

COMPOSITIONS AND METHODS FOR THE TREATMENT AND PREVENTION OF NEUROLOGICAL DISORDERS

Sequence Listing

5 The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on June 19, 2019, is named 51061-029WO2_Sequence_Listing_6.19.19_ST25 and is 18,129 bytes in size.

Field of the Invention

10 The invention relates to the field of therapeutic treatment of neurological disorders in patients, such as human patients.

Background of the Invention

 Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is an aggressive,
15 debilitating neurological disorder in which affected patients succumb within 2 to 5 years after diagnosis. ALS presents with heterogeneous clinical features but has a common underlying pathology of motor neuron loss that limits the central nervous system's ability to effectively regulate voluntary and involuntary muscle activity. Additionally, without neuronal trophic support muscles being to atrophy, further
20 exacerbating motor deterioration. Cellular and tissue degeneration results in motor impairment such as fasciculations and weakening in the arms, legs and neck, difficulty swallowing, slurred speech and ultimately failure of the diaphragm muscles that control breathing. There remains a need for a treatment paradigm for ALS, as well as various other neurological disorders.

Summary

25 The present disclosure relates to compositions and methods for treating neurological disorders, such as amyotrophic lateral sclerosis, among others, including neuromuscular disorders and various other neurological conditions. Using the compositions and methods described herein, a patient having a neurological disorder, such as amyotrophic lateral sclerosis, frontotemporal degeneration (also referred to as frontotemporal lobar degeneration and frontotemporal dementia), Alzheimer's disease, Parkinson's
30 disease, dementia with Lewy Bodies, corticobasal degeneration, progressive supranuclear palsy, dementia parkinsonism ALS complex of Guam, Huntington's disease, Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia (IBMPFD), sporadic inclusion body myositis, myofibrillar myopathy, dementia pugilistica, chronic traumatic encephalopathy, Alexander disease, or hereditary inclusion body myopathy may be administered an inhibitor of cytochrome P450 (CYP450)
35 isoform 51A1 (CYP51A1), also referred to herein as lanosterol 14-alpha demethylase, so as to treat an underlying etiology of the disorder and/or to alleviate one or more symptoms of the disease.

 The inhibitor of CYP51A1 may be, e.g., a small molecule, such as LEK-935, CP-320626, itraconazole, posaconazole, cyproconazole, voriconazole, fluconazole, clotrimazol, fenticonazole, epoxiconazole, ketoconazole, ravuconazole, isavuconazole, holothurin A, theasaponin, capsicosine,
40 betulafolientriol, prochloraz, propiconazole, prothioconazole, prothioconazole-desthio, tebuconazole,

triadimenol, azalanstat, or a variant thereof. In some examples, the CYP51A1 inhibitor is an anti-CYP51A1 antibody or antigen-binding fragment thereof, or a compound, such as an interfering RNA molecule, that attenuates CYP51A1 expression.

5 Patients that may be treated using the compositions and methods described herein include those that exhibit, and/or that are prone to develop, aggregation of TAR-DNA binding protein (TDP)-43. Example of patients that may exhibit or may be prone to exhibit TDP-43 aggregation are those that express a mutant TDP-43 isoform containing a mutation that renders this protein susceptible to aggregation. For example, patients that may be treated using the compositions and methods described herein include those expressing a TDP-43 isoform having a mutation selected from Q331K, M337V,
10 Q343R, N345K, R361S, and N390D, among others that are associated with TDP-43 aggregation and toxicity in vivo.

In one example, the disclosure features a method of treating a neurological disorder in a patient, such as a human patient, by providing to the patient a therapeutically effective amount of a CYP51A1 inhibitor. In one aspect, the present disclosure refers to use of a CYP51A1 inhibitor in the manufacture of
15 a medicament for treating a neurological disorder in a human patient.

In another example, the disclosure features a method of treating a neurological disorder in a patient, such as a human patient, identified as likely to benefit from treatment with a CYP51A1 inhibitor on the basis of TDP-43 aggregation. In one aspect, the present disclosure refers to use of a CYP51A1 inhibitor in the manufacture of a medicament for treating a human patient having a neurological disorder,
20 wherein the patient is informed of the patient's likely benefiting from treatment with the CYP51A1 inhibitor, as the patient is determined as being susceptible to developing TDP-43 aggregation. In this example, the method may include (i) determining that the patient exhibits, or is prone to develop, TDP-43 aggregation, and (ii) providing to the patient a therapeutically effective amount of a CYP51A1 inhibitor. In some examples, the patient has previously been determined to exhibit, or to be prone to developing, TDP-43
25 aggregation, and the method includes providing to the patient a therapeutically effective amount of a CYP51A1 inhibitor. The susceptibility of the patient to developing TDP-43 aggregation may be determined, e.g., by determining whether the patient expresses a mutant isoform of TDP-43 containing a mutation that is associated with TDP-43 aggregation and toxicity, such as a mutation selected from Q331K, M337V, Q343R, N345K, R361S, and N390D. This may be performed, for example, by
30 determining the amino acid sequence of a TDP-43 isoform isolated from a sample obtained from the patient or by determining the nucleic acid sequence of a TDP-43 gene isolated from a sample obtained from the patient. In some examples, the method includes the step of obtaining the sample from the patient.

In one aspect, the present disclosure refers to use of a CYP51A1 inhibitor in the manufacture of a
35 medicament for treating a human patient having a neurological disorder, wherein the patient is informed of the patient's likely benefiting from treatment with the CYP51A1 inhibitor, as the patient is determined as expressing a mutant of TDP-43 having a mutation associated with TDP-43 aggregation.

In an additional example, the disclosure features a method of treating a neurological disorder in a patient, such as a human patient, identified as likely to benefit from treatment with a CYP51A1 inhibitor on the basis of TDP-43 expression. In this example, the method includes (i) determining that the patient expresses a mutant form of TDP-43 having a mutation associated with TDP-43 aggregation (e.g., a mutation selected from Q331K, M337V, Q343R, N345K, R361S, and N390D), and (ii) providing to the patient a therapeutically effective amount of a CYP51A1 inhibitor. In some examples, the patient has previously been determined to express a mutant form of TDP-43 having a mutation associated with TDP-
40 43 aggregation, such as a Q331K, M337V, Q343R, N345K, R361S, or N390D mutation, and the method includes providing to the patient a therapeutically effective amount of a CYP51A1 inhibitor.

In another example, the disclosure features a method of determining whether a patient (e.g., a human patient) having a neurological disorder is likely to benefit from treatment with a CYP51A1 inhibitor by (i) determining whether the patient exhibits, or is prone to develop, TDP-43 aggregation and (ii)

identifying the patient as likely to benefit from treatment with a CYP51A1 inhibitor if the patient exhibits, or is prone to develop, TDP-43 aggregation. In some examples, the method further includes the step of (iii) informing the patient whether he or she is likely to benefit from treatment with a CYP51A1 inhibitor. The susceptibility of the patient to developing TDP-43 aggregation may be determined, e.g., by determining
5 whether the patient expresses a mutant isoform of TDP-43 containing a mutation that is associated with TDP-43 aggregation and toxicity, such as a mutation selected from Q331K, M337V, Q343R, N345K, R361S, and N390D. This may be performed, for example, by determining the amino acid sequence of a TDP-43 isoform isolated from a sample obtained from the patient or by determining the nucleic acid sequence of a TDP-43 gene isolated from a sample obtained from the patient. In some examples, the
10 method includes the step of obtaining the sample from the patient.

In another example, the disclosure features a method of determining whether a patient (e.g., a human patient) having a neurological disorder is likely to benefit from treatment with a CYP51A1 inhibitor by (i) determining whether the patient expresses a TDP-43 mutant having a mutation associated with TDP-43 aggregation (e.g., a mutation selected from Q331K, M337V, Q343R, N345K, R361S, and
15 N390D) and (ii) identifying the patient as likely to benefit from treatment with a CYP51A1 inhibitor if the patient expresses a TDP-43 mutant. In some examples, the method further includes the step of (iii) informing the patient whether he or she is likely to benefit from treatment with a CYP51A1 inhibitor. The TDP-43 isoform expressed by the patient may be assessed, for example, by isolated TDP-43 protein from a sample obtained from the patient and sequencing the protein using molecular biology techniques
20 described herein or known in the art. In some examples, the TDP-43 isoform expressed by the patient is determined by analyzing the patient's genotype at the TDP-43 locus, for example, by sequencing the TDP-43 gene in a sample obtained from the patient. In some examples, the method includes the step of obtaining the sample from the patient.

In some examples of any of the above aspects, the CYP51A1 inhibitor is provided to the patient
25 by administration of the CYP51A1 inhibitor to the patient. In some examples, the CYP51A1 inhibitor is provided to the patient by administration of a prodrug that is converted in vivo to the CYP51A1 inhibitor.

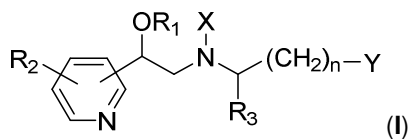
In some examples of any of the above aspects, the neurological disorder is a neuromuscular disorder, such as a neuromuscular disorder selected from amyotrophic lateral sclerosis, congenital myasthenic syndrome, congenital myopathy, cramp fasciculation syndrome, Duchenne muscular
30 dystrophy, glycogen storage disease type II, hereditary spastic paraplegia, inclusion body myositis, Isaac's Syndrome, Kearns-Sayre syndrome, Lambert-Eaton myasthenic syndrome, mitochondrial myopathy, muscular dystrophy, myasthenia gravis, myotonic dystrophy, peripheral neuropathy, spinal and bulbar muscular atrophy, spinal muscular atrophy, Stiff person syndrome, Troyer syndrome, and Guillain-Barré syndrome. In some examples, the neurological disorder is amyotrophic lateral sclerosis.

In some examples of any of the above aspects, the neurological disorder is selected from
35 frontotemporal degeneration (also referred to as frontotemporal lobar degeneration and frontotemporal dementia), Alzheimer's disease, Parkinson's disease, dementia with Lewy Bodies, corticobasal degeneration, progressive supranuclear palsy, dementia parkinsonism ALS complex of Guam, Huntington's disease, Inclusion body myopathy with early-onset Paget disease and frontotemporal

dementia (IBMPFD), sporadic inclusion body myositis, myofibrillar myopathy, dementia pugilistica, chronic traumatic encephalopathy, Alexander disease, and hereditary inclusion body myopathy.

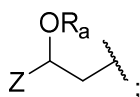
In some examples of any of the above aspects, the CYP51A1 inhibitor is a small molecule antagonist of CYP51A1 activity. The CYP51A1 inhibitor may be, for example, a compound represented

5 by formula (I)

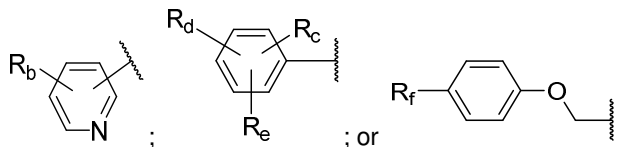


wherein n is 1 or 2;

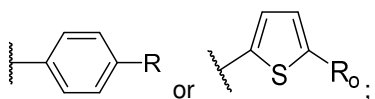
X is hydrogen, lower alkyl, lower alkoxy-lower alkyl, or a group X_a of the formula:



10 Z is a group of the formula:



Y is a group of the formula:



R₀ is lower alkyl, COR₄ or C(R₅)=CHCOR₄;

15 R is R₀ or is OR["];

R["] is hydrogen, lower-alkyl, lower alkanoyl, (CH₂)₁₋₆-OH, (CH₂)₁₋₆-O(CH₂)₁₋₆-R₆, or (CH₂)₁₋₆-COR₄;

R₁ and R_a are hydrogen, lower alkanoyl, benzoyl or (CH₂)₁₋₆-OH;

R₂ and R_b are hydrogen, Cl, Br or CF₃;

R₃ and R₅ are hydrogen or CH₃;

20 R₄ is hydroxy, lower-alkoxy or N(R₇, R₈);

R₆ is hydrogen, R_g, OH or COR₄;

R₇ and R₈ are hydrogen or lower alkyl;

R_c and R_e are hydrogen, Cl, F, Br or CF₃;

R_d is hydrogen or NH₂;

25 R_f is hydrogen, CH₃CONH-, NH₂COCH₂- or R₉CH₂CH₂OCH₂CH₂O-;

R_g and R₉ are phenyl or phenyl substituted by Cl, F or Br;

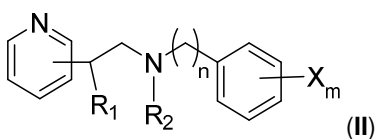
or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples of formula (I), n is 1, R₁ is hydrogen, R₂ is chlorine in the 6-position of a 2-pyridyl residue and Y is phenyl substituted in the p-position by R.

30 In some examples of formula (I), X is X^a; R^a is hydrogen; Z is 6-chloro-2-pyridyl, and Y is phenyl substituted in the p-position by 2-ethoxyethoxy, 2-phenethoxyethoxy or methoxycarbonylmethoxy.

In some examples of formula (I), the compound is methyl α,α' -[[[(R)-p-(2-ethoxyethoxy)- α -methylphen-ethyl]imino]dimethylene]bis[(RS)-6-chloro-2-pyridinemethanol]; (RS)-6-chloro- α -[[[(R)-p-(2-ethoxyethoxy)- α -methyl-phenethyl]amino]methyl]-2-pyridinemethanol; α,α' -[[[p-(2-ethoxyethoxy)phenethyl]imino]dimethylene]bis[(RS)-6-chloro-2-pyridinemethanol]; (R)-6-bromo- α -[[[(RS)-2-(6-bromo-2-pyridyl)-2-hydroxyethyl]][(R)-p-(2-ethoxyethoxy)- α -methylphenethyl]-amino]methyl]-2-pyridimidinemethanol; (R)-6-chloro- α -[[[(S)-2-(6-chloro-2-pyridyl)-2-hydroxyethyl]][(R)-.alpha.-methyl-p-(2-phenethoxyethoxy)phenethyl]amino]methyl]-2-pyridinemethanol, or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples, the CYP51A1 inhibitor is a compound represented by formula (II)



wherein n is 1, 2, 3, or 4 and m is 0, 1, 2, 3, 4, or 5;

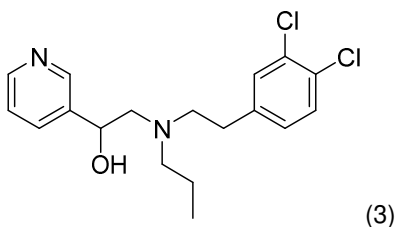
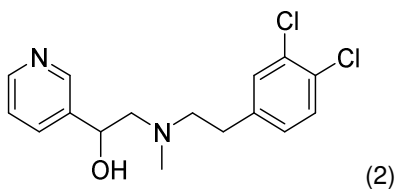
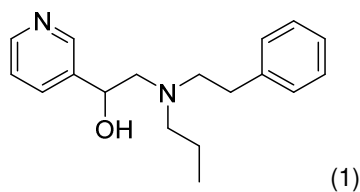
R₁ is a hydrogen atom, hydroxyl group, or lower C₁₋₆ alkoxy group;

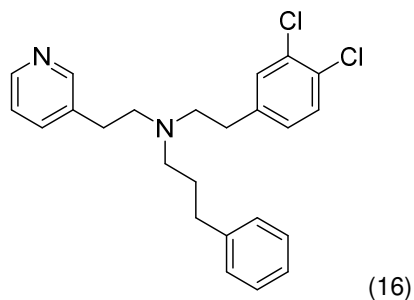
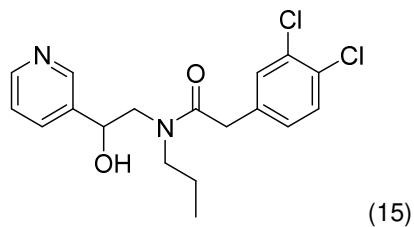
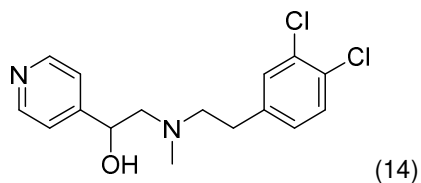
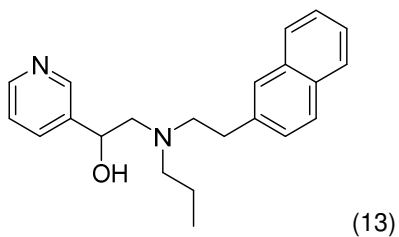
R₂ is a hydrogen atom or an optionally substituted straight or branched lower C₁₋₆ alkyl group (e.g., an aryl lower alkyl group, such as a phenyl lower alkyl group); and

each X is independently fluorine, chlorine, bromine, hydroxyl group, trifluoromethyl group, 3,4-di-Cl, 2,4-di-Cl or lower C₁₋₆ alkoxy group, and wherein the phenyl ring containing the X is optionally fused (so as to form, e.g., a naphthyl ring);

or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples, the CYP51A1 inhibitor is a compound represented by formula (1), (2), (3), (13), (14), (15), or (16)

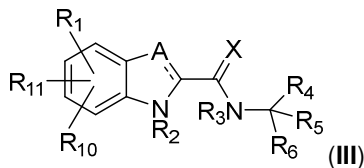




5 or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples, n is an integer 2, R₁ is a hydroxyl group, R₂ a methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl group and X is a hydrogen atom or phenyl disubstituted with two chlorine atoms in the positions 3 and 4 or in the positions 2 and 4.

In some examples, the CYP51A1 inhibitor is a compound represented by formula (III)



10

wherein the dotted line (---) is an optional bond;

X is O or S;

A is —C(H)=, —C((C₁-C₄)alkyl)=, —C(halo)= or —N=, when the dotted line (---) is a bond, or A is methylene or —CH((C₁-C₄)alkyl)—, when the dotted line (---) is not a bond;

15

R₁, R₁₀, and R₁₁ are each independently H, halo, cyano, 4-, 6-, or 7-nitro, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, fluoromethyl, difluoromethyl or trifluoromethyl;

R₂ is H;

R₃ is H or (C₁-C₆)alkyl;

R₁₂ is morpholino, thiomorpholino, 1-oxothiomorpholino, 1,1-dioxothiomorpholino, thiazolidin-3-yl, 1-oxothiazolidin-3-yl, 1,1-dioxothiazolidin-3-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, piperazin-4-yl, azetidin-1-yl, 1,2-oxazinan-2-yl, pyrazolidin-1-yl, isoxazolidin-2-yl, isothiazolidin-2-yl, 1,2-oxazetidin-2-yl, oxazolidin-3-yl, 3,4-dihydroisoquinolin-2-yl, 1,3-dihydroisoindol-2-yl, 3,4-dihydro-2H-quinol-1-yl, 2,3-dihydro-benzo[1,4]oxazin-4-yl, 2,3-dihydro-benzo[1,4]-thiazine-4-yl, 3,4-dihydro-2H-quinoxalin-1-yl, 3,4-dihydro-benzo[c][1,2]oxazin-1-yl, 1,4-dihydro-benzo[d][1,2]oxazin-3-yl, 3,4-dihydro-benzo[e][1,2]-oxazin-2-yl, 3H-benzo[d]isoxazol-2-yl, 3H-benzo[c]isoxazol-1-yl or azepan-1-yl,

wherein the R₁₂ rings are optionally mono-, di- or tri-substituted independently with halo, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, hydroxy, amino, mono-N— or di-N,N—(C₁-C₅)alkylamino, formyl, carboxy, carbamoyl, mono-N— or di-N,N—(C₁-C₅)alkylcarbamoyl, (C₁-C₆)alkoxy(C₁-C₃)alkoxy, (C₁-C₅)alkoxycarbonyl, benzyloxycarbonyl, (C₁-C₅)alkoxycarbonyl(C₁-C₅)alkyl, (C₁-C₄)alkoxycarbonylamino, carboxy(C₁-C₅)alkyl, carbamoyl(C₁-C₅)alkyl, mono-N— or di-N,N—(C₁-C₅)alkylcarbamoyl(C₁-C₅)alkyl, hydroxy(C₁-C₅)alkyl, (C₁-C₄)alkoxy(C₁-C₄)alkyl, amino(C₁-C₄)alkyl, mono-N— or di-N,N—(C₁-C₄)alkylamino(C₁-C₄)alkyl, oxo, hydroxylmino or (C₁-C₆)alkoxylmino and wherein no more than two substituents are selected from oxo, hydroxylmino or (C₁-C₆)alkoxylmino and oxo, hydroxylmino or (C₁-C₆)alkoxyimino are on nonaromatic carbon; and

the R₁₂ rings are optionally additionally mono- or di-substituted independently with (C₁-C₅)alkyl or halo;

or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples of formula (III), R₈ and R₉, together with the nitrogen to which they are bound, form an optionally fused, optionally substituted 5 or 6-membered heterocyclic ring, such as an optionally substituted piperazine ring (e.g., a 4-hydroxypiperazine ring).

