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(54) Title: THIAZOLO(3,2-A) PYRIMIDINONE AND OTHER HETEROBICYCLIC PYRIMIDINONE COMPOUNDS FOR USE IN MEDICAL THERAPY

(57) Abstract: The invention provides heterobicyclic pyrimidinone compounds such as thiazolo[3,2-a]pyrimidinone compounds, compositions containing such compounds, medical kits, and methods for using such compounds and compositions to treat medical disorders, e.g., Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy, in a patient. Exemplary heterobicyclic pyrimidinone compounds described herein include 5-oxo- 2,3-dihydro-5H-hiazolo[3,2-a]pyrimidine-6-carboxarnide compounds.

THIAZOLO[3,2-*a*]PYRIMIDINONE AND OTHER HETEROBICYCLIC PYRIMIDINONE COMPOUNDS FOR USE IN MEDICAL THERAPY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to United States Provisional Patent Application serial number 62/214,486, filed September 4, 2015, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The invention provides heterobicyclic pyrimidinone compounds such as thiazolo[3,2-*a*]pyrimidinone compounds, compositions containing such compounds, medical kits, and methods for using such compounds and compositions to treat medical disorders in a patient.

BACKGROUND

[0003] Gaucher disease is a genetic disorder associated with a deficiency of the lysosomal enzyme, glucocerebrosidase. Gaucher disease has been reported to have an incidence of approximately 1 in 20,000 live births in the general population, and it is a common lysosomal storage disorder. Current treatments for patients suffering from this disease include enzyme replacement therapy, which tends to be expensive, analgesics for bone pain relief, and medical procedures such as blood and platelet transfusions, splenectomy, and joint replacement for patients who experience bone erosion. However, new treatment options are needed having improved efficacy across a broader range of patients and/or reduced adverse side effects.

[0004] Mutations in the gene encoding glucocerebrosidase are also a risk factor for Parkinson's disease and diffuse Lewy Body Disease. Parkinson's disease is a degenerative disorder of the central nervous system associated with death of dopamine-containing cells in a region of the midbrain. Parkinson's disease afflicts millions of people, and the incidence of the disease increases with age. Treatment of Parkinson's disease frequently involves use of levodopa and dopamine agonists. However, these drugs can produce significant side effects such as hallucinations, insomnia, nausea, and constipation. Further, patients often develop

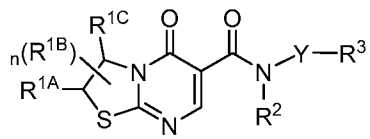
tolerance to these drugs such that the drugs become ineffective at treating the symptoms of the disease, while sometimes also producing a movement disorder side effect called dyskinesia. Diffuse Lewy Body disease is a dementia that is sometimes confused with Alzheimer's disease.

[0005] Accordingly, the need exists for new therapeutic agents for treating Gaucher disease, Parkinson's disease, and related medical disorders. The present invention addresses this need and provides other related advantages.

SUMMARY

[0006] The invention provides heterobicyclic pyrimidinone compounds such as thiazolo[3,2-*a*]pyrimidinone compounds, compositions containing such compounds, medical kits, and methods for using such compounds and compositions to treat medical disorders, *e.g.*, Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, and multiple myeloma, in a patient. Various aspects and embodiments of the invention are described in further detail below.

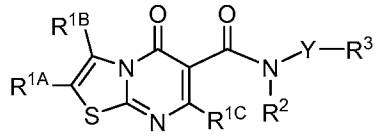
[0007] One aspect of the invention provides a family of heterobicyclic pyrimidinone compounds embraced by Formula I that may be used in the methods, compositions, and kits described herein, wherein Formula I is represented by:



(I)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description.

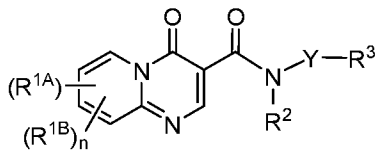
[0008] Another aspect of the invention provides a family of heterobicyclic pyrimidinone compounds embraced by Formula III that may be used in the methods, compositions, and kits described herein, wherein Formula III is represented by:



(III)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description.

[0009] Another aspect of the invention provides a family of heterobicyclic pyrimidinone compounds embraced by Formula V that may be used in the methods, compositions, and kits described herein, wherein Formula V is represented by:



(V)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description. Additional collections of generic and specific heterobicyclic pyrimidinone formulae are provided in the detailed description.

[0010] Another aspect of the invention provides a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a heterobicyclic pyrimidinone compound described herein, such as a compound of Formula I, III, or V.

[0011] Yet another aspect of the invention provides a method of treating a disorder, e.g., Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, and multiple myeloma, in a patient. The method comprises administering to a patient in need thereof a therapeutically effective amount of a heterobicyclic pyrimidinone compound described herein, such as a compound of Formula I, II, III, IV, V, or VI to treat the disorder, e.g., Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, or multiple myeloma. In certain embodiments, the compound is a compound of Formula II, IV, or VI.

DETAILED DESCRIPTION

[0012] The invention provides heterobicyclic pyrimidinone compounds such as thiazolo[3,2-*a*]pyrimidinone compounds, compositions containing such compounds, medical kits, and methods for using such compounds and compositions to treat medical disorders in a patient. The practice of the present invention employs, unless otherwise indicated, conventional techniques of organic chemistry, pharmacology, cell biology, and biochemistry. Such techniques are explained in the literature, such as in "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992); "Current protocols in molecular biology" (F.M. Ausubel *et al.*, eds., 1987, and periodic updates); and "Current protocols in immunology" (J.E. Coligan *et al.*, eds., 1991), each of which is herein incorporated by reference in its entirety. Various aspects of the invention are set forth below in sections; however, aspects of the invention described in one particular section are not to be limited to any particular section.

I. DEFINITIONS

[0013] To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

[0014] The terms "a" and "an" as used herein mean "one or more" and include the plural unless the context is inappropriate.

[0015] The term "alkyl" as used herein refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-12, 1-10, or 1-6 carbon atoms, referred to herein as C_1-C_{12}alkyl, C_1-C_{10}alkyl, and C_1-C_6alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

[0016] The term "alkylene" refers to a diradical of an alkyl group. An exemplary alkylene group is $-CH_2CH_2-$.

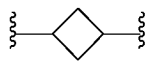
[0017] The term "haloalkyl" refers to an alkyl group that is substituted with at least one halogen. For example, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, and the like.

[0018] The term "heteroalkyl" as used herein refers to an "alkyl" group in which at least one carbon atom has been replaced with a heteroatom (e.g., an O, N, or S atom). The heteroalkyl may be, for example, an –O-C_1-C_{10}alkyl group, an -C_1-C_6alkylene-O-C_1-C_6alkyl group, or a C_1-C_6 alkylene-OH group. In certain embodiments, the "heteroalkyl" may be 2-8 membered heteroalkyl, indicating that the heteroalkyl contains from 2 to 8 atoms selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. In yet other embodiments, the heteroalkyl may be a 2-6 membered, 4-8 membered, or a 5-8 membered heteroalkyl group (which may contain for example 1 or 2 heteroatoms selected from the group oxygen and nitrogen). One type of heteroalkyl group is an "alkoxyl" group.

[0019] The term "alkenyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond, such as a straight or branched group of 2-12, 2-10, or 2-6 carbon atoms, referred to herein as C_2-C_{12}alkenyl, C_2-C_{10}alkenyl, and C_2-C_6alkenyl, respectively. Exemplary alkenyl groups include vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl, and the like.

[0020] The term "alkynyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond, such as a straight or branched group of 2-12, 2-10, or 2-6 carbon atoms, referred to herein as C_2-C_{12}alkynyl, C_2-C_{10}alkynyl, and C_2-C_6alkynyl, respectively. Exemplary alkynyl groups include ethynyl, prop-1-yn-1-yl, and but-1-yn-1-yl.

[0021] The term "cycloalkyl" refers to a monovalent saturated cyclic, bicyclic, or bridged cyclic (e.g., adamantyl) hydrocarbon group of 3-12, 3-8, 4-8, or 4-6 carbons, referred to herein, e.g., as "C_{4-8}cycloalkyl," derived from a cycloalkane. Unless specified otherwise, the cycloalkyl group is optionally substituted by 1 or 2 C_1-C_6 alkyl groups. In certain embodiments, the cycloalkyl group is unsubstituted. Exemplary cycloalkyl groups include, but are not limited to, cyclohexanes, cyclopentanes, cyclobutanes and cyclopropanes.

[0022] The term "cycloalkylene" refers to a diradical of an cycloalkyl group. An exemplary cycloalkylene group is .

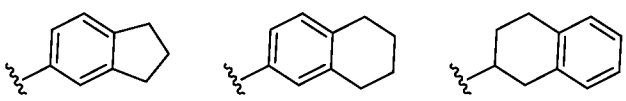
[0023] The term "cycloalkenyl" as used herein refers to a monovalent unsaturated cyclic, bicyclic, or bridged cyclic (e.g., adamantyl) hydrocarbon group of 3-12, 3-8, 4-8, or 4-6

carbons containing one carbon-carbon double bond, referred to herein, e.g., as "C_{4-8}cycloalkenyl," derived from a cycloalkane. Exemplary cycloalkenyl groups include, but are not limited to, cyclohexenes, cyclopentenes, and cyclobutenes. Unless specified otherwise, cycloalkenyl groups are optionally substituted at one or more ring positions with, for example, alkanoyl, alkoxy, alkyl, alkenyl, alkynyl, amido, amidino, amino, aryl, arylalkyl, azido, carbamate, carbonate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, imino, ketone, nitro, phosphate, phosphonato, phosphinato, sulfate, sulfide, sulfonamido, sulfonyl or thiocarbonyl. In certain embodiments, the cycloalkenyl group is not substituted, i.e., it is unsubstituted.

[0024] The term "aryl" is art-recognized and refers to a carbocyclic aromatic group. Representative aryl groups include phenyl, naphthyl, anthracenyl, and the like. The term "aryl" includes polycyclic ring systems having two or more carbocyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic and, e.g., the other ring(s) may be cycloalkyls, cycloalkenyls, cycloalkynyls, and/or aryls. Unless specified otherwise, the aromatic ring may be substituted at one or more ring positions with, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, carboxylic acid, -C(O)alkyl, -CO_2alkyl, carbonyl, carboxyl, alkylthio, sulfonyl, sulfonamido, sulfonamide, ketone, aldehyde, ester, heterocyclyl, aryl or heteroaryl moieties, -CF_3, -CN, or the like. In certain embodiments, the aromatic ring is substituted at one or more ring positions with halogen, alkyl, hydroxyl, or alkoxyl. In certain other embodiments, the aromatic ring is not substituted, i.e., it is unsubstituted. In certain embodiments, the aryl group is a 6-10 membered ring structure.

[0025] The term "aralkyl" refers to an alkyl group substituted with an aryl group.

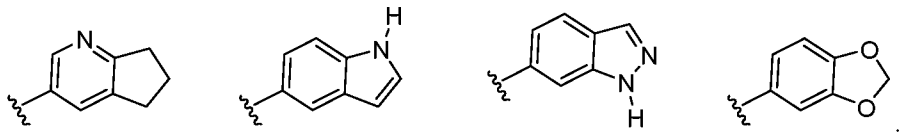
[0026] The term "partially unsaturated bicyclic carbocyclyl" refers to a bicyclic carbocyclic group containing at least one double bond between ring atoms and at least one ring in the bicyclic carbocyclic group is not aromatic. Representative examples of a bicyclic carbocyclyl that is partially unsaturated include, for example:



[0027] The terms ortho, meta and para are art-recognized and refer to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

[0028] The terms "heterocyclyl" and "heterocyclic group" are art-recognized and refer to saturated, partially unsaturated, or aromatic 3- to 10-membered ring structures, alternatively 3- to 7-membered rings, whose ring structures include one to four heteroatoms, such as nitrogen, oxygen, and sulfur. The number of ring atoms in the heterocyclyl group can be specified using C_x-C_x nomenclature where x is an integer specifying the number of ring atoms. For example, a C_3-C_7heterocyclyl group refers to a saturated or partially unsaturated 3- to 7-membered ring structure containing one to four heteroatoms, such as nitrogen, oxygen, and sulfur. The designation "C_3-C_7" indicates that the heterocyclic ring contains a total of from 3 to 7 ring atoms, inclusive of any heteroatoms that occupy a ring atom position. One example of a C_3heterocyclyl is aziridinyl. Heterocycles may also be mono-, bi-, or other multi-cyclic ring systems. A heterocycle may be fused to one or more aryl, partially unsaturated, or saturated rings. Heterocyclyl groups include, for example, biotinyl, chromenyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, homopiperidinyl, imidazolidinyl, isoquinolyl, isothiazolidinyl, isooxazolidinyl, morpholinyl, oxolanyl, oxazolidinyl, phenoxanthenyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazolinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidin-2-onyl, pyrrolinyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydropyranyl, tetrahydroquinolyl, thiazolidinyl, thiolanyl, thiomorpholinyl, thiopyranyl, xanthenyl, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. Unless specified otherwise, the heterocyclic ring is optionally substituted at one or more positions with substituents such as alkanoyl, alkoxy, alkyl, alkenyl, alkynyl, amido, amidino, amino, aryl, arylalkyl, azido, carbamate, carbonate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, imino, ketone, nitro, oxo, phosphate, phosphonato, phosphinato, sulfate, sulfide, sulfonamido, sulfonyl and thiocarbonyl. In certain embodiments, the heterocyclyl group is not substituted, i.e., it is unsubstituted.

[0029] The term "bicyclic heterocyclyl" refers to a heterocyclyl group that contains two rings that are fused together. Representative examples of a bicyclic heterocyclyl include, for example:



In certain embodiments, the bicyclic heterocyclyl is an carbocyclic ring fused to partially unsaturated heterocyclic ring, that together form a bicyclic ring structure having 8-10 ring atoms (e.g., where there are 1, 2, 3, or 4 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur).

[0030] The term "heterocycloalkyl" is art-recognized and refers to a saturated heterocyclyl group as defined above. In certain embodiments, the "heterocycloalkyl" is a 3- to 10-membered ring structures, alternatively a 3- to 7-membered rings, whose ring structures include one to four heteroatoms, such as nitrogen, oxygen, and sulfur.

[0031] The term "heteroaryl" is art-recognized and refers to aromatic groups that include at least one ring heteroatom. In certain instances, a heteroaryl group contains 1, 2, 3, or 4 ring heteroatoms. Representative examples of heteroaryl groups include pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl and pyrimidinyl, and the like. Unless specified otherwise, the heteroaryl ring may be substituted at one or more ring positions with, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, carboxylic acid, -C(O)alkyl, -CO_2alkyl, carbonyl, carboxyl, alkylthio, sulfonyl, sulfonamido, sulfonamide, ketone, aldehyde, ester, heterocyclyl, aryl or heteroaryl moieties, -CF_3, -CN, or the like. The term "heteroaryl" also includes polycyclic ring systems having two or more rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is heteroaromatic, e.g., the other cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, and/or aryls. In certain embodiments, the heteroaryl ring is substituted at one or more ring positions with halogen, alkyl, hydroxyl, or alkoxyl. In certain other embodiments, the heteroaryl ring is not substituted, i.e., it is unsubstituted. In certain embodiments, the heteroaryl group is a 5- to 10-membered ring structure, alternatively a 5- to 6-membered ring structure, whose ring structure includes 1, 2, 3, or 4 heteroatoms, such as nitrogen, oxygen, and sulfur.

[0032] The term "heteroaralkyl" refers to an alkyl group substituted with a heteroaryl group.

[0033] The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety represented by the general formula $-N(R^{50})(R^{51})$, wherein R^{50} and R^{51} each independently represent hydrogen, alkyl, cycloalkyl, heterocyclyl, alkenyl, aryl, aralkyl, or $-(CH_2)_m-R^{61}$; or R^{50} and R^{51}, taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R^{61} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range of 1 to 8. In certain embodiments, R^{50} and R^{51} each independently represent hydrogen, alkyl, alkenyl, or $-(CH_2)_m-R^{61}$.

[0034] The terms "alkoxyl" or "alkoxy" are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as may be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, $-O-(CH_2)_m-R_{61}$, where m and R_{61} are described above.

[0035] The term "carbamate" as used herein refers to a radical of the form $-R_gOC(O)N(R_h)-$, $-R_gOC(O)N(R_h)R_i-$, or $-OC(O)NR_hR_i$, wherein R_g, R_h and R_i are each independently alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, sulfide, sulfonyl, or sulfonamide. Exemplary carbamates include arylcarbamates and heteroaryl carbamates, e.g., wherein at least one of R_g, R_h and R_i are independently aryl or heteroaryl, such as phenyl and pyridinyl.

[0036] The term "carbonyl" as used herein refers to the radical -C(O)-.

[0037] The term "carboxamido" as used herein refers to the radical -C(O)NRR', where R and R' may be the same or different. R and R' may be independently alkyl, aryl, arylalkyl, cycloalkyl, formyl, haloalkyl, heteroaryl, or heterocyclyl.

[0038] The term "carboxy" as used herein refers to the radical -COOH or its corresponding salts, e.g. –COONa, etc.

[0039] The term "amide" or "amido" as used herein refers to a radical of the form $-R_aC(O)N(R_b)-$, $-R_aC(O)N(R_b)R_c-$, $-C(O)NR_bR_c$, or $-C(O)NH_2$, wherein R_a, R_b and R_c are each independently alkoxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate,

cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, or nitro. The amide can be attached to another group through the carbon, the nitrogen, R_b, R_c, or R_a. The amide also may be cyclic, for example R_b and R_c, R_a and R_b, or R_a and R_c may be joined to form a 3- to 12-membered ring, such as a 3- to 10-membered ring or a 5- to 6-membered ring.

[0040] The term "amidino" as used herein refers to a radical of the form -C(=NR)NR'R'' where R, R', and R'' are each independently alkyl, alkenyl, alkynyl, amide, aryl, arylalkyl, cyano, cycloalkyl, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, or nitro.

[0041] The term "alkanoyl" as used herein refers to a radical -O-CO-alkyl.

[0042] The term "oxo" is art-recognized and refers to a "=O" substituent. For example, a cyclopentane susbsituted with an oxo group is cyclopentanone.

[0043] The term "sulfonamide" or "sulfonamido" as used herein refers to a radical having the structure $-N(R_r)-S(O)_2-R_s-$ or $-S(O)_2-N(R_r)R_s$, where R_r, and R_s can be, for example, hydrogen, alkyl, aryl, cycloalkyl, and heterocyclyl. Exemplary sulfonamides include alkylsulfonamides (e.g., where R_s is alkyl), arylsulfonamides (e.g., where R_s is aryl), cycloalkyl sulfonamides (e.g., where R_s is cycloalkyl), and heterocyclyl sulfonamides (e.g., where R_s is heterocyclyl), etc.

[0044] The term "sulfonyl" as used herein refers to a radical having the structure R_uSO_2-, where R_u can be alkyl, aryl, cycloalkyl, and heterocyclyl, e.g., alkylsulfonyl. The term "alkylsulfonyl" as used herein refers to an alkyl group attached to a sulfonyl group.

[0045] The symbol "〰" indicates a point of attachment.

[0046] For clarity, the depiction of variable R^{1B} in Formulae I and II indicates that an occurrence of R^{1B} may be attached to a carbon atom in either the 5-membered ring or the 6-membered ring of the 5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidinyl group when n is 1, in accordance with the rules of valence. When n is 3 in Formulae I and II, one occurrence of R^{1B} is attached to a carbon atom in the 6-membered ring of the 5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidinyl group and two occurrences of R^{1B} are attached to carbon atoms in the 5-membered ring of the 5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidinyl group, in accordance with the rules of valence.

[0047] The compounds of the disclosure may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as geometric isomers, enantiomers or diastereomers. The term "stereoisomers" when used herein consist of all geometric isomers, enantiomers or diastereomers. These compounds may be designated by the symbols "R" or "S," depending on the configuration of substituents around the stereogenic carbon atom. The present invention encompasses various stereoisomers of these compounds and mixtures thereof. Stereoisomers include enantiomers and diastereomers. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. It is understood that graphical depictions of chemical structures, e.g., generic chemical structures, encompass all stereoisomeric forms of the specified compounds, unless indicated otherwise.

[0048] Individual stereoisomers of compounds of the present invention can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, or (3) direct separation of the mixture of optical enantiomers on chiral chromatographic columns. Stereoisomeric mixtures can also be resolved into their component stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Further, enantiomers can be separated using supercritical fluid chromatographic (SFC) techniques described in the literature. Still further, stereoisomers can be obtained from stereomerically-pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

[0049] Geometric isomers can also exist in the compounds of the present invention. The symbol  denotes a bond that may be a single, double or triple bond as described herein. The present invention encompasses the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a carbocyclic ring. Substituents around a carbon-carbon double bond are designated as being in the "*Z*" or "*E*" configuration wherein the terms "*Z*" and "*E*" are used in

accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the "*E*" and "*Z*" isomers.

[0050] Substituents around a carbon-carbon double bond alternatively can be referred to as "cis" or "trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring are designated as "cis" or "trans." The term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

[0051] The invention also embraces isotopically labeled compounds of the invention which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

[0052] Certain isotopically-labeled disclosed compounds (*e.g.,* those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.,* ^{3}H) and carbon-14 (*i.e.,* ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.,* ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.,* increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the invention can generally be prepared by following procedures analogous to those disclosed in, e.g., the Examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0053] As used herein, the terms "subject" and "patient" refer to organisms to be treated by the methods of the present invention. Such organisms are preferably mammals (*e.g.*, murines, simians, equines, bovines, porcines, canines, felines, and the like), and more preferably humans.

[0054] As used herein, the term "effective amount" refers to the amount of a compound (*e.g.*, a compound of the present invention) sufficient to effect beneficial or desired results. An

effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route. As used herein, the term "treating" includes any effect, *e.g.*, lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

[0055] As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

[0056] As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, see Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975].

[0057] As used herein, the term "pharmaceutically acceptable salt" refers to any pharmaceutically acceptable salt (*e.g.*, acid or base) of a compound of the present invention which, upon administration to a subject, is capable of providing a compound of this invention or an active metabolite or residue thereof. As is known to those of skill in the art, "salts" of the compounds of the present invention may be derived from inorganic or organic acids and bases. Examples of acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic acid, and the like. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

[0058] Examples of bases include, but are not limited to, alkali metal (*e.g.*, sodium) hydroxides, alkaline earth metal (*e.g.*, magnesium) hydroxides, ammonia, and compounds of formula NW_4^+, wherein W is C_{1-4} alkyl, and the like.

[0059] Examples of salts include, but are not limited to: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate,

cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, and the like. Other examples of salts include anions of the compounds of the present invention compounded with a suitable cation such as Na^+, NH_4^+, and NW_4^+ (wherein W is a C_{1-4} alkyl group), and the like.

