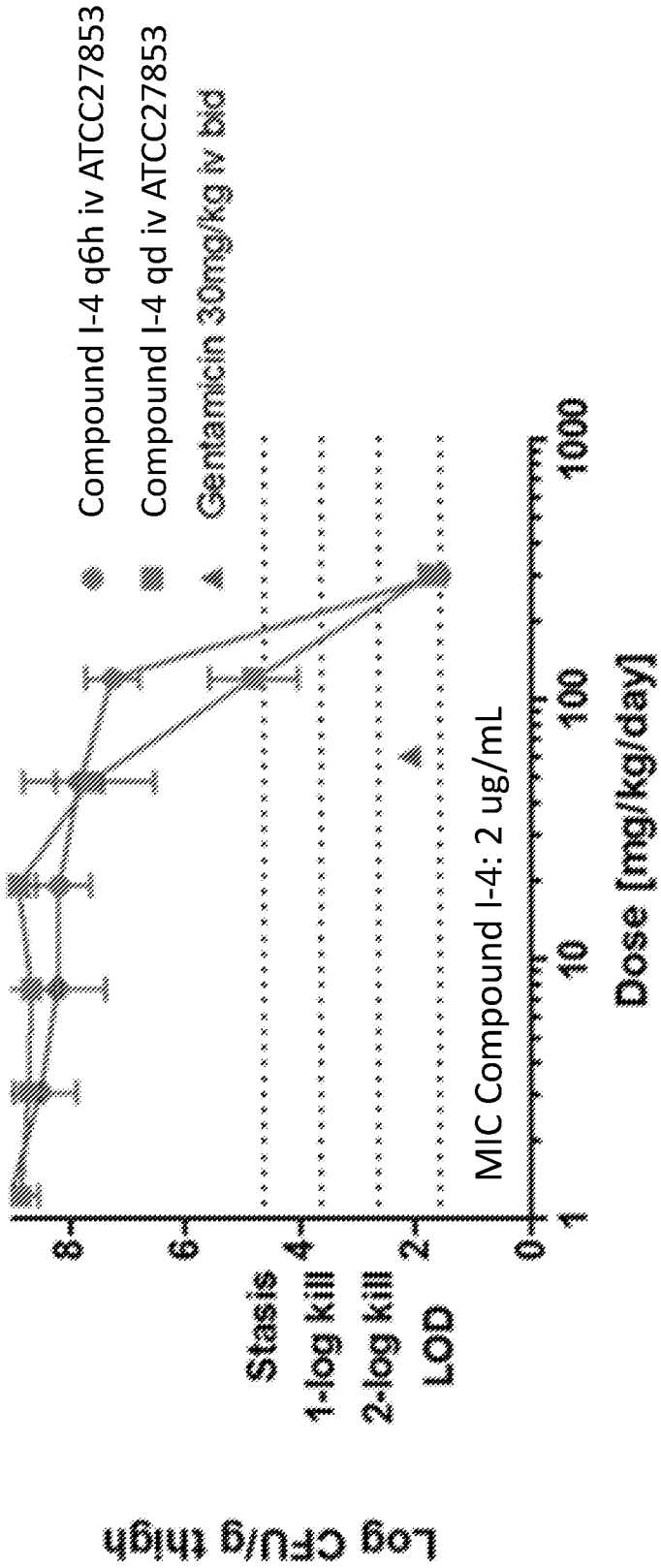

Compound I-4 q6h iv ATCC27853
Compound I-4 qd iv ATCC27853
Gentamicin 30mg/kg iv bid
MIC Compound I-4: 2 ug/mL
Stasis
1-log kill
2-log kill
LOD
Log CFU/g thigh
Dose [mg/kg/day]
0
2
4
6
8
1
10
100
1000

