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(54) Title: COMPOUNDS WITH ANTIFUNGAL PROPERTIES

(57) Abstract: Fungal infections are treated by administering MBX-7591, MBX-7498, an analog thereof, a derivative thereof, or a pharmaceutically acceptable salt of any compound. Analogs and derivatives of MBX-7591 and MBX-7498 are synthesized, and pharmaceutical compositions comprising such compounds are made and used for treating fungal infections, including drug-resistant fungal infections. The compounds and pharmaceutical compositions are used for potentiating antifungal agents, such as azoles, against drug-resistant fungus. The compounds, compositions and methods inhibit growth of fungus more effectively, including with lower concentrations of antifungal agents.



COMPOUNDS WITH ANTIFUNGAL PROPERTIES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This patent application claims priority to U.S. Provisional Patent Application No. 63/469,306, filed on May 26, 2023, the entire contents of which is fully incorporated herein by reference.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with government support under R21/R33 grant AI140878-awarded by the National Institutes of Health. The government has certain rights in the invention.

TECHNICAL FIELD

[0003] The present invention relates to compounds and methods for treating fungal infections.

BACKGROUND

[0004] Fungi are members of a kingdom of eukaryotic organisms that are considered distinct from plants and animals. Unlike plant and animal cells, they are characterised by the presence of a cell wall containing chitin. Many plant and animal diseases are attributed to fungi, either from infection of a host or through their production of toxic metabolites. Serious fungal infections, usually caused by fungal species such as *Candida* spp. and *Aspergillus* spp., are common in immunocompromised and other susceptible patient populations. They are frequent causes of morbidity and mortality in hospitalized patients and in HIV, cancer, transplant, COVID-19, and influenza A patients.

[0005] Infections caused by eukaryotic multicellular filamentous fungi (also referred to as molds) are exceedingly difficult to treat with contemporary antifungal therapies. Many molds are resistant to all 3 main classes of contemporary antifungals, and infections caused by drug susceptible molds such as *Aspergillus fumigatus* are now faced with rising drug resistance. There

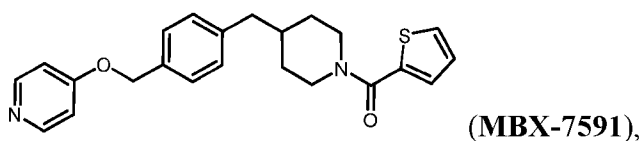
remains an urgent need for antifungal drug development focused on pathogenic filamentous fungi. However, antifungal drug discovery programs targeted against molds have significantly lagged behind that of other eukaryotic pathogens. One reason for this lack of drug development around these increasingly important pathogens is their complex multicellular lifestyles highlighted by the formation of complex biofilms that makes high throughput screening difficult. A second reason is that understanding of essential genes and pathways utilized by molds at the site of infections remains low.

[0006] *Aspergillus fumigatus* is the major *Aspergillus* species causing invasive aspergillosis, which is a life-threatening disease with a high mortality rate of 60-90%. Incidence of aspergillosis has increased, with increasing numbers of immunocompromised patients. Infections by *Candida* are commonly treated with antifungal azoles which target lanosterol demethylase, an essential enzyme in ergosterol synthesis, the major component of the fungal membrane. However the usefulness of azoles is impaired by the emergence of azole-resistant fungus, such as in *Candida* species such as *Candida glabrata*. Further, azole treatment can result in trailing growth, with surviving fungal cells becoming reservoirs for rebound infection.

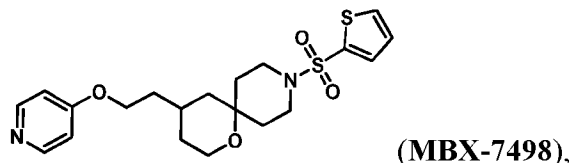
[0007] There is a need for pharmaceutical compositions and methods to treat fungal infection, including drug-resistant fungal infections. There is also a need for compounds that potentiate antifungal agents and/or enhancing the activity of such agents against fungal infections.

SUMMARY OF THE INVENTION

[0008] As one aspect of the invention, methods are provided for treating fungal infection in a subject. The methods comprise administering to the subject

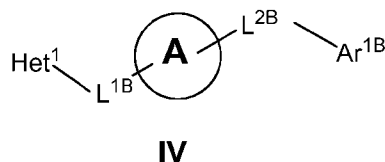
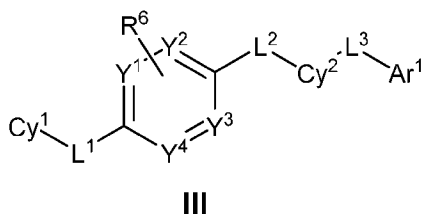


an analog thereof, a derivative thereof, or a pharmaceutically acceptable salt of any of the foregoing; or



an analog thereof, a derivative thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0009] As another aspect of the invention, novel compounds are provided which have a structure of Formula (III) or Formula (IV):



as well as pharmaceutically acceptable salts of such compounds. Also provided are pharmaceutical compositions comprising one or more of the novel compounds.

[0010] As another aspect, methods are provided for potentiating antifungal activity of an azole antifungal agent, by administering to a subject one or more of the compounds or pharmaceutical compositions described herein. In some embodiments, the subject has, is suspected of having, or is at risk of having has an azole-resistant fungal infection, such as an infection caused an azole-resistant *Aspergillus* species.

[0011] These and other features and advantages of the present methods and compounds will be apparent from the following detailed description, in conjunction with the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] FIG. 1 shows Synthetic Scheme 1, which can be used for the synthesis of MBX-7591, an analog thereof, or a derivative thereof.

[0013] FIG. 2 shows Synthetic Scheme 2, which can be used for the synthesis of MBX-7498, an analog thereof, or a derivative thereof.

DETAILED DESCRIPTION

[0014] The present invention relates to compounds and pharmaceutical compositions, as well as methods of treating a subject having a fungal infection by administering such compounds and compositions. The present invention also relates to compounds, compositions, and their use for potentiating antifungal agents, such as azoles, against drug-resistant fungus. The present disclosure provides compounds, compositions and methods which inhibit growth of fungus more effectively, including with lower concentrations of antifungal agents.

[0015] It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present teachings will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those working in the fields to which this disclosure pertain. The defined terms are in addition to the technical and scientific meanings of the defined terms as commonly understood and accepted in the technical field of the present teachings.

[0016] As used herein, and in addition to their ordinary meanings, the terms “substantial” or “substantially” mean to within acceptable limits or degree to one having ordinary skill in the art. For example, “substantially cancelled” means that one skilled in the art considers the cancellation to be acceptable.

[0017] As used herein and in addition to its ordinary meaning, the terms “approximately” and “about” mean to within an acceptable limit or amount to one having ordinary skill in the art. The term “about” generally refers to plus or minus 15% of the indicated number. For example, “about 10” may indicate a range of 8.5 to 11.5. For example, “approximately the same” means that one of ordinary skill in the art considers the items being compared to be the same.

[0018] As used herein, the terms “a,” “an,” and “the” include both singular and plural referents, unless the context clearly dictates otherwise. Thus, for example, “a compound” includes one compound and plural compounds. The terms “first” and “second” are terms to distinguish different elements, not terms supplying a numerical limit, and a composition having first and second element can also include a third, a fourth, a fifth, and so on, unless otherwise indicated.

[0019] As disclosed herein, numeric ranges are provided for various parameters or data. It should be understood that numeric ranges also disclose include each intervening value within the range, to the tenth of the unit of the lower limit, unless the context clearly dictates otherwise. It should also be understood that the upper and lower limits may each be included or excluded in a range.

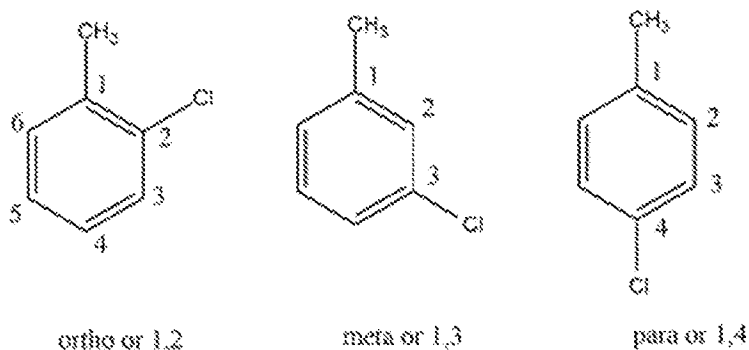
[0020] It should be recognized that chemical structures and formula may be elongated or enlarged for illustrative purposes.

[0021] As used herein, the term “analog” refers to a compound that has a structure similar to an “original” compound (*i.e.*, the compound of which it is an analog), but having one or more structural variations (such as by having one, two, or more different atoms, or by having one, two or more different functional groups), and that retains the same or a substantially similar biological function as the original compound. The term “derivative” as used herein refers to a chemical compound related structurally to an original compound, and which can be made from the original compound in one or more steps. The general physical and chemical properties of a derivative are also similar to the original compound.

[0022] The terms “substituted” and “substituent”, in the context of the chemical molecules or groups discussed herein, refer to replacement of one or more hydrogen atoms on such molecules with a non-hydrogen atom or group. Typical substituents include, but are not limited to, —X, —R, —O[−], =O, —OR, —SR, —S[−], —NR₂, —N⁺R₃, =NR, —CX₃, —CN, —OCN, —SCN, —N=C=O, —NCS, —NO, —NO₂, =N₂, —N₃, —NHC(=O)R, —NHS(=O)₂R, —C(=O)R, —C(=O)NRR—S(=O)₂O[−], —S(=O)₂OH, —S(=O)₂R, —OS(=O)₂OR, —S(=O)₂NR, —S(=O)R, —OP(=O)(OR)₂, —P(=O)(OR)₂, —P(=O)(O[−])₂, —P(=O)(OH)₂, —P(O)(OR)(O[−]), —C(=O)R, —C(=O)OR, —C(=O)X, —C(=S)R, —C(=O)OR, —C(=O)O[−], —C(=S)OR, —C(=O)SR, —C(=S)SR, —C(=O)NRR, —C(=S)NRR, —C(=NR)NRR, where each X is independently a halogen: F, Cl, Br, or I; and each R is independently H, alkyl, aryl, arylalkyl, a heterocycle, or a protecting group. Examples of substituents include C₁–C₃-alkyl, C₁–C₃-haloalkyl, halo, C₁–C₃-alkoxy, and oxo. A “substituted” molecule or group, for example, “substituted alkyl”, “substituted heteroalkyl”, “substituted alkenyl”, substituted hetroalkenyl”, “substituted alkynyl”, “substituted hetoeralkynyl”, “substituted aryl”, “substituted heteroaryl”, and “substituted

heterocycle” means alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, aryl, heteroaryl, and heterocycle, respectively, having one or more substituents.

[0023] The terms "para", "meta", and "ortho" refer to the positions of substituents on a ring with respect to a first atom on the ring. By way of example, a chloro substituent in ortho-, meta-, and para-positions on a benzene ring are shown below.



The first atom can be another substituent or a point of attachment to another group in the compound. When referring to substituents on a five-membered group, the terms "para", "meta", and "ortho" refer to the placement of a substituent relative to the point of attachment of the pyridyl ring. For example the structure below is described as 4 pyridyl with the X substituent in the ortho position and the Y substituent in the meta position:

[0024] The term “alkyl” and “alkane” refers to a linear, branched or cyclic alkyl, unless the context indicates otherwise. For instance, an alkyl can have 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 carbons, or a range formed by any of those numbers, including but not limited to C₁-C₃, C₁-C₄, C₁-C₆, C₃-C₈, or C₄-C₈. Examples of such alkyl groups include methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, pentyl, isoamyl, hexyl, and the like. Alkyl groups may be unsubstituted or substituted, as defined above. The term “haloalkyl” refers to an alkyl group substituted with one or more halogen atoms. Nonlimiting examples include trifluoromethyl, trifluoroethyl, pentafluoroethyl, 2,2,2-trichloroethyl, chloromethyl, and the like. The term “cycloalkyl” refers to a ring system comprising alkyl groups, such as a monocyclic ring, a bicyclic ring, a fused ring system, or a bridged ring system, each which may be optionally substituted by one or more substituents.

[0025] The terms “alkenyl” and “alkene” refers to a linear, branched or cyclic hydrocarbon, unless the context indicates otherwise, and having one or more carbon-carbon double bonds. For instance, an alkenyl can have 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 carbons, or a range formed by any of those numbers, including but not limited to C₂-C₃ alkene, C₂-C₄ alkene, C₂-C₆ alkene, and C₃-C₆ alkene. Examples of alkenyl groups include ethenyl, 1-propenyl, 2-propenyl (allyl), *iso*-propenyl, 2-methyl-1-propenyl, 1-butenyl, and 2-butenyl. Alkenyl groups may be unsubstituted or substituted by one or more suitable substituents, as defined above. The term “haloalkenyl” refers to an alkenyl group substituted with one or more halogen atoms. The term “cycloalkenyl” refers to one or more rings having an alkenyl group, such as a monocyclic ring, a bicyclic ring, a fused ring system, or a bridged ring system, each which may be optionally substituted by one or more substituents.

[0026] The term “alkynyl” or “alkyne” refers to a linear, branched or cyclic hydrocarbon, unless the context indicates otherwise, and having one or more carbon-carbon triple bonds. For instance, an alkynyl can have 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 carbons, or a range formed by any of those numbers, including but not limited to C₂-C₃ alkyne, C₂-C₆ alkyne, and C₃-C₆ alkyne. Alkynyl groups include, but are not limited to, ethynyl, propynyl, and butynyl. Alkynyl groups may be unsubstituted or substituted by one or more suitable substituents, as defined above. The term “haloalkynyl” refers to an alkynyl group substituted with one or more halogen atoms. The term “cycloalkynyl” refers a ring system having an alkynyl group, such as a monocyclic ring, a bicyclic ring, a fused ring system, or a bridged ring system, each which may be optionally substituted by one or more substituents.

[0027] Whenever a range of the number of atoms in a structure is indicated (e.g., a C₁-C₂₄ alkyl, C₂-C₂₄ alkenyl, C₂-C₂₄ alkynyl, etc.), it is hereby disclosed that the substituent can be described by any of the carbon atoms in the sub-range or by any individual number of carbon atoms falling within the indicated range. By way of example, a description of the group such as an alkyl group using the recitation of a range of 1-24 carbon atoms (e.g., C₁-C₂₄), 1-6 carbon atoms (e.g., C₁-C₆), 1-4 carbon atoms (e.g., C₁-C₄), 1-3 carbon atoms (e.g., C₁-C₃), or 2-24 carbon atoms (e.g., C₂-C₂₄) encompasses and specifically describes an alkyl group having any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24 carbon atoms,

as appropriate, as well as any sub-range thereof (e.g., 1-2 carbon atoms, 1-3 carbon atoms, 1-4 carbon atoms, 1-5 carbon atoms, 1-6 carbon atoms, 1-7 carbon atoms, 1-8 carbon atoms, 1-9 carbon atoms, 1-10 carbon atoms, 1-11 carbon atoms, 1-12 carbon atoms, 1-13 carbon atoms, 1-14 carbon atoms, 1-15 carbon atoms, 1-24 carbon atoms, 2-3 carbon atoms, 2-4 carbon atoms, 2-5 carbon atoms, 2-6 carbon atoms, 2-7 carbon atoms, 2-8 carbon atoms, 2-9 carbon atoms, 2-10 carbon atoms, 2-11 carbon atoms, 2-12 carbon atoms, 2-13 carbon atoms, 2-14 carbon atoms, 2-15 carbon atoms, 2-16 carbon atoms, 3-4 carbon atoms, 3-5 carbon atoms, 3-6 carbon atoms, 3-7 carbon atoms, 3-8 carbon atoms, 3-9 carbon atoms, 3-10 carbon atoms, 3-11 carbon atoms, 3-12 carbon atoms, 3-13 carbon atoms, 3-14 carbon atoms, 3-15 carbon atoms, 3-16 carbon atoms, 3-17 carbon atoms, 3-18 carbon atoms, 3-19 carbon atoms, 3-20 carbon atoms, 3-21 carbon atoms, 3-22 carbon atoms, 3-23 carbon atoms and/or 3-24 carbon atoms, as appropriate). When a number of carbon atoms is designated for a substituted molecule or group, the number of carbon atoms refers to the group, not the substituent (unless otherwise indicated). For example, a C₁₋₄ substituted alkyl refers to a C₁₋₄ alkyl, which can be substituted with groups having more than, e.g., 4 carbon atoms.

[0028] “Heteroalkyl”, “heteroalkenyl” and “heteroalkynyl” refers respectively to an alkyl group, an alkenyl group and an alkynyl group, in which one or more carbon atoms have been replaced with a heteroatom, such as, O, N, or S. Any carbons within the alkyl group, the alkenyl group or the alkynyl group can be replaced independently with a heteroatom (O, N, or S), meaning the first carbon, the terminal carbon or an internal carbon. For example, if the carbon atom of an alkyl group which is attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkoxy group (e.g., —OCH₃, etc.), an amine alkyl (e.g., —NHCH₃, —N(CH₃)₂, etc.), or a thioalkyl group (e.g., —SCH₃). If a non-terminal carbon atom of the alkyl group which is not attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkyl ether (e.g., —CH₂CH₂—O—CH₃, etc.), an alkyl amine (e.g., —CH₂NHCH₃, —CH₂N(CH₃)₂, etc.), or a thioalkyl ether (e.g., —CH₂—S—CH₃). If a terminal carbon atom of the alkyl group is replaced with a heteroatom (e.g., O, N, or S), the resulting heteroalkyl groups are, respectively, a hydroxyalkyl group (e.g., —CH₂CH₂—OH), an

aminoalkyl group (e.g., $\text{—CH}_2\text{NH}_2$), or an alkyl thiol group (e.g., $\text{—CH}_2\text{CH}_2\text{—SH}$). A heteroalkyl group, a heteroalkenyl group, or a heteroalkynyl group can have, for example, 1 to 24 carbon atoms. A $\text{C}_1\text{—C}_6$ heteroalkyl group means a heteroalkyl group having 1 to 6 carbon atoms. A “substituted heteroalkyl”, a “substituted heteroalkenyl”, or a “substituted heteroalkynyl” means a heteroalkyl, a heteroalkenyl or a heteroalkynyl as defined herein in which one or more hydrogen atom has been replaced with a non-hydrogen substituent as defined in the “substituted” definition.

[0029] The term “aryl” refers to an unsubstituted or substituted aromatic carbocyclic substituent, as commonly understood in the art, such as phenyl, naphthyl, anthracyl, indanyl, and the like. It is understood that the term aryl applies to cyclic substituents that are planar and comprise $4n+2$ electrons, according to Hückel's Rule. Aryl groups may be unsubstituted or substituted by one or more suitable substituents, as defined above. The term “halosubstituted aryl” refer to aryl substituted with one or more halogen atoms or halogen-containing substituents. The term “fluorosubstituted aryl” refer to aryl substituted with one or more fluorine atoms or fluorine-containing substituents.

[0030] “Arylalkyl” refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal carbon atom, is replaced with an aryl group. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group can comprise 6 to 24 carbon atoms, e.g., the alkyl carbon atoms and the aryl carbon atoms add up to 6 to 24 carbon atoms. Aryl groups may be unsubstituted or substituted by one or more suitable substituents, as defined above.

[0031] The term “carbonyl” refers to a substituent comprising a carbon double bonded to an oxygen. Examples of such substituents include aldehydes, ketones, carboxylic acids, esters, amides, carbonates, and carbamates. Carbonyl groups may be unsubstituted or substituted by one or more suitable substituents, as defined above.

[0032] The term “amino” refers to any nitrogen-containing moiety. Non-limiting examples of the amino group are $\text{NH}_2\text{—}$ (primary), RHN— (secondary), and $\text{R}_2\text{N—}$ (tertiary) where R is alkyl,

alkenyl, alkynyl, aryl, heterocyclic, or heteroaryl. RHN- and R₂N groups may be unsubstituted or substituted, as defined above.

[0033] The term “azole” refers to a five-membered aromatic heterocyclic system with at least one nitrogen in the ring which typically has additional oxygen, sulfur or additional nitrogen(s) within the five-membered ring. Examples of azole include imidazoles, pyrazoles, triazoles, tetrazoles, oxazoles, isoxazoles, and oxadiazoles such as furazan (1,2,5-oxadiazoles). A large number of active antifungal agents have an azole functionality as part of their structure; such an antifungal agent is generally referred to as an “antifungal azole”, an “azole antifungal agent” or an “azole”. Examples of azole antifungal agents include ketoconazole, fluconazole, itraconazole, miconazole, voriconazole, posaconazole and ravuconazole.

[0034] The term “heteroaryl” refers to a monocyclic or bicyclic 5- or 6-membered ring system, wherein the heteroaryl group is unsaturated and satisfies Hückel's rule. Non-limiting examples of heteroaryl groups include furanyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-2-yl, 5-methyl-1,3,4-oxadiazole, 3-methyl-1,2,4-oxadiazole, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, benzothiophenyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazoliny, benzothiazoliny, quinazoliny, and the like. Heteroaryl groups may be unsubstituted or substituted, as defined above.

[0035] The term “heterocycle” or “heterocyclyl” refers to a monocyclic, bicyclic, or tricyclic moiety containing 1 to 4 heteroatoms selected from O, N, and S. Heterocyclyl groups optionally contain one or more double bonds. Heterocyclyl groups include, but are not limited to, azetidiny, tetrahydrofuranyl, imidazolidiny, pyrrolidiny, piperidiny, piperaziny, oxazolidiny, thiazolidiny, pyrazolidiny, thiomorpholiny, tetrahydrothiaziny, tetrahydro-thiadiaziny, morpholiny, oxetany, tetrahydrodiaziny, oxaziny, oxathiaziny, indoliny, isoindoliny, quinuclidiny, chromany, isochromany, and benzoxaziny. Nonlimiting examples of monocyclic saturated or partially saturated ring systems are tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-4-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, 1,3-oxazolidin-3-yl, isothiazolidine, 1,3-thiazolidin-3-yl, 1,2-

pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, thiomorpholin-yl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazin-yl, morpholin-yl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, 1,4-oxazin-2-yl, and 1,2,5-oxathiazin-4-yl. Heterocyclic groups may be unsubstituted or substituted by one or more suitable substituents, as defined above.

[0036] “Halogen” or “halo” refers to fluorine, chlorine, bromine, and iodine.

[0037] As used herein, the term “chiral” refers to molecules which have the property of non-superimposability of the minor image partner, while the term “achiral” refers to molecules which are superimposable on their minor image partner. The compounds of the present disclosure may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as geometric isomers, enantiomers or diastereomers.

[0038] The present compounds and pharmaceutical compositions include various stereoisomers of these compounds and mixtures thereof. Mixtures of enantiomers or diastereomers may be designated ($\pm$) in nomenclature, but it should also be noted that a chemical structure or formula may denote a chiral center implicitly. In the present disclosure, all graphical depictions of chemical compounds, structures and formulas encompass and constitute disclosures of all stereoisomers of the depicted specified compounds, structures and formulas, unless the depiction indicates otherwise.

[0039] The term “stereoisomers” refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. These compounds may be designated by using one or more symbols “R” or “S,” or “+” or “–” depending on the configuration of substituents around the stereogenic carbon atom(s) and or the optical rotation observed.

[0040] “Diastereomer” refers to a stereoisomer with two or more centers or axes of chirality and whose molecules are not mirror images of one another. Diastereomers typically have different physical properties, e.g., melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

[0041] “Enantiomers” refer to two stereoisomers of a compound which are non-superimposable mirror images of one another. A mixture of enantiomers at a ratio other than 1:1 is a “scalemic” mixture.