[0060] For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

[0061] Exemplary abbreviations that may appear herein include *O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*- tetramethyluronium hexafluorophosphate (HATU); diisopropylethylamine (DIPEA); dimethylformamide (DMF); methylene chloride (DCM); tert-butoxycarbonyl (Boc); tetrahydrofuran (THF); trifluoroacetic acid (TFA); N-methylmorpholine (NMM); triethylamine (TEA); Boc anhydride ($(Boc)_2O$); dimethylsulfoxide (DMSO); diisopropylethylamine (DIEA); *N,N*-Dimethylpyridin-4-amine (DMAP); flash column chromatography (FCC); and supercritical fluid chromatography (SFC).

[0062] Throughout the description, where compositions and kits are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions and kits of the present invention that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

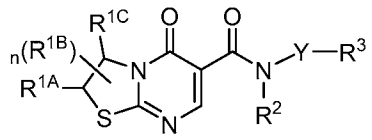
[0063] As a general matter, compositions specifying a percentage are by weight unless otherwise specified. Further, if a variable is not accompanied by a definition, then the previous definition of the variable controls.

II. HETEROBICYCLIC PYRIMIDINONE COMPOUNDS

[0064] One aspect of the invention provides heterobicyclic pyrimidinone compounds. The heterobicyclic pyrimidinone compounds are contemplated to be useful in the methods, compositions, and kits described herein. Exemplary heterobicyclic pyrimidinone compounds are described in more detail below.

Part A – Dihydro-Thiazolo[3,2-*a*]Pyrimidinone Compounds

[0065] One aspect of the invention provides a family of compounds represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1A}, R^{1B}, and R^{1C} each represent independently for each occurrence hydrogen, C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 3-8 membered heterocyclyl, or 6-membered aryl; or R^{1A} and R^{1C} are taken together with intervening atoms to form a 5-7 membered carbocyclic ring;

R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

R^3 is -(C_3-C_8 cycloalkylene)-(C_4-C_8 alkyl), -(C_3-C_8 cycloalkylene)-(C_3-C_8 cycloalkyl), 9-13 membered spiroheterocycloalkyl, or a partially unsaturated 9-10 membered bicyclic carbocyclyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, aryl, heteroaryl, and saturated 3-8 membered heterocyclyl;

Y is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or -C(O)-; and

n is 1 or 2.

[0066] Definitions of the variables in Formula I above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth

above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), *e.g.*, such as where R^{1A} and R^{1B} are hydrogen, R^2 is hydrogen, Y is a bond; and R^3 is -(C_3-C_8 cycloalkylene)-(C_4-C_8 alkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl.

[0067] Accordingly, in certain embodiments, R^{1A} is hydrogen or C_1-C_6 alkyl. In certain other embodiments, R^{1A} is hydrogen. In certain embodiments, R^{1B} is hydrogen or C_1-C_6 alkyl. In certain other embodiments, R^{1B} is hydrogen. In certain embodiments, R^{1C} is hydrogen or C_1-C_6 alkyl. In certain other embodiments, R^{1C} is hydrogen. In certain embodiments, R^{1A}, R^{1B}, and R^{1C} are independently hydrogen or C_1-C_6 alkyl. In certain embodiments, R^{1A}, R^{1B}, and R^{1C} are independently hydrogen or C_1-C_3 alkyl. In certain embodiments, R^{1A}, R^{1B}, and R^{1C} are hydrogen.

[0068] In certain embodiments, R^2 is hydrogen.

[0069] In certain embodiments, Y is a bond. In certain other embodiments, Y is C_1-C_6 alkylene.

[0070] In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_4-C_8 alkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, and -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy. In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_4-C_8 alkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, and C_2-C_4 alkynyl. In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_5-C_8 alkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, and C_2-C_4 alkynyl. In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_4-C_8 alkyl) optionally substituted by C_1-C_6 alkyl. In certain embodiments, R^3 is -(C_5-C_7 cycloalkylene)-(C_5-C_8 alkyl) optionally substituted by C_1-C_6 alkyl. In certain embodiments, R^3 is -(C_5-C_7 cycloalkylene)-(C_5-C_8 alkyl) optionally substituted by C_1-C_6 alkyl.

[0071] In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_3-C_8 cycloalkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, and

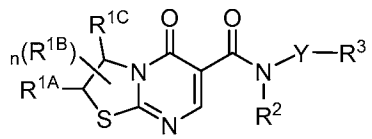
-(C_2-C_4 alkynyl)-C_1-C_6 alkoxy. In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_3-C_8 cycloalkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, and C_2-C_4 alkynyl. In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_3-C_8 cycloalkyl) optionally substituted by C_1-C_6 alkyl. In certain embodiments, R^3 is -(C_5-C_7 cycloalkylene)-(C_5-C_7 cycloalkyl) optionally substituted by C_1-C_6 alkyl.

[0072] In certain embodiments, R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, aryl, heteroaryl, and saturated 3-8 membered heterocyclyl. In certain embodiments, R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, and C_2-C_4 alkynyl. In certain embodiments, R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by C_1-C_6 alkyl.

[0073] In certain embodiments, n is 1. In certain embodiments, n is 2.

[0074] The description above describes multiple embodiments relating to compounds of Formula I. The patent application specifically contemplates all combinations of the embodiments.

[0075] Another aspect of the invention provides a compound represented by Formula II:



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1A}, R^{1B}, and R^{1C} each represent independently for each occurrence hydrogen, C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 3-8 membered heterocyclyl, or 6-membered aryl; or R^{1A} and R^{1C} are taken together with intervening atoms to form a 5-7 membered carbocyclic ring;

R^2 and R^4 are independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

R^3 is C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 9-13 membered spiroheterocycloalkyl, -(C_2-C_6 alkylene)-O-phenyl, phenyl, heteroaryl, a partially unsaturated 9-10 membered bicyclic carbocyclyl, or a partially unsaturated 8-10 membered bicyclic heterocyclyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, -(C_1-C_6 alkylene,)-(C_3-C_6 cycloalkyl), hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, aryl, -O-aryl, heteroaryl, saturated 3-8 membered heterocyclyl, amino, and -CO_2R^4;

Y is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or -C(O)-; and

n is 1 or 2.

[0076] Definitions of the variables in Formula II above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), *e.g.*, such as where R^{1A} is hydrogen, R^2 is hydrogen, and R^3 is C_3-C_8 cycloalkyl or phenyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl.

[0077] Accordingly, in certain embodiments, R^{1A} is hydrogen or C_1-C_6 alkyl. In certain other embodiments, R^{1A} is hydrogen. In certain embodiments, R^{1B} is hydrogen or C_1-C_6 alkyl. In certain other embodiments, R^{1B} is hydrogen. In certain embodiments, R^{1C} is hydrogen or C_1-C_6 alkyl. In certain other embodiments, R^{1C} is hydrogen. In certain embodiments, R^{1A}, R^{1B}, and R^{1C} are independently hydrogen or C_1-C_6 alkyl. In certain embodiments, R^{1A}, R^{1B}, and R^{1C} are independently hydrogen or C_1-C_3 alkyl. In certain embodiments, R^{1A}, R^{1B}, and R^{1C} are hydrogen.

[0078] In certain embodiments, R^2 is hydrogen.

[0079] In certain embodiments, Y is a bond. In certain other embodiments, Y is C_1-C_6 alkylene.

[0080] In certain embodiments, R^3 is phenyl substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-

C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, 5-membered heteroaryl, and saturated 3-8 membered heterocyclyl. In certain embodiments, R^3 is phenyl substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, and C_2-C_4 alkynyl. In certain embodiments, R^3 is phenyl substituted by (i) a 5-6 membered heteroaryl or saturated 3-8 membered heterocyclyl, and (ii) optionally 1 or 2 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, and C_1-C_6 haloalkyl. In certain embodiments, R^3 is phenyl substituted by (i) a 5-membered heteroaryl or saturated 5-6 membered heterocycloalkyl, and (ii) optionally 1 or 2 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, and C_1-C_6 haloalkyl.

[0081] In certain embodiments, R^3 is C_3-C_8 cycloalkyl or a partially unsaturated 9-10 membered bicyclic carbocyclyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, and C_2-C_4 alkynyl.

[0082] In certain embodiments, R^3 is C_3-C_8 cycloalkyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, aryl, heteroaryl, and saturated 3-8 membered heterocyclyl. In certain embodiments, R^3 is C_3-C_7 cycloalkyl substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, and C_1-C_6 alkoxy.

[0083] In certain embodiments, R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, and C_1-C_6 alkoxy. In certain embodiments, R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, and C_1-C_6 alkoxy.

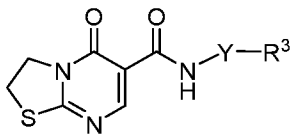
[0084] In certain embodiments, R^3 is a partially unsaturated 8-10 membered bicyclic heterocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, and C_1-C_6 alkoxy.

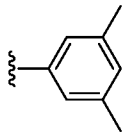
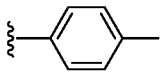
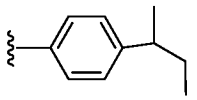
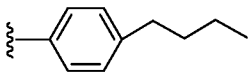
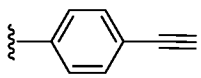
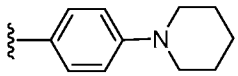
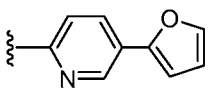
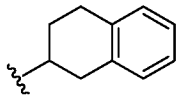
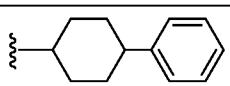
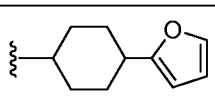
[0085] In certain embodiments, n is 1. In certain embodiments, n is 2.

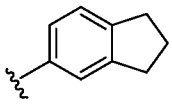
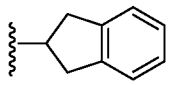
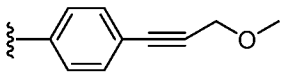
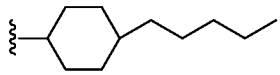
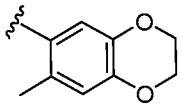
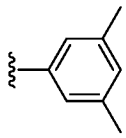
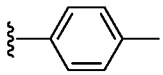
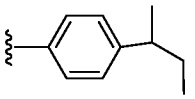
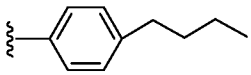
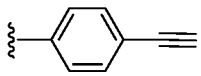
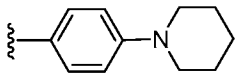
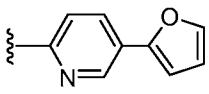
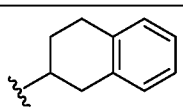
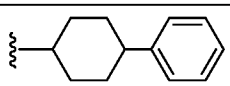
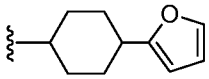
[0086] The description above describes multiple embodiments relating to compounds of Formula II. The patent application specifically contemplates all combinations of the embodiments.

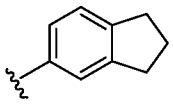
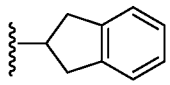
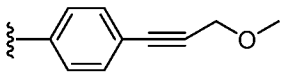
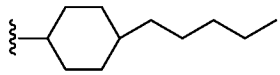
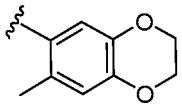
[0087] In certain other embodiments, the compound is one of the compounds listed in Table 1 below or a pharmaceutically acceptable salt thereof.

TABLE 1.



Compound No.	Y	R^3
I-1	a bond	
I-2	a bond	
I-3	a bond	
I-4	a bond	
I-5	a bond	
I-6	a bond	
I-7	a bond	
I-8	a bond	
I-9	a bond	
I-10	a bond	

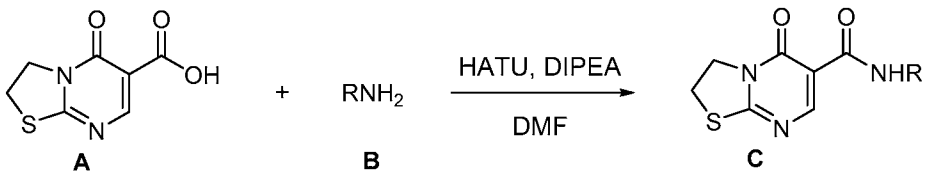
Compound No.	Y	R^3
I-11	a bond	
I-12	a bond	
I-13	a bond	
I-14	a bond	
I-15	a bond	
I-16	C_1-C_4 alkylene	
I-17	C_1-C_4 alkylene	
I-18	C_1-C_4 alkylene	
I-19	C_1-C_4 alkylene	
I-20	C_1-C_4 alkylene	
I-21	C_1-C_4 alkylene	
I-22	C_1-C_4 alkylene	
I-23	C_1-C_4 alkylene	
I-24	C_1-C_4 alkylene	
I-25	C_1-C_4 alkylene	

Compound No.	Y	R^3
I-26	C_1-C_4 alkylene	
I-27	C_1-C_4 alkylene	
I-28	C_1-C_4 alkylene	
I-29	C_1-C_4 alkylene	
I-30	C_1-C_4 alkylene	

[0088] Methods for preparing compounds described herein are illustrated in the following synthetic scheme. These scheme is provided for the purpose of illustrating the invention, and should not be regarded in any manner as limiting the scope or the spirit of the invention. Starting materials shown in the scheme can be obtained from commercial sources or can be prepared based on procedures described in the literature.

[0089] The synthetic route illustrated in Scheme 1 depicts an exemplary procedure for preparing 2,3-dihydro-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamides. The synthetic route involves reacting carboxylic acid **A** with the desired amine **B** in an amide coupling reaction, which may involve an amide coupling reagent such as HATU, to produce amide **C**.

SCHEME 1



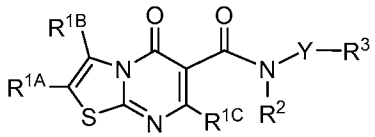
R is, for example, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each of which is optionally substituted.

[0090] The reaction procedures in Scheme 1 are contemplated to be amenable to preparing a wide variety of carboxamide compounds having different substituents at variable R. Furthermore, if a functional group that is part of variable R would not be amenable to a reaction

condition described in Scheme 1, it is contemplated that the functional group can first be protected using standard protecting group chemistry and strategies, and then the protecting group is removed after completing the desired synthetic transformation. See, for example, Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991, for further description of protecting chemistry and strategies. In certain other embodiments, a functional group in substituent R can converted to another functional group using standard functional group manipulation procedures known in the art. See, for example, "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992).

Part B – Thiazolo[3,2-*a*]Pyrimidinone Compounds

[0091] Another aspect of the invention provides a family of compounds represented by Formula III:



(III)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1A}, R^{1B}, and R^{1C} are independently hydrogen, C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, or 3-8 membered heterocyclyl; or R^{1A} and R^{1B} are taken together with intervening atoms to form a 5-7 membered carbocyclic ring;

R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

R^3 is -(C_3-C_8 cycloalkylene)-(C_6-C_8 alkyl), -(C_3-C_8 cycloalkylene)-(C_3-C_8 cycloalkyl), 9-13 membered spiroheterocycloalkyl, or a partially unsaturated 9-10 membered bicyclic carbocyclyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, aryl, heteroaryl, and saturated 3-8 membered heterocyclyl; and

Y is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or -C(O)-.

[0092] Definitions of the variables in Formula III above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the

definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), *e.g.*, such as where R^{1A} and R^{1B} are hydrogen, R^2 is hydrogen, Y is a bond; and R^3 is -(C_3-C_8 cycloalkylene)-(C_6-C_8 alkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl.

[0093] Accordingly, in certain embodiments, R^{1A} is hydrogen or C_1-C_6 alkyl. In certain other embodiments, R^{1A} is hydrogen. In certain embodiments, R^{1B} is hydrogen or C_1-C_6 alkyl. In certain other embodiments, R^{1B} is hydrogen. In certain embodiments, R^{1A} and R^{1B} are independently hydrogen or C_1-C_6 alkyl. In certain embodiments, R^{1A} and R^{1B} are independently hydrogen or C_1-C_3 alkyl. In certain embodiments, R^{1A} and R^{1B} are hydrogen. In certain embodiments, R^{1A}, R^{1B}, and R^{1C} are independently hydrogen or C_1-C_3 alkyl. In certain embodiments, R^{1A}, R^{1B}, and R^{1C} are hydrogen.

[0094] In certain embodiments, R^2 is hydrogen.

[0095] In certain embodiments, Y is a bond. In certain other embodiments, Y is C_1-C_6 alkylene.

[0096] In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_6-C_8 alkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, and -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy. In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_6-C_8 alkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, and C_2-C_4 alkynyl. In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_6-C_8 alkyl) optionally substituted by C_1-C_6 alkyl. In certain embodiments, R^3 is -(C_5-C_7 cycloalkylene)-(C_6-C_8 alkyl) optionally substituted by C_1-C_6 alkyl.

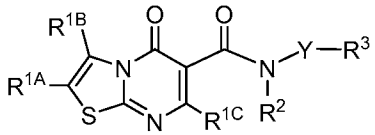
[0097] In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_3-C_8 cycloalkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, and -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy. In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_3-C_8 cycloalkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, and C_2-C_4

alkynyl. In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_3-C_8 cycloalkyl) optionally substituted by C_1-C_6 alkyl. In certain embodiments, R^3 is -(C_5-C_7 cycloalkylene)-(C_5-C_7 cycloalkyl) optionally substituted by C_1-C_6 alkyl.

[0098] In certain embodiments, R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, aryl, heteroaryl, and saturated 3-8 membered heterocyclyl. In certain embodiments, R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, and C_2-C_4 alkynyl. In certain embodiments, R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by C_1-C_6 alkyl.

[0099] The description above describes multiple embodiments relating to compounds of Formula III. The patent application specifically contemplates all combinations of the embodiments.

[00100] Another aspect of the invention provides a compound represented by Formula IV:



(IV)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1A}, R^{1B}, and R^{1C} are independently hydrogen, C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 3-8 membered heterocyclyl, or 6-membered aryl; or R^{1A} and R^{1B} are taken together with intervening atoms to form a 5-7 membered carbocyclic ring;

R^2 and R^4 are independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

R^3 is C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 9-13 membered spiroheterocycloalkyl, -(C_2-C_6 alkylene)-O-phenyl, phenyl, heteroaryl, a partially unsaturated 9-10 membered bicyclic carbocyclyl, or a partially unsaturated 8-10 membered bicyclic heterocyclyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, -(C_1-C_6 alkylene,)-(C_3-C_6 cycloalkyl), hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-

C_1-C_6 alkoxy, aryl, -O-aryl, heteroaryl, saturated 3-8 membered heterocyclyl, amino, and $-CO_2R^4$; and

Y is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or -C(O)-.

[00101] Definitions of the variables in Formula IV above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), *e.g.*, such as where R^{1A} is hydrogen, R^2 is hydrogen, and R^3 is C_3-C_8 cycloalkyl or phenyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl.

[00102] Accordingly, in certain embodiments, R^{1A} is hydrogen or C_1-C_6 alkyl. In certain other embodiments, R^{1A} is hydrogen. In certain embodiments, R^{1B} is hydrogen or C_1-C_6 alkyl. In certain other embodiments, R^{1B} is hydrogen. In certain embodiments, R^{1A} and R^{1B} are independently hydrogen or C_1-C_6 alkyl. In certain embodiments, R^{1A} and R^{1B} are independently hydrogen or C_1-C_6 alkyl. In certain embodiments, R^{1A} and R^{1B} are hydrogen. In certain embodiments, R^{1A}, R^{1B}, and R^{1C} are independently hydrogen or C_1-C_3 alkyl. In certain embodiments, R^{1A}, R^{1B}, and R^{1C} are hydrogen.

[00103] In certain embodiments, R^2 is hydrogen.

[00104] In certain embodiments, Y is a bond. In certain other embodiments, Y is C_1-C_6 alkylene.

[00105] In certain embodiments, R^3 is phenyl substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, 5-membered heteroaryl, and saturated 3-8 membered heterocyclyl. In certain embodiments, R^3 is phenyl substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, and C_2-C_4 alkynyl. In certain embodiments, R^3 is phenyl substituted by (i) a 5-6 membered heteroaryl or saturated 3-8 membered heterocyclyl, and (ii) optionally 1 or 2 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, and C_1-C_6 haloalkyl. In certain embodiments, R^3 is

phenyl substituted by (i) a 5-membered heteroaryl or saturated 5-6 membered heterocycloalkyl, and (ii) optionally 1 or 2 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, and C_1-C_6 haloalkyl.

[00106] In certain embodiments, R^3 is C_3-C_8 cycloalkyl or a partially unsaturated 9-10 membered bicyclic carbocyclyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, and C_2-C_4 alkynyl.

[00107] In certain embodiments, R^3 is C_3-C_8 cycloalkyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, aryl, heteroaryl, and saturated 3-8 membered heterocyclyl. In certain embodiments, R^3 is C_3-C_7 cycloalkyl substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, and C_1-C_6 alkoxy.

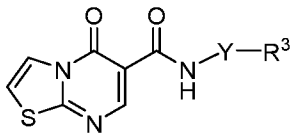
[00108] In certain embodiments, R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, and C_1-C_6 alkoxy. In certain embodiments, R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, and C_1-C_6 alkoxy.

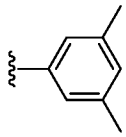
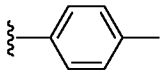
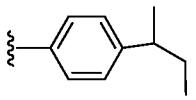
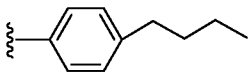
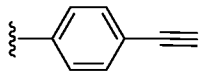
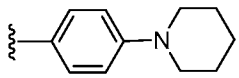
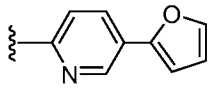
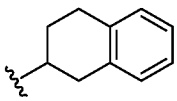
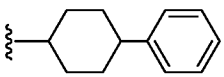
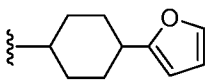
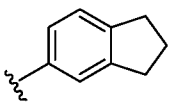
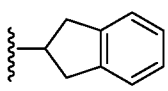
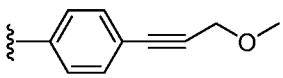
[00109] In certain embodiments, R^3 is a partially unsaturated 8-10 membered bicyclic heterocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, and C_1-C_6 alkoxy.

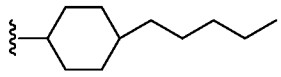
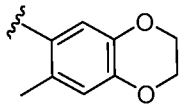
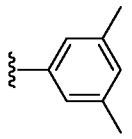
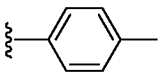
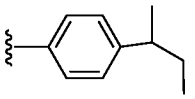
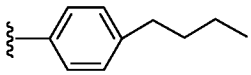
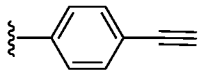
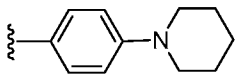
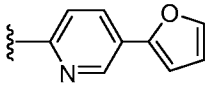
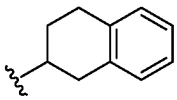
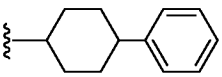
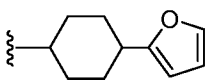
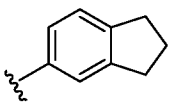
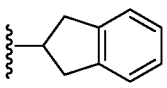
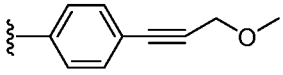
[00110] The description above describes multiple embodiments relating to compounds of Formula IV. The patent application specifically contemplates all combinations of the embodiments.