In some examples of formula (III), when R₆ is (C₁-C₅)alkoxycarbonyl or benzyloxycarbonyl then R₁ is 5-halo, 5-(C₁-C₄)alkyl or 5-cyano and R₄ is (phenyl)(hydroxy)(C₁-C₄)alkyl, (phenyl)((C₁-C₄)alkoxy)(C₁-C₄)alkyl, hydroxymethyl or Ar(C₁-C₂)alkyl, wherein Ar is thien-2- or -3-yl, fur-2- or -3-yl or phenyl wherein the Ar is optionally mono- or di-substituted independently with halo; with the provisos that when R₄ is benzyl and R₅ is methyl, R₁₂ is not 4-hydroxy-piperidin-1-yl or when R₄ is benzyl and R₅ is methyl R₆ is not C(O)N(CH₃)₂.

In some examples of formula (III), when R₁, R₁₀, and R₁₁ are H, R₄ is not imidazol-4-ylmethyl, 2-phenylethyl or 2-hydroxy-2-phenylethyl.

In some examples of formula (III), when both R₈ and R₉ are n-pentyl, none of R₁ is 5-chloro, 5-bromo, 5-cyano, 5(C₁-C₅)alkyl, 5(C₁-C₅)alkoxy or trifluoromethyl.

In some examples of formula (III), when R₁₂ is 3,4-dihydroisoquinol-2-yl, the 3,4-dihydroisoquinol-2-yl is not substituted with carboxy((C₁-C₄)alkyl).

In some examples of formula (III), when R₈ is H and R₉ is (C₁-C₆)alkyl, R₉ is not substituted with carboxy or (C₁-C₄)alkoxycarbonyl on the carbon which is attached to the nitrogen atom N of NHR₉.

In some examples of formula (III), when R₆ is carboxy and R₁, R₁₀, R₁₁ and R₅ are all H, then R₄ is not benzyl, H, (phenyl)(hydroxy)methyl, methyl, ethyl or n-propyl.

Exemplary compounds of formula (III) are those belonging to a first group of compounds in which:

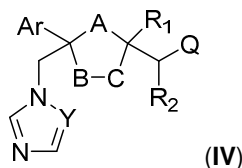
R₁ is 5H, 5-halo, 5-methyl, 5-cyano or 5-trifluoromethyl;

R₁₀ and R₁₁ are H; and

R₄ is H.

Further exemplary compounds of formula (III) that may be used in conjunction with the compositions and methods described herein include those in which R₁ is 5-chloro.

5 In some examples, the CYP51A1 inhibitor is a compound represented by formula (IV)

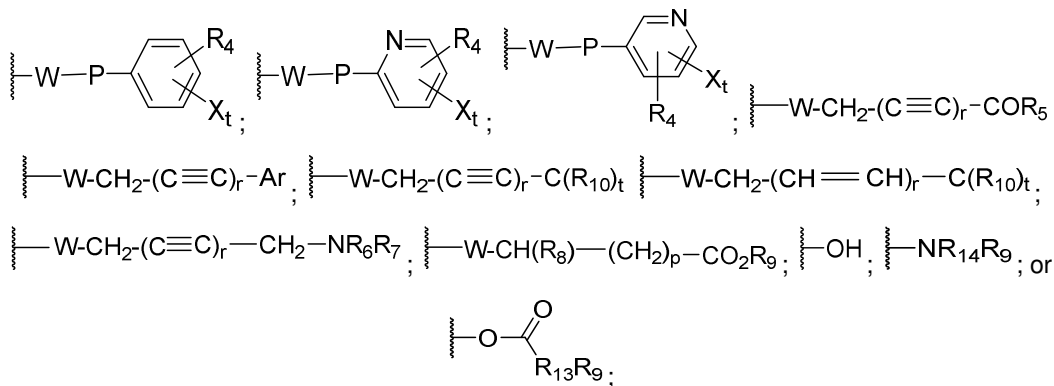


wherein Ar is thienyl, pyridyl, biphenyl, phenyl or phenyl substituted by one or more of halo, nitro, cyano, lower alkyl, lower alkoxy or perhalo(lower)alkyl;

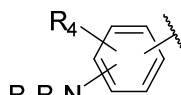
Y is CH or N;

10 either one of A, B and C is oxygen and the remaining two of A, B and C are CH₂; or A is oxygen, B is CH₂, and C is a direct bond;

Q is:



W is -NR₅-, -O-, or -S(O)_n-;

X is -NO₂, -P-NR₆R₇, , , Ar, OR₃ or halogen;

P is a direct bond, -CHR₁₁- or -CHR₁₁CHR₁₂-;

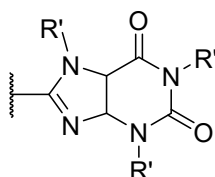
20 R₁, R₈, R₉ and R₁₀ are independently hydrogen, lower alkyl or lower alkyl substituted by one or more hydroxy groups;

R₂, R₄, R₁₁, R₁₂ and R₁₄ are hydrogen, hydroxy, lower alkyl or lower alkyl substituted by one or more hydroxy groups;

R₃ and R₁₃ are independently hydrogen, lower alkyl, (C₂-C₈) perhaloalkanoyl or (C₂-C₈) alkanoyl;

25 R₆ and R₇ are independently hydrogen, lower alkyl, phenyl or phenyl substituted by one or more of halo, perhalo(lower)alkyl, (C₂-C₈)alkanoyl, lower alkyl, lower alkyl substituted by one or more hydroxy groups, lower alkoxy, or 2-(lower)alkyl-3-oxo-1,2,4-triazol-4-yl, or R₆ and R₇ taken together with the nitrogen atom in NR₆ R₇ form unsubstituted or substituted 5- or 6-membered heterocyclyl ring systems containing carbon and one to four heteroatoms chosen from N, O and S, the heterocyclyl substituents
30 being (C₁-C₈)alkanoyl, lower alkyl, lower alkoxy, aminocarbonyl, N-lower alkylaminocarbonyl,

N,N-di(lower alkyl)amino carbonyl, aminothiocarbonyl, N-lower alkylaminothiocarbonyl, N,N-di(lower alkyl)aminothiocarbonyl, lower alkyl sulfonyl, phenyl-substituted lower alkyl sulfonyl, N-lower alkylamino, N,N-di(lower alkyl)amino, 1,3-imidazol-1-yl, 2-loweralkylsulfenyl-1,3-imidazol-1-yl, 2-pyridinyl, 2-thiazolyl, 2-lower alkyl-3-oxo-1,2,4-triazol-4-yl, 1-lower alkylbenzimidazol-2-yl, phenyl or phenyl substituted by one or more of halo, perhalo lower alkyl, (C₂-C₈) alkanoyl, lower alkyl, lower alkyl substituted by one or more hydroxy group, lower alkoxy, 1H,2,4-triazol-1-yl, 2-lower alkyl-3-oxo-1,2,4-triazol-4-yl, or a substituent represented by the formula:



R₅ is a lower alkyl, lower alkoxy, amino, N,N-dilower alkylamino, phenyl or phenyl substituted by one or more of halo, perhalo lower alkyl, lower alkoxy, nitro, cyano, (C₂-C₈)alkanoyl;

p is 0, 1, 2, 3, 4 or 5;

n is 0, 1 or 2;

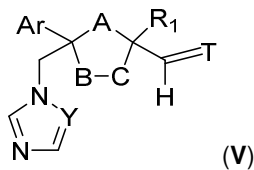
r is 1 or 2; and

t is 0, 1, 2 or 3;

or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples of formula (IV), when R₂, R₁₁, or R₁₂ is attached to a carbon atom adjacent to -NR₅, -S(O)_n or -O-, the R₂, R₁₁, or R₁₂ is not hydroxy.

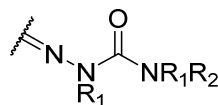
In some examples, the CYP51A1 inhibitor is a compound represented by formula (V)



wherein Y and Ar are as defined for formula (IV) herein;

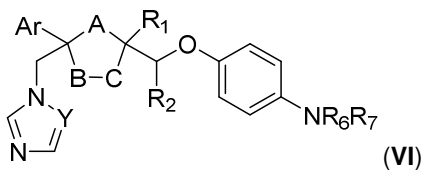
one of A, B or C is oxygen and the remaining two of A, B, or C are -CH₂-;

T is =O, =NOR₁, =NNR₁ R₂ or



wherein R₁ is hydrogen, lower alkyl or lower alkyl substituted by one or more hydroxy groups; and R₂ is hydrogen, hydroxy, lower alkyl or lower alkyl substituted by one or more hydroxy groups; or a pharmaceutically acceptable salt, ester, or ether thereof.

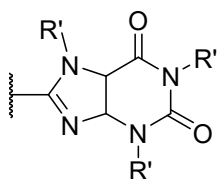
In some examples, the CYP51A1 inhibitor is a compound represented by formula (VI)



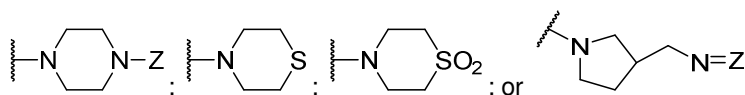
wherein Y, Ar, R₁, R₂, R₆ and R₇ are as previously defined for formula (IV) herein, and either one of A, B and C is oxygen and the remaining two of A, B and C are CH₂, or A is oxygen, B is CH₂, and C is a direct bond;

5 or a pharmaceutically acceptable salt, ester, or ether thereof.

Exemplary compound of formula (VI) for use in conjunction with the compositions and methods described herein are those in which NR₆ R₇ form unsubstituted or substituted 5- or 6-membered heterocyclyl ring systems containing carbon and one to four heteroatoms chosen from N, O and S, the heterocyclyl substituents being (C₁ -C₈) alkanoyl, lower alkyl, lower alkoxy, carbonyl, aminocarbonyl, N-lower alkylaminocarbonyl, N,N-di(lower alkyl)aminocarbonyl, aminothiocarbonyl, N-lower alkylaminothiocarbonyl, N,N-di(lower alkyl)aminothiocarbonyl, lower alkyl sulfonyl, phenyl-substituted lower alkyl sulfonyl, N-lower alkyl-amino, N,N-di(lower alkyl)amino, 1,3-imidazol-1-yl, 2-loweralkylsulfenyl-1,3-imidazol-1-yl, 2-pyridinyl, 2-thiazolyl, 2-lower alkyl-3-oxo-1,2,4-triazol-4-yl, 1-lower alkylbenzimidazol-2-yl, phenyl, phenyl substituted by one or more of halo, perhalo lower alkyl, (C₂ -C₈) alkanoyl, lower alkyl, lower alkyl substituted by one or more hydroxy groups, lower alkoxy, 1H,2,4-triazol-1-yl or 2-lower alkyl-3-oxo-1,2,4-triazol-4-yl; R₅ is a lower alkyl, amino, N,N-dilower alkylamino, or

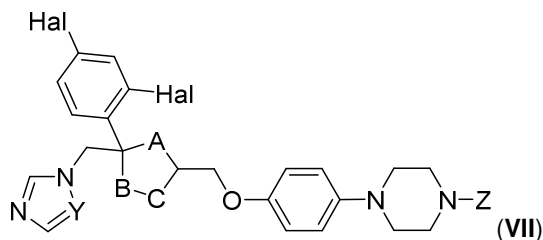


In some examples of formula (VI), the NR₆R₇ is:



20 wherein Z is hydrogen, (C₁ -C₈) alkanoyl, lower alkyl, (C₁ -C₈) perhaloalkanoyl or phenyl substituted by 2-loweralkyl-3-oxo-1,2,4-triazol-4-yl.

In some examples, the CYP51A1 inhibitor is a compound represented by formula (VII)

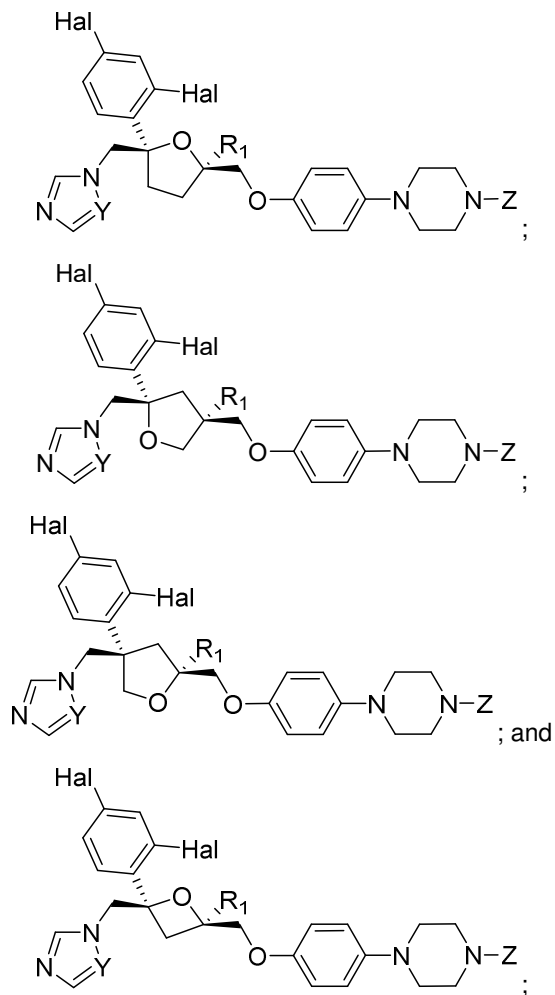


25 wherein one of A, B and C is oxygen and the remaining two of A, B and C are -CH₂-, or two of A, B and C are -CH₂-;

each Hal is independently a halogen, such as Cl or F; and

Z is lower alkyl, (C₂-C₈)alkanoyl, or optionally substituted phenyl, such as phenyl substituted by 2-loweralkyl-3-oxo-1,2,4triazol-4-yl;
or a pharmaceutically acceptable salt, ester, or ether thereof.
In some examples of formula (VII), the compound is selected from:

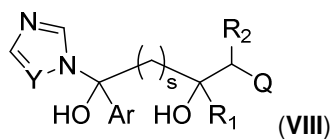
5



or a pharmaceutically acceptable salt, ester, or ether thereof.

10

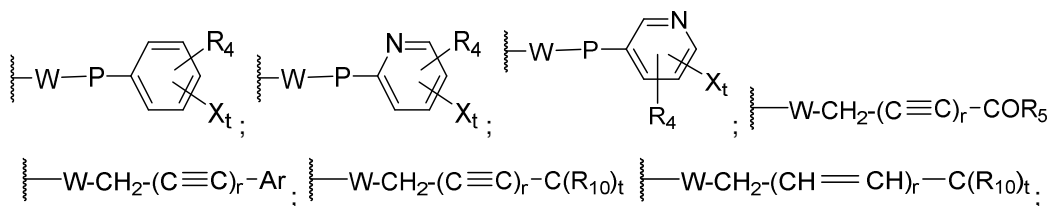
In some examples, the CYP51A1 inhibitor is a compound represented by formula (VIII)



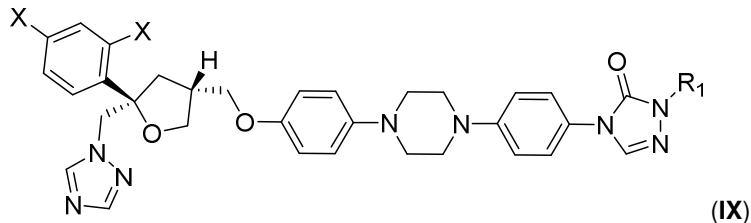
wherein Ar is thienyl, pyridyl, biphenyl, phenyl, or phenyl substituted by one or more of halo, nitro, cyano, lower alkyl, lower alkoxy or perhalo(lower)alkyl;

Q is:

15



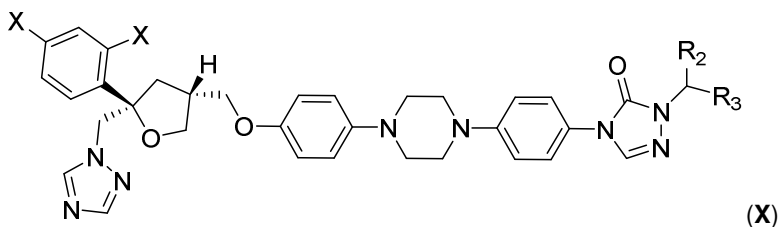
In some examples, the CYP51A1 inhibitor is a compound represented by formula (IX)



wherein each X is independently a halogen, such as F or Cl; and

- R₁ is a straight or branched chain (C₃ to C₈) alkyl group optionally substituted by one or two hydroxy moieties or by one or two groups convertible in vivo into hydroxy moieties; or a pharmaceutically acceptable salt, ester, or ether thereof.

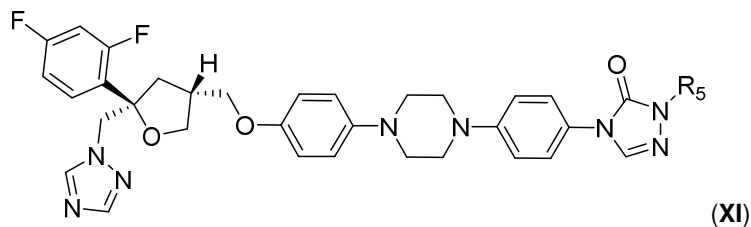
In some examples of formula (IX), the compound is represented by formula (X)



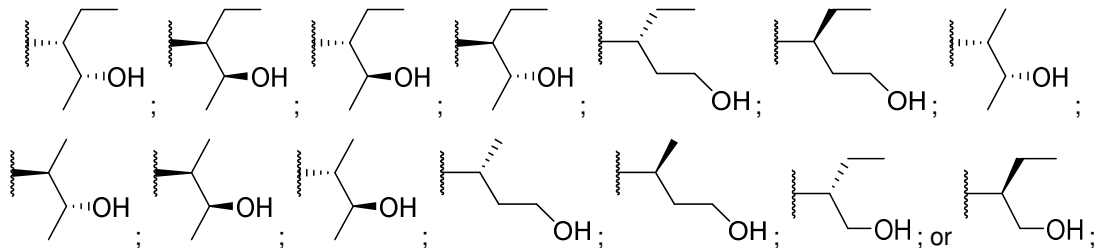
wherein each X is independently a halogen, such as F or Cl; and

- R₂ is H or (C₁-C₃) alkyl and R₃ is (C₁-C₃) alkyl optionally substituted by one hydroxy moiety or by a group convertible in vivo into a hydroxy moiety; or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples of formula (X), the compound is represented by formula (XI)

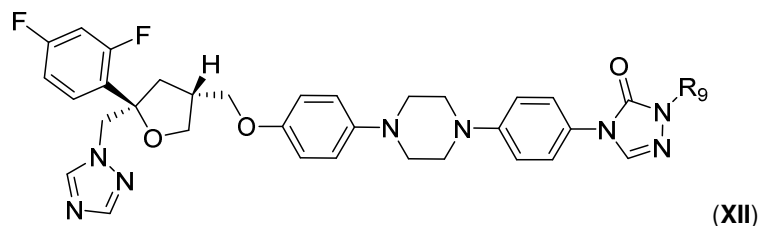


- wherein R₅ is:



or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples of formula (XI), the compound is represented by formula (XII)

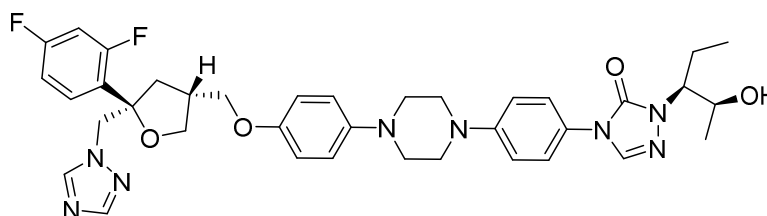


wherein R_9 is $-H(C_2H_5)CH(R_6)CH_3$ or $-H(CH_3)CH(R_6)CH_3$;

R_6 is OH or a group convertible in vivo into OH;

or a pharmaceutically acceptable salt, ester, or ether thereof.

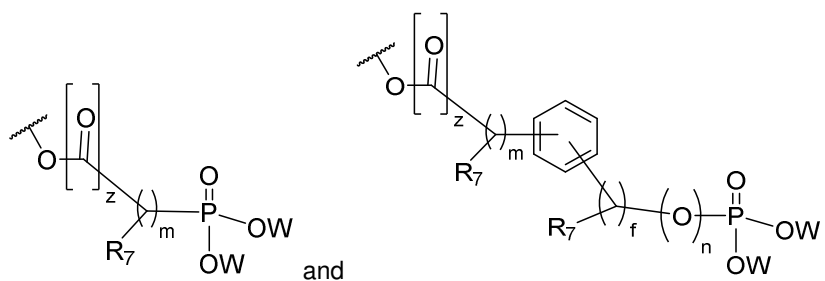
5 In some examples of formula (XII), the compound is:



or a pharmaceutically acceptable salt, ester, or ether thereof.