[0042] The compounds of the present disclosure may have chiral centers, e.g., chiral carbon atoms. Such compounds thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds disclosed herein include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. Similarly, compositions disclosed herein also include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers of compounds disclosed herein. In addition, the present compounds include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures can be separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. The desired optical isomer can also be synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

[0043] The present compounds include any or all of the stereochemical forms, including any enantiomeric or diastereomeric forms and geometric isomers of the compounds described, or mixtures thereof. Unless stereochemistry is explicitly indicated in a chemical structure or name, the structure or name is intended to embrace all possible stereoisomers, including geometric isomers, of a compound depicted. Compositions comprising a compound of the invention are also intended, such as a composition of substantially pure compound, including a specific stereochemical form, including a specific geometric isomer, thereof. Compositions comprising a mixture of compounds of the invention in any ratio are also embraced by the invention, including mixtures of two or more stereochemical forms of a compound of the invention in any ratio, such

that racemic, non-racemic, enantio-enriched and scalemic mixtures of a compound are embraced, or mixtures thereof.

[0044] It is to be understood that for compounds disclosed herein when a bond is drawn in a non-stereochemical manner (e.g., flat) the atom to which the bond is attached includes all stereochemical possibilities. It is also to be understood that when a bond is drawn in a stereochemical manner (e.g., bold, bold-wedge, dashed or dashed-wedge) the atom to which the stereochemical bond is attached has the stereochemistry as shown unless otherwise noted. Accordingly, in some embodiments, a compound disclosed herein is greater than 50% a single enantiomer, alternatively at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% a single enantiomer. In some embodiments, a compound disclosed herein is greater than 50% a single diastereomer, alternatively at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% a single diastereomer.

[0045] Accordingly, in some embodiments, a pharmaceutical composition comprises a compound as disclosed herein, where the compound is greater than 50% a single enantiomer, alternatively at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% a single enantiomer. In some embodiments, a composition disclosed herein is greater than 50% a single diastereomer. In some embodiments, a pharmaceutical composition comprises a compound as disclosed herein, where the compound is greater than 50% a single diastereomer, alternatively at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% a single diastereomer.

[0046] Also contemplated herein are pharmaceutical compositions comprising, consisting essentially of, or consisting of an enantiopure compound, which composition may comprise, consist essentially of, or consist of at least about 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% of a single enantiomer of a given compound (e.g., at least about 99% of an R enantiomer of a given compound).

[0047] As used herein, “pharmaceutically acceptable salt” refers to a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Pharmaceutically acceptable salts are generally regarded as safe and suitable for use without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio. Examples of

“pharmaceutically acceptable salts” of the compounds disclosed herein include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth metal (for example, magnesium), ammonium and NX_4^+ (wherein X is $\text{C}_1\text{-C}_4$ alkyl). Pharmaceutically acceptable salts of a nitrogen atom or an amino group include for example salts of organic carboxylic acids such as acetic, benzoic, camphorsulfonic, citric, glucoheptonic, gluconic, lactic, fumaric, tartaric, maleic, malonic, malic, mandelic, isethionic, lactobionic, succinic, 2-naphthalenesulfonic, oleic, palmitic, propionic, stearic, and trimethylacetic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric and sulfamic acids. Pharmaceutically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X is independently selected from H or a $\text{C}_1\text{-C}_4$ alkyl group). Pharmaceutically acceptable salts also include salts formed when an acidic proton present in the parent compound is replaced by either a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as diethanolamine, triethanolamine, N-methylglucamine and the like. Also included in this definition are ammonium and substituted or quaternized ammonium salts. Representative non-limiting lists of pharmaceutically acceptable salts can be found in S. M. Berge et al., J. Pharma Sci., 66(1), 1-19 (1977), and Remington: The Science and Practice of Pharmacy, R. Hendrickson, ed., 21st edition, Lippincott, Williams & Wilkins, Philadelphia, Pa., (2005), at p. 732, Table 38-5, both of which are hereby incorporated by reference herein.

[0048] For therapeutic use, salts of active ingredients of the present compounds will typically be pharmaceutically acceptable, i.e., they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not pharmaceutically acceptable may also find use, for example, in the preparation or purification of a compound disclosed herein. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

[0049] Metal salts typically are prepared by reacting the metal hydroxide with a compound disclosed herein. Examples of metal salts which are prepared in this way are salts containing Li^+ ,

Na⁺, and K⁺. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

[0050] In addition, salts may be formed from acid addition of certain organic and inorganic acids, e.g., HCl, HBr, H₂SO₄, H₃PO₄ or organic sulfonic acids, to basic centers, such as amines. Finally, it is to be understood that the compositions herein comprise compounds disclosed herein in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

[0051] The term “fungal infection” is used broadly herein to indicate that a subject may have, or contain, or carry, the fungus in question, i.e. that the fungus may be present in or on the subject, and this may include any site or location in or on the body of the subject. It is not necessary that the infection of the subject present as a clinical disease (i.e. that the infection result in clinical symptoms in the subject), although this is of course encompassed. A subject who is suspected to be infected or who is at risk of infection may be a subject who has been exposed to the fungus or to an infected subject, or a subject presenting with clinical signs or symptoms of infection (in the case of a suspected infection), or a subject who is susceptible to infection, whether generally (e.g. due to the clinical status of the subject) or particularly to the fungus in question. The term “fungal infection of a plant” should be construed in line with this.

[0052] The term “effective amount” as employed herein is an amount of a compound of the invention that achieves the effect which is intended with its application. The amount of a compound of the invention which constitutes an “effective amount” will vary depending on the compound, the intended use, the disease state and its severity, the age of the patient to be treated, and the like. The effective amount can be determined routinely by one of ordinary skill in the art.

[0053] The term “subject” as used herein includes humans and other animals, particularly mammals, and other organisms. Thus, the compounds, compositions and methods of the present invention are applicable to both human therapy and veterinary applications. In a preferred embodiment the subject is a mammal, and in a most preferred embodiment the subject is human.

[0054] The terms “treating” or “treatment” as used herein covers the treatment of a disease-state in an animal or plant, which disease-state is characterized by pathogen invasion and includes at least one of: (i) preventing the disease-state from occurring in an animal or plant, in

particular, when such animal or plant is predisposed to the disease-state but has not yet been diagnosed as having it; (ii) inhibiting the disease-state, i.e., arresting its development; and (iii) relieving the disease-state, i.e., causing regression of the disease-state. In a preferred embodiment of the present invention the animal is a mammal, more preferably a human. As is known, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary or desirable. The present methods are not intended to be limited to administration to humans and may also be employed for veterinary, agricultural and aquatic treatments and uses, including for example, methods for treating fungal infections of non-human mammals, fish and plants.

[0055] The term “in a subject” is used broadly herein to include sites or locations inside a subject or on a subject, e.g. an external body surface, and may include in particular infection of a medical device e.g. an implanted or “in-dwelling” medical device. The term “in a patient” should be understood in the same way.

[0056] The term “antifungal agent” is intended to mean a substance capable of inhibiting or preventing the growth, viability and/or reproduction of a fungal cell. Preferable antifungal agents are those capable of preventing or treating a fungal infection in an animal or plant. A preferable antifungal agent is a broad spectrum antifungal agent. However, an antifungal agent can also be specific to one or more particular species of fungus. The term antimycotic agent may be used in place of antifungal agent, and is considered to be interchangeable unless the context indicates otherwise.

[0057] The terms “potentiating antifungal activity” and “improving efficacy of an antifungal agent” generally encompass any improving or enhancing of the antifungal effect of the antifungal agent, e.g. so that the antifungal effect of the antifungal agent is increased or enhanced in any way over the antifungal effect of the antifungal agent seen in the absence of the present compounds. This may be seen for example in a stronger effect of the anti-fungal agent in inhibiting growth and/or viability of the fungi, a requirement for less anti-fungal agent in order to achieve the same effect seen in the absence of the present compounds, or a increased effectiveness seen as increased speed or rate of action, an inhibitory effect being seen in less time than in the absence of the present compounds.

[0058] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present teachings, some exemplary methods and materials are now described.

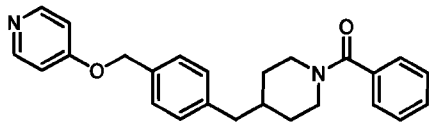
[0059] All patents and publications referred to herein are expressly incorporated by reference.

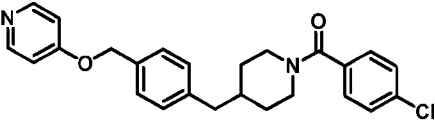
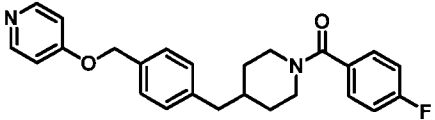
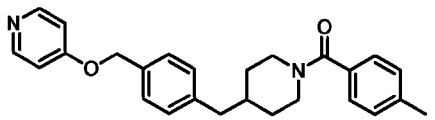
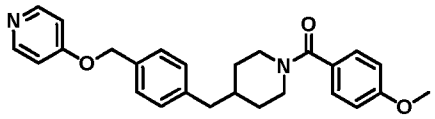
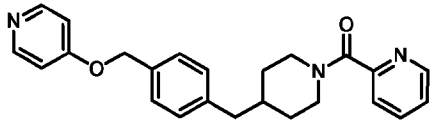
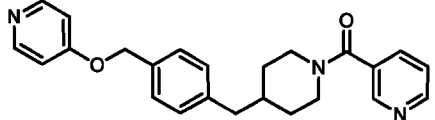
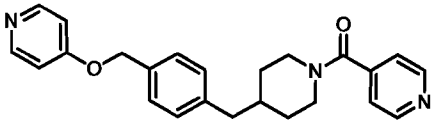
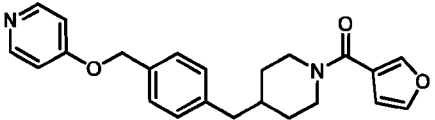
COMPOUNDS

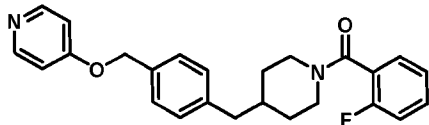
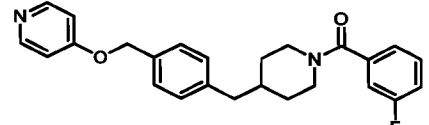
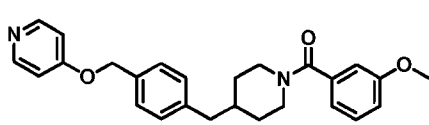
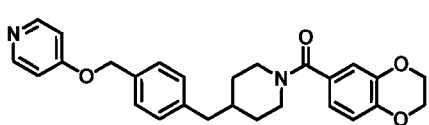
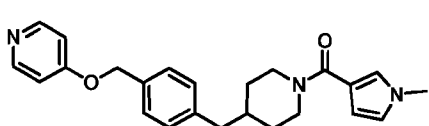
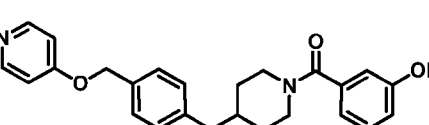
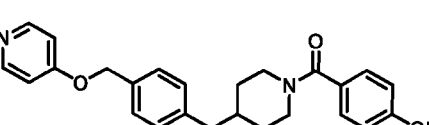
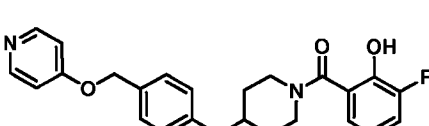
[0060] As one aspect of the present disclosure, novel compounds which are analogs or derivatives of MBX-7591 or MBX-7498 are provided. The inventors discovered that MBX-7498 and MBX-7591 exhibit consistent potentiation activity with fluconazole, are highly selective, moderately water soluble, and have a good ratio of sp^3/sp^2 carbons. Analogs were designed with the objective of overcoming low microsomal stability and high CYP3A4 inhibition, while maintaining/ improving the antifungal activity.

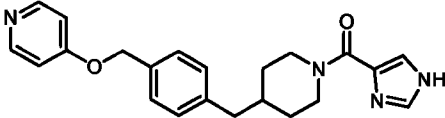
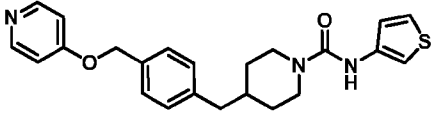
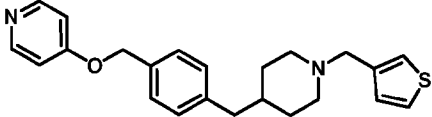
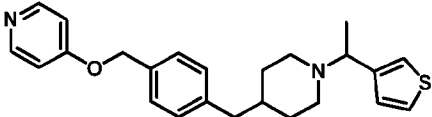
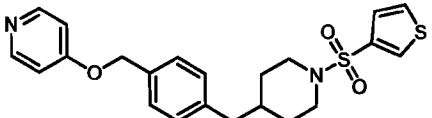
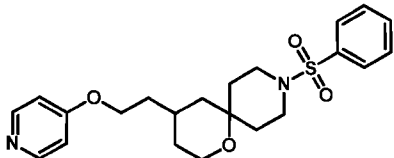
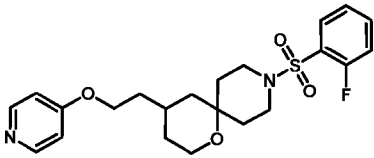
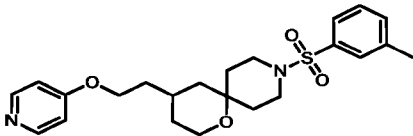
[0061] *A. fumigatus* possess intrinsic resistance to fluconazole with MICs well over 256 $\mu\text{g/ml}$ for *A. fumigatus* clinical isolates. It was theorized that screening for fluconazole potentiators would be a promising first step in identifying potentially novel small molecules that increase the activity of a well-tolerated and widely available class of antifungal drugs. Identifying small molecules that potentiate fluconazole activity and inhibit mold growth significantly increases likelihood of identifying inhibitors and/or identifying a new class of established infection relevant antifungal drugs.

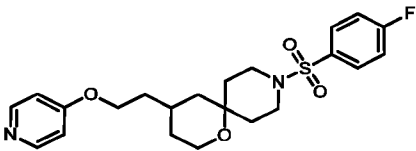
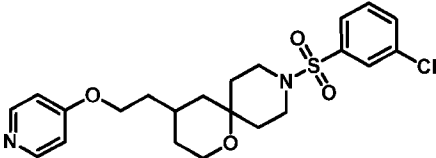
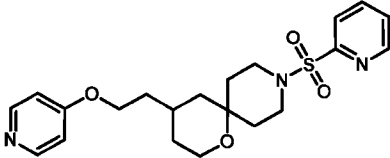
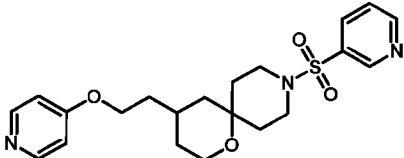
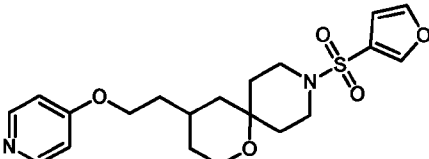
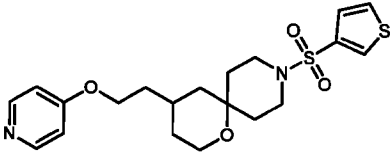
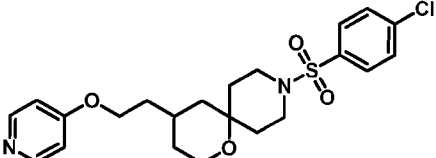
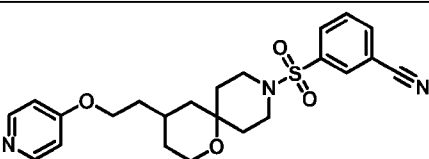
[0062] Exemplary analogs and derivatives of MBX-7591 and MBX-7498 (along with m/z data of those compounds) include, but are not limited, to the following:

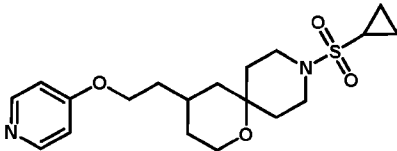
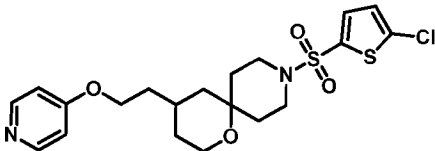
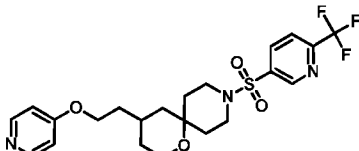
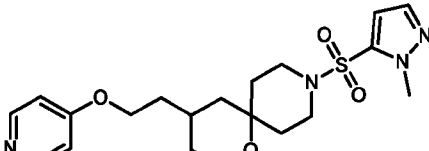
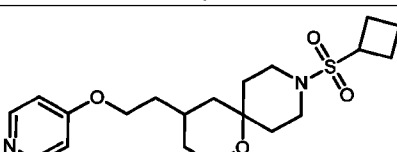
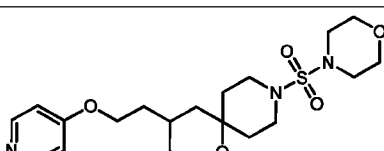
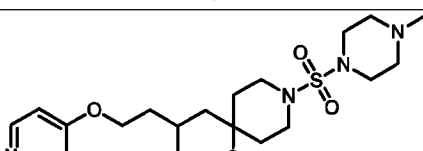
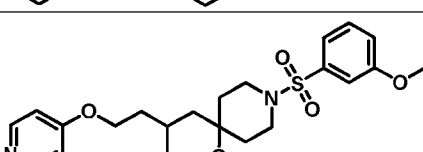
MBX #	Structure	m/z; [M+H]
MBX-7704		386.9

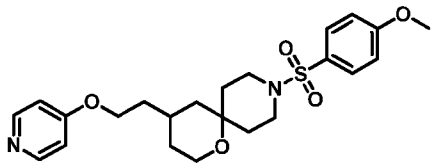
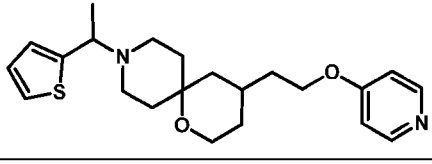
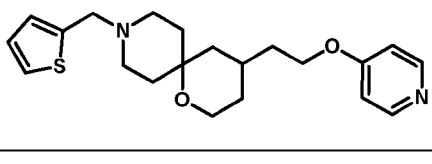
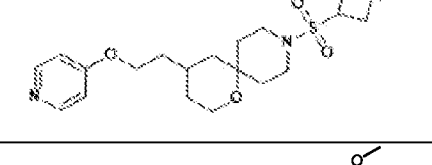
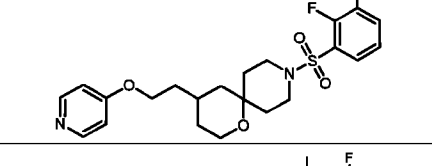
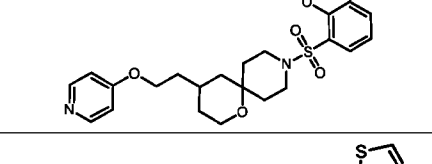
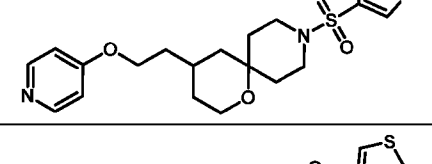
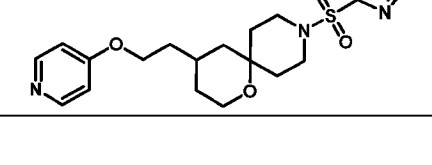
MBX #	Structure	m/z; [M+H]
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MBX-7706		404.9
MBX-7707		401.2
MBX-7728		417.0
MBX-7729		387.9
MBX-7730		387.9
MBX-7731		388.0
MBX-7732		377.0

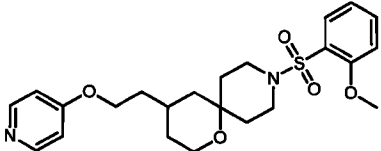
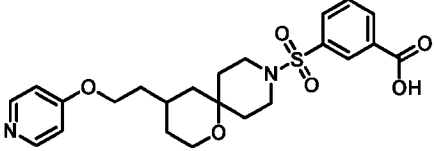
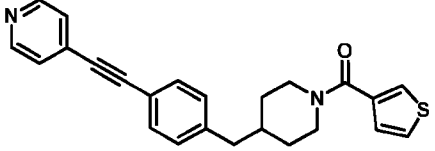
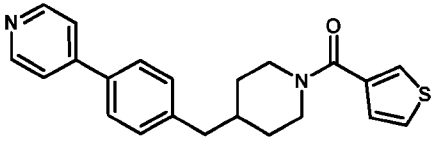
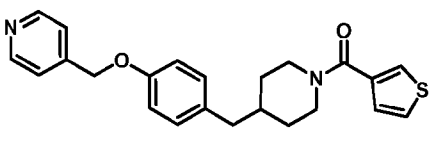
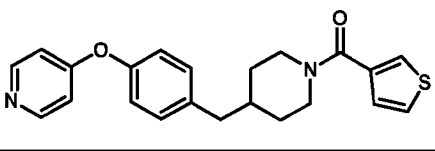
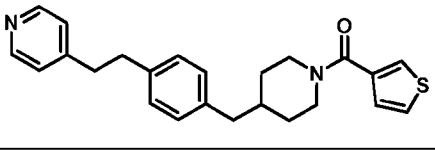
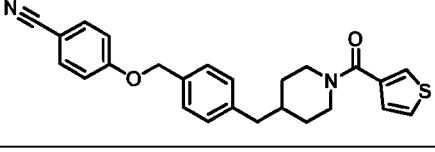
MBX #	Structure	m/z; [M+H]
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MBX-7770		405.0
MBX-7771		416.9
MBX-7772		444.9
MBX-7773		390.0
MBX-7801		403.1
MBX-7802		402.9
MBX-7803		420.9

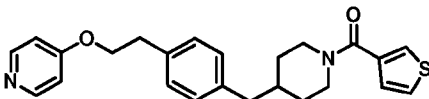
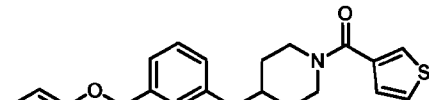
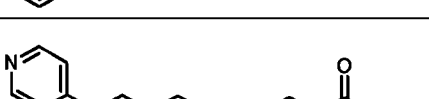
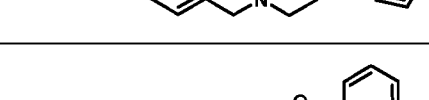
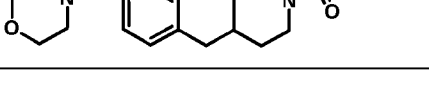
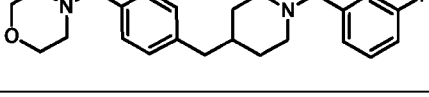
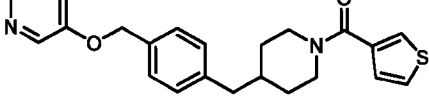
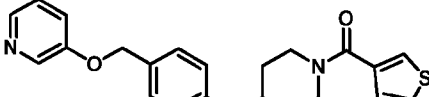
MBX #	Structure	m/z; [M+H]
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MBX-7806		379.0
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MBX-7822		429.0
MBX-7868		417.1
MBX-7869		435.0
MBX-7870		431.1

