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(54) **Title:** 1,2-BENZISOSELENAZOL-3(2H)-ONE AND 1,2-BENZISOTHIAZOL-3(2H)-ONE DERIVATIVES AS BETA-LACTAM ANTIBIOTIC ADJUVANTS

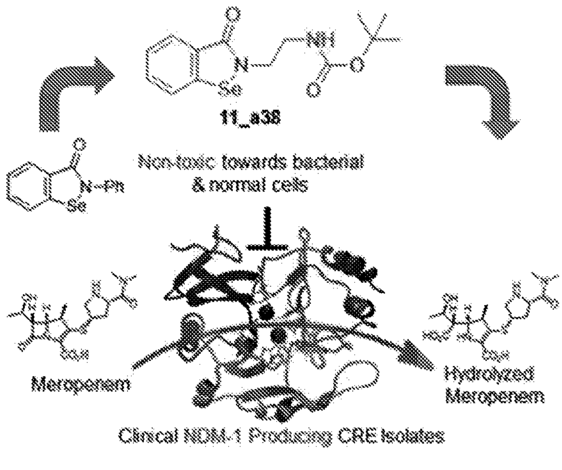


Figure. 1

(57) **Abstract:** Provided herein are compositions and methods useful in the treatment of beta-lactam antibiotic resistant bacteria.

1,2-BENZISOSELENAZOL-3(2H)-ONE AND 1,2-BENZISOTHIAZOL-3(2H)-ONE DERIVATIVES AS BETA-LACTAM ANTIBIOTIC ADJUVANTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[01] This application claims the benefit of priority of United States Provisional Application Number 62/642,053, filed on March 13, 2018, the contents of which being hereby incorporated by reference in their entirety for all purposes.

BACKGROUND

[02] Carbapenem-resistant *Enterobacteriaceae* (CRE) comprise a family of Gram-negative bacteria that exhibit antimicrobial resistance to multiple antibiotics, notably carbapenems, which are the drugs of last resort for treating lethal infections. CRE are the major causes of community- and healthcare-associated bacterial infections, such as those in the urinary tract, bloodstream, surgical site, and intra-abdominal region. Because of their phenotypic resistance to various antibiotics, infections due to such “nightmare bacteria” are often difficult to treat, resulting in a significantly increased mortality.

[03] According to a recent report published by the Centers for Disease Control and Prevention (CDC), more than 9,000 hospitalized patients are infected by CRE annually and half of these patients who developed CRE-associated bloodstream infections died eventually. Moreover, about 600 death cases are due to infection by the two most common types of CRE, carbapenem-resistant *Klebsiella* spp. and *E. coli*, annually. More importantly, recent surveillance reports on antimicrobial resistance also provided evidence which suggests that there is increasing prevalence of CRE strains in the European countries and China. CRE infections have now been regarded as a serious threat to public health. This situation has been be further deteriorated with the recent emergence of MCR-1 positive, colistin-resistant CRE, which do not respond to any known antibiotics.

[04] A list of antibiotic-resistant "priority pathogens" released by the World Health Organization (WHO) early this year indicates that CRE are among the most critical group of bacteria which cause infections that require new antibiotics for treatment.

[05] One of the principal resistance mechanisms of carbapenems in CRE involves the production of carbapenemases, which are carbapenem-hydrolyzing beta-lactamases that possess

versatile hydrolytic capacities to break down nearly all beta-lactam antibiotics and render them ineffective. These broad-spectrum carbapenemases belong to members of the class A, B, and D beta-lactamases, among which the most efficient carbapenemases are class B metallo-beta-lactamases (MBLs). MBLs employ a central zinc ion as essential cofactor to catalyze hydrolysis of the beta-lactam ring. The hydrolytic process of beta-lactam antibiotics does not involve a covalent enzyme-beta-lactam intermediate, but rather a nucleophilic attack by a water/hydroxyl ion which is stabilized by the divalent zinc ion in the active site. MBLs can be further divided into three subclasses (B1, B2 and B3) according to their amino acid sequence. As illustrated in **Figure 2**, for example, New Delhi metallo-beta-lactamase-1 (NDM-1) of subclass B1 MBLs contains a dinuclear zinc center and a water molecule in the active site, in which both zinc ions are coordinated with the 3H site (His116, His118, His196) and the DCH site (Asp120, Cys221, His263), and the water molecule is located in between both zinc ions. Clinically, subclass B1 MBLs are the most significant and prevalent carbapenemases, particularly, NDM-1. The rapid worldwide dissemination of NDM-1-producing “superbugs” further emphasizes the significant role of this type of carbapenemases in conferring antimicrobial resistance, and a pressing need for development of effective NDM-1 inhibitors for clinical applications.

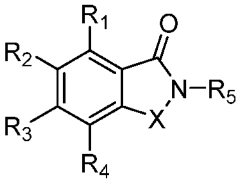
[06] Despite the discovery of a NDM-1-producing *K. pneumoniae* isolate in year 2009, huge success has been made in combating organisms that produce beta-lactamases through clinical usage of beta-lactam antibiotic/beta-lactamase inhibitor combinations. In particular, development of small molecules targeting NDM-1 have been actively pursued in the past decade. Numerous reports on construction of NDM-1 inhibitors and covalent inhibitors have appeared in the literature. Despite ongoing efforts, clinically useful inhibitors of MBLs, in particular NDM-1, are still not available. Thus, there is a need to develop additional useful NDM-1 inhibitors.

SUMARY OF THE INVENTION

[07] Provided herein are compositions and methods useful in the treatment of bacterial infections when administered alone or co-administered with a beta-lactam antibiotic. The compositions described herein are useful as inhibitors of various beta-lactamases, such as NDM-1, and in certain embodiments possess antibacterial properties.

[08] In a first aspect, provided herein is a method of treating a bacterial infection in a patient in need thereof, comprising the step of co-administering a pharmaceutically effective amount of

a beta-lactam antibiotic and a compound of formula **I** to the patient, wherein the compound of formula **I** has the structure:



I

or a pharmaceutically acceptable salt thereof, wherein

X is S or Se;

R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halide, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, heteroaryl, $-N(R_6)_2$, $-(C{=}O)N(R_6)_2$, $-N(R_6)(C{=}O)R_6$, $-OR_6$, $-(C{=}O)R_6$, $-(C{=}O)OR_6$, $-OC(C{=}O)R_6$, $-O(C{=}O)OR_6$, $-O(P{=}O)(OR_6)_2$, $-O(C{=}O)N(R_6)_2$, $-N(R_6)(C{=}O)OR_6$, $-N(R_6)(C{=}O)N(R_6)_2$, and $-SO_2R_6$;

R_5 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-(C{=}O)R_9$, $-SO_2R_9$, or $-(CR_7)_nR_8$;

R_6 for each instance is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, and heteroaryl; or two instances of R_6 taken together with the nitrogen to which they are attached form a 3-6 membered heterocyloalkyl;

R_7 independently for each instance is hydrogen, alkyl, cycloalkyl, heterocycloalkyl aryl, araalkyl, or heteroaryl;

R_8 is nitrile, hydroxyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-N(R_9)_2$, $-(C{=}O)N(R_9)_2$, $-N(R_9)(C{=}O)R_9$, $-OR_9$, $-(C{=}O)R_9$, $-(C{=}O)OR_9$, $-OC(C{=}O)R_9$, $-O(C{=}O)OR_9$, $-O(P{=}O)(OR_9)_2$, $-N(R_9)(P{=}O)(OR_9)_2$, $-O(C{=}O)N(R_9)_2$, $-N(R_9)(C{=}O)OR_9$, $-N(R_9)(C{=}O)N(R_9)_2$, or $-(C{=}O)R_9$;

R_9 for each instance is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, heteroaryl, and $-(CR_7)_nCO_2H$; or two instances of R_9 taken together with the atoms to which they are covalently bonded form a 3-6 membered heterocyloalky; and n for each occurrence is independently an integer selected from 1-6, with the proviso that when R_1, R_2, R_3, and R_4 are hydrogen, R_5 is not phenyl.

[09] In a first embodiment of the first aspect, provided herein is the method of the first aspect, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halide, nitrile, nitro, hydroxyl, and alkyl.

[010] In a second embodiment of the first aspect, provided herein is the method of the first aspect, wherein R_5 is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-(C=O)R_9$, $-SO_2R_9$, or $-(CR_7)_nR_8$.

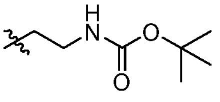
[011] In a third embodiment of the first aspect, provided herein is the method of the first aspect, wherein X is Se; R_5 is $-(CR_7)_nR_8$; and R_8 is hydroxyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-N(R_9)_2$, $-(C=O)N(R_9)_2$, $-N(R_9)(C=O)R_9$, $-(C=O)R_9$, $-(C=O)OR_9$, $-N(R_9)(P=O)(OR_9)_2$, or $-N(R_9)(C=O)OR_9$.

[012] In a fourth embodiment of the first aspect, provided herein is the method of the third embodiment of the first aspect, wherein R_9 for each instance is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, heteroaryl, and $-(CR_7)_nCO_2H$.

[013] In a fifth embodiment of the first aspect, provided herein is the method of the first aspect, wherein X is Se; n is 2, 3, or 4; R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halide, nitrile, nitro, hydroxyl, and alkyl; R_5 is or $-(CR_7)_nR_8$; R_7 for each instance is independently selected from the group consisting of hydrogen and alkyl; and R_8 is heterocycloalkyl, heteroaryl, $-N(R_9)_2$, $-N(R_9)(C=O)R_9$, $-N(R_9)(C=O)OR_9$, or $-N(R_9)(P=O)(OR_9)_2$.

[014] In a sixth embodiment of the first aspect, provided herein is the method of the fifth embodiment of the first aspect, wherein R_5 is $-N(R_9)(C=O)OR_9$.

[015] In an seventh embodiment of the first aspect, provided herein is the method of the fifth embodiment of the first aspect, wherein R_5 is selected from the group consisting of: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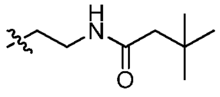
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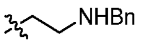
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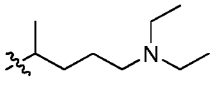
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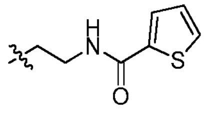
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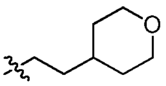
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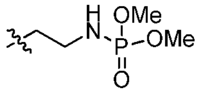
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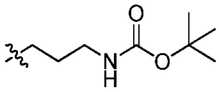
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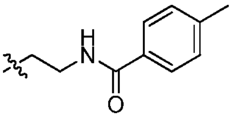
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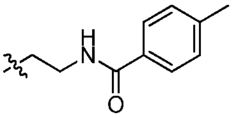
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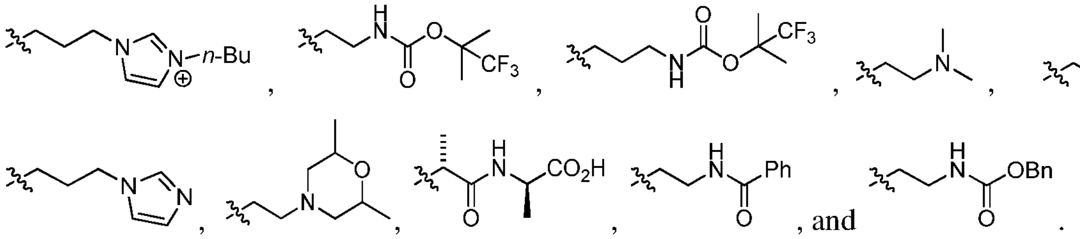
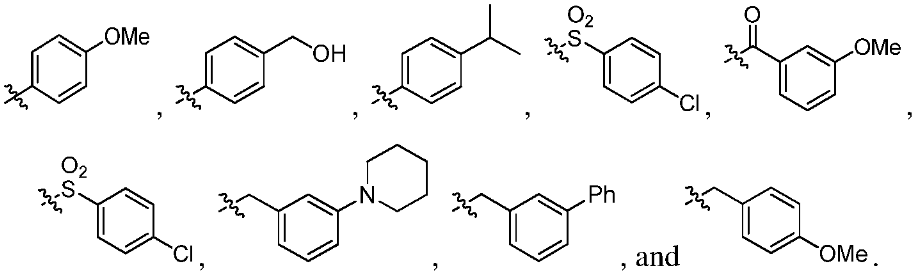


[016] In an eighth embodiment of the first aspect, provided herein is the method of the seventh embodiment of the first aspect, wherein R_1, R_2, R_3, and R_4 are hydrogen.

[017] In a ninth embodiment of the first aspect, provided herein is the method of first aspect, wherein X is Se; R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halide, nitrile, nitro, hydroxyl, and alkyl; and R_5 is 4-substitued aryl, 3-substituted aryl, aralkyl, -(C=O)Ar, and $-SO_2Ar$.

[018] In a tenth embodiment of the first aspect, provided herein is the method of the ninth embodiment of the first aspect, wherein R_5 is selected from the group consisting of:

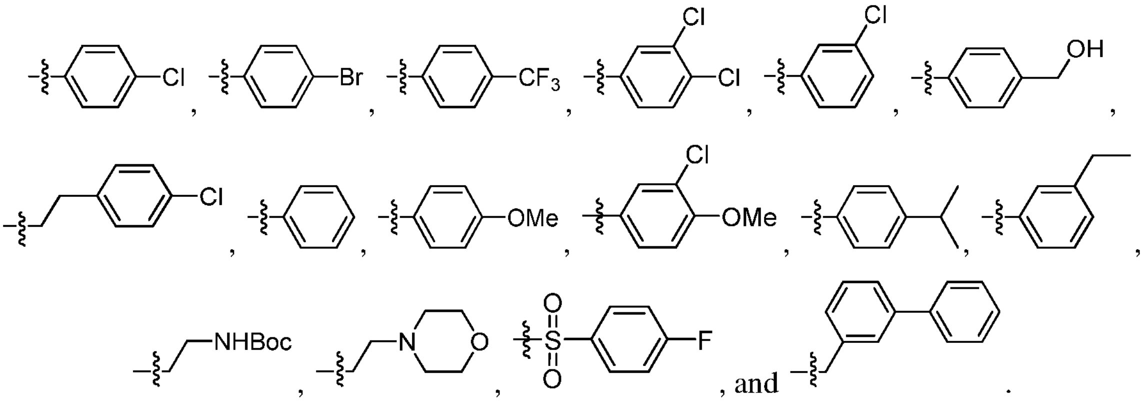


[019] In an eleventh embodiment of the first aspect, provided herein is the method of the tenth embodiment of the first aspect, wherein R_1, R_2, R_3, and R_4 are hydrogen.

[020] In a twelfth embodiment of the first aspect, provided herein is the method of the eleventh embodiment of the first aspect, wherein X is S and R_5 is aryl, $-SO_2R_9$, or $-(CR_7)_nR_8$, wherein n is 1, 2, or 3.

[021] In a thirteenth embodiment of the first aspect, provided herein is the method of the twelfth embodiment of the first aspect, wherein R_5 is phenyl, 4-substituted aryl, 3-substituted aryl, or 3,4-disubsitituted aryl.

[022] In a fourteenth embodiment of the first aspect, provided herein is the method of the twelfth embodiment of the first aspect, wherein R_5 is selected from the group consisting of:



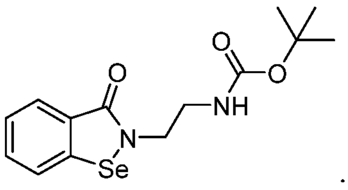
[023] In a fifteenth embodiment of the first aspect, provided herein is the method of the fourteenth embodiment of the first aspect, wherein R_1, R_2, R_3, and R_4 are hydrogen.

[024] In a sixteenth embodiment of the first aspect, provided herein is the method of the first aspect, wherein the bacterial infection is caused by a bacteria that expresses a carbapenemase beta-lactamase or a penicillinase.

[025] In a seventeenth embodiment of the first aspect, provided herein is the method of the first aspect, wherein the bacterial infection is caused by a bacteria that expresses New Delhi metallo-beta-lactamase 1.

[026] In an eighteenth embodiment of the first aspect, provided herein is the method of the first aspect, wherein the bacterial infection is caused by bacteria from the genus Staphylococcus, Micrococcus, Bacillus, Listerella, Escherichia, Klebsiella, Proteus, Salmonella, Shigella, Enterobacter, Serratia, Pseudomonas, Acinetobacter, Nocardia, or Mycobacterium.

[027] In a nineteenth embodiment of the first aspect, provided herein is the method of the seventeenth embodiment of the first aspect, wherein the beta-lactam antibiotic is a carbapenem and the compound of formula **I** has the structure:



BRIEF DESCRIPTION OF THE DRAWINGS

[028] The above and other objects and features of the present invention will become apparent from the following description of the invention, when taken in conjunction with the accompanying drawings, in which:

[029] **Figure 1** depicts a schematic illustrating compound **11_a38** and its inhibitory action on NDM-1

[030] **Figure 2** depicts the active site of NDM-1 and various NDB-1 inhibitors.

[031] **Figure 3** depicts the Kaplan-Meier survival analysis of monotherapy with **11_a38** or meropenem (Mem) and combination therapy with **11_a38** and Mem in protecting *Galleria mellonella* larvae infected with a lethal dose of the clinical NDM-1-producing CRE isolate EL10 (2.5 x 10^5 CFU/larva). Data are the means of three independent experiments.

[032] **Figure 4** depicts compound **11_a38** exhibiting *in vitro* dose-dependent inhibition of NDM-1 enzyme with an IC_{50} of 13 μM.

[033] **Figure 5** depicts (A) Time-dependent and concentration-dependent inhibition of NDM-1 enzyme by compound **11_a38**; (B) Hyperbolic plot of K_{obs} of compound 11_a38 versus concentration of compound **11_a38**.

[034] **Figure 6** depicts Residual activity of NDM-1 enzyme after rapid high dilution of enzyme-compound **11_a38** complex.

[035] **Figure 7** depicts the tolerability of *Galleria mellonella* larvae treated with compound **11_a38**.

[036] **Figure 8** depicts the nano-ESI-MS analysis and their cartoon representations of wild-type (A) and denatured (C) NDM-1 enzyme as well as compound **11_a38**-treated wild-type (B) and denatured (D) NDM-1 enzyme.

[037] **Figure 9** depicts the cytotoxicity profile of compound **11_a38** against HeLa and L929 cell lines.

[038] **Figure 10** depicts HPLC chromatogram of compound **11_a38** under the following HPLC conditions: Column: Agilent Prep-Sil Scalar column (4.6 x 250 mm, 5-μm); Temperature: room temperature (23°C); Flow rate: 1 mL/min; UV detection: 256 nm (reference 450 nm); Mobile phase: 96% DCM, 4% methanol; Retention time: 9.22 min; Purity: 98%.

[039] **Figure 11** depicts HPLC chromatogram of compound **3a** under the following HPLC conditions: HPLC conditions: Column: Agilent Prep-Sil Scalar column (4.6 x 250 mm, 5-µm); Temperature: 23°C; Flow rate: 1 mL/min; UV detection: 256 nm (reference 450 nm); Mobile phase: 98% DCM, 2% methanol; Retention time: 9.364 min; Purity: 99.7%.

[040] **Figure 12** depicts the residual activity after fast dilution of enzyme-inhibitor **3a** complex.

[041] **Figure 13** depicts a plot of velosity of NDM-1 against nitrocefin concentration with different concentrations of compound **3a**.

[042] **Figure 14** depicts a bar graph showing the mammalian cytotoxicity of compound **3a** against HEK-293T cell lines.

[043] **Figure 15** depicts compound **3a** exhibiting *in vitro* dose-dependent inhibition of NDM-1 enzyme.

DETAILED DESCRIPTION OF THE INVENTION

[044] The present disclosure generally relates to 1,2-benzisoselenazol-3(2H)-one and 1,2-benzisothiazol-3(2H)-one analogs their methods of making and intermediates thereto. The present disclosure also provides methods of use of these compounds in the inhibition of beta-lactamases, such as NDM-1. The present disclosure also provides method of treating bacterial infections using the compounds described herein. The compound described herein have been found to be useful in treating antibiotic resistant strains of bacteria and more particularly antibiotic strains of bacteria in which the bacteria expresses one or more beta-lactamases.

[045] **Definitions**

[046] The definitions of terms used herein are meant to incorporate the present state-of-the-art definitions recognized for each term in the chemical and pharmaceutical fields. Where appropriate, exemplification is provided. The definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

[047] Where stereochemistry is not specifically indicated, all stereoisomers of the inventive compounds are included within the scope of the invention, as pure compounds as well as mixtures thereof. Unless otherwise indicated, individual enantiomers, diastereomers, geometrical isomers, and combinations and mixtures thereof are all encompassed by the present invention.

Polymorphic crystalline forms and solvates are also encompassed within the scope of this invention.

[048] As used herein, the term "amino acid" refers to molecules containing both a carboxylic acid moiety and an amino moiety. The carboxylic acid and amino moieties are as defined below. Both naturally occurring and synthetically derived amino acids are encompassed in the scope of this invention.

[049] The term "heteroatom" is art-recognized and refers to an atom of any element other than carbon or hydrogen. Illustrative heteroatoms include boron, nitrogen, oxygen, phosphorus, sulfur and selenium.

[050] The term "alkyl" is art-recognized, and includes saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In certain embodiments, a straight chain or branched chain alkyl has about 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chain, C_3-C_{30} for branched chain), and alternatively, about 20 or fewer. Likewise, cycloalkyls have from about 3 to about 10 carbon atoms in their ring structure, and alternatively about 5, 6 or 7 carbons in the ring structure.

[051] Unless the number of carbons is otherwise specified, "lower alkyl" refers to an alkyl group, as defined above, but having from one to about ten carbons, alternatively from one to about six carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths.

[052] The term "aralkyl" is art-recognized and refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

[053] The terms "alkenyl" and "alkynyl" are art-recognized and refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

[054] The term "aryl" is art-recognized and refers to 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, naphthalene, anthracene, pyrene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" or "heteroaromatics." The aromatic ring may be substituted at one or more ring positions with such

substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, -CF_3, -CN, or the like. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls.

[055] The terms ortho, meta and para are art-recognized and refer to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

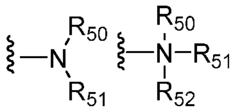
[056] The terms "heterocyclyl", "heteroaryl", or "heterocyclic group" are art-recognized and refer to 3- to about 10-membered ring structures, alternatively 3- to about 7-membered rings, whose ring structures include one to four heteroatoms. Heterocycles may also be polycycles. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxanthene, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring may be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, -CF_3, -CN, or the like.

[057] The term "optionally substituted" refers to a chemical group, such as alkyl, cycloalkyl aryl, and the like, wherein one or more hydrogen may be replaced with a with a substituent as described herein, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl,

carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, $-CF_3$, -CN, or the like

[058] The term "nitro" is art-recognized and refers to NO_2; the term "halogen" is art-recognized and refers to -F, -Cl, -Br or -I; the term "sulfhydryl" is art-recognized and refers to -SH; the term "hydroxyl" means -OH; and the term "sulfonyl" is art-recognized and refers to $-SO_2-$. "Halide" designates the corresponding anion of the halogens, and "pseudohalide" has the definition set forth on 560 of "Advanced Inorganic Chemistry" by Cotton and Wilkinson.

[059] The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that may be represented by the general formulas:



[060] wherein R_{50}, R_{51} and R_{52} each independently represent a hydrogen, an alkyl, an alkenyl, $-(CH_2)_mR_{61}$, or R_{50} and R_{51}, taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R_{61} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range of 1 to 8. In other embodiments, R_{50} and R_{51} (and optionally R_{52}) each independently represent a hydrogen, an alkyl, an alkenyl, or $-(CH_2)_mR_{61}$. Thus, the term "alkylamine" includes an amine group, as defined above, having a substituted or unsubstituted alkyl attached thereto, i.e., at least one of R_{50} and R_{51} is an alkyl group.

[061] The terms "alkoxyl" or "alkoxy" are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, *tert*-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as may be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, $-O-(CH_2)_mR_{61}$, where m and R_{61} are described above.

[062] The terms triflyl, tosyl, mesyl, and nonaflyl are art-recognized and refer to trifluoromethanesulfonyl, p-toluenesulfonyl, methanesulfonyl, and nonafluorobutanesulfonyl groups, respectively. The terms triflate, tosylate, mesylate, and nonaflate are art-recognized and refer to trifluoromethanesulfonate ester, p-toluenesulfonate ester, methanesulfonate ester, and nonafluorobutanesulfonate ester functional groups and molecules that contain said groups, respectively.

[063] The abbreviations Me, Et, Ph, Tf, Nf, Ts, and Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, p-toluenesulfonyl and methanesulfonyl, respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the Journal of Organic Chemistry; this list is typically presented in a table entitled Standard List of Abbreviations.

[064] Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, polymers of the present invention may also be optically active. The present invention contemplates all such compounds, including cis- and trans-isomers, R- and S-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[065] If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

[066] It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction.

[067] The term "substituted" is also contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents may be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have

hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

[068] For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

[069] The term "pharmaceutically acceptable salt" or "salt" refers to a salt of one or more compounds. Suitable pharmaceutically acceptable salts of compounds include acid addition salts which may, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, benzoic acid, acetic acid, citric acid, tartaric acid, phosphoric acid, carbonic acid, or the like. Where the compounds carry one or more acidic moieties, pharmaceutically acceptable salts may be formed by treatment of a solution of the compound with a solution of a pharmaceutically acceptable base, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, tetraalkylammonium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, ammonia, alkylamines, or the like.

[070] The term "subject" as used herein, refers to an animal, typically a mammal or a human, that will be or has been the object of treatment, observation, and/or experiment. When the term is used in conjunction with administration of a compound or drug, then the subject has been the object of treatment, observation, and/or administration of the compound or drug.

[071] The terms "co-administration" and "co-administering" refer to both concurrent administration (administration of two or more therapeutic agents at the same time) and time varied administration (administration of one or more therapeutic agents at a time different from that of the administration of an additional therapeutic agent or agents), as long as the therapeutic agents are present in the patient to some extent at the same time.

[072] The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a cell culture, tissue system, animal, or human that is being sought by a researcher, veterinarian, clinician, or physician, which includes alleviation of the symptoms of the disease, condition, or disorder being treated.

[073] The term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product that results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

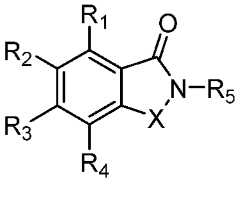
[074] The term "pharmaceutically acceptable carrier" refers to a medium that is used to prepare a desired dosage form of a compound. A pharmaceutically acceptable carrier can include one or more solvents, diluents, or other liquid vehicles; dispersion or suspension aids; surface active agents; isotonic agents; thickening or emulsifying agents; preservatives; solid binders; lubricants; and the like. Remington's Pharmaceutical Sciences, Fifteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1975) and Handbook of Pharmaceutical Excipients, Third Edition, A. H. Kibbe ed. (American Pharmaceutical Assoc. 2000), disclose various carriers used in formulating pharmaceutical compositions and known techniques for the preparation thereof.

Abbreviations

[075] The following abbreviations are used throughout this disclosure, the meanings of which are as follows: CRE, carbapenem-resistant *Enterobacteriaceae*; CDC, Centers for Diseases Control and Prevention; WHO, World Health Organization; MBLs, metallo-beta-lactamases; NDM-1, New Delhi metallo-beta-lactamase-1; Eb, ebselen; IPTG, isopropyl-beta-D-thiogalactoside; Mem, meropenem; MIC, minimum inhibition concentration; FIC, fractional inhibitory concentration; SAR, structure-activity relationship; ESI-MS, electrospray ionization mass spectrometry; DMF, dimethylformamide; EDCI, *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide; DCM, dichloromethane; CLSI, Clinical and Laboratory Standards Institute.

Compositions

[076] In certain embodiments, the present disclosure provides a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein

X is S or Se;

R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halide, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, heteroaryl, $-N(R_6)_2$, $-(C=O)N(R_6)_2$, $-N(R_6)(C=O)R_6$, $-OR_6$, $-(C=O)R_6$, $-(C=O)OR_6$, $-OC(C=O)R_6$, $-O(C=O)OR_6$, $-O(P=O)(OR_6)_2$, $-O(C=O)N(R_6)_2$, $-N(R_6)(C=O)OR_6$, $-N(R_6)(C=O)N(R_6)_2$, and $-SO_2R_6$;

R_5 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-(C=O)R_9$, $-SO_2R_9$, or $-(CR_7)_nR_8$;

R_6 for each instance is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, and heteroaryl; or two instances of R_6 taken together with the nitrogen to which they are attached form a 3-6 membered heterocyloalkyl;

R_7 independently for each instance is hydrogen, alkyl, cycloalkyl, heterocycloalkyl aryl, araalkyl, or heteroaryl;

R_8 is nitrile, hydroxyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-N(R_9)_2$, $-(C=O)N(R_9)_2$, $-N(R_9)(C=O)R_9$, $-OR_9$, $-(C=O)R_9$, $-(C=O)OR_9$, $-OC(C=O)R_9$, $-O(C=O)OR_9$, $-O(P=O)(OR_9)_2$, $-N(R_9)(P=O)(OR_9)_2$, $-O(C=O)N(R_9)_2$, $-N(R_9)(C=O)OR_9$, $-N(R_9)(C=O)N(R_9)_2$, or $-(C=O)R_9$;

R_9 for each instance is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, heteroaryl, and $-(CR_7)_nCO_2H$; or two instances of R_9 taken together with the atoms to which they are covalently bonded form a 3-6 membered heterocyloalky; and

n for each occurrence is independently an integer selected from 1-6.

[077] In certain embodiments, the compound of Formula **I** does not include ebselen, i.e., if R_1, R_2, R_3, and R_4 are hydrogen, R_5 cannot be phenyl.

[078] In certain embodiments, provided is the compound of formula **I**, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halide, nitrile, nitro, hydroxyl, and alkyl.

[079] In certain embodiments, provided is the compound of formula **I** or any of the aforementioned embodiments, wherein R_5 is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -(C=O)R_9, -SO_2R_9, or –$(CR_7)_nR_8$.

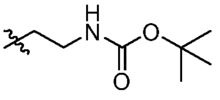
[080] In certain embodiments, provided is the compound of formula **I** or any of the aforementioned embodiments, wherein X is Se; R_5 is –$(CR_7)_nR_8$; and R_8 is hydroxyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -N$(R_9)_2$, -(C=O)N$(R_9)_2$, -N(R_9)(C=O)R_9, -(C=O)R_9, -(C=O)OR_9, -N(R_9)(P=O)$(OR_9)_2$, or -N(R_9)(C=O)OR_9.

[081] In certain embodiments, provided is the compound of formula **I** or any of the aforementioned embodiments, wherein R_9 for each instance is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, heteroaryl, and –$(CR_7)_nCO_2H$.