FIG. 6A

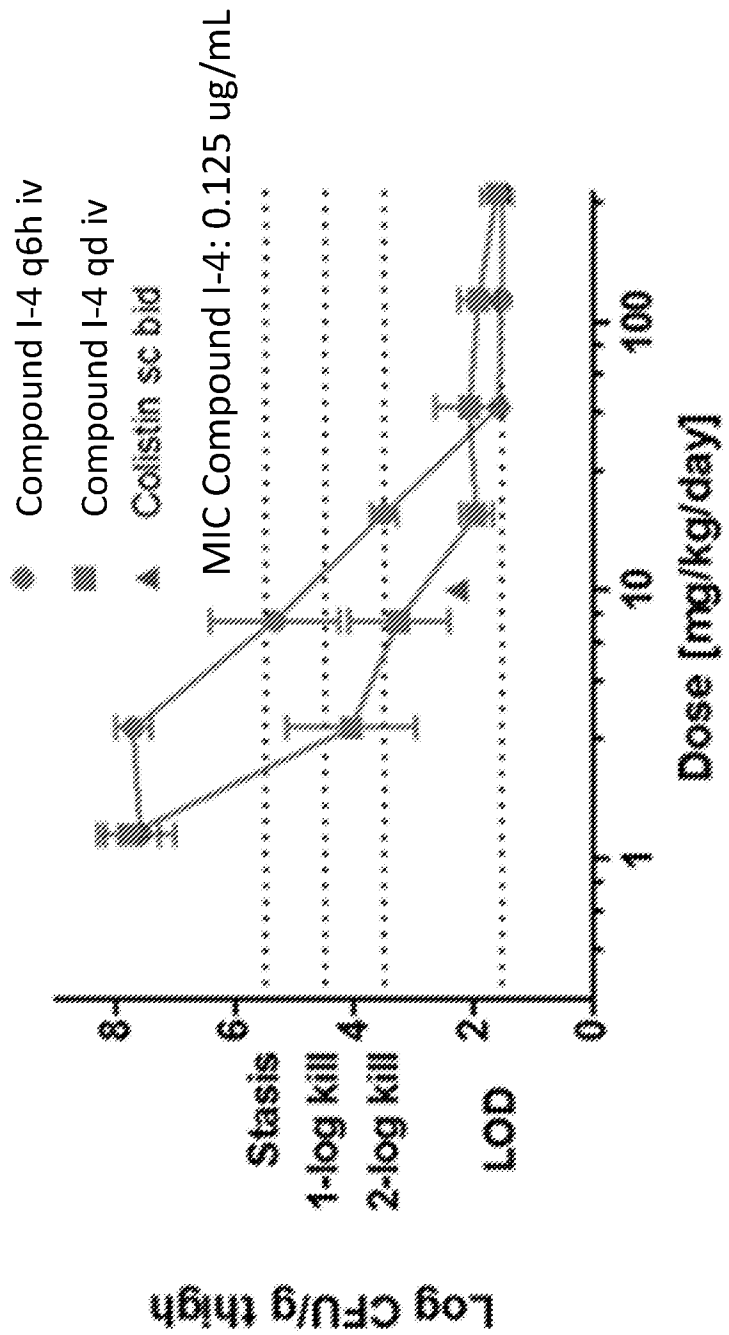

Compound I-4 q6h iv
Compound I-4 qd iv
Colistin sc bid
MIC Compound I-4: 0.125 ug/mL
Log CFU/g thigh
8
6
4
2
0
Stasis
1-log kill
2-log kill
LOD
1
10
100
Dose [mg/kg/day]