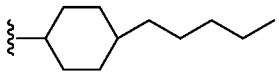
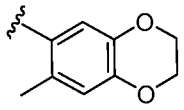
[00111] In certain other embodiments, the compound is one of the compounds listed in Table 2 below or a pharmaceutically acceptable salt thereof.

TABLE 2.



Compound No.	Y	R^3
II-1	a bond	
II-2	a bond	
II-3	a bond	
II-4	a bond	
II-5	a bond	
II-6	a bond	
II-7	a bond	
II-8	a bond	
II-9	a bond	
II-10	a bond	
II-11	a bond	
II-12	a bond	
II-13	a bond	

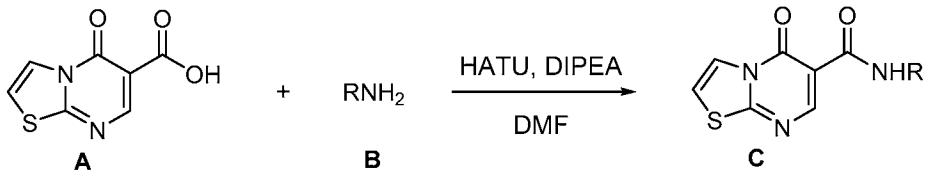
Compound No.	Y	R^3
II-14	a bond	
II-15	a bond	
II-16	C_1-C_4 alkylene	
II-17	C_1-C_4 alkylene	
II-18	C_1-C_4 alkylene	
II-19	C_1-C_4 alkylene	
II-20	C_1-C_4 alkylene	
II-21	C_1-C_4 alkylene	
II-22	C_1-C_4 alkylene	
II-23	C_1-C_4 alkylene	
II-24	C_1-C_4 alkylene	
II-25	C_1-C_4 alkylene	
II-26	C_1-C_4 alkylene	
II-27	C_1-C_4 alkylene	
II-28	C_1-C_4 alkylene	

Compound No.	Y	R^3
II-29	C_1-C_4 alkylene	
II-30	C_1-C_4 alkylene	

[00112] Methods for preparing compounds described herein are illustrated in the following synthetic scheme. The scheme is provided for the purpose of illustrating the invention, and should not be regarded in any manner as limiting the scope or the spirit of the invention. Starting materials shown in the scheme can be obtained from commercial sources or can be prepared based on procedures described in the literature.

[00113] The synthetic route illustrated in Scheme 2 depicts an exemplary procedure for preparing 5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamides. The synthetic route involves reacting carboxylic acid **A** with the desired amine **B** in an amide coupling reaction, which may involve an amide coupling reagent such as HATU, to produce amide **C**.

SCHEME 2



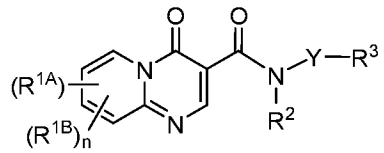
R is, for example, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each of which is optionally substituted.

[00114] The reaction procedures in Scheme 2 are contemplated to be amenable to preparing a wide variety of carboxamide compounds having different substituents at variable R. Furthermore, if a functional group that is part of variable R would not be amenable to a reaction condition described in Scheme 2, it is contemplated that the functional group can first be protected using standard protecting group chemistry and strategies, and then the protecting group is removed after completing the desired synthetic transformation. See, for example, Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991, for further description of protecting chemistry and strategies. In certain other embodiments, a functional group in substituent R can converted to another functional group

using standard functional group manipulation procedures known in the art. See, for example, "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992).

Part C – Pyrido[1,2-*a*]Pyrimidinone Compounds

[00115] Another aspect of the invention provides a family of compounds represented by Formula V:



(V)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1A} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 3-8 membered heterocyclyl, or 6-membered aryl;

R^{1B} represents independently for each occurrence C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 3-6 membered heterocyclyl, or 6-membered aryl;

R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

R^3 is -(C_3-C_8 cycloalkylene)-(C_2-C_8 alkyl), -(C_3-C_8 cycloalkylene)-(C_3-C_8 cycloalkyl), 9-13 membered spiroheterocycloalkyl, or a partially unsaturated 9-10 membered bicyclic carbocyclyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_2-C_4 alkynyl, and -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy;

n is 0, 1, or 2; and

Y is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or -C(O)-;

provided that when both n is 0 and Y is C_1-C_6 alkylene, then R^{1A} is other than methoxy-phenyl.

[00116] Definitions of the variables in Formula V above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), *e.g.*, such as where R^{1A} and R^{1B} are C_1-C_6 alkyl, R^2 is hydrogen, Y is a

bond; and R^3 is -(C_3-C_8 cycloalkylene)-(C_2-C_8 alkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl.

[00117] Accordingly, in certain embodiments, R^{1A} is C_1-C_6 alkyl. In certain other embodiments, R^{1A} is C_1-C_3 alkyl. In certain embodiments, R^{1B} represents independently for each occurrence C_1-C_6 alkyl or halogen. In certain other embodiments, R^{1B} is C_1-C_6 alkyl. In certain other embodiments, R^{1B} is C_1-C_3 alkyl. In certain other embodiments, R^{1A} is C_1-C_3 alkyl, and R^{1B} is C_1-C_3 alkyl.

[00118] In certain embodiments, R^2 is hydrogen.

[00119] In certain embodiments, Y is a bond. In certain other embodiments, Y is C_1-C_6 alkylene.

[00120] In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_2-C_8 alkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_2-C_4 alkynyl, and -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy. In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_2-C_8 alkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl. In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_2-C_8 alkyl) optionally substituted by C_1-C_6 alkyl. In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_5-C_8 alkyl) optionally substituted by C_1-C_6 alkyl. In certain embodiments, R^3 is -(C_5-C_7 cycloalkylene)-(C_2-C_8 alkyl) optionally substituted by C_1-C_6 alkyl. In certain embodiments, R^3 is -(C_5-C_7 cycloalkylene)-(C_5-C_8 alkyl) optionally substituted by C_1-C_6 alkyl.

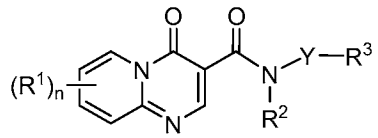
[00121] In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_3-C_8 cycloalkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_2-C_4 alkynyl, and -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy. In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_3-C_8 cycloalkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl. In certain embodiments, R^3 is -(C_3-C_8 cycloalkylene)-(C_3-C_8 cycloalkyl) optionally substituted by C_1-C_6 alkyl. In certain embodiments, R^3 is -(C_5-C_7 cycloalkylene)-(C_5-C_7 cycloalkyl) optionally substituted by C_1-C_6 alkyl.

[00122] In certain embodiments, R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, aryl, heteroaryl, and saturated 3-8 membered heterocyclyl. In certain embodiments, R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl. In certain embodiments, R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by C_1-C_6 alkyl.

[00123] In certain embodiments, n is 1. In certain embodiments, n is 0.

[00124] The description above describes multiple embodiments relating to compounds of Formula V. The patent application specifically contemplates all combinations of the embodiments.

[00125] Another aspect of the invention provides a compound represented by Formula VI:



(VI)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 represents independently for each occurrence C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 3-8 membered heterocyclyl, or 6-membered aryl;

R^2 and R^4 are independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

R^3 is C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 9-13 membered spiroheterocycloalkyl, -(C_2-C_6 alkylene)-O-phenyl, phenyl, heteroaryl, a partially unsaturated 9-10 membered bicyclic carbocyclyl, or a partially unsaturated 8-10 membered bicyclic heterocyclyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, -(C_1-C_6 alkylene,)-(C_3-C_6 cycloalkyl), hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, aryl, -O-aryl, heteroaryl, saturated 3-8 membered heterocyclyl, amino, and -CO_2R^4;

n is 0, 1, or 2; and

Y is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or -C(O)-.

[00126] Definitions of the variables in Formula VI above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), *e.g.*, such as where R^1 is hydrogen, R^2 is hydrogen, and R^3 is C_3-C_8 cycloalkyl or phenyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl.

[00127] Accordingly, in certain embodiments, R^1 represents independently for each occurrence hydrogen or C_1-C_6 alkyl. In certain other embodiments, R^1 is hydrogen. In certain other embodiments, R^1 is C_1-C_6 alkyl.

[00128] In certain embodiments, R^2 is hydrogen.

[00129] In certain embodiments, Y is a bond. In certain other embodiments, Y is C_1-C_6 alkylene.

[00130] In certain embodiments, R^3 is phenyl substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, 5-membered heteroaryl, and saturated 3-8 membered heterocyclyl. In certain embodiments, R^3 is phenyl substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, and C_2-C_4 alkynyl. In certain embodiments, R^3 is phenyl substituted by (i) a 5-6 membered heteroaryl or saturated 3-8 membered heterocyclyl, and (ii) optionally 1 or 2 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, and C_1-C_6 haloalkyl. In certain embodiments, R^3 is phenyl substituted by (i) a 5-membered heteroaryl or saturated 5-6 membered heterocycloalkyl, and (ii) optionally 1 or 2 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, and C_1-C_6 haloalkyl.

[00131] In certain embodiments, R^3 is C_3-C_8 cycloalkyl or a partially unsaturated 9-10 membered bicyclic carbocyclyl; each of which is optionally substituted by 1, 2, or 3

substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, and C_2-C_4 alkynyl.

[00132] In certain embodiments, R^3 is C_3-C_8 cycloalkyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, aryl, heteroaryl, and saturated 3-8 membered heterocyclyl. In certain embodiments, R^3 is C_3-C_7 cycloalkyl substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, and C_1-C_6 alkoxy.

[00133] In certain embodiments, R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, and C_1-C_6 alkoxy. In certain embodiments, R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, and C_1-C_6 alkoxy.

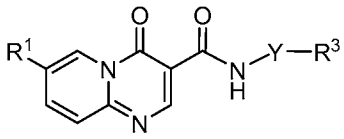
[00134] In certain embodiments, R^3 is a partially unsaturated 8-10 membered bicyclic heterocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, and C_1-C_6 alkoxy.

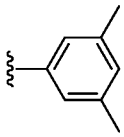
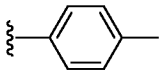
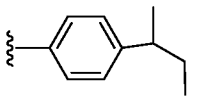
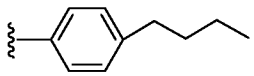
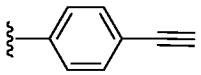
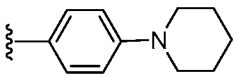
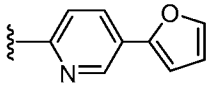
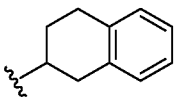
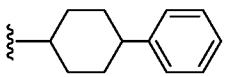
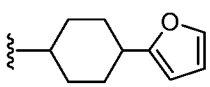
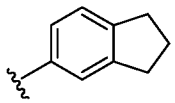
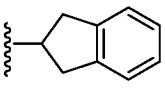
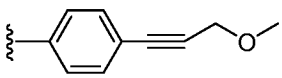
[00135] In certain embodiments, n is 1. In certain embodiments, n is 0.

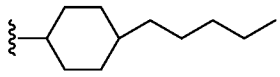
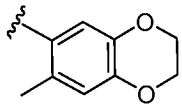
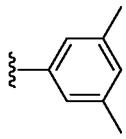
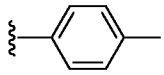
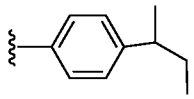
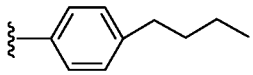
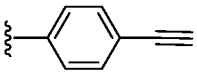
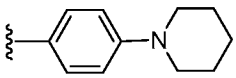
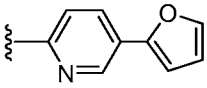
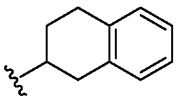
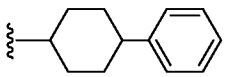
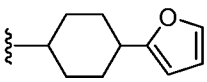
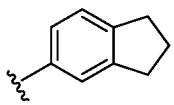
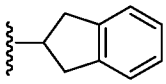
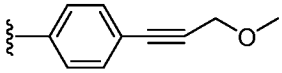
[00136] The description above describes multiple embodiments relating to compounds of Formula VI. The patent application specifically contemplates all combinations of the embodiments.

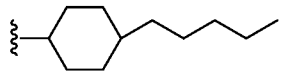
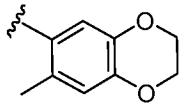
[00137] In certain other embodiments, the compound is one of the compounds listed in Table 3 below or a pharmaceutically acceptable salt thereof.

TABLE 3.



Compound No.	Y	R^1	R^3
III-1	a bond	$-CH_3$	
III-2	a bond	$-CH_3$	
III-3	a bond	$-CH_3$	
III-4	a bond	$-CH_3$	
III-5	a bond	$-CH_3$	
III-6	a bond	$-CH_3$	
III-7	a bond	$-CH_3$	
III-8	a bond	$-CH_3$	
III-9	a bond	H	
III-10	a bond	H	
III-11	a bond	H	
III-12	a bond	H	
III-13	a bond	H	

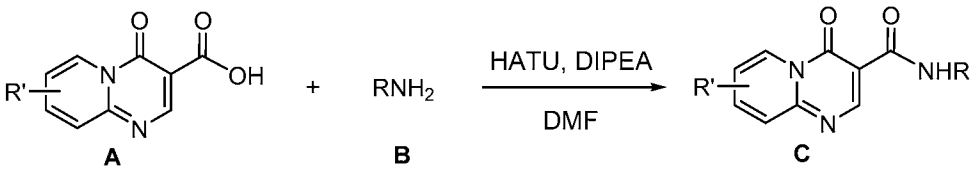
Compound No.	Y	R^1	R^3
III-14	a bond	H	
III-15	a bond	H	
III-16	C_1-C_4 alkylene	$-CH_3$	
III-17	C_1-C_4 alkylene	$-CH_3$	
III-18	C_1-C_4 alkylene	$-CH_3$	
III-19	C_1-C_4 alkylene	$-CH_3$	
III-20	C_1-C_4 alkylene	$-CH_3$	
III-21	C_1-C_4 alkylene	$-CH_3$	
III-22	C_1-C_4 alkylene	$-CH_3$	
III-23	C_1-C_4 alkylene	$-CH_3$	
III-24	C_1-C_4 alkylene	H	
III-25	C_1-C_4 alkylene	H	
III-26	C_1-C_4 alkylene	H	
III-27	C_1-C_4 alkylene	H	
III-28	C_1-C_4 alkylene	H	

Compound No.	Y	R^1	R^3
III-29	C_1-C_4 alkylene	H	
III-30	C_1-C_4 alkylene	H	

[00138] Methods for preparing compounds described herein are illustrated in the following synthetic scheme. These scheme is provided for the purpose of illustrating the invention, and should not be regarded in any manner as limiting the scope or the spirit of the invention. Starting materials shown in the scheme can be obtained from commercial sources or can be prepared based on procedures described in the literature.

[00139] The synthetic route illustrated in Scheme 3 depicts an exemplary procedure for preparing 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamides. The synthetic route involves reacting carboxylic acid **A** with the desired amine **B** in an amide coupling reaction, which may involve an amide coupling reagent such as HATU, to produce amide **C**.

SCHEME 3



R is, for example, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each of which is optionally substituted; and
R' is, for example, methyl or ethyl.

[00140] The reaction procedures in Scheme 3 are contemplated to be amenable to preparing a wide variety of carboxamide compounds having different substituents at variables R and R'. Furthermore, if a functional group that is part of variable R would not be amenable to a reaction condition described in Scheme 3, it is contemplated that the functional group can first be protected using standard protecting group chemistry and strategies, and then the protecting group is removed after completing the desired synthetic transformation. See, for example, Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991, for further description of protecting chemistry and strategies. In certain other

embodiments, a functional group in substituent R can converted to another functional group using standard functional group manipulation procedures known in the art. See, for example, "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992).

III. THERAPEUTIC APPLICATIONS

[00141] The invention provides methods of treating medical disorders, such as Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, and multiple myeloma, using the heterobicyclic pyrimidinone compounds and pharmaceutical compositions described herein. Treatment methods include the use of heterobicyclic pyrimidinone compounds described herein as stand-alone therapeutic agents and/or as part of a combination therapy with another therapeutic agent. Although not wishing to be bound by a particular theory, it is understood that heterobicyclic pyrimidinone compounds described herein may activate glucocerebrosidase (Gcase).

Methods of Treating Medical Disorders

[00142] One aspect of the invention provides a method of treating a disorder selected from the group consisting of Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, and multiple myeloma. The method comprises administering to a patient in need thereof a therapeutically effective amount of a heterobicyclic pyrimidinone compound described herein to treat the disorder. The compound may be a compound of Formula I, II, III, IV, V, or VI, as described above in Section II. In certain embodiments, the compound is a compound of Formula II, IV, or VI, as described above in Section II. In certain embodiments, the compound is a compound of Formula II. In certain embodiments, the compound is a compound of Formula IV. In certain embodiments, the compound is a compound of Formula VI.

[00143] In certain embodiments, the disorder is Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy. In certain other embodiments, the disorder is Gaucher disease. In certain embodiments, the disorder is Parkinson's disease. In certain embodiments, the disorder is Lewy body disease. In certain embodiments, the disorder is dementia. In certain embodiments, the disorder is a dementia selected from the group

consisting of Alzheimer's disease, frontotemporal dementia, and a Lewy body variant of Alzheimer's disease. In certain embodiments, the disorder is multiple system atrophy.

[00144] In certain embodiments, the disorder is an anxiety disorder, such as panic disorder, social anxiety disorder, or generalized anxiety disorder.

[00145] Efficacy of the compounds in treating Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, and multiple myeloma may be evaluated by testing the compounds in assays known in the art for evaluating efficacy against these diseases and/or, *e.g.*, for activation of glucocerebrosidase (Gcase), as discussed in the Examples below.

[00146] In certain embodiments, the patient is a human.

[00147] In certain embodiments, the compound is one of the generic or specific compounds described in Section II, such as a compound of Formula II, a compound embraced by one of the further embodiments describing definitions for certain variables of Formula II, a compound of Formula IV, a compound embraced by one of the further embodiments describing definitions for certain variables of Formula IV, a compound of Formula VI, or a compound embraced by one of the further embodiments describing definitions for certain variables of Formula VI.

[00148] The description above describes multiple embodiments relating to methods of treating various disorders using certain heterobicyclic pyrimidinone compounds. The patent application specifically contemplates all combinations of the embodiments. For example, the invention contemplates methods for treating Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy by administering a therapeutically effective amount of a compound of Formula II wherein R^3 is phenyl substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, 5-membered heteroaryl, and saturated 3-8 membered heterocyclyl.

Medical Use and Preparation of Medicament

[00149] Another aspect of the invention relates to compounds and compositions described herein for use in treating a disorder described herein. Another aspect of the invention pertains

to use of a compound or composition described herein in the preparation of a medicament for treating a disorder described herein.

Combination Therapy

[00150] The invention embraces combination therapy, which includes the administration of a heterobicyclic pyrimidinone compound described herein (such as compound of Formula II, IV, or VI) and a second agent as part of a specific treatment regimen intended to provide the beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination may include pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents.

[00151] Exemplary second agents for use in treating Gaucher disease include, for example, taliglucerase alfa, velaglucerase alfa, eliglustat, ibiglustat and miglustat. Exemplary second agents for use in treating Parkinson's disease include, for example, a glucosylceramide synthase inhibitor (e.g., ibiglustat), an acid ceramidase inhibitor (e.g., carmofur), an acid sphingomyelinase activator, levodopa, pramipexole, ropinirole, rotigotine, apomorphine, or salt thereof. Additional glucosylceramide synthase inhibitors for use in combination therapies include, for example, those described in International Patent Application Publications WO 2015/089067, WO 2014/151291, WO 2014/043068, WO 2008/150486, WO 2010/014554, WO 2012/129084, WO 2011/133915, and WO 2010/091164; U.S. Patent Nos. US 9126993, US 8961959, US 8940776, US 8729075, and US 8309593; and U.S. Patent Application Publications US 2014/0255381 and US 2014/0336174; each of which are hereby incorporated by reference. Additional acid ceramidase inhibitors for use in combination therapies include, for example, those described in International Patent Application Publications WO 2015/173168 and WO 2015/173169, each of which are hereby incorporated by reference.

IV. PHARMACEUTICAL COMPOSITIONS

[00152] The invention provides pharmaceutical compositions comprising a heterobicyclic pyrimidinone compound described herein, such as a compound of Formula I, II, III, IV, V, or VI. In certain embodiments, the pharmaceutical compositions preferably comprise a therapeutically-effective amount of one or more of the heterobicyclic pyrimidinone compounds described above, formulated together with one or more pharmaceutically acceptable carriers. As described in detail below, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the

following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets (e.g., those targeted for buccal, sublingual, and/or systemic absorption), boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration by, for example, subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally.

[00153] The phrase "therapeutically-effective amount" as used herein means that amount of a compound, material, or composition comprising a compound of the present invention which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment.

[00154] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00155] Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[00156] Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[00157] Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be

combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration.

[00158] The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 0.1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

[00159] In certain embodiments, a formulation of the present invention comprises an excipient selected from the group consisting of cyclodextrins, celluloses, liposomes, micelle forming agents, e.g., bile acids, and polymeric carriers, e.g., polyesters and polyanhydrides; and a compound of the present invention. In certain embodiments, an aforementioned formulation renders orally bioavailable a compound of the present invention.

[00160] Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[00161] Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

[00162] In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules, trouches and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as

glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds and surfactants, such as poloxamer and sodium lauryl sulfate; (7) wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and non-ionic surfactants; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, zinc stearate, sodium stearate, stearic acid, and mixtures thereof; (10) coloring agents; and (11) controlled release agents such as crospovidone or ethyl cellulose. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[00163] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[00164] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be formulated for rapid release, e.g., freeze-dried. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions

which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[00165] Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[00166] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[00167] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[00168] Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

[00169] Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

[00170] Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a

pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[00171] The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[00172] Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[00173] Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[00174] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

[00175] Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[00176] Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper

fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[00177] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[00178] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[00179] Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

[00180] When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99% (more preferably, 10 to 30%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[00181] The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given in forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye

lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administrations are preferred.

[00182] The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[00183] The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[00184] These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

[00185] Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

[00186] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[00187] The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with

the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[00188] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[00189] In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Preferably, the compounds are administered at about 0.01 mg/kg to about 200 mg/kg, more preferably at about 0.1 mg/kg to about 100 mg/kg, even more preferably at about 0.5 mg/kg to about 50 mg/kg. When the compounds described herein are co-administered with another agent (*e.g.*, as sensitizing agents), the effective amount may be less than when the agent is used alone.