[082] In certain embodiments, provided is the compound of formula **I** or any of the aforementioned embodiments, wherein X is Se; n is 2, 3, or 4; R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halide, nitrile, nitro, hydroxyl, and alkyl; R_5 is or –$(CR_7)_nR_8$; R_7 for each instance is independently selected from the group consisting of hydrogen and alkyl; and R_8 is heterocycloalkyl, heteroaryl, -N$(R_9)_2$, -N(R_9)(C=O)R_9, -N(R_9)(C=O)OR_9, or -N(R_9)(P=O)$(OR_9)_2$.

[083] In certain embodiments, provided is the compound of formula **I** or any of the aforementioned embodiments, wherein R_5 is –N(R_9)(C=O)OR_9.

[084] In certain embodiments, provided is the compound of formula **I** or any of the aforementioned embodiments, wherein R_5 is selected from the group consisting of:



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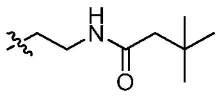

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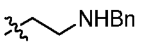

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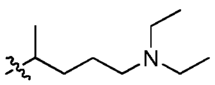

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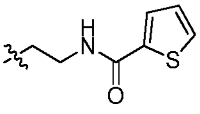

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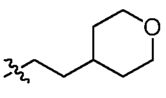

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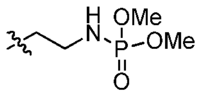

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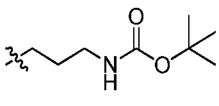

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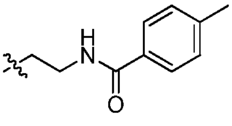

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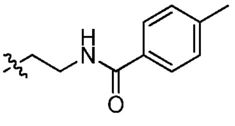

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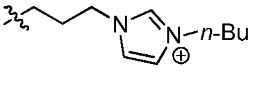

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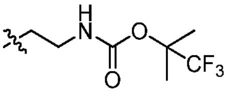

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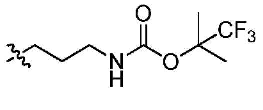

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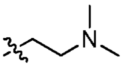

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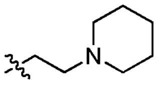

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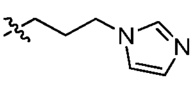

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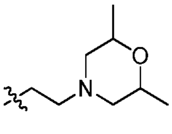

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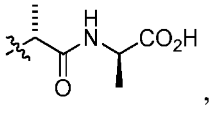

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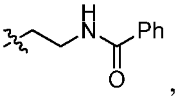

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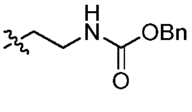

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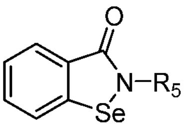
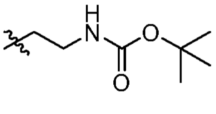
[085] In certain embodiments, provided is the compound of formula **I** is represented by the compound:



[086] or a pharmaceutically acceptable salt, wherein R_5 is selected from the group consisting of: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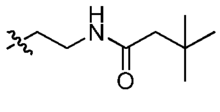
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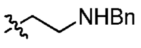
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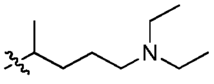
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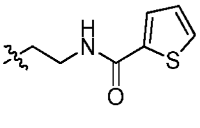
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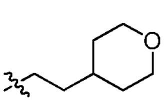
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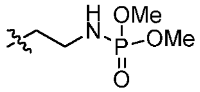
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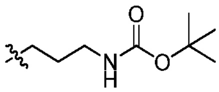
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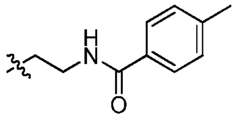
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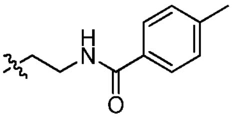
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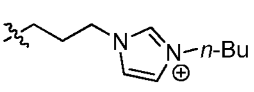
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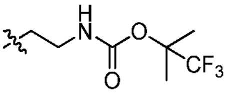
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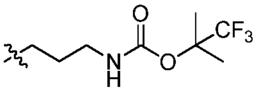
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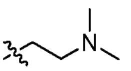
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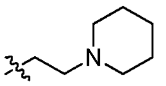
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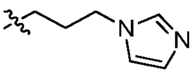
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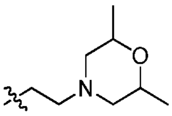
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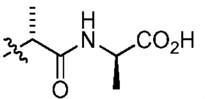
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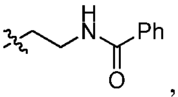
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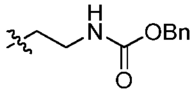
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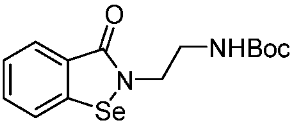
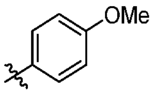
[087] In certain embodiments, provided is the compound of formula **I** is represented by the compound:



[088] In certain embodiments, provided is the compound of formula **I** or any of the aforementioned embodiments, wherein R_1, R_2, R_3, and R_4 are hydrogen.

[089] In certain embodiments, provided is the compound of formula **I** or any of the aforementioned embodiments, wherein X is Se; R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halide, nitrile, nitro, hydroxyl, and alkyl; and R_5 is 4-substitued aryl, 3-substituted aryl, aralkyl, -(C=O)Ar, and -SO_2Ar.

[090] In certain embodiments, provided is the compound of formula **I** or any of the aforementioned embodiments, wherein R_5 is selected from the group consisting of: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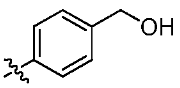
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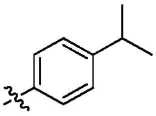
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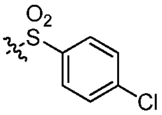
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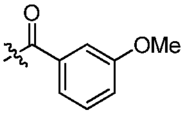
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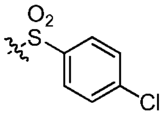
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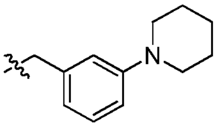
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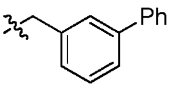
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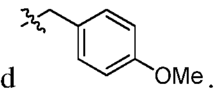
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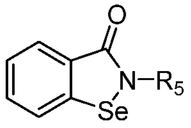
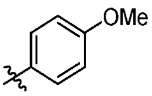
[091] In certain embodiments, provided is the compound of formula **I** is represented by the compound:



[092] or a pharmaceutically acceptable salt, wherein R_5 is selected from the group consisting of: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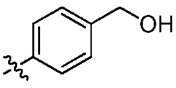
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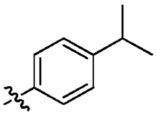
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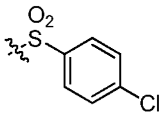
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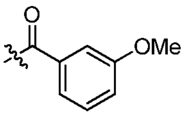
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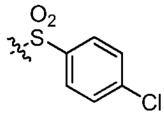
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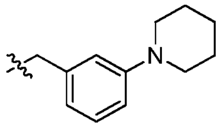
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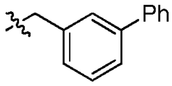
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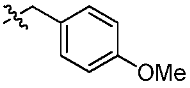
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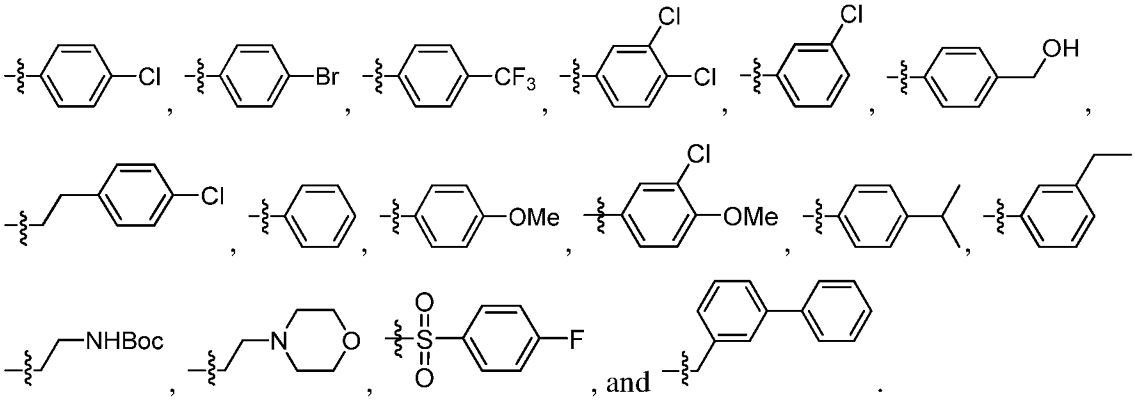
[093] In certain embodiments, provided is the compound of formula **I** or any of the aforementioned embodiments, wherein R_1, R_2, R_3, and R_4 are hydrogen.

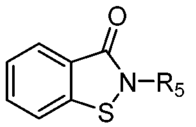
[094] In certain embodiments, provided is the compound of formula **I** or any of the aforementioned embodiments, wherein X is S and R_5 is aryl, $-SO_2R_9$, or $-(CR_7)_nR_8$, wherein n is 1, 2, or 3.

[095] In certain embodiments, provided is the compound of formula **I** or any of the aforementioned embodiments, wherein R_5 is phenyl, 4-substituted aryl, 3-substituted aryl, or 3,4-disubsitituted aryl.

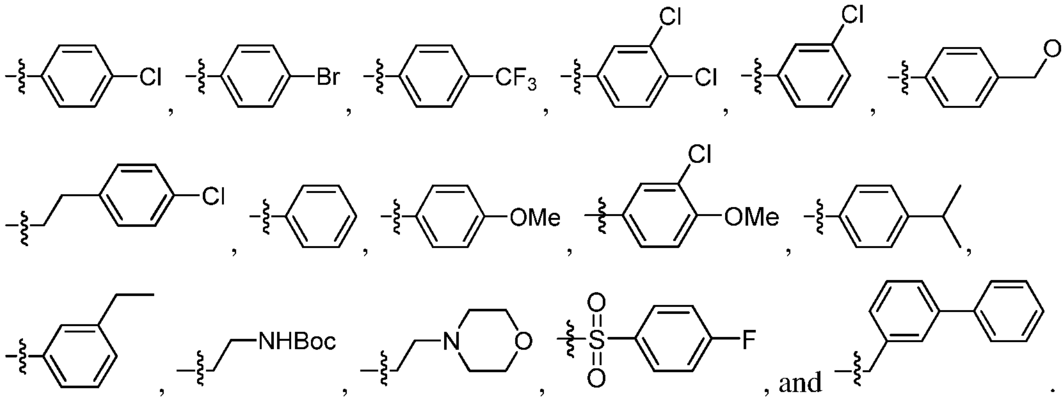
[096] In certain embodiments, provided is the compound of formula **I** or any of the aforementioned embodiments, wherein R_5 is selected from the group consisting of:



[097] In certain embodiments, provided is the compound of formula **I** is represented by the compound:

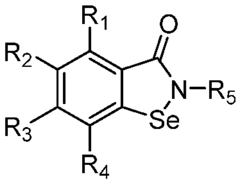


[098] or a pharmaceutically acceptable salt, wherein R_5 is selected from the group consisting of:



[099] In certain embodiments, provided is the compound of formula **I** or any of the aforementioned embodiments, wherein R_1, R_2, R_3, and R_4 are hydrogen.

[0100] In certain embodiments, provided herein is a compound of formula **II**:



II

[0101] or a pharmaceutically acceptable salt thereof, wherein

[0102] R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halide, nitrile, nitro, hydroxyl, alkyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, heteroaryl, -$N(R_6)_2$, -$(C{=}O)N(R_6)_2$, -$N(R_6)(C{=}O)R_6$, -OR_6, -$(C{=}O)R_6$, -$(C{=}O)OR_6$, -$OC(C{=}O)R_6$, -$O(C{=}O)OR_6$, -$O(P{=}O)(OR_6)_2$, -$O(C{=}O)N(R_6)_2$, -$N(R_6)(C{=}O)OR_6$, -$N(R_6)(C{=}O)N(R_6)_2$, and -SO_2R_6;

[0103] R_5 is–$(CR_7)_nR_8$;

[0104] R_6 for each instance is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, and heteroaryl; or two instances of R_6 taken together with the nitrogen to which they are attached form a 3-6 membered heterocyloalkyl;

[0105] R_7 independently for each instance is hydrogen, alkyl, cycloalkyl, heterocycloalkyl aryl, araalkyl, or heteroaryl;

[0106] R_8 is -$N(R_9)(C{=}O)OR_9$;

[0107] R_9 for each instance is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, and heteroaryl; or two instances of R_9 taken together with the atoms to which they are covalently bonded form a 3-6 membered heterocyloalky; and

[0108] n for each occurrence is independently an integer selected from 1-6.

[0109] In certain embodiments, provided herein is the compound of formula **II**, wherein n is 1-3.

[0110] In certain embodiments, provided herein is the compound of formula **II** or any of the aforementioned embodiments of the compound of formula **II**, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halide, nitrile, nitro, hydroxyl, alkyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, heteroaryl, -$N(R_6)_2$, -$(C{=}O)N(R_6)_2$, -$N(R_6)(C{=}O)R_6$, -OR_6, -$(C{=}O)OR_6$, -$O(C{=}O)OR_6$, and -$O(C{=}O)N(R_6)_2$.

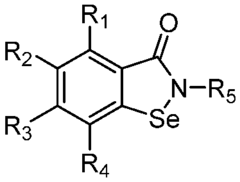
[0111] In certain embodiments, provided herein is the compound of formula **II** or any of the aforementioned embodiments of the compound of formula **II**, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halide, nitrile, nitro, hydroxyl, alkyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, and heteroaryl.

[0112] In certain embodiments, provided herein is the compound of formula **II** or any of the aforementioned embodiments of the compound of formula **II**, R_9 for each instance is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, and heteroaryl; or two instances of R_9 taken together with the atoms to which they are covalently bonded form a 3-6 membered heterocyloalky.

[0113] In certain embodiments, provided herein is the compound of formula **II** or any of the aforementioned embodiments of the compound of formula **II**, R_9 for each instance is independently selected from the group consisting of hydrogen and alkyl; or two instances of R_9 taken together with the atoms to which they are covalently bonded form a 3-6 membered heterocyloalky.

[0114] In certain embodiments, provided herein is the compound of formula **II** or any of the aforementioned embodiments of the compound of formula **II**, wherein R_8 is -N(H)(C=O)OR$_9$.

[0115] In certain embodiments, the compound of formula **II** has the following formula:



[0116] or a pharmaceutically acceptable salt thereof, wherein

[0117] R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halide, nitrile, nitro, hydroxyl, alkyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, heteroaryl, and -N(R_6)$_2$;

[0118] R_5 is –(CR$_7$)$_2$R$_8$;

[0119] R_6 for each instance is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, and heteroaryl; or two instances of R_6 taken together with the nitrogen to which they are attached form a 3-6 membered heterocyloalkyl;

[0120] R_7 independently for each instance is hydrogen and alkyl;

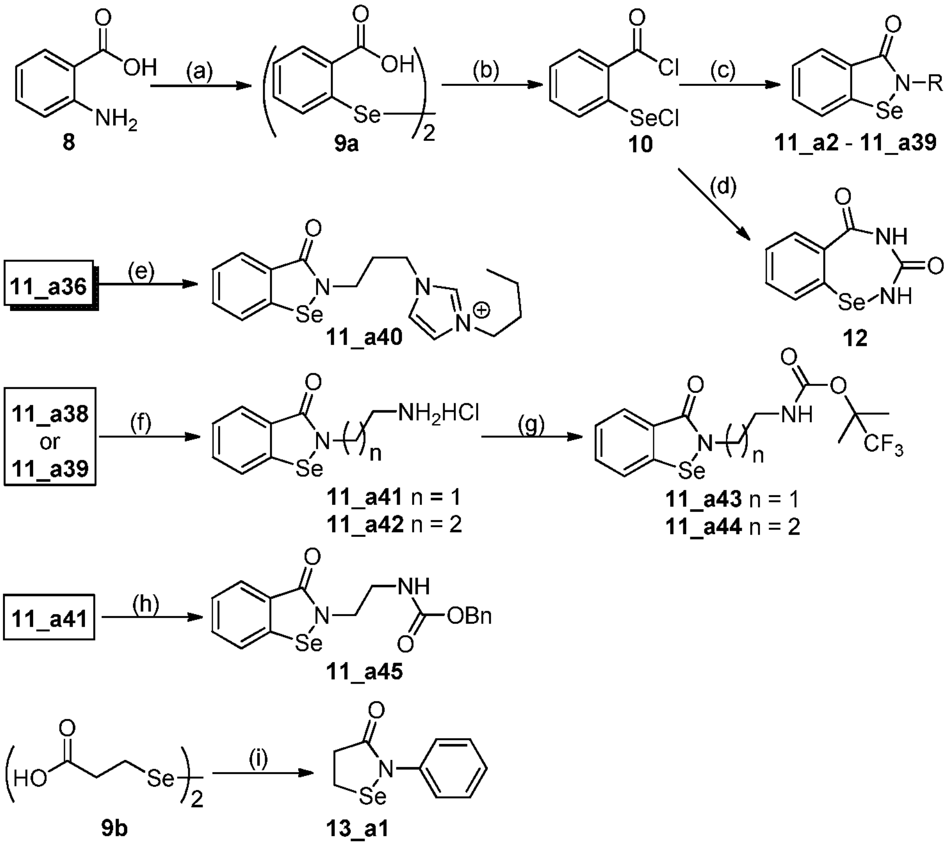
[0121] R_8 is -N(H)(C=O)OR$_9$; and

[0122] R_9 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, and heteroaryl.

Methods of Preparation

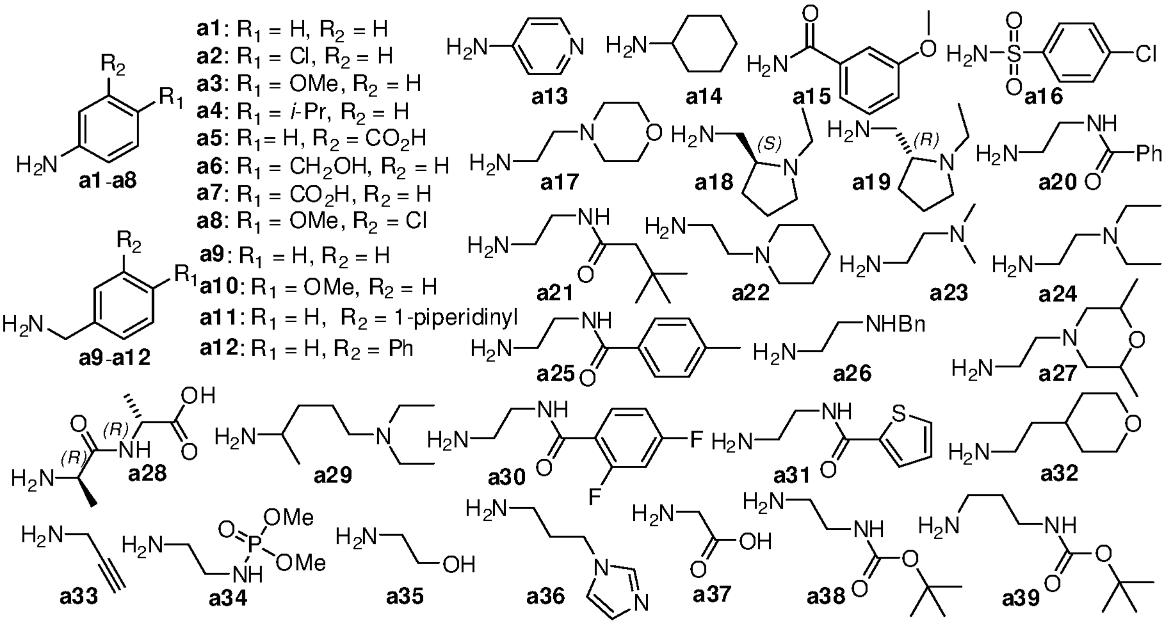
[0123] The synthetic routes of the target compound library of 1,2-benzisoselenazol-3(2*H*)-one derivatives **11** are straightforward and concise, and depicted in **Scheme 1**.[25] Starting from commercially available anthranilic acid (**8**), diazotization with sodium nitrite in hydrochloric acid followed by treatment with a basified solution of disodium diselenide (Na_2Se_2) under inert atmosphere afforded the 2,2'-diselanediyldibenzoic acid (**9a**) in good yield. It is worthy to note that the water used to prepare Na_2Se_2 solution should preferably be degassed to remove oxygen. Further conversion of acid **9a** to 2-(chlorocarbonyl)phenyl hypochloroselenoite (**10**) via treatment with thionyl chloride at refluxing temperature in the presence of a catalytic amount of dimethylformamide (DMF) was achieved in high yield. It is worthy to mention that the acid chloride **10** is unstable and should be kept under the nitrogen atmosphere in a freezer for prolonged storage. The synthesis of the final 1,2-benzisoselenazol-3(2*H*)-one derivatives **11** were successfully accomplished via treatment of acid chloride **10** with various aryl or alkyl substituted primary amines **a1-a14**, **a17-27**, **a29-a36**, **a38-a39**, amide **a15**, and sulfonamide **a16** (**Chart 1**) respectively in the presence of triethylamine with dichloromethane (DCM) as solvent, producing moderate to good yield. Similarly, treatment of acid chloride **10** with D-Ala-D-Ala (**a28**) or glycine (**a37**) in acetonitrile at room temperature furnished **11** with a carboxyl acid moiety. Moreover, three derivatives of **11** were selected for further functionalization, such as alkylation of **11_a36** with 1-butyl iodide in DMF to furnish **11** with an imidazolium moiety, and acidic deprotection of Boc group of **11_a38** and **11_a39** to yield **11** with an amine group. These amine derivatives were in turn converted to the desired carbamates derivatives **11_a43-11_a45** via standard carbamoylation procedure with 3-methyl-1-(((1,1,1-trifluoro-2-methylpropan-2-yl)oxy)carbonyl)-1*H*-imidazol-3-ium iodide or benzyl chloroformate. Furthermore, two structurally related compounds benzo[*f*][1,2,4]-selenadiazepine-3,5(2*H*,4*H*)-dione (**12**) and 2-phenyl-1,2-selenazolidin-3-one (**13_a1**) were also synthesized for testing. Treatment of acid chloride **10** with urea in DCM afforded the compound **12** with a characteristic seven-members 1,2,4-selenadiazepane ring in moderate yield. In the case of compound **13-a1**, starting from commercially available 3,3'-diselanediyldipropanoic acid (**9b**), *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide (EDCI) catalyzed condensation of acid **9b** with aniline (**a1**), followed by *tert*-butyl hydrogen peroxide assisted cyclization, smoothly generated the desired 1,2-selenazolin-3-one **13_a1** in low yield.

[0124] **Scheme 1.** Chemical synthesis of 1,2-benzisoselenazol-3(2*H*)-one derivatives and structurally related compounds[a].

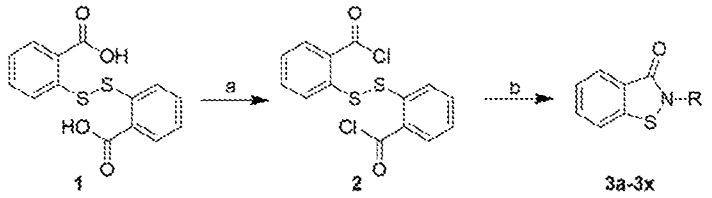


[0125] [a] (a) (1) NaNO$_2$, conc. HCl (aq), 0 °C, 30 min; (2) Na$_2$Se$_2$, H$_2$O, 0 °C to 60 °C., 14 h; (b) SOCl$_2$, DMF (cat.), 0 °C to reflux, 3 h; (c) For compound **11_a2**-**11_a27**, **11_a29**-**11_a36**, **11_a38**-**11_a39**, amine **a2**-**a27**, **a29**-**a36**, **a38**-**a39,** NEt$_3$, DCM, rt, 14 h; For compound **11_a28** and **11_a37**, D-Ala-D-Ala (**a28**) and glycine (**a37**), ACN, rt, 48 h; (d) urea, DCM, acetonitrile, 0 °C to rt, 24 h; (e) 1-butyl iodide, DMF, rt, 14 h; (f) conc. HCl, MeOH, DCM, 0 °C to rt, 14 h; (g) 3-methyl-1-(((1,1,1-trifluoro-2-methylpropan-2-yl)oxy)carbonyl)-1*H*-imidazol-3-ium iodide, NEt$_3$, CHCl$_3$, 14 h; (h) benzyl chloroformate, NEt$_3$, DCM, 0 °C to rt, 14 h; (i) (1) amine **a1**, EDCI, DCM, 0 °C to rt, 14 h; (2) *t*-BuOOH, MeOH, rt, 24 h.

[0126] **Chart 1.** Chemical structures of various amines **a1**-**a14**, **a17-27**, **a29**-**a36**, **a38**-**a39**, amide **a15**, sulfonamide **a16**, D-Ala-D-Ala (**a28**) and glycine (**a37**) used in this study

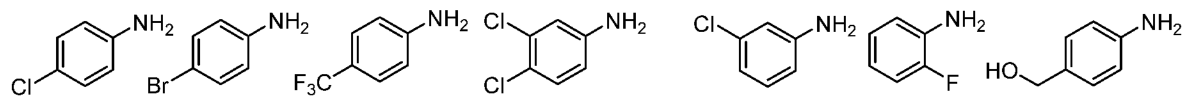


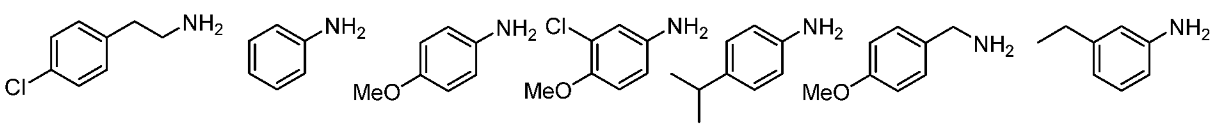
[0127] The synthetic routes of the target compound library of 1,2-benzisothiazol-3(2*H*)-one derivatives **3** are depicted in **Scheme 2**. Starting from commercially available 2-mercapto-methylbenzoate, hydrolysis with hydrochloric acid followed by treatment with iodine affords the 2,2'-dithiodiyldibenzoic acid (**1**). Further conversion of acid **1** to 2,2'-dithiodiyldibenzoyl chloride (**2**) via treatment with thionyl chloride at room temperature in the presence of a catalytic amount of dimethylformamide (DMF). The synthesis of the final 1,2-benzisothiazol-3(2*H*)-one derivatives **3** were successfully accomplished via treatment of acid chloride **2** with various aryl or alkyl substituted primary amines (**Chart 2**).

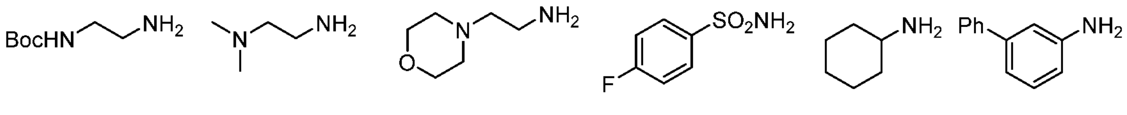


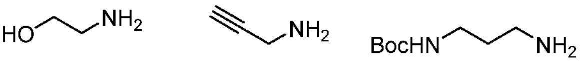
[0128] Reagents and reaction condition: (a) oxalyl chloride, DMF (cat.), DCM, rt., 3h. (b) i: amine (excess), triethylamine, DCM, 0 °C to rt., overnight; ii: Br_2, DCM, 0 °C to rt., overnight.

[0129] **Chart 2.** Chemical structures of various amines used in the preparation of **3a**-**3x**.









Pharmaceutical Compositions

[0130] The present disclosure also provides a pharmaceutical composition comprising any one of the aforementioned compounds and at least one pharmaceutically acceptable excipient.

[0131] The compounds described herein and their pharmaceutically acceptable salts are can be administered to a mammalian subject either alone or in combination with pharmaceutically acceptable carriers or diluents in a pharmaceutical composition according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, preferably parenterally. Parenteral administration includes intravenous, intramuscular, intraperitoneal, subcutaneous and topical, the preferred method being intravenous administration.

[0132] Accordingly, the present disclosure provides pharmaceutically acceptable compositions, which comprise a therapeutically-effective amount of one or more of the compounds described herein, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. The pharmaceutical compositions of the present disclosure may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; and (2) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue. The preferred method of administration of compounds of the present invention is parental administration (intravenous).

[0133] As set out herein, certain embodiments of the compounds described hrein may contain a basic functional group, such as amino or alkylaamino, and are, thus, capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable acids. The term "pharmaceutically-acceptable salts" in this respect, refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared in situ in the administration vehicle or the dosage form manufacturing process, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed during subsequent purification. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like.

[0134] The pharmaceutically acceptable salts of the compounds of the present disclosure include the conventional nontoxic salts or quaternary ammonium salts of the compounds, e.g., from nontoxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids such as hydrochloride, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicyclic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

[0135] In other cases, the compounds described herein may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable bases. The term "pharmaceutically-acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention. These salts can likewise be prepared in situ in the administration vehicle or the dosage form manufacturing process, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically-acceptable metal cation, with ammonia, or with a pharmaceutically-acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

[0136] Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives, solubilizing agents, buffers and antioxidants can also be present in the compositions.

[0137] Methods of preparing these formulations or compositions include the step of bringing into association a compound described herein with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers (liquid formulation), liquid carriers followed by lyophylization (powder formulation for reconstitution with sterile water or the like), or finely divided solid carriers, or both, and then, if necessary, shaping or packaging the product.

[0138] Pharmaceutical compositions of the present disclosure suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, chelating agents, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents. In the examples, the active ingredients are brought together with the pharmaceutically acceptable carriers in solution and then lyophilized to yield a dry powder. The dry powder is packaged in unit dosage form and then reconstituted for parental administration by adding a sterile solution, such as water or normal saline, to the powder.

[0139] Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0140] These compositions may also contain adjuvants, such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the compounds of the present invention may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0141] In some cases, in order to prolong the effect of a drug, it is 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 having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0142] The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[0143] The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[0144] **Methods of Use**

[0145] The present disclosure provides methods of treating bacterial infection, wherein the compounds and compositions described herein are used in combination with at least one beta-lactam antibiotic.

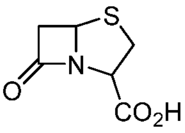
[0146] The compositions described herein are particularly useful for treating bacterial infections caused by bacteria that express a beta lactamase, such as by a carbapenemase or a penicillinase. The beta lactamase can be selected from TEM, SHV, CTX-M TEM, OXA TEM, PER, VEB, GES, IBC, IMP, VIM, KPC, and SME beta-lactamases In certain embodiments the beta lactamase is selected from the group consisting of VIM-1, IMP-4, KPC-2, CTX-M-3, CTX-M-14, CTX-M-15, TEM-1, SHV-12, and NDM-1. In certain embodiments, provided herein is a method of inhibiting a beta lactamase, such as VIM-1, IMP-4, KPC-2, CTX-M-3, CTX-M-14, CTX-M-15, TEM-1, SHV-12, and NDM-1, comprising contacting the beta lactamase with at least one of the compounds described herein.

