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(54) Title: SUBSTITUTED FUSED IMIDAZOLE DERIVATIVES AND METHODS OF TREATING SICKLE CELL DISEASE AND RELATED COMPLICATIONS

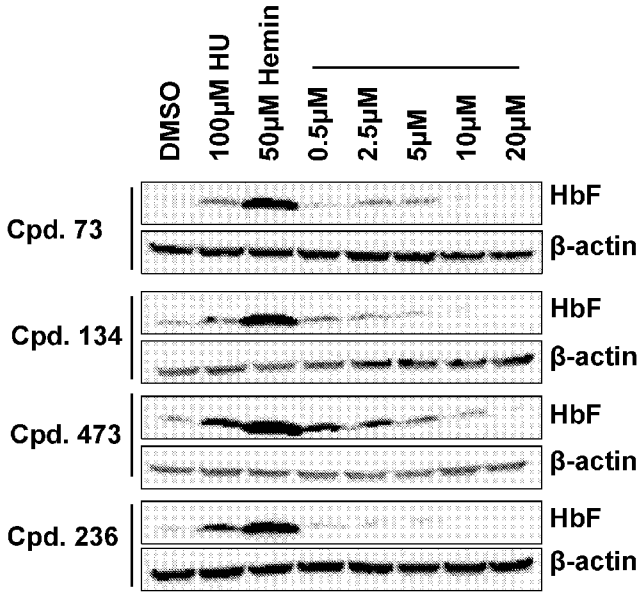

Fig. 1E

(57) Abstract: The present invention provides methods of treating sickle cell disease and related complications using compounds of Formula (I) and pharmaceutical compositions thereof either alone or in combination other active agents.

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TITLE

Substituted Fused Imidazole Derivatives and Methods of Treating Sickle Cell Disease and Related Complications

FIELD OF THE INVENTION

The present invention provides methods of treating sickle cell disease and related complications using compounds of Formula (I) and pharmaceutical compositions thereof either alone or in combination with other active agents. The present invention also provides compounds and pharmaceutical compositions.

BACKGROUND OF THE INVENTION

Sickle cell disease (SCD) is a life-threatening monogenic disorder. SCD is a severe hemoglobinopathy that produces multisystem complications due to the expression of abnormal sickle hemoglobin (HbS). The most common type of SCD is sickle cell anemia (SCA) (also referred to as HbSS or SS disease or hemoglobin S) in which there is homozygosity for the mutation that causes HbS. The more rare types of SCD in which there is heterozygosity (one copy of the mutation that causes HbS and one copy for another abnormal hemoglobin allele) for the mutation include sickle-hemoglobin C (HbSC), sickle β^+ thalassemia (HbS/β^+) and sickle $\beta 0$ thalassemia (HbS/β^0).

Sickle cell disease (SCD) arise from a point mutation that causes erythrocyte deformation or sickle-shaped erythrocytes. Sickled-shaped erythrocytes are associated with clinical manifestations of SCD, such as anemia, recurrent painful vaso-occlusive episodes, infections, acute chest syndrome, pulmonary hypertension, stroke, priapism, osteonecrosis, renal insufficiency, leg ulcers, retinopathies, and cardiac disease.

SCD arises from a single point mutation (GAG>GTG) in codon 6 of the HBB globin gene. The deoxygenated venous circulation causes a process of self-assembly (polymerization) that generates the sickled hemoglobin molecule (HbS) and

damages the membrane and cytoskeleton of the erythrocyte. The HbS repetitively enter into sickling and unsickling cycles incrementally increasing the damage to the erythrocyte membrane (Ischemia-reperfusion (IR) injury) resulting in irreversibly sickle-shaped erythrocytes. As a consequence, these rigid blood cells are unable to deform as they pass through narrow capillaries, leading to vessel occlusion and ischemia. The actual anemia of the illness is caused by hemolysis, the destruction of the red cells, caused by their misshapes.

C-reactive protein (CRP) and the markers of oxidative stress are significantly increased following IR injury. The ensuing oxidative stress contributes to hemolysis, inactivation of nitric oxide (NO), and erythrocyte, leukocyte and platelet adhesive properties.

The sickled-shaped erythrocytes together with endothelial cells, activated leukocytes, platelets and plasma proteins participate in the multistep vaso-occlusion process.

Heme oxygenase-1 (HO-1) and interleukin 10 (IL-10) are characteristically found to be increased in SCD patients in an attempt to counteract the induced inflammation. HO-1 breaks down heme released during hemolysis thereby limiting oxidative stress and inflammation, while IL-10 limits the production of the pro-inflammatory cytokines.

Sickled erythrocytes stimulates leukocyte recruitment: ensuing the inflammatory stimulus, leukocytes are recruited to the activated endothelium of the venous circulation where it forms adhesive interactions with the activated endothelium and sickled erythrocytes, leading to a reduced blood flow and eventually vaso-occlusion.

SCD platelets show increased surface expressions of selectin P (SELP), activated $\alpha_{IIb}\beta_3$ (GPIIbIIIa) and higher concentrations of the platelet activation markers. In healthy individuals, platelet adhesion is inhibited by the antithrombotic factor NO, while SCD platelet adhesion is stimulated by the activated endothelium. Platelets and sickled erythrocytes have been demonstrated

to aggregate via the formation of thrombospondin bridges thereby contributing to vaso-occlusion.

Hydroxyurea (HU) is an approved treatment to modify the disease process of SCD. HU counteracts the pathophysiology of SCD by increasing the production of fetal hemoglobin (HbF)-containing erythrocytes and indirectly altering gene expression and proteins associated with the pathophysiology of SCD. The increased concentration of HbF-containing erythrocytes dilutes the concentration of sickled erythrocytes, may thereby sequentially trigger decreased hemolysis, increased NO bioavailability and decreased endothelium activation. However, HU has been demonstrated to reduce leukocyte counts in patients on therapy. Although HU improved clinical symptoms by reducing pain and vaso-occlusive crises, acute chest syndrome, transfusion requirements, and hospitalization, SCD patients treated with HU have demonstrated side effects such as inducing DNA damage, reducing sperm counts and producing iron nitrosyl Hb.

Thus, there is a need in the art for new, improved, and/or complimentary SCD therapies.

SUMMARY OF THE INVENTION

PCT Publication No. WO 2011/103018 ("WO '018") describes substituted fused imidazole derivatives that upregulate expression of HMOX1 *in vitro*. PCT Publication No. WO 2012/094580 ("WO '580") describes various compounds that modulate cellular oxidative stress including fused imidazole derivatives having a structure similar to or the same as compounds disclosed in WO '018.

The present invention is directed to methods and compositions associated with treatment of one or more blood disorders. Although in particular embodiments the blood disorder is SCD, in specific embodiments, one or more other blood disorders may be treated with the present invention: a bleeding disorder (including clotting disorders, hypercoagulability, hemophilia, or von Willebrand disease, for example), platelet disorder (essential or primary thrombocythemia or

thrombocytopenia, for example), and/or hemophilia or anemia may be treated, for example. In particular embodiments of the invention, there are methods and compositions for treatment and/or prevention of sickle cell disease (which may be referred to as sickle-cell anaemia (or anemia; SCA) or drepanocytosis).

Mammalian and/or non-human mammals or cell lines may be used as sickle cell models. The individual treated with methods and/or compositions of the invention may be experiencing vaso-occlusive crisis, acute chest crisis, painful chest syndrome that may or may not require hospitalization, in specific cases. In specific embodiments, the individual may be experiencing or may experience negative side effects of a drug, such as a drug that directly or indirectly results in increased coagulation and/or increased inflammation; in specific embodiments, the drug is HU.

In certain embodiments of the invention, a compound of the invention is administered alone. In other embodiment, a compound of the invention is administered with one or more other drugs (some of which may or may not induce HbF production) for the treatment of SCD. For example, a compound of the invention may be administered in combination with HU for the treatment of SCD. In another example, a compound of the invention may be administered in combination with an Nrf2 activator, such as a fumarate ester (MMF or DMF) and bardoxolone methyl.

The individual treated may be known to have SCD, is suspected of or at risk for having SCD. In embodiments of the invention, an individual is diagnosed with sickle cell disease prior to receiving the inventive treatment.

The present invention is also directed to compounds of Formula (I) and pharmaceutically acceptable salts thereof and to pharmaceutical compositions comprising Formula (I) and pharmaceutically acceptable salts thereof, and methods of making thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1D show the relative cell growth and percent cell viability of KU812 cells in the presence of various concentrations (0, 0.5, 2.5, 5, 10, and 20 μM) of Compounds 73, 134, 473, and 236, respectively. Data are presented mean ± SD (n=3). *, $p<0.05$

Figure 1E comprises Western Blots showing the level of induction of HbF following treatment of KU812 cells with various concentrations (0, 0.5, 2.5, 5, 10, and 20 μM) of Compounds 73, 134, 473, and 236. Hydroxyurea (HU) and hemin were used as HbF induction positive controls, and ß-actin was used as a protein loading control.

Figure 2 shows HbF protein expression levels of KU812 cells obtained by FACs and analyzed as the mean concentration of HbF per cell measured by mean fluorescence intensity (MFI).

Figure 3A comprises Western Blots showing the level of induction of HbF and HbS when sickle erythroid progenitor cells were treated with Compound 473 (0.5 and 2.5 μM) for 48 hours. Hydroxyurea (HU) and hemin were used as HbF induction positive controls, and ß-actin was used as a protein loading control.

Figure 3B shows the percent of HbF positive cells (F-cells) when sickle erythroid progenitor cells were treated with Compound 473 (0.5 and 2.5 μM) for 48 hours and analyzed by flow cytometry. Hydroxyurea (HU) and hemin were used as HbF induction positive controls.

Figure 4A contains images of sickle erythroid progenitor cells after culturing for 10 days, treating with Compound 473 for 48 hours at concentrations of 0.5 μM and 2.5 μM or with hemin (about 50 μM) or with hydroxyurea (HU) (about 100 μM), and then subjecting the cells to hypoxia conditions (1% O_2 and 5% CO_2).

Figure 4B shows the percent of sickled cells when sickle erythroid progenitor cells were cultured for 10 days and then treated with Compound 473 for 48 hours at concentrations of 0.5 μM and 2.5 μM or with hemin (about 50 μM) or with hydroxyurea (HU) (about 100 μM), and then subjected to hypoxia conditions (1% O_2 and 5% CO_2).

DETAILED DESCRIPTION OF INVENTION

I. Definitions

The following definitions are intended to clarify the terms defined. If a particular term used herein is not specifically defined, the term should not be considered to be indefinite. Rather, such undefined terms are to be construed in accordance with their plain and ordinary meaning to a person of ordinary skill in the field(s) of art to which the invention is directed.

As used herein the term "alkyl" refers to a straight or branched chain saturated hydrocarbon having one to ten carbon atoms, which may be optionally substituted, as herein further described, with multiple degrees of substitution being allowed. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, isobutyl, n-butyl, sec-butyl, tert-butyl, isopentyl, n-pentyl, neopentyl, n-hexyl, and 2-ethylhexyl.

The number carbon atoms in an alkyl group is represented by the phrase "C_{x-y} alkyl," which refers to an alkyl group, as herein defined, containing from x to y, inclusive, carbon atoms. Thus, C_{1-6} alkyl represents an alkyl chain having from 1 to 6 carbon atoms and, for example, includes, but is not limited to, methyl, ethyl, n-propyl, isopropyl, isobutyl, n-butyl, sec-butyl, tert-butyl, isopentyl, n-pentyl, neopentyl, and n-hexyl.

As used herein, the term "alkylene" refers to a straight or branched chain divalent saturated hydrocarbon radical having from one to ten carbon atoms, which may be optionally substituted as herein further described, with multiple degrees of substitution being allowed. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, n-propylene, 1-methylethylene, 2-methylethylene, dimethylmethylene, n-butylene, 1-methyl-n-propylene, and 2-methyl-n-propylene.

The number of carbon atoms in an alkylene group is represented by the phrase "C_{x-y} alkylene," which refers to an alkylene group, as herein defined,

containing from x to y, inclusive, carbon atoms. Similar terminology will apply for other terms and ranges as well. Thus, C_{1-4} alkylene represents an alkylene chain having from 1 to 4 carbons atoms, and, for example, includes, but is not limited to, methylene, ethylene, n-propylene, 1-methylethylene, 2-methylethylene, dimethylmethylene, n-butylene, 1-methyl-n-propylene, and 2-methyl-n-propylene.

As used herein, the term "cycloalkyl" refers to a saturated, three- to ten-membered, cyclic hydrocarbon ring, which may be optionally substituted as herein further described, with multiple degrees of substitution being allowed. Such "cycloalkyl" groups are monocyclic, bicyclic, or tricyclic. Examples of "cycloalkyl" groups as used herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and adamantyl.

The number of carbon atoms in a cycloalkyl group will be represented by the phrase "C_{x-y} cycloalkyl," which refers to a cycloalkyl group, as herein defined, containing from x to y, inclusive, carbon atoms. Similar terminology will apply for other terms and ranges as well. Thus, C_{3-10} cycloalkyl represents a cycloalkyl group having from 3 to 10 carbons as described above, and for example, includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and adamantyl.

As used herein, the term "heterocycle" or "heterocyclyl" refers to an optionally substituted mono- or polycyclic saturated ring system containing one or more heteroatoms. Such "hetercycle" or "heterocyclyl" groups may be optionally substituted as herein further described, with multiple degrees of substitution being allowed. The term "heterocycle" or "heterocyclyl," as used herein, does not include ring systems that contain one or more aromatic rings. Examples of heteroatoms include nitrogen, oxygen, or sulfur atoms, including N-oxides, sulfur oxides, and sulfur dioxides. Typically, the ring is three- to twelve-membered. Such rings may be optionally fused to one or more of another heterocyclic ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" groups, as used herein include, but are not limited to, tetrahydrofuran, tetrahydropyran, 1,4-dioxane, 1,3-dioxane, piperidine, pyrrolidine, morpholine,

tetrahydrothiopyran, and tetrahydrothiophene, where attachment can occur at any point on said rings, as long as attachment is chemically feasible. Thus, for example, "morpholine" refers to morpholin-2-yl, morpholin-3-yl, and morpholin-4-yl.

As used herein, when "heterocycle" or "heterocyclyl" is recited as a possible substituent, the "heterocycle" or "heterocyclyl" group can attach through either a carbon atom or any heteroatom, to the extent that attachment at that point is chemically feasible. For example, "heterocyclyl" would include pyrrolidin-1-yl, pyrrolidin-2-yl, and pyrrolidin-3-yl. When "heterocycle" or "heterocyclyl" groups contain a nitrogen atom in the ring, attachment through the nitrogen atom can alternatively be indicated by using an "-ino" suffix with the ring name. For example, pyrrolidino refers to pyrrolidin-1-yl.

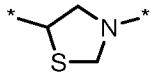
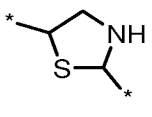
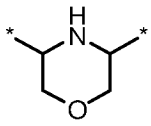
As used herein the term "halogen" refers to fluorine, chlorine, bromine, or iodine.

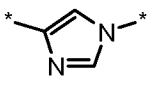
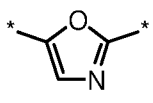
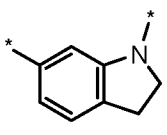
As used herein, the term "oxo" refers to a >C=O substituent. When an oxo substituent occurs on an otherwise saturated group, such as with an oxo-substituted cycloalkyl group (e.g., 3-oxo-cyclobutyl), the substituted group is still intended to be a saturated group.

As used herein, the term "heteroaryl" refers to a five- to fourteen-membered optionally substituted mono- or polycyclic ring system, which contains at least one aromatic ring and also contains one or more heteroatoms. Such "heteroaryl" groups may be optionally substituted as herein further described, with multiple degrees of substitution being allowed. In a polycyclic "heteroaryl" group that contains at least one aromatic ring and at least one non-aromatic ring, the aromatic ring(s) need not contain a heteroatom. Thus, for example, "heteroaryl," as used herein, would include indolinyl. Further, the point of attachment may be to any ring within the ring system without regard to whether the ring containing the attachment point is aromatic or contains a heteroatom. Thus, for example, "heteroaryl," as used herein, would include indolin-1-yl, indolin-3-yl, and indolin-5-yl. Examples of heteroatoms include

nitrogen, oxygen, or sulfur atoms, including N-oxides, sulfur oxides, and sulfur dioxides, where feasible. Examples of "heteraryl" groups, as used herein include, but are not limited to, furyl, thiophenyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,4-triazolyl, pyrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, indolyl, isoindolyl, benzo[b]thiophenyl, benzimidazolyl, benzothiazolyl, pteridinyl, and phenazinyl, where attachment can occur at any point on said rings, as long as attachment is chemically feasible. Thus, for example, "thiazolyl" refers to thiazol-2-yl, thiazol-4-yl, and thiaz-5-yl.

As used herein, when "heteroaryl" is recited as a possible substituent, the "heteroaryl" group can attach through either a carbon atom or any heteroatom, to the extent that attachment at that point is chemically feasible.

As used herein, the term "heterocyclylene" refers to an optionally substituted bivalent heterocyclyl group (as defined above). The points of attachment may be to the same ring atom or to different ring atoms, as long as attachment is chemically feasible. The two points of attachment can each independently be to either a carbon atom or a heteroatom, as long as attachment is chemically feasible. Examples include, but are not limited to,  ,  , and  , where the asterisks indicate points of attachment.