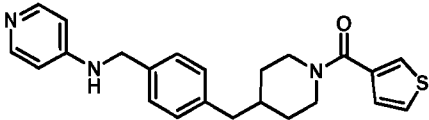
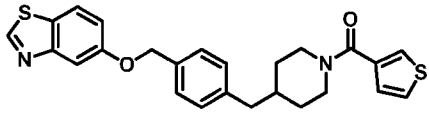
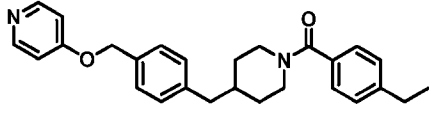
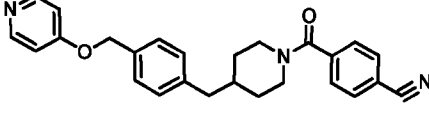
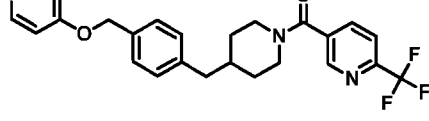
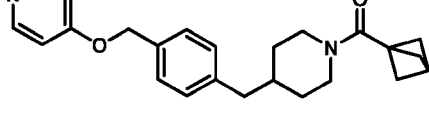
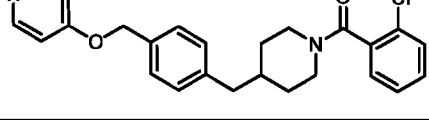
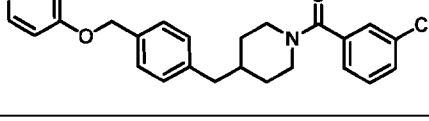
MBX #	Structure	m/z; [M+H]
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MBX-7873		418.1
MBX-7874		418.1
MBX-7875		407.1
MBX-7876		423.0
MBX-7877		451.1
MBX-7910		442.1

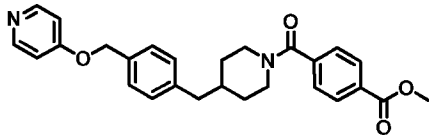
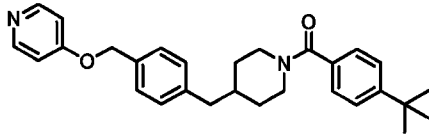
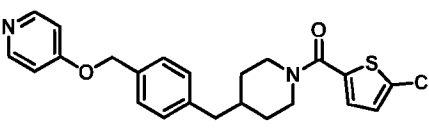
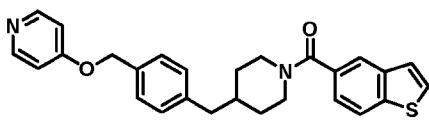
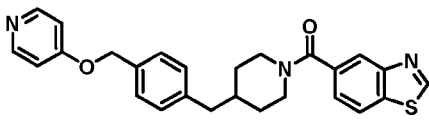
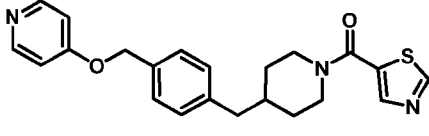
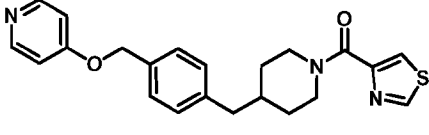
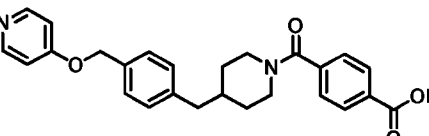
MBX #	Structure	m/z; [M+H]
MBX-7911		381.1
MBX-7912		457.0
MBX-7913		486.1
MBX-7914		421.1
MBX-7915		395.1
MBX-7950		426.0
MBX-7951		439.1
MBX-7952		447.2

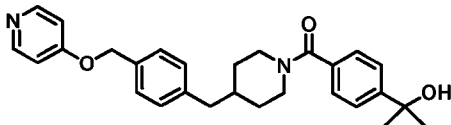
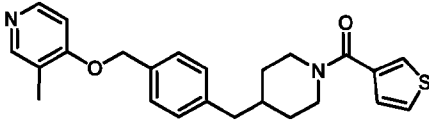
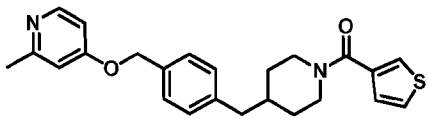
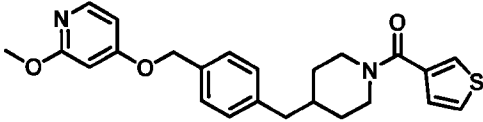
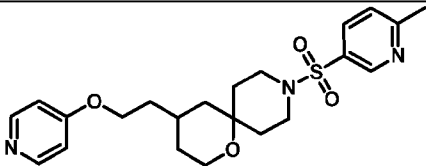
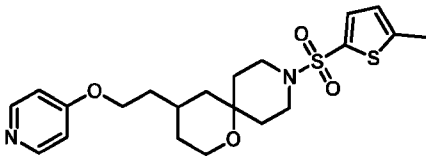
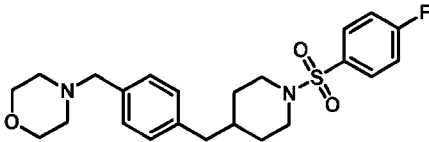
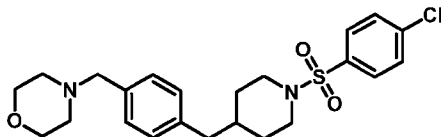
MBX #	Structure	m/z; [M+H]
MBX-7953		447.1
MBX-7954		386.9
MBX-7955		373.0
MBX-7956		397.2
MBX-7957		464.1
MBX-7958		464.2
MBX-7959		423.9
MBX-7960		424.0

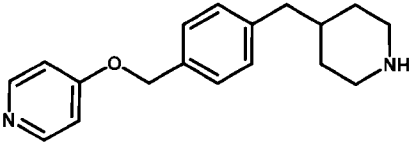
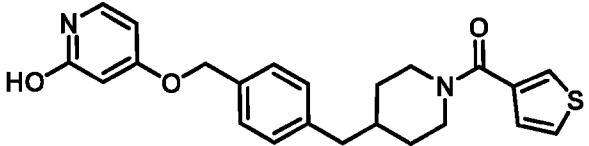
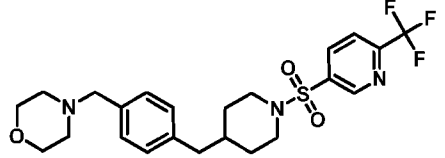
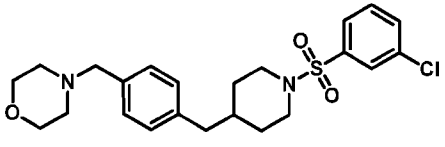
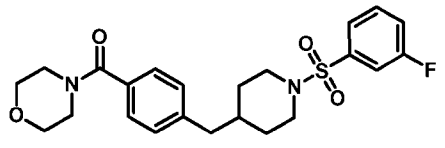
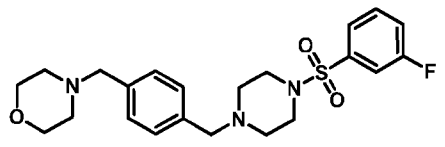
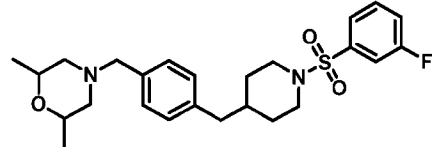
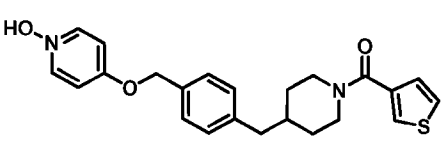
MBX #	Structure	m/z; [M+H]
MBX-7961		447.3
MBX-7962		461.1
MBX-7963		387.1
MBX-7964		363.1
MBX-8024		393.1
MBX-8025		378.9
MBX-8026		391.0
MBX-8027		417.1

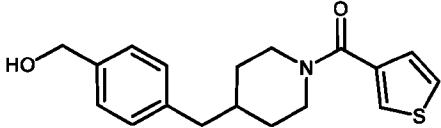
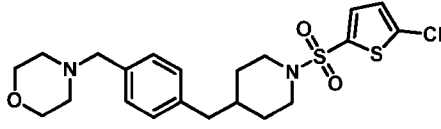
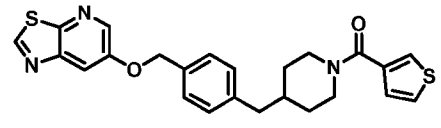
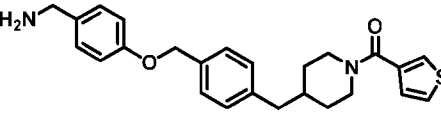
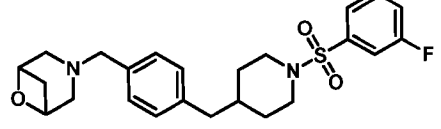
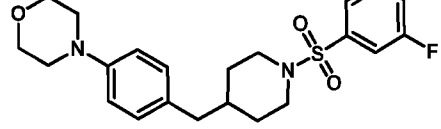
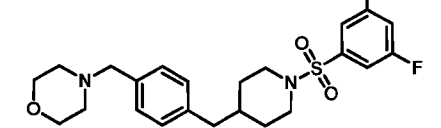
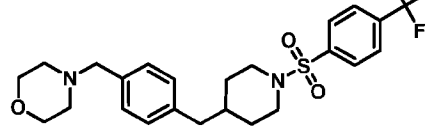
MBX #	Structure	m/z; [M+H]
MBX-8028		406.9
MBX-8029		393.2
MBX-8030		394.0
MBX-8031		397.1
MBX-8032		397.0
MBX-8033		394.1
MBX-8065		392.9
MBX-8066		379.0

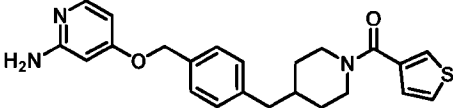
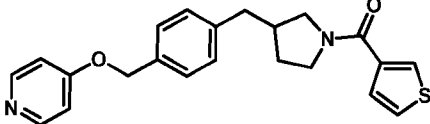
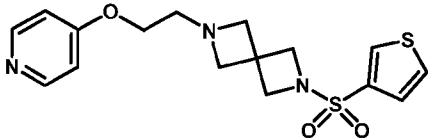
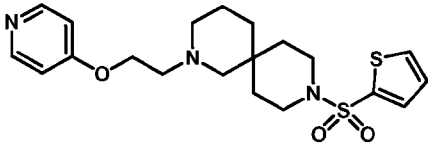
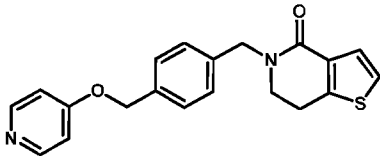
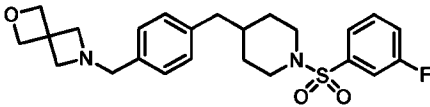
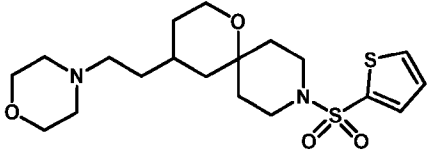
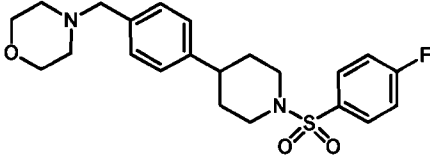
MBX #	Structure	m/z; [M+H]
MBX-8085		392.1
MBX-8086		449.0
MBX-8087		415.2
MBX-8088		412.1
MBX-8089		456.0
MBX-8090		377.1
MBX-8091		421.0
MBX-8092		421.1

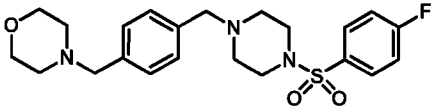
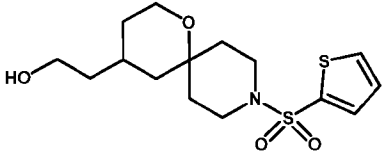
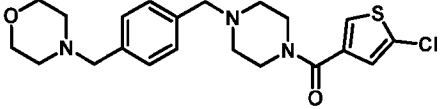
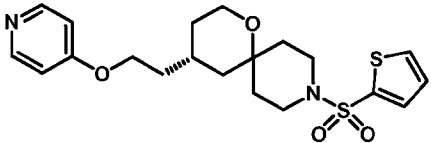
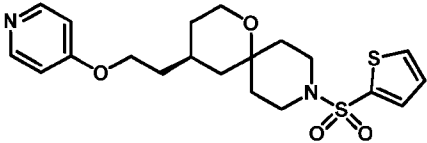
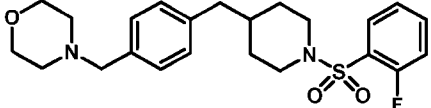
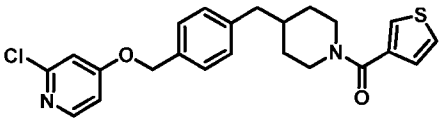
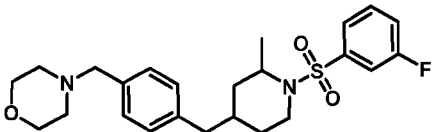
MBX #	Structure	m/z; [M+H]
MBX-8093		445.0
MBX-8094		443.1
MBX-8095		427.0
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MBX-8098		394.1
MBX-8099		394.3
MBX-8138		431.0

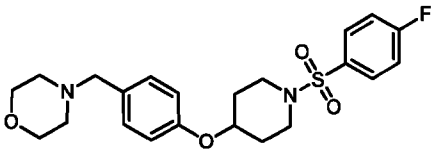
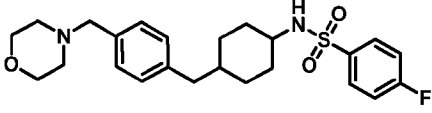
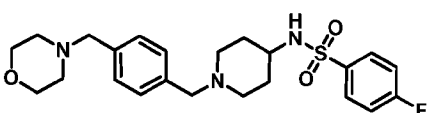
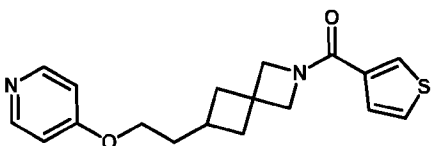
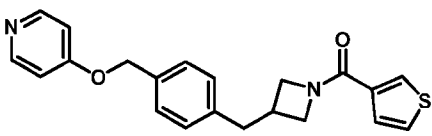
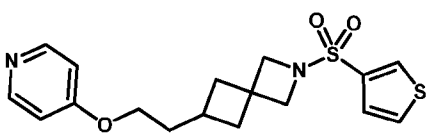
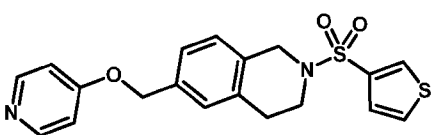
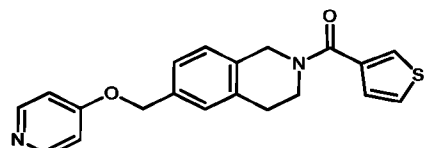
MBX #	Structure	m/z; [M+H]
MBX-8139		445.1
MBX-8140		407.1
MBX-8141		407.0
MBX-8142		423.0
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MBX-8144		437.0
MBX-8145		433.0
MBX-8146		449.0

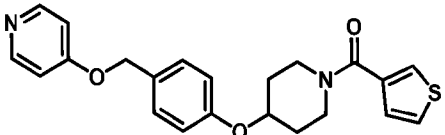
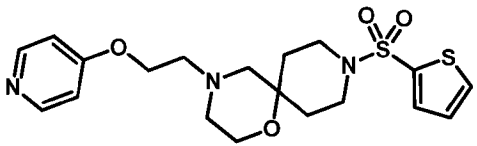
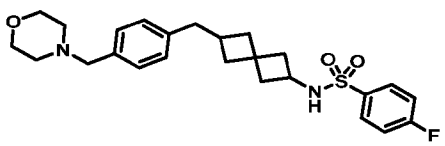
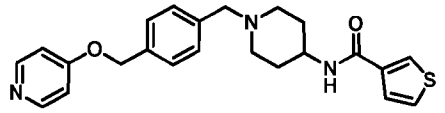
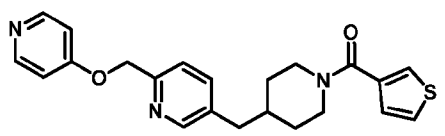
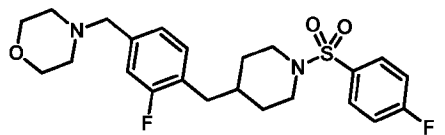
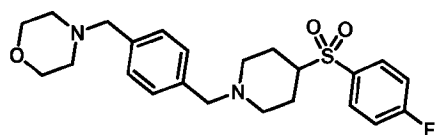
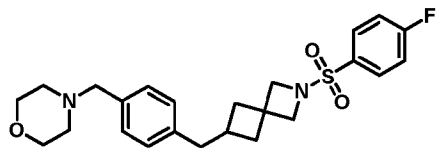
MBX #	Structure	m/z; [M+H]
MBX-8147		283.1
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MBX-8186		484.0
MBX-8187		449.0
MBX-8188		447.0
MBX-8189		434.2
MBX-8190		461.2
MBX-8191		409.0

MBX #	Structure	m/z; [M+H]
MBX-8192		316.1
MBX-8193		455.1
MBX-8219		450.1
MBX-8220		421.2
MBX-8221		445.2
MBX-8222		419.2
MBX-8223		451.2
MBX-8224		483.2

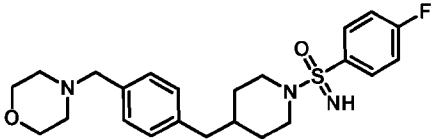
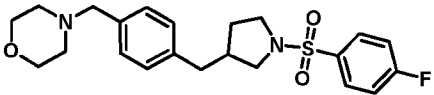
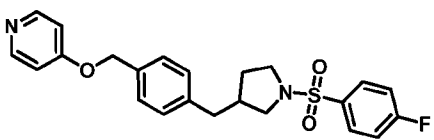
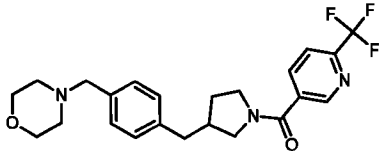
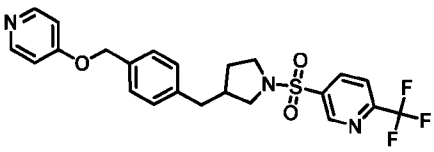
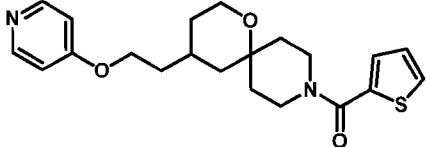
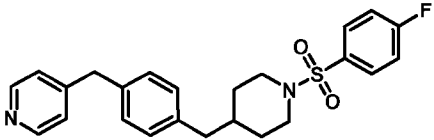
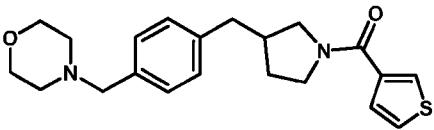
MBX #	Structure	m/z; [M+H]
MBX-8226		408.2
MBX-8240		379.1
MBX-8241		366.1
MBX-8242		422.2
MBX-8243		351.1
MBX-8244		445.2
MBX-8245		415.2
MBX-8246		434.2

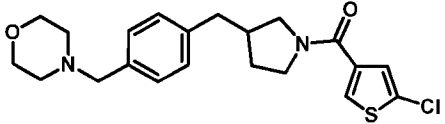
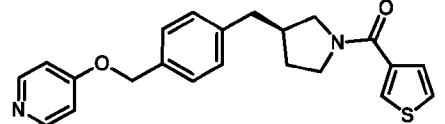
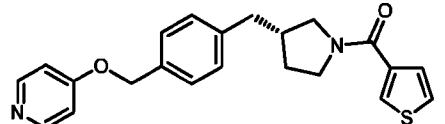
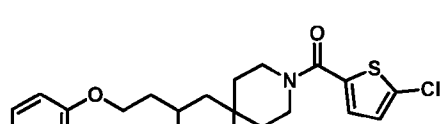
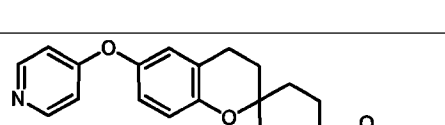
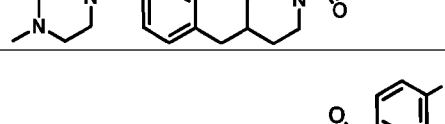
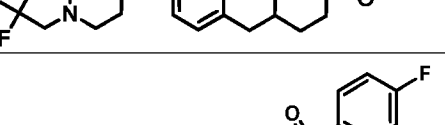
MBX #	Structure	m/z; [M+H]
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MBX-8248		346.3
MBX-8249		420.9
MBX-8250		423.1
MBX-8251		423.2
MBX-8252		433.4
MBX-8253		427.1
MBX-8281		447.2

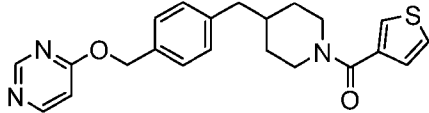
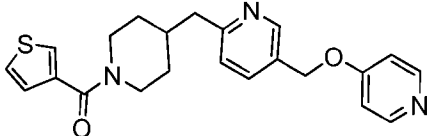
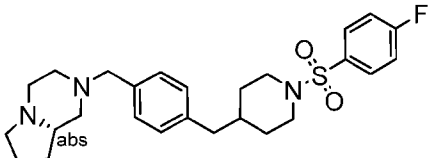
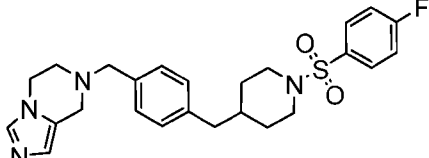
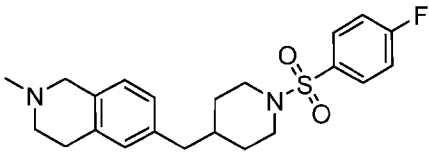
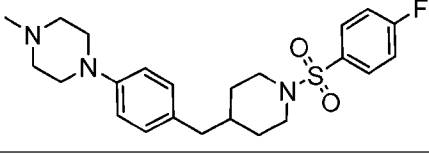
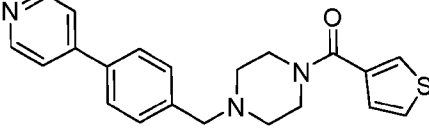
MBX #	Structure	m/z; [M+H]
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MBX-8283		447.2
MBX-8284		448.2
MBX-8285		329.1
MBX-8305		365.1
MBX-8306		365.1
MBX-8307		387.1
MBX-8308		351.1

MBX #	Structure	m/z; [M+H]
MBX-8309		395.2
MBX-8310		424.1
MBX-8311		459.2
MBX-8312		408.1
MBX-8323		394.1
MBX-8324		451.2
MBX-8325		433.2
MBX-8345		445.2

MBX #	Structure	m/z; [M+H]
MBX-8346		447.2
MBX-8347		432.2
MBX-8354		365.1
MBX-8355		449.2
MBX-8356		451.4
MBX-8357		447.2
MBX-8358		447.1
MBX-8359		461.2

MBX #	Structure	m/z; [M+H]
MBX-8389		432.3
MBX-8390		419.2
MBX-8391		427.1
MBX-8392		434.2
MBX-8393		478.1
MBX-8394		387.2
MBX-8428		425.2
MBX-8429		371.2

MBX #	Structure	m/z; [M+H]
MBX-8430		413.1
MBX-8431		379.2
MBX-8432		379.1
MBX-8433		421.1
MBX-8435		443.2
MBX-8436		446.3
MBX-8438		514.2
MBX-8439		391.3

MBX #	Structure	m/z; [M+H]
MBX-8529		394.2
MBX-8619		394.2
MBX-8668		472.2
MBX-8684		469.3
MBX-8700		403.2
MBX-8701		432.2
MBX-8702		364.2

SYNTHETIC SCHEMES

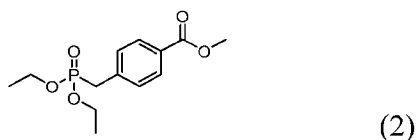
[0063] As another aspect of the present disclosure, methods of making the present compounds are provided. For example, a method is provided for making MBX-7591, an analog thereof, a derivative thereof, or a pharmaceutically acceptable salt of any of the foregoing; or

MBX-7498, an analog thereof, a derivative thereof, or a pharmaceutically acceptable salt of any of the foregoing.