[0147] The results provided below demonstrate the efficacy of the compounds described herein in the inhibition of NDM-1 and the resulting resensitization of beta-lactam resistant *E. coli* to menoprem. Since the NDM-1 gene is normally carried on a variety of plasmids, which will allow the gene to be readily transferred between different strains of bacteria by horizontal gene transfer, other bacteria have been shown to express NDM-1 besides *E. coli.*

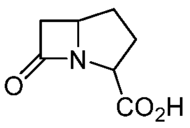
[0148] Thus, the compounds and methods described herein can be used to treat bacterial infection caused by bacteria other than *E. coli*, such as for example, bacteria from the genus Staphylococcus, such as Staphylococcus aureus or Staphylococcus epidermidis, Streptococcus, such as Streptococcus agalactiae, Streptococcus pneumoniae or Streptococcus faecalis, Micrococcus, such as Micrococcus luteus, Bacillus, such as Bacillus subtilis, Listerella, such as Listerella monocytogene, other members of the Escherichia genus, Klebsiella, such as Klebsiella pneumoniae, Proteus, such as Proteus mirabilis or Proteus vulgaris, Salmonella, such as Salmonella typhosa, Shigella, such as Shigella sonnef, Enterobacter, such as Enterobacter aerogenes or Enterobacter cloacae, Serratia, such as Serratia marcescens, Pseudomonas, such as Pseudomonas aeruginosa, Acinetobacter, such as Acinetobacter baumanii, Nocardia, such as

Nocardia autotrophica, or Mycobacterium, such as Mycobacterium fortuitum, and combinations thereof.

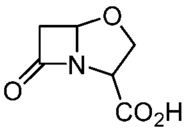
[0149] Some examples of beta-lactam antibiotics that can be used in combination with the methods of the present disclosure include, in general beta-lactams comprising penam, carbapenam, oxapenam, penem, carbapenem, monobactam, cephem, carbacephem, or oxacephem cores as shown below.



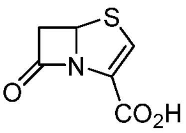
Penam



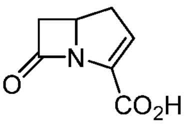
Carpenam



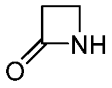
Oxopenam



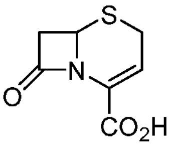
Penem



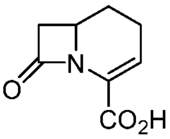
Carpenem



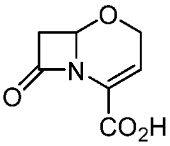
Monobactam



Cephem



Carbocephem



Oxacephem

[0150] Particularly useful members of those classes include, for example, penams, such as Benzylpenicillin (G), Benzathine Benzylpenicillin, Procaine Benzylpenicillin, Phenoxymethylpenicillin (V), Propicillin, Pheneticillin, Pzidocillin, Plometocillin, Penamecilli, Cloxacillin, Dicloxacillin, Flucloxacillin, Oxacillin, Nafcillin, Methicillin, Amoxicillin, Ampicilli, Pivampicillin, Hetacillin, Bacampicillin, Metampicillin, Talampicillin, Epicillin, Ticarcillin Carbenicillin, Carindacillin, Temocillin, Piperacillin, Azlocillin, Mezlocillin, Mecillinam, Pivmecillinam, and Sulbenicillin, penems, such as Faropenem and Ritipenem, carbapenem, such as Ertapenem, Doripenem, Imipenem, Meropenem, Biapenem, and Panipenem, Cephems, such as Cefazoli, Cefalexin, Cefadroxil, Cefapirin, Cefazedone, Cefazaflur, Cefradine, Cefroxadine, Ceftezole, Cefaloglycin, Cefacetrile, Cefalonium, Cefaloridine, Cefalotin, Cefatrizine, Cefaclor, Cefotetan, Cephamycin, Cefoxitin, Cefprozil, Cefuroxime, Cefuroxime axetil, Cefamandole, Cefminox, Cefonicid, Ceforanide, Cefotiam, Cefbuperazone, Cefuzonam, Cefmetazole, Carbacephem, Loracarbef, Cefixime, Ceftriaxon, Ceftazidime, Cefoperazone, Cefdinir, Cefcapene, Cefdaloxime, Ceftizoxime, Cefmenoxime, Cefotaxime, Cefpiramide, Cefpodoxime, Ceftibuten, Cefditoren, Cefetamet, Cefodizime, Cefpimizole, Cefsulodin, Cefteram, Ceftiolene, Oxacephem, Flomoxef, Latamoxef, Cefepime, Cefozopran, Cefpirome, Cefquinome, Ceftaroline fosamil, Ceftolozane, Ceftobiprole, Ceftiofur, Cefquinome, and Cefovecin, and monobactams, such as Aztreonam Tigemonam, Carumonam, and Nocardicin A.

[0151] In certain embodiments, the compounds described herein can be co-administered with two more beta-lactam antibiotics.

[0152] In certain embodiments, the compounds described herein can be co-administered with a beta-lactam antibiotic and an additional beta-lactamase inhibitor. In such instances, the additional beta-lactamase inhibitor can be selected from the group consisting of Sulbactam, Tazobactam, Clavulanic acid), Avibactam, and Vaborbactam.

[0153] The compounds described herein can be administered according to therapeutic protocols well known in the art. It will be apparent to those skilled in the art that the administration of the compounds described herein and the beta-lactam antibiotic can be varied depending on the disease being treated and the known effects of the beta-lactam antibiotic on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g., dosage amounts and times of administration) can be varied in view of the observed effects of the administered therapeutic agents (i.e., beta-lactam antibiotic) on the patient, and in view of the observed responses of the disease to the administered therapeutic agents.

[0154] Also, in general, compounds described herein and the beta-lactam antibiotic do not have to be administered in the same pharmaceutical composition, and may, because of different physical and chemical characteristics, have to be administered by different routes. For example, compounds described herein may be administered intravenously to generate and maintain good blood levels, while the beta-lactam antibiotic may be administered orally. The determination of the mode of administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the skilled clinician. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

[0155] The particular choice of beta-lactam antibiotic will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol.

[0156] A compound described and beta-lactam antibiotic may be administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the bacterial infection, the condition of the patient, and the actual choice of beta-lactam antibiotic to be administered in conjunction (i.e., within a single treatment protocol) with a compound described herein.

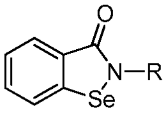
[0157] If a compound described herein and the beta-lactam antibiotic are not administered simultaneously or essentially simultaneously, then the optimum order of administration of the compound described herein and the beta-lactam antibiotic, may be different for different bacterial infections. Thus, in certain situations the compound described herein may be administered first followed by the administration of the beta-lactam antibiotic; and in other situations the beta-lactam antibiotic may be administered first followed by the administration of a compound described herein. This alternate administration may be repeated during a single treatment protocol. The determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the patient. For example, the beta-lactam antibiotic may be administered first and then the treatment continued with the administration of a compound described herein followed, where determined advantageous, by the administration of the beta-lactam antibiotic, and so on until the treatment protocol is complete.

[0158] Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of a component (compound described herein and beta-lactam antibiotic) of the treatment according to the individual patient's needs, as the treatment proceeds.

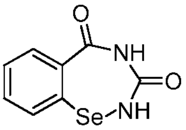
[0159] To generate a Mem resistant strain with a clean background for preliminary screening of compounds, a parental *E. coli* Tg1 strain was transformed into a resistant strain of *E. coli* Tg1 (NDM-1) by introducing a full-length *bla*$_{\text{NDM-1}}$ beta-lactamase gene isolated from a clinical *K. pneumoniae* isolate. *E. coli* Tg1 (NDM-1) is believed to better mimic clinical CRE strain than *E.*

coli BL21 (NDM-1). In line with the Clinical and Laboratory Standards Institute (CLSI) approved guidelines, antimicrobial tests were performed accordingly and the reproducibility was within one 2-fold dilution. The MIC of Mem against this screening strain was found to be 64 μg/mL (**Table 1**, entry 1), which was 128-fold higher than the parental *E. coli* Tg1 (MIC of Mem = 0.5 μg/mL), demonstrating that this strain was capable of producing the NDM-1 enzyme. The antimicrobial activities of all compounds were evaluated by measuring the MICs against this screening strain, and the results for the 1,2-benzisoselenazol-3(2H)-one analogs are presented in **Table 1** and the and 1,2-Benzisothiazol-3(2H)-one analogs in **Table 2**. In general, most of these compounds exhibited relatively weak or substantially no antibacterial activity when administered alone, with MICs ≥64 μg/mL (Entry 3-42), suggesting that these compounds were well-tolerated, relatively less toxic and exhibited little or no off-target side effects. However, six compounds (Entry 43-48) were found to exhibit mild antibacterial activity when administered alone, with MIC values ranging from 4 μg/mL to 32 μg/mL, indicating that these compounds are likely to undergo non-specific interaction with protein targets other than NDM-1. Structurally, these compounds possess polar functional groups, such as alcohol, amine and carboxylic acid; an exception is compound **11_a9**, which has a benzyl group.

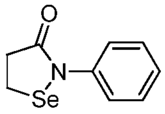
[0160] **Table 1.** MIC screening of compounds **11-13**, Eb and their combination with Mem against *E. coli* Tgl (NDM-1), calculated cLogP, FIC indices and synergistic efficiency of compounds [a]



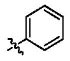
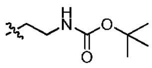
11_a2 - 11_a45

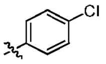
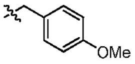
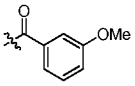
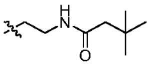
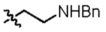
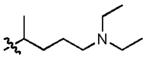
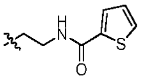
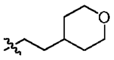
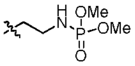
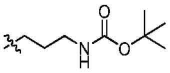
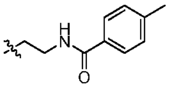
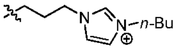
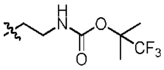
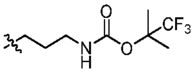
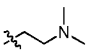
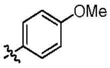
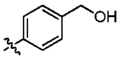


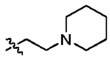
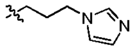
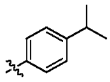
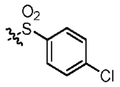
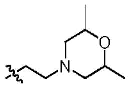
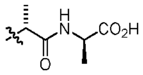
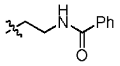
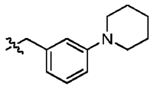
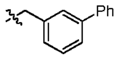
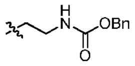
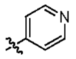
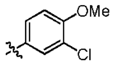
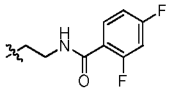
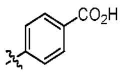
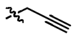
12

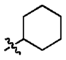
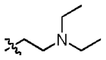
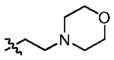
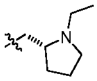
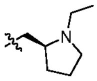
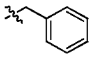
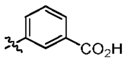
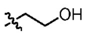
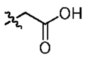
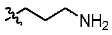
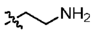


13_a1

Entry	Cpd	R	cLogP	MIC (μg/mL)		FIC	Synergistic
				Cpd	Cpd + Mem	Index	Efficiency
1	Mem	N.A.	N.A.	64	N.A.	N.A.	N.A.
2	Eb		3.71	64	16	0.500	0.043
3	**11_a38**		3.04	≥128	2	0.047	0.153

4	**11_a2**		4.42	≥128	4	0.094	0.139
5	**11_a10**		3.65	≥128	8	0.188	0.088
6	**11_a15**		3.31	≥128	8	0.188	0.084
7	**11_a21**		2.95	≥128	8	0.188	0.084
8	**11_a26**		3.45	≥128	8	0.188	0.084
9	**11_a29**		3.71	≥128	8	0.188	0.084
10	**11_a31**		2.66	≥128	8	0.188	0.084
11	**11_a32**		2.74	≥128	8	0.188	0.084
12	**11_a34**		0.77	≥128	8	0.188	0.084
13	**11_a39**		3.33	≥128	8	0.188	0.080
14	**11_a25**		3.32	≥128	8	0.188	0.076
15	**11_a40**		-0.24	≥128	8	0.188	0.076
16	**11_a43**		4.68	≥128	8	0.188	0.073
17	**11_a44**		4.97	≥128	8	0.188	0.070
18	**11_a23**		2.11	≥128	16	0.375	0.065
19	**11_a3**		3.62	≥128	16	0.375	0.054
20	**11_a6**		2.67	≥128	16	0.375	0.054

21	**11_a22**		3.16	≥128	16	0.375	0.054
22	**11_a36**		2.01	≥128	16	0.375	0.054
23	**11_a4**		5.13	≥128	16	0.375	0.052
24	**11_a16**		3.28	≥128	16	0.375	0.049
25	**11_a27**		2.89	≥128	16	0.375	0.049
26	**11_a28**		1.71	≥128	16	0.375	0.049
27	**11_a20**		2.82	≥128	16	0.375	0.047
28	**11_a11**		4.57	≥128	16	0.375	0.043
29	**11_a12**		5.62	≥128	16	0.375	0.043
30	**11_a45**		3.52	≥128	16	0.375	0.043
31	**13_a1**	N.A.	2.52	≥128	32	0.750	0.024
32	**11_a13**		2.21	≥128	32	0.750	0.018
33	**11_a8**		4.25	≥128	32	0.750	0.015
34	**11_a30**		2.97	≥128	32	0.750	0.013
35	**11_a7**		3.45	64	4	0.125	0.109
36	**11_a33**		2.06	64	8	0.250	0.107
37	**12**	N.A.	0.84	64	8	0.250	0.107

38	**11_a14**		3.99	64	8	0.250	0.087
39	**11_a24**		3.17	64	16	0.500	0.041
40	**11_a17**		2.60	64	16	0.500	0.039
41	**11_a19**		3.12	64	16	0.500	0.039
42	**11_a18**		3.12	64	16	0.500	0.039
43	**11_a9**		3.73	32	8	0.375	0.058
44	**11_a5**		3.45	32	8	0.375	0.052
45	**11_a35**		1.16	32	16	0.750	0.022
46	**11_a37**		1.39	8	2	0.281	0.091
47	**11_a42**		1.55	8	2	0.281	0.091
48	**11_a41**		1.24	4	4	1.063	-0.005

[0161] [a]Compound cLogP were calculated using ChemDraw Ultra (Version 12.0). The synergistic effect is determined by the FIC index, which is calculated as FIC (cpd) + FIC (Mem), where FIC (cpd) is the (MIC of cpd in combination with Mem)/(MIC of cpd alone) while FIC (Mem) is (MIC of cpd in combination with Mem)/(MIC of Mem alone). The drug combination is considered synergistic if the FIC Index is ≤ 0.5. Synergistic efficiency is calculated by measuring –ln(FIC index)/non-hydrogen atom. N.A.: Not Applicable. All experiments were performed in at least triplicates and inhibition of bacterial growth was assessed by naked eye upon incubation overnight.

Combination studies with Mem against E. coli Tg1 (NDM-1) and clinical NDM-1 producing CRE isolates

[0162] Next, to assess the synergistic activities of the test compounds when used in combination with Mem, MICs of Mem were evaluated by mixing Mem with the compounds at a mass ratio of

1:1. The FIC indices, which quantified the degree of interaction between antibiotic and adjuvant, were calculated as previously described, with FIC indices ≤ 0.5 depicting synergistic interaction. To better differentiate the compounds which have exactly the same FIC index values, here we proposed, for the first time, a simple idea of synergistic efficiency, which is a similar concept to the ligand efficiency as previously proposed. The synergistic efficiency is proposed to be calculated by using the equation as shown below,

$$\text{Synergistic efficiency} = \frac{-\ln(FIC\ index\ of\ a\ molecule)}{number\ of\ heavy\ atom\ in\ the\ molecule}$$

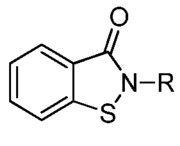
[0163] , where the heavy atom means non-hydrogen atom in a molecule. In fact, synergistic efficiency is a normalized FIC index to enable comparisons of synergistic activities between different molecular scaffolds but with the same FIC index. The larger the value of the synergistic efficiency, the stronger the synergistic interaction will be. It provides a useful parameter for medicinal chemists to choose a lead compound for further optimization. The results of Mem MICs when tested in combination with the compounds, cLogP, calculated FIC indices and synergistic efficiencies of all compounds are summarized in **Table 1**, in which compounds were prioritized according to the FIC indices and synergistic efficiency respectively. The parental compound Eb was used as a positive control for comparison purpose. The MIC of Mem in combination with Eb was 16 µg/mL with a calculated FIC index of 0.50 and synergistic efficiency of 0.043 (**Table 1**, entry 2), exhibiting only moderate synergistic activity. Generally, most of the compounds were found to exhibit stronger synergistic activity than Eb, with FIC indices ranging from 0.047 to 0.375. These compounds were divided into two series to investigate their SARs: (1) 1,2-benzisoselenazol-3(2*H*)-one derivatives with a 2-aryl or benzyl side chain and (2) 1,2-benzisoselenazol-3(2*H*)-one derivatives with a flexible 2-alkyl side chain.

[0164] For series 1, installation of various functional groups on the phenyl ring C of Eb, such as 4-Cl, 4-MeO, 4-CH_2OH, 3-CO_2H, 4-CO_2H, and 4-^{i}Pr improved the synergistic activities dramatically with FIC indices ranging from 0.094 to 0.375 (Entry 4, 19, 20, 23, 35, 44). Furthermore, replacing the phenyl ring C of Eb with different benzyl groups also helped improve the synergistic activities (Entry 5, 28, 29, 43). It is worthy to mention that replacing the freely rotatable benzylic carbon with a carbonyl or sulfonyl group of high rigidity maintained the synergistic activities (Entry 6, 24). Compound **12** with an unusual seven-members 1,2,4-

selenadiazepane ring also exhibited synergy (Entry 37). On the other hand, removal of the phenyl ring B or replacing the phenyl ring C of Eb with pyridine ring or 3-Cl-4-MeO di-substituted phenyl ring resulted in no synergistic activities (Entry 31-33). Among these derivatives, it should be mentioned that compound **11_a2** with a 4-Cl phenyl group demonstrated the most promising synergy, with a FIC index of 0.094 (Entry 4). However, its relatively high cLogP value of 4.42 indicate that it may have lower hydrophilicity and poorer aqueous solubility than Eb, which may impede *in vivo* efficacy study.

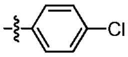
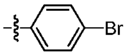
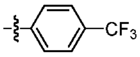
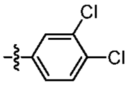
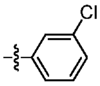
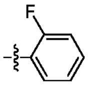
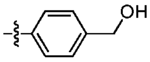
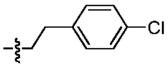
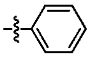
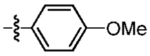
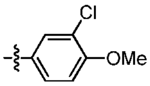
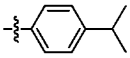
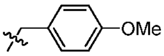
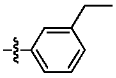
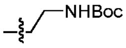
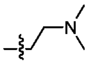
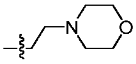
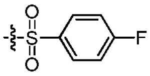
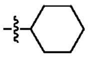
[0165] For series 2, replacing the 2-phenyl ring of Eb with various flexible alkyl side chains generated many compounds of promising synergistic activities, with FIC indices ranging from 0.047 to 0.500 (Entry 3, 7-18, 21-22, 25-27, 30, 36, 38-42). Among these compounds, compound **11_a38** exhibited the most promising synergistic activity, with a FIC index of 0.047 (Entry 3), which is about 10-fold that of Eb. At a concentration of 2 μg/mL, it could re-sensitize Mem resistant screening strain back to the susceptible level. The bulky Boc group of **11_a38** may be essential in conferring synergistic activity as its replacement with other functional groups, such as 3,3-dimethylbutanone (Entry 7), benzyl group (Entry 8), 2-thiophenylmethone (Entry 10), dimethylphosphonate (Entry 12), trifluoro-Boc (Entry 16), benzyl carbamate (Entry 30) and substituted phenylmethanones (Entry 14, 27, 34), resulted in weaker synergistic activities. Installation of heterocyclic rings at the terminal position, like 4-tetrahydropyran (Entry 11), *n*-butyl imidazolium (Entry 15), 1-piperidine (Entry 21), 1-imidazole (Entry 12) and 4-morpholine (Entry 25, 40), also caused weaker synergy. The CH_2CH_2 group of **11_a38** may be crucial for strong synergistic activity as increasing its length to $CH_2CH_2CH_2$ resulted in weaker synergy (Entry 13).

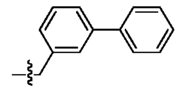
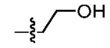
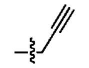
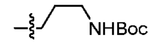
[0166] **Table 2.** MIC screening of compounds **3a-3x**, Eb and their combination with Mem against *E. coli* Tg1 (NDM-1), calculated cLogP, FIC indices and synergistic efficiency of compounds



3a-3x

Cpd	R	MIC (μg/mL)	cLogP	tPSA	FIC	Synergistic

		Cpd	Cpd + Mem			Index	Efficiency
Mem	N.A.	64	N.A.	N.A.	N.A.	N.A.	N.A.
Ebs	N.A.	64	16	3.70	20.31	0.50	0.043
3a		≥128	8	4.07	20.31	0.19	0.098
3b		≥128	8	4.22	20.31	0.19	0.098
3c		≥128	8	4.24	20.31	0.19	0.084
3d		≥128	8	4.66	20.31	0.19	0.093
3e		≥128	8	4.07	20.31	0.19	0.098
3f		≥128	64	3.50	20.31	1.50	-0.024
3g		≥128	16	2.32	40.54	0.38	0.054
3h		≥128	8	4.29	20.31	0.19	0.088
3i		≥128	16	3.35	20.31	0.38	0.061
3j		≥128	16	3.27	29.54	0.38	0.054
3k		≥128	32	3.90	29.54	0.75	0.015
3l		≥128	16	4.78	20.31	0.38	0.051
3m		64	32	2.82	29.54	1.00	0
3n		≥128	16	4.38	20.31	0.38	0.054
3o		≥128	32	2.67	58.64	0.75	0.014
3p		16	8	1.74	23.55	0.63	0.031
3q		≥128	32	1.54	32.78	0.75	0.016
3r		≥128	32	2.71	54.54	0.75	0.014
3s		64	8	3.52	20.31	0.25	0.087

3t		≥128	8	4.79	20.31	0.19	0.073
3u		32	16	0.79	40.54	0.75	0.022
3v		32	8	1.58	20.31	0.38	0.075
3w		≥128	32	2.92	58.64	0.75	0.014
3x	H	32	8	0.61	29.10	0.38	0.098
5a	N.A.	≥128	64	3.92	29.54	1.50	-0.019
5b	N.A.	≥128	32	3.40	20.31	0.75	0.016
5c	N.A.	≥128	≥128	4.12	40.64	3.00	-0.046
5d	N.A.	≥128	32	2.18	37.88	0.75	0.016
5e	N.A.	32	8	1.41	32.67	0.38	0.057
5f	N.A.	2	1	2.47	20.31	0.52	0.051

[0167] cLogP and tPSA were calculated by ChemDraw Ultra (Version 12.0). FICI was defined as FIC (cpd) + FIC (Mem), where FIC (cpd) was the ratio of $\mathrm{MIC_{combination}}$ to $\mathrm{MIC_{cpd}}$ and FIC (Mem) was the ratio of $\mathrm{MIC_{combination}}$ to $\mathrm{MIC_{Mem}}$. MIC value was determined with naked eye using the double dilution method at least triplicate. SE, Synergistic efficiency, it was calculated by –ln(FIC)/non-hydrogen atom. N.A.: Not Applicable.

[0168] A study on the effect of the mass ratio of meropenem to the compound **3a** in *E. coli* strain BL21 and BL21 containing NDM-1 was undertaken. The results of these experiments are shown in Table 3 below. Generally, the MIC of the mixtures of meropenem and the compound **3a** decreased with an increasing mass ratio of the compound of **3a**.

[0169] **Table 3** MIC (μg/mL) of **3a**, meropenem and different combinations of **3a** and meropenem recorded when tested against E. coli strain BL 21 with or without harboring the NDM-1-encoding plasmid.

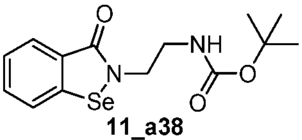
Treatments (ratio)	*E. coli* strains	
	BL21	BL21(NDM-1)
3a alone	≥1024	≥1024
Meropenem alone	<0.125	128

Meropenem + **3a** (1:0.15)	<0.125	4 (32 fold)
Meropenem + **3a** (1:0.188)	<0.125	4 (32 fold)
Meropenem + **3a** (1:0.25)	<0.125	4 (32 fold)
Meropenem + **3a** (1:0.375)	<0.125	2 (64 fold)
Meropenem + **3a** (1:0.75)	<0.125	2 (64 fold)
Meropenem + **3a** (1:1.5)	<0.125	2 (64 fold)
Meropenem + **3a** (1:3)	<0.125	1 (128 fold)
Meropenem + **3a** (1:6)	<0.125	0.5 (256 fold)
Meropenem + **3a** (1:9)	<0.125	0.5 (256 fold)
Meropenem + **3a** (1:12)	<0.125	0.5 (256 fold)
Meropenem + **3a** (1:15)	<0.125	0.5 (256 fold)

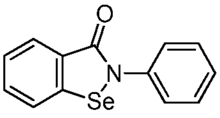
[0170] N = 1-3 independent experiments.

[0171] On the basis of the favorable FIC index of compound **11_a38** and MIC of Mem, we tested whether the observed synergy in the screening strain could also be reproduced in our in-house collection of clinically isolated NDM-1-producing strains, including four *E. coli*, two *K. oxytoca*, four *C. freundii*, nine *E. cloacae*, two *K. pneumoniae* and two *M. morganii* strains. These CRE strains were all NDM-1 positive and highly Mem resistant, with half of the strains exhibiting Mem MICs ≥128 μg/mL (**Table 4**). Apart from producing NDM-1, several of these strains also produced other beta-lactamases such as VIM-1, IMP-4, KPC-2, CTX-M-3, CTX-M-14, CTX-M-15, TEM-1 and SHV-12. As illustrated in **Table 4**, compound **11_a38** demonstrated no antibacterial activity itself (MICs ≥128 μg/mL), but strong synergy with Mem across this panel of clinical isolates, except for KP04 and EL18, with FIC indices ranging from 0.09 to 0.25 (**Table 4**, entry 1, 17). Compared with the parental compound Eb, compound **11_a38** exhibited much stronger synergy as well as the optimal cLogP value of 3.04 for the *in vivo* efficacy assay.

[0172] **Table 4.** MIC screening of compound **11_a38** and Eb in combination with Mem against clinically isolated, NDM-1-producing CRE strains[a]



11_a38



Eb

Entry	CRE Strains	Additional beta-lactamase determinants	MIC (µg/mL)			FIC index	MIC (µg/mL)		FIC index
			Mem	**11_a38**	**11_a38** + Mem		Eb	Eb + Mem	
1	KP04	b5, b1, b7, b8	≥128	≥128	32	0.50	≥128	64	1.00
2	KP14	b5, b3, b8	≥128	≥128	8	0.13	≥128	≥128	2.00
3	EC06	b4, b5, b8	≥128	≥128	8	0.13	≥128	64	1.00
4	EC33	b6	64	≥128	8	0.19	≥128	16	0.38
5	EC34	b6, b7, b8	64	≥128	4	0.09	≥128	16	0.38
6	EC45	none	≥128	≥128	4	0.06	≥128	16	0.25
7	KO03	b8	≥128	≥128	8	0.13	≥128	32	0.50
8	KO16	b8	≥128	≥128	8	0.13	≥128	32	0.50
9	CF05	b8	≥128	≥128	8	0.13	≥128	16	0.25
10	CF17	b8	64	≥128	4	0.09	≥128	16	0.38
11	CF35	b4, b3, b8	≥128	≥128	8	0.13	≥128	32	0.50
12	CF43	none	≥128	≥128	16	0.25	≥128	32	0.50
13	EL07	b5, b7, b8	64	≥128	8	0.19	≥128	16	0.38
14	EL08	b5, b7, b8	32	≥128	4	0.16	≥128	32	1.25
15	EL09	b4, b5, b7, b8	≥128	≥128	8	0.13	≥128	≥128	2.00
16	EL10	b5, b7, b8	64	≥128	8	0.19	≥128	64	1.50
17	EL18	b2, b7	32	≥128	16	0.63	≥128	64	2.50

18	EL19	b5, b3	≥128	≥128	16	0.25	≥128	≥128	2.00
19	EL22	b5, b7, b8	≥128	≥128	16	0.25	≥128	≥128	2.00
20	EL27	b4, b5, b7, b8	32	≥128	4	0.16	≥128	64	2.50
21	EL28	b7, b8	32	≥128	4	0.16	≥128	64	2.50
22	MM23	none	64	≥128	8	0.19	≥128	64	1.50
23	MM26	none	64	≥128	2	0.05	≥128	64	1.50

[0173] [a]EC, *Escherichia coli*; KO, *Klebsiella oxytoca*; CF, *Citrobacter freundii;* EL, *Enterobacter cloacae*; KP, *Klebsiella pneumoniae*; MM, *Morganella morganii*. Additional beta-lactamase determinants: b1: VIM-1, b2: IMP-4, b3: KPC-2, b4: CTX-M-3, b5: CTX-M-14, b6: CTX-M-15, b7: TEM-1, and b8: SHV-12. The synergistic effect is depicted by the FIC index, which is calculated as FIC (cpd) + FIC (Mem), where FIC (cpd) is the (MIC of cpd in combination with Mem)/(MIC of cpd alone) while FIC (Mem) is (MIC of cpd in combination with Mem)/(MIC of Mem alone). The drug combination is considered synergistic if the FIC Index ≤0.5. All experiments were performed in at least triplicates; the degree of inhibition of bacterial growth was determined with the naked eye after incubation.

[0174] Compound **3a** was also tested against our in-house collection of clinically isolated NDM-1-producing strains, including four *E. coli*, two *K. oxytoca*, four *C. freundii*, nine *E. cloacae*, two *K. pneumoniae* and two *M. morganii* strains. These CRE strains were all NDM-1 positive and highly Mem resistant, with half of the strains exhibiting Mem MICs ≥128 μg/mL (**Table 3**). Apart from producing NDM-1, several of these strains also produced other beta-lactamases such as VIM-1, IMP-4, KPC-2, CTX-M-3, CTX-M-14, CTX-M-15, TEM-1 and SHV-12.