As used herein, the term "heteroarylene" refers to an optionally substituted bivalent heteroaryl group (as defined above). The points of attachment may be to the same ring atom or to different ring atoms, as long as attachment is chemically feasible. The two points of attachment can each independently be to either a carbon atom or a heteroatom, as long as attachment is chemically feasible. Examples include, but are not limited to,  ,  , and  , where the asterisks indicate ponts of attachment.

Various other chemical terms or abbreviations have their standard meaning to the skilled artisan. For example: "hydroxyl" refers to -OH; "methoxy" refers to -OCH_3; "cyano" refers to -CN; "amino" refers to -NH_2; "methylamino" refers to -$NHCH_3$; "sulfonyl" refers to -SO_2-; "carbonyl" refers to -C(O)-; "carboxy" or "carboxyl" refer to -CO_2H, and the like. Further, when a name recited multiple moieties, e.g., "methylaminocarbonyl-methyl", an earlier-recited moiety is further from the point of attachment than any later-recited moieties. Thus, a term such as "methylaminocarbonylmethyl" refers to -CH_2-C(O)-NH-CH_3.

As used herein, the term "substituted" refers to substitution of one or more hydrogens of the designated moiety with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated, provided that the substitution results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one in which the chemical structure is not substantially altered when kept at a temperature from about -80°C to about +40°C, in the absence of moisture or other chemically reactive conditions, for at least a week, or a compound which maintains its integrity long enough to be useful for therapeutic or prophylactic administration to a subject. As used herein, the phrases "substituted with one or more…" or "substituted one or more times…" refer to a number of substituents that equals from one to the maximum number of substituents possible based on the number of available bonding sites, provided that the above conditions of stability and chemical feasibility are met.

As used herein, the various functional groups represented will be understood to have a point of attachment at the functional group having the hyphen or dash (–) or an asterisk (*). In other words, in the case of -$CH_2CH_2CH_3$, it will be understood that the point of attachment is the CH_2 group at the far left. If a group is recited without an asterisk or a dash, then the attachment point is indicated by the plain and ordinary meaning of the recited group.

When any variable occurs more than one time in any one constituent (e.g., R^d), or multiple constituents, its definition on each occurrence is independent of its definition on every other occurrence.

As used herein, multi-atom bivalent species are to be read from left to right. For example, if the specification or claims recite A-D-E and D is defined as -OC(O)-, the resulting group with D replaced is: A-OC(O)-E and not A-C(O)O-E.

As used herein, the term “optionally” means that the subsequently described event(s) may or may not occur.

As used herein, "administer” or “administering” means to introduce, such as to introduce to a subject a compound or composition. The term is not limited to any specific mode of delivery, and can include, for example, intravenous delivery, transdermal delivery, oral delivery, nasal delivery, and rectal delivery. Furthermore, depending on the mode of delivery, the administering can be carried out by various individuals, including, for example, a health-care professional (e.g., physician, nurse, etc.), a pharmacist, or the subject (i.e., self-administration).

As used herein, “treat” or “treating” or “treatment” can refer to one or more of delaying the progress of a disease or condition, controlling a disease or condition, delaying the onset of a disease or condition, ameliorating one or more symptoms characteristic of a disease or condition, or delaying the recurrence of a disease or condition or characteristic symptoms thereof, depending on the nature of a disease or condition and its characteristic symptoms. "Treat" or "treating" or "treatment" may also refers to inhibiting the disease, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both, and to inhibiting at least one physical parameter that may or may not be discernible to the subject. In certain embodiments, "treat" or "treating" or "treatment" refers to delaying the onset of the disease or at least one or more symptoms thereof in a subject which may be exposed to or predisposed to a disease even though that subject does not yet experience or display symptoms of the disease.

As used herein, "subject" may refer any mammal such as, but not limited to, humans. In one embodiment, the subject is a human. In another embodiment, the host is a human who exhibits one or more symptoms characteristic of a disease or condition. The term “subject” does not require one to have any particular status

with respect to any hospital, clinic, or research facility (e.g., as an admitted patient, a study participant, or the like). In an embodiment, the subject may be "a subject in need thereof."

"Therapeutically effective amount" refers to the amount of a compound that, when administered to a subject for treating a disease, or at least one of the clinical symptoms of a disease, is sufficient to affect such treatment of the disease or symptom thereof. The "therapeutically effective amount" may vary depending, for example, on the compound, the disease and/or symptoms of the disease, severity of the disease and/or symptoms of the disease or disorder, the age, weight, and/or health of the subject to be treated, and the judgment of the prescribing physician. An appropriate amount in any given instance may be ascertained by those skilled in the art or capable of determination by routine experimentation.

As used herein, the term “compound of the invention” includes free acids, free bases, and any salts thereof of the compound of Formula (I). Thus, phrases such as “compound of embodiment 1” or “compound of claim 1” refer to any free acids, free bases, and any salts thereof that are encompassed by embodiment 1 or claim 1, respectively.

II. Methods of Treatment

A. Treatment of SCD and Related Disorders with Compounds of the Invention

In an embodiment, the present invention provides methods of increasing expression of HbF in cells by contacting certain cells, for example erythroid or retinal pigment epithelial (RPE) cells, with a therapeutically effective amount of a compound of the invention. In other embodiments, the present invention provides methods of increasing expression of HbF in cells by administering a compound of the invention to a subject in need thereof. In embodiment, the expression of HbF is increased such that HbF is greater than or equal to 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 80%, or 90% of the total

hemoglobin in a subject or in a sample taken from a subject. In embodiment, the expression of HbF is increased such that HbF is increased by at least 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, percentage point of the total hemoglobin in a subject or in a sample taken from a subject relative to a baseline sample taken prior to treatment of the subject. In another embodiment where the subject is a human less than 19 years of age, the expression of HbF is increased such that HbF is greater than or equal to 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 80%, or 90% of the total hemoglobin in a subject or in a sample taken from a subject. The methods can be used to compensate for a mutation in the human beta-globin gene in cells that have one or more mutations in the beta-globin gene or an expression control sequence thereof, for example mutations that result in the expression of the HbS form of hemoglobin. Compensating for the mutation includes, but is not limited to, increasing the amount of HbF and reducing the amount of HbS in the subject compared to untreated subjects or prior to treatment of a subject. In another embodiment, the method of treatment results in an increase in the ratio of HbF to HbS expressed in cells in a subject in need thereof. The methods can be used for treating sickle cell disease, for example sickle cell anemia, and other hemoglobinopathies or thalassemias as well as complications related to SCD, for example retinopathy.

In another embodiment, the present invention provides a method of inhibiting polymerization of HbS, of increasing dissolved oxygen levels in a subject's blood, of reducing levels of reactive oxygen species (ROS), or any combination thereof by administering a compound of the invention to a subject in need thereof.

In another embodiment, the present invention provides a method of reducing sickling in response to reduced air pressure, reduced barometric pressure, reduced partial pressure of oxygen or hypoxia, reducing incidences or rate of painful crises, reducing incidences or rate of painful crises requiring hospitalization, reducing the incidences of chest syndrome, reducing the number of transfusion events, reducing

the number of units of blood transfused per event or any combination thereof by administering a compound of the invention to a subject in need thereof. The reduction of incidences or rate may be over a week, month, or year.

In another embodiment, the invention provides a method of treatment comprising administering a compound (or salt) of any one of embodiments 1 to 250 to a subject. In another embodiment, the invention provides a method of treatment comprising administering between 0.1 milligrams and 2 grams of a compound (or salt) of any one of embodiments 1 to 250 to a subject.

In each of the methods described above or below, a compound (or salt) of any of embodiments 1 to 250 may be administered to a subject as part of a pharmaceutically formulation, as described herein.

In each of the methods described herein, the method may further include the step of determining whether the subject has one or more genetic alterations associated with SCD or first determining whether the subject has biochemical or morphological alterations associated with SCD.

In each of the methods described herein, the method may further include the step of determining whether administration of a compound of the invention has increased expression of HbF, decreased biomarkers associated with SCD such ROS, or reduced the symptoms associated with SCD. The method may further comprise the step of administering a higher dose of a compound of the invention if the subject has not increased expression of HbF, does not have decreased biomarkers associated with SCD such ROS, or does not have reduced the symptoms associated with SCD.

B. Treatments in Combination with HU or an Nrf2 Activator

Methods for treating SCD or complications thereof described herein may also include administering a compound of the invention in combination with or alternation with HU or an Nrf2 activator. The combination may be administered in amounts effective to induce or increase expression of HbF.

C. Diseases to be Treated

The compounds of the invention and the combinations described herein can be used to treat subjects with one or more mutations in the beta-globin gene (HBB gene). Mutations in the beta globin gene can cause sickle cell disease, beta thalassemia, or related diseases or conditions thereof. As discussed in more detail below, mutations in the beta-globin gene can be identified before or after manifestations of a disease's clinical symptoms. The compositions can be administered to a subject with one or more mutations in the beta-globin gene before or after the onset of clinical symptoms. Therefore, in some embodiments, the compositions are administered to a subject that has been diagnosed with one or more mutations in the beta-globin gene, but does not yet exhibit clinical symptoms. In some embodiments, the compositions are administered to a subject that is exhibiting one or more symptoms of a disease, condition, or syndrome associated with, or caused by one or more mutations in the beta-globin gene.

1. Sickle Cell Disease

Sickle cell disease (SCD) typically arises from a mutation substituting thymine for adenine in the sixth codon of the beta-chain gene of hemoglobin (i.e., GAG to GTG of the HBB gene). This mutation causes glutamate to valine substitution in position 6 of the Hb beta chain. The resulting Hb, referred to as HbS, has the physical properties of forming polymers under deoxy conditions. SCD is typically an autosomal recessive disorder. Therefore, in some embodiments, the disclosed compositions and methods are used to treated a subject homozygous for an autosomal recessive mutation in beta-chain gene of hemoglobin (i.e., homozygous for sickle cell hemoglobin (HbS)). Also referred to as HbSS disease or sickle cell anemia (the most common form), subjects homozygote for the S globin typically exhibit a severe or moderately severe phenotype and have the shortest survival of the hemoglobinopathies.

Sickle cell trait or the carrier state is the heterozygous form characterized by the presence of around 40% HbS, absence of anemia, inability to concentrate urine (isosthenuria), and hematuria. Under conditions leading to hypoxia, it may become

a pathologic risk factor. Accordingly, in some embodiments, the disclosed compositions and methods are used to treat a subject heterozygous for an autosomal recessive mutation in the beta-chain gene of hemoglobin (i.e., heterozygous for HbS).

2. Beta-Thalassemia

Beta-thalassemias (ß-thalassemias) are a group of inherited blood disorders caused by a variety of mutational mechanisms that result in a reduction or absence of synthesis of ß-globin and leading to accumulation of aggregates of unpaired, insoluble α-chains that cause ineffective erythropoiesis, accelerated red cell destruction, and severe anemia. Subjects with beta-thalassemia exhibit variable phenotypes ranging from severe anemia to clinically asymptomatic individuals. The genetic mutations present in ß-thalassemias are diverse, and can be caused by a number of different mutations. The mutations can involve a single base substitution or deletions or inserts within, near or upstream of the ß-globin gene. For example, mutations occur in the promoter regions preceding the beta-globin genes or cause production of abnormal splice variants. Examples of thalassemias include thalassemia minor, thalassemia intermedia, and thalassemia major.

3. Sickle Cell Related Disorders

Although carriers of sickle cell trait do not suffer from SCD, individuals with one copy of HbS and one copy of a gene that codes for another abnormal variant of hemoglobin, such as HbC or Hb beta-thalassemia, have a less severe form of the disease. A subject that is a double heterozygote for HbS and HbC (HbSC disease) is typically characterized by symptoms of moderate clinical severity. Another common structural variant of beta-globin is hemoglobin E or hemoglobin E (HbE). A subject that is a double heterozygote for HbS and HbE has HbS/HbE syndrome, which usually causes a phenotype similar to HbS/b+ thalassemia, discussed below.

Some mutations in the beta-globin gene can cause other structural variations of hemoglobin or can cause a deficiency in the amount of ß-globin being produced. These types of mutations are referred to as beta-thalassemia mutations. The

absence of beta-globin is referred to as beta-zero (ß-0) thalassemia. A subject that is a double heterozygote for HbS and ß-0 thalassemia (i.e., HbS/ß-0 thalassemia) can suffer symptoms clinically indistinguishable from sickle cell anemia. A reduced amount of beta-globin is referred to as ß-plus (ß+) thalassemia. A subject that is a double heterozygote for HbS and ß+ thalassemia (i.e., HbS/ß+ thalassemia) can have mild-to-moderate severity of clinical symptoms with variability among different ethnicities. Rare combinations of HbS with other abnormal hemoglobins include HbD Los Angeles, G-Philadelphia, HbO Arab, and others.

Therefore, in some embodiments, the disclosed compositions and methods are used to treat a subject with an HbS/ß-0 genotype, an HbS/ß+ genotype, an HBSC genotype, an HbS/HbE genotype, an HbD Los Angeles genotype, a G-Philadelphia genotype, or an abHbO Arab genotype.

As discussed above, retinopathy due to SCD can also be treated by administering an effective amount of a compound of the invention, optionally in combination or alternation with HU or with an Nrf2 activator in amounts effective to induce expression of HbF in retinal cells, for example in RPE cells. Administration of a compound of the invention optionally in combination with HU or with an Nrf2 activator may reduce or inhibit the formation of occlusions in the peripheral retina of a sickle cell patient.

4. Non-Erythroid Cell Related Disorders

Although red blood cells are the primary producers of hemoglobin, reports indicate that other, non-hematopoietic cells, including, but not limited to, macrophage, retinal pigment cells, and alveolar epithelial cells such as alveolar type II (ATII) cells and Clara cells also synthesize hemoglobin. In some embodiments, the compositions disclosed herein are used to increase HbF expression in non-erythroid cells including, but not limited to, macrophage, retinal pigment cells, and alveolar epithelial cells such as alveolar type II (ATII) cells and Clara cells. In some embodiments, the compositions disclosed herein are used to increase HbF expression in non-erythroid cells at interfaces where oxygen-carbon dioxide diffusion occurs, including, but not limited to the eyes and lungs. In some

embodiments, the compositions are used to induce, increase, or enhance hemoglobin synthesis in retinal pigment cells in an effective amount to prevent, reduce, or alleviate one or more symptoms of age-related macular degeneration or diabetic retinopathy.

D. Symptoms of SCD, Beta-Thalassemias, and Related Disorders

In some embodiments, the compositions disclosed herein are administered to a subject in an amount effective to treat one or more symptoms of sickle cell disease, a beta-thalassemia, or a related disorder.

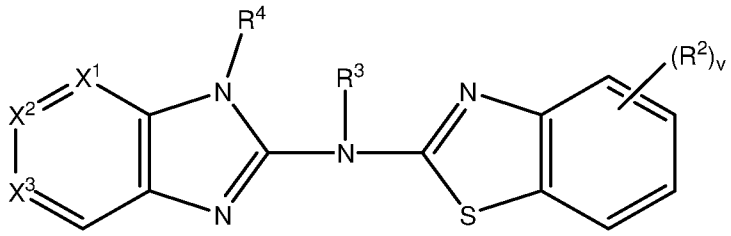
Beta-thalassemia can include symptoms such as anemia, fatigue and weakness, pale skin or jaundice, protruding abdomen with enlarged spleen and liver, dark urine, abnormal facial bones, poor growth, and poor appetite.

In subjects with sickle cell disease, or a related disorder, physiological changes in RBCs can result in a disease with the following signs: (1) hemolytic anemia; (2) vaso-occlusive crisis; and (3) multiple organ damage from microinfarcts, including heart, skeleton, spleen, and central nervous system.