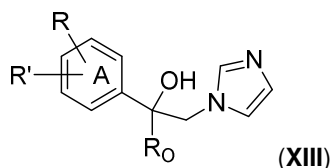
In some examples of formulas (IX) – (XII), the compound is an ester of the corresponding structural formula, such as a phosphate ester. The phosphate ester may be, for example, a phosphate ester selected from

10



wherein z is 0 or 1, R_7 is a $(C_1 - C_6)$ straight or branched chain alkyl group or H, f and n are independently an integer from 0 to 6, m is zero or 1 and W is H, CH_2 Ar or and Ar is phenyl, phenyl substituted by halo, nitro, cyano or trihalomethyl.

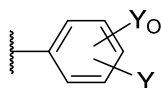
15 In some examples, the CYP51A1 inhibitor is a compound represented by formula (XIII)



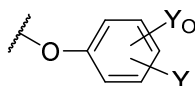
wherein R_0 is alkyl of 2 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, cycloalkyl-alkyl in which the cycloalkyl is of 3 to 6 carbon atoms and the alkyl portion of 1 to 3 carbon atoms, the cycloalkyl and cycloalkyl-alkyl being optionally ring substituted by one or two alkyl groups of 1 to 3 carbon atoms;

20 R is hydrogen, fluoro, chloro, bromo, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkylthio of 1 to 4 carbon atoms or nitro;

R' is hydrogen, fluoro, chloro, bromo, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkylthio of 1 to 4 carbon atoms, -CF₃ in the 3-position of Ring A, nitro, -CN, -COOR", an optionally substituted phenyl group of the formula:



5 or an optionally substituted phenoxy group in the 4-position of Ring A and having the formula:



R" is hydrogen, alkyl of 1 to 4 carbon atoms or a cation, preferably an agriculturally acceptable cation, or R and R' together represent alkylenedioxy of 1 or 2 carbon atoms substituted onto adjacent carbon atoms of the phenyl Ring A; and

10 Y_O and Y are independently hydrogen, fluoro, chloro, bromo, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms;

or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples of formula (XIII), when R_O is n-butyl: (a) at least one of R and R' is other than hydrogen and (b) R and R' are not both halo.

15 In some examples, the CYP51A1 inhibitor is an α-[aryl(alkylene)_m]-α-[CR₁R₂-(CHR₃)_n-R₄]1H-1,2,4-triazole-1-ethanol (formula (XIV-A)) or an α-[aryl(alkylene)_m]-α-[CR₁R₂-(CHR₃)_n-R₄]1H-imidazole-1-ethanol (formula (XIV-B)), or a pharmaceutically acceptable salt, ester, or ether thereof, wherein:

20 R₁ is C₁₋₅ alkyl, unsubstituted or substituted by halogen, by C₁₋₅ -alkoxy, by phenyl-C₁₋₃ alkoxy, by phenoxy, by C₁₋₅ alkylthio, by phenyl-C₁₋₃ alkylthio or by phenylthio, whereby optional phenyl groups may be substituted by C₁₋₅ alkyl, halogen, halogen substituted C₁₋₅ alkyl, C₁₋₅ alkoxy or halogen substituted C₁₋₅ alkoxy; or

is C₂₋₅ alkenyl or C₂₋₅ alkynyl, unsubstituted or substituted by halogen; or

is cycloalkyl, unsubstituted or substituted by C₁₋₅ alkyl; or

25 is phenyl, unsubstituted or substituted by substituents selected from the group consisting of halogen and C₁₋₅ alkyl;

R₂ and R₃, independently, are H or have an R₁ significance, whereby R₁ and R₂ may be linked together to form a C₃₋₇ cycloalkyl group;

m is 0 or 1;

n is 0, 1 or 2; and

30 R₄ is C₃₋₇ cycloalkyl, unsubstituted or substituted by C₁₋₅ alkyl.

The aryl portion in the α-[aryl(alkylene)_m] moiety of formula (XIV-A) or (XIV-B) (collectively "formula (XIV)") may be an aromatic hydrocarbon (e.g. naphthyl, preferably phenyl) unsubstituted or substituted, or a heteroaromatic ring linked by one of its ring carbon atoms (e.g. a 5- or 6-membered ring with 1 or 2 heteroatoms from the group O, N and S, preferably furyl, thienyl or pyridyl), and may be unsubstituted or substituted.

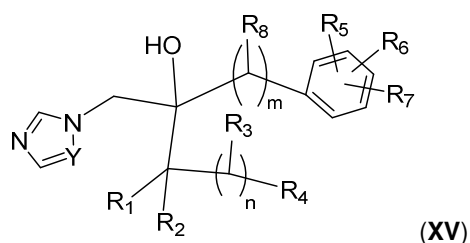
Examples of suitable α-[aryl(alkylene)_m] groups that may be present in formula (XIV) are phenyl, benzyl and α-C₁₋₅ alkylbenzyl (e.g., unsubstituted, mono- or multiple-substituted in the phenyl moiety by

NO₂, halogen, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, or C₁₋₅ alkoxy (unsubstituted or halogenated), phenyl, or phenoxy, unsubstituted or substituted). Further examples of suitable α-aryl groups are the heteroaromatic 3-pyridyl group and 2-thienyl and 2-furyl, which may be, for example, unsubstituted or singly substituted by halogen or lower alkyl (e.g. 5-Cl-2-thienyl and 5-tert.butyl-2-furyl).

For example, the α-[aryl(alkylene)_m] group may be phenyl, benzyl, or α-C₁₋₅ alkylbenzyl substituted in the phenyl moiety by R₅, R₆ and/or R₇, wherein:

R₅ and R₆, independently, are H; halogen, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, or C₁₋₅ alkoxy, (e.g., unsubstituted or halogenated), phenyl or phenoxy (e.g., unsubstituted or substituted), or NO₂; and R₇ is H, C₁₋₅ alkyl or halogen.

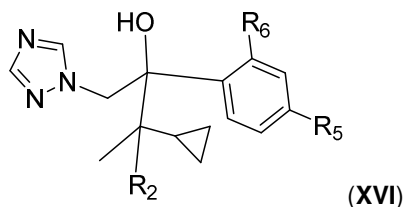
In some examples, the compound represented by formula (XIV) is a compound represented by formula (XV)



wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, m and n are as defined for formula (XIV) herein, R₈ is H or C₁₋₅ alkyl, and Y is CH or N;

or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples, the compound represented by formula (XV) is a compound represented by formula (XVI)

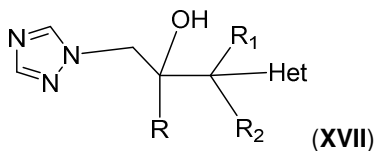


wherein R₂ is hydrogen or optionally substituted alkyl, such as optionally substituted lower alkyl (e.g., methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, or the like); and

R₅ and R₆ are each independently hydrogen or a halogen atom, such as chloro; or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples, the CYP51A1 inhibitor is 2-(4-chlorophenyl)-3-cyclopropyl-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol, 2-(4-chlorophenyl)-3-cyclopropyl-3-methyl-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol, 2-(2,4-dichlorophenyl)-3-cyclopropyl-1-(1H-1,2,4-triazol-1-yl) butan-2-ol, or 2-(2,4-dichlorophenyl)-3-cyclopropyl-3-methyl-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

In some examples, the CYP51A1 inhibitor is a compound represented by formula (XVII)



wherein R is phenyl optionally substituted by 1 to 3 substituents each independently selected from halo and CF₃ ;

R¹ is C₁ -C₄ alkyl;

5 R₂ is H or C₁ -C₄ alkyl; and

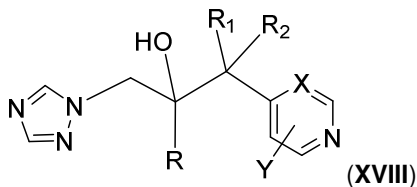
"Het", which is attached to the adjacent carbon atom by a ring carbon atom, is selected from pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl. "Het" may be optionally substituted by C₁ -C₄ alkyl, C₁ -C₄ alkoxy, halo, CF₃, CN, NO₂, NH₂, -NH(C₁-C₄ alkanoyl) or -NHCO₂ (C₁ -C₄ alkyl); or a pharmaceutically acceptable salt, ester, or ether thereof.

10 In some examples of formula (XVII), "Het" is selected from 2- and 4-pyridinyl, pyridazinyl, 2- and 4-pyrimidinyl, pyrazinyl and triazinyl, and may be optionally substituted by C₁ -C₄ alkyl, C₁ -C₄ alkoxy, halo, CF₃, CN, NO₂, NH₂, -NH(C₁ -C₄ alkanoyl) or -NHCO₂ (C₁ -C₄ alkyl). In some examples, "Het" is pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl, and may be optionally substituted by C₁ -C₄ alkyl, C₁ -C₄ alkoxy, halo, CF₃, NO₂, NH₂ or -NH(C₁ -C₄ alkanoyl).

15 In some examples of formula (XVII), R is a substituted phenyl moiety, such as 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 2-iodophenyl, 2-trifluoromethylphenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-chlorophenyl, 2,5-difluorophenyl, 2,4,6-trifluorophenyl, or 4-bromo-2,5-difluorophenyl. In some examples, R is a phenyl group substituted by from 1 to 3 halo (preferably F or Cl) substituents. In some examples, R is a phenyl group substituted by from 1 or 2 halo
20 (preferably F or Cl) substituents. In some examples, R is 2,4-difluorophenyl, 2,4-dichlorophenyl, 2-fluorophenyl or 2-chlorophenyl.

In some examples, the CYP51A1 inhibitor is 2-(2,4-difluorophenyl)-3-(pyridin-2-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, 2-(2,4-difluorophenyl)-3-(pyridin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, or 2-(2,4-difluorophenyl)-3-(pyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

25 In some examples, the CYP51A1 inhibitor is a compound represented by formula (XVIII)



wherein R is optionally substituted phenyl (e.g., substituted by from 1 to 3 substituents each independently selected from halo, -CF₃ and -OCF₃);

R¹ is optionally substituted alkyl, such as optionally substituted lower alkyl (e.g., C₁-C₄ alkyl);

30 R₂ is H or optionally substituted alkyl, such as optionally substituted lower alkyl (e.g., C₁ -C₄ alkyl);

X is CH or N; and

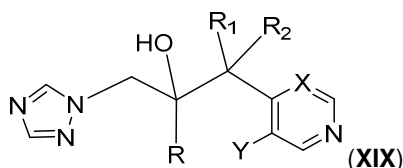
Y is a halogen, such as F or Cl;

or a pharmaceutically acceptable salt, ester, or ether thereof.

Examples of R in formula (XVIII) are 2-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 2-iodophenyl, 2-trifluoromethylphenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-chlorophenyl, 2,5-difluorophenyl, 2,4,6-trifluorophenyl, 4-bromo-2,5-difluorophenyl, and 2-trifluoromethoxyphenyl.

5

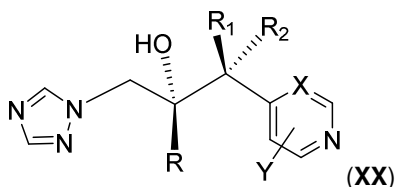
In some examples of formula (XVIII), the compound is represented by formula (XIX)



wherein R, R₁, R₂, X, and Y are as defined for formula (XVIII);
or a pharmaceutically acceptable salt, ester, or ether thereof.

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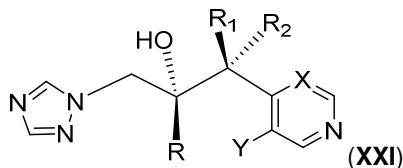
In some examples of formula (XVIII), the compound is represented by formula (XX)



wherein R, R₁, R₂, X, and Y are as defined for formula (XVIII);
or a pharmaceutically acceptable salt, ester, or ether thereof.

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In some examples of formula (XVIII), the compound is represented by formula (XXI)

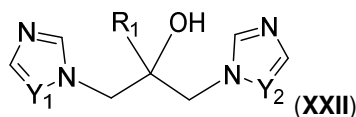


wherein R, R₁, R₂, X, and Y are as defined for formula (XVIII);
or a pharmaceutically acceptable salt, ester, or ether thereof.

20

In some examples, the CYP51A1 inhibitor is 2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, or a pharmaceutically acceptable salt, ester, or ether thereof. In some examples, the CYP51A1 inhibitor is (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples, the CYP51A1 inhibitor is a compound represented by formula (XXII)



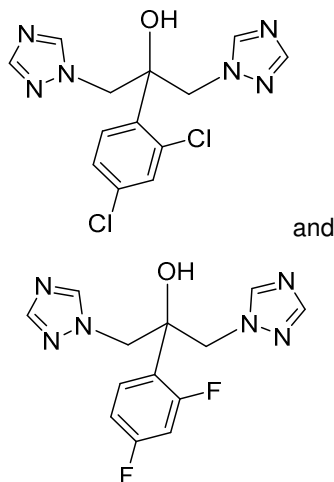
25

wherein R₁ is an optionally substituted alkyl, cycloalkyl (e.g. cyclopentyl or cyclohexyl), aryl (e.g. phenyl) or arylalkyl (e.g. benzyl) group; and
Y₁ and Y₂ are each independently =CH- or =N-;
or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples of formula (XXII), R₁ is alkyl, cycloalkyl, optionally substituted aryl, or optionally substituted arylalkyl; and Y¹ and Y² are either both =CH- or both =N-.

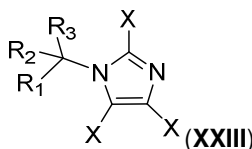
In some examples of formula (XXII), R₁ is phenyl or benzyl, optionally substituted with one or more of halogen, alkyl or haloalkyl each containing from 1 to 5 carbon atoms, alkoxy or haloalkoxy each containing from 1 to 4 carbon atoms, nitro, cyano, hydroxy, alkylthio containing from 1 to 40 carbon atoms, vinyl, phenyl or phenoxy. In some examples, the alkyl moiety of the benzyl is unsubstituted, or substituted with alkyl containing from 1 to 4 carbon atoms, phenyl or chlorophenyl.

In some examples, the CYP51A1 inhibitor is selected from:

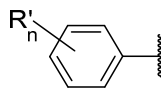


or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples, the CYP51A1 inhibitor is a compound represented by formula (XXIII)



wherein each of R₁, R₂, and R₃ is independently an aryl group represented by the formula:



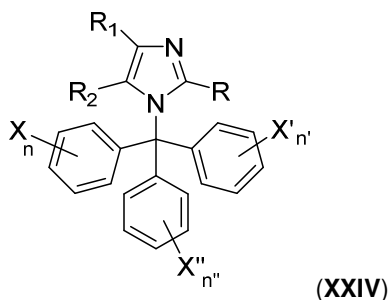
n is 0, 1, 2, 3, 4, or 5 (e.g., 0, 1, or 2) and each R' is independently halogen or optionally substituted alkyl (e.g., optionally substituted lower alkyl); and

each X is independently selected from hydrogen, optionally substituted alkyl (e.g., optionally substituted lower alkyl), or optionally substituted aryl (e.g., optionally substituted phenyl);

or a pharmaceutically acceptable salt, ester, or ether thereof. In some examples, the total number of carbon atoms in all X substituents is an integer of from 0 to 15.

In some examples, the CYP51A1 inhibitor is a compound selected from 1-(tris(m-tert-butylphenyl)methyl)imidazole, 1-(tris(p-tert-butylphenyl)methyl)imidazole, 1-(tris(2,4-difluorophenyl)methyl)-2,4,5-trimethylimidazole, 1-(tris(p-chlorophenyl)methyl)-2-methyl-4,5-diphenylimidazole, 1-(tris(m-tolyl)methyl)-2-n-propylimidazole, and 1-trityl-2-methylimidazole.

In some examples, the CYP51A1 inhibitor is a compound represented by formula (XXIV)



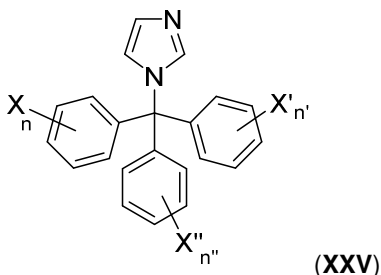
wherein each of R, R₁, and R₂ is independently hydrogen, optionally substituted alkyl (e.g., optionally substituted lower alkyl), or optionally substituted and optionally fused aryl (e.g., optionally substituted phenyl);

5 each of X, X', and X''' is independently hydrogen, halogen, optionally substituted alkyl (e.g., optionally substituted lower alkyl), or optionally substituted and optionally fused aryl (e.g., optionally substituted phenyl); and

each of n, n', and n'' is independently 1, 2, 3, 4, or 5 (e.g., 1, 2, or 3);

or a pharmaceutically acceptable salt, ester, or ether thereof.

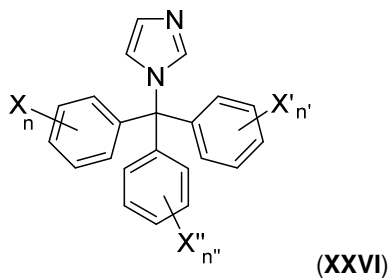
10 In some examples of formula (XXIV), the compound is represented by formula (XXV)



wherein X, X', X''', n, n', and n'' are as defined for formula (XXIV);

or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples of formula (XXIV), the compound is represented by formula (XXVI)



15 wherein X, X', X''', n, n', and n'' are as defined for formula (XXIV);

or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples, the CYP51A1 inhibitor is 1-(3,4-Dimethylphenyl-phenyl-2-pyridyl)-methyl-imidazole, 1-(2,4-dimethylphenyl-phenyl-2-pyridyl)-methyl-imidazole, 1-(2,6-dimethylphenyl-phenyl-2-pyridyl)-methyl-imidazole, 1-(2,4-dimethylphenyl-phenyl-4-pyridyl)-methyl-imidazole, 1-(3,4-dimethylphenyl-phenyl-4-pyridyl)-methyl-imidazole, 1-(2,5-dimethylphenyl-phenyl-4-pyridyl)-methyl-imidazole, 1-(2,3-dimethylphenyl-phenyl-2-pyridyl)-methyl-imidazole, 1-(2,3-dimethylphenyl-phenyl-2-pyridyl)-methyl-imidazole, 1-(2,3-dimethylphenyl-phenyl-2-pyridyl)-methyl-imidazole, 1-(2,3-

dimethylphenyl-phenyl-4-pyridyl)-methyl-imidazole, 1-(3,4-dimethylphenyl-phenyl-4-pyridyl)-methyl-imidazole, or a pharmaceutically acceptable salt thereof, such as the 1,5-naphthalene-disulphonate salt thereof or the hydrochloride salt thereof.

In some examples, the CYP51A1 inhibitor is a compound represented by formula (XXVII)

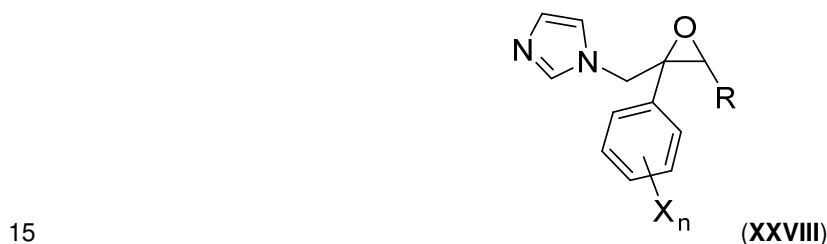


wherein A and B are independently selected from optionally substituted alkyl (e.g., optionally substituted lower alkyl, such as alkyl of 1 to 4 carbon atoms), optionally substituted naphthyl, optionally substituted biphenyl, and optionally substituted phenyl, and Z is CH or N;

or a pharmaceutically acceptable salt, ester, or ether thereof.

10 In some examples of formula (XXVII), A and/or B is an optionally substituted phenyl group, such as a phenyl group substituted by one or more of halogen, nitro, alkyl (e.g., of from 1 to 4 carbon atoms), alkoxy (e.g., of from 1 to 4 carbon atoms), haloalkyl (e.g., of from 1 to 4 carbon atoms), phenoxy, or phenylsulfonyl.