[0175] **Table 5** MIC (μg/mL) screening of **3a**, Ebs and their combination with Mem against clinically isolated CRE strains carrying NDM-1

Strains	Additional β-lactamase	MRM alone	**3a**	**3a**+ MRM	FICI	Ebs alone	Ebs+ MRM	FICI
KP04	CTX-M-14, VIM-	≥128	≥128	32	0.50	≥128	64	1.00

	1,TEM-1,SHV-12							
KP14	CTX-M-14, KPC-2,SHV-12	≥128	≥128	16	0.25	≥128	≥128	2.00
EC06	CTX-M-3, CTX-M-14,SHV-12	≥128	≥128	16	0.25	≥128	64	1.00
EC33	CTX-M-15	64	≥128	16	0.38	≥128	16	0.38
EC34	CTX-M-15, TEM-1,SHV-12	64	≥128	16	0.38	≥128	16	0.38
EC45		≥128	≥128	16	0.25	≥128	16	0.25
KO03	SHV-12	≥128	≥128	16	0.25	≥128	32	0.50
KO16	SHV-12	≥128	≥128	16	0.25	≥128	32	0.50
CF05	SHV-12	≥128	≥128	64	1.00	≥128	16	0.25
CF17	SHV-12	64	≥128	4	0.09	≥128	16	0.38
CF35	CTX-M-3, KPC-2,SHV-12	≥128	≥128	16	0.25	≥128	32	0.50
CF43		≥128	≥128	16	0.25	≥128	32	0.50
ECL07	CTX-M-14, TEM-1,SHV-12	64	≥128	16	0.38	≥128	16	0.38
ECL08	CTX-M-14 ,TEM-1,SHV-12	32	≥128	8	0.32	≥128	32	1.25
ECL09	CTX-M-3, CTX-M-14, TEM-1,SHV-12	≥128	≥128	16	0.25	≥128	≥128	2.00
ECL10	CTX-M-14, TEM-1,SHV-12	64	≥128	16	0.38	≥128	64	1.50
ECL18	IMP-4,TEM-1	32	≥128	8	0.32	≥128	64	2.50

ECL19	CTX-M-14 ,KPC-2	≥128	≥128	16	0.25	≥128	≥128	2.00
ECL22	CTX-M-14, TEM-1,SHV-12	≥128	≥128	16	0.25	≥128	≥128	2.00
ECL27	CTX-M-3, CTX-M-14, TEM-1,SHV-12	32	≥128	8	0.32	≥128	64	2.50
ECL28	TEM-1,SHV-12	32	≥128	8	0.32	≥128	64	2.50
MM23	-	64	≥128	4	0.09	≥128	64	1.50
MM26	-	64	≥128	16	0.38	≥128	64	1.50

[0176] *EC, Escherichia coli; KO, Klebsiella oxytoca; CF, Citrobacter freundii; ECL, Enterobacter cloacae; KP, Klebsiella pneumoniae; MM, Morganella morganii.* N = 1-3 independent experiments.

*In vivo efficacy study of compound **11_a38** in combination with Mem*

[0177] To shed light on the potential clinical benefits of compound **11_a38**, evaluation of *in vivo* toxicity and antimicrobial efficacy was performed by employing a *Galleria mellonella* infection model. First, the tolerable dose of compound **11_a38** was investigated by injecting a solution of compound **11_a38** formulated in 50% PEG solution at different dosages (0, 10 or 30 mg/kg) into the hemocoel of larvae and the percent of survival were monitored at 12 h interval for 48 h. As shown in **Figure 7**, 100% survival rates were observed after 48 h for all treatment groups, indicating the relative safety of both the vehicle and the compound at the dosages tested. Next, the therapeutic abilities of compound **11_a38** alone, Mem alone or their combinations to protect the larvae against a lethal dose infection of clinical NDM-1-producing CRE isolate EL10 were determined at single doses of 0 or 10 mg/kg in drug monotherapy or 2 + 2 mg/kg, 10 + 10 mg/kg in drug combinations (**Figure 3**). 100% mortality of larvae were observed for the treatment groups of the vehicle, 10 mg/kg monotherapy of compound **11_a38**, and combination therapy at 2 + 2 mg/kg doses after 12 h. Encouragingly, 10 mg/kg monotherapy of Mem and combination therapy at 10 + 10 mg/kg doses after 48 h resulted in 20% and 60% survival rate respectively, demonstrating the excellent ability of compound **11_a38** to potentiate Mem antibacterial activity against clinical NDM-1-producing CRE strains. Compared to the treatment groups of monotherapy of compound **11_a38** and Mem at 10 mg/kg, it was found to be highly significant

($p < 0.05$). These results suggest that the therapeutic efficacy of the combination of Mem and compound **11_a38** should be further evaluated in a mouse infection model in future.

*Biochemical studies of compound **11_a38** with purified NDM-1 protein*

[0178] To confirm whether the observed synergy is due to the inhibition of the NDM-1 activity of compound **11_38**, standard enzymatic assays using purified NDM-1 protein and colorimetric beta-lactamase substrate nitrocefin were performed as previously described.[24] Compound **11_a38** demonstrated a potent *in vitro* dose-dependent inhibition of the NDM-1 enzyme, with a calculated IC_{50} value of about 13 μM (**Figure 4**). Previous studies of Eb indicated that it inhibited the activity of NDM-1 in a time-dependent and concentration-dependent manner. Based on the similarity of the core structure of Eb and compound **11_38**, we reasoned that both compounds might exhibit similar NDM-1 inhibition mechanism. To test this hypothesis, the rapid high dilution method was performed to test the reversibility of inhibition of compound **11_a38**. The results revealed that approximately 40% residual NDM-1 activity was observed after the rapid high dilution of a 20-minutes pre-incubation mixture when compared to positive control with no addition of compound **11_a38** (**Figure 6**), implying that the inhibitory effect of compound **11_a38** most likely involves slowly reversible binding to the NDM-1 protein. Compared with Eb, which has 11% residual activity after the rapid high dilution, compound **11_a38** exhibited weaker binding to NDM-1. As illustrated in **Figure 5A**, inhibition of NDM-1 by compound **11_a38** was also time-dependent and concentration-dependent. Moreover, plots of natural logarithm of percentage residual activity versus incubation time at different concentrations of compound **11_a38** indicated that inhibition of DNM-1 follows *pseudo*-first order kinetics with calculated kinetic parameters K_I of 17 ± 2 μM, k_{inact} of 0.068 ± 0.007 min^{-1} and k_{inact}/K_I of 0.067 $mM^{-1}s^{-1}$ respectively (**Figure 5B**).

[0179] To better illustrate the nature of potential interaction between NDM-1 protein and compound **11_a38**, we examined the wild-type and denatured NDM-1 protein treated with compound **11_a38** respectively, using nano-ESI-MS. First, we obtained the ESI mass spectra of wild-type and denatured NDM-1 protein for comparison (**Figure 8**). The deconvoluted ESI mass spectra of wild-type and denatured NDM-1 protein revealed an intact mass of 25,995 Da and 25,866 Da respectively, with a difference of 129 Da, suggesting that there were two zinc ions (2 × 65 Da) in the wild-type NDM-1 protein. In contrast, the deconvoluted ESI-MS spectra of compound **11_a38**-treated wild-type and denatured NDM-1 protein revealed a complex where the majority of protein had a mass of 26,272 Da and 26,208 Da respectively, with a difference of 64 Da, indicating that there was only one zinc ion in the compound **11_a38**-treated wild-type NDM-1 protein. Since the molecular mass of compound **11_a38** is about 341 and there is only one cysteine present in the NDM-1 protein, the protein mass difference between the denatured NDM-1 protein and compound **11_a38**-treated denatured NDM-1 protein is 342 Da, indicating that only one covalent interaction event occurred between compound **11_a38** and a cysteine molecule. The major peak (26,272 Da) in the deconvoluted ESI-MS spectra of compound **11_a38**-treated wild-type NDM-1 protein, therefore, represented the sum of the molecular mass of a denatured NDM-1 protein (25,866 Da), compound **11_a38** (341 Da) and one zinc ion (65 Da). These results are consistent with those of the parental compound Eb.

[0180] Based on the above data, the mechanism of inhibition of compound **11_a38** against NDM-1 protein was proposed. Both cationic divalent zinc ions in the active site of NDM-1 may act as Lewis acids to interact with the carbonyl oxygen of compound **11_a38**, causing the 1,2-benzisoselenazol-3(2*H*)-one being susceptible to nucleophilic attack by the nearby thiol group of cysteine. Not wishing to be bound by theory, it is believed that the thiol group of the cysteine reacts with compound **11_a38** to form a new S-Se covalent bond, leading to the loss of one zinc ion and thereby inhibiting the NDM-1 activity.

*[0181] Cytotoxicity studies of compound **11_a38** against eukaryotic cells*

[0182] As mentioned before, overcoming compound toxicity has been a great concern for the development of clinically useful NDM-1 inhibitors. Although a recent report of phase 2 clinical trial of Eb in an unrelated study indicated that treatment of Eb at a dose of 400 mg twice daily in human was safe, a potential problem usually associated with cysteine modifying agents is their high toxicity towards eukaryotic cells. To verify the safety of compound **11_a38**, its toxicity was tested against human cervical cancer HeLa cell line and mouse peritoneal fibroblast L929 cell line respectively. As shown in **Figure 9**, compound **11_a38** exhibited relatively low cytotoxicity against Hela and L929 cell lines, with a cell viability of 70% or higher at a concentration of 2 mg/mL, which is the effective synergistic concentration in the combination study. Microscopic investigation of both cell lines also indicated that there were no morphological changes after incubation with compound **11_a38** at these concentrations, displaying negligible cytotoxicity.

[0183] In this study, we demonstrated that structural modification of Eb allows generation of a focused compound library of 1,2-benzisoselenazol-3(2*H*)-one derivatives including forty-six candidates. Many compounds displayed stronger synergistic activity with Mem (FIC index $\leq$0.5) than Eb as well as better physiochemical properties (cLogP < that of Eb), but negligible antibacterial activity (MIC $\geq$128 μg/mL) when tested alone. One of these compounds was also demonstrated to exhibit potent synergistic activities with Mem against a panel of clinical NDM-1-producing CRE isolates. These promising results led to the efficacy testing of the lead compound **11_a38** in the *Galleria mellonella* infection model. Investigation of the mode of action suggests that compound **11_a38** exerted synergistic antimicrobial effect with meropenem by covalently binding to the NDM-1 protein. In summary, because of its structural simplicity, potent synergistic activity in combination with Mem, and low cytotoxicity towards eukaryotic cells, a new class of 1,2-benzisoselenazol-3(2*H*)-one derivatives may represent excellent leads for the development of next-generation carbapenem adjuvant co-therapy.

EXPERIMENTALS

Chemical Synthesis

[0184] All NMR spectra were recorded on a Bruker Advance-III spectrometer at 400 MHz for ^{1}H, 101 MHz for ^{13}C, and 376 MHz for ^{19}F. All NMR measurements were carried out at room temperature. The chemical shifts are reported as parts per million (ppm) in unit relative to the resonance of $CDCl_3$, DMSO-d_6, D_2O, Acetone-d_6, or MeOH-d_4. Mass spectra of low-resolution and high-resolution mass spectrometry were obtained on a Micromass Q-TOF-2 by electron spray ionization (ESI) mode. All chemical reagents and organic solvents were reagent grade and were used without further purification unless otherwise stated. The plates used for analytical thin-layer chromatography (TLC) were E. Merck Silica Gel $60F_{254}$ aluminum-backed plates (0.25 mm thickness) and were visualized under short and long UV light (254 and 365 nm) or stained with acidified potassium permanganate solution followed by gentle heating. Column chromatographic purifications were carried out on MN silica gel 60 (230–400 mesh) with gradient elution. Compound purity was determined by an Agilent 1100 series HPLC installed with a normal phase Prep-Sil Scalar column (4.6 mm × 250 mm, 5 μm) at UV detection of 254 nm (reference at 450 nm). All tested compounds were shown to have >95% purity according to the HPLC. 3-Methyl-1-(((1,1,1-trifluoro-2-methylpropan-2-yl)oxy)carbonyl)-1*H*-imidazol-3-ium iodide was synthesized using known methods Amines **a20, a21**, **a25**, **a30**, **a31** and **a34** were prepared in two steps by mixing the corresponding acid chlorides, such as benzoyl chloride, 3,3-dimethylbutanoyl chloride, 4-methylbenzoyl chloride, 2,4-difluorobenzoyl chloride and thiophene-2-carbonyl chloride, or dimethyl chlorophosphate with amine **a38** respectively, followed by acidic treatment of TFA using known methods. Amines **a1**-**a19**, **a22**-**a24**, **a26**-**a29**, **a33**, **a35**-**a39**, anthranilic acid (**8**) and 3,3'-diselanediyldipropanoic acid (**9b**) are commercially available.

[0185] **Preparation of 1,2-Benzisoselenazol-3(2H)-one Analogs**

[0186] **2,2'-Diselanediyldibenzoic acid (9a)**

[0187] Anthranilic acid (**8**) (18 g, 131 mmol) was dissolved in a solution of 37% hydrochloric acid (30 mL) and H_2O (30 mL). After the solution was cooled to 0 °C, a solution of $NaNO_2$ (10 g, 145 mmol in 10 mL H_2O) was added dropwise and the reaction mixture was stirred at 0 °C for 30 mins until all solid has been dissolved. The obtained diazonium salt was used immediately without further purification. To a well-stirred mixture of selenium powder (5.1 g, 65 mmol) in degassed H_2O (50 mL) under a nitrogen atmosphere, a $NaBH_4$ aqueous solution (4.45 g, 130 mmol in 10 mL H_2O) was added dropwise. After the Se powder has been completely dissolved, another batch of 5.1 g Se powder was added to the solution in portions. The reaction mixture was heated for 30 mins to ensure all the Se powder has been dissolved completely. The obtained brownish-red solution was basified with NaOH (10 g) in an ice bath. After cooling the basified solution to 5 °C, the diazonium salt prepared above was added dropwise at a rate at which the reaction temperature was maintained below 10 °C. Afterwards, the mixture was stirred under the nitrogen atmosphere at 60 °C for 11 h and another 3 h at room temperature. The mixture was acidified with hydrochloric acid to pH = 3 ~ 4 and then filtered. The obtained brownish-red precipitates were re-dissolved in NaOH solution (pH = 9 ~ 10) and any undissolved black solid was removed by filtration. The brownish-red filtrate was re-acidified with hydrochloric acid to pH = 1 and the red precipitates were filtered and washed twice with water. The desired product was obtained by recrystallization in acetic acid as a light yellow solid (15.6 g) in 60% yield. ^1H NMR (400MHz, DMSO-d_6) δ 13.56 (br. s., 1 H), 8.04 (d, J = 6.4 Hz, 1 H), 7.68 (d, J = 7.6 Hz, 1

H), 7.49 (t, $J = 7.6$ Hz, 1 H), 7.36 (t, $J = 7.0$ Hz, 1 H); ^{13}C NMR (101MHz, DMSO-d_6) δ 169.0, 134.1, 134.0, 132.0, 130.0, 129.2, 127.0.

[0188] **2-(Chlorocarbonyl)phenyl hypochloroselenoite (10)**

[0189] To a solution of $SOCl_2$ (10 mL) in a three-necked round bottom flask under a nitrogen atmosphere at 0 °C, compound **9a** (2.0 g, 8 mmol) in portions and serval drops of DMF were added. The mixture was heated to reflux at 80 °C for 3 h. After heating, excess $SOCl_2$ was removed by blowing with nitrogen and 20 mL hexane were added to the flask to extract the product for three times. After evaporating the hexane under reduced pressure, a bright yellow product of compound **10** (2.0 g) was obtained in 80% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.38 (d, $J = 7.0$ Hz, 1 H), 8.13 (d, $J = 8.3$ Hz, 1 H), 7.82 (t, $J = 7.6$ Hz, 1 H), 7.52 (t, $J = 7.6$ Hz, 1 H); ^{13}C NMR (101MHz, $CDCl_3$) δ 172.6, 146.3, 136.2, 134.6, 129.0, 127.1, 126.7.

[0190] **2-(4-Chlorophenyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a2)**

[0191] To a well-stirred solution of 4-chloroaniline (**a2**) (0.57 g, 4.5 mmol) and NEt_3 (5 mL) in dry DCM (25 mL) was added dropwise a solution of compound **10** (0.51 g, 2.0 mmol) at room temperature. The reaction mixture was stirred at room temperature for 14 h. The crude mixture was obtained by removal of the organic solvents under reduced pressure and was re-dissolved in DCM, followed by washing with H_2O for 3 times. The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuum. Purification of the product was performed by flash column chromatography on silica gel to afford the desired compound **11_a2** (0.28 g) in 45% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.04 (d, $J = 7.8$ Hz, 1 H), 7.59 (d, $J = 3.9$ Hz, 2 H), 7.51 (d, $J = 1.0$ Hz, 2 H), 7.41 (t, $J = 3.9$, 7.8 Hz, 1 H), 7.32 (d, $J = 1.0$ Hz, 2 H); ^{13}C NMR (101MHz, $CDCl_3$) δ 185.4, 134.7, 134.0, 129.4, 128.1, 126.7, 126.6, 125.2, 123.8, 121.0; HRMS *m/z* calcd for $(C_{13}H_8ClNOSe + H)^+$ 309.9532, found 309.9531.

[0192] **2-(4-Methoxyphenyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a3)**

[0193] Following the experimental procedure for the preparation of compound **11_a2** described above, but with 4-methoxyaniline (**a3**) (0.55 g, 4.5 mmol) as a starting material, compound **11_a3** (0.32 g) was obtained in 52% yield. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.08 (d, $J = 7.8$ Hz, 1 H), 7.89 (d, $J = 7.8$ Hz, 1 H), 7.67 (t, $J = 1.0$ Hz, 1 H), 7.53 - 7.45 (m, 3 H), 7.01 (d, $J = 8.8$ Hz, 2 H), 3.79 (s, 3 H); ^{13}C NMR (101MHz, DMSO-d_6) δ 165.4, 157.8, 139.5, 132.7, 132.5, 128.8, 128.3, 127.0, 126.6, 126.3, 114.8, 55.9; HRMS *m/z* calcd for $(C_{14}H_{11}NO_2Se + H)^+$ 306.0028, found 306.0033.

[0194] **2-(4-Isopropylphenyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a4)**

[0195] Following the experimental procedure for the preparation of compound **11_a2** described above, but with 4-isopropylaniline (**a4**) (0.61 g, 4.5 mmol) as a starting material, compound **11_a4** (0.35 g) was obtained in 55% yield. ^{1}H NMR (400MHz, DMSO-*d*$_6$) δ 8.09 (d, *J* = 7.8 Hz, 1 H), 7.90 (d, *J* = 7.8 Hz, 1 H), 7.68 (t, *J* = 7.8 Hz, 1 H), 7.53 (d, *J* = 1.0 Hz, 2 H), 7.48 (t, *J* = 1.0 Hz, 1 H), 7.33 - 7.30 (m, *J* = 7.8 Hz, 2 H), 2.91 (d, *J* = 6.8 Hz, 1 H), 1.22 (d, *J* = 6.8 Hz, 6 H); ^{13}C NMR (101MHz, DMSO-*d*$_6$) δ 165.4, 146.6, 139.4, 137.8, 132.6, 129.0, 128.4, 127.5, 126.7, 126.3, 125.3, 33.5, 24.3; HRMS *m/z* calcd for $(C_{16}H_{15}NOSe + H)^+$ 318.0392, found 318.0396.

[0196] **3-(3-Oxobenzo[*d*][1,2]selenazol-2(3*H*)-yl)benzoic acid (11_a5)**

[0197] Following the experimental procedure for the preparation of compound **11_a2** described above, but with 3-aminobenzoic acid (**a5**) (0.62 g, 0.45 mmol) as a starting material, compound **11_a5** (0.19 g) was obtained in 30% yield. ^{1}H NMR (400MHz, DMSO-*d*$_6$) δ 13.14 (br. s., 1 H), 8.25 (s, 1 H), 8.11 (d, *J* = 8.3 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.89 (d, *J* = 8.3 Hz, 1 H), 7.84 (d, *J* = 7.6 Hz, 1 H), 7.71 (t, *J* = 7.3 Hz, 1 H), 7.60 (t, *J* = 1.0 Hz, 1 H), 7.50 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR (101MHz, DMSO-*d*$_6$) δ 167.3, 165.7, 140.5, 139.3, 132.9, 132.2, 130.1, 129.2, 128.8, 128.5, 126.9, 126.8, 126.4, 125.4; HRMS *m/z* calcd for $(C_{14}H_9NO_3Se + H)^+$ 319.9820, found 319.9822.

[0198] **2-(4-(Hydroxymethyl)phenyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a6)**

[0199] Following the experimental procedure for the preparation of compound **11_a2** described above, but with 4-aminobenzyl alcohol (**a6**) (0.55 g, 4.5 mmol) as a starting material, compound **11_a6** (0.25 g) was obtained in 40% yield. ^{1}H NMR (400MHz, DMSO-*d*$_6$) δ 8.11 (d, *J* = 8.3 Hz, 1 H), 7.91 (d, *J* = 7.6 Hz, 1 H), 7.69 (t, *J* = 7.3 Hz, 1 H), 7.59 (d, *J* = 1.0 Hz, 2 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.40 (d, *J* = 1.0 Hz, 2 H), 5.25 (t, *J* = 5.4 Hz, 1 H), 4.53 (d, *J* = 5.1 Hz, 2 H); ^{13}C NMR (101MHz, DMSO-*d*$_6$) δ 165.4, 140.7, 139.4, 138.7, 132.6, 129.0, 128.4, 127.7, 126.7, 126.3, 124.9, 62.9; HRMS *m/z* calcd for $(C_{14}H_{11}NO_2Se + H)^+$ 306.0028, found 306.0030.

[0200] **4-(3-Oxobenzo[*d*][1,2]selenazol-2(3*H*)-yl)benzoic acid (11_a7)**

[0201] Following the experimental procedure for the preparation of compound **11_a2** described above, but with 4-aminobenzoic acid (**a7**) (0.62 g, 4.5 mmol) as a starting material, compound **11_a7** (0.24 g) was obtained in 38% yield. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.10 (d, *J* = 7.8 Hz, 1 H), 8.01 (d, *J* = 7.8 Hz, 2 H), 7.93 (d, *J* = 7.8 Hz, 1 H), 7.85 (d, *J* = 8.8 Hz, 2 H), 7.70 (t, *J* = 6.8 Hz, 1 H), 7.49 (t, *J* = 1.0 Hz, 1 H); ^{13}C NMR (101MHz, DMSO-d_6) δ 165.8, 139.2, 133.1, 131.0, 129.1, 128.6, 126.9, 126.4, 123.9; HRMS *m/z* calcd for $(C_{14}H_9NO_3Se + H)^+$ 319.9820, found 319.9825.

[0202] **2-(3-Chloro-4-methoxyphenyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a8)**

[0203] Following the experimental procedure for preparation of compound **11_a2** as described above but with 3-chloro-4-methoxyaniline (**a8**) (0.71 g, 4.5 mmol) as a starting material, compound **11_a8** (0.28 g) was obtained in 41% yield. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.08 (br. s., 1 H), 7.90 (br. s., 1 H), 7.77 (br. s., 1 H), 7.69 (br. s., 1 H), 7.48 (br. s., 2 H), 7.23 (br. s., 1 H), 3.89 (br. s., 3 H); ^{13}C NMR (101MHz, DMSO-d_6) δ 165.6, 153.1, 139.5, 133.3, 132.7, 128.6, 128.4, 126.9, 126.7, 126.3, 125.4, 121.4, 113.5, 56.8; HRMS *m/z* calcd for $(C_{14}H_{10}ClNO_2Se + H)^+$ 339.9638, found 339.9639.

[0204] **2-Benzylbenzo[*d*][1,2]selenazol-3(2*H*)-one (11_a9)**

[0205] Following the experimental procedure for the preparation of compound **11_a2** described above but with benzyl amine (**a9**) (0.49 g, 4.5 mmol) as a starting material, compound **11_a9** (0.35 g) was obtained in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.83 Hz, 1H), 7.59 (d, *J* = 3.91 Hz, 2H), 7.42 - 7.49 (m, 1H), 7.38 (s, 5H), 5.04 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 138.1, 137.2, 132.0, 129.0, 128.9, 128.6, 128.3, 127.4, 126.2, 124.0, 48.7; HRMS *m/z* calcd for $(C_{14}H_{11}NOSe + H)^+$ 290.0079, found 290.0085.

[0206] **2-(4-Methoxybenzyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a10)**

[0207] Following the experimental procedure for the preparation of compound **11_a2** described above but with 4-methoxybenzyl amine (**a10**) (0.62 g, 4.5 mmol) as a starting material, compound **11_a10** (0.31 g) was obtained in 45% yield. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.97 (d, *J* = 7.8 Hz, 1 H), 7.82 (d, *J* = 7.8 Hz, 1 H), 7.57 (t, *J* = 7.8 Hz, 1 H), 7.43 - 7.37 (m, 1 H), 7.26 (d, *J* = 8.8 Hz, 2 H), 6.89 (d, *J* = 7.8 Hz, 2 H), 4.81 (s, 2 H), 3.71 (s, 3 H); ^{13}C NMR (101MHz, DMSO-*d*$_6$) δ 166.6, 159.2, 139.7, 132.0, 130.7, 130.1, 128.5, 127.9, 126.3, 114.4, 55.6, 46.8; HRMS *m/z* calcd for $(C_{15}H_{13}NO_2Se + Na)^+$ 342.0010, found 342.0010.

[0208] **2-(3-(Piperidin-1-yl)benzyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a11)**

[0209] Following the experimental procedure for the preparation of compound **11_a2** described above but with 3-(1-piperidinyl)benzyl amine (**a11**) (0.86 g, 4.5 mmol) as a starting material, compound **11_a11** (0.07 g) was obtained in 10% yield. ^{1}H NMR (400MHz, MeOH-*d*$_4$) δ 7.97 (d, *J* = 7.8 Hz, 1 H), 7.88 (d, *J* = 7.8 Hz, 1 H), 7.60 (t, *J* = 7.3 Hz, 1 H), 7.45 (t, *J* = 1.0 Hz, 1 H), 7.22 (t, *J* = 1.0 Hz, 1 H), 6.98 (s, 1 H), 6.93 (d, *J* = 7.8 Hz, 1 H), 6.81 (d, *J* = 6.8 Hz, 1 H), 4.93 (s, 2 H), 3.13 (t, *J* = 4.9 Hz, 4 H), 1.71 - 1.65 (m, *J* = 5.4, 5.4 Hz, 4 H), 1.59 - 1.54 (m, 2 H); ^{13}C NMR (101MHz, MeOH-*d*$_4$) δ 167.8, 152.6, 139.8, 138.1, 131.7, 129.1, 127.6, 127.5, 125.8, 124.8, 119.2, 116.5, 116.4, 50.6, 25.4, 23.9; HRMS *m/z* calcd for $(C_{19}H_{20}N_2OSe + H)^+$ 373.0814, found 373.0817.

[0210] **2-([1,1'-Biphenyl]-3-ylmethyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a12)**

[0211] Following the experimental procedure for the preparation of compound **11_a2** described above but with 3-phenylbenzyl amine (**a12**) (0.82 g, 4.5 mmol) as a starting material, compound **11_a12** (0.58 g) was obtained in 80% yield. ^{1}H NMR (400MHz, MeOH-*d*$_4$) δ 7.98 (d, *J* = 7.8 Hz, 1 H), 7.89 (d, *J* = 8.8 Hz, 1 H), 7.62 - 7.55 (m, 5 H), 7.47 - 7.39 (m, 4 H), 7.33 (d, *J* = 7.8 Hz, 2 H), 5.06 (s, 2 H); ^{13}C NMR (101MHz, MeOH-*d*$_4$) δ 167.5, 141.7, 140.6, 139.8, 138.1, 131.7, 129.0, 128.5, 127.6, 127.5, 127.2, 126.9, 126.6, 126.6, 126.4, 125.8, 124.9; HRMS *m/z* calcd for $(C_{20}H_{15}NOSe + H)^+$ 366.0393, found 366.0395.

[0212] **2-(Pyridin-4-yl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a13)**

[0213] Following the experimental procedure for the preparation of compound **11_a2** described above but with 4-aminopyridine (**a13**) (0.41 g, 4.5 mmol) as a starting material, compound **11_a13** (0.26 g) was obtained in 48% yield. ^{1}H NMR (400MHz, DMSO-*d*$_6$) δ 8.56 (d, *J* = 4.9 Hz, 2 H), 8.08 (d, *J* = 7.8 Hz, 1 H), 7.93 (d, *J* = 6.8 Hz, 1 H), 7.83 (d, *J* = 4.9 Hz, 2 H), 7.71 (t, *J* = 7.3 Hz, 1 H), 7.49 (t, *J* = 7.3 Hz, 1 H); ^{13}C NMR (101MHz, DMSO-*d*$_6$) δ 166.5, 151.2, 147.8, 138.8, 133.5, 129.2, 128.6, 127.0, 126.4, 117.3; HRMS *m/z* calcd for $(C_{12}H_8NO_2Se + H)^+$ 276.9875, found 276.9881.

[0214] **2-Cyclohexylbenzo[*d*][1,2]selenazol-3(2*H*)-one (11_a14)**

[0215] Following the experimental procedure for the preparation of compound **11_a2** described above but with cyclohexylamine (**a14**) (0.45 g, 4.5 mmol) as a starting material, compound **11_a14** (0.25 g) was obtained in 44% yield. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.05 (d, *J* = 7.8 Hz, 1 H), 7.81 (d, *J* = 7.8 Hz, 1 H), 7.59 (t, *J* = 1.0 Hz, 1 H), 7.41 (t, *J* = 1.0 Hz, 1 H), 4.23 (br. s., 1 H), 1.92 (d, *J* = 9.8 Hz, 2 H), 1.80 (d, *J* = 11.7 Hz, 2 H), 1.64 (d, *J* = 12.7 Hz, 1 H), 1.49 - 1.33 (m, 4 H), 1.25 - 1.14 (m, 1 H); ^{13}C NMR (101MHz, DMSO-d_6) δ 166.1, 139.4, 131.7, 129.3, 127.7, 126.3, 126.2, 53.2, 34.0, 25.7, 25.3; HRMS *m/z* calcd for $(C_{13}H_{15}NOSe + H)^+$ 282.0392, found 282.0395.

[0216] **2-(3-Methoxybenzoyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a15)**

[0217] Following the experimental procedure for the preparation of compound **11_a2** described above but with 3-methoxybenzamide (**a15**) (0.68 g, 4.5 mmol) as a starting material, compound **11_a15** (0.37 g) was obtained in 55% yield. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.05 (d, *J* = 8.3 Hz, 1 H), 7.83 (d, *J* = 7.6 Hz, 1 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 7.46 (t, *J* = 7.0 Hz, 1 H), 7.38 (t, *J* = 8.3 Hz, 1 H), 7.24 - 7.16 (m, 2 H), 7.14 (d, *J* = 8.3 Hz, 1 H), 3.79 (s, 3 H); ^{13}C NMR (101MHz, DMSO-d_6) δ 171.1, 164.9, 159.1, 139.9, 136.4, 134.8, 129.8, 129.5, 129.1, 127.0, 126.6, 121.0, 117.5, 114.1, 55.8; HRMS *m/z* calcd for $(C_{15}H_{11}NO_3Se + Na)^+$ 355.9796, found 355.9806.