III. Compositions for Use in Treating SCD and Related Disorders

A. Compounds of the Invention (Compounds of Formula (I)))

A compound of Formula (I) has the structure shown below



(I)

wherein

X^1 is =N- or =CH-;

X^2 is =C(R^1)- and X^3 is =C(-L-G)-; or X^2 is =C(-L-G)- and X^3 is =C(R^1)-;

G is hydrogen, -C_{1-8} alkyl, -C_{3-10} cycloalkyl, -C_{1-6} alkylene-C_{3-10} cycloaklyl, heterocyclyl, -C_{1-6} alkylene-C_{3-10} heterocyclyl, phenyl, heteroaryl, or NR^hR^k, where the alkyl, alkylene, cycloalkyl, heterocyclyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^c; or G is -CH_2Y^3, -$CH_2CH_2Y^3$, -$CH_2CH_2CH_2Y^3$, -$CH(CH_3)CH_2Y^3$, -$CH_2CH(Y^3)CH_3$, -$CH(Y^3)CH_3$, -$CH_2C(Y^3)(CH_3)_2$, -$C(Y^3)(CH_3)_2$, or  , where Y^3 is cyclopropyl, -CF_3, -OCF_3, -OCH_3, -OCH_2CH_3, -F, -Cl, -OH, -$O(CH_2)_2$-OH, -$O(CH_2)_2$-F, -SCH_3, -$S(O)_2$-CH_3, -SCH_2CH_3, -$S(O)_2CH_2CH_3$, -NH-CH_3, -NH-CH_2CH_3, -$N(CH_3)_2$, tetrahydropyran-4-yl, tetrahydrofuran-2-yl, morpholin-2-yl, morpholin-4-yl, piperidin-1-yl, 4-hydroxy-piperidin-1-yl, 3-hydroxy-piperidin-1-yl, -NH-C(O)-CH_3, -NH-C(O)-CH_2CH_3, tetrahydrofuran-2-yl-methyloxy, or -C(O)-Y^4, where Y^4 is -OH, -OCH_3, -OCH_2CH_3, -$OC(CH_3)_3$, -NH_2, -NH-CH_3, -NH-CH_2CH_3, -$N(CH_3)_2$, -$N(CH_2CH_3)_2$, morpholin-4-yl, 4-methyl-piperazin-1-yl, pyrrolidin-1-yl, or piperazin-1-yl;

L is -CH_2-C(O)$N(R^6)$-, -C(O)$N(R^6)$-, -C(O)-O-, -SO_2-, -C(O)-, heteroarylene optionally substituted one or more times with substituents independently selected from R^x, or heterocyclylene optionally substituted one or more times with substituents independently selected from R^x; or the group -L-G is -cyano;

R^1 is hydrogen, R^a, phenyl, or heteroaryl, where the phenyl and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^x;

R^2 is R^b;

R^3 is hydrogen, -C_{1-6} alkyl, or -C_{1-6} alkylene-C_{3-10} cycloaklyl, where the alkyl, alkylene, and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^z;

R^4 is -C_{1-6} alkyl or -C_{1-6} alkylene-C_{3-10} cycloaklyl, where the alkyl, alkylene, and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^y;

R^6 is hydrogen, -C_{1-6} alkyl, -C_{1-6} alkylene-C_{3-10} cycloaklyl, where the alkyl, alkylene, and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^x;

R^a is

a) -halogen,
b) -C_{1-6} alkyl,
c) -C_{3-10} cycloalkyl,
d) -heterocyclyl,
e) -cyano,
f) -CF_3,
g) -OCF_3,
h) -O-R^d,
i) -$S(O)_w$-R^d,
j) -$S(O)_2O$-R^d,
k) -NR^dR^e,
l) -C(O)-R^d,
m) -C(O)-O-R^d,
n) -OC(O)-R^d,
o) -C(O)NR^d R^e,
p) -C(O)-heterocyclyl,
q) -NR^d C(O)R^e,
r) -OC(O)NR^d R^e,
s) -NR^d C(O)OR^d, or
t) -NR^d C(O)NR^d R^e,

where the alkyl, cycloalkyl, and heterocyclyl groups are optionally substituted one or more times with substituents independently selected from R^y;

R^b is

a) -halogen,
b) -C_{1-6} alkyl,

c) -C_{3-10} cycloalkyl,
d) -heterocyclyl,
e) -phenyl,
f) -heteroaryl,
g) -cyano,
h) -CF_3,
i) -OCF_3,
j) -O-R^f,
k) -$S(O)_w$-R^f,
l) -$S(O)_2O$-R^f,
m) –NR^fR^g,
n) -C(O)-R^f,
o) -C(O)-O-R^f,
p) -OC(O)-R^f,
q) -$C(O)NR^f R^g$,
r) -C(O)-heterocyclyl,
s) -NR^f $C(O)R^g$,
t) -$OC(O)NR^f$ R^g,
u) -NR^f $C(O)OR^f$, or
v) -NR^f $C(O)NR^f$ R^g,

where the alkyl, cycloalkyl, heterocyclyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^z;

R^c is

a) -halogen,
b) -C_{1-6} alkyl,
c) -C_{3-10} cycloalkyl,
d) -heterocyclyl,
e) -cyano,
f) -CF_3,

g) $-OCF_3$,
h) $-O-R^h$,
i) $-S(O)_w-R^h$,
j) $-S(O)_2O-R^h$,
k) $-NR^hR^k$,
l) $-C(O)-R^h$,
m) $-C(O)-O-R^h$,
n) $-OC(O)-R^h$,
o) $-C(O)NR^h R^k$,
p) -C(O)-heterocyclyl,
q) $-NR^h C(O)R^k$,
r) $-OC(O)NR^h R^k$,
s) $-NR^h C(O)OR^k$,
t) $-NR^h C(O)NR^h R^k$,
u) $-NR^h S(O)_wR^k$,
v) -phenyl,
w) -heteroaryl, or
x) $-O-(C_{1-4}$ alkylene)$-O-(C_{1-4}$ alkylene)$-N(R^h)C(O)-OR^k$,

where the alkylene, alkyl, cycloalkyl, heterocyclyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^x;

R^d and R^e are independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl, where the alkyl and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^y; or, if R^d and R^e are both attached to the same nitrogen atom, together with that nitrogen atom may optionally form a heterocyclic ring selected from the group consisting of azetidino, pyrrolidino, pyrazolidino, imidazolidino, oxazolidino, isoxazolidino, thiazolidino, isothiazolidino, piperidino, piperazino, morpholino, thiomorpholino, and azepano, where each ring is optionally substituted one or more times with substituents independently selected from R^y;

R^f and R^g are independently hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, phenyl, or heteroaryl, where the alkyl, cycloalkyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^z; or, if R^f and R^g are both attached to the same nitrogen atom, together with that nitrogen atom may optionally form a heterocyclic ring selected from the group consisting of azetidino, pyrrolidino, pyrazolidino, imidazolidino, oxazolidino, isoxazolidino, thiazolidino, isothiazolidino, piperidino, piperazino, morpholino, thiomorpholino, and azepano, where each ring is optionally substituted one or more times with substituents independently selected from R^z;

R^h and R^k are independently hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, heterocyclyl, phenyl, or heteroaryl, where the alkyl, cycloalkyl, heterocyclyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^x; or, if R^h and R^k are both attached to the same nitrogen atom, together with that nitrogen atom may optionally form a heterocyclic ring selected from the group consisting of azetidino, pyrrolidino, pyrazolidino, imidazolidino, oxazolidino, isoxazolidino, thiazolidino, isothiazolidino, piperidino, piperazino, morpholino, thiomorpholino, and azepano, where each ring is optionally substituted one or more times with substituents independently selected from R^x;

R^y is

a) -halogen,

b) $-NH_2$,

c) -cyano,

d) -carboxy,

e) -hydroxy,

f) -thiol,

g) $-CF_3$,

h) $-OCF_3$,

i) $-C(O)-NH_2$,

j) $-S(O)_2-NH_2$,

k) oxo,

l) $-C_{1-6}$ alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}\text{ alkyl})_2$,

m) -heterocyclyl optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}\text{ alkyl})_2$,

n) $-C_{3-10}$ cycloalkyl optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}\text{ alkyl})_2$,

o) $-O-C_{1-6}$ alkyl optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}\text{ alkyl})_2$,

p) $-O-C_{3-10}$ cycloalkyl optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}\text{ alkyl})_2$,

q) $-NH-C_{1-6}$ alkyl optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}\text{ alkyl})_2$,

r) $-N(C_{1-6}\text{ alkyl})_2$ optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}\text{ alkyl})_2$,

s) $-C(O)-C_{1-6}$ alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}\text{ alkyl})_2$,

t) $-C(O)-O-C_{1-6}$ alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}\text{ alkyl})_2$,

u) -S-C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

v) -$S(O)_2$-C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

w) -C(O)-NH-C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

x) -C(O)-N(C_{1-6} alkyl)$_2$, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

y) -$S(O)_2$-NH-C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

z) -$S(O)_2$-N(C_{1-6} alkyl)$_2$, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

aa)-NH-C(O)-C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$, or

bb)-NH-$S(O)_2$-C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$;

R^x is

a) -R^y

b) -phenyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

c) -heteroaryl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

d) -O-phenyl,

e) -O-heteroaryl,

f) -C(O)-phenyl,

g) -C(O)-heteroaryl,

h) -C(O)-O-phenyl, or

i) -C(O)-O-heteroaryl;

R^z is

a) $-R^y$

b) -phenyl,

c) -heteroaryl;

d) -O-phenyl,

e) -O-heteroaryl,

f) -C(O)-phenyl,

g) -C(O)-heteroaryl,

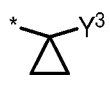
h) -C(O)-O-phenyl, or

i) -C(O)-O-heteroaryl;

v is an integer from 0 to 4, and

w is an integer from 0 to 2.

Embodiment 2: A compound according to embodiment 1 wherein

G is hydrogen, -C_{1-8} alkyl, -C_{3-10} cycloalkyl, -C_{1-6} alkylene-C_{3-10} cycloaklyl, heterocyclyl, phenyl, heteroaryl, or $NR^h R^k$, where the alkyl, alkylene, cycloalkyl, heterocyclyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^c; or G is $-CH_2Y^3$, $-CH_2CH_2Y^3$, $-CH_2CH_2CH_2Y^3$, $-CH(CH_3)CH_2Y^3$, $-CH_2CH(Y^3)CH_3$, $-CH(Y^3)CH_3$, $-CH_2C(Y^3)(CH_3)_2$, $-C(Y^3)(CH_3)_2$, or  ,

where Y^3 is -cyclopropyl, $-CF_3$, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, -F, -Cl, -OH, $-O(CH_2)_2$-OH, $-O(CH_2)_2$-F, $-SCH_3$, $-S(O)_2$-CH_3, $-SCH_2CH_3$, $-S(O)_2CH_2CH_3$, $-NH$-CH_3, $-NH$-CH_2CH_3, $-N(CH_3)_2$, tetrahydropyran-4-yl, tetrahydrofuran-2-yl, morpholin-2-yl, morpholin-4-yl, piperidin-1-yl, 4-hydroxy-piperidin-1-yl, 3-hydroxy-piperidin-1-yl, $-NH$-$C(O)$-CH_3, $-NH$-$C(O)$-CH_2CH_3, tetrahydrofuran-2-yl-methyloxy, or $-C(O)$-Y^4, where Y^4 is -OH, $-OCH_3$, $-OCH_2CH_3$, $-OC(CH_3)_3$, $-NH_2$, $-NH$-CH_3, $-NH$-CH_2CH_3, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, morpholin-4-yl, 4-methyl-piperazin-1-yl, pyrrolidin-1-yl, or piperazin-1-yl;

R^c is

a) -halogen,
b) $-C_{1\text{-}6}$ alkyl,
c) $-C_{3\text{-}10}$ cycloalkyl,
d) -heterocyclyl,
e) -cyano,
f) $-CF_3$,
g) $-OCF_3$,
h) $-O$-R^h,
i) $-S(O)_w$-R^h,
j) $-S(O)_2O$-R^h,
k) $-NR^hR^k$,
l) $-C(O)$-R^h,
m) $-C(O)$-O-R^h,
n) $-OC(O)$-R^h,
o) $-C(O)NR^h\,R^k$,
p) $-C(O)$-heterocyclyl,
q) $-NR^h\,C(O)R^k$,
r) $-OC(O)NR^h\,R^k$,
s) $-NR^h\,C(O)OR^k$,
t) $-NR^h\,C(O)NR^h\,R^k$,
u) -phenyl,

v) -heteroaryl, or

w) -O-(C_{1-4} alkylene)-O-(C_{1-4} alkylene)-N(R^h)C(O)-OR^k,

where the alkylene, alkyl, cycloalkyl, heterocyclyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^x;

R^h and R^k are independently hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, phenyl, or heteroaryl, where the alkyl, cycloalkyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^x; or, if R^h and R^k are both attached to the same nitrogen atom, together with that nitrogen atom may optionally form a heterocyclic ring selected from the group consisting of azetidino, pyrrolidino, pyrazolidino, imidazolidino, oxazolidino, isoxazolidino, thiazolidino, isothiazolidino, piperidino, piperazino, morpholino, thiomorpholino, and azepano, where each ring is optionally substituted one or more times with substituents independently selected from R^x; and

R^y is

a) -halogen,

b) -NH_2,

c) -cyano,

d) -carboxy,

e) -C_{1-6} alkyl, optionally substituted one or more times with halogen,

f) -heterocyclyl, optionally substituted one or more times with halogen,

g) -C_{3-10} cycloalkyl, optionally substituted one or more times with halogen,

h) -O-C_{1-6} alkyl, optionally substituted one or more times with halogen,

i) -O-C_{3-10} cycloalkyl, optionally substituted one or more times with halogen,

j) -hydroxy,

k) -thiol,

l) -CF_3,

m) -OCF_3,

n) –C(O)-C_{1-6} alkyl, optionally substituted one or more times with halogen,

o) -C(O)-O-C_{1-6} alkyl, optionally substituted one or more times with halogen,

p) -S-C_{1-6} alkyl, optionally substituted one or more times with halogen, or

q) -$S(O)_2$-C_{1-6} alkyl, optionally substituted one or more times with halogen.

Embodiment 3: A compound according to embodiment 2, wherein

R^3 is hydrogen.

Embodiment 4: A compound according to embodiment 2, wherein

R^3 is methyl.

Embodiment 5: A compound according to any one of embodiments 2 to 4, wherein

X^1 is =N-.

Embodiment 6: A compound according to any one of embodiments 2 to 4, wherein

X^1 is =CH-.

Embodiment 7: A compound according to any one of embodiments 2 to 6, wherein

v is an integer from 0 to 2.

Embodiment 8: A compound according to any one of embodiments 2 to 6, wherein

v is 0 or 1.

Embodiment 9: A compound according to any one of embodiments 2 to 6, wherein

v is 1.

Embodiment 10: A compound according to any one of embodiments 2 to 6, wherein

v is 1, and R^2 is attached at either the 5-position or the 6-position of the benzothiazole ring.

Embodiment 11: A compound according to any one of embodiments 2 to 6, wherein

v is 1, and R^2 is attached at the 6-position of the benzothiazole ring.

Embodiment 12: A compound according to any one of embodiments 2 to 68, wherein

v is 2, and one R^2 is attached at the 6-position of the benzothiazole ring.

Embodiment 13: A compound according to any one of embodiments 2 to 6, wherein

v is 2, and R^2 is attached at the 5-position and the 6-position of the benzothiazole ring.

Embodiment 14: A compound according to any one of embodiments 2 to 13, wherein

R^2 is -halogen, -C_{1-6} alkyl, -CF_3, -OCF_3, -O-R^f, or -$S(O)_w$-R^f, where the alkyl group is optionally substituted one or more times with substituents independently selected from R^z.

Embodiment 15: A compound according to any one of embodiments 2 to 13, wherein R^2 is -halogen, -methyl, -CF_3, -OCF_3, -SCF_3, -O-heteroaryl, or -$S(O)_2$-CH_3.

Embodiment 16: A compound according to any one of embodiments 2 to 13, wherein R^2 is selected from -Cl, -F, -CF_3, and -OCF_3.

Embodiment 17: A compound according to any one of embodiments 2 to 13, wherein R^2 is -OCF_3.

Embodiment 18: A compound according to any one of embodiments 2 to 13, wherein R^2 is -CF_3.

Embodiment 19: A compound according to any one of embodiments 2 to 13, wherein R^2 is -F.

Embodiment 20: A compound according to any one of embodiments 2 to 13, wherein R^2 is -Cl.

Embodiment 21: A compound according to any one of embodiments 2 to 20, wherein R^4 is -methyl, -ethyl, -n-propyl, -isopropyl, -n-butyl, -sec-butyl, -isobutyl, -tert-butyl, -$(CH_2)_{1-2}$-OCH_3, -$(CH_2)_{1-2}$-F, -$(CH_2)_{1-2}$-Cl, -$(CH_2)_{1-2}$-OCF_3, -$(CH_2)_{1-2}$-NH_2, -$(CH_2)_{1-2}$-CN, -$(CH_2)_{1-2}$-OH, -$(CH_2)_{1-2}$-CF_3, -$(CH_2)_{1-2}$-CO_2H, -$(CH_2)_{1-2}$-SH, -$(CH_2)_{1-2}$-SCH_3, -$(CH_2)_{1-2}$-$S(O)_2CH_3$, -$(CH_2)_{1-2}$-OCH_2CH_3, -$(CH_2)_{1-2}$-SCH_2CH_3, -$(CH_2)_{1-2}$-$S(O)_2CH_2CH_3$, -$(CH_2)_{1-2}$-NH-CH_3, or -$(CH_2)_{1-2}$-$N(CH_3)_2$.

Embodiment 22: A compound according to any one of embodiments 2 to 21, wherein R^4 is -methyl, -ethyl, -isopropyl, -isobutyl, -CH_2CH_2-OCH_3, -CH_2CH_2-F, or -CH_2CH_2-NH_2.

Embodiment 23: A compound according to any one of embodiments 2 to 22, wherein R^4 is -methyl, -ethyl, -isopropyl, or -isobutyl.

Embodiment 24: A compound according to any one of embodiments 2 to 23, wherein R^4 is -methyl.

Embodiment 25: A compound according to any one of embodiments 2 to 23, wherein

R^4 is -ethyl.

Embodiment 26: A compound according to any one of embodiments 2 to 21, wherein R^4 is $-(CH_2)_2-OCH_3$, $-(CH_2)_2-F$, $-(CH_2)_2-Cl$, $-(CH_2)_2-OCF_3$, $-(CH_2)_2-NH_2$, $-(CH_2)_2-CN$, $-(CH_2)_2-OH$, $-(CH_2)_2-CF_3$, $-(CH_2)_2-CO_2H$, $-(CH_2)_2-SH$, $-(CH_2)_2-SCH_3$, or $-(CH_2)_2-S(O)_2CH_3$.

Embodiment 27: A compound according to any one of embodiments 2 to 26, wherein R^1 is selected from hydrogen, $-OCH_3$, -F, -Cl, $-NH_2$, -cyano, -OH, $-CF_3$, $-OCF_3$, -SH, -S-C_{1-6} alkyl, $-S(O)_2-C_{1-6}$ alkyl, $-CO_2H$, -NH-C_{1-6} alkyl, $-N(C_{1-6}$ alkyl$)_2$, and -NH-C_{1-6} alkyl.

Embodiment 28: A compound according to any one of embodiments 2 to 26, wherein R^1 is selected from $-OCH_3$, -F, $-CF_3$, $-OCF_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, and $-N(CH_3)(CH_2CH_3)$.

Embodiment 29: A compound according to any one of embodiments 2 to 26, wherein R^1 is selected from hydrogen, $-OCH_3$, and -F.