[00190] If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. Preferred dosing is one administration per day.

V. KITS FOR USE IN MEDICAL APPLICATIONS

[00191] Another aspect of the invention provides a kit for treating a disorder. The kit comprises: i) instructions for treating a medical disorder, such as Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy; and ii) a heterobicyclic pyrimidinone compound described herein, such as a compound of Formula I, II, III, IV, V, or VI. The kit may comprise one or more unit dosage forms containing an amount of a heterobicyclic pyrimidinone compound described herein, such as a compound of Formula I, that is effective for treating said medical disorder, *e.g.*, Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy.

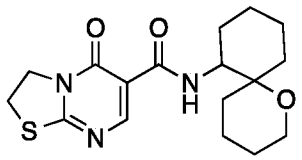
[00192] The description above describes multiple aspects and embodiments of the invention, including heterobicyclic pyrimidinone compounds, compositions comprising a heterobicyclic pyrimidinone compound, methods of using the heterobicyclic pyrimidinone compounds, and

kits. The patent application specifically contemplates all combinations and permutations of the aspects and embodiments. For example, the invention contemplates treating Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy in a human patient by administering a therapeutically effective amount of a compound of Formula II. Further, for example, the invention contemplates a kit for treating Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy, the kit comprising (i) instructions for treating Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy and (ii) a heterobicyclic pyrimidinone compound described herein, such as a compound of Formula II.

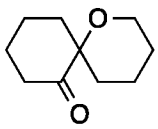
EXAMPLES

[00193] The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

EXAMPLE 1 – PREPARATION OF 5-OXO-*N*-(1-OXASPIRO[5.5]UNDECAN-7-YL)-2,3-DIHYDRO-5*H*-THIAZOLO[3,2-*a*]PYRIMIDINE-6-CARBOXAMIDE



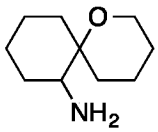
Part I – Preparation of 1-oxaspiro[5.5]undecan-7-one



[00194] A round-bottom flask was charged with potassium tert-butoxide (236 mg, 6.33 mmol) purged with N_2, then THF (15 mL) was added. A solution of cyclohexanone (207 mg, 6.33 mmol) in THF (15 mL) was added dropwise and the reaction mixture was stirred for 15 minutes. Next, a solution of 1-(*tert*-butylperoxy)-4-iodobutane (574 mg, 2.11 mmol) in THF (5 mL) was added dropwise. After disappearance of starting material (as analyzed by TLC), the reaction was quenched by dropwise addition of water to the reaction mixture. Then, the organic phase was separated, and the aqueous phase was extracted with ethyl ether/ethyl

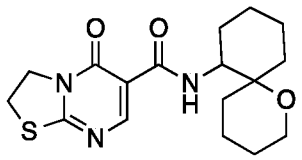
acetate. The organic phases were combined and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (eluting with 5% ethyl acetate/hexane) to give 1-oxaspiro[5.5]undecan-7-one (120 mg, 33%) as a pale oil. LC-MS m/z: 169.1 $[M+H]^+$. LCMS: t_R = 1.75 min.

Part II – Preparation of 1-oxaspiro[5.5]undecan-7-amine



[00195] A suspension of 1-oxaspiro[5.5]undecan-7-one (120 mg, 0.71 mmol) and NH_4OAc (1.099 g, 14.28 mmol) in *i*-PrOH (10 mL) was heated at 70 °C for 2 hours. Then, the reaction mixture was cooled to room temperature. Next, $NaBH_3CN$ (89 mg, 1.42 mmol) was added, and the reaction mixture was stirred at 50 °C for 2 hours, then concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (eluting with DCM/MeOH: 20/1) to give 1-oxaspiro[5.5]undecan-7-amine (cis/trans mixture, 80 mg, 66%) as a pale oil. LC-MS m/z: 170.3 $[M+H]^+$. LCMS: t_R = 1.46 min, 1.50 min.

Part III – Preparation of 5-oxo-*N*-(1-oxaspiro[5.5]undecan-7-yl)-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide



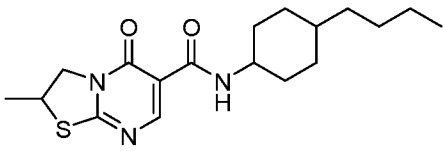
[00196] A mixture of 5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid (60 mg, 0.3 mmol), HATU (228 mg, 0.6 mmol) and DIPEA (104 mg, 0.8 mmol) in DMF (2 mL) was stirred at room temperature for 0.5 hour. Then, 1-oxaspiro[5.5]undecan-7-amine (60 mg, 0.35 mmol) was added, and the reaction mixture was stirred for another 12 hours, and the resulting crude product was purified by prep-HPLC (10 mM NH_4HCO_3/MeCN) to separate the diastereoisomeric mixture to give **Stereoisomer No. 1** (4.9 mg, 4.7%) as pale white solid and **Stereoisomer No. 2** (17.7 mg, 17%) as a pale white solid.

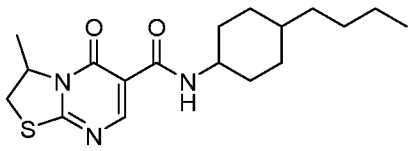
[00197] **Stereoisomer No. 1**: ^1H NMR (500 MHz, DMSO-d_6) δ 9.11 (d, J = 8.0 Hz, 1H), 8.78 (s, 1H), 4.56-4.60 (m, 2H), 3.90 (m, 1H), 3.74-3.76 (m, 1H), 3.52-3.57 (m, 3H), 2.46 (d, J

= 15.0 Hz, 1H), 1.59-1.63 (m, 5H), 1.4-1.49 (m, 5H),1.22-1.24 (m, 2H), 0.98-1.03 (m, 1H). LC-MS m/z: 350.2 $[M+H]^+$. HPLC: Purity (254 nm): >99%; t_R = 9.46 min.

[00198] **Stereoisomer No. 2**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (d, J = 9.5 Hz, 1H), 8.81 (s, 1H), 4.8 (t, J = 8.0 Hz, 1H), 4.48-4.50 (m, 1H), 3.66-3.82 (m, 2H), 3.56 (t, J = 8.0 Hz, 1H), 1.94-2.00 (m, 1H), 1.80-1.83 (m, 1 H), 1.62-1.73 (m, 2H), 1.35-1.56 (m, 10H). LC-MS m/z: 350.2 $[M+H]^+$. HPLC: Purity (254 nm): >99%; t_R = 9.14 min.

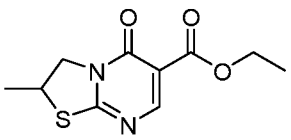
EXAMPLE 2 – PREPARATION OF *N*-(4-BUTYLCYCLOHEXYL)-2-METHYL-5-OXO-2,3-DIHYDRO-5*H*-THIAZOLO[3,2-*a*]PYRIMIDINE-6-CARBOXAMIDE OR *N*-(4-BUTYLCYCLOHEXYL)-3-METHYL-5-OXO-2,3-DIHYDRO-5*H*-THIAZOLO[3,2-*a*]PYRIMIDINE-6-CARBOXAMIDE



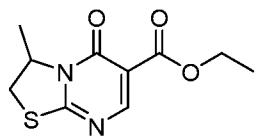


[00199] The synthetic procedures below provide a single compound, which is either *N*-(4-butylcyclohexyl)-2-methyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide or *N*-(4-butylcyclohexyl)-3-methyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide.

Part I – Preparation of ethyl 2-methyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate or ethyl 3-methyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate



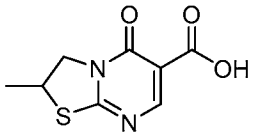
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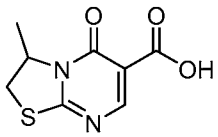


[00200] To a solution of 1,2-dibromopropane (500 mg, 2.5 mmol) in dry toluene (15 mL) in a round-bottom flask equipped with a condenser was added anhydrous Cs_2CO_3 (1.63 g, 5 mmol), tetrabutylammonium bromide (242 mg, 0.75 mmol), and ethyl 2-mercapto-6-oxo-1,6-dihydropyrimidine-5-carboxylate (505 mg, 2.5 mmol). T he reaction mixture was vigorously stirred overnight at 120 °C. Then, the reaction mixture was cooled to room temperature, filtered, and the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica (petroleum ether / ethyl acetate: 1/5) to give either ethyl 3-methyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate or ethyl 2-methyl-5-oxo-2,3-

dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate as an off-white solid (322 mg, 54%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.36 (s, 1H), 5.13 (t, J = 6.5 Hz, 1H), 4.23-4.18 (m, 2H), 3.88 (dd, J = 8.0 Hz, 1H), 3.23 (d, J = 11.5 Hz, 1H), 1.40 (d, J = 6.5 Hz, 3H), 1.26 (t, J = 7.5 Hz, 3H). LC-MS m/z: 241.1 $[M+H]^+$.

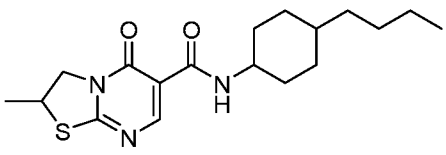
Part II – Preparation of 2-methyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid or 3-methyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid

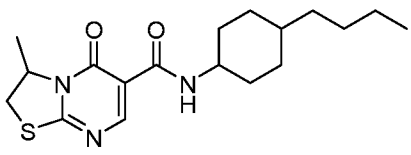


or


[00201] To a solution of either the 2-methyl or 3-methyl ester (65 mg, 0.271 mmol) in toluene (15 mL) was added $(Bu_3Sn)_2O$ (323 mg, 0.542 mmol). The mixture was stirred at reflux overnight, then cooled to room temperature, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica (eluting with DCM:Methanol = 30:1 to 5:1) to give 2-methyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid or 3-methyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid as an off-white solid (61 mg, 85%). LC-MS m/z: 213.2 $[M+H]^+$. LC-MS Purity (214 nm): >90 %; t_R = 0.35 min

Part III – Preparation of *N*-(4-butylcyclohexyl)-2-methyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide or *N*-(4-butylcyclohexyl)-3-methyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide



or


[00202] The following procedure produce one of the above regiosomeric compounds. The compound produced by the procedure was a mixture of two stereoisomers (i.e., the cis-stereoisomer and the trans-stereoisomer).

[00203] To the solution of acid (50 mg, 0.236 mmol) from Part II above in DMF (5 mL) was added 4-butylcyclohexan-1-amine (75 mg, 0. 472 mmol), HATU (110 mg, 0.283 mmol) and DIPEA (150 mg, 1.180 mmol), and the mixture was stirred at room temperature overnight.

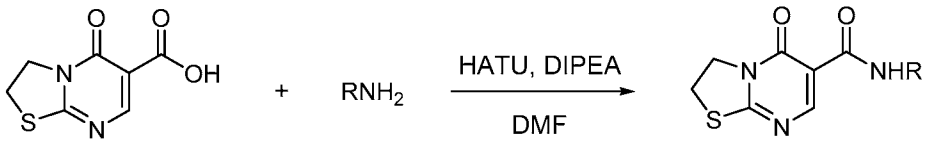
Then, the reaction mixture was diluted with EtOAc (100 mL), washed with water (50 mL two times) and brine (50 mL two times). The organic phases were then dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. The resulting residue was purified by prep-HPLC (Mobile Phase A: 10 mmol/L NH_4HCO_3 in water, B: MeCN; Gradient:5%B increase to 95%B) to give the cis-steroisomer and trans-stereoisomer separately. **Stereoisomer No. 1** (20.7 mg) and **Stereoisomer No. 2** (16.6 mg) as light yellow solids (total yield: 38.4%).

[00204] **Stereoisomer No. 1**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.14 (d, J = 8.0 Hz, 1H), 8.49 (s, 1H), 5.21-5.18 (m, 1H), 4.07-4.06 (m, 1H), 3.89 (dd, J = 11.5, 8.0 Hz, 1H), 3.28 (d, J = 11.5 Hz, 1H), 1.65~1.53 (m, 6H), 1.43 (d, J = 8.0 Hz, 3H), 1.31~1.13 (m, 7H), 1.10 (t, J = 5.5 Hz, 2H), 0.89 (t, J = 6.5 Hz, 3H). LC-MS m/z: 350.0 $[M+H]^+$. HPLC Purity (214 nm): 98.9%; t_R = 11.28 min.

[00205] **Stereoisomer No. 2**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (d, J = 8.0 Hz, 1H), 8.48 (s, 1H), 5.16~5.13 (m, 1H), 3.89 (dd, J = 11.5, 8.0 Hz, 1H), 3.68~3.64 (m, 1H), 3.25 (d, J = 11.5 Hz, 1H), 1.91 (t, J = 9.5 Hz, 2H), 1.75 (d, J = 13.5 Hz, 2H), 1.42 (d, J = 6.5 Hz, 3H), 1.27-1.18 (m, 9H), 1.01-0.94 (m, 2H), 0.87 (t, J = 6.5 Hz, 3H). LC-MS m/z: 350.0 $[M+H]^+$. HPLC Purity (214 nm): >99.5%; t_R = 11.41 min.

EXAMPLE 3 – PREPARATION OF ADDITIONAL 2,3-DIHYDRO-5-OXO-5*H*-THIAZOLO[3,2-*a*]PYRIMIDINE-6-CARBOXAMIDE COMPOUNDS

[00206] Compounds in Table 4 below were prepare based on the following procedure.

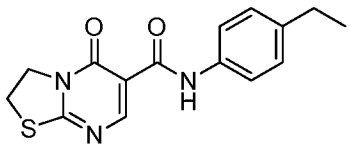
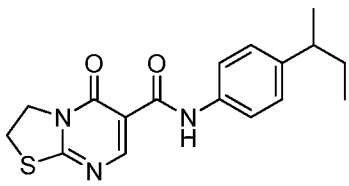
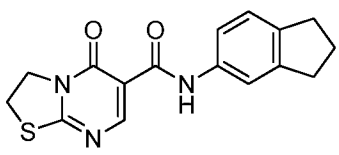


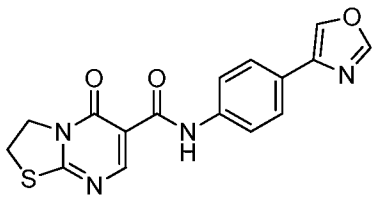
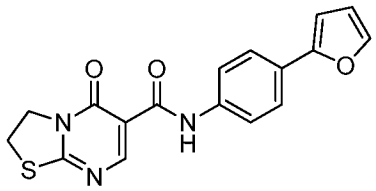
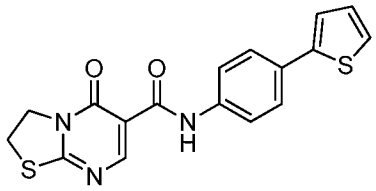
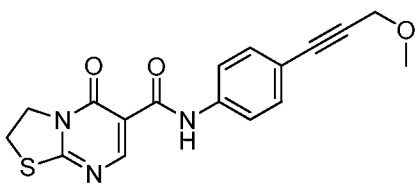
R is, for example, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl.

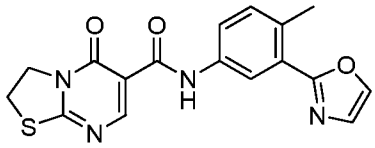
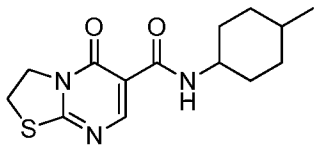
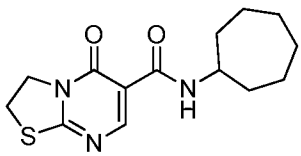
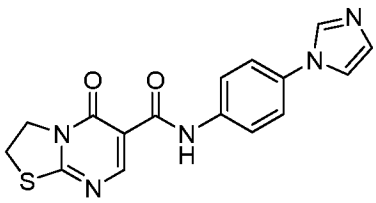
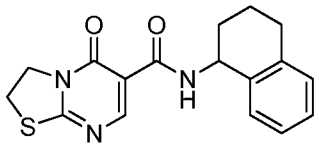
[00207] A mixture of carboxylic acid (1 equiv.), amine (1 equiv.), HATU (1 equiv.) and DIPEA (3 equiv.) in DMF are stirred at room temperature or 65℃ for 16 hr. Then, water is added to the reaction mixture, and the resulting mixture is filtered, and resulting solid is washed with water, and dried in vacuum to give the carboxamide product. If no solid forms when water is added to the reaction mixture, the reaction mixture may be extracted with EtOAc three times, and then the combined organic phase is washed with 10% Na_2CO_3 solution, brine, dried

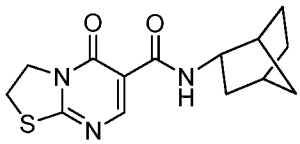
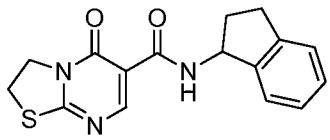
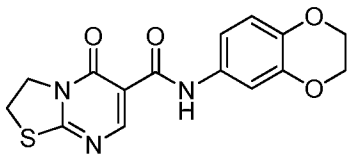
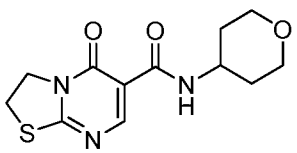
(Na_2SO_4), filtered, and evaporated to give the carboxamide product. Generally, the product is sufficiently pure (e.g., >95% purity). However, if the crude product is not sufficiently pure, then the crude product may be purified by flash chromatography.

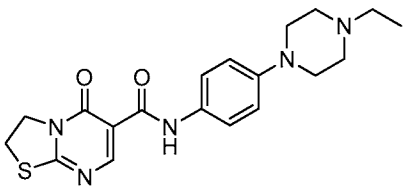
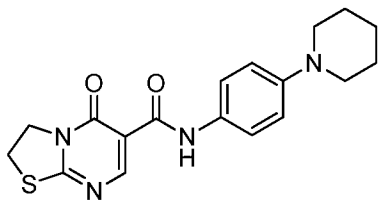
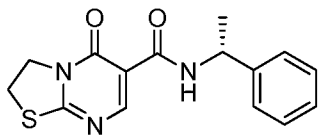
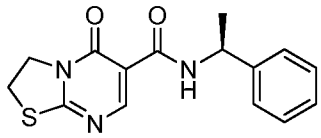
TABLE 4.

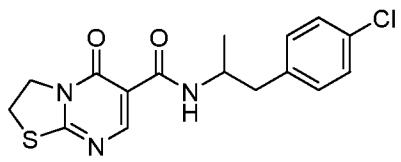
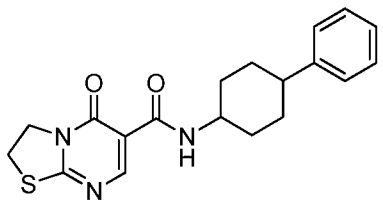
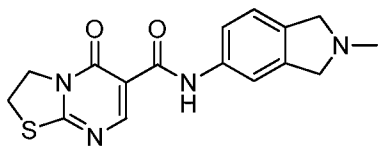
No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
3A		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.80 (s, 1H), 8.86 (s, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 4.58 (t, *J* = 7.8 Hz, 2H), 3.57 (t, *J* = 7.8 Hz, 2H), 2.62 (q, *J* = 7.4 Hz, 2H), 1.22 (t, *J* = 7.5 Hz, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 160.9, 160.4, 159.5, 140.4, 135.7, 128.3, 120.4, 113.4, 49.1, 28.3, 26.7, 15.6	ESI-MS m/z: 324 $(M+Na)^+$
3B		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.78 (s, 1H), 8.86 (s, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 4.58 (t, *J* = 7.9 Hz, 2H), 3.56 (t, *J* = 7.9 Hz, 2H), 2.60-2.51 (m, 1H), 1.59-1.53 (m, 2H), 1.20 (d, *J* = 6.9 Hz, 3H), 0.80 (t, *J* = 7.4 Hz, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 160.9, 160.4, 159.5, 143.8, 135.8, 127.5, 120.3, 113.4, 49.1, 41.2, 31.1, 26.7, 21.8, 12.2	ESI-MS m/z: 352 $(M+Na)^+$
3C		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.78 (s, 1H), 8.85 (s, 1H), 7.62 (s, 1H), 7.34 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 4.57 (t, *J* = 7.9 Hz, 2H), 3.55 (t, *J* = 7.9 Hz, 2H), 2.89 (t, *J* = 7.5 Hz, 2H), 2.85 (t, *J* = 7.4 Hz, 2H), 2.08-2.02 (m, 2H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 161.0, 160.5, 159.6, 145.2, 140.4, 136.3, 124.6, 118.5, 116.8, 113.6, 49.2, 33.1, 32.5, 26.8, 25.7	ESI-MS m/z: 336 $(M+Na)^+$

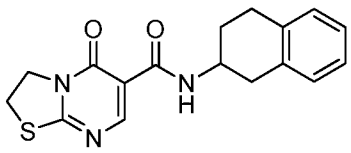
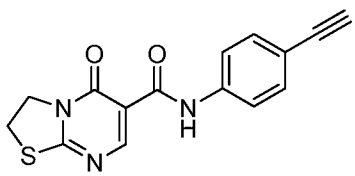
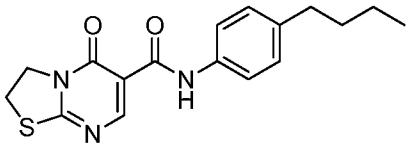
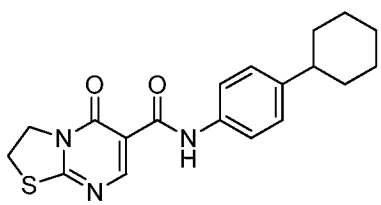
No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
3D		^{1}H NMR (500 MHz, d6-DMSO) δ 11.13 (s, 1H), 8.62 (d, *J* = 15.2 Hz, 2H), 8.46 (s, 1H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.76 (d, *J* = 8.6 Hz, 2H), 4.55 (t, *J* = 8.0 Hz, 2H), 3.68 (t, *J* = 8.0 Hz, 2H).	^{13}C NMR (125 MHz, d6-DMSO) δ 170.5, 160.6, 160.4, 158.3, 152.5, 138.8, 137.7, 134.6, 126.4, 125.9, 119.8, 112.2, 49.4, 26.8	ESI-MS m/z: 363 $(M+Na)^+$
3E		^{1}H NMR (500 MHz, d6-DMSO) δ 11.13 (s, 1H), 8.63 (s, 1H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 3.3 Hz, 1H), 6.60 (dd, *J* = 3.3, 1.8 Hz, 1H), 4.59 – 4.50 (m, 2H), 3.68 (t, *J* = 8.0 Hz, 2H).	^{13}C NMR (125 MHz, d6-DMSO) δ 170.5, 160.6, 160.4, 158.3, 152.8, 142.6, 137.3, 126.1, 124.2, 119.9, 112.3, 112.0, 105.1, 49.4, 26.8	ESI-MS m/z: 362 $(M+Na)^+$
3F		^{1}H NMR (500 MHz, d6-DMSO) δ 11.12 (s, 1H), 8.63 (s, 1H), 7.73 (d, *J* = 8.7 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.55 – 7.50 (m, 1H), 7.48 (dd, *J* = 3.5, 0.9 Hz, 1H), 7.14 (dd, *J* = 5.0, 3.6 Hz, 1H), 4.54 (t, *J* = 8.0 Hz, 2H), 3.67 (t, *J* = 8.0 Hz, 2H).	^{13}C NMR (125 MHz, d6-DMSO) δ 170.9, 161.0, 160.9, 158.8, 143.4, 137.9, 129.9, 128.9, 126.5, 125.6, 123.6, 120.5, 112.7, 49.8, 27.3	ESI-MS m/z: 378 $(M+Na)^+$
3G		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.94 (s, 1H), 8.84 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 4.58 (t, *J* = 8.0 Hz, 2H), 4.30 (s, 2H), 3.57 (t, *J* = 8.0 Hz, 2H), 3.43 (s, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 160.8, 160.6, 159.7, 138.2, 132.5, 119.9, 118.2, 113.1, 86.2, 84.5, 60.4, 57.6, 49.1, 26.7	ESI-MS m/z: 364 $(M+Na)^+$