[0218] **2-((4-Chlorophenyl)sulfonyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a16)**

[0219] Following the experimental procedure for the preparation of compound **11_a2** described above but with 4-chlorobenzenesulfonamide (**a16**) (0.86 g, 4.5 mmol) as a starting material, compound **11_a16** (0.35 g) was obtained in 47% yield. ^{1}H NMR (400MHz, Acetone-d_6) δ 8.06 (d, *J* = 8.8 Hz, 2 H), 7.89 (d, *J* = 7.8 Hz, 1 H), 7.77 (d, *J* = 7.8 Hz, 1 H), 7.67 (d, *J* = 1.0 Hz, 1 H), 7.62 (d, *J* = 8.8 Hz, 2 H), 7.40 (t, *J* = 7.3 Hz, 1 H); ^{13}C NMR (101MHz, Acetone-d_6) δ 158.5, 133.8, 130.7, 128.3, 124.3, 123.3, 122.8, 120.9, 120.8, 119.4; HRMS *m/z* calcd for $(C_{13}H_8ClNO_3SSe + Na)^+$ 395.8971, found 395.8972.

[0220] **2-(2-Morpholinoethyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a17)**

[0221] Following the experimental procedure for the preparation of compound **11_a2** described above but with 4-(2-aminoethyl)morpholine (**a17**) (0.54 g, 4.5 mmol) as a starting material, compound **11_a17** (0.21 g) was obtained in 33% yield. ^{1}H NMR (400MHz, CDCl$_3$) δ 7.94 (d, *J* = 7.8 Hz, 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.45 (t, *J* = 7.8 Hz, 1 H), 7.28 (t, *J* = 7.3 Hz, 1 H), 3.95

- 3.85 (m, 2 H), 3.81 - 3.66 (m, 5 H), 2.53 (br. s., 6 H); ^{13}C NMR (101MHz, MeOH-d_4) δ 168.4, 142.8, 131.4, 127.3, 127.0, 125.5, 124.5, 66.4, 57.1, 53.0, 40.4; HRMS *m/z* calcd for $(C_{13}H_{16}N_2O_2Se + H)^+$ 313.0450, found 313.0460.

[0222] **(*S*)-2-((1-ethylpyrrolidin-2-yl)methyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a18)**

[0223] Following the experimental procedure for the preparation of compound **11_a2** described above but with (*S*)-(−)-2-aminomethyl-1-ethylpyrrolidine (**a18**) (0.58 g, 4.5 mmol) as a starting material, compound **11_a18** (0.34 g) was obtained in 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.82 Hz, 1H), 7.60 (d, *J* = 7.82 Hz, 1H), 7.55 (t, *J* = 7.34 Hz, 1H), 7.38 (t, *J* = 7.34 Hz, 1H), 4.60 (d, *J* = 13.69 Hz, 1H), 3.42 (dd, *J* = 1.96, 13.69 Hz, 1H), 3.31 (t, *J* = 6.85 Hz, 1H), 2.95 - 3.08 (m, 1H), 2.83 - 2.92 (m, 1H), 2.36 - 2.45 (m, 1H), 2.27 - 2.35 (m, 1H), 1.67 - 1.96 (m, 4H), 1.27 (t, *J* = 7.34 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 143.8, 131.4, 128.0, 127.7, 125.5, 123.3, 62.1, 52.8, 48.4, 44.6, 27.2, 23.3, 13.5; HRMS *m/z* calcd for $(C_{14}H_{18}N_2OSe + H)^+$ 312.0652, found 312.0654.

[0224] **(*R*)-2-((1-ethylpyrrolidin-2-yl)methyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a19)**

[0225] Following the experimental procedure for the preparation of compound **11_a2** described above but with (*R*)-(+)-2-aminomethyl-1-ethylpyrrolidine (**a19**) (0.58 g, 4.5 mmol) as a starting material, compound **11_a19** (0.33 g) was obtained in 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.82 Hz, 1H), 7.55 - 7.63 (m, 1H), 7.47 - 7.55 (m, 1H), 7.31 - 7.39 (m, 1H), 4.52 - 4.63 (m, 1H), 3.39 (dd, *J* = 2.93, 14.67 Hz, 1H), 3.27 (t, *J* = 7.34 Hz, 1H), 2.97 (dd, *J* = 7.34, 12.23 Hz, 1H), 2.79 - 2.89 (m, 1H), 2.32 - 2.41 (m, 1H), 2.23 - 2.32 (m, 1H), 1.82 - 1.94 (m, 1H), 1.63 - 1.82 (m, 3H), 1.24 (t, *J* = 7.34 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 143.8, 131.4, 127.9, 127.6, 125.4, 123.3, 62.1, 52.8, 48.3, 44.6, 27.2, 23.3, 13.5; HRMS *m/z* calcd for $(C_{14}H_{18}N_2OSe + H)^+$ 312.0659, found 312.0657.

[0226] ***N*-(2-(3-oxobenzo[*d*][1,2]selenazol-2(3*H*)-yl)ethyl)benzamide (11_a20)**

[0227] Following the experimental procedure for the preparation of compound **11_a2** described above but with *N*-(2-aminoethyl)benzamide (**a20**) (0.74 g, 4.5 mmol) as a starting material, compound **11_a20** (89 mg) was obtained in 13% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (t, *J* = 4.89 Hz, 1H), 8.01 (d, *J* = 7.82 Hz, 1H), 7.81 - 7.88 (m, 3H), 7.60 (t, *J* = 6.85 Hz, 1H), 7.52 (d, *J* = 6.85 Hz, 1H), 7.47 (d, *J* = 7.83 Hz, 2H), 7.41 - 7.45 (m, 1H), 3.91 (t, *J* = 5.87 Hz, 2H), 3.49 -

3.59 (m, 2H); ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 167.3, 167.2, 140.1, 134.7, 132.1, 131.8, 128.8, 128.8, 128.0, 127.8, 127.6, 127.6, 126.3, 126.1, 43.3; HRMS *m/z* calcd for $(C_{16}H_{14}N_2O_2Se + H)^+$ 347.0293, found 347.0294.

[0228] **3,3-Dimethyl-*N*-(2-(3-oxobenzo[*d*][1,2]selenazol-2(3*H*)-yl)ethyl)butanamide (11_a21)**

[0229] Following the experimental procedure for the preparation of compound **11_a2** described above but with *N*-(2-aminoethyl)-3,3-dimethylbutanamide (**a21**) (0.71 g, 4.5 mmol) as starting material, compound **11_a21** (0.18 g) was obtained in 27% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.82 Hz, 1H), 7.70 (d, *J* = 7.82 Hz, 1H), 7.61 (t, *J* = 7.34 Hz, 1H), 7.38 - 7.49 (m, 1H), 6.51 (br. s., 1H), 4.00 (t, *J* = 5.87 Hz, 2H), 3.52 - 3.66 (m, 2H), 2.06 (s, 2H), 0.98 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 168.2, 138.3, 132.2, 128.7, 126.8, 126.3, 124.2, 50.4, 44.2, 40.3, 30.8, 29.8; HRMS *m/z* calcd for $(C_{15}H_{20}N_2O_2Se + H)^+$ 341.0763, found 341.0766.

[0230] **2-(2-(Piperidin-1-yl)ethyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a22)**

[0231] Following the experimental procedure for the preparation of compound **11_a2** described above but with 1-(2-aminoethyl)piperidine (**a22**) (0.58 g, 4.5 mmol) as a starting material, compound **11_a22** (0.32 g) was obtained in 52% yield. ^{1}H NMR (400MHz, MeOH-*d*$_4$) δ 7.90 (d, *J* = 7.8 Hz, 1 H), 7.93 (d, *J* = 7.8 Hz, 1 H), 7.58 (t, *J* = 7.3 Hz, 1 H), 7.40 (t, *J* = 1.0 Hz, 1 H), 3.95 (t, *J* = 5.4 Hz, 2 H), 2.65 - 2.51 (m, 6 H), 1.73 (t, *J* = 1.0 Hz, 4 H); ^{13}C NMR (101MHz, MeOH-*d*$_4$) δ 168.3, 131.3, 127.4, 126.9, 126.9, 125.4, 124.4, 57.3, 54.0, 40.9, 25.5, 24.0; HRMS *m/z* calcd for $(C_{14}H_{18}N_2OSe + H)^+$ 311.0717, found 311.0659.

[0232] **2-(2-(Dimethylamino)ethyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a23)**

[0233] Following the experimental procedure for the preparation of compound **11_a2** described above but with *N*,*N*-dimethylethylenediamine (**a23**) (0.40 g, 4.5 mmol) as a starting material, compound **11_a23** (0.22 g) was obtained in 41% yield. ^{1}H NMR (400MHz, MeOH-*d*$_4$) δ 7.93 (d, *J* = 7.8 Hz, 1 H), 7.86 (d, *J* = 7.8 Hz, 1 H), 7.56 (t, *J* = 7.8 Hz, 1 H), 7.39 (t, *J* = 1.0 Hz, 1 H), 3.93 (t, *J* = 5.9 Hz, 2 H), 2.62 (t, *J* = 5.9 Hz, 2 H), 2.34 (s, 7 H); ^{13}C NMR (101MHz, MeOH-*d*$_4$) δ 168.5, 133.9, 132.1, 122.7, 66.3, 55.9, 53.2, 34.2; HRMS *m/z* calcd for $(C_{11}H_{14}N_2OSe + H)^+$ 271.0344, found 271.0351.

[0234] **2-(2-(Diethylamino)ethyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a24)**

[0235] Following the experimental procedure for the preparation of compound **11_a2** described above but with *N*,*N*-diethylethylenediamine (**a24**) (0.52 g, 4.5 mmol) as a starting material, compound **11_a24** (0.38 g) was obtained in 64% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.82 Hz, 1H), 7.59 (d, *J* = 7.82 Hz, 1H), 7.49 (t, *J* = 7.83 Hz, 1H), 7.26 - 7.39 (m, 1H), 3.87 - 4.01 (m, 2H), 2.61 - 2.76 (m, 6H), 1.07 (t, *J* = 6.85 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 143.1, 131.3, 127.9, 127.6, 125.5, 123.5, 52.6, 45.7, 41.5, 10.8; HRMS *m/z* calcd for $(C_{13}H_{18}N_2OSe + H)^+$ 300.0652, found 300.0654.

[0236] **4-Methyl-*N*-(2-(3-oxobenzo[*d*][1,2]selenazol-2(3*H*)-yl)ethyl)benzamide (11_a25)**

[0237] Following the experimental procedure for the preparation of compound **11_a2** described above but with *N*-(2-aminoethyl)-4-methylbenzamide (**a25**) (0.80 g, 4.5 mmol) as a starting material, compound **11_a25** (0.39 g) was obtained in 55% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 - 8.70 (m, 1H), 8.02 (d, *J* = 7.83 Hz, 1H), 7.84 (d, *J* = 7.83 Hz, 1H), 7.71 - 7.81 (m, *J* = 7.82 Hz, 2H), 7.60 (t, *J* = 7.82 Hz, 1H), 7.36 - 7.49 (m, 1H), 7.20 - 7.33 (m, *J* = 7.82 Hz, 2H), 3.91 (t, *J* = 5.38 Hz, 2H), 3.53 (d, *J* = 5.87 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.0, 166.8, 141.5, 140.2, 132.1, 131.9, 129.3, 128.2, 127.8, 127.7, 126.3, 126.2, 43.3, 21.4; HRMS *m/z* calcd for $(C_{17}H_{16}N_2O_2Se + H)^+$ 361.0450, found 361.0456.

[0238] **2-(2-(Benzylamino)ethyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a26)**

[0239] Following the experimental procedure for the preparation of compound **11_a2** described above but with N^1-benzylethane-1,2-diamine (**a26**) (0.68 g, 4.5 mmol) as a starting material, compound **11_a26** (0.07 g) was obtained in 11% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.82 Hz, 1H), 7.64 (d, *J* = 7.82 Hz, 1H), 7.57 (t, *J* = 7.34 Hz, 1H), 7.33 - 7.47 (m, 5H), 7.25 - 7.33 (m, 1H), 3.94 - 4.06 (m, 2H), 3.90 (s, 2H), 2.91 - 3.07 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 141.0, 139.6, 131.7, 128.6, 128.3, 128.2, 127.4, 127.2, 125.9, 123.7, 53.6, 48.7, 44.1; HRMS *m/z* calcd for $(C_{16}H_{16}N_2OSe + H)^+$ 333.0501, found 333.0504.

[0240] **2-(2-(2,6-Dimethylmorpholino)ethyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a27)**

[0241] Following the experimental procedure for the preparation of compound **11_a2** described above but with 2-(2,6-dimethylmorpholin-4-yl)ethanamine (**a27**) (0.71 g, 4.5 mmol) as a starting material, compound **11_a28** (0.22 g) was obtained in 32% yield. ^{1}H NMR (400MHz, MeOH-d_4) δ 7.91 (d, *J* = 7.8 Hz, 1 H), 7.94 (d, *J* = 7.8 Hz, 1 H), 7.60 (t, *J* = 6.8 Hz, 1 H), 7.42 (t, *J* = 7.3 Hz, 1 H), 4.00 (t, *J* = 1.0 Hz, 2 H), 3.95 - 3.86 (m, 2 H), 2.96 (d, *J* = 10.8 Hz, 2 H), 2.70 - 2.65 (m, 2 H), 1.90 (t, *J* = 11.2 Hz, 2 H), 1.18 (d, *J* = 5.9 Hz, 6 H); ^{13}C NMR (101MHz, MeOH-d_4) δ 158.0, 143.0, 131.4, 126.9, 125.4, 124.4, 121.0, 71.6, 58.7, 56.7, 40.5, 17.9; HRMS *m/z* calcd for $(C_{15}H_{20}N_2O_2Se + H)^+$ 341.0763, found 341.0770.

[0242] **(*R*)-2-((*R*)-2-(3-oxobenzo[*d*][1,2]selenazol-2(3*H*)-yl)propanamido)propanoic acid (11_a28)**

[0243] A solution of compound **10** (0.51 g, 2 mmol) in DCM was added dropwise into the solution of D-Ala-D-Ala (**a28**) (0.72 g, 4.5 mmol) in acetonitrile. The mixture was stirred under room temperature for 48 hours. After the reaction was completed, acetonitrile was removed under reduced pressure. The oily residue was dissolved in water and the product was extracted by EA and purified by column chromatography on silica gel with DCM and EA/MeOH (10:1) as eluent to afford the title compound **11_a28** (0.03 g) in 5% yield. ^{1}H NMR (400MHz, MeOH-d_4) δ 7.94 (t, *J* = 9.3 Hz, 2 H), 7.62 (t, *J* = 7.8 Hz, 1 H), 7.44 (t, *J* = 1.0 Hz, 1 H), 5.32 - 5.25 (m, 1 H), 4.31 - 4.16 (m, 1 H), 1.52 (d, *J* = 6.8 Hz, 3 H), 1.36 (d, *J* = 7.8 Hz, 3 H); ^{13}C NMR (101MHz, MeOH-d_4) δ 178.0, 170.5, 168.0, 141.5, 131.6, 127.3, 127.2, 125.5, 124.6, 53.0, 50.7, 17.8; HRMS *m/z* calcd for $(C_{13}H_{14}N_2O_4Se + H)^+$ 343.0192, found 343.0197.

[0244] **2-(5-(Diethylamino)pentan-2-yl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a29)**

[0245] Following the experimental procedure for preparation of compound **11_a2** described above but with *N^1*,*N^1*-diethylpentane-1,4-diamine (**a29**) (0.72 g, 4.5 mmol) as a starting material, compound **11_a29** (0.33 g) was obtained in 48% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.97 (d, *J* = 6.85 Hz, 2H), 7.59 (t, *J* = 7.34 Hz, 1H), 7.44 (t, *J* = 7.34 Hz, 1H), 4.61 - 4.77 (m, 1H), 2.31 - 2.59 (m, 6H), 1.67 (d, *J* = 6.85 Hz, 2H), 1.41 - 1.57 (m, 2H), 1.35 (d, *J* = 5.87 Hz, 3H), 0.97 (t, *J* = 7.34 Hz, 6H); ^{13}C NMR (101 MHz, MeOH-d_4) δ 167.7, 139.2, 131.6, 128.5, 127.5, 125.9, 125.0, 51.7, 50.2, 46.3, 35.4, 22.7, 21.2, 10.0; HRMS *m/z* calcd for $(C_{16}H_{24}N_2OSe + H)^+$ 341.1127, found 341.1133.

[0246] **2,4-Difluoro-*N*-(2-(3-oxobenzo[*d*][1,2]selenazol-2(3*H*)-yl)ethyl)benzamide (11_a30)**

[0247] Following the experimental procedure for the preparation of compound **11_a2** described above but with *N*-(2-aminoethyl)-2,4-difluorobenzamide (**a30**) (0.90 g, 4.5 mmol) as a starting material, compound **11_a30** (0.17 g) was obtained in 22% yield. ^{1}H NMR (400 MHz, MeOH-d_4)

δ 7.94 (t, *J* = 7.82 Hz, 2H), 7.80 (q, *J* = 7.83 Hz, 1H), 7.62 (t, *J* = 7.34 Hz, 1H), 7.38 - 7.53 (m, 1H), 7.05 (t, *J* = 8.80 Hz, 2H), 4.07 (t, *J* = 4.89 Hz, 2H), 3.73 (t, *J* = 5.38 Hz, 2H); ^{13}C NMR (101 MHz, MeOH-*d*$_4$) δ 168.3, 164.8 (d, *J* = 2.20 Hz), 164.6 (dd, *J* = 253.09, 12.47 Hz), 160.7 (dd, *J* = 253.09, 12.47 Hz), 140.0, 132.0 (dd, *J* = 10.27, 3.67 Hz), 131.7, 127.4, 127.3, 125.7, 124.9, 124.8, 119.2 (dd, *J* = 13.20, 3.67 Hz), 111.4 (dd, *J* = 22.01, 3.67 Hz), 104.0 (dd, *J* = 27.14, 25.68 Hz), 43.2, 39.7; HRMS *m/z* calcd for $(C_{16}H_{12}\ F_2N_2O_2Se + H)^+$ 383.0105, found 383.0100.

[0248] ***N*-(2-(3-oxobenzo[*d*][1,2]selenazol-2(3*H*)-yl)ethyl)thiophene-2-carboxamide (11_a31)**

[0249] Following the experimental procedure for the preparation of compound **11_a2** described above but with *N*-(2-aminoethyl)thiophene-2-carboxamide (**a31**) (0.76 g, 4.5 mmol) as a starting material, compound **11_a31** (56 mg) was obtained in 8% yield. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.71 (br. s., 1H), 8.02 (d, *J* = 6.85 Hz, 1H), 7.84 (d, *J* = 6.85 Hz, 1H), 7.75 (br. s., 2H), 7.61 (br. s., 1H), 7.29 - 7.52 (m, 1H), 7.15 (br. s., 1H), 3.89 (m., 2H), 3.51 (m., 2H); ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 167.0, 161.9, 140.3, 140.2, 131.9, 131.2, 128.7, 128.3, 128.2, 127.8, 126.3, 126.2, 43.3. LRMS *m/z* calcd for $(C_{16}H_{12}\ F_2N_2O_2Se + H)^+$ 353.3, found 353.4.

[0250] **2-(2-(Tetrahydro-2*H*-pyran-4-yl)ethyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a32)**

[0251] Following the experimental procedure for the preparation of compound **11_a2** described above but with 2-(tetrahydro-2*H*-pyran-4-yl)ethanamine (**a32**) (0.58 g, 4.5 mmol) as a starting material, compound **11_a32** (0.40 g) was obtained in 64% yield. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, *J* = 7.83 Hz, 1H), 7.68 (d, *J* = 7.82 Hz, 1H), 7.56 (t, *J* = 7.34 Hz, 1H), 7.33 - 7.48 (m, 1H), 3.82 - 4.01 (m, 4H), 3.32 (t, *J* = 11.74 Hz, 2H), 1.61 - 1.71 (m, 4H), 1.53 - 1.61 (m, 1H), 1.25 - 1.38 (m, 2H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 167.2, 137.8, 131.9, 128.7, 127.6, 126.2, 124.2, 67.9, 42.0, 37.5, 32.8, 32.2; HRMS *m/z* calcd for $(C_{14}H_{17}NO_2Se + H)^+$ 313.0498, found 313.0512.

[0252] **2-(Prop-2-yn-1-yl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a33)**

[0253] Following the experimental procedure for the preparation of compound **11_a2** described above but with prop-2-yn-1-amine (**a33**) (0.25 g, 4.5 mmol) as a starting material, compound **11_a33** (0.24 g) was obtained in 51% yield. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.06 (d, *J* = 7.82 Hz, 1H), 7.55 - 7.72 (m, 2H), 7.44 (t, *J* = 7.34 Hz, 1H), 4.67 (d, *J* = 1.96 Hz, 2H), 2.49 (t, *J* = 2.45 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 138.1, 132.3, 128.9, 127.0, 126.3, 124.1, 74.4, 34.3; HRMS *m/z* calcd for $(C_{10}H_7NOSe + H)^+$ 238.9745, found 238.9768.

[0254] **Dimethyl (2-(3-oxobenzo[*d*][1,2]selenazol-2(3*H*)-yl)ethyl)phosphoramidate (11_a34)**

[0255] Following the experimental procedure for the preparation of compound **11_a2** described above but with dimethyl (2-aminoethyl)phosphoramidate (**a34**) (0.63 g, 4.5 mmol) as a starting material, compound **11_a34** (0.18 g) was obtained in 26% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.83 Hz, 1H), 7.70 (d, *J* = 7.82 Hz, 1H), 7.54 - 7.62 (m, 1H), 7.40 (t, *J* = 7.82 Hz, 1 H), 3.94 (t, *J* = 5.87 Hz, 2H), 3.66 (s, 3H), 3.64 (s, 4H), 3.22 - 3.32 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 138.5, 132.1, 128.6, 127.0, 126.2, 124.2, 77.4, 77.1, 76.8, 53.2, 53.1, 45.9, 45.9, 41.5, 28.4; HRMS *m/z* calcd for $(C_{11}H_{15}N_2O_4PSe + H)^+$ 351.0007, found 351.0012.

[0256] **2-(2-Hydroxyethyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a35)**

[0257] Following the experimental procedure for the preparation of compound **11_a2** described above but with 2-aminoethanol (**a35**) (0.27 g, 4.5 mmol) as a starting material, compound **11_a35** (0.24 g) was obtained in 50% yield. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.05 (d, *J* = 7.8 Hz, 1 H), 7.83 (d, *J* = 7.8 Hz, 1 H), 7.60 (t, *J* = 7.3 Hz, 1 H), 7.40 (t, *J* = 7.3 Hz, 1 H), 5.11 (br. s., 1 H), 3.81 (t, *J* = 5.4 Hz, 2 H), 3.71 - 3.58 (m, 2 H); ^{13}C NMR (101MHz, MeOH-d_4) δ 168.3, 140.7, 131.6, 127.3, 127.2, 125.6, 124.7, 60.7, 46.6; HRMS *m/z* calcd for $(C_9H_9NO_2Se + H)^+$ 243.9877, found 243.9869.

[0258] **2-(3-(1*H*-imidazol-1-yl)propyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (11_a36)**

[0259] Following the experimental procedure for the preparation of compound **11_a2** described above but with 1-(3-aminopropyl)imidazole (**a36**) (0.58 g, 4.5 mmol) as a starting material, compound **11_a36** (0.22 g) was obtained in 36% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.96 (d, *J* = 7.82 Hz, 2H), 7.84 (s, 1H), 7.65 (t, *J* = 7.34 Hz, 1H), 7.48 (t, *J* = 7.34 Hz, 1H), 7.26 (s, 1H), 7.03 (s, 1H), 4.15 (t, *J* = 7.34 Hz, 2H), 3.88 (t, *J* = 6.36 Hz, 2H), 2.26 (quin, *J* = 6.85 Hz, 2H); ^{13}C NMR (101 MHz, MeOH-d_4) δ 168.2, 139.5, 137.0, 131.8, 127.5, 127.2, 125.9, 125.0, 119.4, 119.3, 44.1, 41.2, 31.3; HRMS *m/z* calcd for $(C_{13}H_{13}N_3OSe + H)^+$ 308.0300, found 308.0302.

[0260] **2-(3-Oxobenzo[*d*][1,2]selenazol-2(3*H*)-yl)acetic acid (11_a37)**

[0261] A solution of compound **10** (0.51 g, 2 mmol) in DCM was added dropwise into the solution of glycine (**a37**) (0.34 g, 4.5 mmol) in acetonitrile. The mixture was stirred under room temperature for 48 hours. After the stirring, acetonitrile was removed under reduced pressure. The oily residue was dissolved in diethyl ether and stirred in diluted hydrochloric acid solution (1.5 mL HCl in 40 mL H_2O) overnight until the formation precipitate. The precipitate was filtered off, washed with H_2O and recrystallized in MeOH/H_2O (3:2) to furnish the title compound **11_a37** (0.35 g) in 68% yield. ^1H NMR (400MHz, Acetone-*d*$_6$) δ 8.08 (d, *J* = 7.8 Hz, 1 H), 7.93 (d, *J* = 7.8 Hz, 1 H), 7.64 (t, *J* = 6.8 Hz, 1 H), 7.45 (t, *J* = 7.3 Hz, 1 H), 4.53 (s, 2 H); ^{13}C NMR (101MHz, Acetone-*d*$_6$) δ 170.1, 167.3, 140.3, 131.7, 127.7, 127.3, 125.7, 125.5, 44.8; HRMS *m/z* calcd for $(C_9H_7NO_3Se + H)^+$ 256.9591, found 257.9664.

[0262] ***tert*-Butyl (2-(3-oxobenzo[*d*][1,2]selenazol-2(3*H*)-yl)ethyl)carbamate (11_a38)**

[0263] Following the experimental procedure for the preparation of compound **11_a2** described above but with *N*-Boc-ethylenediamine (**a38**) (0.72 g, 4.5 mmol) as a starting material, compound **11_a38** (0.52 g) was obtained in 76% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.82 Hz, 1H), 7.55 - 7.72 (m, 2H), 7.44 (t, *J* = 7.34 Hz, 1H), 5.12 (br. s., 1H), 3.98 (t, *J* = 5.38 Hz, 2H), 3.40 - 3.54 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 132.1, 128.8, 126.9, 126.3, 124.0, 79.6, 44.5, 40.9, 28.4; HRMS *m/z* calcd for $(C_{14}H_{18}N_2O_3Se + Na)^+$ 366.0370, found 366.0372.

[0264] ***tert*-Butyl (3-(3-oxobenzo[*d*][1,2]selenazol-2(3*H*)-yl)propyl)carbamate (11_a39)**

[0265] Following the experimental procedure for the preparation of compound **11_a2** described above but with *N*-Boc-1,3-propanediamine (**a39**) (0.78 g, 4.5 mmol) as a starting material, compound **11_a39** (0.32 g) was obtained in 46% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.83 Hz, 1H), 7.67 (d, *J* = 7.83 Hz, 1H), 7.52 (t, *J* = 6.85 Hz, 1H), 7.31 - 7.40 (m, 1H), 5.56 (br. s., 1H), 3.87 (t, *J* = 6.36 Hz, 2H), 3.03 - 3.14 (m, 2H), 1.80 (quin, *J* = 6.36 Hz, 2H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 156.1, 138.1, 132.0, 128.7, 127.1, 126.2, 124.3, 79.0, 77.5, 77.2, 76.9, 41.9, 36.9, 30.4, 28.4; HRMS *m/z* calcd for $(C_{15}H_{20}N_2O_3Se + H)^+$ 357.0713, found 357.0726.

[0266] **3-Butyl-1-(3-(3-oxobenzo[*d*][1,2]selenazol-2(3*H*)-yl)propyl)-1*H*-imidazol-3-ium iodide (11_a40)**

[0267] Reaction of compound **11_a36** (0.30 g, 1 mmol) with 1-butyl iodide (0.22 g, 1.2 mmol) using DMF (5 mL) as the solvent at room temperature gave the title compound **11_a40** (0.04 g) in 12% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.77 (d, *J* = 1.71 Hz, 1H), 7.69 - 7.74 (m, 1H), 7.59 (d, *J* = 7.82 Hz, 1H), 7.50 (dd, *J* = 1.47, 7.58 Hz, 1H), 7.41 (dt, *J* = 1.34, 7.64 Hz, 1H), 7.26 - 7.36 (m, 1H), 4.42 (t, *J* = 6.72 Hz, 2H), 4.22 - 4.34 (m, 2H), 3.44 (t, *J* = 6.36 Hz, 2H), 3.04 - 3.13 (m, 2H), 1.85 - 2.01 (m, 2H), 1.68 - 1.76 (m, 2H), 1.28 - 1.37 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 141.7, 135.0, 134.7, 134.4, 131.3, 129.7, 126.5, 126.4, 61.5, 57.1, 53.4, 46.2, 46.2, 39.7, 35.6, 35.5, 33.7, 30.2, 26.6, 23.3, 23.1, 16.5, 16.5, 16.4, 14.2; HRMS *m/z* calcd for $(C_{17}H_{22}N_3OSe + H)^+$ 364.0928, found 364.0925.

[0268] **2-(2-Aminoethyl)benzo[*d*][1,2]selenazol-3(2*H*)-one hydrochloride (11_a41)**

[0269] Hydrochloric acid (3 mL) was added dropwise into a solution of compound **11_a38** (0.50 g, 1.5 mmol) in MeOH (5 mL) and DCM (5 mL) at 0 °C. The mixture was stirred for 14 h. The solvent was evaporated under reduced pressure. MeOH and ether were added to form precipitates, which were filtered and washed twice with ether to furnish the title compound **11_a41** (0.25 g) in 61% yield. ^{1}H NMR (400 MHz, D_2O) δ 7.76 (d, *J* = 7.82 Hz, 2H), 7.57 (t, *J* = 7.34 Hz, 1H), 7.36 - 7.43 (m, 1H), 3.98 - 4.05 (m, 2H), 3.23 - 3.30 (m, 2H); ^{13}C NMR (101 MHz, D_2O) δ 169.8, 139.7, 132.8, 127.7, 126.6, 126.2, 124.9, 42.1, 39.6; HRMS *m/z* calcd for $(C_9H_{10}N_2OSe + H)^+$ 243.0037, found 243.0036.

[0270] **2-(3-Aminopropyl)benzo[*d*][1,2]selenazol-3(2*H*)-one hydrochloride (11_a42)**

[0271] Hydrochloric acid (3 mL) was added dropwise into a mixture of compound **11_a39** (0.50 g, 1.4 mmol) in MeOH (5 mL) and DCM (5 mL) at 0 °C. The mixture was stirred for 14 h. The solvent was evaporated under reduced pressure. MeOH and ether were added to form precipitates, which were filtered and washed twice with ether to furnish the title compound **11_a42** (0.21 g) in 51% yield. ^{1}H NMR (400 MHz, D_2O) δ 7.55 (d, *J* = 7.82 Hz, 1H), 7.48 (d, *J* = 7.82 Hz, 1H), 7.33 (t, *J* = 7.34 Hz, 1H), 7.15 (t, *J* = 7.34 Hz, 1H), 3.63 (t, *J* = 6.85 Hz, 2H), 2.84 (t, *J* = 7.34 Hz, 2H), 1.82 - 1.94 (m, 2H); ^{13}C NMR (101 MHz, D_2O) δ 168.5, 139.3, 132.3, 127.3, 126.3, 126.1, 124.7, 41.4, 36.7, 27.4; HRMS *m/z* calcd for $(C_{10}H_{12}N_2OSe + H)^+$ 257.0184, found 257.0193.