Embodiment 30: A compound according to any one of embodiments 2 to 26, wherein R^1 is hydrogen.

Embodiment 31: A compound according to any one of embodiments 2 to 30, wherein G is hydrogen, -C_{1-8} alkyl, -C_{3-10} cycloalkyl, -C_{1-6} alkylene-C_{3-8} cycloaklyl, heterocyclyl, or $NR^h R^k$, where the alkyl, alkylene, cycloalkyl, and heterocyclyl groups are optionally substituted one or more times with substituents independently selected from R^c; or G is $-CH_2Y^3$, $-CH_2CH_2Y^3$, $-CH_2CH_2CH_2Y^3$, $-CH(CH_3)CH_2Y^3$, $-CH_2CH(Y^3)CH_3$, $-CH(Y^3)CH_3$, $-CH_2C(Y^3)(CH_3)_2$, $-C(Y^3)(CH_3)_2$, or  , where Y^3 is -cyclopropyl, $-CF_3$, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, -F, -Cl, -OH, $-O(CH_2)_2-OH$, $-O(CH_2)_2-F$, $-SCH_3$, $-S(O)_2-CH_3$, $-SCH_2CH_3$, $-S(O)_2CH_2CH_3$, $-NH-CH_3$, $-NH-CH_2CH_3$, $-N(CH_3)_2$, tetrahydropyran-4-yl, tetrahydrofuran-2-yl, morpholin-2-yl, morpholin-4-yl, piperidin-1-yl, 4-hydroxy-piperidin-1-yl, 3-hydroxy-piperidin-1-yl, $-NH-C(O)-CH_3$, $-NH-C(O)-CH_2CH_3$, tetrahydrofuran-2-yl-methyloxy, or $-C(O)-Y^4$, where Y^4 is -OH, $-OCH_3$, $-OCH_2CH_3$, $-OC(CH_3)_3$, $-NH_2$, $-NH-CH_3$, -NH-

CH_2CH_3, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, morpholin-4-yl, 4-methyl-piperazin-1-yl, pyrrolidin-1-yl, or piperazin-1-yl;

L is $-CH_2-C(O)N(R^6)-$, $-C(O)N(R^6)-$, $-C(O)-O-$, $-SO_2-$, $-C(O)-$, or heterocyclylene optionally substituted one or more times with substituents independently selected from R^x; or the group -L-G is -cyano;

R^1 is hydrogen or R^a;

R^c is

a) -halogen,

b) $-C_{1-6}$ alkyl,

c) $-C_{3-10}$ cycloalkyl,

d) -heterocyclyl,

e) -cyano,

f) $-CF_3$,

g) $-OCF_3$,

h) $-O-R^h$,

i) $-S(O)_w-R^h$,

j) $-S(O)_2O-R^h$,

k) $-NR^hR^k$,

l) $-C(O)-R^h$,

m) $-C(O)-O-R^h$,

n) $-OC(O)-R^h$,

o) $-C(O)NR^h R^k$,

p) -C(O)-heterocyclyl,

q) $-NR^h C(O)R^k$,

r) $-OC(O)NR^h R^k$,

s) $-NR^h C(O)OR^k$,

t) $-NR^h C(O)NR^h R^k$, or

u) $-O-(C_{1-4}$ alkylene$)-O-(C_{1-4}$ alkylene$)-N(R^h)C(O)-OR^k$,

where the alkylene, alkyl, cycloalkyl, and heterocyclyl groups are optionally substituted one or more times with substituents independently selected from R^x;

R^h and R^k are independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl, where the alkyl, and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^x; or, if R^h and R^k are both attached to the same nitrogen atom, together with that nitrogen atom may optionally form a heterocyclic ring selected from the group consisting of azetidino, pyrrolidino, pyrazolidino, imidazolidino, oxazolidino, isoxazolidino, thiazolidino, isothiazolidino, piperidino, piperazino, morpholino, thiomorpholino, and azepano, where each ring is optionally substituted one or more times with substituents independently selected from R^x; and

R^x is R^y.

Embodiment 32: A compound according to any one of embodiments 2 to 31, wherein -L-G is not -cyano.

Embodiment 33: A compound according to any one of embodiments 2 to 32, wherein -L-G is $-C(O)NR^h R^k$.

Embodiment 34: A compound according to any one of embodiments 2 to 32, wherein L is $-C(O)N(R^6)-$ or $-C(O)-O-$.

Embodiment 35: A compound according to any one of embodiments 2 to 32, wherein L is $-C(O)N(R^6)-$.

Embodiment 36: A compound according to any one of embodiments 2 to 32, wherein L is not $-CH_2-C(O)N(R^6)-$.

Embodiment 37: A compound according to any one of embodiments 2 to 32, wherein L is -C(O)-O-.

Embodiment 38: A compound according to any one of embodiments 2 to 32, wherein L is -C(O)-.

Embodiment 39: A compound according to any one of embodiments 2 to 32, wherein L is $-S(O)_2-$.

Embodiment 40: A compound according to any one of embodiments 2 to 30, wherein

L is heteroarylene optionally substituted one or more times with substituents independently selected from R^x.

Embodiment 41: A compound according to any one of embodiments 2 to 40, wherein R^6 is hydrogen.

Embodiment 42: A compound according to any one of embodiments 2 to 40, wherein R^6 is hydrogen or -methyl.

Embodiment 43: A compound according to any one of embodiments 2 to 42, wherein G is hydrogen, -C_{1-8} alkyl, -C_{3-10} cycloalkyl, or -C_{1-6} alkylene-C_{3-8} cycloaklyl, where the alkyl, cycloalkyl, and alkylene groups are optionally substituted one or more times with substituents independently selected from R^x.

Embodiment 44: A compound according to any one of embodiments 2 to 42, wherein G is -H, -methyl, -ethyl, -n-propyl, -isopropyl, -isobutyl, -CH_2Y^3, -$CH_2CH_2Y^3$, -$CH_2CH_2CH_2Y^3$, -$CH(CH_3)CH_2Y^3$, -$CH_2CH(Y^3)CH_3$, -$CH(Y^3)CH_3$, -$CH_2C(Y^3)(CH_3)_2$, or -$C(Y^3)(CH_3)_2$, where Y^3 is -cyclopropyl, -CF_3, -OCF_3, -OCH_3, -OCH_2CH_3, -F, -OH, -$O(CH_2)_2$-OH, -$O(CH_2)_2$-F, -SCH_3, -$S(O)_2$-CH_3, -SCH_2CH_3, -$S(O)_2CH_2CH_3$, -NH-CH_3, -NH-CH_2CH_3, -$N(CH_3)_2$, -NH-C(O)-CH_3, -NH-C(O)-CH_2CH_3, or C(O)-Y^4, where Y^4 is -OH, -OCH_3, -OCH_2CH_3, -$OC(CH_3)_3$, -NH_2, -NH-CH_3, -NH-CH_2CH_3, -$N(CH_3)_2$, or -$N(CH_2CH_3)_2$.

Embodiment 45: A compound according to any one of embodiments 2 to 42, wherein G is -methyl, -ethyl, -n-propyl, -isopropyl, or -isobutyl, where each is optionally substituted one or more times with substituents independently selected from -CF_3, -OCF_3, -OCH_3, -OCH_2CH_3, -F, -OH, -$O(CH_2)_2$-OH, -$O(CH_2)_2$-F, -SCH_3, -SCH_2CH_3, -NH-CH_3, -NH-CH_2CH_3, and -$N(CH_3)_2$.

Embodiment 46: A compound according to any one of embodiments 2 to 42, wherein G is H.

Embodiment 47: A compound according to any one of embodiments 2 to 42, wherein G is C_{1-8} alkyl optionally substituted one or more times with halogen.

Embodiment 48: A compound according to any one of embodiments 2 to 42, wherein G is C_{3-10} cycloalkyl optionally substituted one or more times with halogen.

Embodiment 49: A compound according to any one of embodiments 2 to 42, wherein G is heterocyclyl optionally substituted one or more times with halogen.

Embodiment 50: A compound according to any one of embodiments 2 to 42, wherein G is -C_{1-6} alkylene-C_{3-10} cycloalkyl optionally substituted one or more times with halogen.

Embodiment 51: A compound according to any one of embodiments 2 to 42, wherein G is $NR^h R^k$.

Embodiment 52: A compound according to any one of embodiments 2 to 42, wherein G is -CH_2-R^c.

Embodiment 53: A compound according to any one of embodiments 2 to 42, wherein G is –CH_2CH_2-R^c.

Embodiment 54: A compound according to any one of embodiments 2 to 42, wherein G is -$CH_2CH_2CH_2$-R^c.

Embodiment 55: A compound according to any one of embodiments 2 to 42, wherein G is -$CH(CH_3)CH_2R^c$.

Embodiment 56: A compound according to any one of embodiments 2 to 42, wherein G is -$CH_2CH(R^c)CH_3$.

Embodiment 57: A compound according to any one of embodiments 2 to 42, wherein G is -$CH(R^c)CH_3$.

Embodiment 58: A compound according to any one of embodiments 2 to 42, wherein G is -$CH_2C(R^c)(CH_3)_2$.

Embodiment 59: A compound according to any one of embodiments 2 to 42, wherein G is -$C(R^c)(CH_3)_2$.

Embodiment 60: A compound according to any one of embodiments 2 to 42, wherein G is imidazol-2-yl, thiazol-2yl, oxazol-2-yl, pyrazol1-yl, furan-2yl, thiophen-2-yl, pyrrol-1-yl, 1H-1,2,4-triazolyl-3-yl, 5-methyl-1H-1,2,4-triazolyl-3-yl, -$(CH_2)_{1-3}$-(imidazol-2-yl), -$(CH_2)_{1-3}$-(thiazol-2yl), -$(CH_2)_{1-3}$-(oxazol-2-yl), -$(CH_2)_{1-3}$-(pyrazol1-yl), -$(CH_2)_{1-3}$-(furan-2yl), -$(CH_2)_{1-3}$-(thiophen-2-yl), -

$(CH_2)_{1-3}$-(pyrrol-1-yl), -$(CH_2)_{1-3}$-(1H-1,2,4-triazolyl-3-yl), or -$(CH_2)_{1-3}$-(5-methyl-1H-1,2,4-triazolyl-3-yl).

Embodiment 61: A compound according to any one of embodiments 2 to 60, wherein the compound is in its free (non-salted) form.

Embodiment 62: A compound according to any one of embodiments 2 to 60, wherein the compound is in the form of a pharmaceutically acceptable salt.

Embodiment 63: A compound according to any one of embodiments 1 to 62, wherein any "heterocyclyl" group present in the compound is selected from the group consisting of: azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothiophen-2-yl, tetrahydrothiophen-3-yl, pyrazolidin-1-yl, pyrazolidin-3-yl, pyrazolidin-4-yl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-4-yl, oxazolidin-2-yl, oxazolidin-3-yl, oxazolidin-4-yl, oxazolidin-5-yl, isoxazolidin-2-yl, isoxazolidin-3-yl, isoxazolidin-4-yl, isoxazolidin-5-yl, thiazolidin-2-yl, thiazolidin-3-yl, thiazolidin-4-yl, thiazolodin-5-yl, isothiazolidin-2-yl, isothiazolidin-3-yl, isothiazolidin-4-yl, isothiazolodin-5-yl, 1,3-dioxolan-2-yl, 1,3-dioxolan-4-yl, 1,3-oxathiolan-2-yl, 1,3-oxathiolane-4-yl, 1,3-oxathiolan-5-yl, 1,2-dithiolan-3-yl, 1,2-dithiolan-4-yl, 1,3-dithiolan-2-yl, 1,3-dithiolan-4-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, thian-2-yl, thian-3-yl, thian-4-yl, piperazin-1-yl, piperazin-2-yl, morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, thiomorpholin-2-yl, thiomorpholin-3-yl, thiomorpholin-4-yl, 1,4-dioxan-2-yl, 1,3-dioxan-2-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl, 1,4-dithian-2-yl, 1,3-dithian-2-yl, 1,3-dithian-4-yl, 1,3-dithian-5-yl, 1,2-dithian-3-yl, 1,2-dithian-4-yl, azepan-1-yl, azepan-2-yl, azepan-3-yl, and azepan-4-yl, where each of these named rings may optionally be substituted one or more times with substituents independently selected from halogen, -NH_2, cyano, carboxy, C_{1-4} alkyl, C_{3-10} cycloalkyl, hydroxyl, thiol, -CF_3, -OCF_3, -O-C_{1-4} alkyl, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, -S-C_{1-4} alkyl, -S(O)$_2$-C_{1-4} alkyl, -C(O)-C_{1-4} alkyl, -C(O)O-C_{1-4} alkyl, -C(O)NH_2, -C(O)NH-C_{1-4} alkyl,

and -C(O)N(C_{1-4}alkyl)$_2$, and where any nitrogen atom in any of these named rings may optionally be oxidized when chemically feasible, and where any sulfur atom in any of these named rings may optionally be oxidized once or twice when chemically feasible.

Embodiment 64: A compound according to any one of embodiments 1 to 63, wherein any "heteroaryl" group present in the compound is selected from the group consisting of: 1H-pyrrol-1-yl, 1H-pyrrol-2-yl, 1H-pyrrol-3-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, 1H-imidazol-1-yl, 1H-imidazol-2-yl, 1H-imidazol-4-yl, 1H-imidazol-5-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, furazan-3-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrazin-2-yl, 1,3,5-triazin-2-yl, 1H-indol-1-yl, 1H-indol-2-yl, 1H-indol-3-yl, 2H-isoindol-1-yl, 2H-isoindol-2-yl, quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, isoquinolin-1-yl, isoquinolin-3-yl, isoquinolin-4-yl, benzoxazol-2-yl, benzothiazol-2-yl, 1H-benzimidazol-1-yl, 1H-benzimidazol-2-yl, benzofuran-2-yl, benzofuran-3-yl, benzothiophen-2-yl, and benzothiophen-3-yl, where each of these named rings may optionally be substituted one or more times with substituents independently selected from halogen, -NH_2, cyano, carboxy, C_{1-4}alkyl, C_{3-10} cycloalkyl, hydroxyl, thiol, -CF_3, -OCF_3, -O-C_{1-4}alkyl, -NH-C_{1-4}alkyl, -N(C_{1-4}alkyl)$_2$, -S-C_{1-4}alkyl, -S(O)$_2$-C_{1-4}alkyl, -C(O)-C_{1-4}alkyl, -C(O)O-C_{1-4}alkyl, -C(O)NH_2, -C(O)NH-C_{1-4}alkyl, -C(O)N(C_{1-4}alkyl)$_2$, and phenyl.

Embodiment 65: A compound according to any one of embodiments 1 to 64, wherein any "heteroarylene" group present in the compound is selected from the group consisting of: 1H-pyrrol-2,5-diyl, furan-2,5-diyl, thiophen-2,5-diyl,1H-imidazol-2,4-diyl, 1H-imidazol-2,5-diyl, oxazol-2,4-diyl, oxazol-2,5-diyl, thiazol-2,4-diyl, thiazol-2,5-diyl, 1H-1,2,4-triazol-3,5-diyl, and 2H-isoindol-

1,3-diyl, where each of these named rings may optionally be substituted one or more times with substituents independently selected from halogen, -NH_2, cyano, carboxy, -C_{1-4} alkyl, -C_{3-10} cycloalkyl, hydroxyl, thiol, -CF_3, -OCF_3, -O-C_{1-4} alkyl, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, -S-C_{1-4} alkyl, -S(O)$_2$-C_{1-4} alkyl, -C(O)-C_{1-4} alkyl, -C(O)O-C_{1-4} alkyl, -C(O)NH_2, -C(O)NH-C_{1-4} alkyl, -C(O)N(C_{1-4} alkyl)$_2$, and phenyl.

Embodiment 66: A compound according to embodiment 1.

Embodiment 67: A compound according to embodiment 66, wherein R^3 is hydrogen.

Embodiment 68: A compound according to embodiment 66, wherein R^3 is methyl.

Embodiment 69: A compound according to embodiment 66, wherein R^3 is ethyl.

Embodiment 70: A compound according to embodiment 66, wherein R^3 is isopropyl.

Embodiment 71: A compound according to any one of embodiment 66 to 70, wherein X^1 is =N-.

Embodiment 72: A compound according to any one of embodiments 66 to 70, wherein X^1 is =CH-.

Embodiment 73: A compound according to any one of embodiments 66 to 72, wherein v is 0, 1 or 2.

Embodiment 74: A compound according to any one of embodiments 66 to 72, wherein v is 1 or 2.

Embodiment 75: A compound according to any one of embodiments 66 to 72, wherein v is 1.

Embodiment 76: A compound according to any one of embodiments 66 to 72, wherein v is 1, and R^2 is attached at either the 5-position or the 6-position of the benzothiazole ring.

Embodiment 77: A compound according to any one of embodiments 66 to 72, wherein v is 1, and R^2 is attached at the 6-position of the benzothiazole ring.

Embodiment 78: A compound according to any one of embodiments 66 to 72, wherein v is 2, and one R^2 is attached at the 6-position of the benzothiazole ring.

Embodiment 79: A compound according to any one of embodiments 66 to 72, wherein v is 2, and R^2 is attached at the 5-position and the 6-position of the benzothiazole ring.

Embodiment 80: A compound according to any one of embodiments 66 to 79, wherein R^2 is -halogen, -$C_{1\text{-}6}$ alkyl, -CF_3, -OCF_3, -O-R^f, or –$S(O)_w$-R^f, where the alkyl group is optionally substituted one or more times with substituents independently selected from R^z.