FIG. 6B

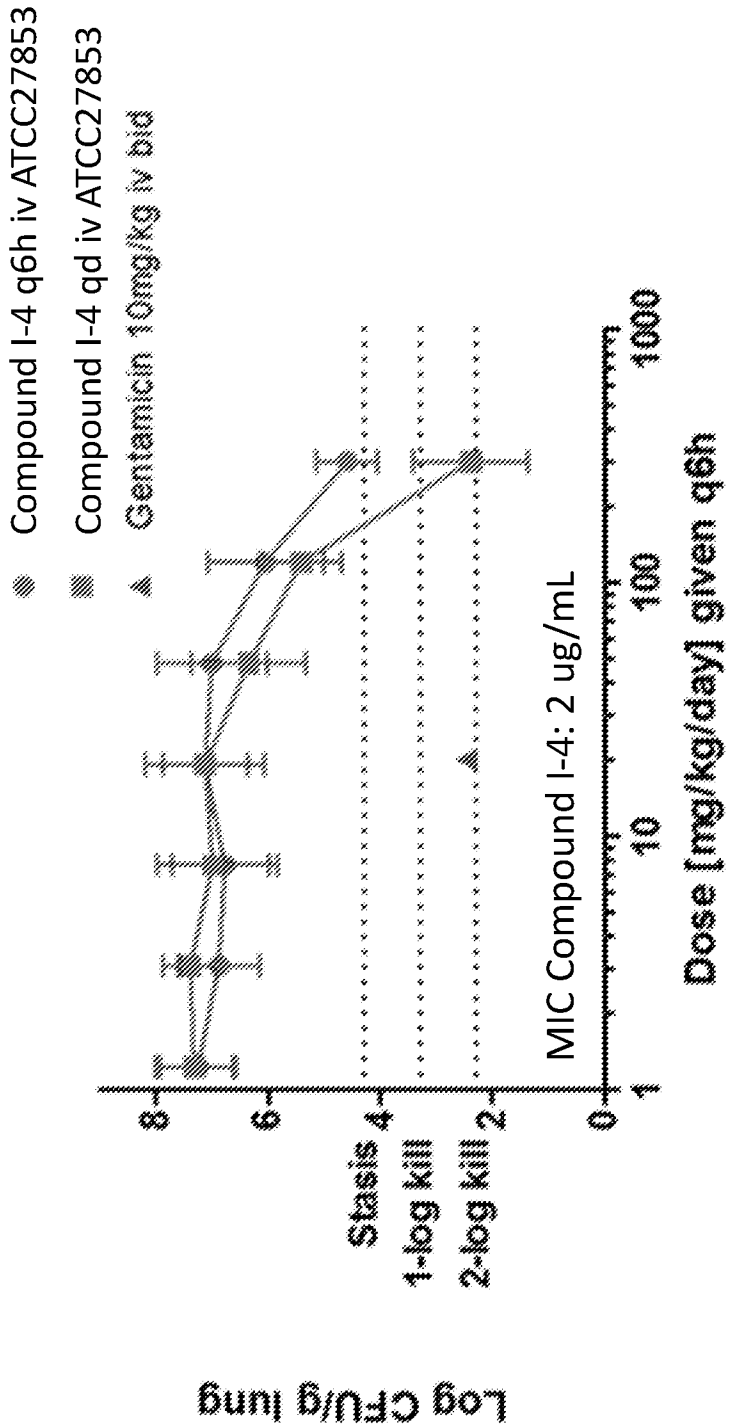

Compound I-4 q6h iv ATCC27853
Compound I-4 qd iv ATCC27853
Gentamicin 10mg/kg iv bid
Log CFU/g lung
8
6
4
2
0
Stasis
1-log kill
2-log kill
MIC Compound I-4: 2 ug/mL
1
10
100
1000
Dose [mg/kg/day] given q6h