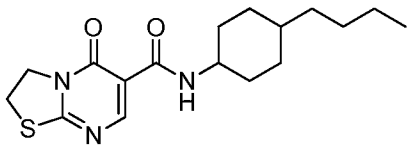
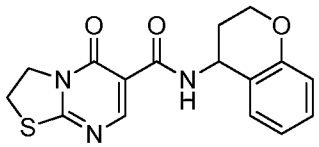
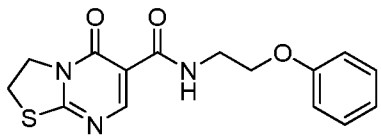
No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
3H		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.89 (s, 1H), 8.84 (s, 1H), 8.23 (d, *J* = 2.3 Hz, 1H), 7.72 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.70 (s, 1H), 7.25 – 7.22 (m, 2H), 4.56 (t, *J* = 8.0 Hz, 2H), 3.55 (t, *J* = 8.0 Hz, 2H), 2.63 (s, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 161.8, 160.8, 160.6, 159.6, 138.2, 136.1, 133.3, 132.2, 128.1, 126.8, 121.8, 120.4, 113.2, 49.1, 26.7, 21.4	ESI-MS m/z: 377 $(M+Na)^+$
3I	 cis/trans mixture	N/A	N/A	ESI-MS m/z: 316 $(M+Na)^+$
3J		^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (d, *J* = 6.9 Hz, 1H), 8.75 (s, 1H), 4.52 (t, *J* = 7.9 Hz, 2H), 4.19 – 4.03 (m, 1H), 3.52 (t, *J* = 7.9 Hz, 2H), 1.98 – 1.79 (m, 2H), 1.71 – 1.36 (m, 10H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 161.3, 160.8, 159.0, 113.4, 50.0, 49.0, 34.8, 28.0, 26.6, 24.0	ESI-MS m/z: 316 $(M+Na)^+$
3K		insoluble	N/A	ESI-MS m/z: 340 $(M+H)^+$
3L		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.08 (d, *J* = 8.1 Hz, 1H), 8.82 (s, 1H), 7.37 – 7.26 (m, 1H), 7.12 (td, *J* = 6.5, 1.6 Hz, 2H), 7.09 – 7.04 (m, 1H), 5.44 – 5.20 (m, 1H), 4.48 (t, *J* = 7.9 Hz, 2H), 3.49 (t, *J* = 7.9 Hz, 2H), 2.89 – 2.64 (m, 2H), 2.19 – 1.99 (m, 1H), 1.93 – 1.72 (m, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 161.9, 160.6, 159.2, 137.3, 136.8, 129.1, 128.6, 127.1, 126.2, 113.3, 48.9, 47.4, 30.2, 29.2, 26.7, 20.1	ESI-MS m/z: 350 $(M+Na)^+$

No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
3M		^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, 2H), 4.51 (t, J = 7.9 Hz, 2H), 3.94 – 3.71 (m, 1H), 3.52 (t, J = 7.9 Hz, 2H), 2.34 – 2.19 (m, 2H), 1.80 (ddd, J = 13.0, 8.0, 2.1 Hz, 1H), 1.54 – 1.42 (m, 2H), 1.42 – 1.37 (m, 1H), 1.32 – 1.21 (m, 2H), 1.19 (d, J = 10.1 Hz, 1H), 1.16 – 1.08 (m, 1H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 161.5, 160.7, 158.9, 113.3, 52.6, 48.9, 42.5, 40.3, 35.7, 35.7, 28.3, 26.6, 26.4	ESI-MS m/z: 314 $(M+Na)^+$
3N		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.06 (d, J = 7.6 Hz, 1H), 8.82 (s, 1H), 7.30 (d, J = 7.1 Hz, 1H), 7.24 – 7.15 (m, 3H), 5.61 (q, J = 7.7 Hz, 1H), 4.53 – 4.46 (m, 2H), 3.51 (t, J = 7.9 Hz, 2H), 3.00 (ddd, J = 15.8, 8.7, 3.5 Hz, 1H), 2.94 – 2.83 (m, 1H), 2.69 – 2.61 (m, 1H), 1.95 – 1.82 (m, 1H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 162.5, 160.6, 159.2, 143.3, 143.3, 127.8, 126.7, 124.7, 124.0, 113.1, 54.6, 49.0, 34.2, 30.3, 26.6	ESI-MS m/z: 336 $(M+Na)^+$
3O		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.84 (s, 1H), 7.34 (s, 1H), 7.06 (d, J = 6.3 Hz, 1H), 6.81 (d, J = 7.3 Hz, 1H), 4.58 (s, 2H), 4.24 (s, 4H), 3.57 (s, 2H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 160.8, 160.2, 159.4, 143.4, 140.4, 131.8, 117.1, 113.8, 113.3, 109.9, 64.4, 64.3, 49.1, 26.7	ESI-MS m/z: 354 $(M+Na)^+$
3P		^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (d, J = 6.4 Hz, 1H), 8.75 (s, 1H), 4.53 (t, J = 7.9 Hz, 2H), 4.20 – 4.07 (m, 1H), 3.98 – 3.86 (m, 2H), 3.58 – 3.43 (m, 4H), 1.94 (d, J = 11.9 Hz, 2H), 1.62 – 1.51 (m, 2H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 161.9, 160.7, 159.2, 113.1, 66.6, 49.0, 45.3, 32.9, 26.6	ESI-MS m/z: 304 $(M+Na)^+$

No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
3Q		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.84 (s, 1H), 7.56 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 4.56 (t, *J* = 7.9 Hz, 2H), 3.54 (t, *J* = 7.9 Hz, 2H), 3.24 – 3.10 (m, 4H), 2.66 – 2.53 (m, 4H), 2.46 (q, *J* = 7.2 Hz, 2H), 1.11 (t, *J* = 7.2 Hz, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 160.9, 160.1, 159.3, 148.2, 130.6, 121.4, 116.5, 113.5, 52.8, 52.3, 49.4, 49.0, 26.7, 11.9	ESI-MS m/z: 386 $(M+H)^+$
3R		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.84 (s, 1H), 7.55 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.57 (t, *J* = 7.9 Hz, 2H), 3.55 (t, *J* = 7.9 Hz, 2H), 3.15 – 3.05 (m, 4H), 1.73 – 1.65 (m, 4H), 1.58 – 1.51 (m, 2H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 160.9, 160.0, 159.3, 149.2, 130.2, 121.3, 117.0, 113.5, 51.0, 49.0, 26.7, 25.8, 24.2	ESI-MS m/z: 357 $(M+H)^+$
3S		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (d, *J* = 7.2 Hz, 1H), 8.75 (s, 1H), 7.38 – 7.26 (m, 4H), 7.24 – 7.20 (m, 1H), 5.29 – 5.21 (m, 1H), 4.53 (t, *J* = 7.9 Hz, 2H), 3.52 (t, *J* = 7.9 Hz, 2H), 1.53 (d, *J* = 6.9 Hz, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 161.7, 160.8, 159.2, 143.5, 128.6, 127.1, 126.0, 113.2, 49.0, 48.9, 26.6, 22.6	ESI-MS m/z: 324 (M+Na)+
3T		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (d, *J* = 7.3 Hz, 1H), 8.75 (s, 1H), 7.40 – 7.26 (m, 4H), 7.24 – 7.19 (m, 1H), 5.29 – 5.21 (m, 1H), 4.52 (t, *J* = 7.9 Hz, 2H), 3.52 (t, *J* = 7.9 Hz, 2H), 1.53 (d, *J* = 6.9 Hz, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 161.7, 160.8, 159.2, 143.5, 128.6, 127.1, 126.0, 113.2, 49.0, 48.9, 26.6, 22.6	ESI-MS m/z: 324 $(M+Na)^+$

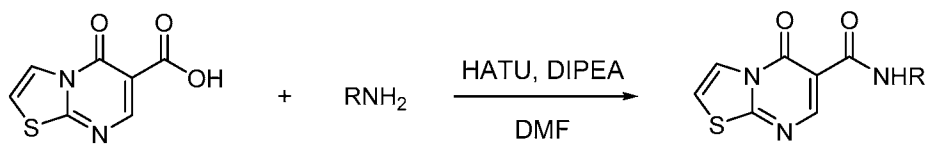
No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
3U		^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 – 8.66 (m, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 4.58 – 4.47 (m, 2H), 4.39 – 4.29 (m, 1H), 3.53 (t, *J* = 7.9 Hz, 2H), 2.87 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.72 (dd, *J* = 13.6, 7.0 Hz, 1H), 1.17 (d, *J* = 6.6 Hz, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 161.9, 160.7, 159.1, 136.8, 132.1, 130.7, 128.4, 113.1, 49.0, 46.3, 42.0, 26.6, 20.1	ESI-MS m/z: 372 $(M+Na)^+$
3V		^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.72 (d, *J* = 7.8 Hz, 1H), 7.31 –7.14 (m, 5H), 4.54 (t, *J* = 7.9 Hz, 2H), 4.03 – 3.93 (m, 1H), 3.53 (t, *J* = 7.9 Hz, 2H), 2.50 (tt, *J* = 12.1, 3.3 Hz, 1H), 2.20 – 2.12 (m, 2H), 1.98 – 1.90 (m, 2H), 1.67 – 1.56 (m, 2H), 1.45 – 1.34 (m, 2H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 161.8, 160.8, 159.1, 146.7, 128.3, 126.7, 126.1, 113.3, 49.0, 48.2, 43.5, 33.3, 32.9, 26.6	ESI-MS m/z: 378 $(M+Na)^+$
3W		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.84 (s, 1H), 8.83 (s, 1H), 7.67 (s, 1H), 7.36 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 4.56 (t, *J* = 8.0 Hz, 2H), 3.90 (s, 2H), 3.87 (s, 2H), 3.55 (t, *J* = 8.0 Hz, 2H), 2.57 (s, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 160.8, 160.5, 159.5, 141.5, 136.9, 136.6, 122.4, 118.8, 114.5, 113.3, 61.0, 60.6, 49.1, 42.4, 26.7	ESI-MS m/z: 329 $(M+H)^+$

No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
3X		^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, *J* = 6.7 Hz, 1H), 8.80 (s, 1H), 7.17 – 6.99 (m, 4H), 4.53 (t, *J* = 7.9 Hz, 2H), 4.48 – 4.34 (m, 1H), 3.53 (t, *J* = 7.9 Hz, 2H), 3.18 (dd, *J* = 16.2, 4.9 Hz, 1H), 2.97 – 2.90 (m, 2H), 2.79 (dd, *J* = 16.2, 8.6 Hz, 1H), 2.21 – 2.08 (m, 1H), 1.94 – 1.76 (m, 1H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 162.1, 160.7, 159.1, 135.5, 134.3, 129.4, 128.8, 126.0, 125.8, 113.2, 49.0, 45.3, 35.6, 28.8, 27.4, 26.6	ESI-MS m/z: 350 $(M+Na)^+$
3Y		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.96 (s, 1H), 8.84 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 4.57 (t, *J* = 7.9 Hz, 2H), 3.57 (t, *J* = 7.9 Hz, 2H), 3.05 (s, 1H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 160.8, 160.6, 159.7, 138.5, 132.9, 119.9, 117.6, 113.0, 83.5, 76.8, 49.1, 26.7	ESI-MS m/z: 320 $(M+Na)^+$
3Z		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.80 (s, 1H), 8.87 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 4.59 (t, *J* = 7.9 Hz, 2H), 3.57 (t, *J* = 7.9 Hz, 2H), 2.64 – 2.49 (m, 2H), 1.66 – 1.52 (m, 2H), 1.41 – 1.28 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 160.9, 160.4, 159.5, 139.0, 135.7, 128.8, 120.3, 113.4, 49.1, 35.1, 33.6, 26.7, 22.3, 13.9	ESI-MS m/z: 352 $(M+Na)^+$
3AA		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.78 (s, 1H), 8.85 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 4.57 (t, *J* = 7.9 Hz, 2H), 3.55 (t, *J* = 7.9 Hz, 2H), 2.51 – 2.40 (m, 1H), 1.91 – 1.76 (m, 4H), 1.72 (d, *J* = 12.5 Hz, 1H), 1.44 – 1.30 (m, 4H), 1.29 – 1.16 (m, 1H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 160.9, 160.4, 159.5, 144.3, 135.7, 127.2, 120.3, 113.4, 49.1, 44.0, 34.5, 26.9, 26.7, 26.1	ESI-MS m/z: 378 $(M+Na)^+$

No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
3AB	 cis/trans mixture	N/A	N/A	ESI-MS m/z: 358 $(M+Na)^+$
3AC		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (d, *J* = 7.3 Hz, 1H), 8.82 (s, 1H), 7.22 (s, 1H), 7.17 – 7.12 (m, 1H), 6.87 (td, *J* = 7.6, 1.0 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 5.34 – 5.28 (m, 1H), 4.53 – 4.46 (m, 2H), 4.30 – 4.24 (m, 1H), 4.22 – 4.15 (m, 1H), 3.52 (t, *J* = 7.9 Hz, 2H), 2.32 – 2.24 (m, 1H), 2.13 – 2.05 (m, 1H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 162.1, 160.6, 159.3, 154.9, 129.3, 129.1, 122.2, 120.8, 117.0, 112.9, 63.3, 49.0, 43.5, 29.1, 26.7	ESI-MS m/z: 352 $(M+Na)^+$
3AD		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.77 (s, 1H), 7.29 – 7.24 (m, 2H), 6.96 – 6.89 (m, 3H), 4.53 (t, *J* = 7.9 Hz, 2H), 4.10 (t, *J* = 5.3 Hz, 2H), 3.81 (q, *J* = 5.5 Hz, 2H), 3.52 (t, *J* = 7.9 Hz, 2H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 162.9, 160.5, 159.1, 158.6, 129.4, 121.0, 114.6, 113.0, 77.3, 77.0, 76.8, 66.5, 49.0, 38.8, 26.6	ESI-MS m/z: 340 $(M+Na)^+$

EXAMPLE 4 – PREPARATION OF 5-OXO-5*H*-THIAZOLO[3,2-*a*]PYRIMIDINE-6-CARBOXAMIDES COMPOUNDS

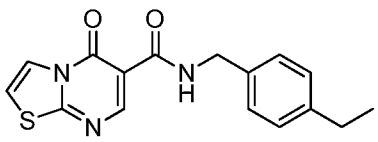
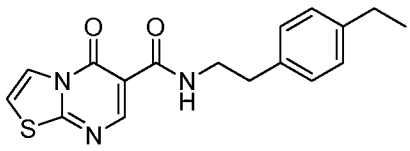
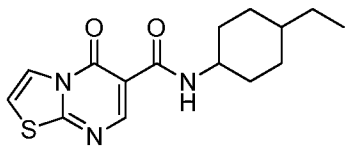
[00208] Compounds in Table 5 below were prepare based on the following general procedure.

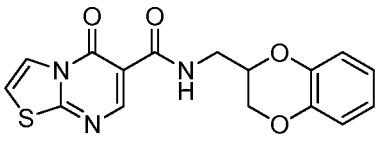
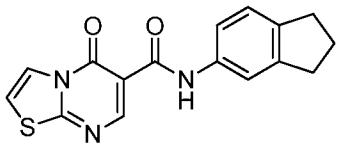
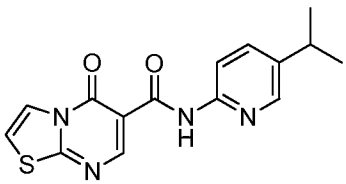
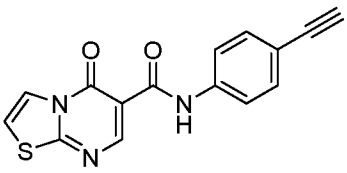


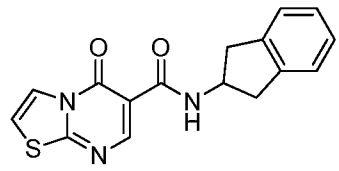
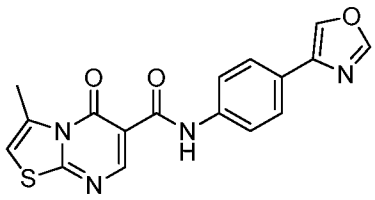
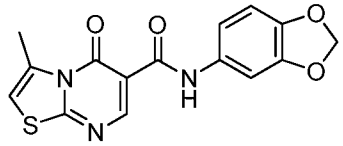
R is, for example, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl.

[00209] A mixture of carboxylic acid (1 equiv.), amine (1 equiv.), HATU (1 equiv.) and DIPEA (3 equiv.) in DMF are stirred at room temperature or 65℃ for 16 hr. Then, water is added to the reaction mixture, and the resulting mixture is filtered, and resulting solid is washed with water, and dried in vacuum to give the carboxamide product. If no solid forms when water is added to the reaction mixture, the reaction mixture may be extracted with EtOAc three times, and then the combined organic phase is washed with 10% Na_2CO_3 solution, brine, dried (Na_2SO_4), filtered, and evaporated to give the carboxamide product. Generally, the product is sufficiently pure (e.g., >95% purity). However, if the crude product is not sufficiently pure, then the crude product may be purified by flash chromatography.

TABLE 5.

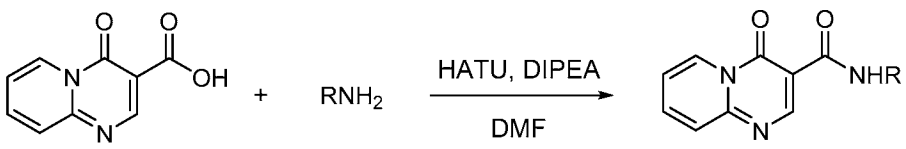
No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
4A		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (s, 2H), 8.17 (d, *J* = 4.9 Hz, 1H), 7.36 – 7.32 (m, 2H), 7.27 – 7.22 (m, 3H), 4.70 (d, *J* = 5.7 Hz, 2H), 2.69 (q, *J* = 7.6 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 163.2, 158.4, 157.9, 143.4, 135.7, 128.2, 127.8, 122.6, 113.8, 109.2, 43.3, 28.6, 15.7	ESI-MS m/z: 336 $(M+Na)^+$
4B		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.87 (s, 1H), 8.12 (d, *J* = 4.9 Hz, 1H), 7.21 – 7.11 (m, 5H), 3.73 – 3.67 (m, 2H), 2.91 (t, *J* = 7.3 Hz, 2H), 2.62 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 163.3, 158.3, 157.8, 142.4, 136.3, 128.8, 128.1, 122.7, 113.7, 109.3, 41.1, 35.6, 28.5, 15.7	ESI-MS m/z: 350 $(M+Na)^+$
4C	 cis/trans mixture	N/A	N/A	ESI-MS m/z: 328 $(M+Na)^+$

No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
4D		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 9.08 (s, 1H), 8.16 (d, *J* = 4.8 Hz, 1H), 7.22 (d, *J* = 4.8 Hz, 1H), 6.96 – 6.90 (m, 1H), 6.90 – 6.80 (m, 3H), 4.39 (d, *J* = 5.9 Hz, 1H), 4.34 (d, *J* = 11.5 Hz, 1H), 4.03 (dd, *J* = 11.4, 7.3 Hz, 1H), 3.90 – 3.82 (m, 1H), 3.78 – 3.70 (m, 1H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 163.9, 158.3, 157.9, 143.2, 143.0, 122.7, 121.7, 121.6, 117.6, 117.2, 113.9, 108.9, 72.1, 66.0, 39.8	ESI-MS m/z: 366 $(M+Na)^+$
4E		^{1}H NMR (500 MHz, d6-DMSO) δ 10.94 (s, 1H), 8.89 (s, 1H), 8.33 (d, *J* = 4.7 Hz, 1H), 7.83 (d, *J* = 4.8 Hz, 1H), 7.64 (s, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 2.93 – 2.79 (m, 4H), 2.10 – 1.97 (m, 2H).	^{13}C NMR (125 MHz, d6-DMSO) δ 166.5, 161.4, 158.7, 156.8, 145.0, 139.7, 136.9, 124.9, 123.3, 118.2, 117.0, 116.2, 108.8, 32.9, 32.3, 25.6	ESI-MS m/z: 334 $(M+Na)^+$
4F		^{1}H NMR (500 MHz, $CDCl_3$) δ 11.25 (s, 1H), 9.14 (s, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 8.23 – 8.17 (m, 2H), 7.57 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.23 (d, *J* = 4.8 Hz, 1H), 2.91 (m, 1H), 1.25 (d, *J* = 6.9 Hz, 6H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 161.4, 158.1, 158.0, 149.6, 146.5, 140.0, 135.9, 122.9, 114.4, 113.9, 109.0, 31.3, 23.8	ESI-MS m/z: 337 $(M+Na)^+$
4G		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.94 (s, 1H), 9.13 (s, 1H), 8.15 (d, *J* = 4.8 Hz, 1H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 4.8 Hz, 1H), 3.03 (s, 1H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 161.2, 158.5, 158.1, 138.6, 132.9, 122.6, 119.9, 117.6, 114.2, 109.0, 83.5	ESI-MS m/z: 318 $(M+Na)^+$

No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
4H		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (s, 1H), 9.05 (d, *J* = 6.5 Hz, 1H), 8.09 (d, *J* = 4.9 Hz, 1H), 7.25 – 7.22 (m, 2H), 7.20 – 7.16 (m, 3H), 4.98 – 4.87 (m, 1H), 3.42 (dd, *J* = 15.9, 7.4 Hz, 2H), 2.96 (dd, *J* = 15.9, 5.7 Hz, 2H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 162.9, 158.3, 157.7, 141.0, 126.7, 124.7, 122.4, 113.7, 109.1, 50.6, 40.1	ESI-MS m/z: 334 $(M+Na)^+$
4I		^{1}H NMR (500 MHz, d6-DMSO) δ 11.11 (s, 1H), 8.81 (s, 1H), 8.60 (s, 1H), 8.46 (s, 1H), 7.80 (s, 4H), 7.35 (s, 1H), 2.84 (s, 3H).	^{13}C NMR (125 MHz, d6-DMSO) δ 168.5, 161.9, 156.8, 153.0, 139.3, 138.4, 137.5, 135.0, 126.4, 120.4, 111.0, 109.5, 18.6	ESI-MS m/z: 375 $(M+Na)^+$
4J		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.84 (s, 1H), 9.02 (s, 1H), 7.46 (d, *J* = 0.7 Hz, 1H), 7.02 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.67 (s, 1H), 5.95 (s, 2H), 2.90 (s, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 161.7, 161.2, 157.6, 147.7, 144.0, 137.8, 132.6, 113.4, 110.0, 108.5, 108.0, 102.9, 101.1, 18.9	ESI-MS m/z: 352 $(M+Na)^+$

EXAMPLE 5 – PREPARATION OF 4-OXO-4*H*-PYRIDO[1,2-*a*]PYRIMIDINE-3-CARBOXAMIDE COMPOUNDS

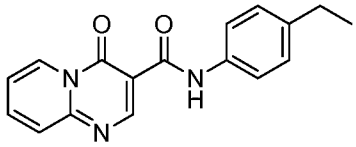
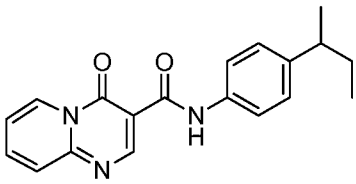
[00210] Compounds in Table 6 below were prepare based on the following general procedure.