[0272] **1,1,1-Trifluoro-2-methylpropan-2-yl (2-(3-oxobenzo[*d*][1,2]selenazol-2(3*H*)-yl)ethyl)carbamate (11_a43)**

[0273] Further treatment of compound **11_a41** (0.28 g, 1.0 mmol) with 3-methyl-1-(((1,1,1-trifluoro-2-methylpropan-2-yl)oxy)carbonyl)-1*H*-imidazol-3-ium iodide (0.44 g, 1.2 mmol) in the NEt_3 (5 mL) using $CHCl_3$ (5 mL) as the solvent produced the title compound **11_a43** (0.36 g) in 46% yield. ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.01 (d, J = 7.83 Hz, 1H), 7.93 (d, J = 7.82 Hz, 1H), 7.59 - 7.71 (m, 1H), 7.42 - 7.52 (m, 1H), 6.79 (br. s., 1H), 3.94 (t, J = 5.87 Hz, 2H), 3.45 (q, J = 5.71 Hz, 2H), 1.65 (s, 6H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 131.7, 127.9, 127.6, 125.8, 125.1, 43.5, 40.7, 29.5, 29.3, 29.1, 28.9, 28.7, 28.6, 28.4, 19.0; ^{19}F NMR (376 MHz, Acetone-d_6) δ –85.23; HRMS *m/z* calcd for $(C_{14}H_{15}F_3N_2O_3Se + H)^+$ 397.0273, found 397.0278.

[0274] **1,1,1-Trifluoro-2-methylpropan-2-yl (3-(3-oxobenzo[*d*][1,2]selenazol-2(3*H*)-yl)propyl)carbamate (11_a44)**

[0275] Further treatment of compound **11_a42** (0.29 g, 1.0 mmol) with 3-methyl-1-(((1,1,1-trifluoro-2-methylpropan-2-yl)oxy)carbonyl)-1*H*-imidazol-3-ium iodide (0.44 g, 1.2 mmol) in the NEt_3 (5 mL) using $CHCl_3$ (5 mL) as the solvent generated the title compound **11_a44** (0.38 g) in 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.82 Hz, 1H), 7.57 - 7.71 (m, 2H), 7.46 (t, J = 6.85 Hz, 1H), 5.75 (br. s., 1H), 3.95 (t, J = 5.87 Hz, 2H), 3.11 - 3.25 (m, 2H), 1.82 - 1.95 (m, 2H), 1.69 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 132.2, 128.9, 126.9, 126.4, 124.1, 79.2, 77.3, 77.0, 76.7, 50.0, 41.8, 37.1, 30.2, 29.7; ^{19}F NMR (376 MHz, Acetone-d_6) δ -84.67, -84.75, -84.98; HRMS *m/z* calcd for $(C_{15}H_{17}F_3N_2O_3Se + H)^+$ 411.0430, found 411.0433.

[0276] **Benzyl (2-(3-oxobenzo[*d*][1,2]selenazol-2(3*H*)-yl)ethyl)carbamate (11_a45)**

[0277] Benzyl chloroformate (0.10 mL) was added dropwise into the mixture of NEt_3 (0.10 mL) and compound **11_a41** (0.10 g, 0.41 mmol) in DCM (10 mL) at 0 °C. The mixture was stirred for 14 h. Then the solvent was removed and the residue was dissolved in DCM, and the organic layer was washed twice with H_2O and brine once. The organic layers were combined and dried over anhydrous $MgSO_4$ and concentrated in vacuum. The crude product was purified by column chromatography on silica gel to give the title compound **11_a45** (26 mg) in 16% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.82 Hz, 1H), 7.59 - 7.67 (m, 2H), 7.41 - 7.49 (m, 1H), 7.29 - 7.41 (m, 5H), 5.39 (br. s., 1H), 5.13 (s, 2H), 3.93 - 4.06 (m, 2H), 3.52 - 3.61 (m, 2H); ^{13}C NMR

(101 MHz, $CDCl_3$) δ 167.8, 156.5, 138.1, 136.5, 132.2, 128.9, 128.5, 128.1, 126.8, 126.3, 124.0, 77.3, 77.2, 77.0, 76.7, 66.8, 44.4, 41.4; HRMS *m/z* calcd for $(C_{17}H_{16}N_2O_3Se + Na)^+$ 399.0219, found 399.0220.

[0278] **Benzo[*f*][1,2,4]selenadiazepine-3,5(*2H,4H*)-dione (12)**

[0279] A solution of compound **10** (0.51 g, 2 mmol) in DCM was added dropwise into a stirred suspension of urea in acetonitrile cooled in an ice salt bath. After stirring for 24 h, the solvent was evaporated under reduced pressure. The residue was washed twice with water and the suspension was neutralized with Na_2CO_3 solution. The crude product was filtered off, washed twice with water, and recrystallized in acetonitril/benzene (4:1) to furnish the title compound **12** (0.14 g) in 30% yield. ^1H NMR (400MHz, DMSO-d_6) δ 8.28 (br. s., 1 H), 8.07 (d, J = 7.8 Hz, 1 H), 7.97 (br. s., 1 H), 7.91 (d, J = 7.8 Hz, 1 H), 7.73 (t, J = 7.3 Hz, 1 H), 7.48 (t, J = 7.3 Hz, 1 H); ^{13}C NMR (101MHz, DMSO-d_6) δ 166.3, 153.8, 139.6, 134.0, 129.5, 128.7, 126.7, 126.5; HRMS *m/z* calcd for $(C_8H_6N_2O_2Se + H)^+$ 241.9594, found 242.2845.

[0280] **2-Phenyl-1,2-selenazolidin-3-one (13_a1)**

[0281] To a suspension of 3,3'-diselanediyldipropanoic acid (**9b**) (0.61g, 2 mmol) in DCM cooled in an ice bath, EDCI (0.37 g, 2.4 mmol.) was added in portions. After stirring for two hours, the reaction mixture became clear and aniline (0.56 g, 6 mmol) was added dropwise into the solution. The mixture was stirred at room temperature for another 14 h. After the reaction was completed, the precipitate was filtered, washed twice with water and acetone to yield 3,3'-diselanediylbis(*N*-phenylpropanamide) (0.73 g) in 80% yield, which was pure enough for use in the next step. To a solution of 3,3'-diselanediylbis(*N*-phenylpropanamide) (0.8 g, 1.5 mmol) in MeOH at room temperature, *t*-BuOOH (0.40 g, 4.5 mmol) dissolved in MeOH was added dropwise. The mixture was stirred at room temperature for 24 h. After the reaction was completed, the mixture was diluted with MeOH, filtered, and the filtrate was collected and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel with EA/Hex (1:4) as eluent to furnish the title compound **13_a1** (15 mg) in 5% yield. ^1H NMR (400MHz, MeOH-d_4) δ 7.55 (d, J = 7.8 Hz, 2 H), 7.30 (t, J = 7.8 Hz, 2 H), 7.14 - 7.06 (m, 1 H), 3.26 (t, J = 7.3 Hz, 2 H), 2.91 (t, J = 7.3 Hz, 2 H); ^{13}C NMR (101MHz, MeOH-d_4) δ 132.3, 122.3, 117.8, 113.8, 31.6, 17.9; HRMS *m/z* calcd for $(C_9H_9NOSe + H)^+$ 227.9922, found 227.9927.

[0282] **Preparation of 1,2-Benzisothiazol-3(2H)-one Analogs**

[0283] The starting material, 2, 2'-dithiodibenzoyl chloride, was synthesized using known methods. To a solution of corresponding amine (14.5 mmol) in dry dichloromethane (25 mL) was added dropwise a solution of 2, 2'-dithiodibenzoyl chloride (1 g, 2.9 mmol) at 0 °C with stirring. The resulting mixture was allowed to slowly warm to room temperature and was stirred at room temperature overnight. Removal of the organic layer under reduced pressure gave a reddish residue. An aqueous 3 M HCl (20 mL) solution was then poured into the residue to remove the excess amine compounds. After 15 min, the precipitate was filtered, washed with dichloromethane, and dried in vacuo to yield the desired intermediate as a pale solid with insufficient purity to be used directly in the next step. To a well stirred solution of corresponding amide compound (1 mmol) in dry dichloromethane (20 mL) was slowly added liquid bromine (1.5 mmol) at 0 °C over a period of 5-10 min. The reaction was allowed to slowly warm to room temperature and stirring was continued overnight. Activated basic aluminum oxide (Sigma Aldrich, 150 mesh) was added to the mixture. Purification of the residue was performed by flash column chromatography on silica gel to afford the desired compound.

[0284] **2-(4-chlorophenyl)-1,2-benzisothiazol-3(2*H*)-one (3a)**

[0285] This compound (0.20 g, yield 75%) was prepared from 2,2'-disulfanediylbis(N-(4-chlorophenyl)benzamide) (0.52 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.82 Hz, 1H), 7.64 - 7.72 (m, 3H), 7.56 - 7.62 (m, 1H), 7.40 - 7.50 (m, 3H), 1.24 - 1.33 (m, 1H), 0.90 (t, *J* = 6.85 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 139.6, 135.9, 132.6, 132.4, 129.4, 127.2, 126.0, 125.5, 124.6, 120.2; HRMS *m/z* calcd for $(C_{13}H_8NClOS + H)^+$ 262.0088, found 262.0086.

[0286] **2-(4-bromophenyl)-1,2-benzisothiazol-3(2*H*)-one (3b)**

[0287] This compound (0.13 g, yield 43%) was prepared from 2,2'-disulfanediylbis(N-(4-bromophenyl)benzamide) (0.61 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.82 Hz, 1H), 7.50 - 7.75 (m, 6H), 7.35 - 7.50 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 139.6, 136.4, 132.6, 132.4, 127.2, 126.0, 125.7, 124.6, 120.2, 120.2; HRMS *m/z* calcd for $(C_{13}H_8BrNOS + H)^+$ 305.9583, found 305.9584.

[0288] **2-(4-(trifluoromethyl)phenyl)-1,2-benzisothiazol-3(2*H*)-one (3c)**

[0289] This compound (0.12 g, yield 41%) was prepared from 2,2'-disulfanediylbis(N-(4-(trifluoromethyl))benzamide) (0.59 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.82 Hz, 1H), 7.94 (d, *J* = 7.82 Hz, 2H), 7.67 - 7.80 (m, 3H), 7.57 - 7.65 (m, 1H), 7.48 (t, *J* = 7.34 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 139.5, 132.9, 127.4, 126.6, 126.5, 126.5, 126.5, 126.1, 124.7, 123.6, 120.2; HRMS *m/z* calcd for $(C_{14}H_8F_3NOS + H)^+$ 296.0351, found 296.0352.

[0290] **2-(3,4-dichlorophenyl)-1,2-benzisothiazol-3(2*H*)-one (3d)**

[0291] This compound (0.11 g, yield 39%) was prepared from 2,2'-disulfanediylbis(N-(3,4-dichlorophenyl)benzamide) (0.59 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.82 Hz, 1H), 7.93 (d, *J* = 1.96 Hz, 1H), 7.67 - 7.75 (m, 1H), 7.58 - 7.66 (m, 2H), 7.52 - 7.57 (m, 1H), 7.49 (t, *J* = 7.82 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 139.5, 133.3, 132.9, 130.9, 127.4, 126.2, 125.8, 123.2, 120.2; HRMS *m/z* calcd for $(C_{13}H_7Cl_2NOS + H)^+$ 295.9698, found 295.9699.

[0292] **2-(3-chlorophenyl)-1,2-benzisothiazol-3(2*H*)-one (3e)**

[0293] This compound (0.14 g, yield 52%) was prepared from 2,2'-disulfanediylbis(N-(3-chlorophenyl)benzamide) (0.52 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.82 Hz, 1H), 7.82 (s, 1H), 7.57 - 7.74 (m, 3H), 7.36 - 7.51 (m, 2H), 7.29 (d, *J* = 7.83 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 139.6, 138.5, 135.0, 132.7, 130.3, 127.3, 127.0, 126.0, 124.6, 124.3, 122.2, 120.1; HRMS *m/z* calcd for $(C_{13}H_8ClNOS + H)^+$ 262.0088, found 262.0094.

[0294] **2-(2-fluorophenyl)-1,2-benzisothiazol-3(2*H*)-one (3f)**

[0295] This compound (0.09 g, yield 38%) was prepared from 2,2'-disulfanediylbis(N-(2-fluorophenyl)benzamide) (0.49 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.83 Hz, 1H), 7.64 - 7.76 (m, 1H), 7.57 - 7.64 (m, 1H), 7.53 (t, *J* = 7.34 Hz, 1H), 7.39 - 7.50 (m, 2H), 7.22 - 7.32 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 158.3 (d, *J* = 254.56 Hz), 141.3, 132.5, 130.6, 130.6 (d, *J* = 8.1 Hz), 130.0, 127.3, 125.8, 124.8 (d, *J* =

3.7 Hz), 123.3, 120.3, 117.0 (d, *J* = 19.8 Hz); HRMS *m/z* calcd for $(C_{13}H_8FNOS + H)^+$ 246.0383, found 246.0385.

[0296] **2-(4-(hydroxymethyl)phenyl)-1,2-benzisothiazol-3(2*H*)-one (3g)**

[0297] This compound (0.13 g, yield 49%) was prepared from 2,2'-disulfanediylbis(N-(4-(hydroxymethyl)phenyl)benzamide) (0.52 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.00 (d, *J* = 7.82 Hz, 1H), 7.84 (d, *J* = 7.83 Hz, 1H), 7.73 (t, *J* = 7.82 Hz, 1H), 7.61 - 7.68 (m, 2H), 7.46 - 7.54 (m, 3H), 4.67 (s, 2H); ^{13}C NMR (101 MHz, MeOH-d_4) δ 164.7, 141.3, 140.7, 135.7, 132.5, 128.4, 127.5, 126.0, 125.8, 125.8, 124.8, 124.7, 124.2, 120.7, 63.1; HRMS *m/z* calcd for $(C_{14}H_{11}NO_2S + H)^+$ 258.0583, found 258.0588.

[0298] **2-(4-chlorophenethyl)-1,2-benzisothiazol-3(2*H*)-one (3h)**

[0299] This compound (0.15 g, yield 53%) was prepared from 2,2'-disulfanediylbis(N-(4-chlorophenethyl)benzamide) (0.58 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.80 Hz, 1H), 7.51 - 7.62 (m, 1H), 7.45 - 7.51 (m, 1H), 7.35 (t, *J* = 7.83 Hz, 1H), 7.23 (d, *J* = 7.82 Hz, 2H), 7.08 - 7.19 (m, 2H), 4.08 (t, *J* = 7.34 Hz, 2H), 3.01 (t, *J* = 7.34 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 140.2, 136.2, 132.6, 131.8, 130.2, 128.7, 126.6, 125.5, 124.4, 120.4, 45.0, 34.9; HRMS *m/z* calcd for $(C_{15}H_{12}ClNOS + H)^+$ 290.0401, found 290.0402.

[0300]

[0301] **2-phenyl-1,2-benzisothiazol-3(2*H*)-one (3i)**

[0302] This compound (0.16 g, yield 72%) was prepared from 2,2'-disulfanediylbis(N-phenylbenzamide) (0.46 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.82 Hz, 1H), 7.72 (d, *J* = 7.58 Hz, 2H), 7.62 - 7.69 (m, 1H), 7.55 - 7.62 (m, 1H), 7.41 - 7.53 (m, 3H), 7.29 - 7.37 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 139.9, 137.3, 132.4, 129.4, 127.2, 127.0, 125.8, 124.9, 124.6, 120.1; HRMS *m/z* calcd for $(C_{13}H_9NOS + Na)^+$ 250.0297, found 250.0308.

[0303] **2-(4-methoxyphenyl)-1,2-benzisothiazol-3(2*H*)-one (3j)**

[0304] This compound (0.16 g, yield 64%) was prepared from 2,2'-disulfanediylbis(N-(4-methoxyphenyl)benzamide) (0.52 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5

mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 7.82 Hz, 1H), 7.72 (d, J = 7.58 Hz, 2H), 7.62 - 7.69 (m, 1H), 7.55 - 7.62 (m, 1H), 7.41 - 7.53 (m, 3H), 7.29 - 7.37 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 158.7, 140.0, 132.2, 129.7, 127.1, 126.8, 125.7, 124.6, 120.1, 114.6, 55.6; HRMS *m/z* calcd for $(C_{14}H_{11}NO_2S + Na)^+$ 280.0403, found 280.0413.

[0305] **2-(3-chloro-4-methoxyphenyl)-1,2-benzisothiazol-3(2*H*)-one (3k)**

[0306] This compound (0.16 g, yield 57%) was prepared from 2,2'-disulfanediylbis(N-(3-chloro-4-methoxyphenyl)benzamide) (0.58 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 7.82 Hz, 1H), 7.70 - 7.73 (m, 1H), 7.68 (d, J = 6.85 Hz, 1H), 7.54 - 7.62 (m, 2H), 7.47 (t, J = 7.34 Hz, 1H), 7.02 (d, J = 8.80 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (101 MHz, MeOH-d_4) δ 164.2, 154.2, 140.0, 132.4, 130.1, 127.2, 126.0, 124.8, 124.4, 123.0, 120.1, 112.2, 56.5; HRMS *m/z* calcd for $(C_{14}H_{10}ClNO_2S + Na)^+$ 314.0013, found 314.0018.

[0307] **2-(4-isopropylphenyl)-1,2-benzisothiazol-3(2*H*)-one (3l)**

[0308] This compound (0.15 g, yield 56%) was prepared from 2,2'-disulfanediylbis(N-(4-isopropylphenyl)benzamide) (0.54 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.00 (d, J = 7.82 Hz, 1H), 7.83 (d, J = 8.80 Hz, 1H), 7.69 - 7.78 (m, 1H), 7.46 - 7.60 (m, 3H), 7.37 (d, J = 8.80 Hz, 2H), 2.96 (dt, J = 6.85, 13.69 Hz, 1H), 1.28 (d, J = 6.85 Hz, 6H); ^{13}C NMR (101 MHz, MeOH-d_4) δ 164.8, 148.8, 134.4, 132.4, 127.1, 126.0, 125.8, 125.2, 120.7, 33.7, 22.9; HRMS *m/z* calcd for $(C_{16}H_{15}NOS + Na)^+$ 292.0767, found 292.0778.

[0309] **2-(4-methoxybenzyl)-1,2-benzisothiazol-3(2*H*)-one (3m)**

[0310] This compound (0.19 g, yield 70%) was prepared from 2,2'-disulfanediylbis(N-(4-methoxybenzyl)benzamide) (0.52 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.82 Hz, 1H), 7.30 - 7.43 (m, 2H), 7.14 - 7.25 (m, 3H), 6.76 (d, J = 8.80 Hz, 2H), 4.86 (s, 2H), 3.63 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 159.6, 140.4, 131.7, 129.9, 128.3, 126.5, 125.4, 124.5, 120.5, 114.1, 55.1, 47.0; HRMS *m/z* calcd for $(C_{15}H_{13}NO_2S + Na)^+$ 294.0559, found 294.0565.

[0311] **2-(3-ethylphenyl)-1,2-benzisothiazol-3(2*H*)-one (3n)**

[0312] This compound (0.15 g, yield 58%) was prepared from 2,2'-disulfanediylbis(N-(3-ethylphenyl)benzamide) (0.51 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.82 Hz, 1H), 7.60 - 7.68 (m, 1H), 7.54 - 7.60 (m, 2H), 7.51 (d, *J* = 7.82 Hz, 1H), 7.38 (t, *J* = 7.34 Hz, 1H), 7.43 (t, *J* = 7.34 Hz, 1H), 7.17 (d, *J* = 7.83 Hz, 1H), 2.66 - 2.80 (m, 2H), 1.29 (t, *J* = 7.83 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 145.7, 140.0, 137.2, 132.3, 129.2, 127.1, 126.8, 125.8, 124.9, 124.2, 121.9, 120.1, 28.8, 15.4; HRMS *m/z* calcd for $(C_{15}H_{13}NOS + H)^+$ 255.0712, found 255.0715.

[0313] ***tert*-butyl(2-(3-oxo-1,2-benzisothiazol-3(2*H*)-yl)ethyl)carbamate (3o)**

[0314] This compound (0.18 g, yield 61%) was prepared from di-*tert*-butyl (((2,2'-disulfanediylbis(benzoyl))bis(azanediyl))bis(ethane-2,1-diyl))dicarbamate (0.59 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol,) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.83 Hz, 1H), 7.47 - 7.61 (m, 2H), 7.36 (t, *J* = 7.83 Hz, 1H), 5.32 (br. s., 1H), 3.98 (t, *J* = 5.38 Hz, 2H), 3.47 (d, *J* = 5.87 Hz, 2H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 156.0, 140.5, 131.8, 126.6, 125.5, 124.2, 120.3, 79.5, 43.8, 40.2, 28.3; HRMS *m/z* calcd for $(C_{14}H1_8N_2O_3S + Na)^+$ 317.0930, found 317.0932.

[0315] **2-(2-(dimethylamino)ethyl)-1,2-benzisothiazol-3(2*H*)-one (3p)**

[0316] This compound (0.08 g, yield 38%) was prepared from 2,2'-disulfanediylbis(N-(2-(dimethylamino)ethyl)benzamide) (0.45 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.82 Hz, 1H), 7.46 - 7.59 (m, 2H), 7.33 (t, *J* = 7.34 Hz, 1H), 3.97 (t, *J* = 5.87 Hz, 2H), 2.62 (t, *J* = 6.36 Hz, 2H), 2.30 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 141.5, 131.5, 126.4, 125.2, 124.4, 120.2, 58.2, 45.3, 41.7; HRMS *m/z* calcd for $(C_{11}H_{14}N_2OS + H)^+$ 223.0900, found 223.0905.

[0317] **2-(2-morpholinoethyl)-1,2-benzisothiazol-3(2*H*)-one (3q)**

[0318] This compound (0.15 g, yield 55%) was prepared from 2,2'-disulfanediylbis(N-(2-morpholinoethyl)benzamide) (0.53 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.82 Hz, 1H), 7.46 - 7.62 (m, 2H), 7.33 (t, *J* = 7.34 Hz, 1H), 3.98 (t, *J* = 5.87 Hz, 2H), 3.66 - 3.74 (m, 4H), 2.65 (t, *J* = 5.87 Hz, 2H), 2.46 - 2.56 (m, 4H); ^{13}C NMR (101

MHz, $CDCl_3$) δ 165.6, 141.5, 131.6, 126.4, 125.2, 124.3, 120.2, 66.9, 57.3, 53.5, 40.8; HRMS *m/z* calcd for $(C_{13}H_{16}N_2O_2S + H)^+$ 265.1005, found 265.1004.

[0319] **2-((4-fluorophenyl)sulfonyl)-1,2-benzisothiazol-3(2*H*)-one (3r)**

[0320] This compound (0.17 g, yield 54%) was prepared from 2,2'-disulfanediylbis(N-((4-fluorophenyl)sulfonyl)benzamide) (0.62 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, J = 5.38, 9.29 Hz, 2H), 7.93 (d, *J* = 7.83 Hz, 1H), 7.79 (d, J = 8.80 Hz, 1H), 7.53 (t, *J* = 7.82 Hz, 1H), 7.37 - 7.47 (m, 1H), 7.24 (t, *J* = 8.31 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 165.0, 153.8, 152.2, 132.1, 132.0, 131.9, 129.3, 125.8, 125.6, 122.9, 120.3, 116.8, 116.5; HRMS *m/z* calcd for $(C_{13}H_8FNO_3S_2 + Na)^+$ 331.9822, found 331.9811.

[0321] **2-cyclohexyl-1,2-benzisothiazol-3(2*H*)-one (3s)**

[0322] This compound (0.12 g, yield 51%) was prepared from 2,2'-disulfanediylbis(N-cyclohexylbenzamide) (0.47 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.83 Hz, 1H), 7.51 - 7.65 (m, 2H), 7.34 - 7.48 (m, 1H), 4.49 - 4.69 (m, 1H), 2.07 (d, *J* = 11.74 Hz, 2H), 1.89 (d, *J* = 12.72 Hz, 2H), 1.75 (d, *J* = 13.69 Hz, 1H), 1.40 - 1.66 (m, 4H), 1.20 - 1.28 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 140.3, 131.4, 126.5, 125.5, 125.3, 120.3, 53.2, 32.9, 25.6, 25.2; HRMS *m/z* calcd for $(C_{13}H_{15}NOS + Na)^+$ 256.0365, found 256.0377.

[0323] **2-((1,1'-biphenyl)-3-ylmethyl)-1,2-benzisothiazol-3(2*H*)-one (3t)**

[0324] This compound (0.16 g, yield 49%) was prepared from 2,2'-disulfanediylbis(N-([1,1'-biphenyl]-4-ylmethyl)benzamide) (0.64 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.82 Hz, 1H), 7.56 - 7.66 (m, 5H), 7.51 (d, *J* = 7.82 Hz, 1H), 7.33 - 7.49 (m, 6H), 5.15 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 141.9, 140.6, 136.7, 131.9, 129.3, 128.8, 127.6, 127.4, 127.3, 127.2, 127.1, 126.9, 125.6, 124.5, 120.4, 47.6; HRMS *m/z* calcd for $(C_{20}H_{15}NOS + H)^+$ 318.0947, found 318.0951.

[0325] **2-(2-hydroxyethyl) -1,2-benzisothiazol-3(2*H*)-one (3u)**

[0326] This compound (0.08 g, yield 44%) was prepared from 2,2'-disulfanediylbis(N-(2-hydroxyethyl)benzamide) (0.39 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, J = 7.82 Hz, 1H), 7.86 (d, J = 7.82 Hz, 1H), 7.60 - 7.75 (m, 1H), 7.36 - 7.49 (m, 1H), 6.52 (br. s., 1H), 3.88 (t, J = 5.38 Hz, 2H), 3.58 - 3.74 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.0, 141.5, 132.1, 125.9, 125.7, 124.4, 122.1, 60.0, 46.4; HRMS *m/z* calcd for $(C_9H_9NO_2S + H)^+$ 196.0427, found 196.0425.

[0327] **2-(prop-2-yl-1yl)-1,2-benzisothiazol-3(2*H*)-one (3v)**

[0328] This compound (0.12 g, yield 61%) was prepared from 2,2'-disulfanediylbis(N-(prop-2-yn-1-yl)benzamide) (0.38 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.82 Hz, 1H), 7.55 - 7.67 (m, 2H), 7.38 - 7.45 (m, 1H), 4.71 (d, J = 2.93 Hz, 2H), 2.43 - 2.51 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 140.5, 132.2, 126.8, 125.7, 124.0, 120.5, 74.4, 33.2; HRMS *m/z* calcd for $(C_{10}H_7NOS + H)^+$ 190.0321, found 190.0323.

[0329] ***tert*-butyl(3-(3-oxo-1,2-benzisothiazol-3(2*H*)-yl)propyl)carbamate (3w)**

[0330] This compound (0.12 g, yield 39%) was prepared from di-*tert*-butyl (((2,2'-disulfanediylbis(benzoyl))bis(azanediyl))bis(propane-3,1-diyl))dicarbamate (0.62 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.82 Hz, 1H), 7.53 - 7.69 (m, 2H), 7.36 - 7.49 (m, 1H), 5.41 (br. s., 1H), 3.93 - 4.05 (m, 2H), 3.10 - 3.22 (m, 2H), 1.87 - 1.99 (m, 2H), 1.39 - 1.52 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 156.1, 140.2, 131.9, 126.7, 125.6, 124.4, 120.4, 79.1, 41.1, 29.6, 28.4, 28.4; HRMS *m/z* calcd for $(C_{15}H_{20}N_2O_3S + Na)^+$331.1087, found 331.1089.

[0331] **1,2-benzisothiazol-3(2*H*)-one (3x)**

[0332] This compound (0.08 g, yield 53%) was prepared from 2,2'-disulfanediyldibenzamide (0.30 g, 1 mmol), DCM (20 mL) and liquid bromine (0.24 g, 1.5 mmol) according to the general preparation procedure described above. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (br. s., 1H), 7.96 (d, J = 7.83 Hz, 1H), 7.85 (d, J = 7.82 Hz, 1H), 7.58 (t, J = 7.34 Hz, 1H), 7.38 (t, J = 7.34 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.3, 147.5, 130.6, 125.3, 125.1, 124.7, 122.0; HRMS *m/z* calcd for $(C_7H_5NOS + H)^+$ 151.1454, found 151.1471.

[0333] **2-(4-(trifluoromethyl)benzyl)benzo[*d*]isoxazol-3(2*H*)-one (5a) and 3-((4-(trifluoromethyl)benzyl)oxy)benzo[d]isoxazole (5g)**

[0334] A mixture of 3-hydroxybenzisoxazole (0.3 g, 2.2 mmol) and 1-(bromomethyl)-4-(trifluoromethyl)benzene (0.64 g, 2.66 mmol) in the presence of NaH (0.06 g, 2.66 mmol) and

DMF was stirred for overnight. Then resulting solution was diluted with DCM, washed with brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated to dryness. The crude residue was purified by flash chromatography on silica gel to afford the desired compound **5a** (0.21 g, 0.72 mmol, 33%) and a side product compound **5g**. For **5a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.82 Hz, 1H), 7.54 (t, *J* = 7.83 Hz, 3H), 7.45 (d, *J* = 7.83 Hz, 2H), 7.20 (t, *J* = 7.34 Hz, 1H), 7.11 (d, *J* = 8.80 Hz, 1H), 5.20 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 160.3, 138.9, 138.9, 133.6, 130.36 (q, *J* = 32 Hz), 125.5 (q, *J* = 3 Hz), 124.3, 124.0 (q, *J* = 271 Hz), 123.6, 116.1, 109.9, 49.1; HRMS *m/z* calcd for $(C_{15}H_{10}F_3NO_2 + H)^+$ 294.0736, found 294.0741. For **5g**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 - 7.68 (m, 5H), 7.36 - 7.51 (m, 2H), 7.17 - 7.28 (m, 1H), 5.52 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 164.1, 139.7, 131.0, 130.5 (q, *J* = 32 Hz), 128.2, 125.5 (q, *J* = 3 Hz), 124.1 (q, *J* = 270 Hz) , 123.1, 120.7, 114.0, 110.1, 70.8; HRMS *m/z* calcd for $(C_{15}H_{10}F_3NO_2 + H)^+$ 294.0736, found 294.0743.