Synthetic Scheme 1

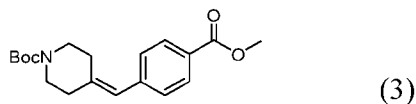
[0064] FIG. 1 shows Synthetic Scheme 1, which can be used for the synthesis of MBX-7591, an analog thereof, or a derivative thereof. The compounds and reactions shown in FIG. 1 are described in more detail below.

Synthesis of methyl 4-((diethoxyphosphoryl)methyl)benzoate (2)



[0065] The mixture methyl 4-(bromomethyl)benzoate (50 g, 218 mmol) and triethyl phosphite (47.1 g, 284 mmol) was stirred at 120 °C for 16 h. The RM was diluted with DCM and the crude was taken for purification. Crude obtained was adsorbed on aluminium oxide and purified by using 0-100% ethyl acetate in pet-ether. Product was eluted in 3% Ethyl acetate in Pet-ether, concentrated under reduced pressure to afford methyl 4-((diethoxyphosphoryl)methyl)benzoate (43.6g, 70 % yield). M+H = 287.10

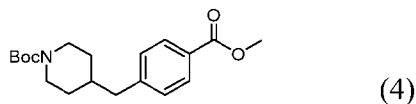
Synthesis of 4-(2-(pyridin-4-yloxy)ethyl)-9-(thiophen-3-ylsulfonyl)-1-oxa-9-azaspiro[5.5]undecane (3)



[0066] To an ice cooled stirred solution of methyl 4-((diethoxyphosphoryl)methyl)benzoate (50 g, 175 mmol) and 15- crown-5 (2.77 ml, 13.97 mmol) in THF (350 ml) was added sodium hydride (6.99 g, 175 mmol) and the mixture was stirred at 0 °C for 30 min. To the mixture was added tert-butyl 4-oxopiperidine-1-carboxylate (27.8 g, 140 mmol) THF (150 ml) dropwise over 20 min at 0 °C, and the mixture was stirred at RT for 16 h. The reaction mixture was diluted with water and extracted with ethyl acetate (3 x 35 mL), combined organic layer was washed with NaHCO₃ (20 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure to give 52 g of crude. Crude was adsorbed on aluminium oxide and purified by using 0-100%

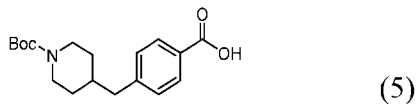
Ethyl acetate in Pet-ether. Product was eluted in 8% Ethyl acetate in Pet-ether, concentrated under reduced pressure to afford tertbutyl 4-(4-(methoxycarbonyl)benzylidene)piperidine-1-carboxylate (47 g, 56.7 mmol, 32.5 % yield) as colourless liquid. M+H = 232.2.

Synthesis of tert-butyl 4-(4-(methoxycarbonyl)benzyl)piperidine-1-carboxylate (4)



[0067] To a solution of tert-butyl 4-(4-(methoxycarbonyl)benzylidene)piperidine-1-carboxylate (47 g, 142 mmol) in THF (200 ml) and MeOH (200 ml) was added Pd-C (4.53 g, 42.5 mmol). The reaction mixture was stirred at RT under hydrogen atmosphere for 16h. The RM was filtered through celite bed and concentrated under reduced pressure to get tert-butyl 4-(4-(methoxycarbonyl)benzyl)piperidine-1-carboxylate (44 g, 58.1 mmol, 40.9 % yield) as colorless liquid. M+H = 234.

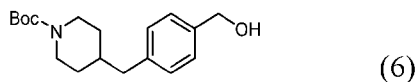
Synthesis of 4-((1-(tert-butoxycarbonyl)piperidin-4-yl)methyl)benzoic acid (5)



[0068] To a solution of tert-butyl 4-(4-(methoxycarbonyl)benzyl)piperidine-1-carboxylate (1 g, 3.00 mmol) in ethanol (15ml) was added NaOH (10%) (15 ml, 3.00 mmol). The reaction was stirred at 60 °C for 6h. The reaction was concentrated and the residue was acidified with 1.5N HCl, the solid appeared was filtered and

[0069] dried to obtain white solid 4-((1-(tert-butoxycarbonyl)piperidin-4-yl)methyl)benzoic acid (0.9g, 95 % yield), M-H = 318.2.

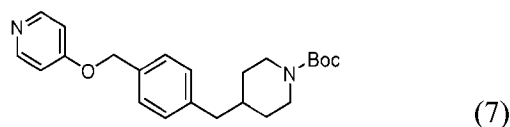
Synthesis of tert-butyl 4-(4-(hydroxymethyl)benzyl)piperidine-1-carboxylate (6)



[0070] To a solution of 4-((1-(tert-butoxycarbonyl)piperidin-4-yl)methyl)benzoic acid (5.7 g, 17.85 mmol) in THF (40 ml) was added BH3.THF (89 ml, 89 mmol) at 0°C. The reaction was

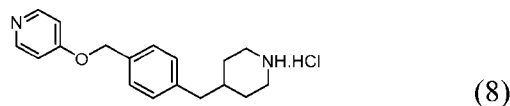
stirred at RT for 16h. The reaction mixture was cooled to 0°C, quenched with methanol, stirred at RT for 20 mins, concentrated under reduced pressure to remove the solvent. The residue for dissolved in water and extracted with ethyl acetate (3 x 50 mL), dried over sodium sulphate, filtered and concentrated to afford tert-butyl 4-(4-(hydroxymethyl)benzyl)piperidine-1-carboxylate (5.34 g, 98 % yield) as orange liquid. M+H = 206.2.

Synthesis of tert-butyl 4-(4-((pyridin-4-yloxy)methyl)benzyl)piperidine-1-carboxylate (7)



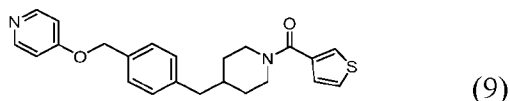
[0071] To a stirred solution of sodium hydride (0.262 g, 6.55 mmol) in DMF (10 ml) was added tert-butyl 4-(4-(hydroxymethyl)benzyl)piperidine-1-carboxylate (1 g, 3.27 mmol) in DMF (10 ml) at 0 °C and stirred for 40 min. After 40 min, 4-iodopyridine (1.007 g, 4.91 mmol) was added at 0°C and then heated to 85°C and continued for stirring and heating. The RM was cooled to 0°C and slowly quenched with ice and stirred for 5mins. Solid precipitated which was filtered to get tert-butyl 4-(4-((pyridin-4-yloxy)methyl)benzyl)piperidine-1-carboxylate (1.1 g, 2.88 mmol, 88 % yield) M+H = 383.

Synthesis of 4-((4-(piperidin-4-ylmethyl)benzyl)oxy)pyridine (8)



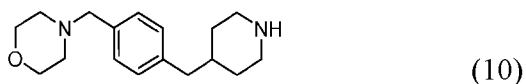
[0072] To a stirred solution of 4-((4-(piperidin-4-ylmethyl)benzyl)oxy)pyridine hydrochloride in DCM (15 ml) was added hydrogen chloride 4.0M in 1,4-dioxane (12.74 ml, 51.0 mmol) at 0 °C. The reaction mixture was stirred at RT for 1 hr. The reaction mixture was concentrated under reduced pressure to get the crude which was taken to the next step without further purification. M+H = 293.

Synthesis of (4-(4-((pyridin-4-yloxy)methyl)benzyl)piperidin-1-yl)(thiophen-3-yl)methanone (9)



[0073] To a mixture of 4-((4-(piperidin-4-ylmethyl)benzyl)oxy)pyridine hydrochloride (0.25 g, 0.784 mmol), thiophene-3-carboxylic acid (0.151 g, 1.176 mmol) in DCM (5.0 ml) was added triethylamine (0.328 ml, 2.352 mmol) and followed by T3P (0.748 g, 2.352 mmol) dropwise under N₂ atm at 0 °C. The resultant reaction mixture was slowly warmed to rt and stirred. The reaction mixture was quenched with ice-cooled water (10 ml) and extracted with DCM (2*60 ml). The combined organic layer was washed with sat. 10% sodium bicarbonate solution, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to get crude product. After Prep.HPLC the solution was as such concentrated under reduced pressure to afford (4-(4-((pyridin-4-yloxy)methyl)benzyl)piperidin-1-yl)(thiophen-3-yl)methanone (0.15 g, 0.382 mmol, 48.7 % yield) as a white solid. M+H = 393.1

Synthesis of 4-(4-(piperidin-4-ylmethyl)benzyl)morpholine (10)

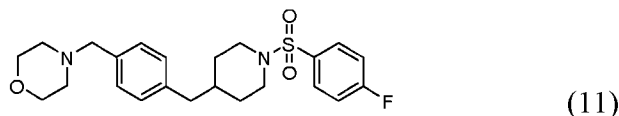


[0074] To a solution of tert-butyl 4-(4-(hydroxymethyl)benzyl)piperidine-1-carboxylate (0.6 g, 1.965 mmol) in DCM (0.5 ml) was added Ms-Cl (0.182 ml, 2.357 mmol) and TEA (0.596 g, 5.89 mmol). After 1h, morpholine (0.342 g, 3.93 mmol) was added to the solution and the reaction mixture was stirred for 1h. The reaction was quenched with water, extracted with DCM, dried over sodium sulphate, filtered and concentrated under reduced pressure to give tert-butyl 4-(4-(morpholinomethyl)benzyl)piperidine-1-carboxylate (0.64g, 90 % yield). M+H = 375.3

[0075] To a cooled solution of tert-butyl 4-(4-(morpholinomethyl)benzyl)piperidine-1-carboxylate (0.25 g, 0.668 mmol) in formic acid (0.256 ml, 6.68 mmol) and the resultant reaction mixture was stirred at rt. The reaction mixture was concentrated under high vacuum, the obtained residue was diluted with methanol in chloroform and basified by using solid NaHCO₃ to adjust pH=8-9. Decanted the MDC layer and concentrated under reduced pressure to afford tert-butyl 4-

(4-(morpholinomethyl)benzyl)piperidine-1-carboxylate (0.25 g, 0.668 mmol) as an off-white solid. $M+H = 275.1$.

Synthesis of 4-(4-((1-((4-fluorophenyl)sulfonyl)piperidin-4-yl)methyl)benzyl)morpholine (11)

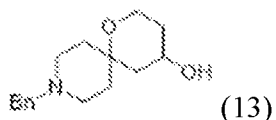


[0076] To a cooled solution of 4-(4-(piperidin-4-ylmethyl)benzyl)morpholine hydrochloride (0.025 g, 0.080 mmol) in DCM (2.0 ml) was added triethylamine (0.024 g, 0.241 mmol) and followed by 4-fluorobenzenesulfonyl chloride (0.024 g, 0.097 mmol). The resultant reaction mixture was stirred at rt. The reaction mixture was quenched with water and concentrated the residue. The obtained residue was submitted for PREP.HPLC. After prep HPLC, the solution was as such lyophilized for 16 h to afford 4-(4-((1-((4-fluorophenyl)sulfonyl)piperidin-4-yl)methyl)benzyl)morpholine (0.03 g, 0.062 mmol, 77 % yield) as a white solid. $M+H = 483.1$.

Synthetic Scheme 2

[0077] FIG. 2 shows Synthetic Scheme 2, which can be used for the synthesis of MBX-7498, an analog thereof, or a derivative thereof. The compounds and reactions shown in FIG. 2 are described in more detail below.

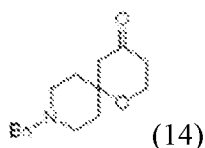
Synthesis of 9-benzyl-1-oxa-9-azaspiro[5.5]undecan-4-ol (13)



[0078] To an ice cooled stirred solution of 1-benzylpiperidin-4-one (4.90 ml, 26.4 mmol) and but-3-en-1-ol (2.501 ml, 29.1 mmol), was added sulfuric acid 70% (3.70 g, 26.4 mmol) at 0 °C dropwise slowly. The mixture was stirred at rt overnight. The reaction mixture was diluted with water (2ml) and neutralized with NaOH solution (4ml) to pH 9 and extracted with ethyl acetate (2*10ml), washed with saturated brine (1*10ml) and dried over sodium sulphate, filtered and concentrated under reduced pressure to afford 9-benzyl-1-oxa-9-azaspiro[5.5]undecan-4-ol (6.8

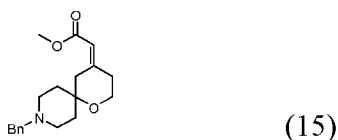
g, 26.0 mmol, 98 % yield) as a yellow oil. The product was taken to the next step without further purification. $M+H = 262.1$

Synthesis of 9-benzyl-1-oxa-9-azaspiro[5.5]undecan-4-one (14)



[0079] To a stirred solution of 9-benzyl-1-oxa-9-azaspiro[5.5]undecan-4-ol (5 g, 19.13 mmol) in DCM (20 ml), Pyridinium chlorochromate (6.19 g, 28.7 mmol) was added at 0 °C. The reaction mixture was stirred overnight. The reaction mixture was filtered with celite and the filtrate was concentrated to get the crude. The obtained crude product (5g) was loaded in column chromatography using DCM and Methanol(10%) as a eluent to afford 9- benzyl-1-oxa-9-azaspiro[5.5]undecan-4-one (3.5 g, 13.50 mmol, 70.5 % yield) as a dark brown semi solid. $M+H = 260.1$

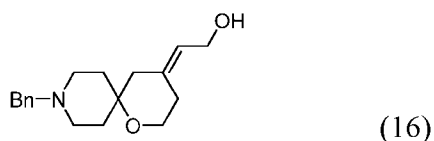
Synthesis of methyl (Z)-2-(9-benzyl-1-oxa-9-azaspiro[5.5]undecan-4-ylidene)acetate (15)



[0080] To a stirred solution of Sodium hydride (1.542 g, 38.6 mmol) in THF (100 ml) , was added methyl 2- (dimethoxyphosphoryl)acetate (7.37 g, 40.5 mmol) dropwise slowly at rt. The reaction mixture was stirred for 30 minutes. After 30 minutes 9-benzyl-1-oxa-9-azaspiro[5.5]undecan-4-one (5 g, 19.28 mmol) was added at 0 °C dropwise. The reaction mixture was stirred overnight. The reaction mixture was quenched with 1M HCl(0.5 ml) and concentrated in vaccum to remove THF and extracted with DCM(2*5ml) washed with saturated brine (1*10ml) and dried over sodium suphate, filtered and concentrated under reduced pressure to afford the crude product as a light yellow solid. The obtained crude product was loaded in column chromatography using DCM and Methanol(10%) as a eluent to afford methyl (Z)-2-(9-

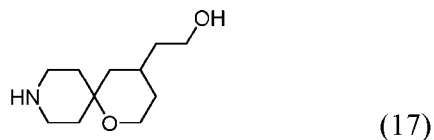
benzyl-1-oxa-9-azaspiro[5.5]undecan-4-ylidene)acetate (5 g, 15.85 mmol, 82 % yield) as a yellow solid. $M+H = 316.3$

Synthesis of (E)-2-(9-benzyl-1-oxa-9-azaspiro[5.5]undecan-4-ylidene)ethan-1-ol (16)



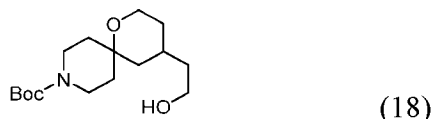
[0081] To stirred solution of methyl (Z)-2-(9-benzyl-1-oxa-9-azaspiro[5.5]undecan-4-ylidene)acetate (5 g, 15.85 mmol) in THF (100 ml), was added lithium aluminium hydride (31.7 ml, 63.4 mmol) at -78 °C. The reaction mixture was stirred overnight at rt. The reaction mixture was cooled to 0 °C and quenched with NH_4Cl (20ml) and extracted with Ethyl acetate(2*50ML). The organic layer was washed with brine, dried over sodium sulphate, filtered and concentrated under reduced pressure to afford (E)-2-(9-benzyl-1-oxa-9-azaspiro[5.5]undecan-4-ylidene)ethan-1-ol (2 g, 6.96 mmol, 43.9 % yield) as a pale yellow liquid. The crude product was taken as such for next step without purification. $M+H = 288.1$

Synthesis of 2-(1-oxa-9-azaspiro[5.5]undecan-4-yl)ethan-1-ol (17)



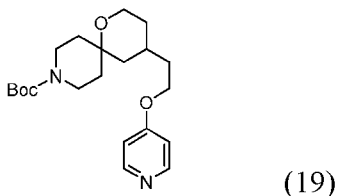
[0082] To a stirred solution of (E)-2-(9-benzyl-1-oxa-9-azaspiro[5.5]undecan-4-ylidene)ethan-1-ol (1.3 g, 4.52 mmol) in methanol (30 ml), was added PdC (1.059 g, 9.95 mmol). The reaction mixture was stirred overnight at rt. The reaction mixture was filtered with celite and concentrated under reduced pressure to afford 2-(1-oxa-9-azaspiro[5.5]undecan-4-yl)ethan-1-ol (0.6 g, 3.01 mmol, 66.6 % yield). The crude was as such taken for next step without purification. $M+H = 200.2$

Synthesis of tert-butyl 4-(2-hydroxyethyl)-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate (18)

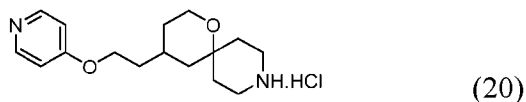


[0083] To a stirred solution of 2-(1-oxa-9-azaspiro[5.5]undecan-4-yl)ethan-1-ol (1.8 g, 9.03 mmol) in DCM (20 ml) was added triethylamine (1.885 ml, 13.55 mmol) and di-tert-butyl dicarbonate (2.282 ml, 9.94 mmol) was added at 0°C. The reaction mixture was stirred overnight, quenched with water (5ml) and extracted with ethyl acetate (2*10ml). The organic layer was washed with brine, dried over sodium sulphate, filtered and concentrated under reduced pressure to get the crude. The obtained crude product was loaded in column chromatography using DCM and methanol(10%) as a eluent to afford tert-butyl 4-(2-hydroxyethyl)-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate (1.8 g, 6.01 mmol, 66.6 % yield). M+H = 300.2

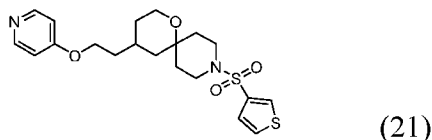
Synthesis of tert-butyl 4-(2-(pyridin-4-yloxy)ethyl)-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate (19)



[0084] To a stirred solution of sodium hydride (0.347 g, 8.68 mmol) in DMF (4 ml) was added tert-butyl 4-(2-hydroxyethyl)-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate (1.3 g, 4.34 mmol) in DMF (4 ml) at 0 °C and stirred for 40 min after 40 min 4-iodopyridine (0.890 g, 4.34 mmol) is added at rt and then heated to 85°C and continued for stirring and heating. The reaction mixture was diluted with water(10ml) and extracted with ethyl acetate(2*10ml). The organic layer was dried with sodium sulphate to get crude compound. The crude was taken for purification. The crude was dissolved with dichloromethane, preabsorbed onto silica gel and eluted with 0-50% Ethyl acetate to get tert-butyl 4-(2-(pyridin-4-yloxy)ethyl)-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate (0.9 g, 2.390 mmol, 55.1 % yield). M+H = 377.3

Synthesis of 4-(2-(pyridin-4-yloxy)ethyl)-1-oxa-9-azaspiro[5.5]undecane (20)

[0085] To a stirred solution of tert-butyl 4-(2-(pyridin-4-yloxy)ethyl)-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate (1 g, 2.66 mmol) in Dioxane (5 ml) was added 4M HCl (7.97 ml, 31.9 mmol) in Dioxane at 0 °C and continued for stirring at rt. After 1 hr the desired product mass was observed by LCMS. The reaction mixture was as such concentrated to get 4-(2-(pyridin-4-yloxy)ethyl)-1-oxa-9-azaspiro[5.5]undecane (0.7 g, 2.53 mmol, 95 % yield) as a yellow semi solid. The crude was taken for next step without purification. M+H = 277.3

Synthesis of 4-(2-(pyridin-4-yloxy)ethyl)-9-(thiophen-3-ylsulfonyl)-1-oxa-9-azaspiro[5.5]undecane (21)

[0086] To a stirred solution of 4-(2-(pyridin-4-yloxy)ethyl)-1-oxa-9-azaspiro[5.5]undecane (0.025 g, 0.090 mmol) in DCM (2 ml), Triethylamine (0.013 ml, 0.090 mmol) and thiophene-3-sulfonyl chloride (0.025 g, 0.136 mmol) was added at 0°C. The mixture was kept for 2 hrs stirring at rt. The reaction mixture was quenched with ice and as such concentrated to get the crude. The crude was purified by PREP HPLC and lyophilized to afford 4-(2-(pyridin-4-yloxy)ethyl)-9-(thiophen-3-ylsulfonyl)-1-oxa-9-azaspiro[5.5]undecane (3.6 mg, 8.43 μmol, 9.32 % yield). M+H = 423.1

[0087] The foregoing synthetic schemes are exemplary and not intended to be limiting, and modifications of those schemes or alternative schemes will be apparent (in view of the present disclosure) to persons skilled in the art of organic chemistry or chemical synthesis. It is contemplated that other suitable starting materials, coupling agents, acids, bases, or other reagents may be used in place of those exemplified above, and are within the scope of the present disclosure. Modification of reaction conditions (such as temperature, reaction duration or combinations thereof) is also considered part of the present disclosure.

METHODS OF TREATMENT

[0088] As another aspect of the present disclosure, methods of treating a subject having a fungal infection are provided. For example, a method is provided for treating a fungal infection in a subject by administering to the subject MBX-7591, an analog thereof, a derivative thereof, or a pharmaceutically acceptable salt of any of the foregoing; or MBX-7498, an analog thereof, a derivative thereof, or a pharmaceutically acceptable salt of any of the foregoing. As another example, a method for treating a fungal infection in a subject comprises administering to the subject a pharmaceutical composition described by the present disclosure, or a compound described by the present disclosure, or a pharmaceutically acceptable salt thereof. In still another example, a method of potentiating antifungal activity of an azole antifungal agent is provided, which comprises administering to a subject a pharmaceutical composition described herein, or a compound described herein, in combination with an azole antifungal agent administered to the subject.

[0089] In some embodiments of the present methods, an antifungal agent is administered to the subject, before, after or simultaneously with the administration of one or more of MBX-7591, an analog thereof, a derivative thereof, or a pharmaceutically acceptable salt of any of the foregoing; or MBX-7498, an analog thereof, a derivative thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0090] Antifungal agents include, but are not limited to, polyene antifungals such as natamycin, rimocidin, nystatin, amphotericin B, candicin, hamycin, perimycin; azole antifungals (which includes imidazole antifungals and triazole antifungals), such as the imidazole antifungals miconazole, ketoconazole, clotrimazole, econazole, omoconazole, bifonazole, butoconazole, fenticonazole, isoconazole, oxiconazole, sertaconazole, sulconazole, tioconazole; and the triazole antifungals fluconazole, fosfluconazole, itraconazole, isavuconazole, ravuconazole, posaconazole, voriconazole, terconazole, albaconazole; thiazole antifungals, such as abafungin; allylamine antifungals such as terbinafine, naftifin, butenafine, amorolfine; echinocandin antifungals such as anidulafungin, caspofungin, micafungin; ciclopirox; tolnaftate; and flucytosine. The antifungal drug may be used in any convenient form, including any

pharmaceutically acceptable salt or hydrate. The references to the antifungal drugs listed above extends to any isomeric form in which the compound may exist as well as mixtures of two or more isomers, e.g. racemic mixtures.