In some examples, the CYP51A1 inhibitor is a compound represented by formula (XXVIII)



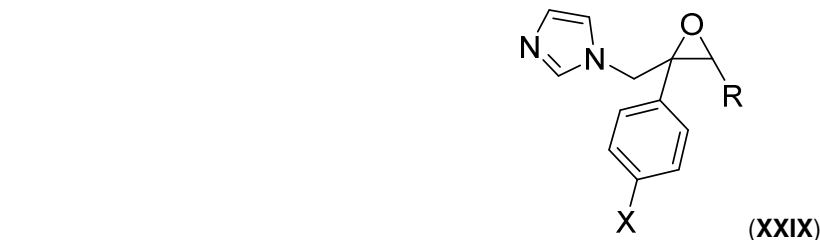
wherein R is optionally substituted aryl, such as phenyl, pyridyl, tetrahydropyranyl, norbornyl, C₃-C₁₂ cycloalkyl or C₅-C₈ cycloalkenyl, each of which may be unsubstituted or monosubstituted to trisubstituted by halogen, nitro, phenoxy, alkyl, amino, alkoxy (e.g., of from 1 to 4 carbon atoms), haloalkoxy (e.g., of from 1 to 4 carbon atoms), or haloalkyl (e.g., of from 1 to 4 carbon atoms);

20 each X is independently fluorine, chlorine, bromine, or iodine; and

each n is independently 1, 2, 3, 4, or 5 (e.g., 1, 2, or 3);

or a pharmaceutically acceptable salt, ester, or ether thereof.

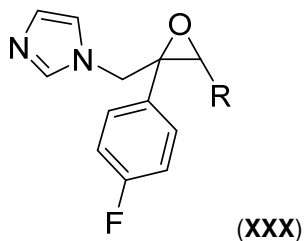
In some examples of formula (XXVIII), the compound is represented by formula (XXIX)



wherein R and X are as defined for formula (XXVIII);

or a pharmaceutically acceptable salt, ester, or ether thereof.

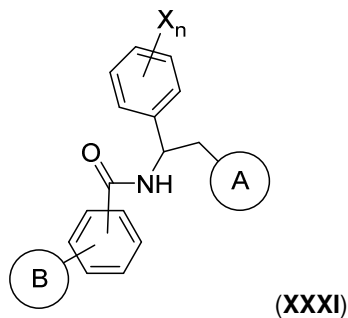
In some examples of formula (XXVIII), the compound is represented by formula (XXX)



wherein R is as defined for formula (XXVIII);

or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples, the CYP51A1 inhibitor is a compound represented by formula (XXXI)



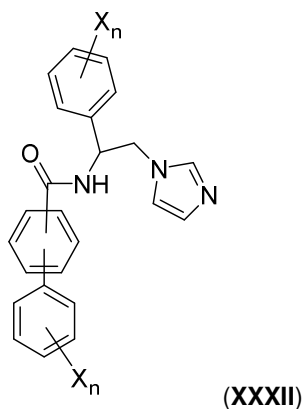
wherein each of rings A and B are independently optionally substituted and optionally fused aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

each X is independently halogen or optionally substituted alkyl (e.g., optionally substituted lower alkyl); and

n is 1, 2, 3, 4, or 5 (e.g., 1, 2, or 3);

or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples of formula (XXXI), the compound is represented by formula (XXXII)

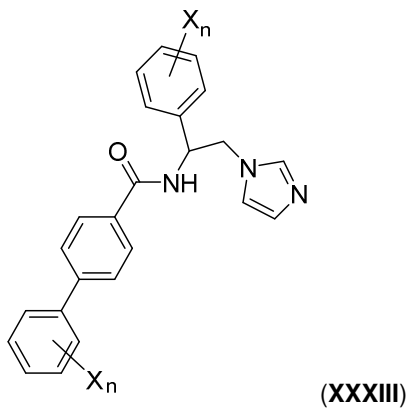


wherein each X is independently halogen or optionally substituted alkyl (e.g., optionally substituted lower alkyl); and

each n is independently 1, 2, 3, 4, or 5 (e.g., 1, 2, or 3);

or a pharmaceutically acceptable salt, ester, or ether thereof.

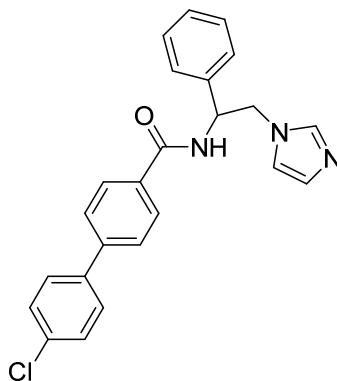
In some examples of formula (XXXII), the compound is represented by formula (XXXIII)



wherein each X and n are as defined for formula (XXXII);

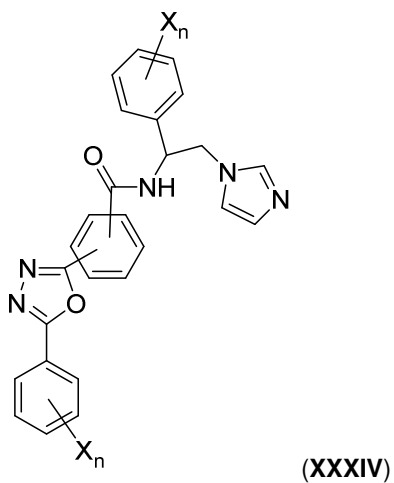
or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples, the CYP51A1 inhibitor is represented by the formula:



5

In some examples, the CYP51A1 inhibitor is a compound represented by formula (XXXIV)

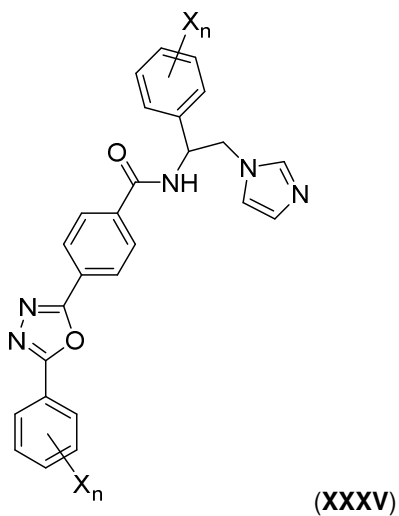


wherein each X is independently halogen or optionally substituted alkyl (e.g., optionally substituted lower alkyl); and

each n is independently 1, 2, 3, 4, or 5 (e.g., 1, 2, or 3);

or a pharmaceutically acceptable salt, ester, or ether thereof.

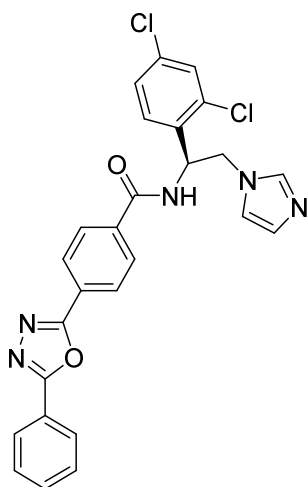
In some examples of formula (XXXIV), the compound is represented by formula (XXXV)



wherein each X and n are as defined for formula (XXXIV);

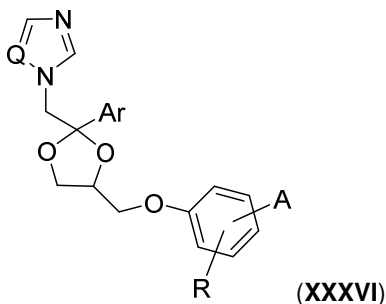
or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples, the CYP51A1 inhibitor is represented by the formula:



5

In some examples, the CYP51A1 inhibitor is a compound represented by formula (XXXVI)



wherein Q is selected from the group consisting of CH and N;

Ar is an optionally substituted, optionally fused aryl group, such as an optionally fused, optionally substituted phenyl group, for example, a phenyl group having from 1 to 3 substituents, such as from 1 to 3 substituents independently selected from the group consisting of halo, lower alkyl and lower alkyloxy;

A is selected from the group consisting of:

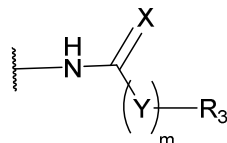
(a) an isothiocyanato group $-N=C=S$;

(b) an amino group of the formula



wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen and lower alkyl;

(c) a group of the formula

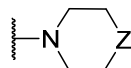


wherein X is selected from the group consisting of O and S , Y is selected from the group consisting of O and NH , m is the integer 0 or 1 , and R_3 is selected from the group consisting of hydrogen, lower alkyl, mono- and dihalo-(lower alkyl), phenyl and substituted phenyl, said substituted phenyl having from 1 to 2 substituents independently selected from the group consisting of halo, lower alkyl and lower alkyloxy, optionally provided that:

i) when said X is S , then said Y is NH and said m is 1 ; and

ii) when said Y is O and said m is 1 , then said R_3 is other than hydrogen; and

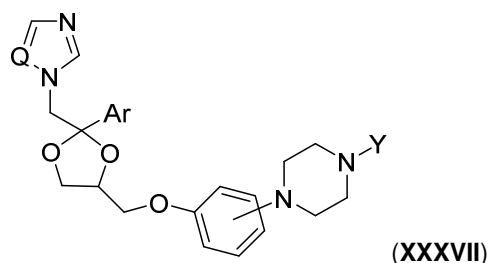
(d) a group of the formula



wherein Z is selected from the group consisting of a direct bond, CH_2 , O and $N-R_4$, wherein R_4 is selected from the group consisting of hydrogen, lower alkyl, hydroxy-(lower alkyl), (lower alkyloxy)-lower alkyl, lower alkanoyl, lower alkylsulfonyl, phenylmethylsulfonyl, lower alkyloxycarbonyl, lower alkyloxycarbonylmethyl, phenoxy carbonyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, aminocarbonylmethyl, (lower alkyl)aminocarbonylmethyl, (lower alkyl)aminothioxomethyl, (lower alkylthio)thioxomethyl, phenyl, phenylmethyl, benzoyl and substituted benzoyl, said substituted benzoyl being benzoyl having from 1 to 2 substituents independently selected from the group consisting of halo, lower alkyl and lower alkyloxy; and R is selected from the group consisting of hydrogen and nitro, optionally provided that when said R is nitro, then said A is amino;

or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples, the CYP51A1 inhibitor is a compound represented by formula (XXXVII)



wherein Q is selected from the group consisting of N and CH;

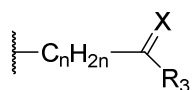
Ar is selected from the group consisting of phenyl, thienyl, halothienyl and substituted phenyl, the substituted phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, lower alkyl, lower alkyloxy and trifluoromethyl; and

5 the group Y is selected from the group consisting of:

a group of the formula $-\text{SO}_2\text{R}_1$, wherein R_1 is selected from the group consisting of trifluoromethyl and aryl;

a group of formula $-\text{alk}-\text{R}_2$, wherein alk is selected from the group consisting of lower alkylene and lower alkenylene and R_2 is selected from the group consisting of cyano, amino, 10 mono- and di(lower alkyl)amino, arylamino, mono- and di(aryllower alkyl)amino, 1-pyrrolidinyl, 1-morpholinyl, 1-piperidinyl, aryloxy and aryl, provided that alk is other than methylene when R_2 is phenyl;

a group of formula

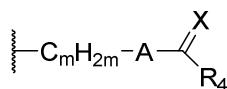


15 wherein n is an integer of from 0 to 6 inclusive, X is O or S and R_3 is selected from the group consisting of hydrogen, mono-, di- and trihalo lower alkyl, amino, mono- and di(lower alkyl)amino, arylamino, mono- and di(aryllower alkyl)amino, amino lower alkyl, mono- and di(lower alkyl)amino lower alkyl, (1-pyrrolidinyl)lower alkyl, (1-morpholinyl)lower alkyl, (1-piperidinyl)lower alkyl, aryl, aryllower alkyl, aryllower alkenyl and lower alkyloxycarbonyl lower alkyloxy, optionally provided that:

(i) said n is other than 0 or 1 when said R_3 is amino or lower alkylamino; and

(ii) said n is other than 0 when said R_3 is di(lower alkyl)amino or aryl; and

a group of formula

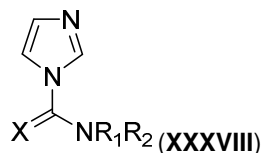


25 wherein m is an integer of from 1 to 6 inclusive, A is O or NH, X is O or S and R_4 is selected from the group consisting of hydrogen, lower alkyl, lower alkyloxy, aryl, aryloxy, aryllower alkyl, amino, mono- and di(lower alkyl)amino, arylamino, mono- and di(aryllower alkyl)amino, 1-pyrrolidinyl, 1-morpholinyl and 1-piperidinyl;

wherein said aryl, as used in the foregoing definitions, is selected from the group consisting of phenyl, 30 substituted phenyl, thienyl, halothienyl, lower alkylthienyl and pyridinyl, said substituted phenyl optionally being a phenyl ring having from 1 to 3 substituents each independently selected from the group consisting of lower alkyl, lower alkyloxy, halo, amino, mono- and di(lower alkyl)amino, lower alkylcarbonylamino, nitro and trifluoromethyl;

or a pharmaceutically acceptable salt, ester, or ether thereof.

35 In some examples, the CYP51A1 inhibitor is a compound represented by formula (XXXVIII)

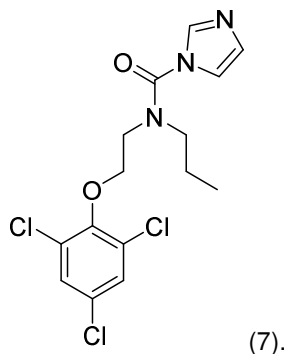


wherein X is oxygen or sulfur, R₁ is optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, phenylalkyl, phenylalkenyl, phenoxyalkyl or phenylthioalkyl and R₂ is optionally substituted phenyl, phenylalkyl, phenylalkenyl, phenoxyalkyl or phenylthioalkyl, provided that when R₁ is methyl or phenyl R₂ is substituted phenyl or optionally substituted phenylalkyl, phenylalkenyl, phenoxyalkyl or phenylthioalkyl;

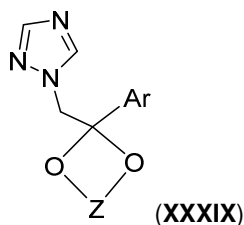
or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples of formula (XXXVIII), X is selected from the group consisting of oxygen and sulfur, R₁ is selected from the group consisting of alkyl of 1 to 10 carbon atoms, alkenyl of 3 or 4 carbon atoms, alkynyl of 3 to 5 carbon atoms, cycloalkyl of 3 to 10 carbon atoms, optionally substituted phenyl, phenylalkyl, of the formula Ph(CH₂)_n where n is 1 to 5, phenylalkenyl of 9 to 11 carbon atoms, phenoxyalkyl of the formula PhO(CH₂)_n where n is 2 to 5 and phenylthioalkyl of the formula PhS(CH₂)_n where n is 2 to 5, wherein the substituted phenyl nucleus has at least one substituent selected from the group consisting of halo, alkoxy of 1 or 2 carbon atoms, alkyl of 1 to 4 carbon atoms, trihalomethyl, cyano, methylthio, nitro and methylsulphonyl, and R₂ is selected from the group consisting of optionally substituted phenylalkyl, of the formula Ph(CH₂)_n where n is 1 to 5, phenylalkenyl of 9 to 11 carbon atoms, phenoxyalkyl of the formula PhO(CH₂)_n where n is 2 to 5 and phenylthioalkyl of the formula PhS(CH₂)_n where n is 2 to 5, wherein the substituted phenyl nucleus has at least one substituent selected from the group consisting of halo, alkoxy of 1 or 2 carbon atoms, alkyl of 1 to 4 carbon atoms, trihalomethyl, cyano, methylthio, nitro and methylsulphonyl.

In some examples, the CYP51A1 inhibitor is prochloraz, represented by formula (7)



In some examples, the CYP51A1 inhibitor is a compound represented by formula (XXXIX)

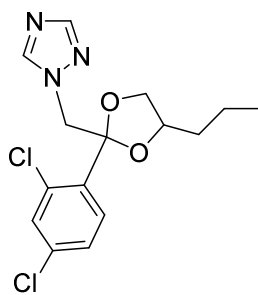


wherein Z is an alkylene selected from the group consisting of -CH₂CH₂-, -CH₂-CH₂CH₂-, -CH(CH₃)CH(CH₃)-, and -CH₂CH(alkyl)-, wherein the alkyl has from 1 to about 10 carbon atoms; and

Ar is an optionally fused, optionally substituted aryl group, such as an optionally fused, optionally substituted phenyl, thienyl, naphthyl, or fluorenyl, for example, phenyl, thienyl, halothienyl, naphthyl and fluorenyl, each optionally containing one or more (e.g., from 1 to 3) substituents, such as substituents selected independently from the group consisting of halo, lower alkyl, lower alkyloxy, cyano, and nitro;

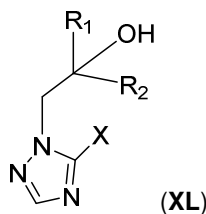
or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples, the CYP51A1 inhibitor is propiconazole, represented by formula (8)



(8).

In some examples, the CYP51A1 inhibitor is a compound represented by formula (XL)



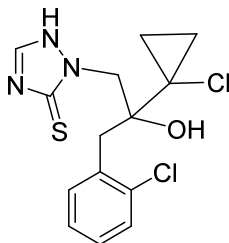
(XL)

wherein R₁ and R₂ are each independently selected from optionally substituted alkyl, optionally substituted alkenyl, optionally substituted cycloalkyl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aroxyalkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

X is -SH, -SR₃, -SO-R₃, -SO₂-R₃, or -SO₃H, wherein R₃ is alkyl which is optionally substituted by one or more halogen moieties (e.g., fluorine and/or chlorine), alkenyl which is optionally substituted by one or more halogen moieties (e.g., fluorine and/or chlorine), optionally substituted aralkyl or optionally substituted aryl;

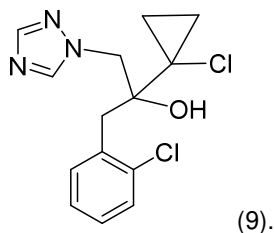
or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples, the CYP51A1 inhibitor is prothioconazole, represented by formula (8)

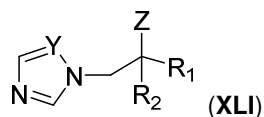


(8).

In some examples, the CYP51A1 inhibitor is prothioconazole-desthio, represented by formula (9)

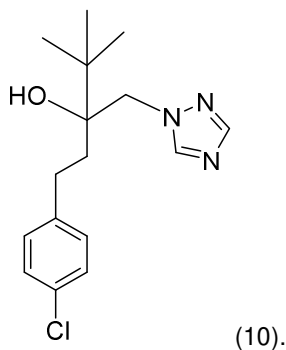


In some examples, the CYP51A1 inhibitor is a compound represented by formula (XLI)

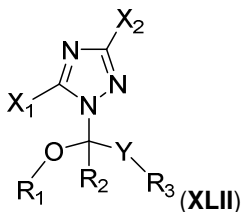


wherein R₁ is -CH=CH-X, -C≡C-X, or -CH₂-CH₂-X, wherein X is hydrogen, alkyl, hydroxyalkyl,
 5 alkoxyalkyl, cycloalkyl or optionally substituted aryl, aralkyl, aryloxy alkyl, or heterocycle;
 R₂ is alkyl, cycloalkyl (e.g. cyclopropyl, cyclopentyl, or cyclohexyl) or optionally substituted aryl;
 Z is Cl, CN, or OR₃, wherein R₃ is hydrogen, acetyl, alkyl, alkenyl or aralkyl; and
 Y is =N- or =CH-,
 or a pharmaceutically acceptable salt, ester, or ether thereof.

10 In some examples, the CYP51A1 inhibitor is tebuconazole, represented by formula (10)



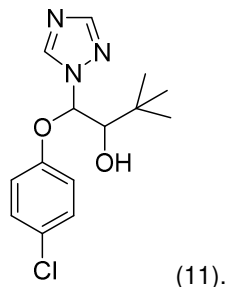
In some examples, the CYP51A1 inhibitor is a compound represented by formula (XLII)



wherein X₁ is hydrogen or an alkyl group,
 15 X₂ is hydrogen or an alkyl group,
 R₁ is an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl or optionally substituted aryl or aralkyl
 group,
 R₂ is hydrogen or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl or optionally substituted aryl
 or aralkyl group,
 20 R₃ is hydrogen or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl or optionally substituted aryl
 or aralkyl group, and
 Y is a keto group or a functional keto derivative.

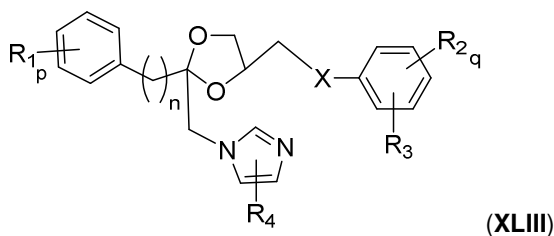
or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples, the CYP51A1 inhibitor is triadimenol, represented by formula (11)



(11).