[0335] **2-(4-chlorobenzyl)isoindolin-1-one (5b)**

[0336] A mixture of 1-isoindolinone (0.2 g, 1.5 mmol) and 1-(bromomethyl)-4-chlorobenzene (0.37 g, 1.8 mmol) in the presence of NaH (0.04 g, 1.8 mmol) and DMF was stirred for overnight. Then resulting solution was diluted with DCM, washed with brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated to dryness. The crude residue was purified by flash chromatography on silica gel to afford the desired compound **5b** (0.23 g). Yield 29%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 6.85 Hz, 1H), 7.38 - 7.53 (m, 2H), 7.35 (d, *J* = 7.82 Hz, 1H), 7.16 - 7.28 (m, 4H), 4.72 (s, 2H), 4.22 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 141.2, 135.6, 133.5, 132.4, 131.5, 129.5, 128.9, 128.1, 123.8, 122.9, 49.4, 45.7; HRMS *m/z* calcd for $(C_{15}H_{13}ClNO + H)^+$ 258.0680, found 258.0679.

[0337] **2-(3-(piperidin-2-yl)benzyl)isoindoline-1,3-dione (5c)**

[0338] A mixture of potassium phthalimide (0.3 g, 1.62 mmol) and 1-(3-(bromomethyl)phenyl)piperidine (0.45 g, 1.78 mmol) in DMF was stirred for overnight. Then resulting solution was diluted with DCM, washed with brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated to dryness. The crude residue was purified by flash chromatography on silica gel to afford the desired compound **5c** (0.32 g, 1 mmol). Yield 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 - 7.88 (m, 2H), 7.71 (d, *J* = 3.91 Hz, 2H), 7.20 (t, *J* = 7.82 Hz, 1H), 7.06 (s, 1H), 6.91 (d, *J* = 7.83 Hz, 1H), 6.85 (d, *J* = 7.82 Hz, 1H), 4.81 (s, 2H), 3.16 (t, *J* = 5.38 Hz, 4H), 1.64 - 1.77 (m, 4H), 1.50 - 1.62 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 152.5, 137.2, 133.9, 132.2, 129.3, 123.3, 119.4, 116.8, 115.8, 50.5, 42.0, 25.8, 24.3; HRMS *m/z* calcd for $(C_{20}H_{20}N_2O_2 + H)^+$ 321.1598, found 321.1601.

[0339] **2-(4-chlorophenyl)-1,2-benzisothiazol-3(2*H*)-one-1-oxide (5d)**

[0340] To a stirred solution of compound **3a** (0.20 g, 0.76 mmol) in DCM (10 mL), 3-chloroperoxybenzoic acid (0.16 g, 0.92 mmol) in DCM (5 mL) was added dropwise at 0 °C. The solution mixture was placed in ice bath and stirred for 3 hours. Water was then added to the mixture. The organic phase was combined and dried by Na_2SO_4, and concentrated in vacuum. Purification of the residue was performed by flash column chromatography on silica gel to afford the desired compound **5d** (0.05 g). Yield 25%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.82 Hz, 1H), 7.99 (d, *J* = 7.82 Hz, 1H), 7.81 - 7.94 (m, 2H), 7.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 145.4, 134.8, 133.6, 130.2, 129.9, 128.5, 128.0, 126.9, 125.3; HRMS *m/z* calcd for $(C_{13}H_8ClNO_2S + H)^+$ 278.0037, found 278.0037.

[0341] **2-benzylisothiazolo[*5,4-b*]pyridin-3(2*H*)-one (5e)**

[0342] A mixture of 2-chloronicotinonitrile (1.0 g, 7.2 mmol) and thiourea (1.81 g, 23.8 mmol) in *n*-butanol (40 mL) was heated at reflux. Four hours later, the precipitate was filtered, rinsed with n-butanol, and dried in vacuo to afford the 2-mercaptonicotinonitrile (0.91 g, 6.7 mmol). Then dissolved the compound in concentrated H_2SO_4 (8 mL) was heated for 4h. The solution was then cooled down and adjusted to pH 6 by addition of KOH to yield the white solid (0.62, 4.1 mmol). Without further purification, the solid was dissolved in DCM and reacted with benzyl bromide (0.77 g, 4.5 mmol) in the presence of K_2CO_3 (0.62g, 4.5 mmol), Et_3N (2.1g, 20.4 mmol), and catalytic amount of KI at room temperature for overnight. The volatile was removed under reduced pressure. The crude residue was extracted with DCM and water. The organic phase was collected, dried over $MgSO_4$ and purified by flash chromatography to obtain the compound **5e** (0.54 g, 2.23 mmol). Yield 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 - 8.78 (m, 1H), 8.32 (d, *J* = 7.82 Hz, 1H), 7.35 - 7.41 (m, 6H), 5.10 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 162.4, 153.6, 135.8, 134.9, 129.2, 129.0, 128.5, 128.5, 128.0, 120.7, 119.3, 77.4, 77.1, 76.7, 47.5; HRMS m/z calcd for $(C_{13}H_{10}N_2OS + H)^+$ 243.0592, found 243.0588.

[0343] **2-(4-chlorophenyl)isothiazol-3(2*H*)-one (5f)**

[0344] To the solution of 3,3'-disulfanediyldipropanoic acid (1 g, 4.76 mmol) in DCM (20 Ml) in ice bath was added dropwise thionyl chloride (1.24 g, 10.46 mmol) with few drops of DMF as the catalyst. The solvent was removed in vacuo and the crude residue was further reacted with excess 4-chloroaniline (1.41 g, 11.04 mmol) in DCM. After 3 hours, the precipitate was filtered, washed with DCM, and dried in vacuo to yield the amide compound as a white solid (1.82 g) with sufficient purity to be used directly in the next step. To a solution of amide compound in DCM (25 mL) was added 1.0 equiv. of SO_2Cl_2 (0.57 g, 4.24 mmol) in ice bath. After 2 hours, the solution was poured into water. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to dryness. The resulting residue was purified by flash chromatography to afford the tittle compound **5f** (0.42 g, 2.0 mmol). Yield 46.8%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 6.85 Hz, 1H), 7.46 - 7.57 (m, 2H), 7.34 - 7.45 (m, J = 8.80 Hz, 2H), 6.29 (d, J = 6.85 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 146.6, 134.3, 133.4, 129.7, 125.9, 114.9; HRMS *m/z* calcd for $(C_9H_6ClNOS + H)^+$ 211.9931, found 211.9926.

[0345] **Materials for biological studies**

[0346] Meropenem, and ebselen were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Luria broth (LB) and nitrocefin were purchased from BD (Franklin Lakes, NJ, USA). Mueller-Hinton broth (MHB) was purchased from Oxoid Co. (Hampshire, United Kingdom). Isopropyl beta-D-1-thiogalactopyranoside (IPTG) was purchased from IBI Inc. (Boca Raton, FL, USA). The *bla*$_{\text{NDM-1}}$ gene was PCR amplified and constructed in an IPTG-inducible pET28b vector.[32] The constructed plasmid was transformed with *E. coli* BL21 to form a strain of *E. coli* BL21 (NDM-1) harboring the recombinant plasmid pET28b-*bla*$_{H6\text{-}NDM\text{-}1}$, which encoded G^{36} to R^{270} and carried an N-terminal His_6 tag for the overexpression and purification of the NDM-1 enzyme. *E. coli* TG1 was transformed with the IncX3 *bla*$_{NDM\text{-}1}$-bearing plasmid (similar as plasmid, pP855-NDM5, MF547508.1) originally isolated from a clinical *K. Pneumoniae* and was used in the preliminary MIC screening of test compounds alone and in combination with Meropenem. Clinically isolated CRE strains shown in **Table 2** were from our in-house bacterial strain library, which were isolated from different specimens (urine, faeces, and sputum) collected from patients in hospitals in Zhejiang Province, China.[33]

[0347] **Antimicrobial susceptibility tests and FIC index determination**

[0348] The MIC values of all compounds and their combination with Mem were determined and interpreted in accordance with the CLSI guidelines[27] and previous report.[24] At least three independent assays were performed for each compound and their combination with Mem. FIC index was calculated as FIC (compound) + FIC (Mem), where FIC (compound) is the (MIC of compound in combination with Mem) / (MIC of compound alone) while FIC (Mem) is (MIC of compound in combination with Mem) / (MIC of Mem alone). FIC index of ≤0.5 was deemed synergistic.

[0349] **Cytotoxicity tests towards normal cells**

[0350] The standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cytotoxicity assay was performed.[34] A solution of compound **11_a38** in DMSO at a concentration of 400 mg/mL was freshly prepared as a stock solution. Eukaryotic cells (L929 or Hela) were seeded into three 96-well plates at a density of 1×10^4 cells per well in DMEM (10% FBS) and incubated for 12 h at 37 °C. The cells were then exposed to various concentrations of compound **11_a38** (0.13 mg/mL to 2 mg/mL) for 48 h. Medium containing 0.5% DMSO and medium without cells were used as negative control and blank control respectively. After incubation, MTT at a concentration of 0.5 mg/mL in PBS was added to each well and the cells were further incubated for 3 h at 37 °C. The medium was removed to afford the formazan crystals followed by dissolving in DMSO. The optical density (OD) of each well was measured at 490 nm using a Microplate Reader (Clariostar, BMG). The percentage of survival cell was calculated using the formula: (corrected reading from test well – corrected reading from blank well)/ (corrected reading from negative well – corrected reading from blank well) × 100%.

[0351] **Evaluation of the *in vivo* synergistic activity using a *G. mellonella* model of infection**

[0352] To evaluate the *in vivo* synergistic efficacy of compound **11_a38** in combination with Mem, an infection model of *G. mellonella* was employed as previously described with little modification.[35] In brief, 1 mL aliquots of overnight cultures of clinical CRE isolate *E. cloacae* EL10 were pelleted and washed twice with sterile phosphate buffered saline (PBS) before being resuspended in 100 μL of PBS. *G. mellonella* larvae (N = 10) at weight 250 – 300 mg were selected for inoculation with a lethal dose of 10 μL bacterial suspensions (2.5×10^5 CFU/larva). Using a 50 μL Hamiton syringe, the bacterial suspension was injected into the hemocoels at the last left proleg of larvae. Larvae were then treated with various treatments at 1 h before bacterial inoculation. Treatments included vehicle, compound **11_a38** along, Mem along, compound **11_a38** in combination with Mem. Treatments were performed in the same manner as infection, except that injections were into the next left proleg moving toward the head of the larvae. Larvae were then incubated in Petri dishes at 37 °C and mortality rates were monitored at 12 h interval for 48 h. Larvae were considered dead if they did not respond to physical stimuli. Data were analyzed for statistical significance using a log-rank and χ square test with 1 degree of freedom.

[0353] **Overexpression, purification and kinetic assay of NDM-1 protein**

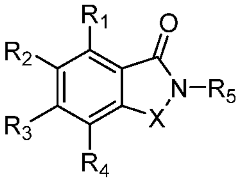
[0354] The purified NDM-1 protein was prepared as previously described.[32] Kinetic assay of NDM-1 was performed to determine the inactivation constants of compounds as previously described.[24] Briefly, followed by addition of 7 fold of Km of the reporter substrate nitrocefin, 1 nM of pure NDM-1 was mixed with different concentrations of compounds in 500 µL of 50 mM phosphate buffer with or without 50 µM $ZnSO_4$. Bovine serum albumin (BSA) was then added to stabilize the activity of diluted NDM-1. The readout of the velocity can be recorded by the wavelength change at 482 nm. Independent assay was performed in triplicate.

[0355] **ESI-MS analysis of NDM-1 with compound 11_a38**

[0356] Waters Synapt G2-Si electrospray ionization/quadrupole-ion mobility-time-of flight mass spectrometer was employed to perform the Electrospray ionization mass spectrometry (ESI-MS) experiments. For qualitative detection of the binding between NDM-1 and compound under non-denaturing conditions, after incubating 20 µM of NDM-1 in 20 mM ammonia acetate with equal molar of compound in the same buffer system for 20 mins, the reaction mixture was infused directly into a nanospray emitter (Econo12, New Objectives, Woburn, USA), which was mounted onto a nano-ESI source for analysis. The spray voltage was carefully raised to initiate the spray process, which was maintained for around 20 mins at the voltage of 150V.[36] For analysis under denaturing conditions, an equal volume of acetonitrile with 0.5% formic acid (v/v) was added to the NDM-1/ligand reaction mixture before being loaded to the ESI source with a syringe pump at a flow rate of 5 µL/min. During data acquisition, positive ion mode was exhibited in the operation of the mass spectrometer in the *m/z* range of 200-5000 for detection of multiply charged ions. The Transform program (MassLynx 4.1, Waters) was used to analyze the obtained raw multiply charged mass spectra.

We claim:

1. A method of treating a bacterial infection in a patient in need thereof, comprising the step of co-administering a pharmaceutically effective amount of a beta-lactam antibiotic and a compound of formula **I** to the patient, wherein the compound of formula **I** has the structure:



I

or a pharmaceutically acceptable salt thereof, wherein

X is S or Se;

R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halide, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, heteroaryl, $-N(R_6)_2$, $-(C{=}O)N(R_6)_2$, $-N(R_6)(C{=}O)R_6$, $-OR_6$, $-(C{=}O)R_6$, $-(C{=}O)OR_6$, $-OC(C{=}O)R_6$, $-O(C{=}O)OR_6$, $-O(P{=}O)(OR_6)_2$, $-O(C{=}O)N(R_6)_2$, $-N(R_6)(C{=}O)OR_6$, $-N(R_6)(C{=}O)N(R_6)_2$, and $-SO_2R_6$;

R_5 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-(C{=}O)R_9$, $-SO_2R_9$, or $-(CR_7)_nR_8$;

R_6 for each instance is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, and heteroaryl; or two instances of R_6 taken together with the nitrogen to which they are attached form a 3-6 membered heterocyloalkyl;

R_7 independently for each instance is hydrogen, alkyl, cycloalkyl, heterocycloalkyl aryl, araalkyl, or heteroaryl;

R_8 is nitrile, hydroxyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-N(R_9)_2$, $-(C{=}O)N(R_9)_2$, $-N(R_9)(C{=}O)R_9$, $-OR_9$, $-(C{=}O)R_9$, $-(C{=}O)OR_9$, $-OC(C{=}O)R_9$, $-O(C{=}O)OR_9$, $-O(P{=}O)(OR_9)_2$, $-N(R_9)(P{=}O)(OR_9)_2$, $-O(C{=}O)N(R_9)_2$, $-N(R_9)(C{=}O)OR_9$, $-N(R_9)(C{=}O)N(R_9)_2$, or $-(C{=}O)R_9$;

R_9 for each instance is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, heteroaryl, and –$(CR_7)_nCO_2H$; or two instances of R_9 taken together with the atoms to which they are covalently bonded form a 3-6 membered heterocyloalky; and

n for each occurrence is independently an integer selected from 1-6,

with the proviso that when R_1, R_2, R_3, and R_4 are hydrogen, R_5 is not phenyl.

2. The method of claim 1, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halide, nitrile, nitro, hydroxyl, and alkyl.

3. The method of claim 1, wherein R_5 is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -$(C{=}O)R_9$, -SO_2R_9, or –$(CR_7)_nR_8$.

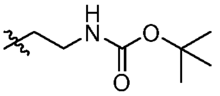
4. The method of claim 1, wherein X is Se; R_5 is –$(CR_7)_nR_8$; and R_8 is hydroxyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -$N(R_9)_2$, -$(C{=}O)N(R_9)_2$, -$N(R_9)(C{=}O)R_9$, -$(C{=}O)R_9$, -$(C{=}O)OR_9$, -$N(R_9)(P{=}O)(OR_9)_2$, or -$N(R_9)(C{=}O)OR_9$.

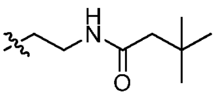
5. The method of claim 4, wherein R_9 for each instance is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, araalkyl, heteroaryl, and –$(CR_7)_nCO_2H$.

6. The method of claim 1, wherein X is Se; n is 2, 3, or 4; R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halide, nitrile, nitro, hydroxyl, and alkyl; R_5 is or –$(CR_7)_nR_8$; R_7 for each instance is independently selected from the group consisting of hydrogen and alkyl; and R_8 is heterocycloalkyl, heteroaryl, -$N(R_9)_2$, -$N(R_9)(C{=}O)R_9$, -$N(R_9)(C{=}O)OR_9$, or -$N(R_9)(P{=}O)(OR_9)_2$.

7. The method of claim 6, wherein R_5 is –$N(R_9)(C{=}O)OR_9$.

8. The method of claim 6, wherein R_5 is selected from the group consisting of:



,


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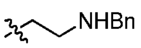
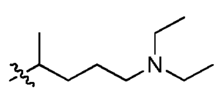


,


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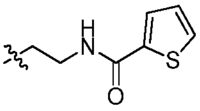

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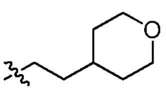
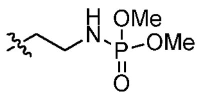


,


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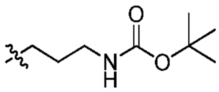

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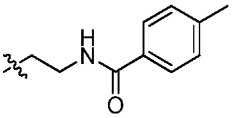
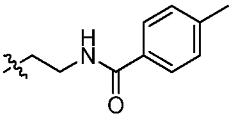
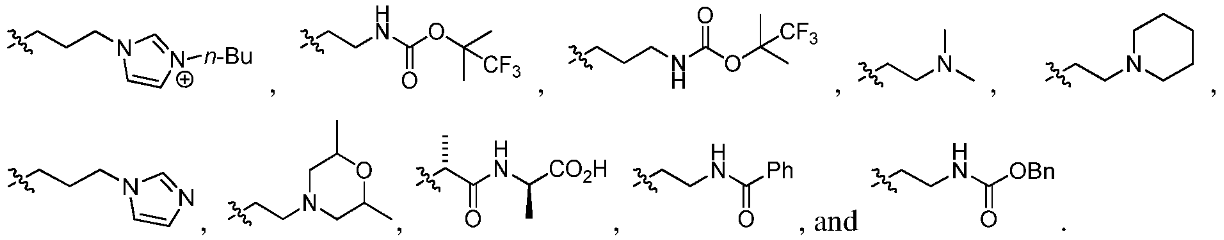


,


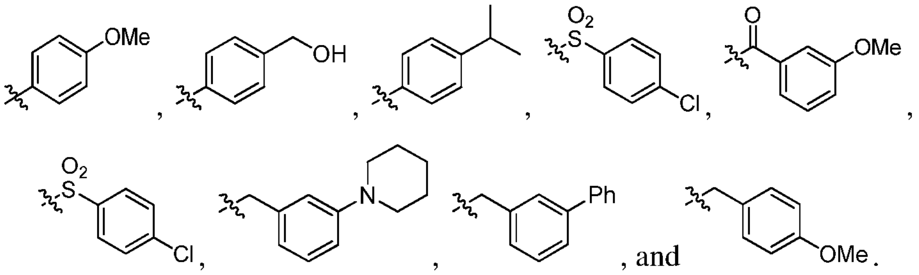
,



9. The method of claim 8, wherein R_1, R_2, R_3, and R_4 are hydrogen.

10. The method of claim 1, wherein X is Se; R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halide, nitrile, nitro, hydroxyl, and alkyl; and R_5 is 4-substitued aryl, 3-substituted aryl, aralkyl, -(C=O)Ar, and $-SO_2Ar$.

11. The method of claim 10, wherein R_5 is selected from the group consisting of:

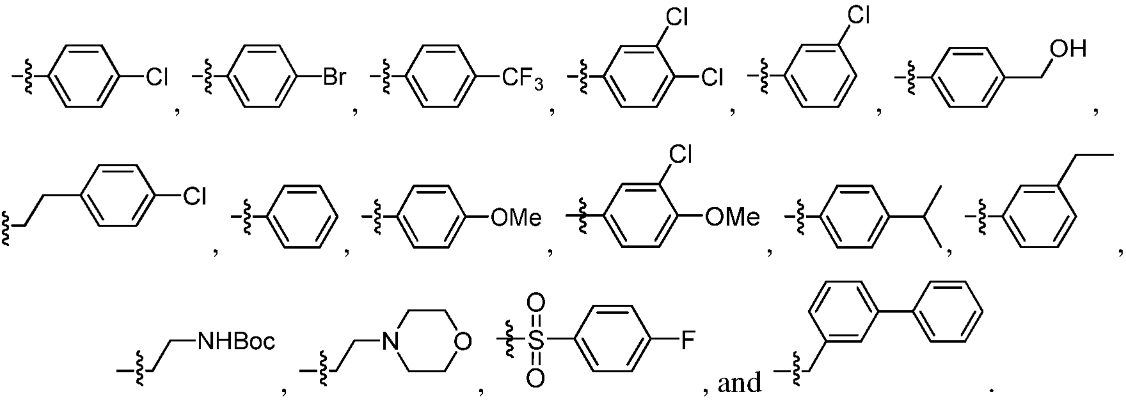


12. The method of claim 11, wherein R_1, R_2, R_3, and R_4 are hydrogen.

13. The method of claim 12, wherein X is S and R_5 is aryl, $-SO_2R_9$, or $-(CR_7)_nR_8$, wherein n is 1, 2, or 3.

14. The method of claim 13, wherein R_5 is phenyl, 4-substituted aryl, 3-substituted aryl, or 3,4-disubsitituted aryl.

15. The method of claim 13, wherein R_5 is selected from the group consisting of:



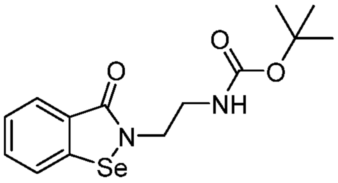
16. The method of claim 15, wherein R_1, R_2, R_3, and R_4 are hydrogen.

17. The method of claim 1, wherein the bacterial infection is caused by a bacteria that expresses a carbapenemase beta-lactamase or a penicillinase.

18. The method of claim 1, wherein the bacterial infection is caused by a bacteria that expresses New Delhi metallo-beta-lactamase 1.

19. The method of claim 1, wherein the bacterial infection is caused by bacteria from the genus Staphylococcus, Micrococcus, Bacillus, Listerella, Escherichia, Klebsiella, Proteus, Salmonella, Shigella, Enterobacter, Serratia, Pseudomonas, Acinetobacter, Nocardia, or Mycobacterium.

20. The method of claim 18, wherein the beta-lactam antibiotic is a carbapenem and the compound of formula **I** has the structure:



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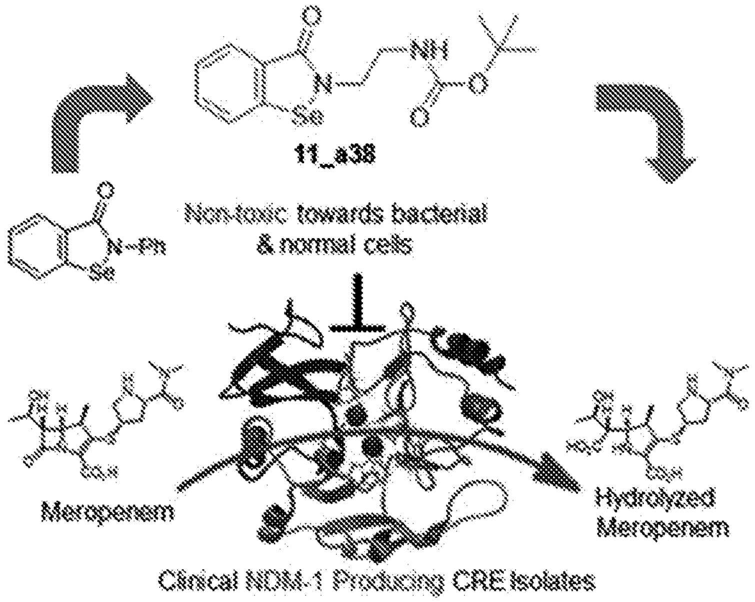

11_a38
N–Ph
Se
Non-toxic towards bacterial & normal cells
Meropenem
Hydrolyzed Meropenem
Clinical NDM-1 Producing CRE Isolates

Figure. 1

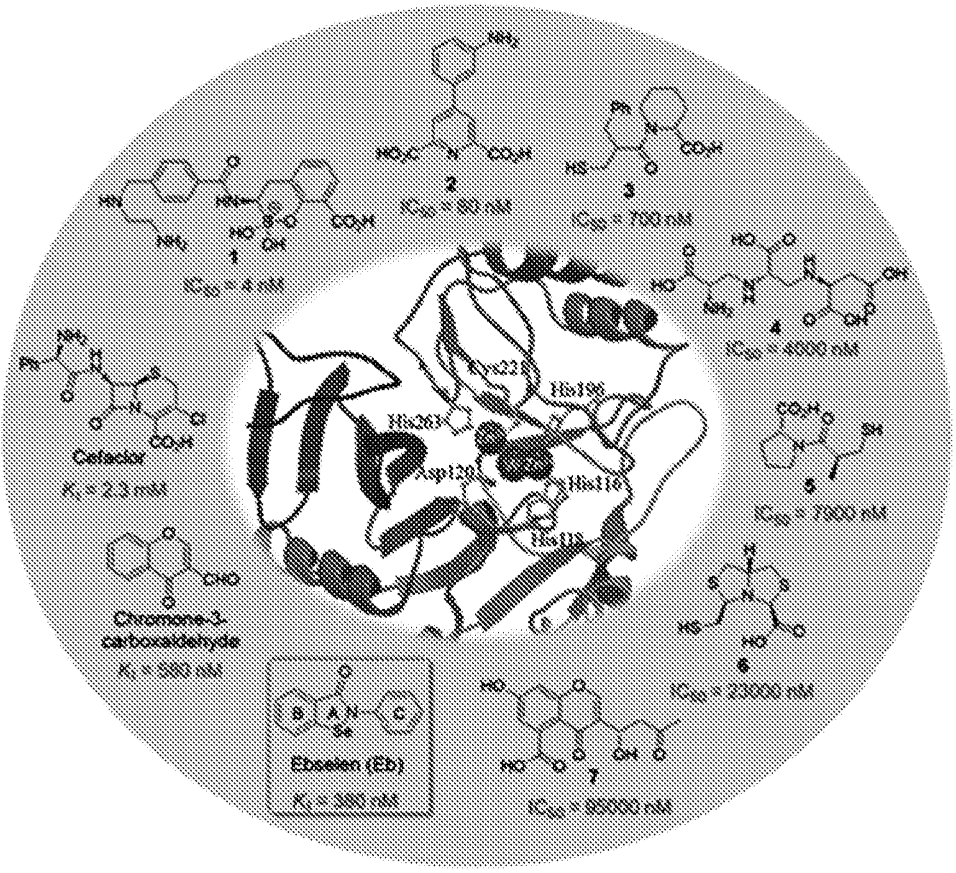

1
IC_{50} = 4 nM
2
IC_{50} = 80 nM
3
IC_{50} = 700 nM
4
IC_{50} = 4000 nM
5
IC_{50} = 7900 nM
6
IC_{50} = 23000 nM
7
IC_{50} = 85000 nM
Cefaclor
K_i = 2.3 nM
Chromone-3-carboxaldehyde
K_i = 380 nM
Ebselen (Eb)
K_i = 380 nM
B
A
C
Se
Cys221
His196
His263
Asp120
His116
His118

Figure. 2

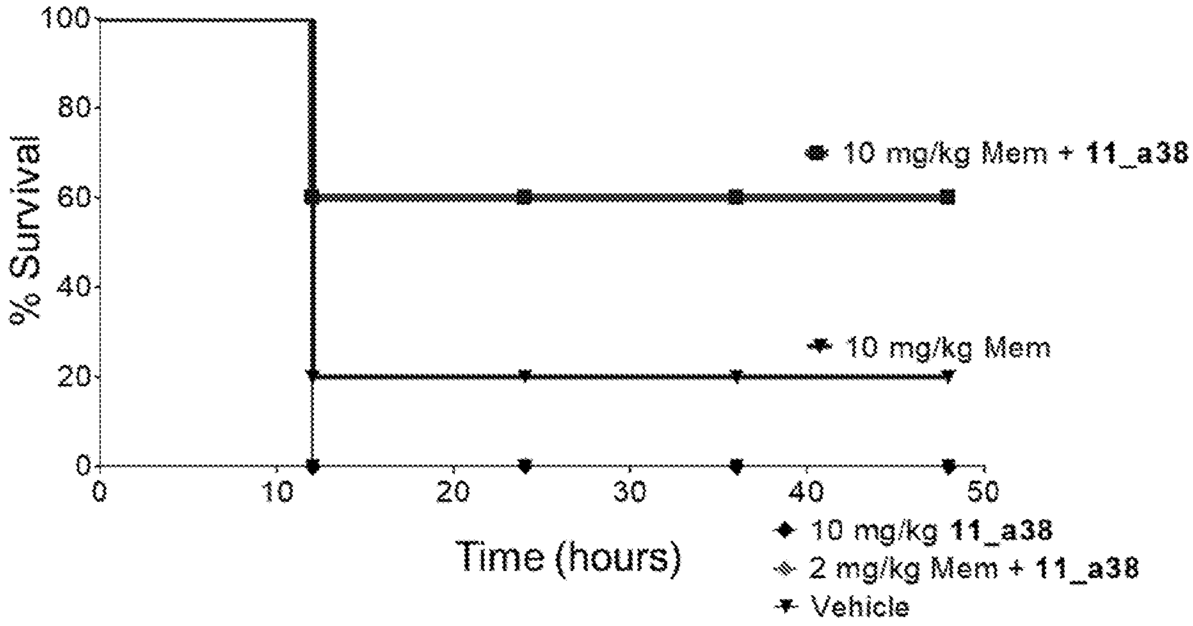

100
80
60
40
20
0
% Survival
0
10
20
30
40
50
Time (hours)
10 mg/kg Mem + 11_a38
10 mg/kg Mem
10 mg/kg 11_a38
2 mg/kg Mem + 11_a38
Vehicle

Figure. 3

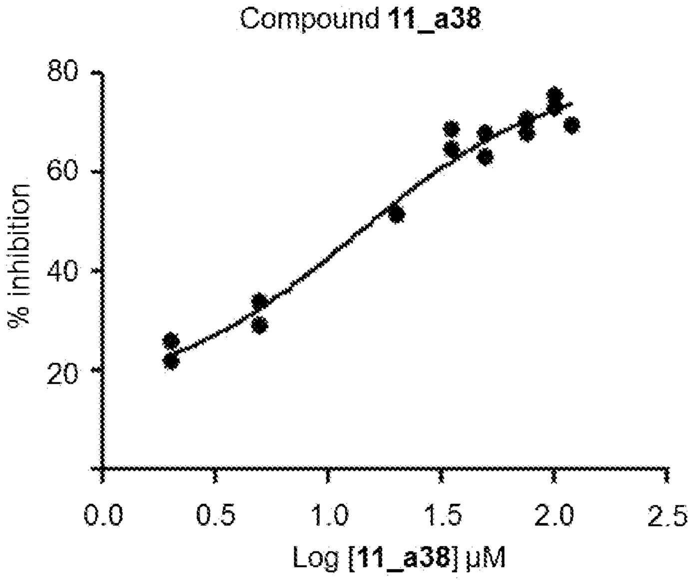

Compound **11_a38**
% inhibition
80
60
40
20
0.0
0.5
1.0
1.5
2.0
2.5
Log [**11_a38**] μM