[0091] In some embodiments, the antifungal agent is a drug that is typically administered systemically, e.g. amphotericin B, hamycin, ketoconazole, fluconazole, fosfluconazole, itraconazole, posaconazole, voriconazole, terbinafine, echinocandin antifungals (e.g. anidulafungin, caspofungin, micafungin), and flucytosine.

[0092] In some embodiments, the antifungal is a drug that is typically administered as a non-systemic treatment, e.g. as a topical treatment. Representative examples of such drugs include, but are not limited to, natamycin, nystatin, amphotericin B, candicin, hamycin, perimycin, miconazole, ketoconazole, clotrimazole, econazole, omoconazole, bifonazole, butoconazole, fenticonazole, isoconazole, oxiconazole, sertaconazole, sulconazole, tioconazole, fluconazole, fosfluconazole, isavuconazole, ravuconazole, terconazole, albaconazole, abafungin, allylamine antifungals (e.g. terbinafine, naftifin, butenafine, amorolfine), ciclopirox and tolnaftate.

[0093] Additional examples of antifungal agents include, but are not limited to, benzimidazole fungicides (e.g. albendazole, benomyl, carbendazim, chlorfenazole, cypendazole, debacarb, fuberidazole, mecarbinzid, rabenzazole, thiabendazole); benzimidazole precursor fungicides (e.g. furophanate, thiophanate, thiophanate-methyl); benzothiazole fungicides (e.g. benthaluron, benthiavalicarb, benthiazole, chlobenthiazole, probenazole); botanical fungicides (e.g. allicin, berberine, carvacrol, carvone, osthol, santonin); bridged diphenyl fungicides (e.g. bithionol, dichlorophen, diphenylamine, hexachlorophene, parinol); carbamate fungicides (e.g. benthiavalicarb, furophanate, iodocarb, iprovalicarb, propamocarb, pyribencarb, thiophanate, thiophanate-methyl); benzimidazolylcarbamate fungicides (e.g. albendazole, benomyl, carbendazim, cypendazole, debacarb, mecarbinzid); carbanilate fungicides (e.g. diethofencarb, lvdngjunzhi, pyraclostrobin, pyrametostrobin); conazole (imidazole) fungicides (e.g. climbazole, clotrimazole, imazalil, oxpoconazole, prochloraz, triflumizole); conazole (triazole) fungicides (e.g. azaconazole, bromuconazole, cyproconazole, diclobutrazol, difenoconazole, diniconazole, diniconazole-M, epoxiconazole, etaconazole, fenbuconazole, fluquinconazole, flusilazole, flutriafol, furconazole, furconazole-cis, hexaconazole, imibenconazole, ipconazole, metconazole,

myclobutanil, penconazole, propiconazole, prothioconazole, quinconazole, simeconazole, tebuconazole, tetraconazole, triadimefon, triadimenol, triticonazole, uniconazole, uniconazole-P); aliphatic nitrogen fungicides (e.g. butylamine, cymoxanil, dodicin, dodine, guazatine, iminoctadine); amide fungicides (e.g. carpropamid, chloraniformethan, cyflufenamid, diclocymet, diclocymet, dimoxystrobin, fenoxanil, flumetover, furametpyr, isopyrazam, mandipropamid, metominostrobin, orysastrobin, penthiopyrad, prochloraz, quinazamid, silthiofam, triforine, xiwojunan); acylamino acid fungicides (e.g. benalaxyl, benalaxyl-M, furalaxyl, metalaxyl, metalaxyl-M, pefurazoate, valifenalate); anilide fungicides (e.g. benalaxyl, benalaxyl-M, bixafen, boscalid, carboxin, fenhexamid, fluxapyroxad, isotianil, metalaxyl, metalaxyl-M, metsulfovax, ofurace, oxadixyl, oxycarboxin, penflufen, pyracarbolid, sedaxane, thifluzamide, tiadinil, vangard); benzanilide fungicides (e.g. benodanil, flutolanil, mebenil, mepronil, salicylanilide, tecloftalam); furanilide fungicides (e.g. fenfuram, furalaxyl, furcarbanil, methfuroxam); sulfonanilide fungicides (e.g. flusulfamide); benzamide fungicides (e.g. benzohydroxamic acid, fluopicolide, fluopyram, tioxymid, trichlamide, zarilamid, zoxamide); furamide fungicides (e.g. cyclofuramid, furmecyclox); phenylsulfamide fungicides (e.g. dichlofluanid, tolylfluanid); sulfonamide fungicides (e.g. amisulbrom, cyazofamid); valinamide fungicides (e.g. benthiavalicarb, iprovalicarb); antibiotic fungicides (e.g. aureofungin, blastocidin-S, cycloheximide, griseofulvin, kasugamycin, moroxydin, polyoxins, polyoxorim, validamycin); strobilurin fungicides (e.g. fluoxastrobin); methoxyacrylate strobilurin fungicides (e.g. azoxystrobin, bifujunzhi, coumoxystrobin, enestroburin, jiaxiangjunzhi, picoxystrobin, pyraoxystrobin); methoxycarbanilate strobilurin fungicides (e.g. lvdjngjunzhi, pyraclostrobin, pyrametostrobin); methoxyiminoacetamide strobilurin fungicides (e.g. dimoxystrobin, metominostrobin, orysastrobin, xiwojunan); methoxyiminoacetate strobilurin fungicides (e.g. kresoxim-methyl, trifloxystrobin); aromatic fungicides (e.g. biphenyl, chlorodinitronaphthalenes, chloroneb, chlorothalonil, cresol, dicloran, fenjuntong, hexachlorobenzene, pentachlorophenol, quintozone, sodium pentachlorophenoxide, tecnazene); arsenical fungicides (e.g. asomate, urbacide); aryl phenyl ketone fungicides (e.g. metrafenone, yriofenone); copper fungicides (e.g. acypetacs-copper, Bordeaux mixture, Burgundy mixture, Cheshunt mixture, copper acetate, copper carbonate (basic), copper hydroxide, copper naphthenate, copper oleate, copper

oxychloride, copper silicate, copper sulfate, copper sulfate (basic), copper zinc chromate, cufraneb, cuproban, cuprous oxide, mancozeb, oxine-copper, saientong, thiodiazole-copper); cyanoacrylate fungicides (e.g. benzamyl, phenamyl); dicarboximide fungicides (e.g. famoxadone, fluoroimide); dichlorophenyl dicarboximide fungicides (e.g. chlozolinate, dichlozoline, iprodione, isovaledione, myclozolin, procymidone, vinclozolin); phthalimide fungicides (e.g. captan, captan, ditalimfos, folpet, thiochlorfenphim); dinitrophenol fungicides (e.g. binapacryl, dinobuton, dinocap, dinocap-4, dinocap-6, meptyldinocap, dinocap dinopent, dinosulfon, dinoterbon, DNOC); dithiocarbamate fungicides (e.g. amobam, asomate, azithiram, carbamorph, cufraneb, cuproban, disulfiram, ferbam, metam, nabam, tecoram, thiram, urbacide, ziram); cyclic dithiocarbamate fungicides (e.g. dazomet, etem, milneb); polymeric dithiocarbamate fungicides (e.g. mancozeb, mancozeb, maneb, metiram, polycarbamate, propineb, zineb); dithiolane fungicides (e.g. isoprothiolane, saijunmao); fumigant fungicides (e.g. dithioether, methyl bromide); hydrazide fungicides (e.g. benquinox, saijunmao); imidazole fungicides (e.g. cyazofamid, fenamidone, fenapanil, glyodin, iprodione, isovaledione, pefurazate, triazoxide); inorganic fungicides (potassium azide, potassium thiocyanate, sodium azide, sulfur); inorganic mercury fungicides (e.g. mercuric chloride, mercuric oxide, mercurous chloride); organomercury fungicides (e.g. (3-ethoxypropyl)mercury bromide, ethylmercury acetate, ethylmercury bromide, ethylmercury chloride, ethylmercury 2,3-dihydroxypropyl mercaptide, ethylmercury phosphate, N-(ethylmercury)-p-toluenesulphonanilide hydrargaphen, 2-methoxyethylmercury chloride, methylmercury benzoate, methylmercury dicyandiamide, methylmercury pentachlorophenoxide, 8-phenylmercurioxyquinoline, phenylmercuriurea, phenylmercury acetate, phenylmercury chloride, phenylmercury derivative of pyrocatechol, phenylmercury nitrate, phenylmercury salicylate, thiomersal, tolylmercury acetate); morpholine fungicides (e.g. aldimorph, benzamorph, carbamorph, dimethomorph, dodemorph, fenpropimorph, flumorph, tridemorph); organophosphorus fungicides (e.g. ampropylfos, ditalimfos, EBP, edifenphos, fosetyl, hexylthiofos, inezin, iprobenfos izopamfos, kejunlin, phosdiphen, pyrazophos, tolclofos-methyl, triamiphos); organotin fungicides (e.g. decafeintin, fentin, tributyltin oxide); oxathiin fungicides (e.g. carboxin, oxycarboxin); oxazole fungicides (e.g. chlozolinate, dichlozoline, dingjunezuo, drazoxolon, famoxadone, hymexazol, metazoxolon,

myclozolin, oxadixyl, vinclozolin); polysulfide fungicides (e.g. barium polysulfide, calcium polysulfide, potassium polysulfide, sodium polysulfide); pyrazole fungicides (e.g. bixafen, fenpyrazamine, fluxapyroxad, furametpyr, isopyrazam, penflufen, penthiopyrad, pyraclostrobin, pyrametostrobin, pyraoxystrobin, rabenzazole, sedaxane); pyridine fungicides (e.g. boscalid, buthiobate, dingjunezuo, dipyrithione, fluazinam, fluopicolide, fluopyram, lvdingjunzhi, parinol, pyribencarb, pyridinitril, pyrifenox, pyroxychlor, pyroxyfur); pyrimidine fungicides (e.g. bupirimate, diflumetorim, dimethirimol, ethirimol, fenarimol, ferimzone, nuarimol, triarimol); anilinopyrimidine fungicides (e.g. cyprodinil, mepanipyrim, pyrimethanil); pyrrole fungicides (e.g. dimetachlone, fenciclonil, fludioxonil, fluoroimide); quaternary ammonium fungicides (e.g. berberine); quinoline fungicides (e.g. ethoxyquin, halacrinat, 8-hydroxyquinoline sulfate, quinacetol, quinoxifen, tebufloquin); quinone fungicides (e.g. chloranil, dichlone, dithianon); quinoxaline fungicides (e.g. chinomethionat, chlorquinox, thioquinox); thiadiazole fungicides (e.g. etridiazole, saisentong, thiodiazole-copper, zinc thiazole); thiazole fungicides (e.g. ethaboxam, isotianil, metsulfovax, othilinone, thiabendazole, thifluzamide); thiazolidine fungicides (e.g. flutianil, thiadifluor); thiocarbamate fungicides (e.g. methasulfocarb, prothiocarb); thiophene fungicides (e.g. ethaboxam, silthiofam); triazine fungicides (e.g. anilazine); triazole fungicides (e.g. amisulbrom, bitertanol, fluotrimazole, huanjunzuo, triazbutil); triazolopyrimidine fungicides (e.g. ametoctradin); urea fungicides (e.g. bentazur, pencycuron, quinazamid); zinc fungicides (e.g. acypetacs-zinc, copper zinc chromate, cufraneb, mancozeb, metiram, polycarbamate, polyoxorim-zinc, propineb, zinc naphthenate, zinc thiazole, zineb, ziram); acibenzolar, acypetacs, allyl alcohol, benzalkonium chloride, bethoxazin, bromothalonil, chitosan, chloropicrin, DBCP, dehydroacetic acid, diclomezine, diethyl pyrocarbonate, ethylcin, fenaminosulf, fenitropan, fenpropidin, furfural, hexachlorobutadiene, methyl iodide, methyl isothiocyanate, nitrostyrene, nitrothai-isopropyl, OCH, 2-phenylphenol, phthalide, piperalin, propamidine, proquinazid, pyroquilon, sodium orthophenylphenoxide, spiroxamine, sultropen, thicyofen or tricyclazole. The antifungal agent may be used in any convenient form, including any functionally acceptable salt. The references to the antifungal agents listed above extends to any isomeric form in which the compound may exist as well as mixtures of two or more isomers, e.g. racemic mixtures.

[0094] In some embodiments of the present methods, the antifungal agent is an azole antifungal, such as fluconazole, itraconazole, ketoconazole, miconazole, voriconazole, or a combination thereof.

[0095] Factors affecting dosage regimens for administration of the present compound to a subject include the type, age, weight, sex, diet, and condition of the subject; the type and severity of the fungal infection; pharmacological considerations, such as the activity, efficacy, pharmacokinetic, and toxicology profiles of the particular compound or salt used; whether a drug delivery system is utilized; and the specific drug combination.

[0096] The present compound may be administered at any suitable frequency and may be administered substantially simultaneous with, or independent from, an antifungal agent. The antifungal agent may be also administered at any suitable frequency and may be administered substantially simultaneous with, or independent from, the present compound.

[0097] The present compound and an antifungal agent may be co-administered to the subject from the same pharmaceutical composition or from separate pharmaceutical compositions. The present compound and an antifungal agent may be co-administered in a substantially simultaneous manner (e.g., or within about 5 min of each other), in a sequential manner, or both. It is contemplated, for example, that such combination therapies may include administering one therapeutic agent multiple times between the administrations of the other. The time period between the administration of each agent may range from a few seconds (or less) to several hours or days, and will depend on, for example, the properties of each composition and active ingredient (e.g., potency, solubility, bioavailability, half-life, and kinetic profile), as well as the condition of the patient.

[0098] The present methods are contemplated for use with a fungus, e.g. any eukaryotic organism with a cell wall containing chitin, or any organism classified as belonging to the taxonomic kingdom Fungi. The fungus may be a member of the taxonomic phyla Ascomycota (i.e. from the taxonomic class Neoelectromycetes, Pneumocystidomycetes, Schizosaccharomycetes, Taphrinomycetes, Arthoniomycetes, Dothideomycetes, Geoglossomycetes, Eurotiomycetes, Laboulbeniomycetes, Lecanoromycetes, Leotiomycetes, Lichinomycetes, Orbiliomycetes, Pezizomycetes, Sordariomycetes, Saccharomycetes);

Basidiomycota (i.e. from the taxonomic class Agaricomycetes, Dacrymycetes, Tremellomycetes, Agaricostilbomycetes, Attractiellomycetes, Classiculomycetes, Cryptomycocolacomycetes, Cystobasidiomycetes, Microbotryomycetes, Mixiomycetes, Pucciniomycetes, Ustilaginomycetes, or Exobasidiomycetes); Chytridiomycota (i.e. from the taxonomic class Chytridiomycetes or Monoblepharidomycetes); Glomeromycota (i.e. from the taxonomic class Glomeromycetes); Zygomycota (i.e. from the taxonomic class Trichomycetes or Zygomycetes); Microsporidia (i.e. from the taxonomic class Aquasporidia, Marinosporidia or Terresporidia); Blastocladiomycota (i.e. from the taxonomic class Blastocladiomycetes); and Neocallimastigomycota (i.e. from the taxonomic class Neocallimastigomycetes). The term “fungus” extends to the spores that may be produced by certain species of fungus, e.g. the “fungus” may be a sporangiospore, a zygospore, an aco-spore, a basidiospore, an aeciospore, a urediospore, a teliospore, a conidiospore, or a mitospore.

[0099] In some embodiments, the fungus is an animal and/or a plant pathogen, an animal and/or a plant parasite, or involved in the spoilage or decomposition of organic materials (e.g. foodstuffs and cellulose-based products). The fungus may be a pathogen that is usually benign to healthy subjects with an uncompromised immune system, but such a fungus can establish an infection in subjects whose immune system is compromised in some way. The fungus may also be a fungus that produces a mycotoxin that affects animals, typically by poisoning them or inducing allergic reactions. The fungus may be a plant pathogen that can establish an infection in one or more types of plants, or specifically on seeds, flowers, fruits, roots, bark or leaves of plants.

[00100] In some embodiments, the fungus of the fungal infection may be the causative agent of an aspergillosis (i.e. fungi from the taxonomic genus *Aspergillus*, e.g. *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus clavatus*, *Aspergillus terreus*, *Aspergillus niger*); a candidiasis (i.e. fungi from the taxonomic genus *Candida*, e.g. *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida lusitanae*, *Candida dubliniensis*, *Candida parapsilosis*, *Candida krusei*, *Candida rugosa*); a coccidioidomycosis (e.g. *Coccidioides immitis*, *Coccidioides posadasii*); a cryptococcosis (e.g. *Cryptococcus neoformans*, *Cryptococcus gattii*, *Cryptococcus laurentii*, *Cryptococcus albidus*); a histoplasmosis (e.g. *Histoplasma capsulatum*, *Histoplasma duboisii*);

blastomycosis (e.g. *Blastomyces dermatitidis*); a mycetoma (e.g. *Actinomadura pelletieri*, *Acremonium strictum*, *Actinomadura madurae*, *Aspergillus nidulans*, *Noettestudina rosatii*, *Phaeoacremonium kraidenii*, *Pseudallescheria boydii*, *Curvularia lunata*, *Exophiala jeanselmei*, *Leptosphaeria senegalensis*, *Leptosphaeria tompkinsii*, *Madurella grisea*, *Madurella mycetomatis*, *Pyrenochaeta romeroi*); paracoccidioidomycosis (e.g. *Paracoccidioides brasiliensis*); pneumocystosis (e.g. *Pneumocystis jirovecii*); fusariosis (e.g. the *Fusarium solani* complex: *Fusarium oxysporum*, *Fusarium verticillioides*, *Fusarium proliferatum*, *Fusarium moniliforme*); a phaeohyphomycosis (e.g. fungi from the genus *Alternaria*, *Exophiala jeanselmei*); an alternariosis (i.e. fungi from the genus *Alternaria*, e.g. *Alternaria alternata*); rhinosporidiosis (e.g. *Rhinosporidium seeberi*); a microsporidiosis (e.g. *Enterocytozoon bieneusi*, *Encephalitozoon intestinalis*); basidiobolomycosis (e.g. *Basidiobolus ranarum*); a conidiobolomycosis (e.g. *Conidiobolus coronatus*, *Conidiobolus incongruus*); a mucormycosis (e.g. *Rhizopus oryzae*, *Mucor indicus*, *Absidia corymbifera*, *Syncephalastrum racemosum*); a trichosporonosis (e.g. *Trichosporon* spp, *Trichosporon asahii*, *Trichosporon inkin*, *Trichosporon asteroides*, *Trichosporon cutaneum*, *Trichosporon mucoides*, *Trichosporon ovoides*, *Trichosporon pullulans*, *Trichosporon loubieri*, *Trichosporon japonicum*); a chromoblastomycosis (*Fonsecaea pedrosoi*, *Fonsecaea compacta*, *Phialophora verrucosa*); geotrichosis (e.g. *Geotrichum candidum*); allescheriasis (e.g. *Pseudallescheria boydii*); sporotrichosis (e.g. *Sporothrix schenckii*); penicilliosis (e.g. *Penicillium marneffei*); lobomycosis (e.g. *Lacazia loboi*); a dermatophytosis (i.e. fungi from the genera *Epidermophyton*, *Microsporum* and *Trichophyton*, e.g. *Epidermophyton floccosum*, *Microsporum canis*, *Microsporum audouinii*, *Microsporum gypseum*, *Trichophyton interdigitale/mentagrophytes*, *Trichophyton verrucosum*, *Trichophyton violaceum*, *Trichophyton canis*, *Trichophyton tonsurans*, *Trichophyton schoenleini*, *Trichophyton rubrum*, *Trichophyton concentricum*); a piedra (e.g. *Hortaea werneckii*, *Piedraia hortae*, *Malassezia furfur*, *Trichosporon* spp, *Trichosporon beigelii*); a pityrosporum folliculitis/malassezia folliculitis (i.e. fungi from the genera *Malassezia*, e.g. *Malassezia globosa*, *Malassezia restricta*). Other fungal species capable of acting as an animal pathogen include, *Malassezia pachydermatis*, *Scedosporium prolificans*, *Acremonium kiliense*, and *Paecilomyces lilacinus*.

[00101] In some embodiments, the fungus is a species from the taxonomic genus *Aspergillus*, such as *Aspergillus niger*, *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus clavatus* or *Aspergillus terreus*, in particular *Aspergillus fumigatus*.

[00102] In some embodiments of the present methods, the fungal infection is a drug-resistant fungal infection. In some embodiments, the fungal infection is a multi-drug resistant (MDR) fungal infection. In some embodiments, the fungal infection is an azole-resistant fungal infection. In some embodiments, the fungal infection is caused by an azole resistant *Aspergillus* species.

[00103] A minimum inhibitory concentration (MIC) of one of the present compounds or an antifungal agent (or both) is the concentration that prevents growth of a fungus, compared to the growth of the fungus in the absence of the present compound or antifungal agent.

[00104] A “drug-resistant fungal infection” refers to infection by a fungus resistant to one or more antifungal agents. An assay that determines minimum inhibitory concentration (MIC) can be used to identify assay whether a fungus is drug-resistant. The relevant tolerance of a fungus to an antifungal agent is measured by determining the lowest concentration of antifungal agent that causes complete inhibition of growth. A fungus resistant to an antifungal agent will have a substantially greater MIC value for the antifungal agent than that of the reference fungus sensitive to the antifungal agent or a typical, or a wild type, version of the fungus. In some contents, a drug-resistant fungus has a MIC value for the antifungal agent that is at least 2, 4, 8, 16, or more, times higher than the MIC value of a reference fungal strain that is sensitive to the antifungal agent or a typical or a wild type version of the fungus. Alternatively, in the context of in vivo or clinical use of an antifungal agent for the treatment of a fungal infection, a fungus may be considered resistant to an antifungal agent if the fungus has a MIC value for the antifungal agent that is greater than the maximum safe circulating concentration of the antifungal agent in the subject. More functionally, a fungus may be considered to be resistant to an antifungal agent if an infection associated with that fungus is unresponsive to or insufficiently affected by the maximum safe dose of the antifungal agent.

[00105] The fungus of a fungal infection may be resistant to more than one antifungal agent, or more particularly it may be resistant to more than one class of antifungal agent, e.g. the fungus

may be resistant to at least 2 or 3, or at least 4, 5, 6, 7, 8, 9 or 10 antifungal agents or classes thereof. Those fungi that are resistant to more than 3 classes of antifungal agent are multi-drug resistant (MDR) or have an MDR phenotype.

[00106] The term “reducing resistance” means a measurable reduction in the above-described indicators of the resistance (or measurable increase in susceptibility or measurable decrease in tolerance) to the antifungal agent displayed by the fungus. It generally refers to the observed phenotype of the treated fungus and should not necessarily be considered to equate to a reversal, to any extent, at the mechanistic level of any particular resistance mechanism. The effects of the present compounds in reducing resistance to an antifungal agent or in potentiating an antifungal agents may be seen irrespective of the mechanism of resistance to the antifungal agent.

[00107] In some embodiments, the present compounds will measurably reduce the MIC value of the resistant fungus for the antifungal agent, e.g. the MIC value for the antifungal will be reduced by a factor of at least 2, at least 3, at least 4, at least 10, or by an even higher factor, compared to the MIC value of the fungus for the antifungal agent in the absence of the present compounds.