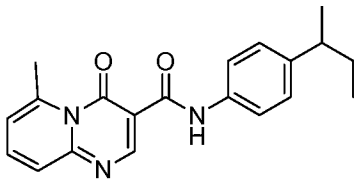
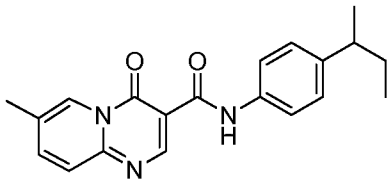
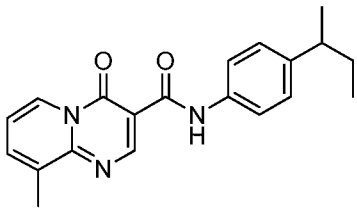
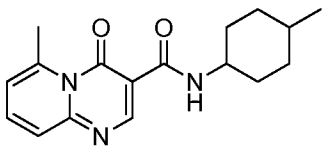


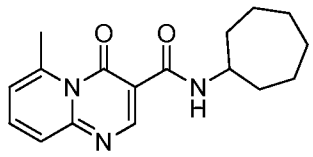
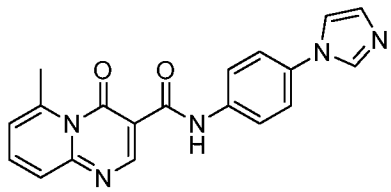
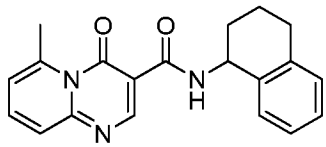
R is, for example, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl.

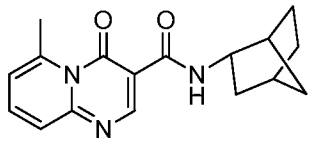
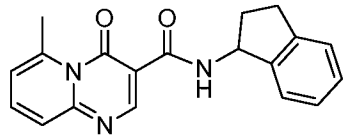
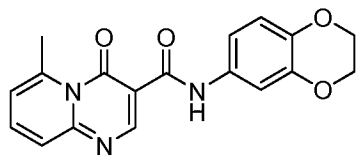
[00211] A mixture of carboxylic acid (1 equiv.), amine (1 equiv.), HATU (1 equiv.) and DIPEA (3 equiv.) in DMF are stirred at room temperature or 65℃ for 16 hr. Then, water is added to the reaction mixture, and the resulting mixture is filtered, and resulting solid is washed with water, and dried in vacuum to give the carboxamide product. If no solid forms when water is added to the reaction mixture, the reaction mixture may be extracted with EtOAc three times, and then the combined organic phase is washed with 10% Na_2CO_3 solution, brine, dried (Na_2SO_4), filtered, and evaporated to give the carboxamide product. Generally, the product is sufficiently pure (e.g., >95% purity). However, if the crude product is not sufficiently pure, then the crude product may be purified by flash chromatography.

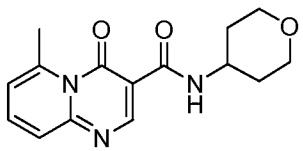
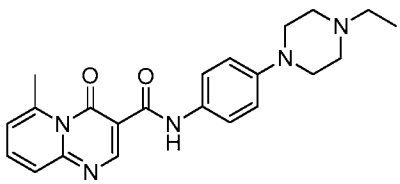
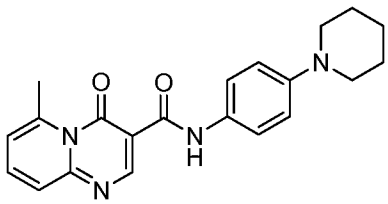
TABLE 6.

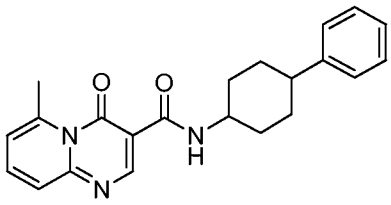
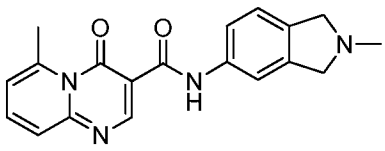
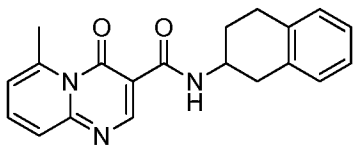
No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
5A		^{1}H NMR (500 MHz, $CDCl_3$) δ 11.01 (s, 1H), 9.42 (s, 1H), 9.26 (d, *J* = 6.8 Hz, 1H), 8.01 – 7.91 (m, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.44 – 7.33 (m, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 158.6, 157.8, 152.4, 140.2, 138.4, 135.9, 128.3, 128.0, 127.2, 120.4, 117.6, 107.5, 28.3, 15.7	ESI-MS m/z: 316 $(M+Na)^+$
5B		^{1}H NMR (500 MHz, $CDCl_3$) δ 11.00 (s, 1H), 9.42 (s, 1H), 9.26 (d, *J* = 6.5 Hz, 1H), 8.00 – 7.92 (m, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.39 (td, *J* = 7.0, 1.3 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 2.62-2.54 (m, 1H), 1.62 – 1.53 (m, 2H), 1.22 (d, *J* = 6.9 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 158.7, 157.8, 152.4, 143.7, 138.3, 136.0, 128.1, 127.5, 127.2, 120.4, 117.5, 107.5, 41.2, 31.2, 21.9, 12.2	ESI-MS m/z: 344 $(M+Na)^+$

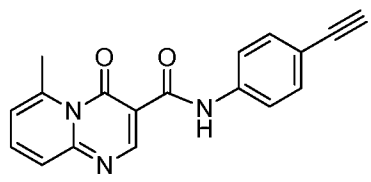
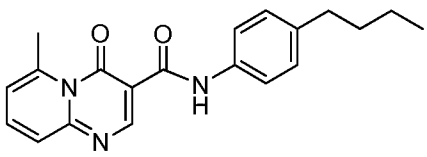
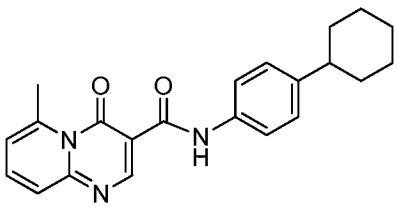
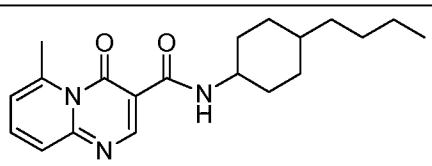
No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
5C		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.92 (s, 1H), 9.21 (d, *J* = 2.1 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 3H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 6.9 Hz, 1H), 3.13 (s, 3H), 2.62-2.53 (m, 1H), 1.62-1.54 (m, 2H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 161.7, 157.8, 155.1, 145.6, 143.5, 137.5, 136.1, 127.4, 125.9, 120.8, 120.4, 109.0, 41.2, 31.2, 25.3, 21.9, 12.2	ESI-MS m/z: 358 $(M+Na)^+$
5D		^{1}H NMR (500 MHz, $CDCl_3$) δ 11.06 (s, 1H), 9.38 (s, 1H), 9.06 (s, 1H), 7.85 – 7.73 (m, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 2.64 – 2.54 (m, 1H), 2.52 (s, 3H), 1.65 – 1.50 (m, 2H), 1.22 (d, *J* = 6.9 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 158.1, 157.7, 151.2, 143.6, 141.2, 136.1, 128.3, 127.5, 126.6, 125.7, 120.3, 107.2, 41.2, 31.2, 21.9, 18.6, 12.2	ESI-MS m/z: 358 $(M+Na)^+$
5E		^{1}H NMR (500 MHz, $CDCl_3$) δ 11.05 (s, 1H), 9.42 (s, 1H), 9.14 (d, *J* = 7.1 Hz, 1H), 7.79 (d, *J* = 6.9 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.27 (t, *J* = 7.0 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 2.68 (s, 3H), 3.60-2.52 m, 1H), 1.62-1.54 (m, 2H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 158.3, 157.7, 151.9, 143.7, 137.5, 136.2, 136.2, 127.6, 126.2, 120.5, 117.2, 107.3, 41.3, 31.3, 22.0, 18.3, 12.3	ESI-MS m/z: 358 $(M+Na)^+$
5F	 cis/trans mixture	N/A	N/A	ESI-MS m/z: 322 $(M+Na)^+$

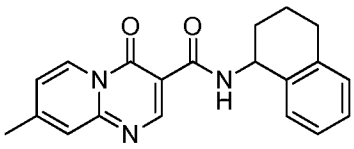
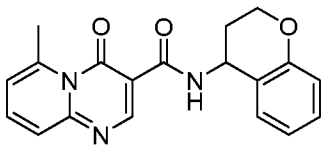
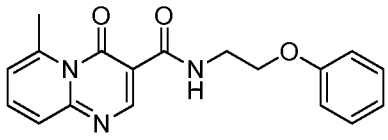
No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
5G		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.87 (d, *J* = 7.1 Hz, 1H), 7.60 (dd, *J* = 8.7, 7.0 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 6.5 Hz, 1H), 4.22-4.10 (m, 1H), 3.09 (s, 3H), 2.03 – 1.92 (m, 2H), 1.71 – 1.40 (m, 10H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 161.9, 157.3, 154.9, 145.3, 137.1, 125.8, 120.4, 109.1, 50.3, 35.0, 28.0, 25.2, 24.2	ESI-MS m/z: 322 $(M+Na)^+$
5H		^{1}H NMR (500 MHz, $CDCl_3$) δ 11.17 (s, 1H), 9.23 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.84 (s, 1H), 7.71 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.27 (s, 1H), 7.20 (s, 1H), 6.97 (d, *J* = 6.9 Hz, 1H), 3.18 (s, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 162.1, 158.0, 155.2, 145.7, 137.9, 135.6, 133.1, 130.2, 126.1, 122.1, 121.4, 121.1, 118.4, 108.5, 25.4	ESI-MS m/z: 346 $(M+H)^+$
5I		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (d, 2H), 7.65 – 7.60 (m, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.22 – 7.04 (m, 3H), 6.86 (d, *J* = 6.7 Hz, 1H), 5.53 – 5.35 (m, 1H), 3.05 (s, 3H), 2.94 – 2.73 (m, 2H), 2.28 – 2.06 (m, 1H), 2.02 – 1.78 (m, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 161.8, 157.6, 155.0, 145.5, 137.4, 137.3, 137.2, 129.0, 128.7, 126.9, 126.1, 125.8, 120.4, 108.8, 47.4, 30.4, 29.3, 25.2, 20.4	ESI-MS m/z: 356 $(M+Na)^+$

No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
5J		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.80 (d, *J* = 6.0 Hz, 1H), 7.60 (dd, *J* = 8.7, 7.0 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 6.85 (d, *J* = 6.8 Hz, 1H), 3.95 – 3.82 (m, 1H), 3.08 (s, 3H), 2.41 – 2.20 (m, 2H), 1.84 (ddd, *J* = 13.0, 8.0, 2.2 Hz, 1H), 1.61 – 1.39 (m, 3H), 1.39 – 1.26 (m, 2H), 1.22 (d, *J* = 10.0 Hz, 1H), 1.19 – 1.12 (m, 1H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 161.9, 157.3, 154.9, 145.3, 137.1, 125.8, 120.4, 109.0, 52.7, 42.5, 40.4, 35.8, 35.7, 28.3, 26.5, 25.2	ESI-MS m/z: 320 $(M+Na)^+$
5K		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (s, 1H), 9.17 (d, *J* = 7.6 Hz, 1H), 7.61 (dd, *J* = 8.8, 6.9 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 6.6 Hz, 1H), 7.28 – 7.13 (m, 3H), 6.85 (d, *J* = 6.8 Hz, 1H), 5.70 (q, *J* = 7.9 Hz, 1H), 3.11 – 2.95 (m, 4H), 2.95 – 2.84 (m, 1H), 2.76 – 2.62 (m, 1H), 2.03 – 1.83 (m, 1H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 161.9, 157.6, 155.1, 145.5, 143.8, 143.3, 137.3, 127.6, 126.7, 125.9, 124.7, 124.1, 120.5, 108.7, 54.6, 34.3, 30.4, 25.2	ESI-MS m/z: 342 $(M+Na)^+$
5L		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.82 (s, 1H), 9.20 (s, 1H), 7.65 (dd, *J* = 8.8, 7.0 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 2.5 Hz, 1H), 7.11 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.91 (d, *J* = 6.8 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 4.32 – 4.15 (m, 4H), 3.13 (s, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 161.5, 157.7, 155.0, 145.6, 143.4, 140.2, 137.5, 132.2, 125.9, 120.8, 117.0, 113.9, 109.9, 109.0, 64.4, 64.3, 25.3	ESI-MS m/z: 360 $(M+Na)^+$

No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
5M		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.90 (d, *J* = 7.1 Hz, 1H), 7.62 (dd, *J* = 8.7, 7.0 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 6.8 Hz, 1H), 4.26 – 4.12 (m, 1H), 3.96 (dt, *J* = 11.8, 3.6 Hz, 2H), 3.62 – 3.46 (m, 2H), 3.10 (s, 3H), 2.04 – 1.91 (m, 2H), 1.69 – 1.52 (m, 2H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 161.9, 157.5, 155.0, 145.4, 137.3, 125.9, 120.6, 108.7, 66.7, 45.4, 33.1, 25.2	ESI-MS m/z: 310 $(M+Na)^+$
5N		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.83 (s, 1H), 9.19 (s, 1H), 7.66 – 7.59 (m, 3H), 7.55 (d, *J* = 8.1 Hz, 1H), 6.97 – 6.77 (m, 3H), 3.25 – 3.15 (m, 4H), 3.12 (s, 3H), 2.67 – 2.54 (m, 4H), 2.46 (q, *J* = 7.2 Hz, 2H), 1.11 (t, *J* = 7.2 Hz, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 161.4, 157.6, 155.0, 148.0, 145.5, 137.4, 131.0, 125.9, 121.4, 120.7, 116.5, 109.1, 52.8, 52.3, 49.5, 25.3, 12.0	ESI-MS m/z: 392 $(M+H)^+$
5O		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.81 (s, 1H), 9.20 (s, 1H), 7.65 – 7.58 (m, 3H), 7.56 (d, *J* = 8.1 Hz, 1H), 6.93 – 6.87 (m, 3H), 3.12 (s, 3H), 3.11 – 3.08 (m, 4H), 1.73 – 1.66 (m, 4H), 1.58 – 1.51 (m, 2H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 161.4, 157.6, 155.0, 149.1, 145.5, 137.3, 130.6, 125.9, 121.3, 120.7, 117.0, 109.2, 51.1, 25.9, 25.3, 24.2	ESI-MS m/z: 363 $(M+H)^+$

No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
5P		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.82 (d, *J* = 7.5 Hz, 1H), 7.61 (dd, *J* = 8.7, 7.0 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.32 – 7.25 (m, 2H), 7.23 – 7.14 (m, 3H), 6.87 (d, *J* = 6.4 Hz, 1H), 4.11 – 3.98 (m, 1H), 3.11 (s, 3H), 2.58 – 2.46 (m, 1H), 2.21 (d, *J* = 12.0 Hz, 2H), 1.96 (d, *J* = 12.8 Hz, 2H), 1.70 – 1.59 (m, 2H), 1.51 – 1.40 (m, 2H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 161.9, 157.6, 155.0, 146.8, 145.3, 137.1, 128.3, 126.8, 126.0, 125.9, 120.4, 109.0, 48.2, 43.6, 33.5, 33.0, 25.2	ESI-MS m/z: 384 $(M+Na)^+$
5Q		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.97 (s, 1H), 9.19 (s, 1H), 7.72 (s, 1H), 7.64 (dd, *J* = 8.7, 7.0 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.42 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 6.90 (d, *J* = 6.7 Hz, 1H), 3.90 (s, 2H), 3.87 (s, 2H), 3.12 (s, 3H), 2.57 (s, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 161.8, 157.8, 155.1, 145.6, 141.5, 137.5, 137.2, 136.3, 126.0, 122.3, 120.8, 118.9, 114.5, 108.9, 61.0, 60.6, 42.4, 25.3	ESI-MS m/z: 335 $(M+H)^+$
5R		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (s, 1H), 9.12 (d, *J* = 7.1 Hz, 1H), 7.75 (dd, *J* = 8.7, 7.0 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.27 – 7.15 (m, 4H), 7.00 (d, *J* = 6.8 Hz, 1H), 4.63 – 4.51 (m, 1H), 3.36 (dd, *J* = 16.2, 5.1 Hz, 1H), 3.21 (s, 3H), 3.15 – 3.00 (m, 2H), 2.95 (dd, *J* = 16.2, 9.3 Hz, 1H), 2.39 – 2.30 (m, 1H), 2.04 – 1.89 (m, 1H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 161.9, 157.5, 155.0, 145.4, 137.2, 135.7, 134.7, 129.3, 128.7, 125.9, 125.8, 125.7, 120.5, 108.9, 45.5, 35.9, 29.2, 27.9, 25.2	ESI-MS m/z: 334 $(M+H)^+$

No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
5S		^{1}H NMR (500 MHz, $CDCl_3$) δ 11.10 (s, 1H), 9.19 (s, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.67 (dd, *J* = 8.7, 7.0 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 6.9 Hz, 1H), 3.14 (s, 3H), 3.03 (s, 1H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 162.0, 157.9, 155.2, 145.7, 138.9, 137.8, 132.9, 126.0, 121.0, 119.9, 117.2, 108.6, 83.6, 76.6, 25.3	ESI-MS m/z: 326 $(M+Na)^+$
5T		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.92 (s, 1H), 9.21 (d, *J* = 2.4 Hz, 1H), 7.68 – 7.51 (m, 4H), 7.14 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 6.9 Hz, 1H), 3.13 (s, 3H), 2.60 – 2.53 (m, 2H), 1.62 – 1.53 (m, 2H), 1.39 – 1.28 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 161.7, 157.8, 155.1, 145.6, 138.7, 137.5, 136.0, 128.8, 125.9, 120.8, 120.3, 109.0, 35.1, 33.7, 25.3, 22.3, 13.9	ESI-MS m/z: 358 $(M+Na)^+$
5U		^{1}H NMR (500 MHz, $CDCl_3$) δ 10.93 (s, 1H), 9.22 (s, 1H), 7.67-7.64 (m, 3H), 7.62 – 7.55 (m, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 6.9 Hz, 1H), 3.15 (s, 3H), 2.56 – 2.41 (m, 1H), 1.94 – 1.78 (m, 4H), 1.74 (d, *J* = 12.7 Hz, 1H), 1.48 – 1.30 (m, 4H), 1.30 – 1.16 (m, 1H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 161.7, 157.8, 155.1, 145.6, 144.0, 137.5, 136.1, 127.2, 125.9, 120.8, 120.3, 109.0, 44.0, 34.5, 26.9, 26.1, 25.3	ESI-MS m/z: 362 $(M+H)^+$
5V	 cis/trans mixture	N/A	N/A	ESI-MS m/z: 342 $(M+H)^+$

No.	Compound Structure	^{1}H NMR	^{13}C NMR	Mass Spec. Data
5W		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 9.26 (d, *J* = 7.3 Hz, 1H), 9.02 (d, *J* = 7.3 Hz, 1H), 7.59 (s, 1H), 7.38 – 7.34 (m, 1H), 7.17 – 7.07 (m, 4H), 5.47 – 5.40 (m, 1H), 2.91 – 2.74 (m, 2H), 2.55 (s, 3H), 2.19 – 2.11 (m, 1H), 1.97 – 1.85 (m, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 158.9, 157.7, 152.3, 151.1, 137.4, 137.3, 129.1, 128.8, 127.3, 127.1, 126.3, 125.4, 119.9, 106.5, 47.5, 30.4, 29.4, 21.7, 20.3	ESI-MS m/z: 356 $(M+Na)^+$
5X		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (d, *J* = 7.6 Hz, 1H), 9.18 (s, 1H), 7.63 (dd, *J* = 8.8, 7.0 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.21 – 7.12 (m, 1H), 6.93 – 6.79 (m, 3H), 5.44 – 5.34 (m, 1H), 4.33 – 4.27 (m, 1H), 4.26-4.22 (m, 1H), 3.04 (s, 3H), 2.35-2.28 (m, 1H), 2.18 – 2.11 (m, 1H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 161.9, 157.7, 155.1, 155.0, 145.6, 137.4, 129.4, 128.9, 125.9, 122.7, 120.7, 120.6, 116.9, 108.5, 63.6, 43.5, 29.3, 25.2	ESI-MS m/z: 358 $(M+Na)^+$
5Y		^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, 1H), 9.13 (s, 1H), 7.62 (dd, *J* = 8.7, 7.0 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.29 – 7.24 (m, 2H), 6.97 – 6.91 (m, 3H), 6.87 (d, *J* = 7.0 Hz, 1H), 4.15 (t, *J* = 5.4 Hz, 2H), 3.85 (q, *J* = 5.6 Hz, 2H), 3.09 (s, 3H).	^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 161.8, 158.7, 157.5, 155.1, 145.5, 137.4, 129.4, 125.8, 120.9, 120.5, 114.7, 108.6, 66.7, 38.9, 25.2	ESI-MS m/z: 346 $(M+Na)^+$

EXAMPLE 6 – BIOLOGICAL ACTIVITY EVALUATION

[00212] The ability of exemplary compounds to activate glucocerebrosidase (Gcase) was measured. Experimental procedures and results are provided below.