Figure. 4

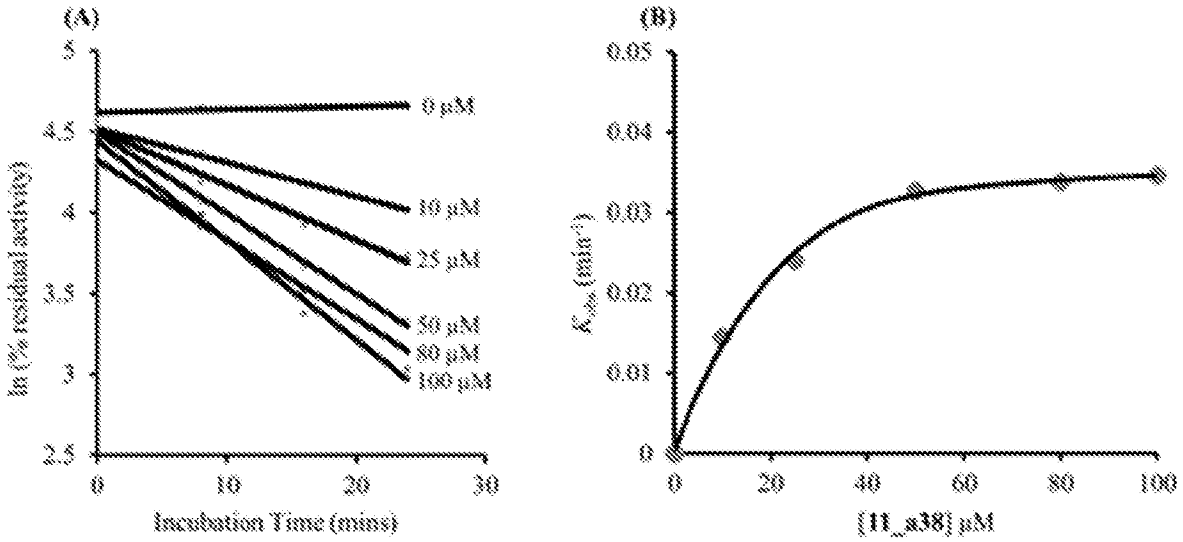

(A)
5
4.5
4
3.5
3
2.5
ln (% residual activity)
0 µM
10 µM
25 µM
50 µM
80 µM
100 µM
0
10
20
30
Incubation Time (mins)
(B)
0.05
0.04
0.03
0.02
0.01
0
K_{obs} (min^{-1})
0
20
40
60
80
100
[11_a38] µM

Figure. 5

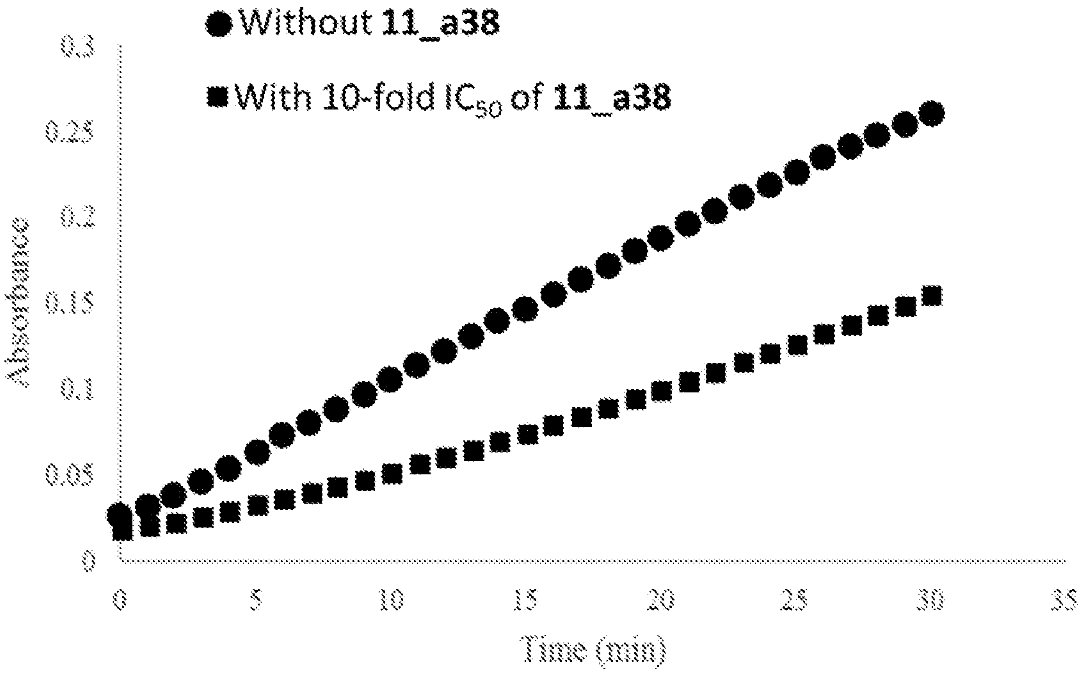

● Without **11_a38**
■ With 10-fold IC50 of **11_a38**
Absorbance
0.3
0.25
0.2
0.15
0.1
0.05
0
0
5
10
15
20
25
30
35
Time (min)

Figure. 6

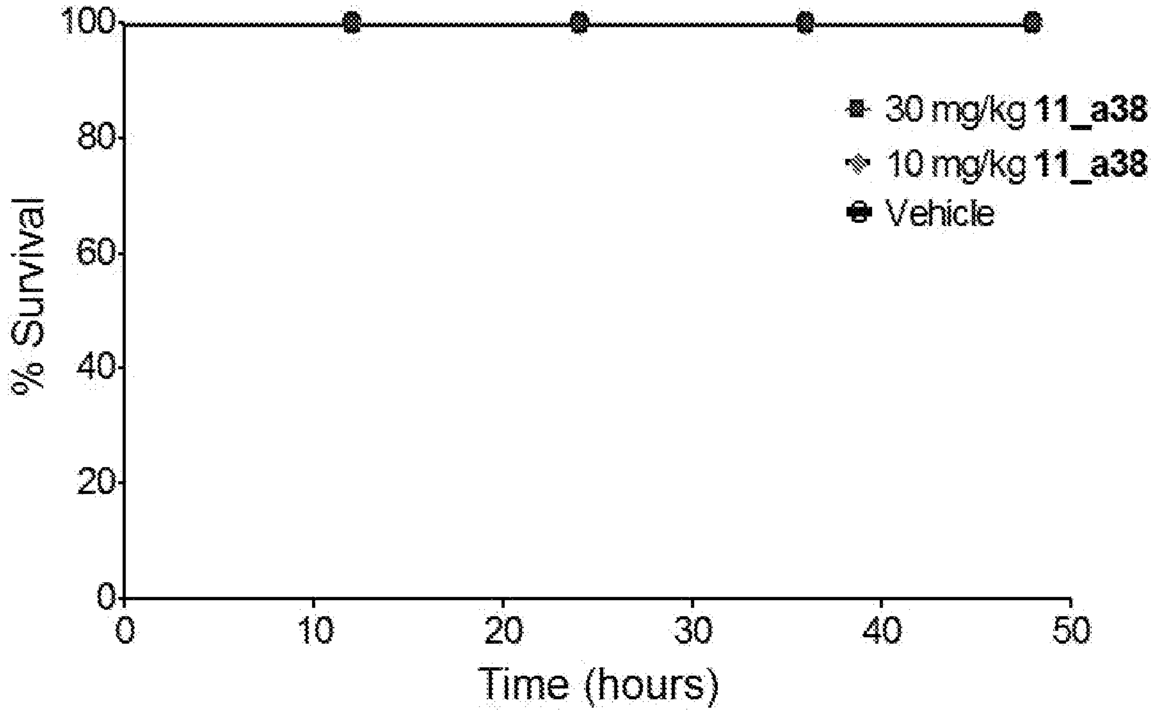

100
80
60
40
20
0
% Survival
0
10
20
30
40
50
Time (hours)
30 mg/kg **11_a38**
10 mg/kg **11_a38**
Vehicle

Figure. 7

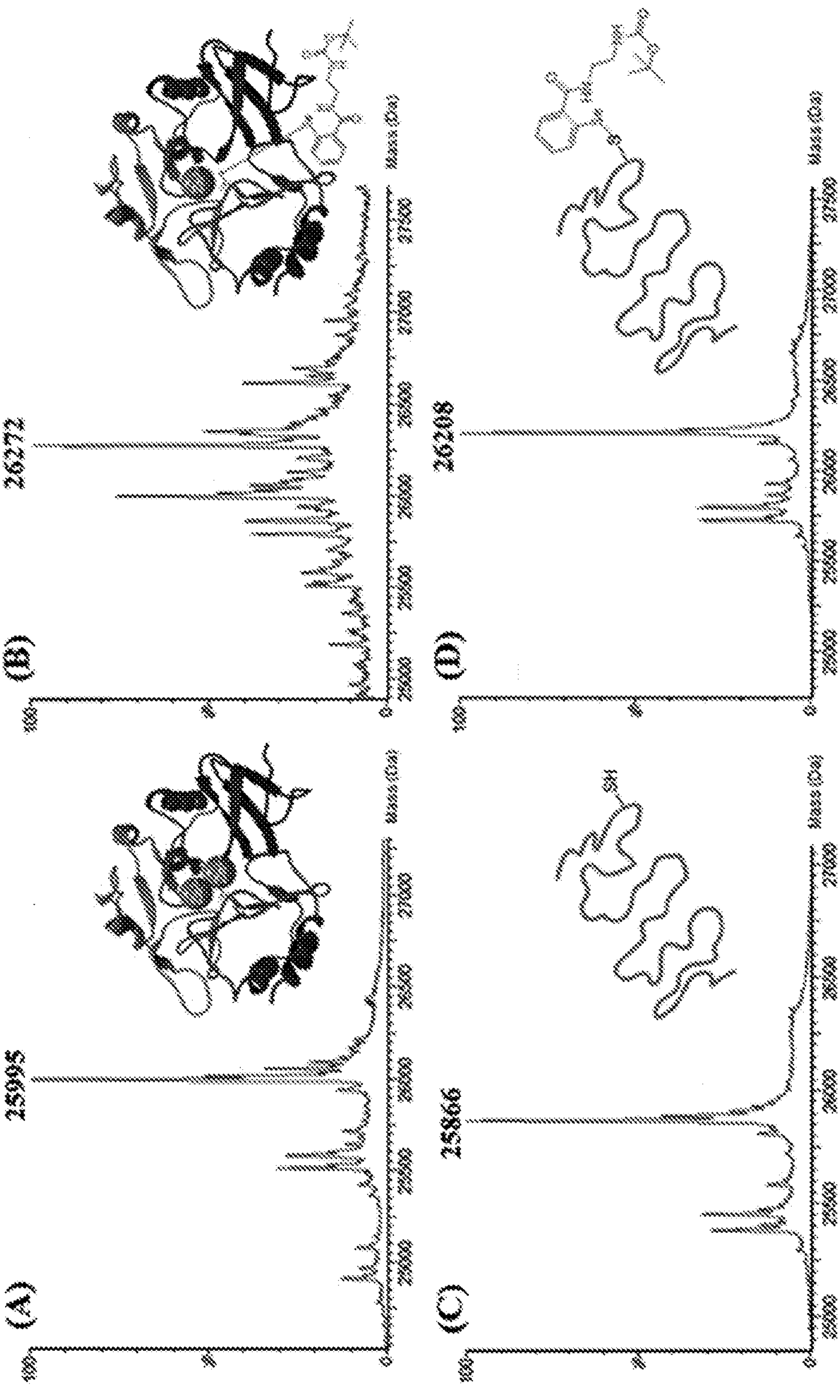


Figure. 8

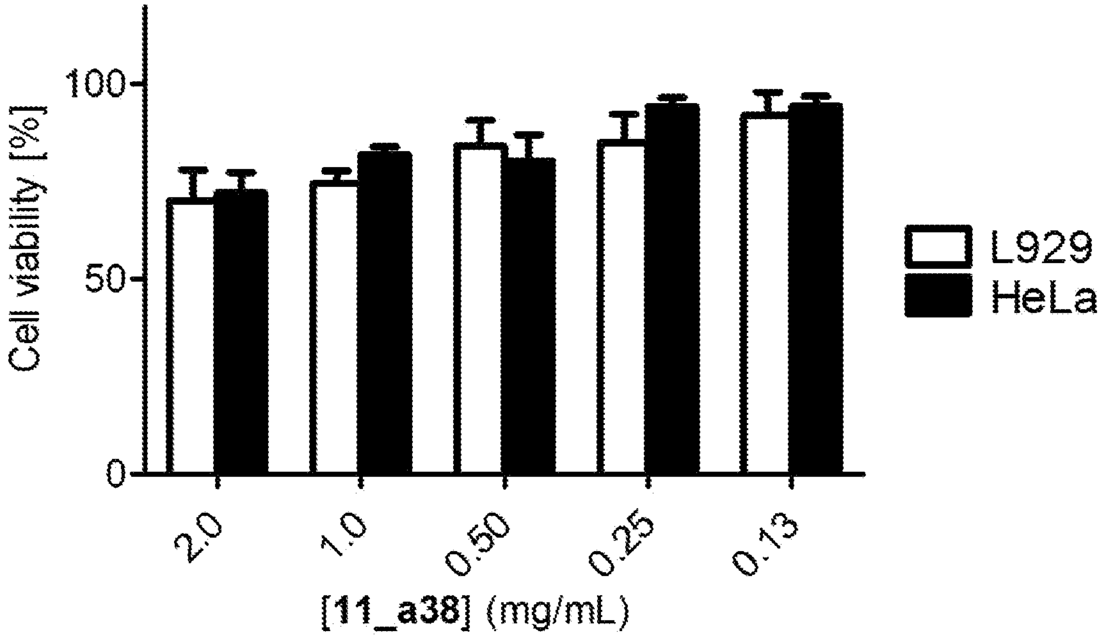


Figure. 9

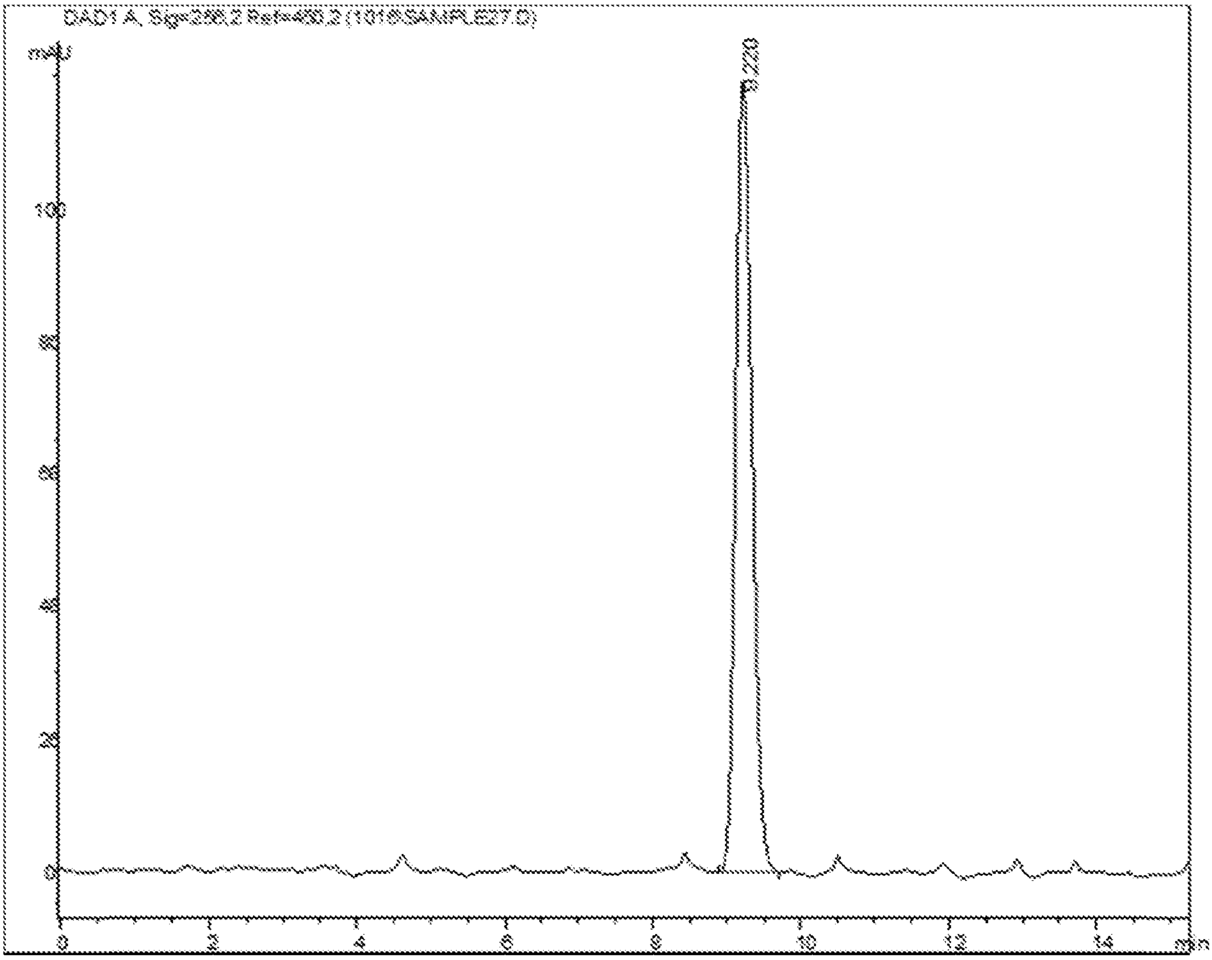
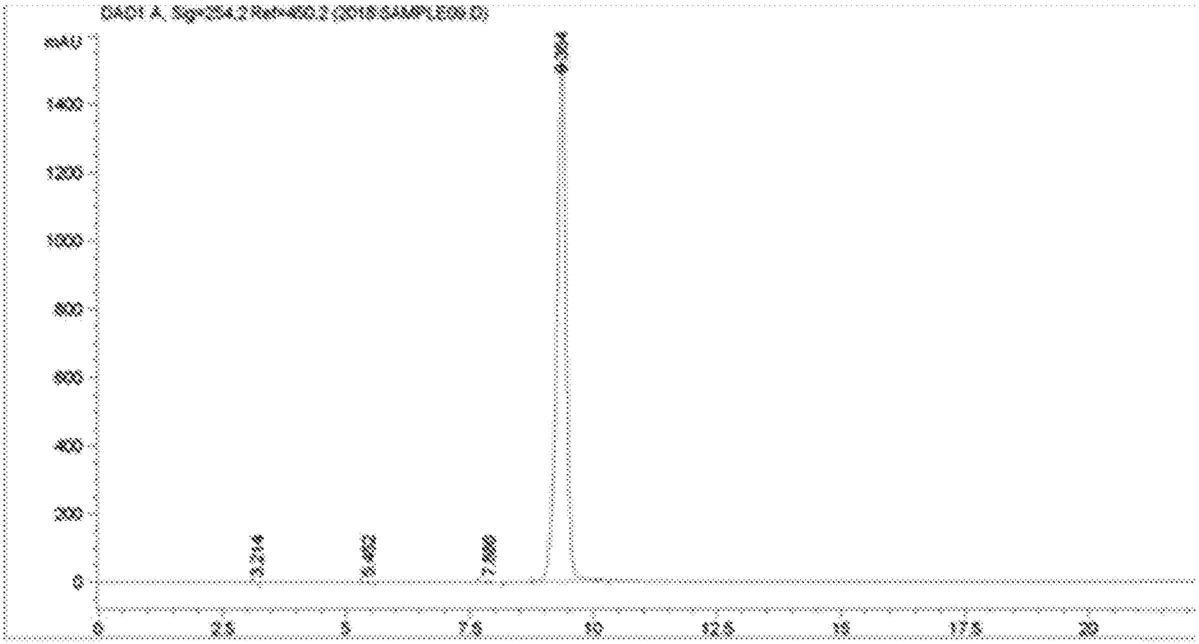

DAD1 A, Sig=256,2 Ref=450,2 (1018SAMPLE27.D)
mAU
100
80
60
40
20
0
9.220
0
2
4
6
8
10
12
14
min

Figure. 10



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=====================================================================
                         Area Percent Report
=====================================================================

Sorted By             :      Signal
Calib. Data Modified  :      Friday, April 27, 2018 3:14:40 PM
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,2 Ref=450,2

Peak RetTime  Type   Width     Area       Area    Name
  #   [min]          [min]    [mAU*s]      %
----|-------|------|-------|----------|--------|---------------------
   1   3.214 BB      0.0713    6.10227   0.0305 ?
   2   5.452 BV      0.1075   14.51774   0.0725 ?
   3   7.866 BB      0.1535   32.30332   0.1613 ?
   4   9.364 BB      0.1940 1.99714e4   99.7357

Totals :                     2.00243e4
```

Figure. 11

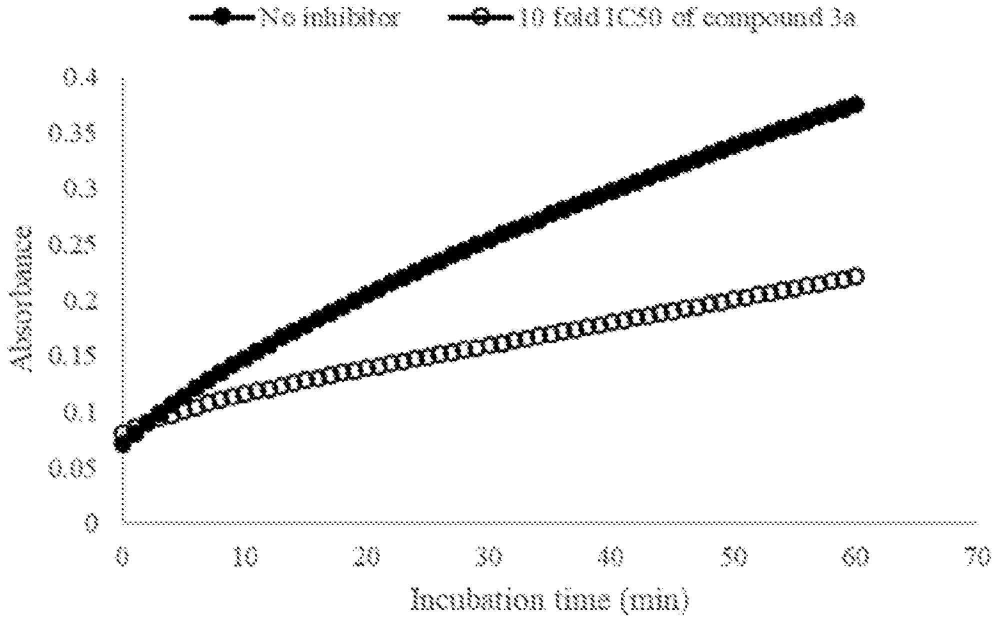

Figure. 12

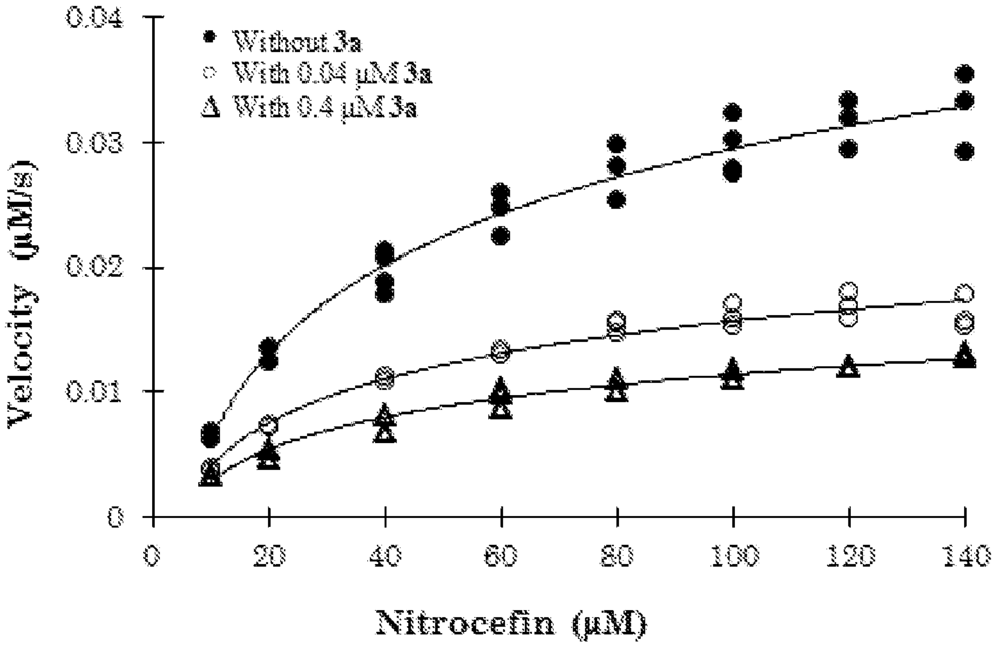

Figure. 13

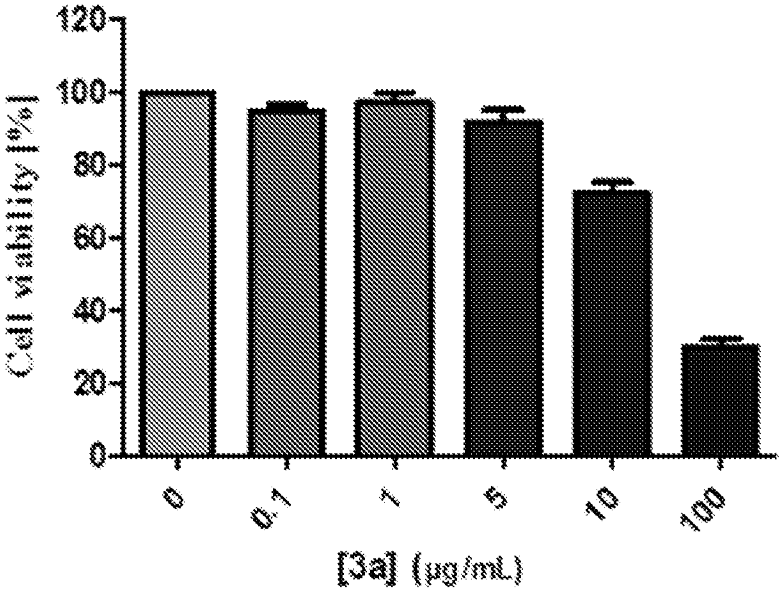

Figure. 14

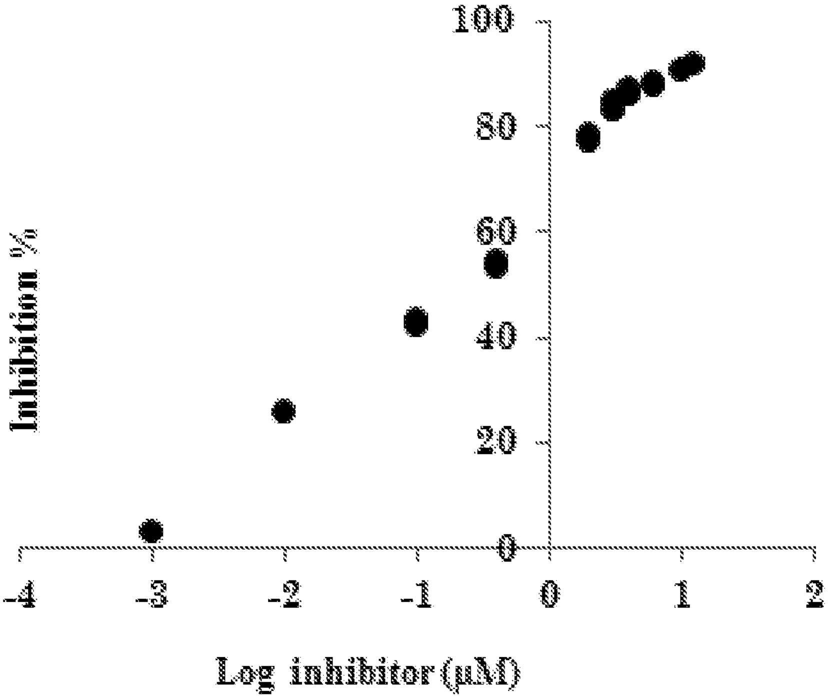

Figure. 15

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2018/114268

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/428(2006.01)i； A61K 31/43(2006.01)i； A61P 31/04(2006.01)i； C07D 275/04(2006.01)i； C07D 293/00(2006.01)i

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)

A61K31/-, A61P31/-, C07D275/-, C07D293/-

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)

CNKI, CNPAT, EPODOC, WPI, STN: 香港理工大学, 苯并异噻唑啉, 苯并异硒唑, 酮, 内酰胺, 抗生素, 青霉烯, 细菌, 抗菌, hong kong polytechnic university, benzisothiazol, benzisoselenazol, benzisothiazolinone, lactam, antibiotic, carbapenem, bacteria, antimicrobial, structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	JIN，W.B. "Investigation of synergistic antimicrobial effects of the drug combinations of meropenem and 1，2-benzisoselenazol-3(2H)-one derivatives on carbapenem-resistant Enterobacteriaceae producing NDM-1" *European Journal of Medicinal Chemistry,* Vol. 155, 06 June 2018 (2018-06-06), ISSN: 0223-5234, pages 285-302	1-20
X	US 2014/0296310 A1 (GEORGETOWN UNIVERSITY) 02 October 2014 (2014-10-02) see paragraphs [0004]-[0006]，[0027]，[0074]-[0075]，[0080]	1-3，19
Y	US 2014/0296310 A1 (GEORGETOWN UNIVERSITY) 02 October 2014 (2014-10-02) see paragraphs [0004]-[0006]，[0027]，[0074]-[0075]，[0080]	1-20
Y	WO 2017/091737 A1 (MOLECULAR DEFENSES CORPORATION) 01 June 2017 (2017-06-01) see page 42 line 31 to page 43 line 17，page 43 lines 30-31	1-20
A	WO 2011/116355 A2 (SANFORD-BURNHAM MEDICAL RESEARCH INSTITUTE ET AL.) 22 September 2011 (2011-09-22) see the whole document	1-20

☐ 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 **15 January 2019**	Date of mailing of the international search report **30 January 2019**
Name and mailing address of the ISA/CN **National Intellectual Property Administration, PRC** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing** **100088** **China** Facsimile No. **(86-10)62019451**	Authorized officer **LIU,Hongyan** Telephone No. **86-(10)-53962141**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2018/114268

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **1-20**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 1-20 are directed to a method of treatment of the human or animal body, but the search has been carried out and based on the alleged effect of the composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2018/114268

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
US 2014/0296310 A1	02 October 2014	AU 2012296543 A1	06 March 2014
		US 2014296310 A1	02 October 2014
		CA 2845551 A1	21 February 2013
		US 9428472 B2	30 August 2016
		AU 2012296543 B2	11 August 2016
		WO 2013025897 A1	21 February 2013
WO 2017/091737 A1	01 June 2017	None	
WO 2011/116355 A2	22 September 2011	WO 2011116355 A3	01 March 2012
		US 2011257233 A1	20 October 2011