[00108] In some embodiments, the fungal infection to be treated occurs in or on a surface in a human subject, a non-human animal subject, or a plant. Such surfaces including human, animal or plant bodies or parts thereof, for instance limbs, organs, seeds, flowers, fruits, roots, bark and leaves, including tissues and organs. Examples of surfaces of human or non-human animal bodies also include, but are not limited to, any surface in the oral cavity (e.g. teeth, gingiva, gingival crevice, periodontal pocket) the reproductive tract (e.g. cervix, uterus, fallopian tubes), the peritoneum, middle ear, prostate, urinary tract, vascular intima, the eye (i.e. ocular tissue, e.g. the conjunctiva, corneal tissue, lachrymal duct, lachrymal gland, eyelid) the respiratory tract, lung tissue (e.g. bronchial and alveolar), heart valves, gastrointestinal tract, skin, scalp, nails and the interior of wounds, particularly chronic wounds and surgical wounds, which may be topical or internal wounds. Other surfaces include the exterior of organs, particularly those undergoing transplantation, for example, heart, lungs, kidney, liver, heart valve, pancreas, intestine, corneal tissue, arterial and venous grafts and skin.

[00109] The location of the subject's infection is not restricted and may be any of the sites or locations in a subject described above. Administering the present compounds and the antifungal agent to the subject preferably results in the infected location being contacted with the present compounds and antifungal agent in amounts sufficient to treat the infection. The subject's infection may be acute, or alternatively chronic, e.g. an infection that has persisted for at least 5 or at least 10 days, particularly at least 20 days, more particularly at least 30 days, most particularly at least 40 days.

[00110] In some embodiment, the present methods or uses of the compounds and pharmaceutical compositions comprises a step in which the subject is identified (e.g. diagnosed) as having or suspected to have a fungal infection or being a candidate that is at risk of or susceptible to an fungal infection. In some embodiments, the subject is diagnosed as having a drug-resistant fungal infection, before being administered one or more of the present compounds and an antifungal agent. In some embodiments, the subject is diagnosed as having an azole-resistant fungal infection, before being administered one or more of the present compounds and an azole antifungal agent.

PHARMACEUTICAL COMPOSITIONS

[00111] As another aspect of the present disclosure, pharmaceutical compositions comprising one or more of the present compounds are provided. Such compositions comprise an effective amount of the present compound in combination with a pharmaceutically acceptable carrier, and, optionally, one or more other active agents, diluents, fillers, or excipients. An excipient is a compound that improves or provides a desirable physical property to a composition. An excipient useful in a composition described herein includes, but is not limited to, emulsifying agents, pH buffering agents, approved dyes and colorants; dispersing agents, cosolvents, gelling agents, and drying agents.

[00112] Pharmaceutical compositions comprising the present compound include those suitable for administration to an individual by any medically acceptable route including, but not limited to, parenteral, subcutaneous, intramuscular, intravenous, auricular (ear), ocular, intra-articular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelical,

intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary (e.g., by inhalation or insufflation), intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, oral, rectal, buccal, sublingual, intranasal, and transdermal. The pharmaceutical compositions may, where appropriate, be conveniently presented in discrete dosage units. As indicated above, the pharmaceutical compositions may also comprise an antifungal agent. In some embodiments, the present compound is present in the pharmaceutical composition in an amount effective to potentiate the antifungal agent or increase its efficacy in inhibiting fungal growth.

[00113] Oral pharmaceutical compositions or dosage units include capsules, cachets, or tablets which contain a predetermined amount of the present compound in a powder or granule form, in a solution, in a suspension, or as an emulsion. The present compound may also be in a bolus, electuary, or paste. Tablets and capsules for oral administration may contain excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated. Oral liquid pharmaceutical compositions include aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be provided as a dry product for reconstitution before use. Such liquid preparations may contain additives such as suspending agents, emulsifying agents, nonaqueous vehicles (such as edible oils), or preservatives.

[00114] In some embodiments, the pharmaceutical composition is formulated for parenteral administration (e.g., by injection as a bolus or by continuous infusion) and may be provided in unit doses within ampoules, prefilled syringes, small volume infusion, or in multidose containers with an added preservative. Pharmaceutical compositions may be suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing, and/or dispersing agents. Alternatively, the present compound may be provided in powder form, for reconstitution with a suitable vehicle, such as sterile water.

[00115] For topical administration, pharmaceutical compositions may be as ointments, creams, gels, jellies, or lotions, or incorporated into a transdermal patch. Such transdermal patches may contain penetration enhancers. Ointments and creams may be formulated with an aqueous or oily base comprising one or more suitable thickening and/or gelling agents. Lotions

may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Compositions suitable for topical administration in the oral cavity include lozenges; pastilles; and mouthwashes comprising the present compound in a suitable liquid carrier.

[00116] Pharmaceutical compositions may be for rectal administration (e.g., a suppository), wherein the carrier is a solid. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of a present compound with the softened or melted carrier(s) followed by chilling and shaping in molds.

[00117] Pharmaceutical compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or sprays containing in addition to a present compound.

[00118] For intranasal administration the present compounds may be provided in a liquid spray or dispersible powder or in the form of drops. Drops may be formulated with an aqueous or nonaqueous base also comprising one more dispersing agents, solubilizing agents, or suspending agents. Liquid sprays may conveniently be delivered from pressurized packs.

[00119] For administration by inhalation, the present compounds may be delivered from an insufflator, nebulizer, a pressurized pack, or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant. For administration by inhalation or insufflation, the present compounds may be within a dry powder composition. The powder composition may be presented in unit dosage form in capsules or cartridges, or in gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

[00120] Pharmaceutical compositions comprising one of the present compounds may also be formulated for treating a fungal infection of the eye (via eye drops) or of the ear (via ear drops).

[00121] When desired, the pharmaceutical compositions may be adapted or formulated to give a sustained or time-delayed release of the present compound.

EXEMPLARY EMBODIMENTS

[00122] Before various exemplary embodiments and examples are described, it is to be understood that the teachings of this disclosure are not limited to the particular embodiments described, and as such can, of course, vary.

[00123] Exemplary embodiments are described and illustrated throughout the present application, including by Claims 1 to 66 set forth below.

EXAMPLES

Example 1

[00124] In this Example, various analogs and derivatives of MBX-7498 and MBX-7591 were screened for potentiation if the activity of the triazole antifungal drug fluconazole.

[00125] A screening protocol that utilizes a bioluminescent *A. fumigatus* strain to identify small molecules that potentiate the activity of the triazole antifungal drug fluconazole is described in Opperman TJ, et al., “Luciferase-Based High-Throughput Screen with *Aspergillus fumigatus* to Identify Antifungal Small Molecules”, *Methods Mol Biol.* 2023; 2658:17-34. In this assay, 10^3 spores of a luminescent strain of *A. fumigatus* are added to each well of an assay plate containing 40 μ L glucose minimal medium (GMM) supplemented with 32 μ g fluconazole/mL. A discreet small molecule was added to each test well (final concentration of 10 μ M). Negative control wells contained 1% DMSO and positive control wells contained 8 μ g voriconazole/mL. The assay plates were incubated at 37 °C with 5% CO₂ for 18 h, after which BrightGlo luminescence reagent (Promega) was added and the luminescence of each well was measured using an Envision plate reader (Perkin Elmer). Test wells that exhibited 70% inhibition of luminescence signal as compared to the negative control were scored as primary hits.

[00126] Screening assays were developed and optimized to identify compounds that A) increase filamentous fungal susceptibility to the azole anti-fungal agent fluconazole, and B) inhibit filamentous fungal growth in hypoxic conditions. The rationale for the dual screen was based on the phenotypes associated with inhibition of the *Aspergillus fumigatus* SrbA pathway in work previously published by the Cramer laboratory. Willger SD, et al., “A sterol-regulatory

element binding protein is required for cell polarity, hypoxia adaptation, azole drug resistance, and virulence in *Aspergillus fumigatus*.” PLoS Pathog. 2008 Nov;4(11):e1000200. Chung D, et al., “ChIP-seq and in vivo transcriptome analyses of the *Aspergillus fumigatus* SREBP SrbA reveals a new regulator of the fungal hypoxia response and virulence”, PLoS Pathog. 2014 Nov 6;10(11):e1004487. These phenotypes are: clinically relevant MIC to fluconazole (<8 ug/ml), elimination of voriconazole drug resistance in azole resistant strains, complete loss of hypoxic growth (oxygen levels <5% ambient), and elimination of fungal virulence in multiple murine models of invasive aspergillosis.

[00127] The sensitive luminescence-based reporter assay was chosen for screening compounds for activity, as it had been validated at Microbiotix, Inc. for use in a robust and sensitive cell-based assay for compounds that potentiate fluconazole and inhibit hypoxic growth. Several assay parameters were optimized for each screen, including growth medium, incubation time and temperature, density of fungal spores in the inoculum, and luminescence detection reagent. Additional optimized parameters were the concentration of fluconazole that was used in the screen for compounds that increase susceptibility to fluconazole, and the oxygen concentration for the hypoxic growth screen. The optimized parameters for both screening assays are summarized below.

[00128] *Fluconazole potentiator screen.* To assess antifungal activity, MICs were measured against the *A. fumigatus* CEA10 reference strain utilizing the standard CLSI microbroth dilution platform (Clinical and Laboratory Standards Institute. 2017. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi, 3rd ed Clinical and Laboratory Standards Institute, Wayne, PA) under the following conditions: (A) Normoxia (20% O₂, 5% CO₂), and (B) Normoxia in the presence of 32 µg/ml fluconazole. The optimized parameters are as follows: growth medium, glucose minimal medium (GMM); incubation time, 18 h; temperature, 37 °C; spore density, 10³ spores/well; fluconazole concentration, 8× the MIC of the *ArbdB* mutant (32 pg/ml)]; positive control, 4× the MIC of voriconazole (1 µg/ml) *vs.* WT; luminescence detection reagent, 5 µl BrightGlo reagent (Promega) per well.

[00129] This optimized assay was evaluated in a pilot screen of >2000 compounds with known biological activities (Spectrum Library, Microsource Discovery Systems). The assay

exhibited the following statistics in the pilot screen, which are indicative of a robust screening assay: signal/noise ratio >50, $Z' = 0.50$, throughput >6400 cmpds/day. While the Z' is at the lower limit of the range of values required for a robust screen, the assay performed well in the pilot screen, resulting in the identification of 22 hit compounds, all of which were triazole anti-fungal agents or other compounds known to have antifungal activity. As the pilot screen was so successful in identifying known antifungal compounds from the library, we proceeded to conduct the fluconazole potentiator screen.

[00130] The results of this screening campaign are summarized in Table 1. Twenty-nine compounds were identified that meet the criteria specified by the protocol.

Table 1

Summary of <i>A. fumigatus</i> Fluconazole Potentiator High Throughput Screen		
Screening Stage	Number of Compounds	% Total
Total Screened	206,240	100
Primary Hits	1266	0.614
Med. Chem. Pass	1203	0.583
Confirmed Hits	236	0.114
Re-Ordered from Vendor	53	0.026
MIC ≤ 10 μ M (with 32 μ g/ml Fluc.)	39	0.019
MIC _{-Fluc} /MIC _{+Fluc} ≥ 4	29	0.014

Example 2

[00131] Two prioritized hit compounds, MBX-7498 and MBX-7591, were chosen for further development. Various analogs and derivatives of those compounds were synthesized as described herein and were evaluated in the fluconazole potentiator screen. Results from the fluconazole potentiator screen are shown in Table 2. The results set forth in Table 2 provide several teachings regarding the structure-activity relationship between analogs and derivatives of MBX-7591 and MBX-7498 and fluconazole potentiation activity.

Table 2

MBX #	MIC (ug/mL) (-) Fluc	MIC (ug/mL) (+) Fluc
MBX-7498	2.60	0.30
MBX-7591	0.50	0.15
MBX-7704	>15	>15

MBX #	MIC (ug/mL) (-) Fluc	MIC (ug/mL) (+) Fluc
MBX-7705	1.49	1.05
MBX-7706	1.01	8.09
MBX-7707	1.18	0.59
MBX-7728	8.30	8.30
MBX-7729	15.00	15.00
MBX-7730	15.00	7.70
MBX-7731	7.70	7.70
MBX-7732	5.32	1.88
MBX-7769	11.40	8.09
MBX-7770	8.09	8.09
MBX-7771	11.80	16.70
MBX-7772	12.60	12.60
MBX-7773	7.79	15.60
MBX-7801	>16	>16
MBX-7802	>16	>16
MBX-7803	>16	>16
MBX-7804	>15	>15
MBX-7805	>16	>16
MBX-7806	>15	>15
MBX-7821	>15	>15
MBX-7822	>6	1.07
MBX-7868	8.33	2.08
MBX-7869	>17	3.07
MBX-7870	>17	6.09
MBX-7871	8.69	1.09
MBX-7872	>18	6.38
MBX-7873	>16	>16
MBX-7874	>16	>16
MBX-7875	>16	8.00
MBX-7876	>12	2.99
MBX-7877	3.19	0.80
MBX-7910	>88	22.00
MBX-7911	76.10	38.10
MBX-7912	0.36	0.18
MBX-7913	2.41	0.96
MBX-7914	8.34	3.31
MBX-7915	39.50	49.70
MBX-7950	26.80	13.40
MBX-7951	>87	>87
MBX-7952	11.20	2.79

MBX #	MIC (ug/mL) (-) Fluc	MIC (ug/mL) (+) Fluc
MBX-7953	5.58	1.11
MBX-7954	>77	>77
MBX-7955	>74	>74
MBX-7956	>79	>79
MBX-7957	>92	46.50
MBX-7958	>92	>92
MBX-7959	21.20	4.20
MBX-7960	42.00	10.60
MBX-7961	>89	>89
MBX-7962	>92	>92
MBX-7963	>77	>77
MBX-7964	2.27	1.13
MBX-8024	19.60	19.60
MBX-8025	>37	>37
MBX-8026	2.40	0.80
MBX-8027	>83	>83
MBX-8028	0.40	0.60
MBX-8029	27.00	19.00
MBX-8030	1.90	0.50
MBX-8031	2.10	0.30
MBX-8032	3.10	8.80
MBX-8033	39.00	27.00
MBX-8065	>19	>19
MBX-8066	1.20	0.90
MBX-8085	>19	>19
MBX-8086	>19	>19
MBX-8087	13.00	>18
MBX-8088	6.50	14.50
MBX-8089	>22	>20
MBX-8090	18.80	13.30
MBX-8091	>21	>21
MBX-8092	21.00	>21
MBX-8093	>22	>20
MBX-8094	>22	>22
MBX-8095	6.70	3.80
MBX-8096	>22	>22
MBX-8097	>22	>22
MBX-8098	5.50	2.50
MBX-8099	7.81	3.10
MBX-8138	>21	>21

MBX #	MIC (ug/mL) (-) Fluc	MIC (ug/mL) (+) Fluc
MBX-8139	>22	>22
MBX-8140	>20	>20
MBX-8141	>20	>20
MBX-8142	>21	>21
MBX-8143	10.80	3.81
MBX-8144	0.77	0.21
MBX-8145	0.30	0.08
MBX-8146	0.28	0.14
MBX-8147	>14	>14
MBX-8185	>20	>20
MBX-8186	4.80	1.90
MBX-8187	4.45	2.50
MBX-8188	>22	>22
MBX-8189	>21	>21
MBX-8190	>23	>23
MBX-8191	>20	>20
MBX-8192	>15.8	>15.8
MBX-8193	0.63	0.18
MBX-8219	2.81	2.81
MBX-8220	>21	>21
MBX-8221	>17	>22
MBX-8222	>21	>21
MBX-8223	12.60	3.50
MBX-8224	1.10	0.50
MBX-8226	20.00	11.00
MBX-8240	4.73	2.37
MBX-8241	>18	>18
MBX-8242	>21	>21
MBX-8243	8.76	4.92
MBX-8244	>22	>22
MBX-8245	>20	>20
MBX-8246	>21	12.20
MBX-8247	5.23	2.08
MBX-8248	>17	>17
MBX-8249	>21	21.00
MBX-8250	2.64	0.52
MBX-8251	5.28	1.32
MBX-8252	5.40	1.07
MBX-8253	>21	>21
MBX-8281	7.03	1.40

MBX #	MIC (ug/mL) (-) Fluc	MIC (ug/mL) (+) Fluc
MBX-8282	5.43	1.36
MBX-8283	>22	>22
MBX-8284	>22	>22
MBX-8285	4.11	2.05
MBX-8305	9.10	4.50
MBX-8306	9.10	4.50
MBX-8307	4.80	2.40
MBX-8308	4.30	1.90
MBX-8309	19.00	19.00
MBX-8310	21.00	5.20
MBX-8311	19.00	22.00
MBX-8312	>20	>20
MBX-8323	2.40	1.20
MBX-8324	1.20	0.17
MBX-8325	>20	>20
MBX-8345	>22	11.00
MBX-8346	1.10	0.15
MBX-8347	>21	>21
MBX-8354	9.00	14.00
MBX-8355	>22	>22
MBX-8356	0.60	0.09
MBX-8357	>22	5.60
MBX-8358	2.79	0.44
MBX-8359	>23	>23
MBX-8389	>43	>43
MBX-8390	2.00	0.40
MBX-8391	1.00	0.20
MBX-8392	>43	>43
MBX-8393	>47	>47
MBX-8394	19.00	9.70
MBX-8428	10.61	6.37
MBX-8429	18.53	18.53
MBX-8430	10.12	5.26
MBX-8431	3.78	1.14
MBX-8432	4.16	1.51
MBX-8433	2.53	0.84
MBX-8435	>22	>22
MBX-8436	4.46	0.45
MBX-8438	>25	>25
MBX-8439	9.76	0.78

MBX #	MIC (ug/mL) (-) Fluc	MIC (ug/mL) (+) Fluc
MBX-8529	9.84	>15
MBX-8619	4.92	1.23
MBX-8668	11.80	1.47
MBX-8684	7.38	1.30
MBX-8700	8.97	1.26
MBX-8701	0.67	0.19
MBX-8702	1.14	0.32

[00132] Analogs of MBX-7591 were made by changing the thiophene group, thereby scanning the binding pocket for a potential hydrogen bonding. It was found that swapping the thiophene of MBX-7591 for another electron rich furan (MBX-7732) resulted in a 4-fold loss in potency compared to MBX-7591. Analogs reducing the electron density of thiophene (MBX-8095) or the thiazole isomers (MBX-8098 & MBX-8099) led to more than 4-fold loss in potentiating the fluconazole. Switching to a nitrogen-based pyrrole analog (MBX-7773) resulted in an antagonistic potentiation effect with the fluconazole, while the basic imidazole (MBX-7804) was not tolerated. Similarly, the basic pyridine isomers (MBX-7731, MBX-7730, MBX-7729) and its electron deficient congener (MBX-8089) did not result in appreciable increase in potency. Similar to heteroaromatics, neither the phenyl replacement (MBX-7704), its isostere (MBX-8090), the electron donating substituents (MBX-7728, MBX-7771, MBX-7772, MBX-7801, MBX-7802), the acidic substituents (MBX-7803, MBX-8138) nor the sterically hindered alcohol (MBX-8139) had any effect on the potency relative to MBX-7591. Compared to the sterically hindered tert-butyl substitution (MBX-8094), the methylated analog (MBX-7707) exhibited comparable activity to MBX-7591. Further exploration with electronegative substituents (MBX-7706, MBX-8088) resulted in antagonistic effect in contrast to MBX-7705 where a low potentiation effect was observed. Overall, it can be inferred that the potency of the analogs is dictated by the electron density and the sterics of the substituted aromatic ring in MBX-7591.

[00133] With regard to the pyridine moiety of MBX-7591, while contributing to CYP3A4 inhibition, it can also undergo N-oxidation. To circumvent CYP inhibition and consequently the N-oxidation of pyridine, analogs of the pyridine in MBX-7591 were designed by (a) isomerizing pyridine (MBX-8065); (b) reducing the electron density of nitrogen (MBX-8033); (c) changing

the orientation (MBX-8140) and (d) increasing steric hindrance (MBX-8141, MBX-8142, MBX-8185, MBX-8191). All the analogs resulted in complete loss of activity reinforcing the role of pyridine for maintaining potency. Shifting to heteroaryloxy methyl variations, analogs having directly attached pyridine ring (MBX-7964) and ethylene linker (MBX-8026) maintained potency but the methyl aryloxy (MBX-8024), diaryl ether (MBX-8025), alkyne and amino pyridine linkers were not optimal for potentiation of fluconazole. Further analogs of the amide linker bridging piperidine with thiophene (MBX-7591, MBX-7806, MBX-7821, MBX-7805, MBX-7822) the sulfonamide analog (MBX-7822) is the only linker reasonably tolerated, apart from the amide.

[00134] Analogues were also synthesized in a combinatorial fashion, with concurrent variations to multiple groups, based in part on a commercially available morpholine analogue (MBX-8031) that maintained potency similar to MBX-7591 but with lowered CYP3A4 inhibition at 67%. Unexpectedly, switching to a para-fluorophenyl substitution (MBX-8145) resulted in 6-fold increase in potentiation of fluconazole. This is further augmented by a similar trend in activity with para-chlorophenyl (MBX-8146) compared to its congener (MBX-8187). The heteroaromatic substituents (MBX-8146, MBX-8186) also maintain activity in the morpholine series, in contrast to the variations observed in MBX-8089 and MBX-8095, while an amide linker (MBX-8188) replacing a methylene and a sterically hindered morpholine (MBX-8190) are not tolerated.

[00135] With regard to analogs of MBX-7498, in contrast to some of the results for analogs of MBX-7591, analogs with electronically modulated thiophene (MBX-7912) and pyridine variations (MBX-7913) were the most potent while the non-aromatic analogs (MBX-7911, MBX-7915, MBX-7956, MBX-7950, MBX-7951) led to complete loss of activity. Variations of the sulfonamide linker of MBX-7498 revealed sulfonamide as the optimal linker in maintaining antifungal activity.

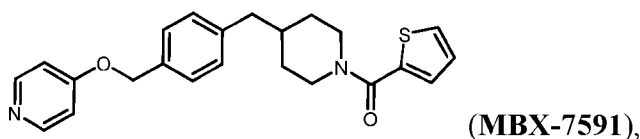
[00136] In view of this disclosure, it is noted that the methods can be implemented in keeping with the present teachings. Further, the various components, materials, structures and parameters are included by way of illustration and example only and not in any limiting sense. In view of this disclosure, the present teachings can be implemented in other applications and components,

materials, structures and equipment to implement these applications can be determined, while remaining within the scope of the appended claims.

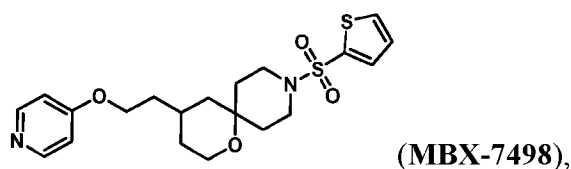
CLAIMS

What is claimed is:

Claim 1. A method for treating fungal infection in a subject, the method comprising administering to the subject



an analog thereof, a derivative thereof, or a pharmaceutically acceptable salt of any of the foregoing; or



an analog thereof, a derivative thereof, or a pharmaceutically acceptable salt of any of the foregoing.

Claim 2. The method of **Claim 1**, further comprising administering to the subject an antifungal agent.

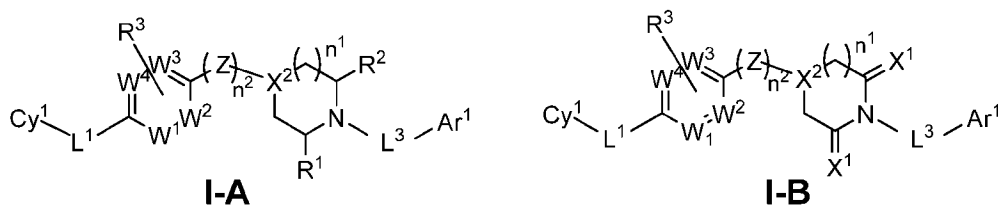
Claim 3. The method of **Claim 2**, wherein the antifungal agent is an azole antifungal, such as fluconazole, itraconazole, ketoconazole, miconazole, voriconazole, or a combination thereof.