Embodiment 81: A compound according to any one of embodiments 66 to 79, wherein R^2 is -halogen, -methyl, ethyl, isopropyl, -OCH_3, -OCH_2CH_3, -$OCH(CH_3)_2$, -CF_3, -OCF_3, -SCF_3, -$S(O)_2$-CH_3, -O-phenyl, -O-(2-pyridyl), -O-(3-pyridyl), or -O-(4-pyridyl).

Embodiment 82: A compound according to any one of embodiments 66 to 79, wherein R^2 is -halogen, -methyl, ethyl, isopropyl, -OCH_3, -OCH_2CH_3, -$OCH(CH_3)_2$, -CF_3, -OCF_3, -SCF_3, -$S(O)_2$-CH_3, or -O-(3-pyridyl).

Embodiment 83: A compound according to any one of embodiments 66 to 79, wherein R^2 is -Cl, -F, -CF_3, or -OCF_3.

Embodiment 84: A compound according to any one of embodiments 66 to 79, wherein R^2 is -OCF_3.

Embodiment 85: A compound according to any one of embodiments 66 to 79, wherein R^2 is -CF_3.

Embodiment 86: A compound according to any one of embodiments 66 to 79, wherein R^2 is -F.

Embodiment 87: A compound according to any one of embodiments 66 to 79, wherein R^2 is -Cl.

Embodiment 88: A compound according to any one of embodiments 66 to 79, wherein R^2 is -SO_2CH_3.

Embodiment 89: A compound according to any one of embodiments 66 to 79, wherein R^2 is methyl, ethyl, or isopropyl.

Embodiment 90: A compound according to any one of embodiments 66 to 79, wherein R^2 is methyl.

Embodiment 91: A compound according to any one of embodiments 66 to 79, wherein R^2 is $-OCH_2CH_3$.

Embodiment 92: A compound according to any one of embodiments 66 to 79, wherein R^2 is -O-phenyl.

Embodiment 93: A compound according to any one of embodiments 66 to 79, wherein R^2 is -O-(2-pyridyl), -O-(3-pyridyl), or -O-(4-pyridyl).

Embodiment 94: A compound according to any one of embodiments 66 to 79, wherein R^2 is -O-(3-pyridyl).

Embodiment 95: A compound according to any one of embodiments 66 to 94, wherein

R^4 is -methyl, -ethyl, -n-propyl, -isopropyl, -n-butyl, -sec-butyl, -isobutyl, -tert-butyl, $-(CH_2)_{1-2}-OCH_3$, $-(CH_2)_{1-2}-F$, $-(CH_2)_{1-2}-Cl$, $-(CH_2)_{1-2}-OCF_3$, $-(CH_2)_{1-2}-NH_2$, $-(CH_2)_{1-2}-CN$, $-(CH_2)_{1-2}-OH$, $-(CH_2)_{1-2}-CF_3$, $-(CH_2)_{1-2}-CO_2H$, $-(CH_2)_{1-2}-SH$, $-(CH_2)_{1-2}-SCH_3$, $-(CH_2)_{1-2}-S(O)_2CH_3$, $-(CH_2)_{1-2}-OCH_2CH_3$, $-(CH_2)_{1-2}-SCH_2CH_3$, $-(CH_2)_{1-2}-S(O)_2CH_2CH_3$, $-(CH_2)_{1-2}-NH-CH_3$, or $-(CH_2)_{1-2}-N(CH_3)_2$.

Embodiment 96: A compound according to any one of embodiments66 to 94, wherein R^4 is -methyl, -ethyl, -isopropyl, -isobutyl, $-CH_2CH_2-OCH_3$, $-CH_2CH_2-F$, $-CH_2CH_2-NH_2$, or $-CH_2CH_2-NH-CH_3$.

Embodiment 97: A compound according to any one of embodiments66 to 94, wherein R^4 is -methyl, -ethyl, -isopropyl, or -isobutyl.

Embodiment 98: A compound according to any one of embodiments 66 to 94, wherein R^4 is methyl.

Embodiment 99: A compound according to any one of embodiments 66 to 94, wherein R^4 is -ethyl.

Embodiment 100: A compound according to any one of embodiments 66 to 94, wherein R^4 is -isopropyl.

Embodiment 101: A compound according to any one of embodiments 66 to 94, wherein R^4 is -isobutyl.

Embodiment 102: A compound according to any one of embodiments 66 to 94, wherein R^4 is $-CH_2CH_2-OCH_3$.

Embodiment 103: A compound according to any one of embodiments 66 to 94, wherein R^4 is $-CH_2CH_2-F$.

Embodiment 104: A compound according to any one of embodiments 66 to 94, wherein R^4 is $-CH_2CH_2-NH_2$.

Embodiment 105: A compound according to any one of embodiments 66 to 94, wherein R^4 is $-CH_2CH_2-NH-CH_3$.

Embodiment 106: A compound according to any one of embodiments 66 to 105, wherein

R^1 is hydrogen, $-OCH_3$, -F, -Cl, $-NH_2$, -cyano, -OH, $-CF_3$, $-OCF_3$, -SH, $-S-C_{1-6}$ alkyl, $-S(O)_2-C_{1-6}$ alkyl, $-CO_2H$, $-NH-C_{1-6}$ alkyl, $-N(C_{1-6}\text{ alkyl})_2$, or $-NH-C_{1-6}$ alkyl.

Embodiment 107: A compound according to any one of embodiments 66 to 105, wherein

R^1 is $-OCH_3$, -F, $-CF_3$, $-OCF_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, or $-N(CH_3)(CH_2CH_3)$.

Embodiment 108: A compound according to any one of embodiments 66 to 105, wherein R^1 is hydrogen, $-OCH_3$, or -F.

Embodiment 109: A compound according to any one of embodiments 66 to 105, wherein R^1 is hydrogen.

Embodiment 110: A compound according to any one of embodiments 66 to 105, wherein R^1 is -F.

Embodiment 111: A compound according to any one of embodiments 66 to 105, wherein R^1 is $-OCH_3$.

Embodiment 112: A compound according to any one of embodiments 66 to 105 wherein R^1 is $-N(CH_2CH_3)_2$.

Embodiment 113: A compound according to any one of embodiments 66 to 112, wherein

G is hydrogen, -C_{1-8} alkyl, -C_{3-10} cycloalkyl, -C_{1-6} alkylene-C_{3-10} cycloaklyl, heterocyclyl, -C_{1-6} alkylene-C_{3-10} heterocyclyl, or NR^hR^k, where the alkyl, alkylene, cycloalkyl, and heterocyclyl groups are optionally substituted one or more times with substituents independently selected from R^c; or G is -CH_2Y^3, -$CH_2CH_2Y^3$, -$CH_2CH_2CH_2Y^3$, -$CH(CH_3)CH_2Y^3$, -$CH_2CH(Y^3)CH_3$, -$CH(Y^3)CH_3$, -$CH_2C(Y^3)(CH_3)_2$, -$C(Y^3)(CH_3)_2$, or  , where Y^3 is cyclopropyl, -CF_3, -OCF_3, -OCH_3, -OCH_2CH_3, -F, -Cl, -OH, -$O(CH_2)_2$-OH, -$O(CH_2)_2$-F, -SCH_3, -$S(O)_2$-CH_3, -SCH_2CH_3, -$S(O)_2CH_2CH_3$, -NH-CH_3, -NH-CH_2CH_3, -$N(CH_3)_2$, tetrahydropyran-4-yl, tetrahydrofuran-2-yl, morpholin-2-yl, morpholin-4-yl, piperidin-1-yl, 4-hydroxy-piperidin-1-yl, 3-hydroxy-piperidin-1-yl, -NH-C(O)-CH_3, -NH-C(O)-CH_2CH_3, tetrahydrofuran-2-yl-methyloxy, or -C(O)-Y^4, where Y^4 is -OH, -OCH_3, -OCH_2CH_3, -$OC(CH_3)_3$, -NH_2, -NH-CH_3, -NH-CH_2CH_3, -$N(CH_3)_2$, -$N(CH_2CH_3)_2$, morpholin-4-yl, 4-methyl-piperazin-1-yl, pyrrolidin-1-yl, or piperazin-1-yl;

L is -CH_2-C(O)$N(R^6)$-, -C(O)$N(R^6)$-, -C(O)-O-, -SO_2-, -C(O)-, or heterocyclylene optionally substituted one or more times with substituents independently selected from R^x; or the group -L-G is -cyano;

R^1 is hydrogen or R^a;

R^c is

a) -halogen,

b) -C_{1-6} alkyl,

c) -C_{3-10} cycloalkyl,

d) -heterocyclyl,

e) -cyano,

f) -CF_3,

g) -OCF_3,

h) -O-R^h,

i) -$S(O)_w$-R^h,

j) -$S(O)_2O$-R^h,

k) $-NR^hR^k$,

l) $-C(O)-R^h$,

m) $-C(O)-O-R^h$,

n) $-OC(O)-R^h$,

o) $-C(O)NR^h R^k$,

p) -C(O)-heterocyclyl,

q) $-NR^h C(O)R^k$,

r) $-OC(O)NR^h R^k$,

s) $-NR^hC(O)OR^k$,

t) $-NR^hC(O)NR^h R^k$,

u) $-NR^hS(O)_wR^k$, or

v) $-O-(C_{1-4}$ alkylene)$-O-(C_{1-4}$ alkylene)$-N(R^h)C(O)-OR^k$,

where the alkylene, alkyl, cycloalkyl, and heterocyclyl groups are optionally substituted one or more times with substituents independently selected from R^x;

R^h and R^k independently are hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, or heterocyclyl, where the alkyl, cycloalkyl, and heterocyclyl groups are optionally substituted one or more times with substituents independently selected from R^x; or, if R^h and R^k are both attached to the same nitrogen atom, together with that nitrogen atom may optionally form a heterocyclic ring selected from azetidino, pyrrolidino, pyrazolidino, imidazolidino, oxazolidino, isoxazolidino, thiazolidino, isothiazolidino, piperidino, piperazino, morpholino, thiomorpholino, and azepano, where each ring is optionally substituted one or more times with substituents independently selected from R^x; and

R^x is R^y.

Embodiment 114: A compound according to any one of embodiments 66 to 112, wherein -L-G is not -cyano.

Embodiment 115: A compound according to any one of embodiments 66 to 112, wherein L is $-C(O)N(R^6)-$.

Embodiment 116: A compound according to embodiment 115 wherein

R^6 is hydrogen.

Embodiment 117: A compound according to embodiment 115 wherein

R^6 is methyl.

Embodiment 118: A compound according to embodiment 117 wherein

G is $-N(CH_3)_2$.

Embodiment 119: A compound according to any one of embodiments 66 to 112, wherein -L-G is $-C(O)NR^h R^k$.

Embodiment 120: A compound according to embodiment 119, wherein

$NR^h R^k$ is pyrrolidino, piperidino, piperazino, 4-methyl-piperazino, or morpholino, where each of the foregoing is optionally substituted once with $-(CH_2)_{1-3}-OH$.

Embodiment 121: A compound according to embodiment 120, wherein

$NR^h R^k$ is pyrrolidino, 4-(2-hydroxyethyl)-piperazino, or 4-(3-hydroxypropyl)-piperidino.

Embodiment 122: A compound according to embodiment 119, wherein

$NR^h R^k$ is $N[(CH_2)_2-OH]_2$.

Embodiment 123: A compound according to any one of embodiments 66 to 114, wherein L is not $-CH_2-C(O)N(R^6)-$.

Embodiment 124: A compound according to any one of embodiments 66 to 123, wherein L is not heterocyclylene.

Embodiment 125: A compound according to any one of embodiments 66 to 112, wherein L is $-S(O)_2-$.

Embodiment 126: A compound according to embodiment 125, wherein

G is methyl or $-CF_3$.

Embodiment 127: A compound according to any one of embodiments 66 to 112, wherein

L is heteroarylene optionally substituted one or more times with substituents independently selected from R^x.

Embodiment 128: A compound according to embodiment 127, wherein

-L-G is imidazol-2-yl, 1,2,4-triazol-3-yl, or 5-methyl-1,2,4-triazol-3-yl.

Embodiment 129: A compound according to any one of embodiments 66 to 112, wherein L is -C(O)-O-.

Embodiment 130: A compound according to embodiment 129, wherein

G is hydrogen, or -C_{1-8} alkyl, where the alkyl group is optionally substituted one or more times with substituents independently selected from R^c.

Embodiment 131: A compound according to embodiment 130, wherein

G is methyl or ethyl.

Embodiment 132: A compound according to embodiment 130, wherein

G is hydrogen.

Embodiment 133: A compound according to any one of embodiments 66 to 116, wherein

G is -C_{1-8} alkyl, -C_{3-10} cycloalkyl, -C_{1-6} alkylene-C_{3-10} cycloaklyl, heterocyclyl, or -C_{1-6} alkylene-C_{3-10} heterocyclyl, where the alkyl, alkylene, cycloalkyl, and heterocyclyl groups are optionally substituted one or more times with substituents independently selected from R^c.

Embodiment 134: A compound according to embodiment 133, wherein

G is -C_{1-8} alkyl optionally substituted one or more times with substituents independently selected from R^c.

Embodiment 135: A compound according to embodiment 134, wherein

G is methyl, ethyl, isopropyl, n-propyl, n-butyl, sec-butyl, or isobutyl.

Embodiment 136: A compound according to embodiment 134, wherein

G is methyl, ethyl, or n-propyl.

Embodiment 137: A compound according to embodiment 134, wherein

G is 2-fluoroethyl, 2,2-difluoroethyl, or 2,2,2-trifluoroethyl.

Embodiment 138: A compound according to embodiment 134, wherein

G is 2-cyanoethyl.

Embodiment 139: A compound according to embodiment 134, wherein

G is -C_{1-8} alkyl substituted once by -C(O)-O-R^h.

Embodiment 140: A compound according to embodiment 139, wherein

G is -CH_2-C(O)-O-R^h.

Embodiment 141: A compound according to embodiment 140, wherein R^h is hydrogen or methyl.

Embodiment 142: A compound according to embodiment 139, wherein G is -CH_2CH_2-C(O)-O-R^h.

Embodiment 143: A compound according to embodiment 142, wherein R^h is hydrogen or methyl.

Embodiment 144: A compound according to embodiment 139, wherein G is -$C(CH_3)_2$-C(O)-O-R^h.

Embodiment 145: A compound according to embodiment 144, wherein R^h is hydrogen or methyl.

Embodiment 146: A compound according to embodiment 139, wherein G is -$CH(CH_3)$-C(O)-O-R^h.

Embodiment 147: A compound according to embodiment 146, wherein R^h is hydrogen or methyl.

Embodiment 148: A compound according to embodiment 134, wherein G is -$C_{1\text{-}8}$ alkyl substituted once by -C(O)$NR^h R^k$.

Embodiment 149: A compound according to embodiment 148, wherein G is CH_2-C(O)-$NR^h R^k$.

Embodiment 150: A compound according to embodiment 149, wherein $NR^h R^k$ is methylamino, dimethylamino, or diethylamino.

Embodiment 151: A compound according to embodiment 149, wherein $NR^h R^k$ is thiomorpholino or 1,1-dioxothiomorpholino.

Embodiment 152: A compound according to embodiment 149, wherein $NR^h R^k$ is morpholino, pyrrolidino, piperidino, piperazino, or 4-methylpiperazino.

Embodiment 153: A compound according to embodiment 149, wherein $NR^h R^k$ is pyrrolidino, 3-hydroxy-pyrrolidino, 3-methoxy-pyrrolidino, 3-amino-pyrrolidino, 3-(methylamino)-pyrrolidino, 3-(dimethylamino)-pyrrolidino, 2-(hydroxymethyl)-pyrrolidino, 2-(dimethylaminocarbonyl)-pyrrolidino or 3,4-dihydroxy-pyrrolidino.

Embodiment 154: A compound according to embodiment 149, wherein

NR^hR^k is piperazino, 4-methylpiperazino, 4-(methylsulfonyl)-piperazino, or 4-(dimethylaminosulfonyl)-piperazino.

Embodiment 155: A compound according to embodiment 149, wherein

NR^hR^k is piperidino, 3-hydroxypiperidino, 4-hydroxypiperidino, 2-(hydroxymethyl)-piperidino, 3-(hydroxymethyl)-piperidino, 4-(hydroxymethyl)-piperidino, 3-methoxy-piperidino, 4-(methoxymethyl)-piperidino, 4-(fluoromethyl)-piperidino, 4-(trifluoromethyl)-piperidino, 4-cyano-piperidino, 4-carbamoyl-piperidino, 4-(methylamino)-piperidino, 4-(dimethylamino)-piperidino, 4-(methylaminomethyl)-piperidino, or 4-(dimethylaminomethyl)-piperidino.

Embodiment 156: A compound according to embodiment 149, wherein

NR^hR^k is NHR^k, where R^k is 2-hydroxypropyl, 2-(methylsulfonyl)-ethyl, tetrahydrofuran-3-yl, tetrahydropyran-4-yl, 1-methylpiperidin-4-yl, piperidin-3-yl, or 1-methylpiperidin-3-yl.

Embodiment 157: A compound according to embodiment 149, wherein

NR^hR^k is $N(CH_3)R^k$, where R^k is 2-hydroxyethyl, tetrahydropyran-4-yl, pyrrolidin-3-yl, 1-methylpyrrolidin-3-yl, or piperazin-3-yl.

Embodiment 158: A compound according to embodiment 149, wherein

NR^hR^k is $N(CH_2CH_2OH)_2$.

Embodiment 159: A compound according to embodiment 148, wherein

G is $-(CH_2)_{2\text{-}3}-C(O)-N(CH_3)_2$.