In some examples, the CYP51A1 inhibitor is a compound represented by formula (XLIII)



(XLIII)

wherein n is 2 or 3;

p is 0, 1 or 2;

q is 0, 1 or 2;

X is oxygen or S(O)_t wherein t is 0, 1, or 2;

each R₁ is independently halo, lower alkyl, lower alkoxy, or trifluoromethyl;

each R₂ is independently halo or lower alkyl;

R₃ is nitro or -N(R₅)R₆ where

R₅ is hydrogen or lower alkyl;

R₆ is hydrogen, lower alkyl, lower alkylsulfonyl or -C(Y)R₇ where Y is oxygen or sulfur and R₇ is

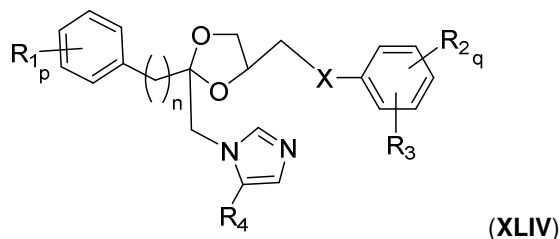
hydrogen, lower alkyl, lower alkoxy or -N(R₈)R₉ where R₈ is hydrogen or lower alkyl and R₉ is hydrogen, lower alkyl or lower alkoxy; or

R₅ and R₆ together with N is pyrrolidino, piperidino, morpholino, thiomorpholino or piperazino, wherein the piperazino is optionally substituted at the 4-position by -C(O)R₁₀ where R₁₀ is hydrogen, lower alkyl, lower alkoxy or amino; and

R₄ is hydrogen or optionally substituted lower alkyl;

or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples of formula (XLIII), the compound is represented by formula (XLIV)

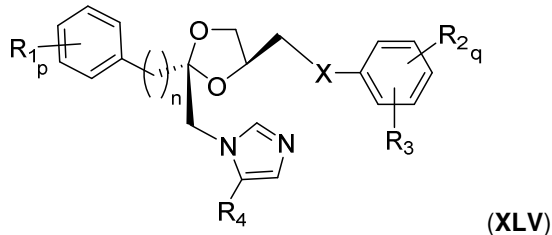


(XLIV)

wherein R₁, R₂, R₃, R₄, X, n, p, and q are as defined for formula (XLIII);

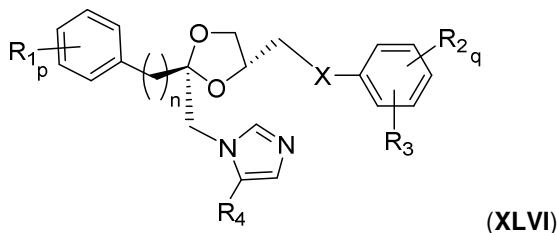
or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples of formula (XLIII), the compound is represented by formula (XLV)



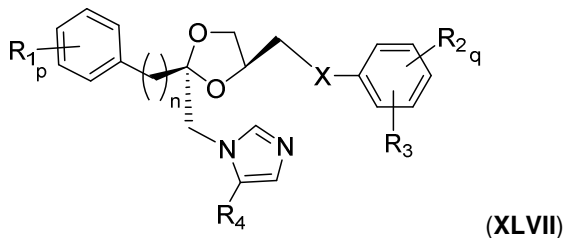
wherein R₁, R₂, R₃, R₄, X, n, p, and q are as defined for formula (XLIII);
or a pharmaceutically acceptable salt, ester, or ether thereof.

5 In some examples of formula (XLIII), the compound is represented by formula (XLVI)



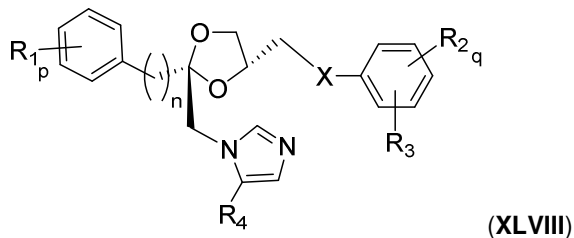
wherein R₁, R₂, R₃, R₄, X, n, p, and q are as defined for formula (XLIII);
or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples of formula (XLIII), the compound is represented by formula (XLVII)



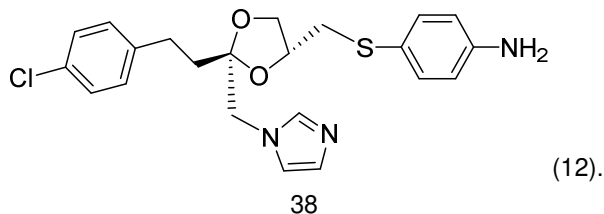
wherein R₁, R₂, R₃, R₄, X, n, p, and q are as defined for formula (XLIII);
or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples of formula (XLIII), the compound is represented by formula (XLVIII)



wherein R₁, R₂, R₃, R₄, X, n, p, and q are as defined for formula (XLIII);
or a pharmaceutically acceptable salt, ester, or ether thereof.

In some examples, the CYP51A1 inhibitor is azalanstat, represented by formula (12)



In some examples, the CYP51A1 inhibitor is LEK-935, CP-320626, itraconazole, posaconazole, cyproconazole, voriconazole, fluconazole, clotrimazol, fenticonazole, epoxiconazole, ketoconazole, ravuconazole, isavuconazole, holothurin A, theasaponin, capsicosine, betulafolientriol, prochloraz, propiconazole, prothioconazole, prothioconazole-desthio, tebuconazole, triadimenol, azalanstat, or a variant thereof.

In some examples, the CYP51A1 inhibitor is an antibody or antigen-binding fragment thereof, such as one that specifically binds to CYP51A1 and/or inhibits CYP51A1 catalytic activity. In some examples, the antibody or antigen-binding fragment thereof is a monoclonal antibody or antigen-binding fragment thereof, a polyclonal antibody or antigen-binding fragment thereof, a humanized antibody or antigen-binding fragment thereof, a bispecific antibody or antigen-binding fragment thereof, a dual-variable immunoglobulin domain, a single-chain Fv molecule (scFv), a diabody, a triabody, a nanobody, an antibody-like protein scaffold, a Fv fragment, a Fab fragment, a F(ab')₂ molecule, and a tandem di-scFv. In some examples, the antibody has an isotype selected from IgG, IgA, IgM, IgD, and IgE.

In some examples, the CYP51A1 inhibitor is an interfering RNA molecule, such as a short interfering RNA (siRNA), micro RNA (miRNA), or short hairpin RNA (shRNA). The interfering RNA may suppress expression of a CYP51A1 mRNA transcript, for example, by way of (i) annealing to a CYP51A1 mRNA or pre-mRNA transcript, thereby forming a nucleic acid duplex; and (ii) promoting nuclease-mediated degradation of the CYP51A1 mRNA or pre-mRNA transcript and/or (iii) slowing, inhibiting, or preventing the translation of a CYP51A1 mRNA transcript, such as by sterically precluding the formation of a functional ribosome-RNA transcript complex or otherwise attenuating formation of a functional protein product from the target RNA transcript.

In some examples, the interfering RNA molecule, such as the siRNA, miRNA, or shRNA, contains an antisense portion that anneals to a segment of a CYP51A1 RNA transcript (e.g., mRNA or pre-mRNA transcript), such as a portion that anneals to a segment of a CYP51A1 RNA transcript having a nucleic acid sequence that is at least 85% identical to the nucleic acid sequence of SEQ ID NO: 2 (e.g., 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% < 96%, 97%, 98%, 99%, 99.9%, or 100% identical to the nucleic acid sequence of SEQ ID NO: 2).

In some examples, the interfering RNA molecule, such as the siRNA, miRNA, or shRNA, contains a sense portion having at least 85% sequence identity to the nucleic acid sequence of a segment of SEQ ID NO: 2 (e.g., 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% < 96%, 97%, 98%, 99%, 99.9%, or 100% identical to the nucleic acid sequence of a segment of SEQ ID NO: 2).

In some examples, the neurological disorder is amyotrophic lateral sclerosis, and following administration of the CYP51A1 inhibitor to the patient, the patient exhibits one or more, or all, of the following responses:

(i) an improvement in condition as assessed using the amyotrophic lateral sclerosis functional rating scale (ALSFRS) or the revised ALSFRS (ALSFRS-R), such as an improvement in the patient's ALSFRS or ALSFRS-R score within one or more days, weeks, or months following administration of the CYP51A1 inhibitor (e.g., an improvement in the patient's ALSFRS or ALSFRS-R score within from about 1 day to about 48 weeks (e.g., within from about 2 days to about 36 weeks, from about 4 weeks to about

weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, or more, following the initial administration of the

5 CYP51A1 inhibitor to the patient.

In another example, the disclosure features a kit containing a CYP51A1 inhibitor. The kit may further contain a package insert, such as one that instructs a user of the kit to perform the method or use of any of the above aspects or examples of the disclosure. In one aspect, the present disclosure refers to a kit comprising a CYP51A1 inhibitor and a package insert, wherein the package insert instructs a user of the kit to administer the CYP51A1 inhibitor to the patient in accordance with any of the uses as disclosed herein. The CYP51A1 inhibitor in the kit may be a small molecule, antibody, antigen-binding fragment thereof, or interfering RNA molecule, such as a small molecule, antibody, antigen-binding fragment thereof, or interfering RNA molecule described above and herein.

15 Definitions

As used herein, the term “about” refers to a value that is within 10% above or below the value being described. For instance, a value of “about 5 mg” refers to a quantity that is from 4.5 mg to 5.5 mg.

As used herein, the term “affinity” refers to the strength of a binding interaction between two molecules, such as a ligand and a receptor. The term “ K_i ”, as used herein, is intended to refer to the inhibition constant of an antagonist for a particular molecule of interest, and is expressed as a molar concentration (M). K_i values for antagonist-target interactions can be determined, e.g., using methods established in the art. The term “ K_d ”, as used herein, is intended to refer to the dissociation constant, which can be obtained, e.g., from the ratio of the rate constant for the dissociation of the two molecules (k_d) to the rate constant for the association of the two molecules (k_a) and is expressed as a molar concentration (M). K_d values for receptor-ligand interactions can be determined, e.g., using methods established in the art. Methods that can be used to determine the K_d of a receptor-ligand interaction include surface plasmon resonance, e.g., through the use of a biosensor system such as a BIACORE® system.

As used herein, the terms “benefit” and “response” are used interchangeably in the context of a subject, such as a human subject undergoing therapy for the treatment of a neurological disorder, for example, amyotrophic lateral sclerosis, frontotemporal degeneration (also referred to as frontotemporal lobar degeneration and frontotemporal dementia), Alzheimer’s disease, Parkinson’s disease, dementia with Lewy Bodies, corticobasal degeneration, progressive supranuclear palsy, dementia parkinsonism ALS complex of Guam, Huntington’s disease, Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia (IBMPFD), sporadic inclusion body myositis, myofibrillar myopathy, dementia pugilistica, chronic traumatic encephalopathy, Alexander disease, and hereditary inclusion body myopathy. The terms “benefit” and “response” refer to any clinical improvement in the subject’s condition. Exemplary benefits in the context of a subject undergoing treatment for a neurological disorder using the compositions and methods described herein (e.g., in the context of a human subject undergoing treatment for a neurological disorder described herein, such as amyotrophic lateral sclerosis, with a cytochrome P450 isoform 51A1 (CYP51A1) inhibitor described herein, such as an inhibitory small molecule, antibody, antigen-binding fragment thereof, or interfering RNA molecule) include the slowing

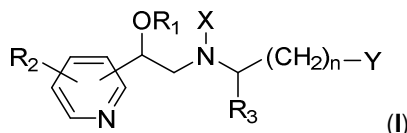
CLAIMS

1. Use of a CYP51A1 inhibitor in the manufacture of a medicament for treating a neurological disorder in a human patient.
2. The use of claim 1, wherein the patient has been identified as likely to benefit from treatment with a CYP51A1 inhibitor, the use further comprising determining that the patient is susceptible to developing TAR-DNA binding protein (TDP)-43 aggregation.
3. The use of claim 1, wherein the patient has previously been determined to be susceptible to developing TDP-43 aggregation.
4. The use of claim 1, wherein the patient has been identified as likely to benefit from treatment with a CYP51A1 inhibitor, the use further comprising determining that the patient expresses a mutant form of TDP-43 having a mutation associated with TDP-43 aggregation.
5. The use of claim 1, wherein the patient has previously been determined to express a mutant form of TDP-43 having a mutation associated with TDP-43 aggregation.
6. Use of a CYP51A1 inhibitor in the manufacture of a medicament for treating a human patient having a neurological disorder, wherein the patient is informed of the patient's likely benefiting from treatment with the CYP51A1 inhibitor, as the patient is determined as being susceptible to developing TDP-43 aggregation.
7. Use of a CYP51A1 inhibitor in the manufacture of a medicament for treating a human patient having a neurological disorder, wherein the patient is informed of the patient's likely benefiting from treatment with the CYP51A1 inhibitor, as the patient is determined as expressing a mutant of TDP-43 having a mutation associated with TDP-43 aggregation.
8. The use of any one of claims 4, 5, and 7, wherein the mutation is selected from the group consisting of Q331K, M337V, Q343R, N345K, R361S, and N390D.
9. The use of any one of claims 1-8, wherein the neurological disorder is a neuromuscular disorder selected from the group consisting of amyotrophic lateral sclerosis, congenital myasthenic syndrome, congenital myopathy, cramp fasciculation syndrome, Duchenne muscular dystrophy, glycogen storage disease type II, hereditary spastic paraplegia, inclusion body myositis, Isaac's Syndrome, Kearns-Sayre syndrome, Lambert–Eaton myasthenic syndrome, mitochondrial myopathy, muscular dystrophy, myasthenia gravis, myotonic dystrophy, peripheral neuropathy, spinal and bulbar muscular atrophy, spinal muscular atrophy, Stiff person syndrome, Troyer syndrome, and Guillain–Barré syndrome.
10. The use of claim 9, wherein the neuromuscular disorder is amyotrophic lateral sclerosis.

11. The use of any one of claims 1-8, wherein the neurological disorder is selected from the group consisting of frontotemporal degeneration, Alzheimer's disease, Parkinson's disease, dementia with Lewy Bodies, corticobasal degeneration, progressive supranuclear palsy, dementia parkinsonism ALS complex of Guam, Huntington's disease, inclusion body myopathy with early-onset Paget disease and frontotemporal dementia, sporadic inclusion body myositis, myofibrillar myopathy, dementia pugilistica, chronic traumatic encephalopathy, Alexander disease, and hereditary inclusion body myopathy.

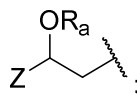
12. The use of any one of claims 1-11, wherein the CYP51A1 inhibitor is a small molecule that binds to and/or inhibits the enzymatic activity of CYP51A1.

13. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (I)

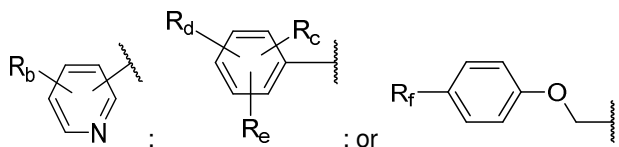


wherein n is 1 or 2;

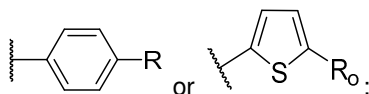
X is hydrogen, lower alkyl, lower alkoxy-lower alkyl, or a group X^a of the formula:



Z is a group of the formula:



Y is a group of the formula:



R₀ is lower alkyl, COR₄ or C(R₅)=CHCOR₄;

R is R₀ or is OR^{''};

R^{''} is hydrogen, lower-alkyl, lower alkanoyl, (CH₂)₁₋₆-OH, (CH₂)₁₋₆-O(CH₂)₁₋₆-R₆, or (CH₂)₁₋₆-COR₄;

R₁ and R_a are hydrogen, lower alkanoyl, benzoyl or (CH₂)₁₋₆-OH;

R₂ and R_b are hydrogen, Cl, Br or CF₃;

R₃ and R₅ are hydrogen or CH₃;

R₄ is hydroxy, lower-alkoxy or N(R₇, R₈);

R₆ is hydrogen, R_g, OH or COR₄;

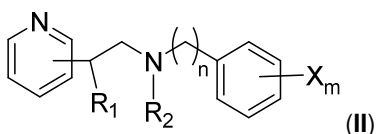
R₇ and R₈ are hydrogen or lower alkyl;

R_c and R_e are hydrogen, Cl, F, Br or CF₃;

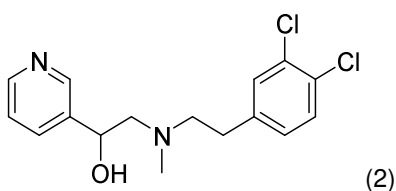
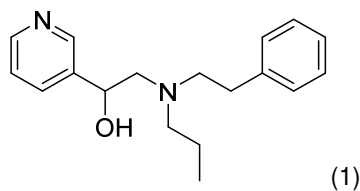
R_d is hydrogen or NH₂;

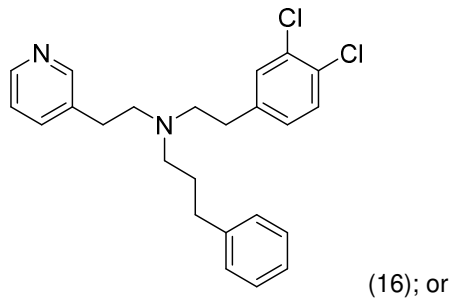
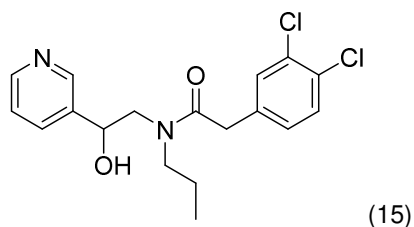
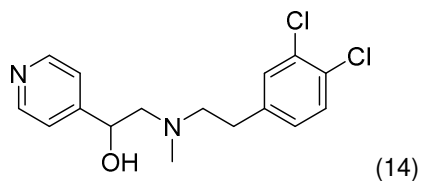
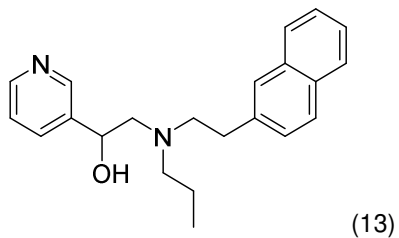
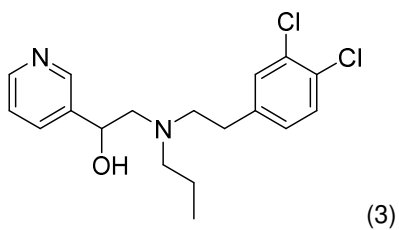
R_f is hydrogen, $\text{CH}_3\text{CONH-}$, $\text{NH}_2\text{COCH}_2\text{-}$ or $\text{R}_9\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{O-}$;
 R_g and R_9 are phenyl or phenyl substituted by Cl, F or Br;
 or a pharmaceutically acceptable salt, ester, or ether thereof; or
 wherein n is 1, R wherein n is 1, R_1 is hydrogen, R_2 is chlorine in the 6-position of a 2-pyridyl residue, and Y is phenyl substituted in the p-position by R; or
 wherein X is X^a , R^a is hydrogen, Z is 6-chloro-2-pyridyl, and Y is phenyl substituted in the p-position by 2-ethoxyethoxy, 2-phenethoxyethoxy or methoxycarbonylmethoxy; or
 wherein the compound is methyl α, α' -[[[(R)-p-(2-ethoxyethoxy)- α -methylphenethyl]imino]dimethylene]bis[(RS)-6-chloro-2-pyridinemethanol]; (RS)-6-chloro- α -[[[(R)-p-(2-ethoxyethoxy)- α -methyl-phenethyl]amino]methyl]-2-pyridinemethanol; α, α' -[[p-(2-ethoxyethoxy)phenethyl]imino]dimethylene]bis[(RS)-6-chloro-2-pyridinemethanol]; (R)-6-bromo- α -[[[(RS)-2-(6-bromo-2-pyridyl)-2-hydroxyethyl][[(R)-p-(2-ethoxyethoxy)- α -methylphenethyl]-amino]methyl]-2-pyridimidinemethanol; (R)-6-chloro- α -[[[(S)-2-(6-chloro-2-pyridyl)-2-hydroxyethyl][[(R)- α -methyl-p-(2-phenethoxyethoxy)phenethyl]amino]methyl]-2-pyridinemethanol.

14. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (II)

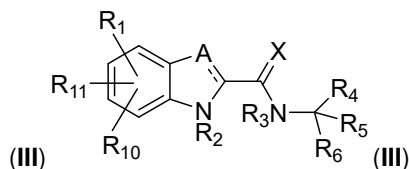


wherein n is 1, 2, 3 or 4 and m is 0, 1, 2, 3, 4, or 5;
 R_1 is a hydrogen atom, hydroxyl group, or lower C_{1-6} alkoxy group;
 R_2 is a hydrogen atom or an optionally substituted straight or branched lower C_{1-6} alkyl group;
 each X is independently fluorine, chlorine, bromine, hydroxyl group, trifluoromethyl group, 3,4-di-Cl, 2,4-di-Cl or lower C_{1-6} alkoxy group, and wherein the phenyl ring containing each X is optionally fused;
 or a pharmaceutically acceptable salt, ester, or ether thereof; or
 wherein n is 2, R_1 is a hydroxyl group, R_2 a methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl group and X is a hydrogen atom or phenyl disubstituted with two chlorine atoms in the positions 3 and 4 or in the positions 2 and 4; or
 wherein the CYP51A1 inhibitor is a compound represented by formula (1), (2), (3), (13), (14), (15), or (16):





15. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula



wherein the dotted line (---) is an optional bond;

X is O or S;

A is —C(H)= , $\text{—C}((\text{C}_1\text{--C}_4)\text{alkyl})\text{=}$, —C(halo)= or —N= , when the dotted line (---) is a bond, or A is methylene or $\text{—CH}((\text{C}_1\text{--C}_4)\text{alkyl})\text{—}$, when the dotted line (---) is not a bond;

R₁, R₁₀ or R₁₁ are each independently H, halo, cyano, 4-, 6-, or 7-nitro, (C₁–C₄)alkyl, (C₁–C₄)alkoxy, fluoromethyl, difluoromethyl or trifluoromethyl;

R₂ is H;

R₃ is H or (C₁–C₆)alkyl;

R₄ is H, methyl, ethyl, n-propyl, hydroxy(C₁-C₃)alkyl, (C₁-C₃)alkoxy(C₁-C₃)alkyl, phenyl(C₁-C₄)alkyl, phenylhydroxy(C₁-C₄)alkyl, (phenyl)((C₁-C₄)-alkoxy)(C₁-C₄)alkyl, thien-2- or -3-yl(C₁-C₄)alkyl or fur-2- or 3-yl(C₁-C₄)alkyl wherein the R₄ rings are mono-, di- or tri-substituted independently on carbon with H, halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, trifluoromethyl, hydroxy, amino, cyano or 4,5-dihydro-1H-imidazol-2-yl; or

R₄ is pyrid-2-, -3- or -4-yl(C₁-C₄)alkyl, thiazol-2-, -4- or -5-yl(C₁-C₄)alkyl, imidazol-2-, -4- or -5-yl(C₁-C₄)alkyl, pyrrol-2- or -3-yl(C₁-C₄)alkyl, oxazol-2-, -4- or -5-yl(C₁-C₄)alkyl, pyrazol-3-, -4- or -5-yl(C₁-C₄)alkyl, isoxazol-3-, -4- or -5-yl(C₁-C₄)alkyl, isothiazol-3-, -4- or -5-yl(C₁-C₄)alkyl, pyridazin-3- or -4-yl(C₁-C₄)alkyl, pyrimidin-2-, -4-, -5- or -6-yl(C₁-C₄)alkyl, pyrazin-2- or -3-yl(C₁-C₄)alkyl, 1,3,5-triazin-2-yl(C₁-C₄)alkyl; or indol-2-(C₁-C₄)alkyl, wherein the preceding R₄ heterocycles are optionally mono- or di-substituted independently with halo, trifluoromethyl, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, amino, hydroxy or cyano and the substituents are bonded to carbon; or

R₄ is R₁₅-carbonyloxymethyl, wherein the R₁₅ is phenyl, thiazolyl, imidazolyl, 1H-indolyl, furyl, pyrrolyl, oxazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazinyl and wherein the preceding R₁₅ rings are optionally mono- or di-substituted independently with halo, amino, hydroxy, (C₁-C₄)alkyl, (C₁-C₄)alkoxy or trifluoromethyl and the mono- or di-substituents are bonded to carbon;

R₅ is H, methyl, ethyl, n-propyl, hydroxymethyl or hydroxyethyl;

R₆ is carboxy, (C₁-C₈)alkoxycarbonyl, benzyloxycarbonyl, C(O)NR₈R₉ or C(O)R₁₂ wherein

R₈ is H, (C₁-C₆)alkyl, cyclo(C₃-C₆)alkyl, cyclo(C₃-C₆)alkyl(C₁-C₅)alkyl, hydroxy or (C₁-C₈)alkoxy;

and

R₉ is H, cyclo(C₃-C₈)alkyl, cyclo(C₃-C₈)alkyl(C₁-C₅)alkyl, cyclo(C₄-C₇)alkenyl, cyclo(C₃-C₇)alkyl(C₁-C₅)alkoxy, cyclo(C₃-C₇)alkyloxy, hydroxy, methylene-perfluorinated(C₁-C₈)alkyl, phenyl, or a heterocycle wherein the heterocycle is pyridyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, pyridinyl, piperidinyl, morpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, thiochromanyl or tetrahydrobenzothiazolyl wherein the heterocycle rings are carbon-nitrogen linked; or

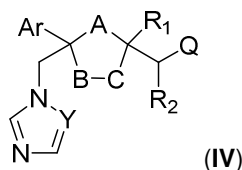
R₉ is (C₁-C₆)alkyl or (C₁-C₈)alkoxy wherein the (C₁-C₆)alkyl or (C₁-C₈)alkoxy is optionally monosubstituted with cyclo(C₄-C₇)alken-1-yl, phenyl, thienyl, pyridyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, piperidinyl, morpholinyl, thiomorpholinyl, 1-oxothiomorpholinyl, 1,1-dioxothiomorpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl or indolyl and wherein the (C₁-C₆)alkyl or (C₁-C₈)alkoxy are optionally additionally independently mono- or di-substituted with halo, hydroxy, (C₁-C₅)alkoxy, amino, mono-N— or di-N,N—(C₁-C₅)alkylamino, cyano, carboxy, or (C₁-C₄)alkoxycarbonyl; and wherein the R₉ rings are optionally mono- or di-substituted independently on carbon with halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, hydroxy, hydroxy(C₁-C₄)alkyl, amino(C₁-C₄)alkyl, mono-N— or di-N,N—(C₁-C₄)alkylamino(C₁-C₄)alkyl, (C₁-C₄)alkoxy(C₁-C₄)alkyl, amino, mono-N— or di-N,N—(C₁-C₄)alkylamino, cyano, carboxy, (C₁-C₅)alkoxycarbonyl, carbamoyl, formyl or trifluoromethyl and the R₉ rings may optionally be additionally mono- or di-substituted independently with (C₁-C₅)alkyl or halo;

optionally with the proviso that no quaternized nitrogen on any R₉ heterocycle is included;

R₁₂ is morpholino, thiomorpholino, 1-oxothiomorpholino, 1,1-dioxothiomorpholino, thiazolidin-3-yl, 1-oxothiazolidin-3-yl, 1,1-dioxothiazolidin-3-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, piperazin-4-yl,

wherein the R₁₂ rings are optionally mono-, di- or tri-substituted independently with halo, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, hydroxy, amino, mono-N— or di-N,N—(C₁-C₅)alkylamino, formyl, carboxy, carbamoyl, mono-N— or di-N,N—(C₁-C₅)alkylcarbamoyl, (C₁-C₆)alkoxy(C₁-C₃)alkoxy, (C₁-C₅)alkoxycarbonyl, benzyloxycarbonyl, (C₁-C₅)alkoxycarbonyl(C₁-C₅)alkyl, (C₁-C₄)alkoxycarbonylamino, carboxy(C₁-C₅)alkyl, carbamoyl(C₁-C₅)alkyl, mono-N— or di-N,N—(C₁-C₅)alkylcarbamoyl(C₁-C₅)alkyl, hydroxy(C₁-C₅)alkyl, (C₁-C₄)alkoxy(C₁-C₄)alkyl, amino(C₁-C₄)alkyl, mono-N— or di-N,N—(C₁-C₄)alkylamino(C₁-C₄)alkyl, oxo, hydroxylmino or (C₁-C₆)alkoxylmino and wherein no more than two substituents are selected from oxo, hydroxylmino or (C₁-C₆)alkoxylmino and oxo, hydroxylmino or (C₁-C₆)alkoxyimino are on nonaromatic carbon; and

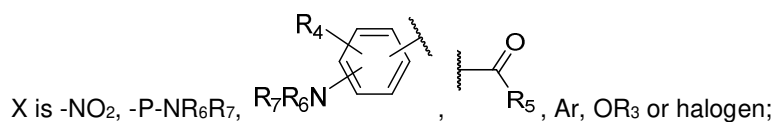
16 The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula
(IV)



either one of A, B and C is oxygen and the remaining two of A, B and C are CH_2 ; or A is oxygen, C_2 , and C is a direct bond;

$$\begin{aligned} & \text{---}W\text{---}P\text{---}\langle \text{benzene ring} \rangle\text{---}X_t; \quad \text{---}W\text{---}P\text{---}\langle \text{pyridine ring} \rangle\text{---}X_t; \quad \text{---}W\text{---}P\text{---}\langle \text{pyridine ring} \rangle\text{---}X_t; \\ & \text{---}W\text{---}CH_2\text{---}(C\equiv C)_r\text{---}Ar; \quad \text{---}W\text{---}CH_2\text{---}(C\equiv C)_r\text{---}C(R_{10})_t; \quad \text{---}W\text{---}CH_2\text{---}(CH=CH)_r\text{---}C(R_{10})_t; \\ & \text{---}W\text{---}CH_2\text{---}(C\equiv C)_r\text{---}CH_2\text{---}NR_6R_7; \quad \text{---}W\text{---}CH(R_8)\text{---}(CH_2)_p\text{---}CO_2R_9; \quad \text{---}OH; \quad \text{---}NR_{14}R_9; \text{ or} \\ & \text{---}O\text{---}C(=O)\text{---}R_{13}R_9. \end{aligned}$$

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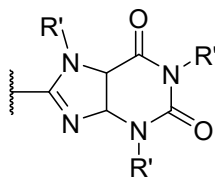
P is a direct bond, -CHR₁₁- or -CHR₁₁CHR₁₂-;

R₁, R₈, R₉ and R₁₀ are independently hydrogen, lower alkyl or lower alkyl substituted by one or more hydroxy groups;

R₂, R₄, R₁₁, R₁₂ and R₁₄ are hydrogen, hydroxy, lower alkyl or lower alkyl substituted by one or more hydroxy groups;

R₃ and R₁₃ are independently hydrogen, lower alkyl, (C₂-C₈) perhaloalkanoyl or (C₂-C₈) alkanoyl;

R₆ and R₇ are independently hydrogen, lower alkyl, phenyl or phenyl substituted by one or more of halo, perhalo(lower)alkyl, (C₂-C₈)alkanoyl, lower alkyl, lower alkyl substituted by one or more hydroxy groups, lower alkoxy, or 2-(lower)alkyl-3-oxo-1,2,4-triazol-4-yl, or R₆ and R₇ taken together with the nitrogen atom in NR₆ R₇ form unsubstituted or substituted 5- or 6-membered heterocyclyl ring systems containing carbon and one to four heteroatoms chosen from N, O and S, the heterocyclyl substituents being (C₁-C₈)alkanoyl, lower alkyl, lower alkoxycarbonyl, aminocarbonyl, N-lower alkylaminocarbonyl, N,N-di(lower alkyl)amino carbonyl, aminothiocarbonyl, N-lower alkylaminothiocarbonyl, N,N-di(lower alkyl)aminothiocarbonyl, lower alkyl sulfonyl, phenyl-substituted lower alkyl sulfonyl, N-lower alkylamino, N,N-di(lower alkyl)amino, 1,3-imidazol-1-yl, 2-loweralkylsulfenyl-1,3-imidazol-1-yl, 2-pyridinyl, 2-thiazolyl, 2-lower alkyl-3-oxo-1,2,4-triazol-4-yl, 1-lower alkylbenzimidazol-2-yl, phenyl or phenyl substituted by one or more of halo, perhalo lower alkyl, (C₂-C₈) alkanoyl, lower alkyl, lower alkyl substituted by one or more hydroxy group, lower alkoxy, 1H,2,4-triazol-1-yl, 2-lower alkyl-3-oxo-1,2,4-triazol-4-yl, or a substituent represented by the formula:



R₅ is a lower alkyl, lower alkoxy, amino, N,N-dilower alkylamino, phenyl or phenyl substituted by one or more of halo, perhalo lower alkyl, lower alkoxy, nitro, cyano, (C₂-C₈)alkanoyl;

p is 0, 1, 2, 3, 4 or 5;

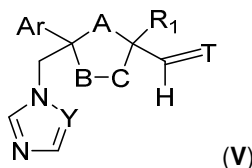
n is 0, 1 or 2;

r is 1 or 2; and

t is 0, 1, 2 or 3;

or a pharmaceutically acceptable salt, ester, or ether thereof ; or

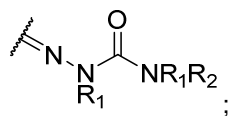
wherein the CYP51A1 inhibitor is a compound represented by formula (V)



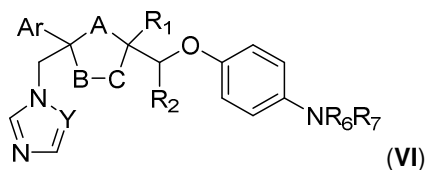
wherein Y and Ar are as defined for formula (IV);

one of A, B or C is oxygen and the remaining two of A, B, or C are -CH₂-;

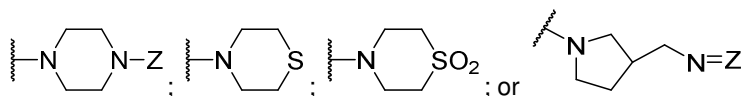
T is =O, =NOR₁, =NNR₁ R₂ or



wherein R₁ is hydrogen, lower alkyl or lower alkyl substituted by one or more hydroxy groups; and R₂ is hydrogen, hydroxy, lower alkyl or lower alkyl substituted by one or more hydroxy groups; or wherein the CYP51A1 inhibitor is a compound represented by formula (VI)

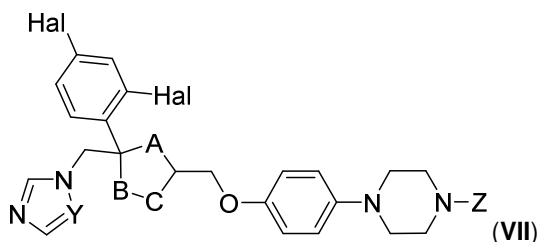


wherein Y, Ar, R₁, R₂, R₆ and R₇ are as defined for formula (IV), and either one of A, B and C is oxygen and the remaining two of A, B and C are CH₂, or A is oxygen, B is CH₂, and C is a direct bond, in particular wherein NR₆R₇ is:



in particular wherein Z is hydrogen, (C₁-C₈) alkanoyl, lower alkyl, (C₁-C₈) perhaloalkanoyl or phenyl substituted by 2-loweralkyl-3-oxo-1,2,4-triazol-4-yl.

17. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (VII)

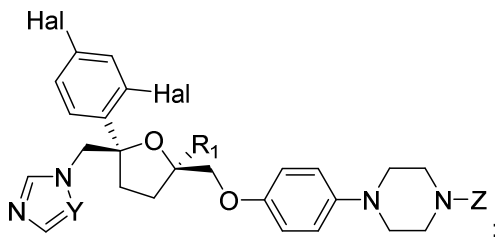


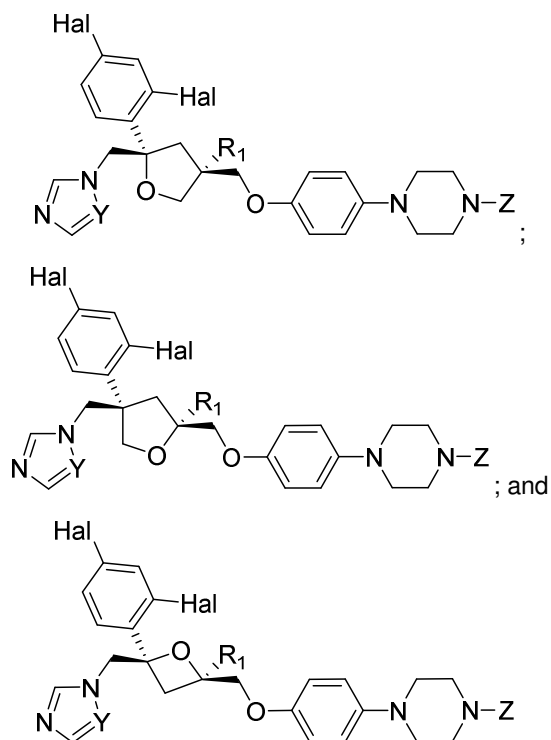
wherein one of A, B and C is oxygen and the remaining two of A, B and C are -CH₂-, or two of A, B and C are -CH₂-;

each Hal is independently Cl or F; and

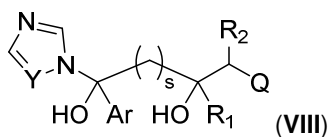
Z is lower alkyl, (C₂-C₈)alkanoyl, or phenyl substituted by 2-loweralkyl-3-oxo-1,2,4-triazol-4-yl; or

wherein the CYP51A1 inhibitor is selected from:



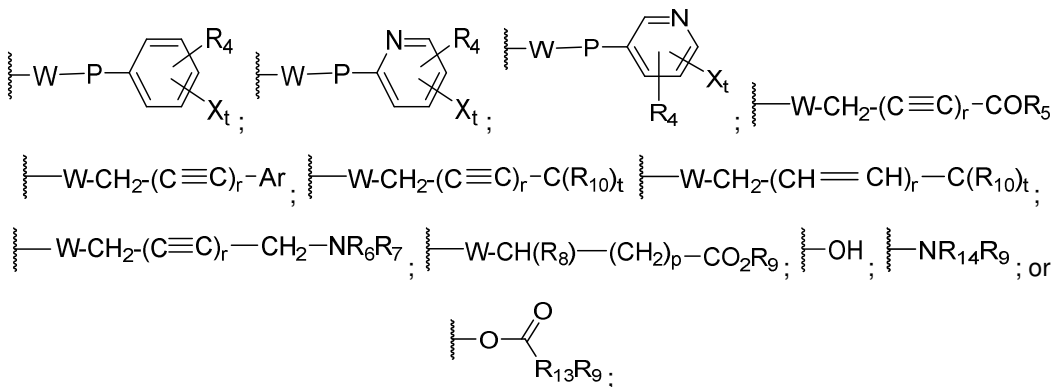


18. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (VIII)



wherein Ar is thienyl, pyridyl, biphenyl, phenyl or phenyl substituted by one or more of halo, nitro, cyano, lower alkyl, lower alkoxy or perhalo(lower)alkyl;

Q is:



W is -NR₅-, -O-, or -S(O)_n-;

X is -NO₂, -P-NR₆R₇, , , Ar, OR₃ or halogen;

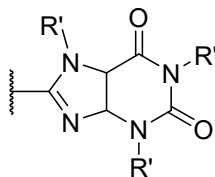
P is a direct bond, -CHR₁₁- or -CHR₁₁CHR₁₂-;

R₈, R₉ and R₁₀ are independently hydrogen, lower alkyl or lower alkyl substituted by one or more hydroxy groups;

R₄, R₁₁, R₁₂ and R₁₄ are hydrogen, hydroxy, lower alkyl or lower alkyl substituted by one or more hydroxy groups;

R₃ and R₁₃ are independently hydrogen, lower alkyl, (C₂-C₈) perhaloalkanoyl or (C₂-C₈) alkanoyl;

R₆ and R₇ are independently hydrogen, lower alkyl, phenyl or phenyl substituted by one or more of halo, perhalo(lower)alkyl, (C₂-C₈)alkanoyl, lower alkyl, lower alkyl substituted by one or more hydroxy groups, lower alkoxy, or 2-(lower)alkyl-3-oxo-1,2,4-triazol-4-yl, or R₆ and R₇ taken together with the nitrogen atom in NR₆ R₇ form unsubstituted or substituted 5- or 6-membered heterocyclyl ring systems containing carbon and one to four heteroatoms chosen from N, O and S, the heterocyclyl substituents being (C₁-C₈)alkanoyl, lower alkyl, lower alkoxy, carbonyl, aminocarbonyl, N-lower alkylaminocarbonyl, N,N-di(lower alkyl)amino carbonyl, aminothiocarbonyl, N-lower alkylaminothiocarbonyl, N,N-di(lower alkyl)aminothiocarbonyl, lower alkyl sulfonyl, phenyl-substituted lower alkyl sulfonyl, N-lower alkylamino, N,N-di(lower alkyl)amino, 1,3-imidazol-1-yl, 2-loweralkylsulfenyl-1,3-imidazol-1-yl, 2-pyridinyl, 2-thiazolyl, 2-lower alkyl-3-oxo-1,2,4-triazol-4-yl, 1-lower alkylbenzimidazol-2-yl, phenyl or phenyl substituted by one or more of halo, perhalo lower alkyl, (C₂-C₈) alkanoyl, lower alkyl, lower alkyl substituted by one or more hydroxy group, lower alkoxy, 1H,2,4-triazol-1-yl, 2-lower alkyl-3-oxo-1,2,4-triazol-4-yl, or a substituent represented by the formula:



R₅ is a lower alkyl, lower alkoxy, amino, N,N-dilower alkylamino, phenyl or phenyl substituted by one or more of halo, perhalo lower alkyl, lower alkoxy, nitro, cyano, (C₂-C₈)alkanoyl;

p is 0, 1, 2, 3, 4 or 5;

n is 0, 1 or 2;

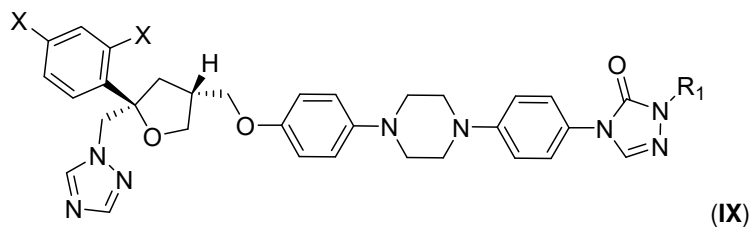
r is 1 or 2; and

t is 0, 1, 2 or 3;

R₁ is hydrogen, lower alkyl or lower alkyl substituted by one or more hydroxy groups; and

R₂ is hydrogen, hydroxy, lower alkyl or lower alkyl substituted by one or more hydroxy groups.

19. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (IX)

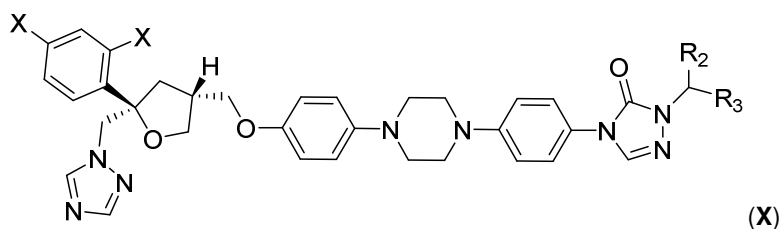


Wherein each X is independently F or Cl;

R₁ is a straight or branched chain (C₃ to C₈) alkyl group optionally substituted by one or two hydroxy moieties or by one or two groups convertible in vivo into hydroxy moieties;

or a pharmaceutically acceptable salt, ester, or ether thereof; or

wherein the CYP51A1 inhibitor is a compound represented by formula (X)

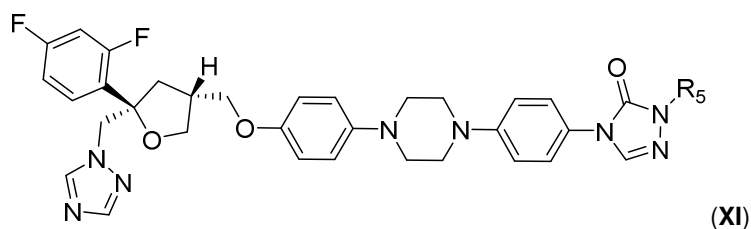


wherein each X is independently F or Cl; and

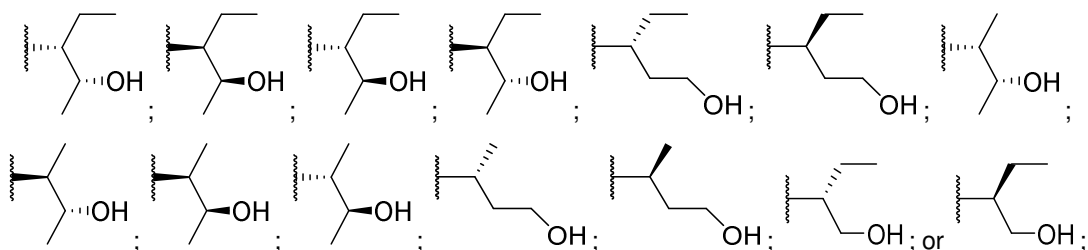
R₂ is H or (C₁ -C₃) alkyl and R₃ is (C₁ -C₃) alkyl optionally substituted by one hydroxy moiety or by a group convertible in vivo into a hydroxy moiety;

or a pharmaceutically acceptable salt, ester, or ether thereof; or

wherein the CYP51A1 inhibitor is a compound represented by formula (XI)

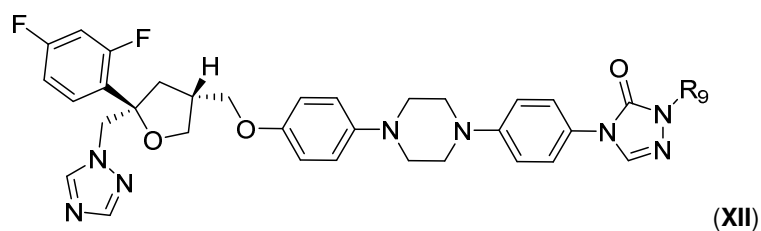


wherein R₅ is:



or a pharmaceutically acceptable salt, ester, or ether thereof; or

wherein the CYP51A1 inhibitor is a compound represented by formula (XII)

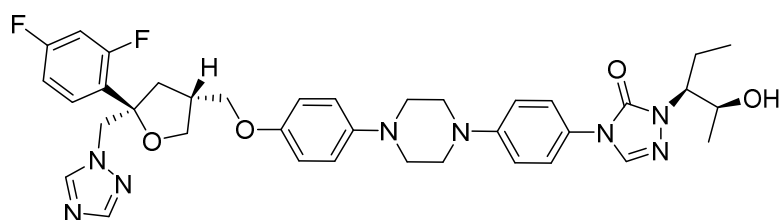


wherein R₉ is -H(C₂H₅)CH(R₆)CH₃ or -H(CH₃)CH(R₆)CH₃;

R₆ is OH or a group convertible in vivo into OH;

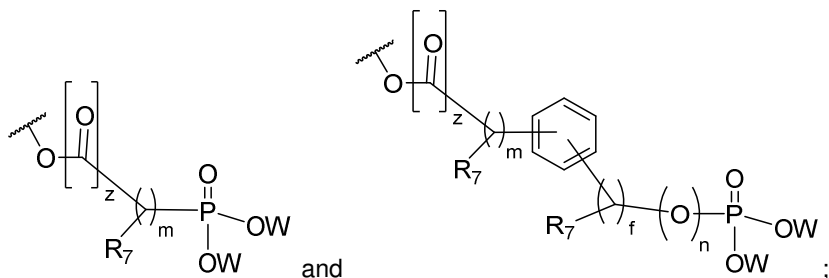
or a pharmaceutically acceptable salt, ester, or ether thereof ; or

wherein the CYP51A1 inhibitor is:



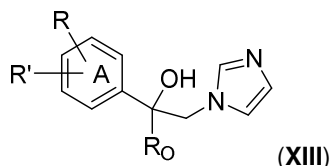
or a pharmaceutically acceptable salt, ester, or ether thereof; or

wherein the CYP51A1 inhibitor is an ester of any one of the indicated compounds, in particular wherein the ester is a phosphate ester, in particular wherein the phosphate ester is selected from



wherein z is 0 or 1, R_7 is a (C_1 - C_6) straight or branched chain alkyl group or H, f and n are independently an integer from 0 to 6, m is zero or 1 and W is H, CH_2 Ar or and Ar is phenyl, phenyl substituted by halo, nitro, cyano or trihalomethyl.

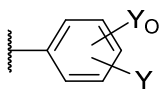
20. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (XIII)



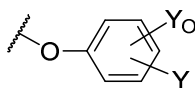
wherein R_O is alkyl of 2 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, cycloalkyl-alkyl in which the cycloalkyl is of 3 to 6 carbon atoms and the alkyl portion of 1 to 3 carbon atoms, the cycloalkyl and cycloalkyl-alkyl being optionally ring substituted by one or two alkyl groups of 1 to 3 carbon atoms;

R is hydrogen, fluoro, chloro, bromo, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkylthio of 1 to 4 carbon atoms or nitro;

R' is hydrogen, fluoro, chloro, bromo, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkylthio of 1 to 4 carbon atoms, $-CF_3$ in the 3-position of Ring A, nitro, $-CN$, $-COOR''$, an optionally substituted phenyl group of the formula:



or an optionally substituted phenoxy group in the 4-position of Ring A and having the formula:



R'' is hydrogen, alkyl of 1 to 4 carbon atoms or a cation, preferably an agriculturally acceptable cation, or R and R' together represent alkylenedioxy of 1 or 2 carbon atoms substituted onto adjacent carbon atoms of the phenyl Ring A; and

Y_O and Y are independently hydrogen, fluoro, chloro, bromo, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms.

21. The use of claim 12, wherein the CYP51A1 inhibitor is an α -[aryl(alkylene)_m]- α -[CR₁R₂-(CHR₃)_n-R₄]1H-1,2,4-triazole-1-ethanol or an α -[aryl(alkylene)_m]- α -[CR₁R₂-(CHR₃)_n-R₄]1H-imidazole-1-ethanol, or a pharmaceutically acceptable salt or ester thereof, wherein:

R₁ is C₁₋₅ alkyl, unsubstituted or substituted by halogen, by C₁₋₅-alkoxy, by phenyl-C₁₋₃ alkoxy, by phenoxy, by C₁₋₅ alkylthio, by phenyl-C₁₋₃ alkylthio or by phenylthio, whereby optional phenyl groups may be substituted by C₁₋₅ alkyl, halogen, halogen substituted C₁₋₅ alkyl, C₁₋₅ alkoxy or halogen substituted C₁₋₅ alkoxy; or

is C₂₋₅ alkenyl or C₂₋₅ alkynyl, unsubstituted or substituted by halogen; or

is cycloalkyl, unsubstituted or substituted by C₁₋₅ alkyl; or

is phenyl, unsubstituted or substituted by substituents selected from the group consisting of halogen and C₁₋₅ alkyl;

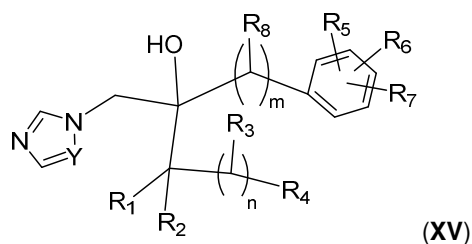
R₂ and R₃, independently, are H or have an R₁ significance, whereby R₁ and R₂ may be linked together to form a C₃₋₇ cycloalkyl group;

m is 0 or 1;

n is 0, 1 or 2; and

R₄ is C₃₋₇ cycloalkyl, unsubstituted or substituted by C₁₋₅ alkyl; or

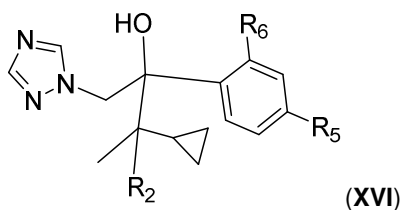
wherein the CYP51A1 inhibitor is a compound represented by formula (XV)



wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, m and n are as defined in claim 35, R₈ is H or C₁₋₅ alkyl, and Y is CH or N;

or a pharmaceutically acceptable salt, ester, or ether thereof; or

wherein the CYP51A1 inhibitor is a compound represented by formula (XVI)

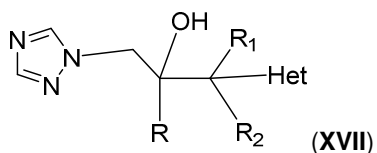


wherein R₂ is hydrogen or optionally substituted alkyl, such as optionally substituted lower alkyl; and

R₅ and R₆ are each independently hydrogen or a halogen atom, such as chloro;

or a pharmaceutically acceptable salt, ester, or ether thereof.

22. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (XVII)



wherein R is phenyl optionally substituted by 1 to 3 substituents each independently selected from halo and CF₃ ;

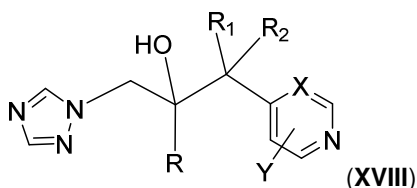
R₁ is C₁ -C₄ alkyl;

R² is H or C₁ -C₄ alkyl; and

"Het", which is attached to the adjacent carbon atom by a ring carbon atom, is selected from pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl. "Het" may be optionally substituted by C₁ -C₄ alkyl, C₁ -C₄ alkoxy, halo, CF₃, CN, NO₂, NH₂, -NH(C₁ -C₄ alkanoyl) or -NHCO₂ (C₁ -C₄ alkyl);

or a pharmaceutically acceptable salt, ester, or ether thereof; or

wherein the CYP51A1 inhibitor is a compound represented by formula (XVIII)



wherein R is optionally substituted phenyl;

R₁ is optionally substituted alkyl, such as optionally substituted lower alkyl;

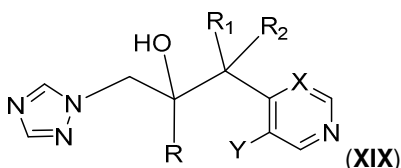
R² is H or optionally substituted alkyl, such as optionally substituted lower alkyl;

X is CH or N; and

Y is a halogen, such as F or Cl;

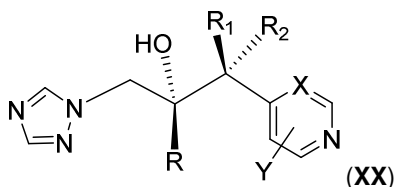
or a pharmaceutically acceptable salt, ester, or ether thereof; or

wherein the CYP51A1 inhibitor is a compound represented by formula (XIX)



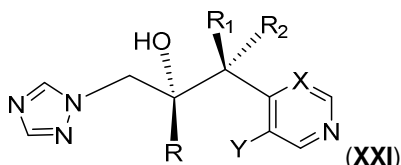
wherein R, R₁, R₂, X, and Y are as defined for formula (XVIII); or

wherein the CYP51A1 inhibitor is a compound represented by formula (XX)



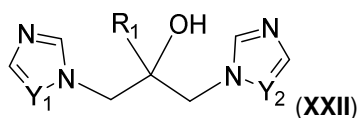
wherein R, R₁, R₂, X, and Y are as defined for formula (XVIII); or

wherein the CYP51A1 inhibitor is a compound represented by formula (XXI)



wherein R, R₁, R₂, X, and Y are as defined for formula (XVIII).

23. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (XXII)

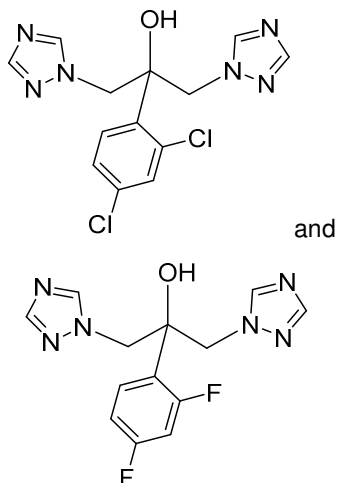


wherein R₁ is an optionally substituted alkyl, cycloalkyl, aryl, or arylalkyl group; and

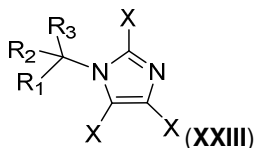
Y₁ and Y₂ are each independently =CH- or =N-;

or a pharmaceutically acceptable salt, ester, or ether thereof; or

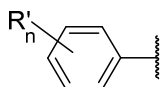
wherein the CYP51A1 inhibitor is a compound selected from:



24. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (XXIII)



wherein each of R₁, R₂, and R₃ is independently an aryl group represented by the formula:



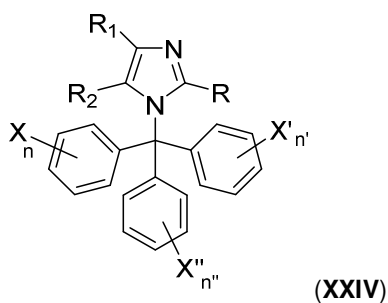
n is an integer of from 0 to 5 and each R' is independently halogen or optionally substituted alkyl;

and

each X is independently selected from hydrogen, optionally substituted alkyl, or optionally substituted aryl;

or a pharmaceutically acceptable salt thereof.

25. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (XXIV)

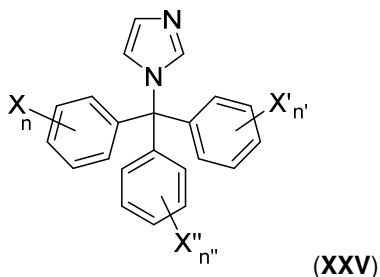


wherein each of R, R₁, and R₂ is independently hydrogen, optionally substituted alkyl, or optionally substituted aryl;

each of X, X', and X''' is independently hydrogen, halogen, optionally substituted alkyl or optionally substituted aryl; and

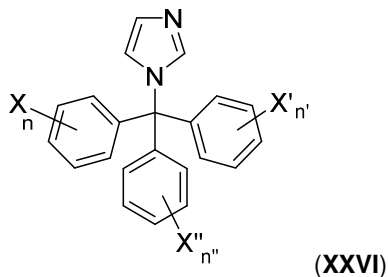
each of n, n', and n'' is independently an integer of from 1 to 5; or

wherein the CYP51A1 inhibitor is a compound represented by formula (XXV)



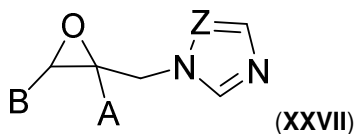
wherein X, X', X''', n, n', and n'' are as defined for formula (XXIV); or

wherein the CYP51A1 inhibitor is a compound represented by formula (XXVI)



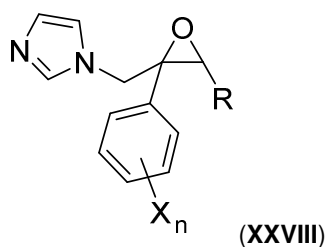
wherein X, X', X''', n, n', and n'' are as defined for formula (XXIV).

26. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (XXVII)



wherein A and B are independently selected from optionally substituted alkyl, optionally substituted naphthyl, optionally substituted biphenyl, and optionally substituted phenyl, and Z is CH or N;
or

wherein the CYP51A1 inhibitor is a compound represented by formula (XXVIII)

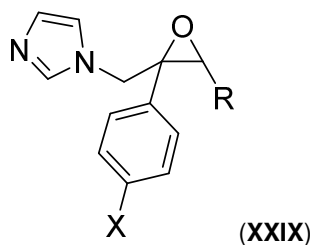


wherein R is optionally substituted aryl, such as phenyl, pyridyl, tetrahydropyranyl, norbornyl, C₃-C₁₂ cycloalkyl or C₅-C₈ cycloalkenyl, each of which may be unsubstituted or monosubstituted to trisubstituted by halogen, nitro, phenoxy, alkyl, amino, alkoxy, haloalkoxy, or haloalkyl;

each X is independently fluorine, chlorine, bromine, or iodine; and

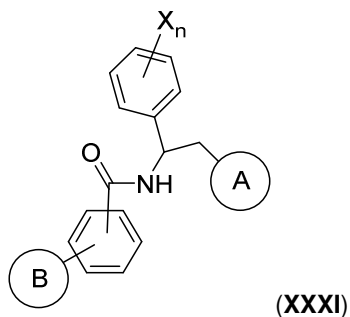
each n is independently an integer of from 1 to 5; or

wherein the CYP51A1 inhibitor is a compound represented by formula (XXIX)



wherein R and X are as defined for formula (XXVIII); or

27. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (XXXI)

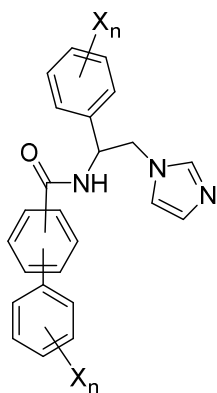


wherein each of rings A and B are independently optionally substituted and optionally fused aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

each X is independently halogen or optionally substituted alkyl; and

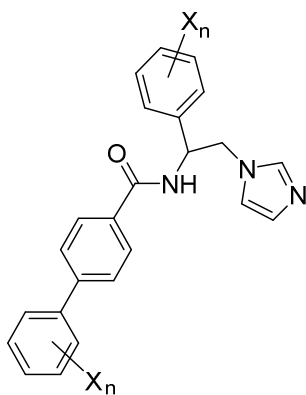
n is an integer of from 1 to 5; or

wherein CYP51A1 inhibitor is a compound represented by formula (XXXII)



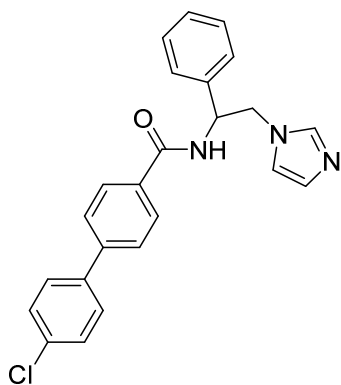
(XXXII)

wherein each X is independently halogen or optionally substituted alkyl; and
 each n is independently an integer of from 1 to 5; or
 wherein the CYP51A1 inhibitor is a compound represented by formula (XXXIII)



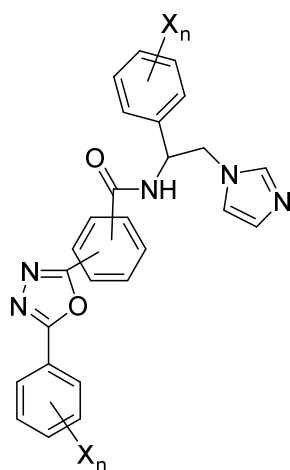
(XXXIII)

wherein each X and n are as defined for formula (XXXII); or
 wherein CYP51A1 inhibitor is:



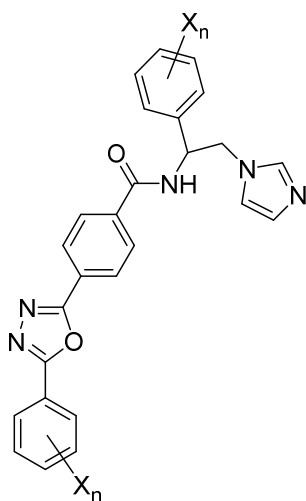
; or

wherein the CYP51A1 inhibitor is a compound represented by formula (XXXIV)



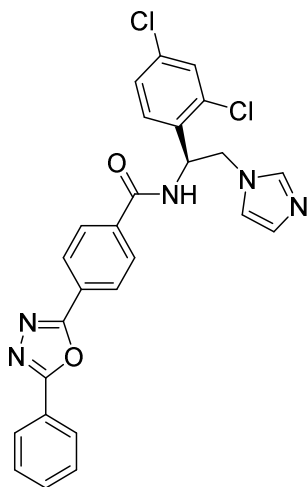
(XXXIV)

wherein each X is independently halogen or optionally substituted alkyl; and
 each n is independently an integer of from 1 to 5; or
 wherein the CYP51A1 inhibitor is a compound represented by formula (XXXV)

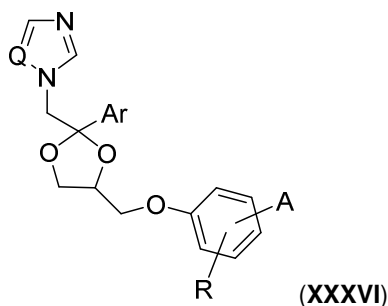


(XXXV)

wherein each X and n are as defined for formula (XXXIV); or
 wherein the CYP51A1 inhibitor is:



28. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (XXXVI)



wherein Q is selected from the group consisting of CH and N;

Ar is an optionally substituted, optionally fused aryl group, such as an optionally fused, optionally substituted phenyl group, for example, a phenyl group having from 1 to 3 substituents, such as from 1 to 3 substituents independently selected from the group consisting of halo, lower alkyl and lower alkyloxy;

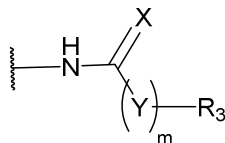
A is selected from the group consisting of:

- (a) an isothiocyanato group -N=C=S ;
- (b) an amino group of the formula



wherein R₁ and R₂ are each independently selected from the group consisting of hydrogen and lower alkyl;

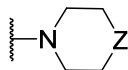
- (c) a group of the formula



wherein X is selected from the group consisting of O and S, Y is selected from the group consisting of O and NH, m is the integer 0 or 1, and R₃ is selected from the group consisting of hydrogen, lower alkyl, mono- and dihalo-(lower alkyl), phenyl and substituted phenyl, said substituted phenyl having from 1 to 2 substituents independently selected from the group consisting of halo, lower alkyl and lower alkyloxy, optionally provided that:

- i) when said X is S, then said Y is NH and said m is 1; and
- ii) when said Y is O and said m is 1, then said R₃ is other than hydrogen; and

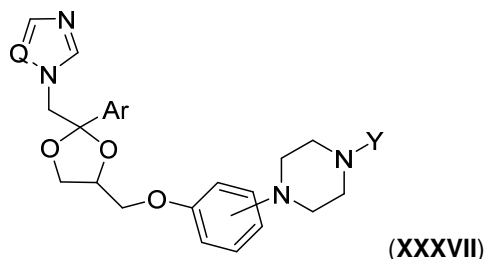
- (d) a group of the formula



wherein Z is selected from the group consisting of a direct bond, CH₂, O and N-R₄, wherein R₄ is selected from the group consisting of hydrogen, lower alkyl, hydroxy-(lower alkyl), (lower alkyloxy)-lower alkyl, lower alkanoyl, lower alkylsulfonyl, phenylmethylsulfonyl, lower alkyloxycarbonyl, lower alkyloxycarbonylmethyl, phenoxycarbonyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, aminocarbonylmethyl, (lower alkyl)aminocarbonylmethyl, (lower alkyl)aminothioxomethyl, (lower alkylthio)thioxomethyl, phenyl, phenylmethyl, benzoyl and

substituted benzoyl, said substituted benzoyl being benzoyl having from 1 to 2 substituents independently selected from the group consisting of halo, lower alkyl and lower alkyloxy; and R is selected from the group consisting of hydrogen and nitro, optionally provided that when said R is nitro, then said A is amino; or

wherein the CYP51A1 inhibitor is a compound represented by formula (XXXVII)



wherein Q is selected from the group consisting of N and CH;

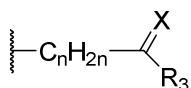
Ar is selected from the group consisting of phenyl, thienyl, halothienyl and substituted phenyl, the substituted phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, lower alkyl, lower alkyloxy and trifluoromethyl; and

the group Y is selected from the group consisting of:

a group of the formula $-\text{SO}_2\text{R}_1$, wherein R_1 is selected from the group consisting of trifluoromethyl and aryl;

a group of formula $-\text{alk}-\text{R}_2$, wherein alk is selected from the group consisting of lower alkylene and lower alkenylene and R_2 is selected from the group consisting of cyano, amino, mono- and di(lower alkyl)amino, arylamino, mono- and di(aryl lower alkyl)amino, 1-pyrrolidinyl, 1-morpholinyl, 1-piperidinyl, aryloxy and aryl, provided that alk is other than methylene when R_2 is phenyl;

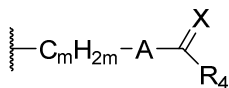
a group of formula



wherein n is an integer of from 0 to 6 inclusive, X is O or S and R_3 is selected from the group consisting of hydrogen, mono-, di- and trihalolower alkyl, amino, mono- and di(lower alkyl)amino, arylamino, mono- and di(aryl lower alkyl)amino, aminolower alkyl, mono- and di(lower alkyl)aminolower alkyl, (1-pyrrolidinyl)lower alkyl, (1-morpholinyl)lower alkyl, (1-piperidinyl)lower alkyl, aryl, aryl lower alkyl, aryl lower alkenyl and lower alkyloxycarbonyl lower alkyloxy, optionally provided that:

- (i) said n is other than 0 or 1 when said R_3 is amino or lower alkylamino; and
- (ii) said n is other than 0 when said R_3 is di(lower alkyl)amino or aryl; and

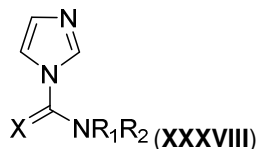
a group of formula



wherein m is an integer of from 1 to 6 inclusive, A is O or NH, X is O or S and R_4 is selected from the group consisting of hydrogen, lower alkyl, lower alkyloxy, aryl, aryloxy, aryl lower alkyl, amino, mono- and di(lower alkyl)amino, arylamino, mono- and di(aryl lower alkyl)amino, 1-pyrrolidinyl, 1-morpholinyl and 1-piperidinyl;

wherein said aryl is selected from the group consisting of phenyl, substituted phenyl, thienyl, halothienyl, lower alkylthienyl and pyridinyl, said substituted phenyl having from 1 to 3 substituents each independently selected from the group consisting of lower alkyl, lower alkyloxy, halo, amino, mono- and di(lower alkyl)amino, lower alkylcarbonylamino, nitro and trifluoromethyl.

29. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by (XXXVIII)

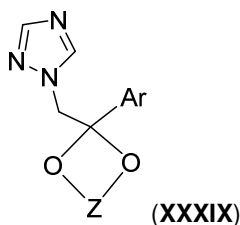


wherein X is oxygen or sulfur, R₁ is optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, phenylalkyl, phenylalkenyl, phenoxyalkyl or phenylthioalkyl and R₂ is optionally substituted phenyl, phenylalkyl, phenylalkenyl, phenoxyalkyl or phenylthioalkyl, provided that when R₁ is methyl or phenyl R₂ is substituted phenyl or optionally substituted phenylalkyl, phenylalkenyl, phenoxyalkyl or phenylthioalkyl; or

wherein X is selected from the group consisting of oxygen and sulfur, R₁ is selected from the group consisting of alkyl of 1 to 10 carbon atoms, alkenyl of 3 or 4 carbon atoms, alkynyl of 3 to 5 carbon atoms, cycloalkyl of 3 to 10 carbon atoms, optionally substituted phenyl, phenylalkyl, of the formula Ph(CH₂)_n where n is 1 to 5, phenylalkenyl of 9 to 11 carbon atoms, phenoxyalkyl of the formula PhO(CH₂)_n where n is 2 to 5 and phenylthioalkyl of the formula PhS(CH₂)_n where n is 2 to 5, wherein the substituted phenyl nucleus has at least one substituent selected from the group consisting of halo, alkoxy of 1 or 2 carbon atoms, alkyl of 1 to 4 carbon atoms, trihalomethyl, cyano, methylthio, nitro and methylsulphonyl, and R₂ is selected from the group consisting of optionally substituted phenylalkyl, of the formula Ph(CH₂)_n where n is 1 to 5, phenylalkenyl of 9 to 11 carbon atoms, phenoxyalkyl of the formula PhO(CH₂)_n where n is 2 to 5 and phenylthioalkyl of the formula PhS(CH₂)_n where n is 2 to 5, wherein the substituted phenyl nucleus has at least one substituent selected from the group consisting of halo, alkoxy of 1 or 2 carbon atoms, alkyl of 1 to 4 carbon atoms, trihalomethyl, cyano, methylthio, nitro and methylsulphonyl; or

wherein the CYP51A1 inhibitor is prochloraz.

30. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (XXXIX)

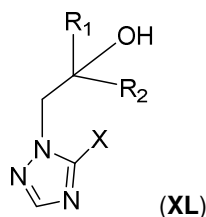


wherein Z is an alkylene selected from the group consisting of -CH₂CH₂-, -CH₂-CH₂CH₂-, -CH(CH₃)CH(CH₃)-, and -CH₂CH(alkyl)-, wherein the alkyl has from 1 to about 10 carbon atoms; and

Ar is an optionally fused, optionally substituted aryl group, such as an optionally fused, optionally substituted phenyl, thienyl, naphthyl, or fluorenyl, for example, phenyl, thienyl, halothienyl, naphthyl and

fluorenyl, each optionally containing one or more (e.g., from 1 to 3) substituents selected independently from the group consisting of halo, lower alkyl, lower alkyloxy, cyano, and nitro; or
wherein the CYP51A1 inhibitor is propiconazole.

31. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (XL)

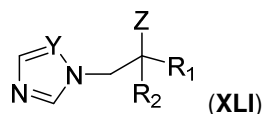


wherein R₁ and R₂ are each independently selected from optionally substituted alkyl, optionally substituted alkenyl, optionally substituted cycloalkyl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aroxyalkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

X is -SH, -SR₃, -SO-R₃, -SO₂-R₃, or -SO₃H, wherein R₃ is alkyl which is optionally substituted by one or more halogen moieties (e.g., fluorine and/or chlorine), alkenyl which is optionally substituted by one or more halogen moieties (e.g., fluorine and/or chlorine), optionally substituted aralkyl or optionally substituted aryl; or

wherein the CYP51A1 inhibitor is prothioconazole or prothioconazole-desthio; or

wherein the CYP51A1 inhibitor is a compound represented by formula (XLI)



wherein R₁ is -CH=CH-X, -C≡C-X, or -CH₂-CH₂-X, wherein X is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl or optionally substituted aryl, aralkyl, aryloxy alkyl, or heterocycle;

R₂ is alkyl, cycloalkyl (e.g. cyclopropyl, cyclopentyl, or cyclohexyl) or optionally substituted aryl;

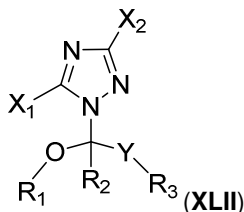
Z is Cl, CN, or OR₃, wherein R₃ is hydrogen, acetyl, alkyl, alkenyl or aralkyl; and

Y is =N- or =CH-,

or a pharmaceutically acceptable salt, ester, or ether thereof; or

wherein the CYP51A1 inhibitor is tebuconazole.

32. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (XLII)



wherein X₁ is hydrogen or an alkyl group,

X₂ is hydrogen or an alkyl group,

R₁ is an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl or optionally substituted aryl or aralkyl group,

R₂ is hydrogen or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl or optionally substituted aryl or aralkyl group,

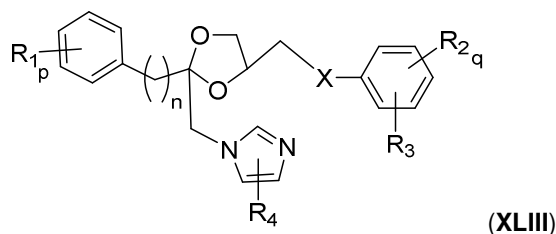
R₃ is hydrogen or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl or optionally substituted aryl or aralkyl group, and

Y is a keto group or a functional keto derivative.

or a pharmaceutically acceptable salt, ester, or ether thereof; or

wherein the CYP51A1 inhibitor is triadimenol.

33. The use of claim 12, wherein the CYP51A1 inhibitor is a compound represented by formula (XLIII)



wherein n is 2 or 3;

p is 0, 1 or 2;

q is 0, 1 or 2;

X is oxygen or S(O)_t wherein t is 0, 1, or 2;

each R₁ is independently halo, lower alkyl, lower alkoxy, or trifluoromethyl;

each R₂ is independently halo or lower alkyl;

R₃ is nitro or -N(R₅)R₆ where

R₅ is hydrogen or lower alkyl;

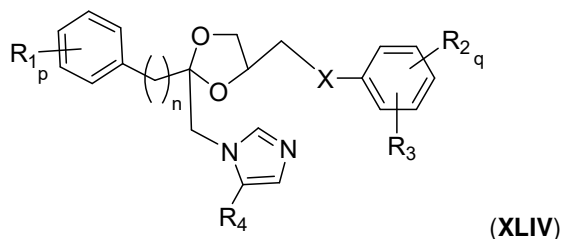
R₆ is hydrogen, lower alkyl, lower alkylsulfonyl or -C(Y)R₇ where Y is oxygen or sulfur and R₇ is hydrogen, lower alkyl, lower alkoxy or -N(R₈)R₉ where R₈ is hydrogen or lower alkyl and R₉ is hydrogen, lower alkyl or lower alkoxy carbonyl; or

R₅ and R₆ together with N is pyrrolidino, piperidino, morpholino, thiomorpholino or piperazino, wherein the piperazino is optionally substituted at the 4-position by -C(O)R₁₀ where R₁₀ is hydrogen, lower alkyl, lower alkoxy or amino; and

R₄ is hydrogen or optionally substituted lower alkyl;

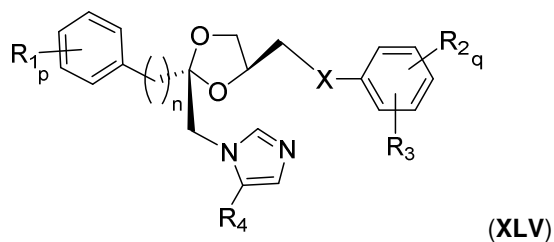
or a pharmaceutically acceptable salt, ester, or ether thereof; or

wherein the compound represented by formula (XLIII) is a compound represented by formula (XLIV)



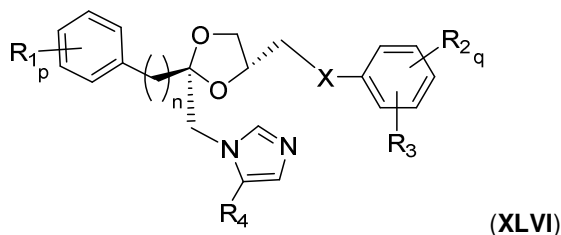
wherein R₁, R₂, R₃, R₄, X, n, p, and q are as defined for formula (XLIII); or

wherein the compound represented by formula (XLIII) is a compound represented by formula (XLV)



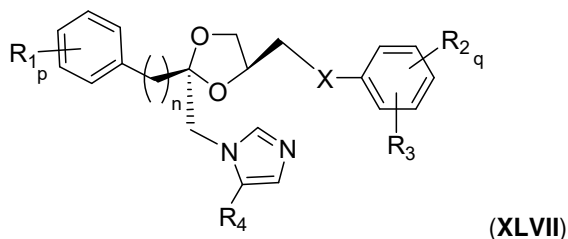
wherein R₁, R₂, R₃, R₄, X, n, p, and q are as defined for formula (XLIII); or

wherein the compound represented by formula (XLIII) is a compound represented by formula (XLVI)



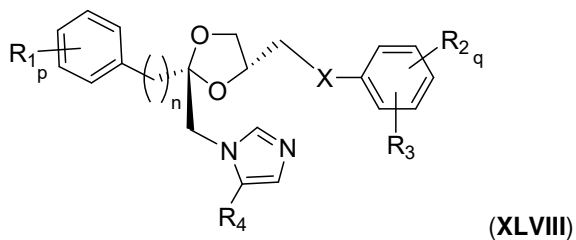
wherein R₁, R₂, R₃, R₄, X, n, p, and q are as defined for formula (XLIII); or

wherein the compound represented by formula (XLIII) is a compound represented by formula (XLVII)



wherein R₁, R₂, R₃, R₄, X, n, p, and q are as defined for formula (XLIII); or

wherein the compound represented by formula (XLIII) is a compound represented by formula (XLVIII)



wherein R₁, R₂, R₃, R₄, X, n, p, and q are as defined for formula (XLIII); or

wherein the CYP51A1 inhibitor is azalanstat.

34. The use of claim 12, wherein the CYP51A1 inhibitor is selected from the group consisting of LEK-935, CP-320626, itraconazole, posaconazole, cyproconazole, voriconazole, fluconazole, clotrimazol, fenticonazole, epoxiconazole, ketoconazole, ravuconazole, isavuconazole, holothurin A, theasaponin, capsicosine, betulafolientriol, prochloraz, propiconazole, prothioconazole, prothioconazole-desthio, tebuconazole, triadimenol, azalanstat, and variants thereof.

35. The use of claim 12, wherein the CYP51A1 inhibitor is an antibody or antigen-binding fragment thereof that specifically binds to CYP51A1 and/or inhibits CYP51A1 catalytic activity.

36. The use of claim 12, wherein the CYP61A1 inhibitor is an interfering RNA molecule, in particular wherein the interfering RNA molecule is a short interfering RNA, micro RNA, or short hairpin RNA.

37. The use of any one of claims 1-5 and 8-36, wherein the neuromuscular disorder is amyotrophic lateral sclerosis, and following the administration of the CYP51A1 inhibitor to the patient, the patient exhibits one or more, or all, of the following responses:

- (i) an improvement in condition as assessed using the amyotrophic lateral sclerosis functional rating scale or the revised ALSFRS;
- (ii) an increase in slow vital capacity;
- (iii) a reduction in decremental responses exhibited by the patient upon repetitive nerve stimulation;
- (iv) an improvement in muscle strength;
- (v) an improvement in quality of life;
- (vi) a decrease in the frequency and/or severity of muscle cramps; and/or
- (vii) a decrease in TDP-43 aggregation.

38. A kit comprising a CYP51A1 inhibitor and a package insert, wherein the package insert instructs a user of the kit to administer the CYP51A1 inhibitor to the patient in accordance with the use of any one of claims 1-5 and 8-36.