Claim 4. The method of any of the preceding claims, wherein the fungal infection is an azole-resistant fungal infection.

Claim 5. The method of any of the preceding claims, wherein the fungal infection is caused by an *Aspergillus* species.

Claim 6. The method of any of the preceding claims, wherein the fungal infection is caused by an azole-resistant *Aspergillus* species.

Claim 7. The method of any one of **Claims 1 – 6**, wherein the analog or derivative of **MBX-7591** has the structure of Formula **(I-A)** or **(I-B)**:



wherein R^1 and R^2 are independently H or C_1 – C_6 alkyl;

R^3 is H, C_1 – C_6 alkyl, $CH=CHR^1$, OCH_3 , halogen, C_1 – C_6 alkoxy, CN, methylenedioxy, $COOH$, $COOR^1$, $C(=O)R^1$, NH_2 , NR^1R^2 , $NHC(=O)R^4$, NO_2 , CF_3 , aryl, SO_3H , $SO_2NR^{4a}R^{4b}$, CHO , $C(=O)NR^{4a}R^{4b}$, OH , OR^1 , $C(=N)NH_2$, $NHC(=NH)NH_2$, $NHOH$, $B(OH)_2$, tetrazole, or C_2 – C_3 alkyne;

R^4 , R^{4a} and R^{4b} are independently H, CH_3 or CH_2CH_3 ;

X^1 is O or S;

X^2 is CH, CR^1 , CR^3 or N;

W^1 through W^4 are independently CH, CR^1 , CR^3 or N, and in some embodiments, at least one, at least two, or at least three of W^1 to W^4 is CH, CR^1 , or CR^3 ;

L^3 is CR^1R^2 , CF_2 , $C(=O)$, $C(=S)$, or $S(O)_2$;

L^1 is a bond, C_1 – C_3 alkyl, $^*-O(CH_2)_{n2}$, $^*-S(CH_2)_{n2}$, $^*-S(O)_2(CH_2)_{n2}$, where * represents the point of attachment to Cy^1 ;

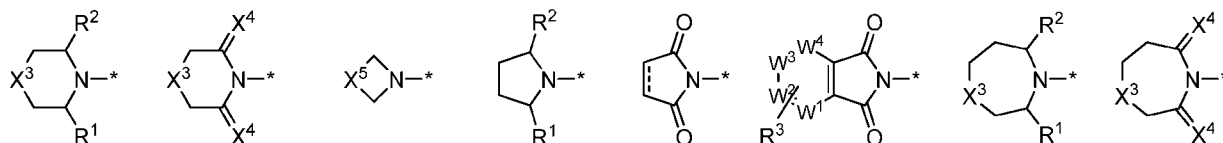
Z is $(CR^1R^2)_{n1}$, CF_2 , O, S, $C(=O)$, SO_2 , or  $_{n2}$;

n^1 is 0 to 2, wherein when n^1 is zero, a chemical bond is present in place of $-(CR^1R^2)-$ in the formula;

n^2 is 0 to 4, wherein when n^2 is zero, a chemical bond is present in place of $-Z-$ in the formula;

Ar^1 is a 5- or 6- membered aryl or heteroaryl, wherein the 5- or 6- membered aryl or heteroaryl is optionally substituted with one or more R^3 ;

Cy¹ is a 5- or 6-membered heteroaryl or heterocycloalkyl containing one or two heteroatoms, or Cy¹ is a 5- or 6 membered cycloalkyl or aryl group, or Cy¹ is 4- to 7-membered-ring having the structure of one of the following formulas:



wherein the attachment point to L¹ is indicated by *;

a dashed line indicates a single bond or double bond may be present;

X³ is CH₂, CR¹R², NR⁴, O, S, SO₂, C(=O), or C(=S);

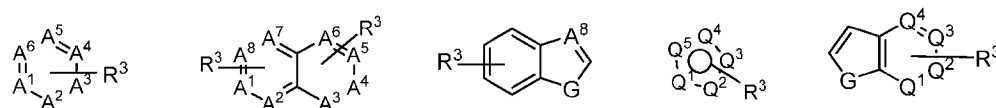
X⁴ is O or S;

X⁵ is CH₂, CR¹R², C(=O) or C(=S); and

Cy¹ is optionally substituted with one or more R³.

Claim 8. The method of **Claim 7**, wherein Cy¹ is a pyridine, a morpholine, a piperazine, or a thiazolo[4.5-b]pyridine.

Claim 9. The method of **Claim 7 or 8**, wherein Ar¹ has the structure of one of the following formulas:



wherein Ar¹ is attached to L³ at any point of attachment;

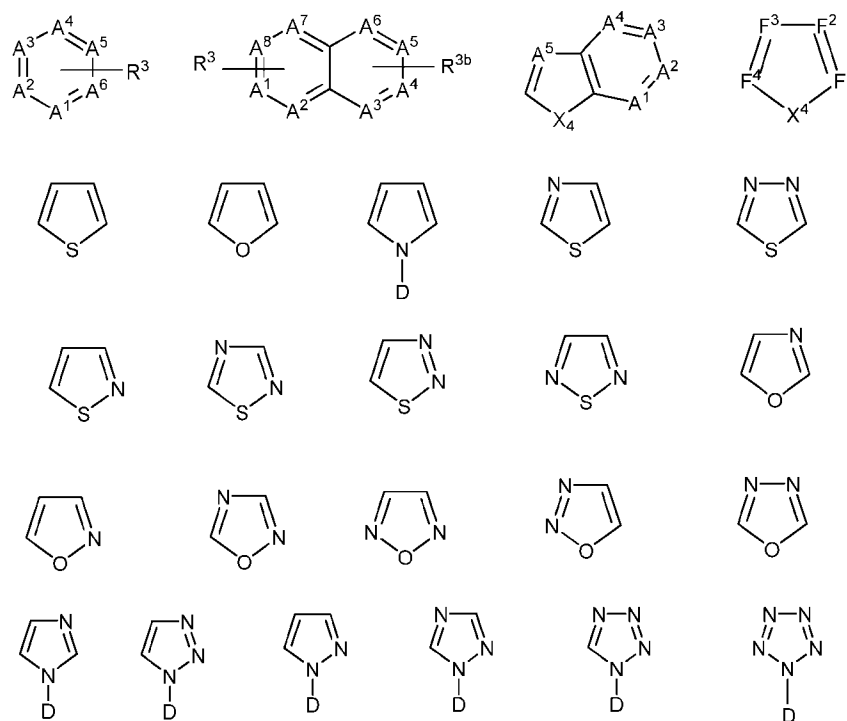
A¹ through A⁸ are independently CH, CR¹, CR³ or N, and in some embodiments, wherein at least one, at least two, at least three or at least four of A¹ through A⁶ is CH, CR¹, or CR³, and at least one, at least two, at least three, at least four or at least five of A¹ through A⁸ is CH, CR¹, or CR³;

G is O, S, NH, or NCH₃;

Q¹ through Q⁵ are independently CH, CR¹, CR³ N, O, or S, and in some embodiments, at least one, at least two, at least three, at least four or at least five of Q¹ to Q⁴ or of Q¹ to Q⁵ is CH, CR¹, or CR³;

R^3 is H, C_1 - C_6 alkyl, $CH=CHR^1$, OCH_3 , halogen, C_1 - C_6 alkoxy, CN, methylenedioxy, $COOH$, $COOR^1$, $C(=O)R^1$, NH^2 , NR^1R^2 , $NHC(=O)R^4$, NO_2 , CF_3 , aryl, SO_3H , $SO_2NR^{4a}R^{4b}$, CHO , $C(=O)NR^{4a}R^{4b}$, OH , OR^1 , $C(=N)NH_2$, $NHC(=NH)NH_2$, $NHOH$, $B(OH)_2$, tetrazole, or C_2 - C_3 alkyne.

Claim 10. The method of any one of **Claims 7 – 9**, wherein Ar^1 is selected from the following ring structures:



wherein A^1 through A^8 are independently CH, CR^1 , CR^3 or N, and in some embodiments, at least one, at least two, at least three or at least four of A^1 through A^6 is CH, CR^1 , or CR^3 , and at least one, at least two, at least three, at least four or at least five of A^1 through A^8 is CH, CR^1 , or CR^3 ; F^1 through F^4 are independently CH, CR^1 , CR^3 , O, S, N, NH, or $NHCH_3$, and in some embodiments, at least one, at least two, or at least three of F^1 to F^4 are CH, CR^1 , or CR^3 ; Ar^1 is attached to L^3 at any point of attachment, and optionally Ar^1 is substituted with one or more substituents independently selected from the group consisting of R^3 ; D is H or CH_3 ; X^4 is O, S, NH, or $NHCH_3$;

R^3 is H, C_1 - C_6 alkyl, $CH=CHR^1$, OCH_3 , halogen, C_1 - C_6 alkoxy, CN, methylenedioxy, $COOH$, $COOR^1$, $C(=O)R^1$, NH_2 , NR^1R^2 , $NHC(=O)R^4$, NO_2 , CF_3 , Aryl, SO_3H , $SO_2NR^{4a}R^{4b}$, CHO , $C(=O)NR^{4a}R^{4b}$, OH , OR_1 , $C(=N)NH_2$, $NHC(=NH)NH_2$, $NHOH$, $B(OH)_2$, tetrazole, or C_2 - C_3 alkyne.

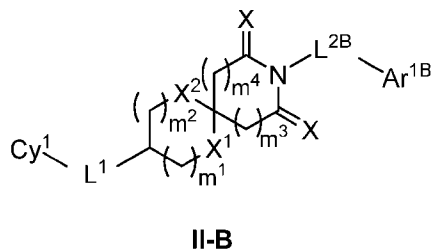
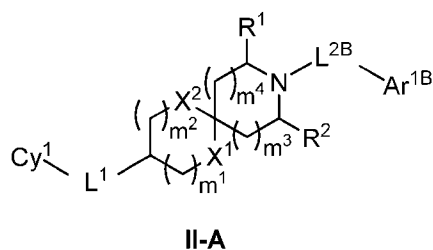
Claim 11. The method of **Claim 7**, wherein Ar^1 is a thiophene, a thiazole, or a substituted phenyl.

Claim 12. The method of **Claim 11**, wherein the thiophene, the thiazole, or the substituted phenyl is substituted with halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or a combination thereof.

Claim 13. The method of **Claim 7**, wherein Ar^1 is a para-substituted phenyl.

Claim 14. The method of **Claim 13**, wherein Cy^1 is unsubstituted morpholine.

Claim 15. The method of **Claims 1 – 6**, wherein the analog of **MBX-7498** has the structure of Formula (II-A) or (II-B):



m^1 , m^2 , m^3 , and m^4 are independently 0 to 3, wherein when m^1 , m^2 , m^3 , or m^4 is zero, a chemical bond is present in place of $-CH_2-$ in the formula;

R^1 and R^2 are independently H or C_1 - C_6 alkyl;

R^3 is H, C_1 - C_6 alkyl, $CH=CHR^1$, OCH_3 , halogen, C_1 - C_6 alkoxy, CN, methylenedioxy, $COOH$, $COOR^1$, $C(=O)R^1$, NH_2 , NR^1R^2 , $NHC(=O)R^4$, NO_2 , CF_3 , aryl, SO_3H , $SO_2NR^{4a}R^{4b}$, CHO , $C(=O)NR^{4a}R^{4b}$, OH , OR_1 , $C(=N)NH_2$, $NHC(=NH)NH_2$, $NHOH$, $B(OH)_2$, tetrazole, or C_2 - C_3 alkyne;

R^4 is CH_3 or CH_2CH_3 ;

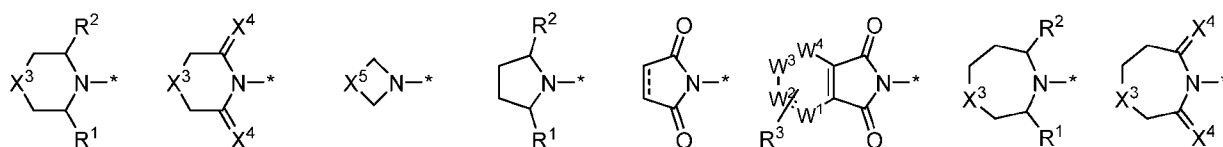
X is O or S;

X^1 and X^2 are independently CR^1R^2 , O, or S;

L^{2B} is CR^1R^2 , CF_2 , $C(=O)$, $C(=S)$, or $S(O)_2$;

Ar^{1B} is a 5- or 6-membered heteroaryl or a phenyl, wherein the 5- or 6-membered heteroaryl or the phenyl is optionally substituted with one or more R^3 ;

Cy^1 is a 5- or 6-membered heteroaryl or heterocycloalkyl containing one or two heteroatoms, or Cy^1 is a 5- or 6 membered cycloalkyl or aryl group, or Cy^1 is 4- to 7-membered-ring having the structure of one of the following formulas:



wherein the attachment point to L^1 is indicated by *;

a dashed line indicates a single bond or double bond may be present;

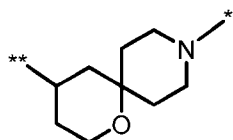
X^3 is CH_2 , CR^1R^2 , NR^4 , O, S, SO_2 , $C(=O)$, or $C(=S)$;

X^4 is O or S;

X^5 is CH_2 , CR^1R^2 , $C(=O)$ or $C(=S)$; and

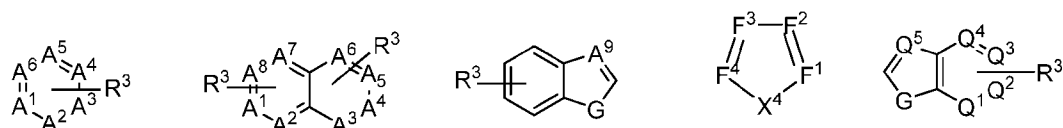
Cy^1 is optionally substituted with one or more R^3 .

Claim 16. The method of **Claim 15**, wherein the analog comprises



wherein * indicates the point of attachment to L^{2B} and ** indicates the point of attachment to L^1 .

Claim 17. The method of any one of **Claims 15 – 16**, wherein Ar^{1B} is a ring structure selected from the group consisting of:



A¹ through A⁹ are independently CH, CR³, or N, and in some embodiments, at least one, at least two, at least three, at least four or at least five of A¹ through A⁹ is CR¹;

F¹ through F⁴ are independently CH, CR¹, CR³, O, S, N, NH, or NHCH₃, and in some embodiments, at least one, at least two, or at least three of F¹ to F⁴ are CH, CR¹, or CR³;

X₄ is independently O, S, NH, or NHCH₃;

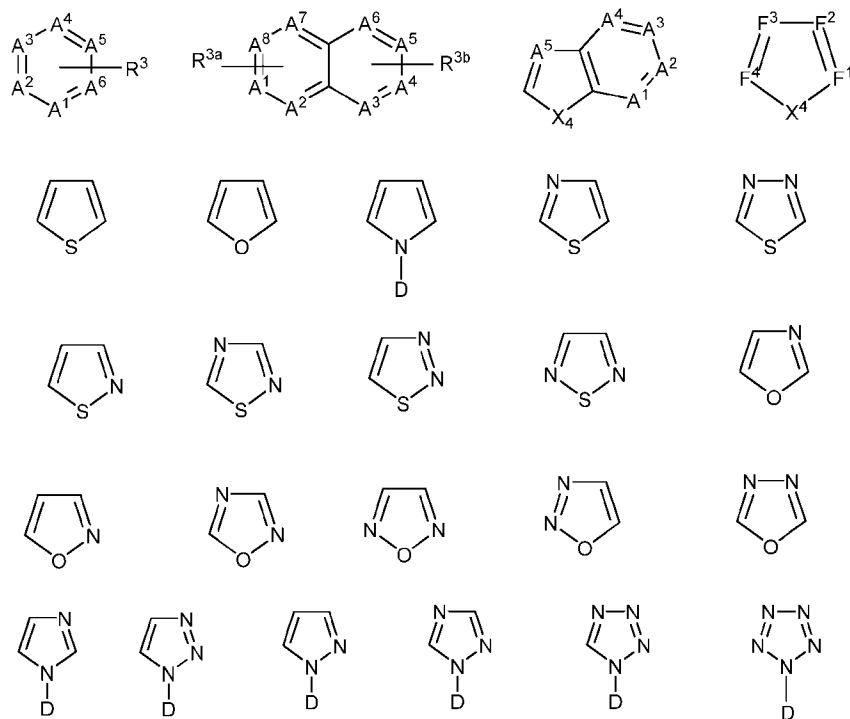
G is O, NH, N(CH₃), or S;

Q¹ through Q⁵ are independently CH, CR¹, CR³ or N, and in some embodiments, at least one, at least two, at least three, at least four or at least five of Q¹ to Q⁵ is CH, CR¹ or CR³;

wherein any of the foregoing ring structures is optionally substituted with one or more R³;

R³ is H, C₁–C₆ alkyl CH=CHR¹, OCH₃, halogen, C₁–C₆ alkoxy, CN, methylenedioxy, COOH, COOR¹, C(=O)R¹, NH₂, NR¹R², NHC(=O)R₄, NO₂, CF₃, Aryl, SO₃H, SO₂NR^{4a}R^{4b}, CHO, C(=O)NR^{4a}R^{4b}, OH, OR¹, C(=N)NH₂, NHC(=NH)NH₂, NHOH, B(OH)₂, tetrazole, or C₂–C₃ alkyne.

Claim 18. The method of **Claims 15 – 17**, wherein Ar^{1B} is a ring structure selected from the group consisting of:



A¹ through A⁸ are independently CH, CR¹, CR³ or N, and in some embodiments, at least one, at least two, at least three or at least four of A¹ through A⁶ is CH, CR¹, or CR³, or at least one, at least two, at least three, at least four or at least five of A¹ through A⁸ is CH, CR¹, or CR³;

F¹ through F⁴ are independently CH, CR¹, CR³, O, S, N, NH, or NHCH₃, and in some embodiments, at least one, at least two, or at least three of F¹ to F⁴ are CH, CR¹, or CR³;

wherein any of the foregoing ring structures is optionally substituted with one or more R³;

D is H or CH₃;

X⁴ is independently is O, S, NH, or NHCH₃;

R³ is H, C₁–C₆ alkyl, OCH₃, halogen, C₁–C₆ alkoxy, CN, methylenedioxy, COOH, COOR¹, C(=O)R¹, NH₂, NR¹R², NHC(=O)R⁴, NO₂, CF₃, Aryl, SO₃H, SO₂NR^{4a}R^{4b}, CHO, C(=O)R¹, C(=O)NR^{4a}R^{4b}, OH, OR¹, C(=N)NH₂, NHC(=NH)NH₂, NHOH, B(OH)₂, tetrazole, or C₂–C₃ alkyne.

Claim 19. The method of **Claim 15**, wherein Ar^{1B} is a thiophene, a thiazole, a phenyl, or a pyridine.

Claim 20. The method of **Claim 19**, wherein Ar^{1B} is an unsubstituted phenyl or a para-substituted phenyl.

Claim 21. The method of **Claim 19**, wherein Ar^{1B} is an unsubstituted thiophene or a halo-substituted thiophene.

Claim 22. The method of **Claim 19**, wherein Ar^{1B} is a para-substituted pyridine.

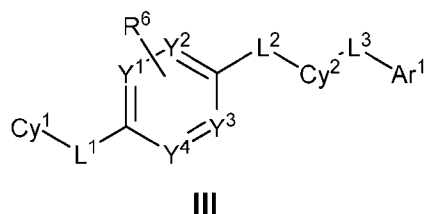
Claim 23. The method of any one of the preceding claims, wherein the analog or derivative of **MBX-7591** or the analog or derivative of **MBX-7498** is selected from the group consisting of MBX-7705, MBX-7706, MBX-7707, MBX-7728, MBX-7729, MBX-7730, MBX-7731, MBX-7732, MBX-7769, MBX-7770, MBX-7771, MBX-7772, MBX-7773, MBX-7822, MBX-7868, MBX-7869, MBX-7870, MBX-7871, MBX-7872, MBX-7875, MBX-7876, MBX-7877, MBX-7910, MBX-7911, MBX-7912, MBX-7913, MBX-7914, MBX-7915, MBX-7950, MBX-7952, MBX-7953, MBX-7957, MBX-7959, MBX-7960, MBX-7964, MBX-8024, MBX-8026, MBX-8028, MBX-8029, MBX-8030, MBX-8031, MBX-8032, MBX-8066, MBX-8087, MBX-8088, MBX-8090, MBX-8092, MBX-8095, MBX-8098, MBX-8099, MBX-8143, MBX-8144, MBX-8145, MBX-8146, MBX-8186, MBX-8187, MBX-8192, MBX-8193, MBX-8219, MBX-8223, MBX-8224, MBX-8226, MBX-8240, MBX-8243, MBX-8246, MBX-8247, MBX-8249, MBX-8250, MBX-8251, MBX-8252, MBX-8281, MBX-8282, MBX-8285, MBX-8305, MBX-8306, MBX-8307, MBX-8308, MBX-8309, MBX-8310, MBX-8311, MBX-8323, MBX-8324, MBX-8345, MBX-8346, MBX-8354, MBX-8356, MBX-8357, MBX-8358, MBX-8390, MBX-8391, MBX-8394, MBX-8428, MBX-8429, MBX-8430, MBX-8431, MBX-8432, MBX-8433, MBX-8436, MBX-8439, MBX-8529, MBX-8619, MBX-8668, MBX-8684, MBX-8700, MBX-8701, MBX-8702, and mixtures thereof.

Claim 24. The method of any one of the preceding claims, the analog or derivative of **MBX-7591** or the analog or derivative of **MBX-7498** is selected from the group consisting of MBX-7705, MBX-7706, MBX-7707, MBX-7728, MBX-7729, MBX-7730, MBX-7731, MBX-7732,

MBX-7769, MBX-7770, MBX-7771, MBX-7772, MBX-7773, MBX-7822, MBX-7964, MBX-8024, MBX-8026, MBX-8028, MBX-8029, MBX-8030, MBX-8031, MBX-8032, MBX-8066, MBX-8087, MBX-8088, MBX-8090, MBX-8092, MBX-8095, MBX-8098, MBX-8099, MBX-8145, MBX-8146, MBX-8186, MBX-8187, MBX-8192, MBX-8193, MBX-8219, MBX-8223, MBX-8224, MBX-8226, MBX-8240, MBX-8243, MBX-8246, MBX-8247, MBX-8249, MBX-8252, MBX-8281, MBX-8282, MBX-8305, MBX-8307, MBX-8308, MBX-8309, MBX-8323, MBX-8324, MBX-8346, MBX-8354, MBX-8356, MBX-8357, MBX-8358, MBX-8390, MBX-8391, MBX-8394, MBX-8428, MBX-8429, MBX-8430, MBX-8431, MBX-8432, MBX-8436, MBX-8439, and mixtures thereof.

Claim 25. The method of any one of the preceding claims, the analog or derivative of **MBX-7591** or the analog or derivative of **MBX-7498** is selected from the group consisting of MBX-7868, MBX-7869, MBX-7870, MBX-7871, MBX-7872, MBX-7875, MBX-7876, MBX-7877, MBX-7910, MBX-7911, MBX-7912, MBX-7913, MBX-7914, MBX-7915, MBX-7950, MBX-7952, MBX-7953, MBX-7957, MBX-7959, MBX-7960, MBX-8143, MBX-8144, MBX-8250, MBX-8251, MBX-8285, MBX-8306, MBX-8310, MBX-8311, MBX-8345, MBX-8394, MBX-8433, and mixtures thereof.