Embodiment 160: A compound according to embodiment 148, wherein

G is $-(CH_2)_3-C(O)-$(4-methylpiperazino).

Embodiment 161: A compound according to embodiment 148, wherein

G is $-CH(CH_3)-C(O)-NR^hR^k$, where NR^hR^k is methylamino, dimethylamino, 4-methylpiperazino, or morpholino.

Embodiment 162: A compound according to embodiment 148, wherein

G is $-C(CH_3)_2-C(O)-N(CH_3)_2$.

Embodiment 163: A compound according to embodiment 134, wherein

G is -CH-[C(O)-N(CH_3)$_2$]-[CH_2OH], -CH-[C(O)-N(CH_3)$_2$]-[(CH_2)$_4$-NH_2], or -CH-[C(O)-N(CH_3)$_2$]-[(CH_2)$_4$-N(CH_3)$_2$].

Embodiment 164: A compound according to embodiment 134, wherein

G is -C_{1-8} alkyl substituted once by -O-R^h.

Embodiment 165: A compound according to embodiment 164, wherein

G is -(CH_2)$_2$-O-R^h.

Embodiment 166: A compound according to embodiment 165, wherein

R^h is hydrogen, methyl, or ethyl.

Embodiment 167: A compound according to embodiment 165, wherein

R^h is trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, or 2,2-difluoroethyl.

Embodiment 168: A compound according to embodiment 165, wherein

R^h is tetrahydrofuran-2-ylmethyl.

Embodiment 169: A compound according to embodiment 165, wherein

R^h is 2-hydroxyethyl.

Embodiment 170: A compound according to embodiment 165, wherein

R^h is 3-hydroxypropyl.

Embodiment 171: A compound according to embodiment 165, wherein

R^h is 2-methoxyethyl.

Embodiment 172: A compound according to embodiment 165, wherein

R^h is 2-(2-hydroxyethoxy)-ethyl.

Embodiment 173: A compound according to embodiment 165, wherein

R^h is 2-hydroxypropyl or 1-hydroxyprop-2-yl.

Embodiment 174: A compound according to embodiment 165, wherein

R^h is 2-cyanoethyl, 2-(methylcarbonylamino)-ethyl, or 2-(methylsulfonylamino)-ethyl.

Embodiment 175: A compound according to embodiment 165, wherein

R^h is 2-aminoethyl, 2-(methylamino)-ethyl, or 2-(dimethylamino)-ethyl.

Embodiment 176: A compound according to embodiment 165, wherein

R^h is carbamoylmethyl.

Embodiment 177: A compound according to embodiment 164, wherein

G is -$(CH_2)_3$-O-R^h.

Embodiment 178: A compound according to embodiment 177, wherein

R^h is hydrogen, methyl, or ethyl.

Embodiment 179: A compound according to embodiment 177, wherein

R^h is 2-hydroxyethyl.

Embodiment 180: A compound according to embodiment 164, wherein

G is -$(CH2)_4$-OH, -$(CH2)_5$-OH, -$CH_2C(CH_3)_2$-OH, -$CH_2C(CH_3)_2$-OCH_3, -$CH_2C(CH_3)_2$-CH_2-OH, -$CH(CH_3)$-CH_2-OCH_3, -$(CH_2)_3C(CH_3)_2$-CH_2-OH, -$(CH_2)_2CH(CH_3)$-CH_2-OH, or -$(CH_2)_2CH(CH_3)$-OH.

Embodiment 181: A compound according to embodiment 164, wherein

G is -$CH_2CH(CH_3)$-O-R^h.

Embodiment 182: A compound according to embodiment 181, wherein

R^h is hydrogen, methyl, or ethyl.

Embodiment 183: A compound according to embodiment 134, wherein

G is -CH_2-CH(OH)-CH_2-OH.

Embodiment 184: A compound according to embodiment 134, wherein

G is -$C_{1\text{-}8}$ alkyl substituted once by -NR^hR^k.

Embodiment 185: A compound according to embodiment 184, wherein

G is -$(CH_2)_2$-NR^hR^k.

Embodiment 186: A compound according to embodiment 185, wherein

NR^hR^k is amino, methylamino, or dimethylamino.

Embodiment 187: A compound according to embodiment 185, wherein

NR^hR^k is methylcarbonylamino.

Embodiment 188: A compound according to embodiment 185, wherein

NR^hR^k is (dimethylamino)methylcarbonylamino, hydroxymethylcarbonylamino, or 1-hydroxyethylcarbonylamino.

Embodiment 189: A compound according to embodiment 185, wherein

NR^hR^k is methylsulfonylamino.

Embodiment 190: A compound according to embodiment 185, wherein

NR^hR^k is piperidino, 4-hydroxypiperidino, or 3-hydroxypiperidino.

Embodiment 191: A compound according to embodiment 185, wherein NR^hR^k is piperidino, 4,4-difluoropiperidino, or 3,3-difluoropiperidino.

Embodiment 192: A compound according to embodiment 185, wherein NR^hR^k is 2-oxo-pyrrolidino, 2-oxo-imidazolidino, or 3-oxo-piperazino.

Embodiment 193: A compound according to embodiment 185, wherein NR^hR^k is piperazino, 4-methylpiperazino, morpholino, or 1,1-dioxo-thiomorpholino.

Embodiment 194: A compound according to embodiment 184, wherein G is $-(CH_2)_3-NR^hR^k$.

Embodiment 195: A compound according to embodiment 194, wherein NR^hR^k is amino, dimethylamino, or diethylamino.

Embodiment 196: A compound according to embodiment 194, wherein NR^hR^k is piperidino, 4-methylpiperazino, or morpholino.

Embodiment 197: A compound according to embodiment 184, wherein G is $-(CH_2)_4-NR^hR^k$.

Embodiment 198: A compound according to embodiment 197, wherein NR^hR^k is amino, dimethylamino, or diethylamino.

Embodiment 199: A compound according to embodiment 133, wherein G is $-C_{1-6}$ alkylene-heterocyclyl, where the alkylene and heterocyclyl groups are optionally substituted one or more times with substituents independently selected from R^c.

Embodiment 200: A compound according to embodiment 199, wherein G is $-CH_2$-heterocyclyl, where the heterocyclyl group is optionally substituted once with a substituent selected from R^c.

Embodiment 201: A compound according to embodiment 200, wherein the heterocyclyl group is tetrahydropyran-4-yl, tetrahydrofuran-2-yl, 1,4-dioxan-2-yl, morpholin-2-yl, tetrahydropyran-2-yl, piperidin-4-yl, 1-(2-hydroxyethyl)-piperidin-4-yl, 1-(dimethylaminomethylcarbonyl)-piperidin-4-yl, piperazin-2-yl, or 1-methyl-piperazin-2-yl.

Embodiment 202: A compound according to embodiment 133, wherein

G is C_{3-10} cycloalkyl optionally substituted one or more times with substituents independently selected from R^c.

Embodiment 203: A compound according to embodiment 202, wherein

G is 4-hydroxy-cyclohexyl, 4-carboxy-cyclohexyl, or 4-(dimethylaminocarbonyl)-cyclohexyl.

Embodiment 204: A compound according to embodiment 202, wherein

G is 1-carboxy-cyclopropyl, 1-(ethoxycarbonyl)-cyclopropyl, or 1-(dimethylamino-carbonyl)-cyclopropyl.

Embodiment 205: A compound according to embodiment 133, wherein

G is C_{1-6} alkylene-C_{3-10} cycloalkyl, where the alkylene and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^c.

Embodiment 206: A compound according to embodiment 205, wherein

G is -CH_2-(4-hydroxy-cyclohexyl).

Embodiment 207: A compound according to embodiment 205, wherein

G is -$(CH_2)_2$-(4-hydroxy-cyclohexyl).

Embodiment 208: A compound according to embodiment 205, wherein

G is -CH_2-[4-(hydroxymethyl)-cyclohexyl].

Embodiment 209: A compound according to embodiment 133, wherein

G is heterocyclyl optionally substituted one or more times with substituents independently selected from R^c.

Embodiment 210: A compound according to embodiment 209, wherein

G is piperidin-4-yl, 1-methyl-piperidin-4-yl, 1-carboxy-piperidin-4-yl, 1-(methylsulfonyl)-piperidin-4-yl, 1-(2-hydroxyethyl)-piperidin-4-yl, 1-(dimethyl-aminocarbonyl)piperidin-4-yl, or 1-(dimethylaminomethylcarbonyl)-piperidin-4-yl.

Embodiment 211: A compound according to embodiment 209, wherein

G is piperidin-3-yl or 1-(dimethylaminomethylcarbonyl)-piperidin-3-yl.

Embodiment 212: A compound according to embodiment 209, wherein

G is 1,1-dioxo-tetrahydrothiophen-3-yl.

Embodiment 213: A compound according to embodiment 209, wherein

G is pyrrolidin-3-yl, 1-methyl-pyrrolidin-3-yl, 1-(2-hydroxyethyl)-pyrrolidin-3-yl, 1-(2-hydroxypropyl)-pyrrolidin-3-yl, 1-(2-hydroxy-2-methylpropyl)-pyrrolidin-3-yl, 1-(1-hydroxyethylcarbonyl)-pyrrolidin-3-yl, 1-(2-carboxyethyl)-pyrrolidin-3-yl, or 1-(2-methylsulfonylamino-ethyl)-pyrrolidin-3-yl.

Embodiment 214: A compound according to embodiment 134, wherein

G is -C_{1-8} alkyl substituted once by -S-R^h.

Embodiment 215: A compound according to embodiment 214, wherein

G is -$(CH_2)_2$-S-R^h.

Embodiment 216: A compound according to embodiment 215, wherein

R^h is methyl or ethyl.

Embodiment 217: A compound according to embodiment 215, wherein

R^h is 2-hydroxyethyl.

Embodiment 218: A compound according to embodiment 214, wherein

G is -$(CH_2)_3$-S-R^h.

Embodiment 219: A compound according to embodiment 218, wherein

R^h is methyl.

Embodiment 220: A compound according to embodiment 134, wherein

G is -C_{1-8} alkyl substituted once by -SO_2-R^h.

Embodiment 221: A compound according to embodiment 220, wherein

G is -$(CH_2)_2$-SO_2-R^h.

Embodiment 222: A compound according to embodiment 221, wherein

R^h is methyl or ethyl.

Embodiment 223: A compound according to embodiment 221, wherein

R^h is 2-hydroxyethyl.

Embodiment 224: A compound according to embodiment 220, wherein

G is -$(CH_2)_3$-SO_2-R^h.

Embodiment 225: A compound according to embodiment 224, wherein

R^h is methyl.

Embodiment 226: A compound according to embodiment 133 wherein

G is -CH(CH_3)-NR^hR^k, where NR^hR^k is pyrrolidino, piperidino, 4-methyl-piperazino, morpholino, or dimethylamino.

Embodiment 227: A compound according to embodiment 133 wherein

G is 1-(2-hydroxypropyl)-pyrrolodin-3-yl or 1-(1-hydroxyethylcarbonyl)-pyrrolidin-3-yl.

Embodiment 228: A compound according to embodiment 133 wherein

G is 1-(dimethylaminomethylcarbonyl)-piperidin-4-yl.

Embodiment 229: A compound according to embodiment 133 wherein

G is -$(CH_2)_{3-5}$-OH.

Embodiment 230: A compound according to embodiment 133 wherein

G is 4-hydroxy-cyclohexylmethyl.

Embodiment 231: A compound according to embodiment 133 wherein

G is -$(CH_2)_2$-NHC(O)-CH_2-$N(CH_3)_2$.

Embodiment 232: A compound according to embodiment 133 wherein

G is 4-hydroxy-cyclohexylmethyl.

Embodiment 233: A compound according to embodiment 133 wherein

G is -CH_2-C(O)-NR^hR^k, where NR^hR^k is 3-hydroxy-pyrrolidino or 3-(dimethyl-amino)-pyrrolidino.

Embodiment 234: A compound according to embodiment 133 wherein

G is -CH_2-C(O)-NR^hR^k, where NR^hR^k is morpholino.

Embodiment 235: A compound according to embodiment 133 wherein

G is -CH_2-C(O)-NR^hR^k, where NR^hR^k is 4-hydroxy-piperidino, 4-methoxy-piperidino, 4-(hydroxymethyl)-piperidino, 3-hydroxy-piperidino, 3-methoxy-piperidino, 3-(hydroxymethyl)-piperidino, or 4,4-difluoropiperidino.

Embodiment 236: A compound according to embodiment 133 wherein

G is -CH_2-C(O)-NR^hR^k, where NR^hR^k is dimethylamino.

Embodiment 237: A compound according to embodiment 133 wherein

G is -$(CH_2)_2$-O-$(CH_2)_2$-OH.

Embodiment 238: A compound according to embodiment 133 wherein

G is -$(CH_2)_2$-O-$(CH_2)_2$-OCH_3.

Embodiment 239: A compound according to embodiment 133 wherein

G is -CH_2-CH(CH_3)-OH.

Embodiment 240: A compound according to any one of embodiments 66 to 112, wherein

L is C(O)NH, and G is C_{1-8} alkyl substituted once by a heteroaryl group, where the heteroaryl group is optionally substituted one or more times with substituents independently selected from R^x.

Embodiment 241: A compound according to embodiment 240, wherein

G is -CH_2-(2-furyl), -CH_2-(2-thienyl), -CH_2-(2-oxazolyl), or -CH_2-(2-thiazolyl).

Embodiment 242: A compound according to embodiment 240, wherein

G is -$(CH_2)_{2-3}$-(1-pyrrolyl), -$(CH_2)_{2-3}$-(1-pyrazolyl), or -$(CH_2)_{2-3}$-(1-imidazolyl).

Embodiment 243: A compound according to any one of embodiments 66 to 112, wherein

L is C(O)NH, and G is C_{1-8} alkyl substituted once by a phenyl group, where the phenyl group is optionally substituted one or more times with substituents independently selected from R^x.

Embodiment 244: A compound according to embodiment 243, wherein

G is -$(-CH_2)_{1-2}$-(4-hydroxyphenyl) or -$(-CH_2)_{1-2}$-(4-methoxy-3-hydroxyphenyl).

Embodiment 245: A compound according to any one of embodiments 66 to 112, wherein

L is C(O)NH, and G is -CH_2-C(O)NH-CH_2-(4-hydroxyphenyl).

Embodiment 246: A compound according to any one of embodiments 66 to 112, wherein

L is C(O)NH, and G is -CH_2-C(O)-[4-(pyrimidin-2-yloxy)-piperidino].

Embodiment 247: A compound according to any one of embodiments 1 to 246, wherein X^2 is =C(R^1)- and X^3 is =C(-L-G)-.

Embodiment 248: A compound according to any one of embodiments 1 to 247, wherein the compound is in the form of a free acid or a free base.

Embodiment 249: A compound according to any one of embodiments 1 to 247, wherein the compound is in the form of a pharmaceutically acceptable salt.

Embodiment 250: A compound according to embodiment 1, wherein the compound is a compound from Table A or a pharmaceutically acceptable salt thereof.

Table A.