Part I: Assay Procedure

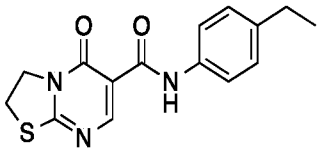
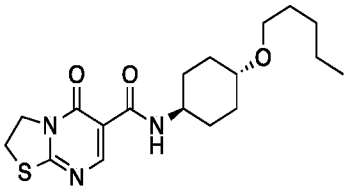
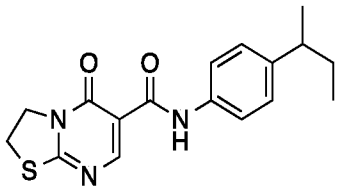
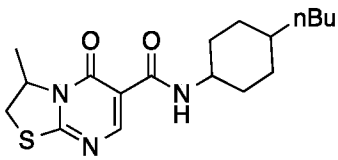
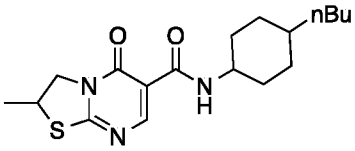
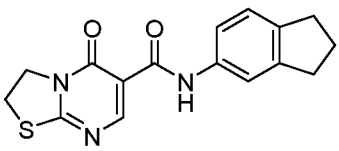
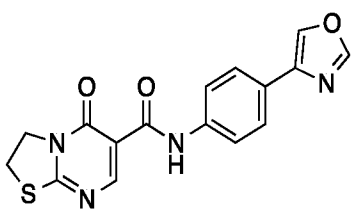
[00213] A 484 μL aliquot of a 1.0 mg/mL solution of phosphatidylserine (PS) (Sigma P7769) in chloroform was evaporated under a stream of nitrogen for 1 hour. The lipid film was dissolved over 4 minutes of vigorous vortexing in 40 mL of 176 mM K_2HPO_4/50 mM citric acid (pH 4.7) containing 7.5 μL of triton X-100, resulting in a mixed micellar preparation with a composition of 0.32 mM triton and 0.37 mol% PS. 4-Methylumbelliferyl-beta-D-glucopyranoside (ACROS-337025000) was dissolved in the micellar solution to a final concentration of 2 mM for use as the reaction substrate.

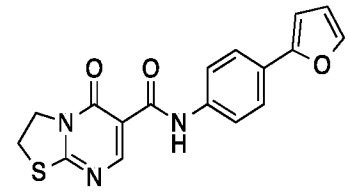
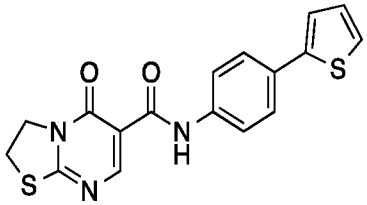
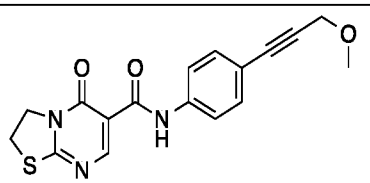
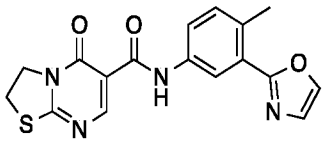
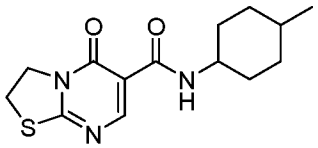
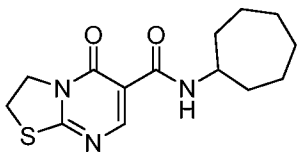
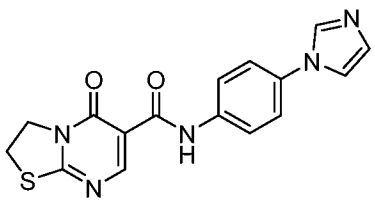
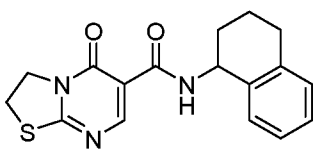
[00214] Test compounds were diluted to the desired concentrations with dimethylsulfoxide (DMSO) from 10 mM stocks, and 0.41 μL of the DMSO compound mixture was added to 100 μL of micellar solution containing 10 nM GCase and 100 nM saposin C (Enzo ALX-201-262-C050). Pre-incubation was allowed to occur for 30 minutes at room temperature, after which the reaction was initiated by combining 25 μL of substrate solution with 25 μL of compound/GCase/saposin mixture. The reaction proceeded for 15 minutes at room temperature and was stopped by adding 150 μL of 1M glycine, pH 12.5. The endpoint of the reaction was monitored by measuring fluorescence intensity (excitation: 365 nm; emission: 440 nm) on a SpectraMax i3 instrument (Molecular Devices). Test compounds were screened at 1.0 and 0.1 μM final concentration, and subsequent 8-point dose response curves were obtained using 3-fold dilutions from a maximum final concentration of 5 μM.

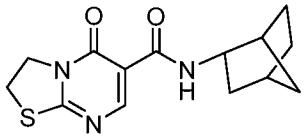
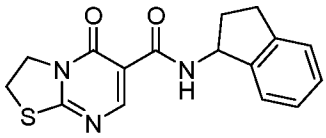
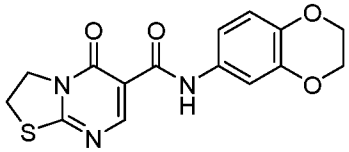
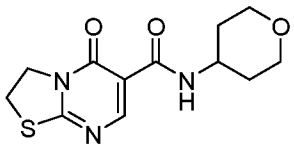
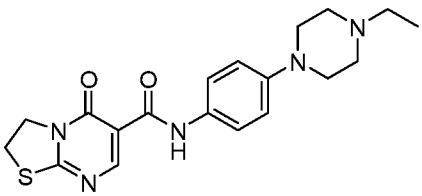
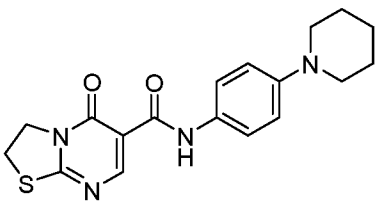
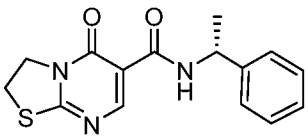
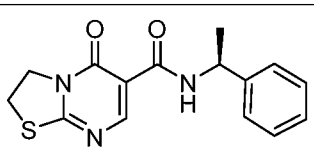
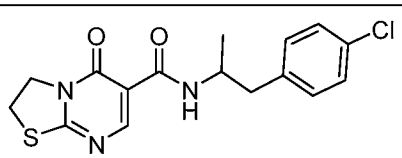
Part II: Results

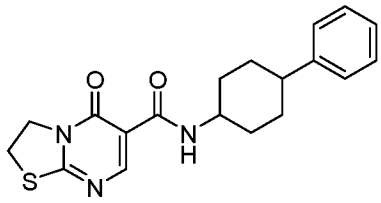
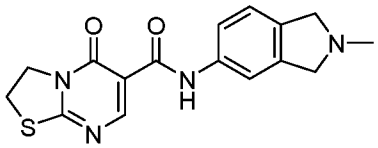
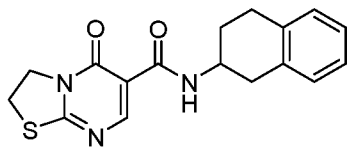
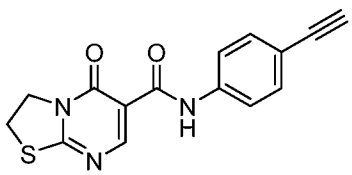
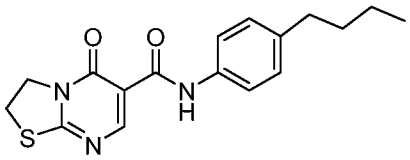
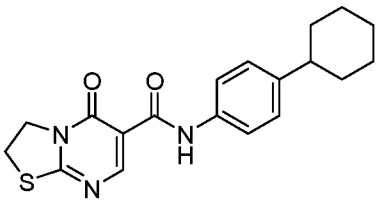
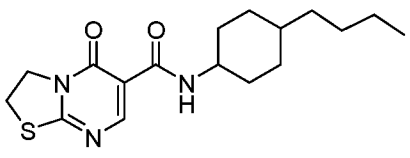
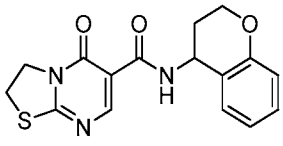
[00215] Gcase activation values for tested compounds are provided in Tables 7, 8, and 9 below, along with cLogP, PSA, and compound solubility in water. The symbol "+" indicates less than 5% Gcase activation; the symbol "++" indicates Gcase activation in the range of 5% up to 20%; and the symbol "+++"indicates Gcase activation greater than 20%. The symbol "N/A" indicates that no data available.

TABLE 7.

Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
				1 μM Test Compound	0.1 μM Test Compound
	1.9	61.8	5.1	+++	+
	1.7	71.0	8.4	++	+
	2.8	61.8	0.3	+++	++
	3.7	61.8	1.3	+++	++
	3.7	61.8	1.2	+++	+
	1.9	61.8	0.3	++	+
	0.8	83.4	N/A	+	+

Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
				1 μM Test Compound	0.1 μM Test Compound
	2.1	71.0	N/A	++	++
	2.6	61.8	N/A	++	++
	0.4	71.0	N/A	++	++
	0.9	83.4	N/A	++	+
	1.6	61.8	21.4	++	+
	1.7	61.8	20.8	++	+
	0.8	77.4	0.8	+	+
	2.0	61.8	7.1	+++	+

Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
				1 μM Test Compound	0.1 μM Test Compound
	2.0	61.8	N/A	+	+
	1.5	61.8	17.6	++	+
	0.7	80.2	9.5	+	+
	-1.3	71.0	26.3	++	+
	1.4	68.3	34.8	++	+
	1.7	65.0	4.0	+	+
	1.4	61.8	36.8	+	+
	1.4	61.8	37.2	++	++
	2.2	61.8	16.7	++	+

Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
				1 μM Test Compound	0.1 μM Test Compound
	2.5	61.8	10.6	+++	++
	0.2	65.0	32.4	++	+
	1.6	61.8	30.7	++	+
	1.2	61.8	1.5	++	+
	3.0	61.8	0.2	+++	++
	3.5	61.8	N/A	+++	++
	3.2	61.8	N/A	+++	++
	0.9	71.0	N/A	++	+

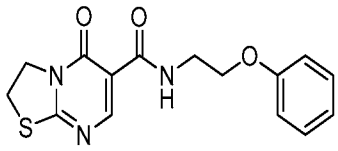
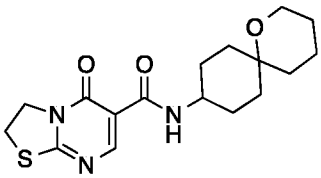
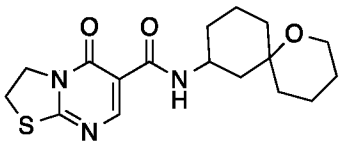
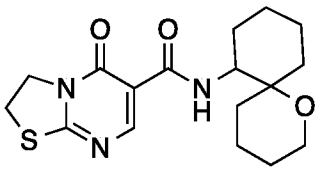
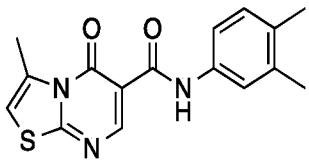
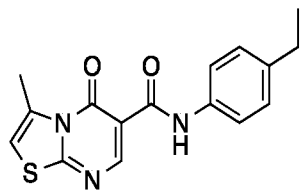
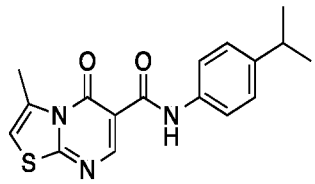
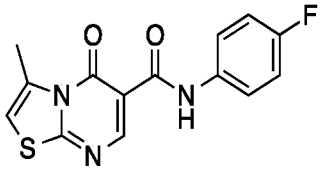
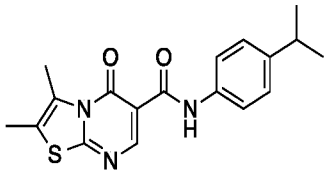
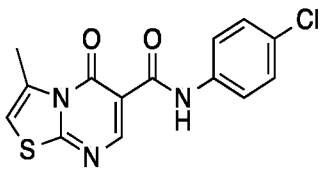
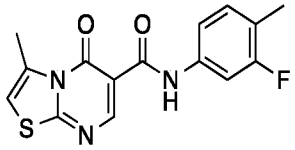
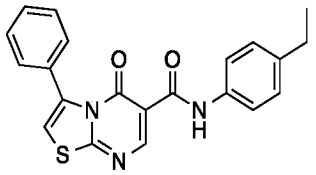
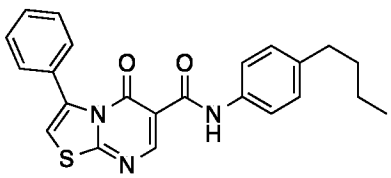
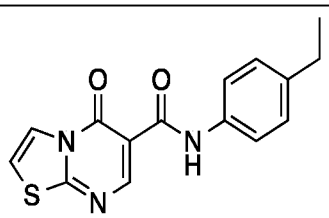
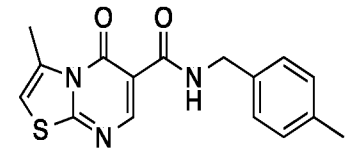
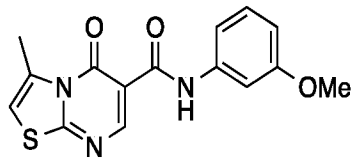
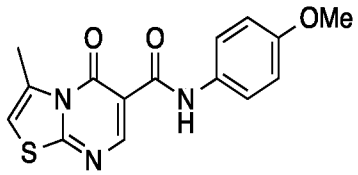
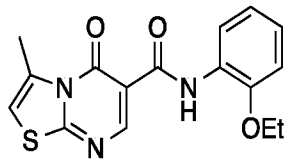
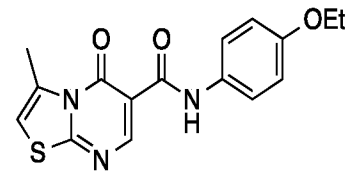
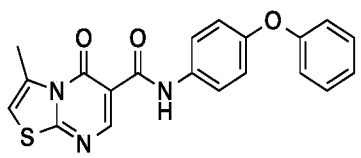
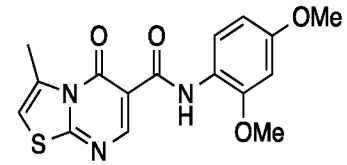
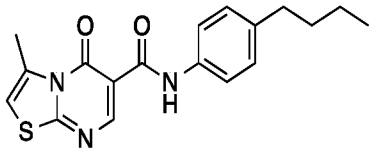
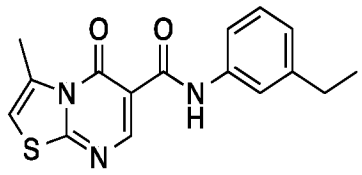
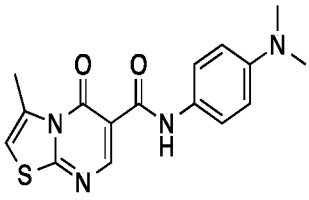
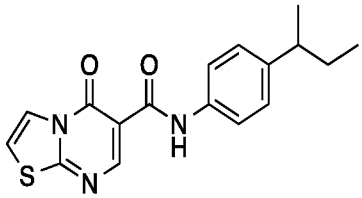
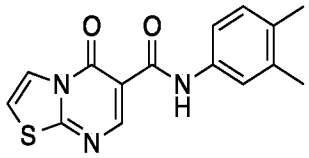
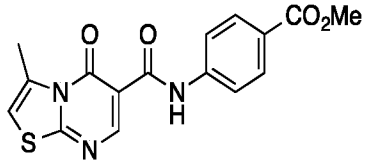
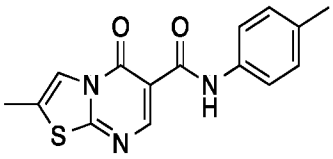
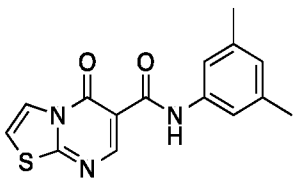
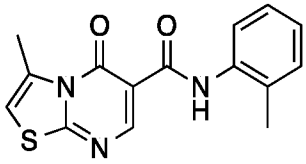
Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
				1 μM Test Compound	0.1 μM Test Compound
	1.1	71.0	N/A	++	+
	0.7	71.0	29.5	+	+
	0.7	71.0	36.0	+	+
	0.7	71.0	37.2	+	+

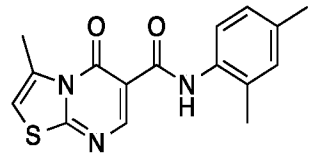
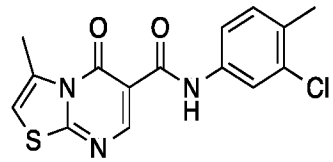
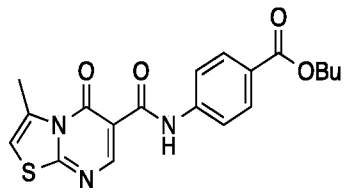
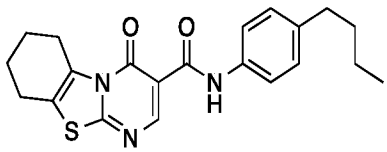
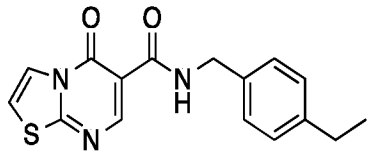
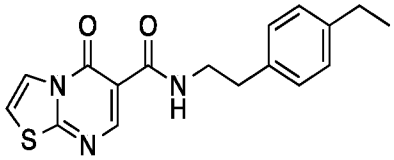
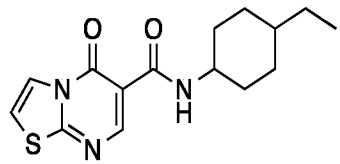
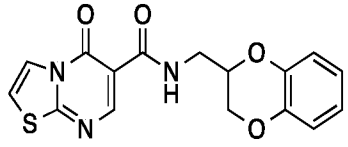
TABLE 8.

Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
				1 μM Test Compound	0.1 μM Test Compound
	3.1	61.8	N/A	++	N/A
	3.1	61.8	1.1	+++	+

Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
				1 μM Test Compound	0.1 μM Test Compound
	3.4	61.8	0.5	+++	++
	2.3	61.8	N/A	+	N/A
	3.6	61.8	N/A	+	N/A
	2.7	61.8	N/A	+++	N/A
	2.8	61.8	N/A	++	N/A
	4.2	61.8	N//A	+++	NA
	5.0	61.8	N/A	+++	NA
	2.9	61.8	N/A	+++	++

Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
				1 μM Test Compound	0.1 μM Test Compound
	2.3	61.8	N/A	++	NA
	2.0	71.0	N/A	++	NA
	2.0	71.0	N/A	+++	NA
	2.3	71.0	N/A	++	NA
	2.3	71.0	N/A	++	NA
	3.6	71.0	N/A	+++	++
	4.8	80.2	N/A	++	NA
	4.0	61.8	N/A	+++	++

Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
				1 μM Test Compound	0.1 μM Test Compound
	3.1	61.8	N/A	+++	NA
	2.2	65.0	N/A	++	NA
	3.6	61.8	N/A	+++	+
	2.9	61.8	N/A	++	NA
	2.1	88.1	N/A	++	NA
	2.7	61.8	N/A	++	NA
	2.9	61.8	N/A	++	NA
	2.6	61.8	N/A	++	NA

Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
				1 μM Test Compound	0.1 μM Test Compound
	3.1	61.8	N/A	+++	NA
	3.2	61.8	N/A	++	NA
	3.4	88.1	N/A	+++	NA
	4.8	61.8	N/A	++	NA
	2.5	61.8	17.0	++	+
	2.6	61.8	2.5	++	+
	2.6	61.8	4.9	+++	++
	1.4	80.2	22.6	+	+