Claim 26. A compound of Formula (III) or a pharmaceutically acceptable salt thereof,



wherein Cy¹ is a 5- to 10-membered heterocycle or 4-(aminomethyl)phenyl, wherein the 5- to 10- membered heterocycle is optionally substituted with a substituent selected from the group consisting of C₁–C₃-alkyl, C₁–C₃-haloalkyl, halo, C₁–C₃-alkoxy, and oxo;

L¹ is a bond, C₁–C₃-alkylene, C₂–C₄-alkynylene, *-OCH₂-, *-CH₂O-, *-NHO-, -O-, where * represents the point of attachment to Cy¹, wherein the C₁–C₃-alkylene is optionally substituted with a C₁–C₃-alkyl;

Y^1 through Y^4 are independently CH, CR^1 , CR^3 or N, and in some embodiments, at least one, at least two, or at least three of Y^1 through Y^4 is CH, CR^1 , or CR^3 ;

R^6 is H, C₁-C₃-alkyl, or halo;

L^2 is C₁-C₃-alkylene, -O-, -NH-, wherein the C₁-C₃-alkylene is optionally substituted with a substituent selected from the group consisting of C₁-C₃-alkyl and OH;

Cy^2 is 4- to 7-membered monocyclic heterocycle, 8- to 10-membered polycyclic heterocycle, phenyl, 5- to 7-membered monocyclic carbocycle, wherein the 4- to 7-membered heterocycle is optionally substituted with a substituent from the group consisting of C₁-C₃ alkyl and oxo;

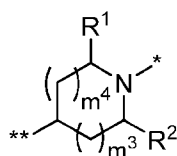
L^3 is -C(=O)-, -S(O)₂-, -N(H)S(O)₂-, -N(H)C(=O)-, -S(O)(NH)-, -C(R^x)₂S(O)₂-, wherein each R^x is independently H or C₁-C₃ alkyl;

Ar¹ is a 5- to 10-membered monocyclic or bicyclic heteroaryl or a phenyl, wherein the 5- to 10-membered heteroaryl or the phenyl is optionally substituted with a substituent selected from the group consisting of C₁ C₃-alkyl, C₁-C₃-haloalkyl, halo, C₁-C₃-alkoxy, cyano, or hydroxyl, with the proviso that the compound is not **MBX-7591**.

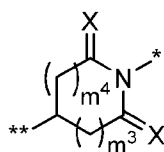
Claim 27. The compound or pharmaceutically acceptable salt of **Claim 26**, wherein Cy^1 is



Claim 28. The compound or pharmaceutically acceptable salt of **Claims 26 – 27**, wherein Cy^2 has the structure of Formula **(III-A)** or **(III-B)**:



III-A



III-B

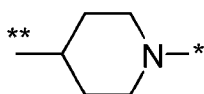
wherein X is O or S;

m^3 and m^4 are independently is 0 to 2, wherein when m_3 or m_4 is zero, a chemical bond is present in place of -CH₂- in the formula;

* represents the point of attachment to L^3 , and ** represents the point of attachment to L^2 ;

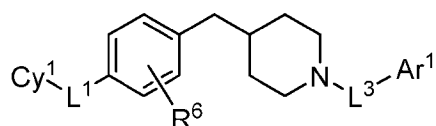
R^1 and R^2 are independently H, C_1 - C_6 alkyl,
wherein Formulas (III-A) and (III-B) are optionally substituted by one or more R^1 and/or R^2 .

Claim 29. The compound or pharmaceutically acceptable salt of **Claim 26 – 28**, wherein Cy^2 is

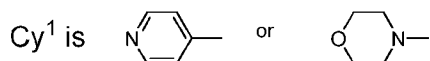


wherein * represents the point of attachment to L^3 , and ** represents the point of attachment to L^2 .

Claim 30. The compound or pharmaceutically acceptable salt of **Claim 26**, having the structure of Formula (III-C):



III-C



L^1 is a bond, C_1 - C_3 alkyl, or $^*-OCH_2-$, where * represents the point of attachment to Cy^1 ;

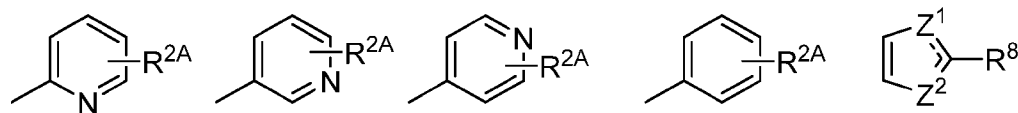
R^6 is H, C_1 - C_3 alkyl, or halogen;

L^3 is $-C(=O)-$ or $-S(O)_2-$;

Ar^1 is a 5- or 6-membered heteroaryl or a phenyl, wherein the 5- or 6-membered heteroaryl or the phenyl is optionally substituted with a substituent selected from the group consisting of C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and halogen;

with the proviso that the compound is not **MBX-7591**.

Claim 31. The compound or pharmaceutically acceptable salt of **Claim 26**, wherein Ar^1 is:



Z^1 is S, O, NR^7 , or CH;

R^7 is C₁-C₃ alkyl;

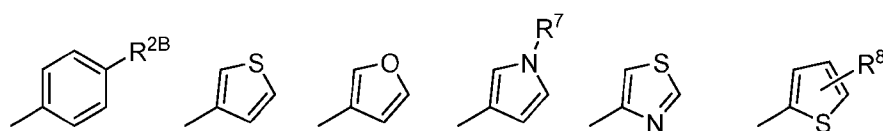
Z^2 is S, N, or CH;

R^{2A} is H, C₁-C₃ alkyl, or halogen;

R^{2B} is C₁-C₃ alkyl, or halogen; and

R^8 is H or halogen.

Claim 32. The compound or pharmaceutically acceptable salt of any one of **Claims 26 - 31**, wherein Ar^1 is:



R^{2B} is C₁-C₃ alkyl or halogen;

R^7 is C₁-C₃ alkyl;

R^{58} is H or halogen.

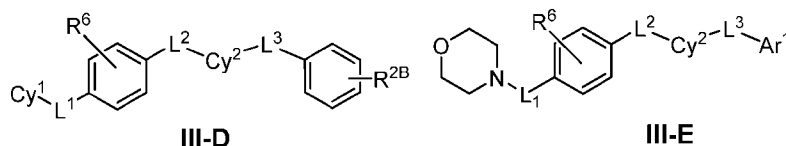
Claim 33. The method of **Claim 26**, wherein Ar^1 is a thiophene, a thiazole, or a substituted phenyl.

Claim 34. The method of **Claim 33**, wherein the thiophene, the thiazole, or the substituted phenyl is substituted with halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, or a combination thereof.

Claim 35. The method of **Claim 26**, wherein Ar^1 is a para-substituted phenyl.

Claim 36. The method of **Claim 35**, wherein Cy^1 is unsubstituted morpholine.

Claim 37. The compound or pharmaceutically acceptable salt of **Claim 26**, having the structure of Formulas **(III-D)** or **(III-E)**:



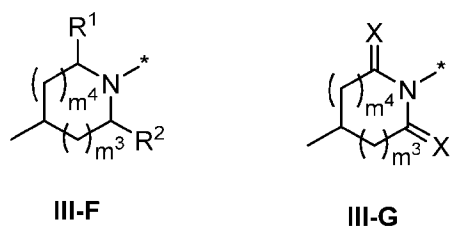
wherein Cy¹ is: or

L¹ is a bond, C₁-C₃ alkyl, or *-OCH₂, where * represents the point of attachment to Cy¹ in Formula (I-B) or the morpholine in Formula (I-C);

R⁶ is H, C₁-C₃ alkyl, or halogen;

L² is C₁-C₃ alkylene, -O-, or -NH-, wherein the C₁-C₃ alkylene is optionally substituted with a substituent selected from the group consisting of C₁-C₃ alkyl and OH;

Cy² is Formula (III-F) or (III-G):



wherein the point of attachment to L³ is indicated by *;

m³ and m⁴ are independently 0 to 2, wherein when m³ or m⁴ are equal to zero, a chemical bond is present in place of -CH₂- in the formula;

R¹ and R² are independently H or C₁-C₄ alkyl;

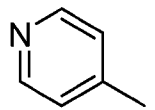
X is O or S;

L³ is -C(=O)- or -S(O)₂-;

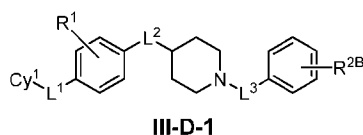
R^{2B} is C₁-C₃ alkyl or halogen; and

Ar¹ is 5- or 6-membered heteroaryl or a phenyl, wherein the 5- or 6-membered heteroaryl or the phenyl is optionally substituted with a substituent selected from the group consisting of C₁-C₃ alkyl, C₁-C₃ haloalkyl, and halogen.

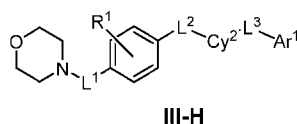
Claim 38. The compound or pharmaceutically acceptable salt of **Claim 37**, wherein Cy¹ is:



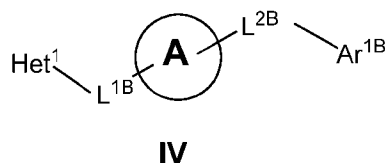
Claim 39. The compound or pharmaceutically acceptable salt of any one of **Claims 37 – 38**, having the structure of Formula **(III-D-1)**:



Claim 40. The compound or pharmaceutically acceptable salt of **Claim 37**, having the structure of Formula **(III-H)**:



Claim 41. A compound of Formula **(IV)** or a pharmaceutically acceptable salt thereof, wherein:



Het¹ is a 6-membered heterocycle or hydroxyalkyl;

L^{1B} is a C₁-C₃ alkylene, *-O(CH₂)-, -O-, where * represents the point of attachment to Het¹;

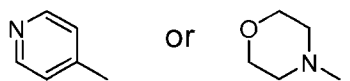
Ring A is a 7 to 15-membered polycyclic ring, said polycyclic ring comprising a spiro ring or a fused ring;

L^{2B} is -C(=O)- or -S(O)₂-;

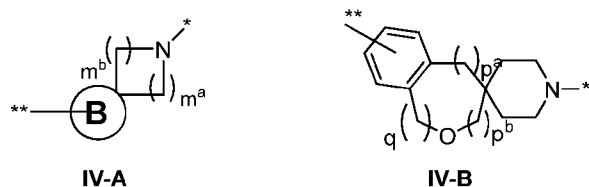
Ar^{1B} is a 5- or 6-membered heteroaryl or a phenyl, wherein the 5- or 6-membered heteroaryl or the phenyl is optionally substituted with a substituent selected from the group consisting of C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, and halogen;

with the proviso that the compound is not **MBX-7498**.

Claim 42. The compound or pharmaceutically acceptable salt of **Claim 41**, wherein Het¹ is



Claim 43. The compound or pharmaceutically acceptable salt of **Claim 41 - 42**, wherein **Ring A** is a structure of Formula (IV) or Formula (IV-B):



wherein m^a and m^b are independently 1 or 2;

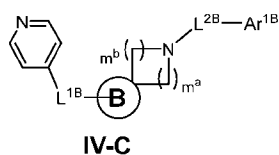
Ring B is a 4- to 10-membered monocyclic or bicyclic ring;

p^a and p^b are independently 0 or 1;

q is 0, 1, or 2;

* represents the point of attachment to L^{2B}, and ** represents the point of attachment to L^{1B}.

Claim 44. The compound or pharmaceutically acceptable salt of **Claim 41**, having the structure of Formula (IV-C):

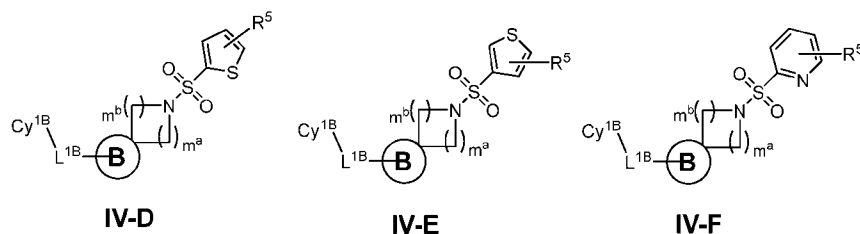


wherein m^a and m^b are independently 1 or 2;

Ring B is a 4- to 10-membered monocyclic or bicyclic ring;

with the proviso that the compound is not **MBX-7498**.

Claim 45. The compound or pharmaceutically acceptable salt of **Claim 41**, having the structure of Formula (IV-D), Formula (IV-E), or Formula (IV-F):



wherein Cy^{1B} is pyridyl or morpholine;

L^{1B} is a C₁-C₃ alkylene, *-O-(CH₂)₂-, -O-, where * represents the point of attachment to the pyridine ring;

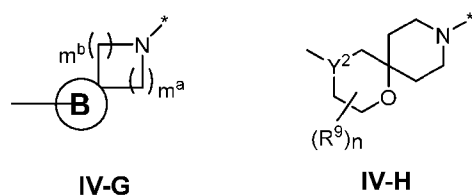
m^a and m^b are independently 1 or 2 and Ring B is a 4- to 10-membered monocyclic or bicyclic ring;

L^{2B} is -C(=O)- or -S(O)₂-;

R² is C₁-C₃ alkyl or C₁-C₃ haloalkyl; and

R⁵ is C₁-C₃ alkyl or halogen.

Claim 46. The compound or pharmaceutically acceptable salt of **Claim 41**, wherein **Ring A** is a structure of Formula (IV-G) or Formula (IV-H):



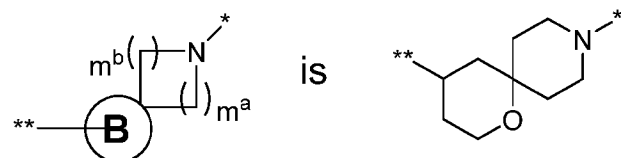
wherein Y² is CH or N;

m^a and m^b are independently 1 or 2;

n is 0 to 3; and

R⁹ is H, C₁-C₃ alkyl, or oxo.

Claim 47. The compound or pharmaceutically acceptable salt of **Claim 46**, wherein:



Claim 48. The compound or pharmaceutically acceptable salt of any one of **Claim 41 - 44** or **46 - 47**, wherein Ar^{1B} is a thiophene, a thiazole, a phenyl, or a pyridine.

Claim 49. The compound or pharmaceutically acceptable salt of **Claim 48**, wherein Ar^{1B} is an unsubstituted phenyl or a para-substituted phenyl.

Claim 50. The compound or pharmaceutically acceptable salt of **Claim 48**, wherein Ar^{1B} is an unsubstituted thiophene or a halo-substituted thiophene.

Claim 51. The compound or pharmaceutically acceptable salt of **Claim 48**, wherein Ar^{1B} is a para-substituted pyridine.

Claim 52. A compound selected from the group consisting of MBX-7705, MBX-7706, MBX-7707, MBX-7728, MBX-7729, MBX-7730, MBX-7731, MBX-7732, MBX-7769, MBX-7770, MBX-7771, MBX-7772, MBX-7773, MBX-7822, MBX-7868, MBX-7869, MBX-7870, MBX-7871, MBX-7872, MBX-7875, MBX-7876, MBX-7877, MBX-7910, MBX-7911, MBX-7912, MBX-7913, MBX-7914, MBX-7915, MBX-7950, MBX-7952, MBX-7953, MBX-7957, MBX-7959, MBX-7960, MBX-7964, MBX-8024, MBX-8026, MBX-8028, MBX-8029, MBX-8030, MBX-8031, MBX-8032, MBX-8066, MBX-8087, MBX-8088, MBX-8090, MBX-8092, MBX-8095, MBX-8098, MBX-8099, MBX-8143, MBX-8144, MBX-8145, MBX-8146, MBX-8186, MBX-8187, MBX-8192, MBX-8193, MBX-8219, MBX-8223, MBX-8224, MBX-8226, MBX-8240, MBX-8243, MBX-8246, MBX-8247, MBX-8249, MBX-8250, MBX-8251, MBX-8252, MBX-8281, MBX-8282, MBX-8285, MBX-8305, MBX-8306, MBX-8307, MBX-8308, MBX-8309, MBX-8310, MBX-8311, MBX-8323, MBX-8324, MBX-8345, MBX-8346, MBX-8354, MBX-8356, MBX-8357, MBX-8358, MBX-8390, MBX-8391, MBX-8394, MBX-8428, MBX-8429, MBX-8430, MBX-8431, MBX-8432, MBX-8433, MBX-8436, MBX-8439, MBX-8529, MBX-8619, MBX-8668, MBX-8684, MBX-8700, MBX-8701, MBX-8702, and mixtures thereof, or a pharmaceutically acceptable salt thereof.

Claim 53. A compound selected from the group consisting of MBX-7705, MBX-7706, MBX-7707, MBX-7728, MBX-7729, MBX-7730, MBX-7731, MBX-7732, MBX-7769, MBX-7770, MBX-7771, MBX-7772, MBX-7773, MBX-7822, MBX-7964, MBX-8024, MBX-8026, MBX-8028, MBX-8029, MBX-8030, MBX-8031, MBX-8032, MBX-8066, MBX-8087, MBX-8088, MBX-8090, MBX-8092, MBX-8095, MBX-8098, MBX-8099, MBX-8145, MBX-8146, MBX-8186, MBX-8187, MBX-8192, MBX-8193, MBX-8219, MBX-8223, MBX-8224, MBX-8226, MBX-8240, MBX-8243, MBX-8246, MBX-8247, MBX-8249, MBX-8252, MBX-8281, MBX-8282, MBX-8305, MBX-8307, MBX-8308, MBX-8309, MBX-8323, MBX-8324, MBX-8346, MBX-8354, MBX-8356, MBX-8357, MBX-8358, MBX-8390, MBX-8391, MBX-8394, MBX-8428, MBX-8429, MBX-8430, MBX-8431, MBX-8432, MBX-8436, MBX-8439, and mixtures thereof.

Claim 54. A compound selected from the group consisting of MBX-7868, MBX-7869, MBX-7870, MBX-7871, MBX-7872, MBX-7875, MBX-7876, MBX-7877, MBX-7910, MBX-7911, MBX-7912, MBX-7913, MBX-7914, MBX-7915, MBX-7950, MBX-7952, MBX-7953, MBX-7957, MBX-7959, MBX-7960, MBX-8143, MBX-8144, MBX-8250, MBX-8251, MBX-8285, MBX-8306, MBX-8310, MBX-8311, MBX-8345, MBX-8394, MBX-8433, and mixtures thereof.

Claim 55. A pharmaceutical composition comprising a compound of any one of **Claims 26 – 54**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

Claim 56. A method for treating a fungal infection in a subject, the method comprising administering to the subject the pharmaceutical composition of **Claim 55**.

Claim 57. A method for treating a fungal infection in a subject, the method comprising administering to the subject the compound of any one of **Claims 26 – 54**, or a pharmaceutically acceptable salt thereof.

Claim 58. The method of **Claim 56 - 57**, further comprising administering an antifungal agent to the subject.

Claim 59. The method of **Claim 2** or **Claim 58**, wherein the antifungal agent is a polyene antifungal, an azole antifungal, a thiazole antifungal, an allylamine antifungal, an echinocandin antifungal, ciclopirox, tolnaftate, flucytosine, or a combination thereof.

Claim 60. The method of **Claim 2** or **Claim 58**, wherein the antifungal agent is selected from the group consisting of natamycin, rimocidin, nystatin, amphotericin B, candicin, hamycin, perimycin, miconazole, ketoconazole, clotrimazole, econazole, omoconazole, bifonazole, butoconazole, fenticonazole, isoconazole, oxiconazole, sertaconazole, sulconazole, tioconazole, fluconazole, fosfluconazole, itraconazole, isavuconazole, ravuconazole, posaconazole, voriconazole, terconazole, albaconazole, abafungin, terbinafine, naftifin, butenafine, amorolfine, anidulafungin, caspofungin, micafungin, ciclopirox, tolnaftate, flucytosine, and a pharmaceutically acceptable salt or hydrate thereof, and combinations of any of the foregoing compounds and salts.

Claim 61. The method of **Claim 2** or **Claim 58**, wherein the antifungal agent is selected from the group consisting of miconazole, ketoconazole, clotrimazole, econazole, omoconazole, bifonazole, butoconazole, fenticonazole, isoconazole, oxiconazole, sertaconazole, sulconazole, tioconazole, fluconazole, fosfluconazole, itraconazole, isavuconazole, ravuconazole, posaconazole, voriconazole, terconazole, albaconazole, and a pharmaceutically acceptable salt or hydrate thereof, and combinations of any of the foregoing compounds and salts.

Claim 62. A method of potentiating antifungal activity of an azole antifungal agent, the method comprising administering to a subject the pharmaceutical composition of **Claim 55**.

Claim 63. The method of **Claim 62**, wherein the azole antifungal agent is fluconazole, itraconazole, ketoconazole, miconazole, voriconazole, posaconazole or ravuconazole.

Claim 64. The method of **Claim 62**, wherein the azole antifungal agent is selected from the group consisting of miconazole, ketoconazole, clotrimazole, econazole, omoconazole, bifonazole, butoconazole, fenticonazole, isoconazole, oxiconazole, sertaconazole, sulconazole, tioconazole, fluconazole, fosfluconazole, itraconazole, isavuconazole, ravuconazole, posaconazole, voriconazole, terconazole, albaconazole, and a pharmaceutically acceptable salt or hydrate thereof, and combinations of any of the foregoing compounds and salts.

Claim 65. The method of any one of **Claims 62 - 64**, further comprising identifying the subject as having a drug-resistant fungal infection.

Claim 66. The method of any one of **Claims 62 - 64**, further comprising identifying the subject as having an azole-resistant fungal infection.

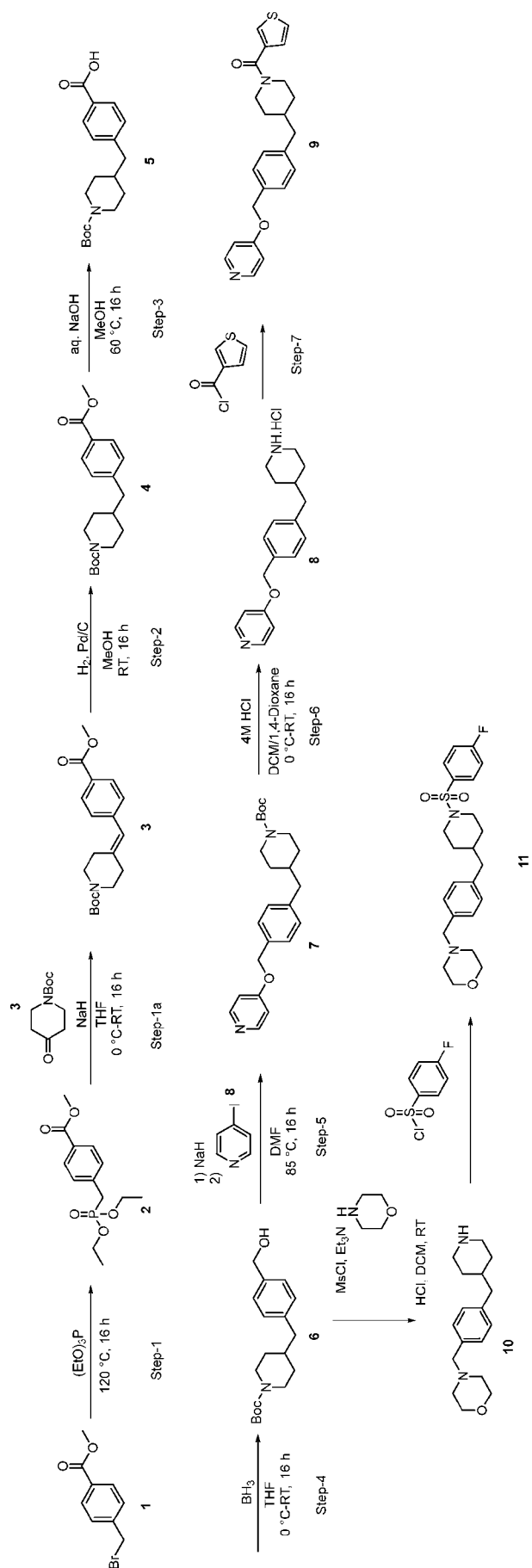


FIG. 1