No.	Name
1	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methyl amide
2	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methyl ester
3	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid
4	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-ethoxy-ethyl)-amide
5	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid cyclopropylmethyl-amide
6	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ethylamide
7	[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazol-5-yl]-pyrrolidin-1-yl-methanone
8	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide
9	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-fluoro-ethyl)-amide
10	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethyl)-amide

No.	Name
11	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (3-pyrazol-1-yl-propyl)-amide
12	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid propylamide
13	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (3-hydroxy-propyl)-amide
14	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (3-ethoxy-propyl)-amide
15	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid morpholin-4-ylamide
16	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2,2,2-trifluoro-ethyl)-amide
17	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide
18	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (tetrahydro-furan-2-ylmethyl)-amide
19	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (3-methoxy-propyl)-amide
20	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-1-methyl-ethyl)-amide
21	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-hydroxy-propyl)-amide
22	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-2-methyl-propyl)-amide
23	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methyl ester
24	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid

No.	Name
25	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide
26	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ethylamide
27	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethyl)-amide
28	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl ester
29	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid
30	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethyl)-amide
31	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide
32	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid ethylamide
33	2-(5,6-Difluoro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl ester
34	2-(5,6-Difluoro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid
35	2-(5,6-Difluoro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid ethylamide
36	2-(5,6-Difluoro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethyl)-amide
37	2-(5,6-Difluoro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide
38	3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-benzoimidazole-5-carboxylic acid methylamide

No.	Name
39	6-Fluoro-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide
40	6-Fluoro-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methyl ester
41	6-Fluoro-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid
42	6-Fluoro-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ethylamide
43	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-morpholin-4-yl-ethyl)-amide
44	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-trifluoromethoxy-ethyl)-amide
45	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-hydroxy-2-methyl-propyl)-amide
46	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-hydroxy-ethoxy)-ethyl]-amide
47	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-fluoro-ethoxy)-ethyl]-amide
48	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (furan-2-ylmethyl)-amide
49	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ([1,4]dioxan-2-ylmethyl)-amide
50	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((S)-2-hydroxy-propyl)-amide
51	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((R)-2-hydroxy-propyl)-amide
52	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (*trans*-4-hydroxy-cyclohexyl)-amide

No.	Name
53	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(tetrahydro-furan-2-ylmethoxy)-ethyl]-amide
54	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-ethoxy-propyl)-amide
55	2-({[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carbonyl]-amino}-methyl)-morpholine-4-carboxylic acid tert-butyl ester
56	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (morpholin-2-ylmethyl)-amide hydrochloride
57	6-Fluoro-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-ethoxy-ethyl)-amide
58	6-Fluoro-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide
59	6-Fluoro-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-morpholin-4-yl-ethyl)-amide
60	6-Fluoro-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-hydroxy-propyl)-amide
61	6-Methoxy-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methyl ester
62	6-Methoxy-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid
63	6-Methoxy-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid dimethylcarbamoyl-methyl-amide
64	6-Methoxy-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ethylamide

No.	Name
65	6-Methoxy-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-ethoxy-ethyl)-amide
66	6-Methoxy-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-morpholin-4-yl-ethyl)-amide
67	6-Methoxy-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide
68	6-Methoxy-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-hydroxy-propyl)-amide
69	6-Diethylamino-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methyl ester
70	6-Diethylamino-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid
71	3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid ethyl ester
72	3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid
73	3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (2-methoxy-ethyl)-amide
74	3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid dimethylcarbamoylmethyl-amide
75	3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (2-ethoxy-ethyl)-amide
76	3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid ethylamide
77	3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (2-morpholin-4-yl-ethyl)-amide
78	3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (2-hydroxy-propyl)-amide

No.	Name
79	{[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carbonyl]-amino}-acetic acid methyl ester
80	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide
81	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid ((S)-1-ethylcarbamoyl-ethyl)-amide
82	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid (2-dimethylamino-ethyl)-amide
83	{[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carbonyl]-amino}-acetic acid
84	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid methylamide
85	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid (2-ethoxy-ethyl)-amide
86	2-(5,6-Difluoro-benzothiazol-2-ylamino)-1-methyl-1*H*-benzoimidazole-5-carboxylic acid methylamide
87	2-(5,6-Difluoro-benzothiazol-2-ylamino)-1-methyl-1*H*-benzoimidazole-5-carboxylic acid (2-ethoxy-ethyl)-amide
88	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1*H*-benzoimidazole-5-carboxylic acid methylamide
89	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1*H*-benzoimidazole-5-carboxylic acid (2-ethoxy-ethyl)-amide
90	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid (1-methanesulfonyl-piperidin-4-yl)-amide
91	{[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carbonyl]-amino}-acetic acid *tert*-butyl ester

No.	Name
92	4-{[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carbonyl]-amino}-piperidine-1-carboxylic acid *tert*-butyl ester
93	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid piperidin-4-ylamide hydrochloride
94	3-{[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carbonyl]-amino}-piperidine-1-carboxylic acid *tert*-butyl ester
95	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid piperidin-3-ylamide hydrochloride
96	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid (thiazol-2-ylmethyl)-amide
97	3-{[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carbonyl]-amino}-propionic acid methyl ester
98	3-{[2-(6-Trifluoromethoxy-benzothiazol-2-ylamino)-1-methyl-1*H*-benzimidazole-5-carbonyl]-amino}-propionic acid
99	1-Methyl-2-(5-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid methyl ester
100	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid (2-acetylamino-ethyl)-amide
101	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid (2-methylsulfanyl-ethyl)-amide
102	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid (2-methanesulfonyl-ethyl)-amide
103	(2-{[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carbonyl]-amino}-ethyl)-carbamic acid *tert*-butyl ester
104	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid (2-amino-ethyl)-amide hydrochloride

No.	Name
105	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid (2-methylamino-ethyl)-amide
106	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid trimethylhydrazide
107	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid (2-ethylsulfanyl-ethyl)-amide
108	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid (3-methylsulfanyl-propyl)-amide
109	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid (2-ethanesulfonyl-ethyl)-amide
110	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid (3-methanesulfonyl-propyl)-amide
111	2-(5-Fluoro-benzothiazol-2-ylamino)-1-methyl-1*H*-benzoimidazole-5-carboxylic acid methyl ester
112	2-(6-Fluoro-benzothiazol-2-ylamino)-1-methyl-1*H*-benzoimidazole-5-carboxylic acid methyl ester
113	2-(6-Methanesulfonyl-benzothiazol-2-ylamino)-1-methyl-1*H*-benzoimidazole-5-carboxylic acid methyl ester
114	1-Methyl-2-(6-methyl-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid methyl ester
115	1-Methyl-2-(5-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid methylamide
116	1-Methyl-2-(5-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide
117	2-(5-Fluoro-benzothiazol-2-ylamino)-1-methyl-1*H*-benzimidazole-5-carboxylic acid
118	2-(6-Fluoro-benzothiazol-2-ylamino)-1-methyl-1*H*-benzimidazole-5-carboxylic acid

No.	Name
119	2-(6-Methanesulfonyl-benzothiazol-2-ylamino)-1-methyl-1*H*-benzimidazole-5-carboxylic acid
120	1-Methyl-2-(6-methyl-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid
121	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid (1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl)-amide
122	2-(5-Fluoro-benzothiazol-2-ylamino)-1-methyl-1*H*-benzimidazole-5-carboxylic acid methylamide
123	2-(5-Fluoro-benzothiazol-2-ylamino)-1-methyl-1*H*-benzimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide
124	2-(6-Fluoro-benzothiazol-2-ylamino)-1-methyl-1*H*-benzimidazole-5-carboxylic acid methylamide
125	2-(6-Fluoro-benzothiazol-2-ylamino)-1-methyl-1*H*-benzimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide
126	2-(6-Methanesulfonyl-benzothiazol-2-ylamino)-1-methyl-1*H*-benzimidazole-5-carboxylic acid methylamide
127	2-(6-Methanesulfonyl-benzothiazol-2-ylamino)-1-methyl-1*H*-benzimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide
128	2-(6-Methyl-benzothiazol-2-ylamino)-1-methyl-1*H*-benzimidazole-5-carboxylic acid methylamide
129	2-(6-Methyl-benzothiazol-2-ylamino)-1-methyl-1*H*-benzimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide
130	2-(6-Methanesulfonyl-benzothiazol-2-ylamino)-1-methyl-1*H*-benzimidazole-5-carboxylic acid (2-methylsulfanyl-ethyl)-amide
131	2-(6-Methanesulfonyl-benzothiazol-2-ylamino)-1-methyl-1*H*-benzimidazole-5-carboxylic acid (2-methylsulfonyl-ethyl)-amide

No.	Name
132	1-Methyl-2-(6-trifluoromethylsulfanyl-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carboxylic acid methyl ester
133	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1*H*-benzimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide
134	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide
135	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid (2-dimethylcarbamoyl-ethyl)-amide
136	3-{[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carbonyl]-amino}-propionic acid *tert*-butyl ester
137	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid [2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide
138	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid (2-morpholin-4-yl-2-oxo-ethyl)-amide
139	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid methylcarbamoylmethyl-amide
140	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid diethylcarbamoylmethyl-amide
141	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid (2-oxo-2-pyrrolidin-1-yl-ethyl)-amide
142	4-(2-{[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carbonyl]-amino}-acetyl)-piperazine-1-carboxylic acid *tert*-butyl ester
143	(S)-2-{[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carbonyl]-amino}-propionic acid methyl ester
144	1-{[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carbonyl]-amino}-cyclopropanecarboxylic acid ethyl ester

No.	Name
145	2-Methyl-2-{[1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carbonyl]-amino}-propionic acid methyl ester
146	(S)-2-{[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carbonyl]-amino}-propionic acid
147	1-{[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carbonyl]-amino}-cyclopropanecarboxylic acid
148	2-Methyl-2-{[1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carbonyl]-amino}-propionic acid
149	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((S)-1-dimethylcarbamoyl-ethyl)-amide
150	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid (1-dimethylcarbamoyl-cyclopropyl)-amide
151	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid (1-dimethylcarbamoyl-1-methyl-ethyl)-amide
152	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzimidazole-5-carboxylic acid (2-oxo-2-piperazin-1-yl-ethyl)-amide hydrochloride
153	1-Ethyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methyl ester
154	1-Ethyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid
155	1-Ethyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methylamide
156	1-Ethyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ethylamide
157	1-Ethyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-ethoxy-ethyl)-amide

No.	Name
158	1-Isopropyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H benzoimidazole-5-carboxylic acid methyl ester
159	1-Isopropyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid
160	1-Isopropyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methylamide
161	1-Isopropyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ethylamide
162	1-Isobutyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methyl ester
163	1-Isobutyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid
164	1-Isobutyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methylamide
165	1-Isobutyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ethylamide
166	1-(2-Methoxy-ethyl)-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid
167	1-(2-Methoxy-ethyl)-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methylamide
168	1-(2-Methoxy-ethyl)-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide
169	1-(2-Methoxy-ethyl)-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-ethoxy-ethyl)-amide
170	1-(2-Fluoro-ethyl)-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methylamide
171	1-(2-Fluoro-ethyl)-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide

No.	Name
172	1-(2-Fluoro-ethyl)-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-ethoxy-ethyl)-amide
173	1-(2-Amino-ethyl)-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methylamide hydrochloride
174	2-(6-Chloro-benzothiazol-2-ylamino)-1-ethyl-1H-benzoimidazole-5-carboxylic acid methylamide
175	2-(6-Chloro-benzothiazol-2-ylamino)-1-ethyl-1H-benzoimidazole-5-carboxylic acid ethylamide
176	2-(6-Chloro-benzothiazol-2-ylamino)-1-ethyl-1H-benzoimidazole-5-carboxylic acid (2-fluoro-ethyl)-amide
177	2-(6-Chloro-benzothiazol-2-ylamino)-1-ethyl-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide
178	2-(6-Chloro-benzothiazol-2-ylamino)-1-ethyl-1H-benzoimidazole-5-carboxylic acid (2-methoxy-2-methyl-propyl)-amide
179	2-(6-Chloro-benzothiazol-2-ylamino)-1-ethyl-1H-benzoimidazole-5-carboxylic acid (2-ethoxy-ethyl)-amide
180	1-Ethyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methylamide
181	1-Ethyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ethylamide
182	1-Ethyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide
183	1-Ethyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-ethoxy-ethyl)-amide
184	1-Ethyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-2-methyl-propyl)-amide
185	1-Ethyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methylsulfanyl-ethyl)-amide

No.	Name
186	1-Ethyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide
187	1-Ethyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide
188	1-(2-Methoxy-ethyl)-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide
189	1-(2-Methoxy-ethyl)-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide
190	1-Ethyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide
191	1-Ethyl-2-[6-(pyridin-3-yloxy)-benzothiazol-2-ylamino]-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide
192	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-hydroxy-piperidin-1-yl)-ethyl]-amide
193	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(3-hydroxy-piperidin-1-yl)-ethyl]-amide
194	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-5-carbonitrile
195	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazole-6-carbonitrile
196	[5-(1*H*-Imidazol-2-yl)-1-methyl-1*H*-benzimidazol-2-yl]-(6-trifluoromethoxy-benzothiazol-2-yl)-amine
197	[1-Methyl-6-(1*H*-1,2,4-triazol-3-yl)-1*H*-benzimidazol-2-yl]-(6-trifluoromethoxy-benzothiazol-2-yl)-amine

No.	Name
198	[1-Methyl-6-(5-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-benzimidazol-2-yl]-(5-trifluoromethoxy-benzothiazol-2-yl)-amine
199	(1-Ethyl-5-trifluoromethanesulfonyl-1*H*-benzoimidazol-2-yl)-(6-trifluoromethoxy-benzothiazol-2-yl)-amine
200	1-[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1*H*-benzoimidazol-5-yl]-ethanone
201	(5-Methanesulfonyl-1-methyl-1*H*-benzoimidazol-2-yl)-(6-trifluoromethoxy-benzothiazol-2-yl)-amine
202	2-[1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazol-6-yl]-acetamide
203	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid ((R)-2-hydroxy-propyl)-amide
204	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid ((S)-2-hydroxy-propyl)-amide
205	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((R)-2-hydroxy-propyl)-amide
206	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((S)-2-hydroxy-propyl)-amide
207	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-methoxy-2-methyl-propyl)-amide
208	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-2-methyl-propyl)-amide
209	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-fluoro-ethyl)-amide
210	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-fluoro-ethyl)-amide
211	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid cyanomethyl-amide

No.	Name
212	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-cyano-ethyl)-amide
213	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-cyano-ethyl)-amide
214	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (3-hydroxy-propyl)-amide
215	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (3-hydroxy-butyl)-amide
216	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (3-hydroxy-butyl)-amide
217	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (3-hydroxy-2,2-dimethyl-propyl)-amide
218	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (3-hydroxy-2,2-dimethyl-propyl)-amide
219	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (4-hydroxy-butyl)-amide
220	2-(6-Chloro-1H-benzoimidazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (4-hydroxy-butyl)-amide
221	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (4-hydroxy-butyl)-amide
222	6-Fluoro-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (4-hydroxy-butyl)-amide
223	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((R)-4-hydroxy-3-methyl-butyl)-amide
224	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid ((R)-4-hydroxy-3-methyl-butyl)-amide
225	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (*trans*-4-hydroxy-cyclohexyl)-amide

No.	Name
226	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (5-hydroxy-pentyl)-amide
227	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (5-hydroxy-pentyl)-amide
228	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (5-hydroxy-pentyl)-amide
229	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (5-hydroxy-4,4-dimethyl-pentyl)-amide
230	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid 4-hydroxy-benzylamide
231	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid 3-hydroxy-4-methoxy-benzylamide
232	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (*trans*-4-hydroxy-cyclohexylmethyl)-amide
233	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (*trans*-4-hydroxy-cyclohexylmethyl)-amide
234	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (*trans*-4-hydroxy-cyclohexylmethyl)-amide
235	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(2-hydroxy-ethoxy)-ethyl]-amide
236	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-hydroxy-ethoxy)-ethyl]-amide
237	6-Fluoro-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-hydroxy-ethoxy)-ethyl]-amide
238	3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid [2-(2-hydroxy-ethoxy)-ethyl]-amide

No.	Name
239	1-(2-Methylamino-ethyl)-2-(6-trifluoromethoxy-benzothiazol-2 ylamino)-1H-benzoimidazole-5-carboxylic acid[2-(2-hydroxy-ethoxy)-ethyl]-amide hydrochloride
240	2-(6-Chloro-benzothiazol-2-ylamino)-1-(2-methylamino-ethyl)-1H-benzoimidazole-5-carboxylic acid [2-(2-hydroxy-ethoxy)-ethyl]-amide hydrochloride
241	1-(2-Methoxy-ethyl)-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-hydroxy-ethoxy)-ethyl]-amide
242	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((R)-2-hydroxy-1-methyl-ethoxy)-ethyl]-amide
243	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-((R)-2-hydroxy-1-methyl-ethoxy)-ethyl]-amide
244	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-hydroxy-propoxy)-ethyl]-amide
245	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-hydroxy-2-methyl-propoxy)-ethyl]-amide
246	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(3-hydroxy-propoxy)-ethyl]-amide
247	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(3-fluoro-propoxy)-ethyl]-amide
248	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(3-hydroxy-propoxy)-ethyl]-amide
249	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(3-fluoro-propoxy)-ethyl]-amide
250	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [3-(2-hydroxy-ethoxy)-propyl]-amide

No.	Name
251	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-hydroxy-phenyl)-ethyl]-amide
252	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(3-hydroxy-phenyl)-ethyl]-amide
253	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-hydroxy-cyclohexyl)-ethyl]-amide
254	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (*trans*-4-hydroxymethyl-cyclohexylmethyl)-amide
255	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (*trans*-4-hydroxymethyl-cyclohexylmethyl)-amide
256	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid {2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethyl}-amide
257	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-fluoro-ethoxy)-ethyl]-amide
258	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2,2-difluoro-ethoxy)-ethyl]-amide
259	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(2,2-difluoro-ethoxy)-ethyl]-amide
260	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-methoxy-ethoxy)-ethyl]-amide
261	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(2-methoxy-ethoxy)-ethyl]-amide
262	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-methoxy-ethoxy)-ethyl]-amide
263	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(tetrahydro-pyran-2-yl)-ethyl]-amide

No.	Name
264	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(tetrahydro-pyran-4-yl)-ethyl]-amide
265	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-cyano-ethoxy)-ethyl]-amide
266	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(2-cyano-ethoxy)-ethyl]-amide
267	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-carbamoylmethoxy-ethyl)-amide
268	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H benzoimidazole-5-carboxylic acid [2-(2-amino-ethoxy)-ethyl]-amide
269	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(2-amino-ethoxy)-ethyl]-amide
270	2-(4-Chloro-benzothiazol-2-ylamino)-1-methyl-1H benzoimidazole-5-carboxylic acid [2-(2-amino-ethoxy)-ethyl]-amide
271	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-methylamino-ethoxy)-ethyl]-amide hydrochloride
272	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(2-methylamino-ethoxy)-ethyl]-amide hydrochloride
273	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-dimethylamino-ethoxy)-ethyl]-amide
274	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(2-dimethylamino-ethoxy)-ethyl]-amide
275	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-acetylamino-ethoxy)-ethyl]-amide

No.	Name
276	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-methanesulfonylamino-ethoxy)-ethyl]-amide
277	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-ethanesulfonyl-ethyl)-amide
278	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(2-hydroxy-ethanesulfonyl)-ethyl]-amide
279	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(2-fluoro-ethylamino)-ethyl]-amide hydrochloride
280	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((S)-2,3-dihydroxy-propyl)-amide
281	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((R)-2,3-dihydroxy-propyl)-amide
282	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((1R,2S,3R,4R)-2,3-dihydroxy-4-hydroxymethyl-cyclopentyl)-amide
283	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((2S,3R,4R,5S,6R)-2,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-3-yl)-amide
284	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid bis-(2-hydroxy-ethyl)-amide
285	3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-benzoimidazole-5-carboxylic acid (4-hydroxy-butyl)-amide
286	3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-benzoimidazole-5-carboxylic acid [2-(2-hydroxy-ethoxy)-ethyl]-amide
287	2-(6-Chloro-benzothiazol-2-ylamino)-3-methyl-3H-benzoimidazole-5-carboxylic acid (4-hydroxy-butyl)-amide