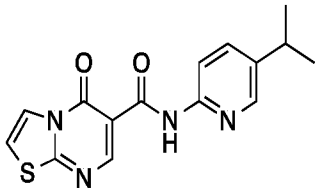
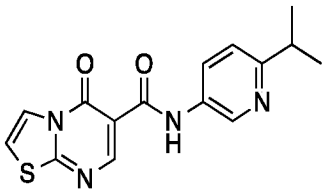
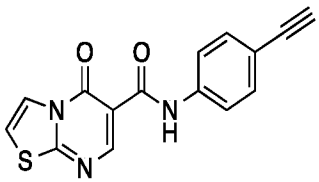
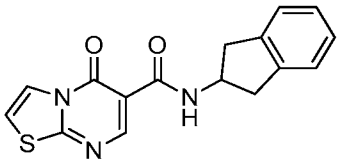
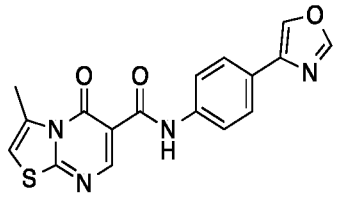
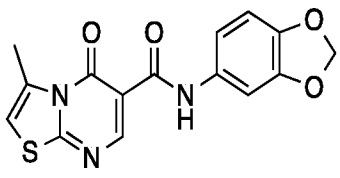
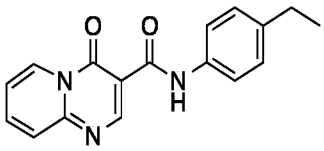
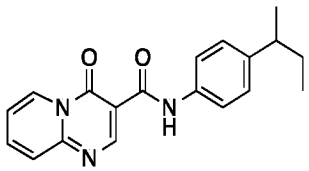
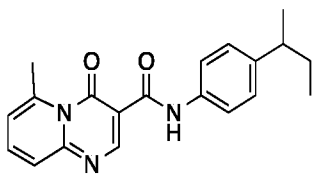
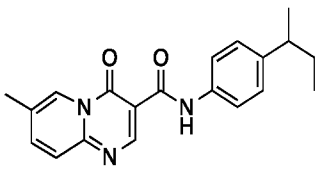
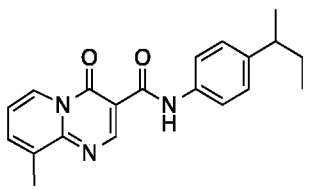
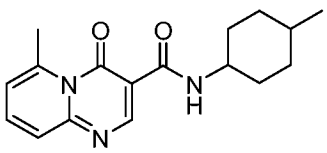
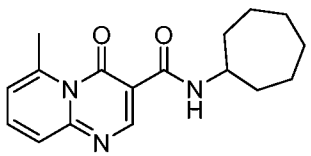
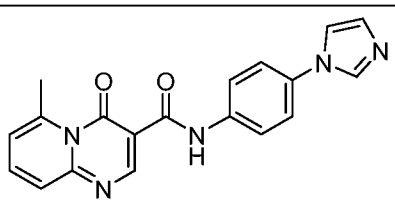
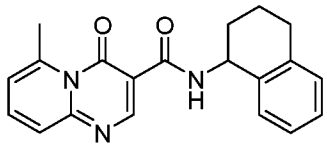
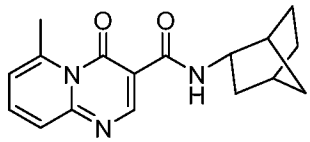
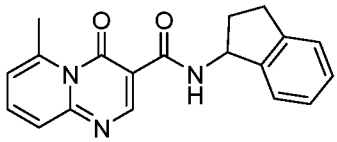
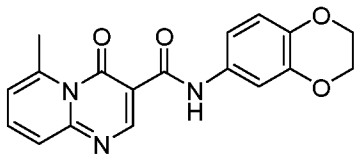
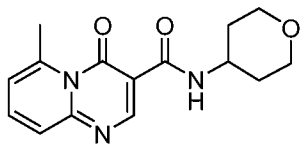
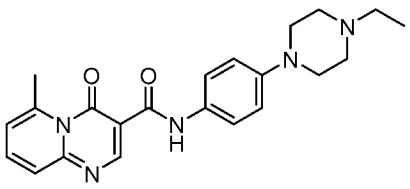
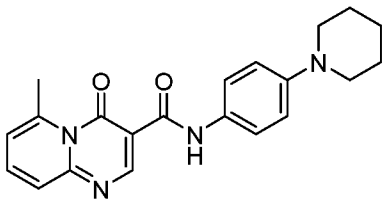
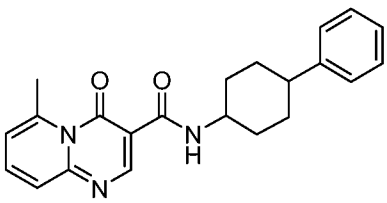
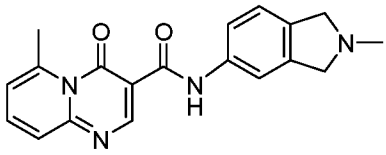
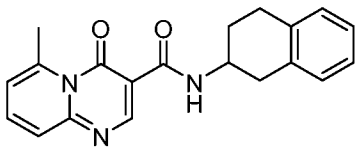
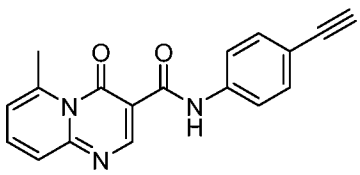
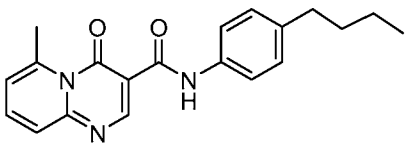
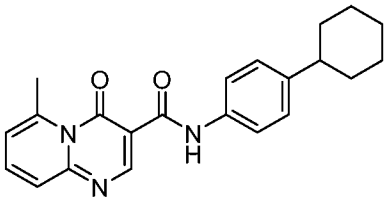
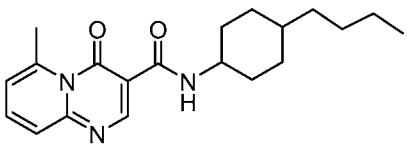
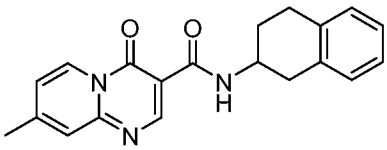
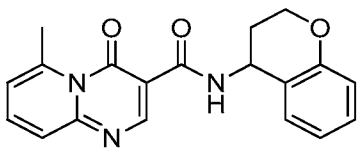
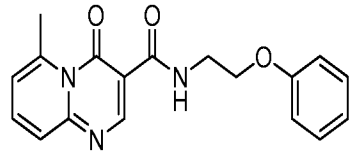
Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
				1 μM Test Compound	0.1 μM Test Compound
	1.5	74.1	2.7	++	+
	1.5	74.1	13.8	+	+
	1.5	61.8	3.4	+++	++
	1.5	61.8	1.2	+++	++
	1.6	83.4	N/A	++	+
	1.6	80.2	N/A	++	+

TABLE 9.

Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
				1 μM Test Compound	0.1 μM Test Compound
	2.6	61.8	1.0	++	+
	3.5	61.8	0.3	++	+
	4.0	61.8	1.0	+++	++
	4.0	61.8	0.05	++	+
	4.0	61.8	0.5	++	+
	2.8	61.8	18.7	+++	+
	2.8	61.8	9.3	+++	+
	1.9	77.4	1.2	++	+

Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
				1 μM Test Compound	0.1 μM Test Compound
	3.2	61.8	13.9	+++	++
	3.1	61.8	N/A	++	+
	2.6	61.8	6.8	+++	+
	1.8	80.2	0.7	++	+
	-0.1	71.0	31.0	++	+
	2.6	68.3	33.3	++	+
	2.9	65.0	1.4	+	+
	3.7	61.8	3.5	+++	++

Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
				1 μM Test Compound	0.1 μM Test Compound
	1.4	65.0	35.4	+	+
	2.8	61.8	4.3	++	+
	2.3	61.8	1.5	++	+
	4.1	61.8	0.05	+++	++
	4.6	61.8	0.2	+++	+
	4.4	61.8	0.4	+++	++
	2.8	61.8	N/A	++	+
	2.1	71.0	NA	++	+

Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
				1 μM Test Compound	0.1 μM Test Compound
	2.2	71.0	NA	++	+

INCORPORATION BY REFERENCE

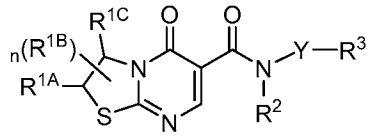
[00216] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[00217] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

What is claimed is:

1. A compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1A}, R^{1B}, and R^{1C} each represent independently for each occurrence hydrogen, C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 3-6 membered heterocyclyl, or 6-membered aryl; or R^{1A} and R^{1C} are taken together with intervening atoms to form a 5-7 membered carbocyclic ring;

R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

R^3 is -(C_3-C_8 cycloalkylene)-(C_4-C_8 alkyl), -(C_3-C_8 cycloalkylene)-(C_3-C_8 cycloalkyl), 9-13 membered spiroheterocycloalkyl, or a partially unsaturated 9-10 membered bicyclic carbocyclyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, aryl, heteroaryl, and saturated 3-8 membered heterocyclyl;

Y is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or -C(O)-; and

n is 1 or 2.

2. The compound of claim 1, wherein R^{1A}, R^{1B}, and R^{1C} are independently hydrogen or C_1-C_3 alkyl.

3. The compound of claim 1, wherein R^{1A}, R^{1B}, and R^{1C} are hydrogen.

4. The compound of any one of claims 1-3, wherein R^2 is hydrogen.

5. The compound of any one of claims 1-4, wherein Y is a bond.

6. The compound of any one of claims 1-4, wherein Y is C_1-C_6 alkylene.

7. The compound of any one of claims 1-6, wherein R^3 is -(C_3-C_8 cycloalkylene)-(C_4-C_8 alkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group

consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, and -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy.

8. The compound of any one of claims 1-6, wherein R^3 is -(C_5-C_7 cycloalkylene)-(C_4-C_8 alkyl) optionally substituted by C_1-C_6 alkyl.

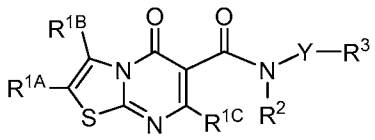
9. The compound of any one of claims 1-6, wherein R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, aryl, heteroaryl, and saturated 3-8 membered heterocyclyl.

10. The compound of any one of claims 1-6, wherein R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by C_1-C_6 alkyl.

11. A compound in Table 1, 4, or 7, or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition, comprising a compound of any one of claims 1-11 and a pharmaceutically acceptable carrier.

13. A compound of Formula III:



(III)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1A}, R^{1B}, and R^{1C} are independently hydrogen, C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, or 3-6 membered heterocyclyl; or R^{1A} and R^{1B} are taken together with intervening atoms to form a 5-7 membered carbocyclic ring;

R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

R^3 is -(C_3-C_8 cycloalkylene)-(C_6-C_8 alkyl), -(C_3-C_8 cycloalkylene)-(C_3-C_8 cycloalkyl), 9-13 membered spiroheterocycloalkyl, or a partially unsaturated 9-10 membered bicyclic carbocyclyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl,

hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, aryl, heteroaryl, and saturated 3-8 membered heterocyclyl; and

Y is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or -C(O)-.

14. The compound of claim 13, wherein R^{1A}, R^{1B}, and R^{1C} are independently hydrogen or C_1-C_3 alkyl.

15. The compound of claim 13, wherein R^{1A}, R^{1B}, and R^{1C} are hydrogen.

16. The compound of any one of claims 13-15, wherein R^2 is hydrogen.

17. The compound of any one of claims 13-16, wherein Y is a bond.

18. The compound of any one of claims 13-16, wherein Y is C_1-C_6 alkylene.

19. The compound of any one of claims 13-18, wherein R^3 is -(C_3-C_8 cycloalkylene)-(C_6-C_8 alkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, and -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy.

20. The compound of any one of claims 13-18, wherein R^3 is -(C_5-C_7 cycloalkylene)-(C_6-C_8 alkyl) optionally substituted by C_1-C_6 alkyl.

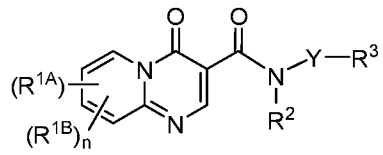
21. The compound of any one of claims 13-18, wherein R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, aryl, heteroaryl, and saturated 3-8 membered heterocyclyl.

22. The compound of any one of claims 13-18, wherein R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by C_1-C_6 alkyl.

23. A compound in Table 2 or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition, comprising a compound of any one of claims 13-23 and a pharmaceutically acceptable carrier.

25. A compound of Formula V:



(V)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1A} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 3-6 membered heterocyclyl, or 6-membered aryl;

R^{1B} represents independently for each occurrence C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 3-6 membered heterocyclyl, or 6-membered aryl;

R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

R^3 is -(C_3-C_8 cycloalkylene)-(C_2-C_8 alkyl), -(C_3-C_8 cycloalkylene)-(C_3-C_8 cycloalkyl), 9-13 membered spiroheterocycloalkyl, or a partially unsaturated 9-10 membered bicyclic carbocyclyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_2-C_4 alkynyl, and -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy;

n is 0, 1, or 2; and

Y is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or -C(O)-;

provided that when both n is 0 and Y is C_1-C_6 alkylene, then R^{1A} is other than methoxy-phenyl.

26. The compound of claim 25, wherein R^{1A} is C_1-C_3 alkyl.

27. The compound of claim 25, wherein R^{1B} represents independently for each occurrence C_1-C_3 alkyl or halogen.

28. The compound of any one of claims 25-27, wherein R^2 is hydrogen.

29. The compound of any one of claims 25-28, wherein Y is a bond.

30. The compound of any one of claims 25-28, wherein Y is C_1-C_6 alkylene.

31. The compound of any one of claims 25-30, wherein R^3 is -(C_3-C_8 cycloalkylene)-(C_2-C_8 alkyl) optionally substituted by 1, 2, or 3 substituents independently selected from the

group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, and -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy.

32. The compound of any one of claims 25-30, wherein R^3 is -(C_5-C_7 cycloalkylene)-(C_2-C_8 alkyl) optionally substituted by C_1-C_6 alkyl.

33. The compound of any one of claims 25-30, wherein R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, aryl, heteroaryl, and saturated 3-8 membered heterocyclyl.

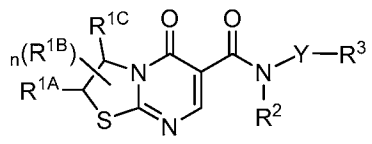
34. The compound of any one of claims 25-30, wherein R^3 is a partially unsaturated 9-10 membered bicyclic carbocyclyl optionally substituted by C_1-C_6 alkyl.

35. The compound of any one of claims 25-34, wherein n is 0.

36. A compound in Table 3, 6, or 9, or a pharmaceutically acceptable salt thereof.

37. A pharmaceutical composition, comprising a compound of any one of claims 25-36 and a pharmaceutically acceptable carrier.

38. A method of treating a disorder selected from the group consisting of Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, and multiple myeloma, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula II, IV, or VI to treat the disorder; wherein Formula II is represented by:



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1A}, R^{1B}, and R^{1C} each represent independently for each occurrence hydrogen, C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 3-8 membered heterocyclyl, or 6-membered

aryl; or R^{1A} and R^{1C} are taken together with intervening atoms to form a 5-7 membered carbocyclic ring;

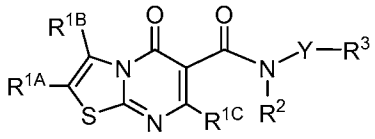
R^2 and R^4 are independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

R^3 is C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 9-13 membered spiroheterocycloalkyl, -(C_2-C_6 alkylene)-O-phenyl, phenyl, heteroaryl, a partially unsaturated 9-10 membered bicyclic carbocyclyl, or a partially unsaturated 8-10 membered bicyclic heterocyclyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, -(C_1-C_6 alkylene,)-(C_3-C_6 cycloalkyl), hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, aryl, -O-aryl, heteroaryl, saturated 3-8 membered heterocyclyl, amino, and -CO_2R^4;

Y is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or -C(O)-; and

n is 1 or 2;

Formula IV is represented by:



(IV)

or a pharmaceutically acceptable salt thereof, wherein:

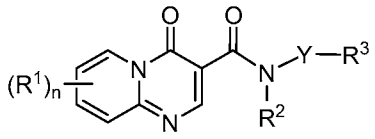
R^{1A}, R^{1B}, and R^{1C} are independently hydrogen, C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 3-6 membered heterocyclyl, or 6-membered aryl; or R^{1A} and R^{1B} are taken together with intervening atoms to form a 5-7 membered carbocyclic ring;

R^2 and R^4 are independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

R^3 is C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 9-13 membered spiroheterocycloalkyl, -(C_2-C_6 alkylene)-O-phenyl, phenyl, heteroaryl, a partially unsaturated 9-10 membered bicyclic carbocyclyl, or a partially unsaturated 8-10 membered bicyclic heterocyclyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, -(C_1-C_6 alkylene,)-(C_3-C_6 cycloalkyl), hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, aryl, -O-aryl, heteroaryl, saturated 3-8 membered heterocyclyl, amino, and -CO_2R^4; and

Y is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or -C(O)-; and

Formula VI is represented by:



(VI)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 represents independently for each occurrence C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 3-6 membered heterocyclyl, or 6-membered aryl;

R^2 and R^4 are independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

R^3 is C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 9-13 membered spiroheterocycloalkyl, -(C_2-C_6 alkylene)-O-phenyl, phenyl, heteroaryl, a partially unsaturated 9-10 membered bicyclic carbocyclyl, or a partially unsaturated 8-10 membered bicyclic heterocyclyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_8 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, -(C_1-C_6 alkylene,)-(C_3-C_6 cycloalkyl), hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, aryl, -O-aryl, heteroaryl, saturated 3-8 membered heterocyclyl, amino, and $-CO_2R^4$;

n is 0, 1, or 2; and

Y is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or -C(O)-.

39. The method of claim 38, wherein the compound is a compound of Formula II.

40. The method of claim 39, wherein R^{1A}, R^{1B}, and R^{1C} are independently hydrogen or C_1-C_3 alkyl.

41. The method of claim 39, wherein R^{1A}, R^{1B}, and R^{1C} are hydrogen.

42. The method of any one of claims 39-41, wherein R^2 is hydrogen.

43. The method of any one of claims 39-42, wherein Y is a bond.

44. The method of any one of claims 39-42, wherein Y is C_1-C_6 alkylene.

45. The method of any one of claims 39-44, wherein R^3 is C_3-C_8 cycloalkyl or a partially unsaturated 9-10 membered bicyclic carbocyclyl; each of which is optionally substituted by

1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, and C_2-C_4 alkynyl.

46. The method of any one of claims 39-44, wherein R^3 is phenyl substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, 5-membered heteroaryl, and saturated 3-8 membered heterocyclyl.

47. The method of claim 38, wherein the compound is a compound of Formula IV.

48. The method of claim 47, wherein R^{1A}, R^{1B}, and R^{1C} are independently hydrogen or C_1-C_3 alkyl.

49. The method of claim 47, wherein R^{1A}, R^{1B}, and R^{1C} are hydrogen.

50. The method of any one of claims 47-49, wherein R^2 is hydrogen.

51. The method of any one of claims 47-50, wherein Y is a bond.

52. The method of any one of claims 47-50, wherein Y is C_1-C_6 alkylene.

53. The method of any one of claims 47-52, wherein R^3 is C_3-C_8 cycloalkyl or a partially unsaturated 9-10 membered bicyclic carbocyclyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, and C_2-C_4 alkynyl.

54. The method of any one of claims 47-52, wherein R^3 is phenyl substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, 5-membered heteroaryl, and saturated 3-8 membered heterocyclyl.

55. The method of claim 38, wherein the compound is a compound of Formula VI.

56. The method of claim 55, wherein R^1 is C_1-C_3 alkyl.

57. The method of claim 55 or 56, wherein n is 1.

58. The method of any one of claims 55-57, wherein R^2 is hydrogen.

59. The method of any one of claims 55-58, wherein Y is a bond.

60. The method of any one of claims 55-58, wherein Y is C_1-C_6 alkylene.

61. The method of any one of claims 55-60, wherein R^3 is C_3-C_8 cycloalkyl or a partially unsaturated 9-10 membered bicyclic carbocyclyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, and C_2-C_4 alkynyl.

62. The method of any one of claims 55-60, wherein R^3 is phenyl substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_4 alkynyl, -(C_2-C_4 alkynyl)-C_1-C_6 alkoxy, 5-membered heteroaryl, and saturated 3-8 membered heterocyclyl.

63. The method of claim 38, wherein the compound is a compound in any one of Tables 1-9 or a pharmaceutically acceptable salt thereof.

64. The method of any one of claims 38-63, wherein the disorder is Gaucher disease.

65. The method of any one of claims 38-63, wherein the disorder is Parkinson's disease.

66. The method of any one of claims 38-63, wherein the disorder is Lewy body disease.

67. The method of any one of claims 38-63, wherein the disorder is dementia.

68. The method of any one of claims 38-63, wherein the disorder is multiple system atrophy.

69. The method of any one of claims 38-68, wherein the patient is a human.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/050029

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

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

1. ☐ Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including

2. ☒ Claims Nos.: **11, 23, 36, 63**

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

See Supplemental Box

3. ☐ Claims Nos:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/050029

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/04 (2006.01) C07D 513/04 (2006.01) A61K 31/519 (2006.01) A61P 25/16 (2006.01) A61P 25/24 (2006.01) A61P 25/28 (2006.01) A61P 27/06 (2006.01) A61P 35/02 (2006.01) A61P 3/10 (2006.01) A61P 13/12 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: Caplus, Registry: Substructure search of Formulae I, II, III, IV, V and VI; and Keywords: cyclo, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, hydro, indene or inden, spiro, naphth,

Esp@cenet: Applicant/Inventor search

Google: Applicant/Inventor search and/or Keywords: depression, Parkinson's disease, dementia, Gaucher disease, Lewy Body disease, multiple system atrophy, neurodegenerative (or neurodegeneration and the like), psychiatric (and the like).

Applicant(s)/Inventor(s) name searched in internal databases provided by IP Australia

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 November 2016	18 November 2016
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Marica Nikac AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61 2 62832087

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/US2016/050029**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CAS registry Number 1197899-54-9; STN Entry Date 16 December 2009 Whole Document	1-4, 6, 9-10
X	CAS registry Number 1240937-65-8; STN Entry Date 14 September 2010 Whole Document	1-3, 5, 9-10
X	CAS registry Number 1331007-59-0; STN Entry Date 11 September 2011 Whole Document	1-3, 5, 9-10
X	CAS registry Number 1626293-14-8; STN Entry Date 25 September 2014 Whole Document	1-5, 9
X	CAS registry Number 1324567-70-5; STN Entry Date 28 August 2011 Whole Document	1-5, 9-10
X	CAS registry Number 1092323-71-1; STN Entry Date 31 December 2008 Whole Document	13-17, 21-22
X	CAS registry Number 1189476-26-3; STN Entry Date 22 October 2009 Whole Document	13, 16-17, 21-22
X	CAS registry Number 1324517-94-3; STN Entry Date 28 August 2011 Whole Document	13-15, 17, 21-22
X	CAS registry Number 1376321-72-0; STN Entry Date 7 June 2012 Whole Document	13-17, 21
X	CAS registry Number 1795480-99-7; STN Entry Date 6 July 2015 Whole Document	13-17, 21
X	CAS registry Number 1029724-27-3; STN Entry Date 22 June 2008 Whole Document	25-26, 28-29, 33-35
X	CAS registry Number 906164-79-2; STN Entry Date 10 September 2006 Whole Document	25-26, 28-29, 33-35
X	CAS registry Number 1388542-77-5; STN Entry Date 9 August 2012 Whole Document	25-26, 28-29, 31-32, 35
X	CAS registry Number 1609765-47-0; STN Entry Date 6 June 2014 Whole Document	25-26, 28, 30, 33, 35
X	WO 2003/070244 A1 (ABBOTT LABORATORIES) 28 August 2003 Abstract; second last compound on page 22; pages 3-5, 15-19; claims 37, 39-40, pages 200-201; also see "Determination of Biological Activity", pages 36-39	38, 55-59, 61, 64-69
P,A	WO 2016/086261 A1 (PRANA BIOTECHNOLOGY LIMITED) 09 June 2016 Abstract; For example see compounds on pages 39-42	25-35, 37-62, 64-69

Supplemental Box

Continuation of **Box II**

The claims do not comply with Rule 6.2(a) because it/they rely on references to the description and/or drawings.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2016/050029**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2003/070244 A1	28 August 2003	WO 03070244 A1	28 Aug 2003
WO 2016/086261 A1	09 June 2016	WO 2016086261 A1	09 Jun 2016

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.