FIG. 7A

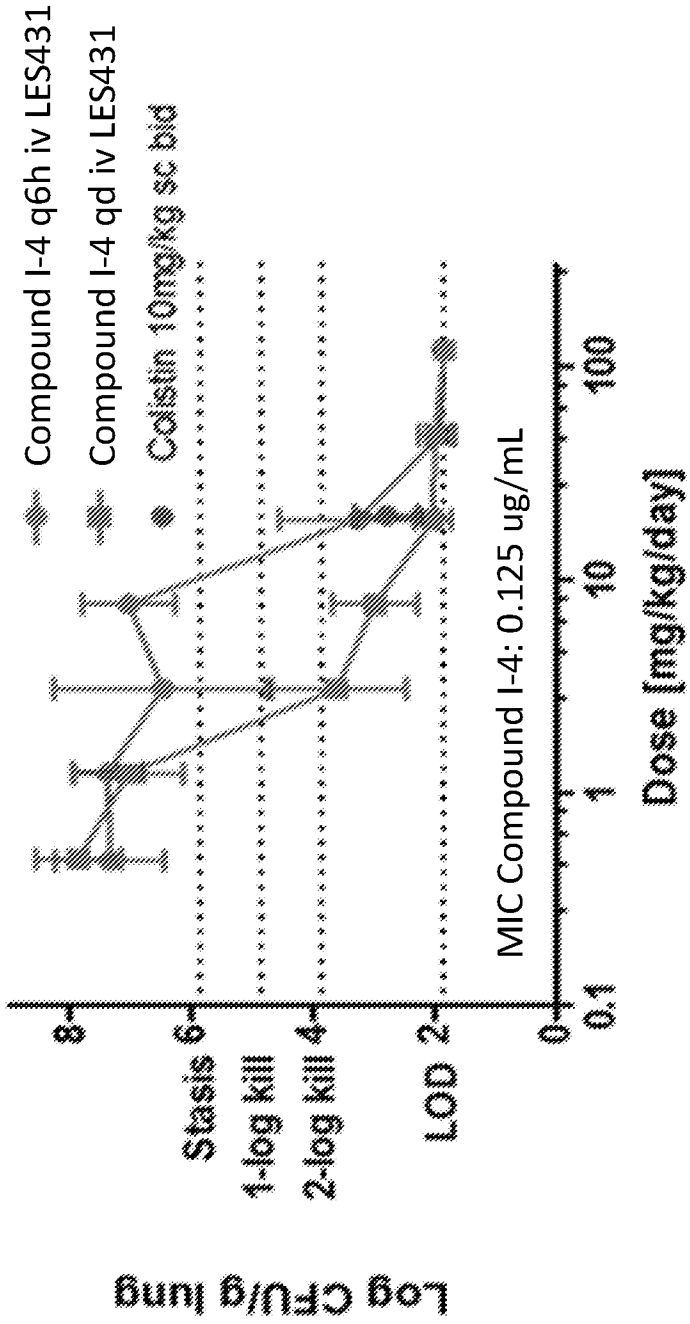

Compound I-4 q6h iv LES431
Compound I-4 qd iv LES431
Colistin 10mg/kg sc bid
Log CFU/g lung
8
6
4
2
0
Stasis
1-log kill
2-log kill
LOD
MIC Compound I-4: 0.125 ug/mL
0.1
1
10
100
Dose [mg/kg/day]

FIG. 7B

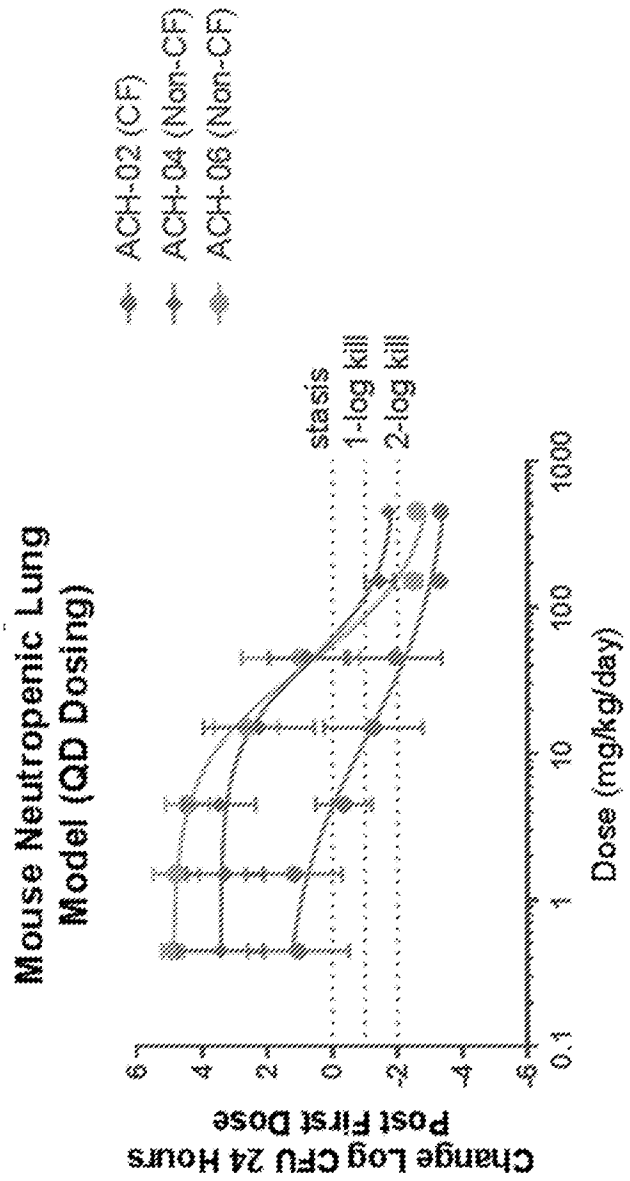

Mouse Neutropenic Lung
Model (QD Dosing)
ACH-02 (CF)
ACH-04 (Non-CF)
ACH-06 (Non-CF)
stasis
1-log kill
2-log kill
Change Log CFU 24 Hours
Post First Dose
6
4
2
0
-2
-4
-6
0.1
1
10
100
1000
Dose (mg/kg/day)

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/038815

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D331/04 C07D205/04 A61K31/397 A61P31/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/154204 A1 (ACHAOGEN INC [US]; KASAR RAMESH [US]; LINSELL MARTIN SHERINGHAM [US];) 15 November 2012 (2012-11-15) see Table I, pp 18-19, Examples I-17 to I-21; pages 1-3	1-88
A	WO 2008/154642 A2 (ACHAOGEN INC [US]; MOSER HEINZ [US]; LU QING [US]; PATTEN PHILLIP A [U]) 18 December 2008 (2008-12-18) page 1; examples 64-7,67-9	1-88

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2017	11/08/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Lauro, Paola

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/038815

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012154204 A1	15-11-2012	AR 083760 A1	20-03-2013
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		WO 2008154642 A2	18-12-2008