No.	Name
288	2-(6-Chloro-benzothiazol-2-ylamino)-3-methyl-3H-benzoimidazole-5-carboxylic acid [2-(2-hydroxy-ethoxy)-ethyl]-amide
289	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid pyrrolidin-3-ylamide hydrochloride
290	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (R)-pyrrolidin-3-ylamide hydrochloride
291	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (S)-pyrrolidin-3-ylamide hydrochloride
292	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [(R)-1-(2-hydroxy-ethyl)-pyrrolidin-3-yl]-amide
293	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [(S)-1-(2-hydroxy-ethyl)-pyrrolidin-3-yl]-amide
294	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [1-((R)-2-hydroxy-propyl)-pyrrolidin-3-yl]-amide
295	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [(R)-1-((S)-2-hydroxy-propionyl)-pyrrolidin-3-yl]-amide
296	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [(R)-1-((R)-2-hydroxy-propyl)-pyrrolidin-3-yl]-amide
297	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [(R)-1-((R)-2-hydroxy-propyl)-pyrrolidin-3-yl]-amide
298	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [1-(2-hydroxy-2-methyl-propyl)-pyrrolidin-3-yl]-amide
299	3-(3-{[2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carbonyl]-amino}-pyrrolidin-1-yl)-propionic acid

No.	Name
300	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [1-(2-methanesulfonylamino-ethyl)-pyrrolidin-3-yl]-amide
301	2-(6-Chloro-benzothiazol-2-ylamino)-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carboxylic acid [1-(2-hydroxy-ethyl)-piperidin-4-yl]-amide
302	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (piperidin-4-ylmethyl)-amide hydrochloride
303	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [1-(2-hydroxy-ethyl)-piperidin-4-ylmethyl]-amide
304	2-(6-Chloro-benzothiazol-2-ylamino)-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carboxylic acid [1-(2-hydroxy-ethyl)-piperidin-4-ylmethyl]-amide
305	[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-[1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazol-5-yl]-methanone
306	[2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazol-5-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone
307	[4-(3-Hydroxy-propyl)-piperidin-1-yl]-[1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H benzoimidazol-5-yl]-methanone
308	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [(R)-1-(2-dimethylamino-acetyl)-pyrrolidin-3-yl]-amide
309	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (R)-piperidin-3-ylamide hydrochloride
310	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (S)-piperidin-3-ylamide hydrochloride
311	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [(R)-1-(2-dimethylamino-acetyl)-piperidin-3-yl]-amide
312	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [(S)-1-(2-dimethylamino-acetyl)-piperidin-3-yl]-amide

No.	Name
313	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [1-(2-dimethylamino-acetyl)-piperidin-4-yl]-amide
314	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [1-(2-dimethylamino-acetyl)-piperidin-4-ylmethyl]-amide
315	2-(6-Chloro-benzothiazol-2-ylamino)-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carboxylic acid [1-(2-dimethylamino-acetyl)-piperidin-4-ylmethyl]-amide
316	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H benzoimidazole-5-carboxylic acid ((R)-1-methyl-pyrrolidin-3-yl)-amide
317	2-(6-Chloro-benzothiazol-2 ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-methyl-pyrrolidin-3-yl)-amide
318	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (1-methyl-piperidin-2-ylmethyl)-amide
319	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (1-methyl-piperidin-4-yl)-amide
320	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (1-methanesulfonyl-piperidin-4-yl)-amide
321	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid morpholin-4-ylamide
322	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methanesulfonylamino-ethyl)-amide
323	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-dimethylamino-acetylamino)-ethyl]-amide
324	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(2-dimethylamino-acetylamino)-ethyl]-amide
325	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-hydroxy-acetylamino)-ethyl]-amide

No.	Name
326	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((S)-2-hydroxy-propionylamino)-ethyl]-amide
327	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-imidazol-1-yl-ethyl)-amide
328	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-pyrazol-1-yl-ethyl)-amide
329	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-oxo-pyrrolidin-1-yl)-ethyl]-amide
330	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-oxo-imidazolidin-1-yl)-ethyl]-amide
331	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(3-oxo-piperazin-1-yl)-ethyl]-amide
332	2-(6-Chloro-benzothiazol-2-ylamino)-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carboxylic acid [2-(3-oxo-piperazin-1-yl)-ethyl]-amide
333	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-piperidin-1-yl-ethyl)-amide
334	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-piperidin-1-yl-ethyl)-amide
335	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(4,4-difluoro-piperidin-1-yl)-ethyl]-amide
336	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(3,3-difluoro-piperidin-1-yl)-ethyl]-amide
337	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-methyl-piperazin-1-yl)-ethyl]-amide
338	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(4-methyl-piperazin-1-yl)-ethyl]-amide

No.	Name
339	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-piperazin-1-yl-ethyl)-amide hydrochloride
340	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-morpholin-4-yl-ethyl)-amide
341	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-morpholin-4-yl-ethyl)-amide
342	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(1,1-dioxo-thiomorpholin-4-yl)-ethyl]-amide
343	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-amino-ethyl)-amide hydrochloride
344	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (3-amino-propyl)-amide hydrochloride
345	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (3-amino-propyl)-amide hydrochloride
346	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (4-amino-butyl)-amide hydrochloride
347	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (4-amino-butyl)-amide hydrochloride
348	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (3-dimethylamino-propyl)-amide
349	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (3-dimethylamino-propyl)-amide
350	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (3-dimethylamino-propyl)-amide
351	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (3-diethylamino-propyl)-amide

No.	Name
352	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (3-diethylamino-propyl)-amide
353	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (3-diethylamino-propyl)-amide
354	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (3-pyrrolidin-1-yl-propyl)-amide
355	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide
356	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide
357	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide
358	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (3-morpholin-4-yl-propyl)-amide
359	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (3-morpholin-4-yl-propyl)-amide
360	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (4-diethylamino-butyl)-amide
361	6-Diethylamino-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide
362	6-Diethylamino-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-morpholin-4-yl-ethyl)-amide
363	1-Methyl-2-(6-methyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide
364	2-(6-Ethoxy-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide

No.	Name
365	2-(6-Isopropyl-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide
366	2-(6-Chloro-benzothiazol-2-ylamino)-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide
367	2-(6-Chloro-benzothiazol-2-ylamino)-1-(2-methylamino-ethyl)-1H-benzoimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide hydrochloride
368	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((S)-1-dimethylcarbamoyl-2-hydroxy-ethyl)-amide
369	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((S)-5-amino-1-dimethylcarbamoyl-pentyl)-amide hydrochloride
370	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((S)-5-dimethylamino-1-dimethylcarbamoyl-pentyl)-amide
371	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-dimethylcarbamoyl-ethyl)-amide
372	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-dimethylcarbamoyl-ethyl)-amide
373	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (3-morpholin-4-yl-3-oxo-propyl)-amide
374	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (3-morpholin-4-yl-3-oxo-propyl)-amide
375	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [3-(4-methyl-piperazin-1-yl)-3-oxo-propyl]-amide

No.	Name
376	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (3-dimethylcarbamoyl-propyl)-amide
377	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [4-(4-methyl-piperazin-1-yl)-4-oxo-butyl]-amide
378	4-{[2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carbonyl]-amino}-*trans*-cyclohexanecarboxylic acid
379	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (4-*trans*-dimethylcarbamoyl-cyclohexyl)-amide
380	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid methylcarbamoylmethyl-amide
381	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methylcarbamoylmethyl-amide
382	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [((R)-2-hydroxy-propylcarbamoyl)-methyl]-amide
383	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [(2-methanesulfonyl-ethylcarbamoyl)-methyl]-amide
384	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [(tetrahydro-furan-3-ylcarbamoyl)-methyl]-amide
385	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [(tetrahydro-pyran-4-ylcarbamoyl)-methyl]-amide
386	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [(1-methyl-piperidin-4-ylcarbamoyl)-methyl]-amide
387	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid ((R)-piperidin-3-ylcarbamoylmethyl)-amide hydrochloride
388	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [((R)-1-methyl-piperidin-3-ylcarbamoyl)-methyl]-amide

No.	Name
389	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [(4-hydroxy-benzylcarbamoyl)-methyl]-amide
390	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid {[(2-hydroxy-ethyl)-methyl-carbamoyl]-methyl}-amide
391	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid {[(2-hydroxy-ethyl)-methyl-carbamoyl]-methyl}-amide
392	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid {[bis-(2-hydroxy-ethyl)-carbamoyl]-methyl}-amide
393	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid {[methyl-(tetrahydro-pyran-4-yl)-carbamoyl]-methyl}-amide
394	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [(methyl-pyrrolidin-3-yl-carbamoyl)-methyl]-amide hydrochloride
395	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid {[methyl-(1-methyl-pyrrolidin-3-yl)-carbamoyl]-methyl}-amide
396	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [(methyl-piperidin-3-yl-carbamoyl)-methyl]-amide hydrochloride
397	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-oxo-2-pyrrolidin-1-yl-ethyl)-amide
398	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

No.	Name
399	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
400	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-((R)-3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
401	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
402	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((R)-3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
403	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
404	2-(6-Chloro-benzothiazol-2-ylamino)-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carboxylic acid [2-((R)-3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
405	2-(6-Chloro-benzothiazol-2-ylamino)-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
406	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((S)-2-hydroxymethyl-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
407	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((3S,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
408	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-((R)-3-methoxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
409	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-methoxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

No.	Name
410	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-methoxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
411	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-amino-pyrrolidin-1-yl)-2-oxo-ethyl]-amide hydrochloride
412	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-amino-pyrrolidin-1-yl)-2-oxo-ethyl]-amide hydrochloride
413	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((R)-3-methylamino-pyrrolidin-1-yl)-2-oxo-ethyl]-amide hydrochloride
414	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-methylamino-pyrrolidin-1-yl)-2-oxo-ethyl]-amide hydrochloride
415	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((R)-3-dimethylamino-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
416	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-dimethylamino-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
417	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-((R)-3-dimethylamino-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
418	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-dimethylamino-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

No.	Name
419	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-((S)-2-dimethylcarbamoyl-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
420	3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (2-morpholin-4-yl-2-oxo-ethyl)-amide
421	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-morpholin-4-yl-2-oxo-ethyl)-amide
422	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-morpholin-4-yl-2-oxo-ethyl)-amide
423	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-oxo-2-thiomorpholin-4-yl-ethyl)-amide
424	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(1,1-dioxo-thiomorpholin-4-yl)-2-oxo-ethyl]-amide
425	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-oxo-2-piperazin-1-yl-ethyl)-amide hydrochloride
426	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide
427	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide
428	2-(6-Chloro-benzothiazol-2-ylamino)-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carboxylic acid [2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide
429	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(4-methanesulfonyl-piperazin-1-yl)-2-oxo-ethyl]-amide
430	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(4-dimethylsulfamoyl-piperazin-1-yl)-2-oxo-ethyl]-amide

No.	Name
431	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(3-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide
432	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((R)-3-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide
433	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide
434	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide
435	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide
436	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide
437	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide
438	2-(6-Chloro-benzothiazol-2-ylamino)-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carboxylic acid [2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide
439	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-hydroxymethyl-piperidin-1-yl)-2-oxo-ethyl]-amide
440	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(3-hydroxymethyl-piperidin-1-yl)-2-oxo-ethyl]-amide

No.	Name
441	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-hydroxymethyl-piperidin-1-yl)-2-oxo-ethyl]-amide
442	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(4-hydroxymethyl-piperidin-1-yl)-2-oxo-ethyl]-amide
443	2-(6-Chloro-benzothiazol-2-ylamino)-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carboxylic acid [2-(4-hydroxymethyl-piperidin-1-yl)-2-oxo-ethyl]-amide
444	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-methoxy-piperidin-1-yl)-2-oxo-ethyl]-amide
445	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-methoxy-piperidin-1-yl)-2-oxo-ethyl]-amide
446	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((R)-3-methoxy-piperidin-1-yl)-2-oxo-ethyl]-amide
447	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-methoxymethyl-piperidin-1-yl)-2-oxo-ethyl]-amide
448	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-fluoromethyl-piperidin-1-yl)-2-oxo-ethyl]-amide
449	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-oxo-2-(4-trifluoromethyl-piperidin-1-yl)-ethyl]-amide
450	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-cyano-piperidin-1-yl)-2-oxo-ethyl]-amide

No.	Name
451	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-carbamoyl-piperidin-1-yl)-2-oxo-ethyl]-amide
452	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid {2-oxo-2-[4-(pyrimidin-2-yloxy)-piperidin-1-yl]-ethyl}-amide
453	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-methylamino-piperidin-1-yl)-2-oxo-ethyl]-amide hydrochloride
454	2-(6-Chloro-benzothiazol-2-ylamino-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(4-methylamino-piperidin-1-yl)-2-oxo-ethyl]-amide hydrochloride
455	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-dimethylamino-piperidin-1-yl)-2-oxo-ethyl]-amide
456	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(4-dimethylamino-piperidin-1-yl)-2-oxo-ethyl]-amide
457	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(4-methylaminomethyl-piperidin-1-yl)-2-oxo-ethyl]-amide hydrochloride
458	1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-dimethylaminomethyl-piperidin-1-yl)-2-oxo-ethyl]-amide
459	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(4-dimethylaminomethyl-piperidin-1-yl)-2-oxo-ethyl]-amide

No.	Name
460	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(3-methylaminomethyl-piperidin-1-yl)-2-oxo-ethyl]-amid hydrochloride
461	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(3-dimethylaminomethyl-piperidin-1-yl)-2-oxo-ethyl]-amide
462	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-dimethylcarbamoyl-ethyl)-amide
463	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((S)-1-dimethylcarbamoyl-ethyl)-amide
464	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [(S)-1-methyl-2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide
465	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-methyl-2-morpholin-4-yl-2-oxo-ethyl)-amide
466	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((S)-1-methyl-2-morpholin-4-yl-2-oxo-ethyl)-amide
467	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid ((R)-1-dimethylcarbamoyl-ethyl)-amide
468	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((R)-1-dimethylcarbamoyl-ethyl)-amide
469	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [(R)-1-methyl-2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide
470	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [(R)-1-methyl-2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide

No.	Name
471	2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid ((R)-1-methyl-2-morpholin-4-yl-2-oxo-ethyl)-amide
472	1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((R)-1-methyl-2-morpholin-4-yl-2-oxo-ethyl)-amide
473	N-[2-(2-Hydroxyethoxy)ethyl]-3-methyl-2-[[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino]imidazo[4,5-b]pyridine-6-carboxamide
474	1-Ethyl-N-[2-(2-hydroxyethoxy)ethyl]-2-[[5-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino]benzimidazole-5-carboxamide

Compounds 1-474 in Table A may be prepared as described in WO '018 or other methods apparent to one of skill in the art. For example, Compounds 473 and 474 in Table A may be prepared as described in the Examples section below.

In another aspect, the present invention provides a pharmaceutical composition comprising the compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in treating sickle cell disease or related disorders. In an embodiment, the present invention provides a pharmaceutical composition comprising a compound (or salt) of any one of embodiments 1 to 250 (recited above) and a pharmaceutical carrier. In another embodiment, the pharmaceutical composition comprises a compound (or salt) of any one of the examples and a pharmaceutically acceptable carrier.

Thus, in another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In another embodiment, the invention provides a pharmaceutical composition comprising a compound (or salt) of any one of embodiments 1 to 250 and a pharmaceutical acceptable carrier.

In another embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in medicine. In

another embodiment, the invention provides a compound (or salt) of any one of embodiments 1 to 250 for use in medicine.

B. Co-Administration

The present invention further provides for the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more active compounds for simultaneous, subsequent, or sequential administration. The invention also provides for the use of a compound (or salt) of any one of embodiments 1 to 250 in combination with one or more medically effective active compounds for simultaneous, subsequent, or sequential administration. Examples of such active ingredients include, but are not limited to, HU, Nrf2 activators, antioxidants, detoxification agents, and anti-inflammatory agents. In one embodiment, the invention provides a pharmaceutical composition comprising a compound (or salt) of any one of embodiments 1 to 250 and at least one other medically effective active ingredient selected from HU, Nrf2 activators, antioxidants, detoxification agents, and anti-inflammatory agents. In another embodiment, the invention provides for the use of a compound (or salt) of any one of embodiments 1 to 250 in combination with at least one other medically effective active ingredient selected from Nrf2 activators, antioxidants, detoxification agents, and anti-inflammatory agents for simultaneous, subsequent, or sequential administration.

Nrf2 Activators may comprise a Michael addition acceptor, one or more fumaric acid esters, i.e. fumaric acid mono- and/or diesters which may be selected from the group of monoalkyl hydrogen fumarate and dialkyl fumarate, such as monomethyl hydrogen fumarate, dimethyl fumarate, monoethyl hydrogen fumarate, and diethyl fumarate, furthermore ethacrynic acid, bardoxolone methyl (methyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate), isothiocyanate such as sulforaphane, 1,2-dithiole-3-thione such as oltipraz, 3,5-di-tert-butyl-4-hydroxytoluene, 3-hydroxycoumarin, or a pharmacologically active derivative or analog of the

aforementioned agents. In an embodiment, Nrf2 Activators for use in combination with a compound of the invention are bardoxolone methyl and fumaric acid esters.

Nrf2 Activators compounds may be classified based on their chemical structures: Diphenols, Michael reaction acceptors, isothiocyanates, thiocarbamates, trivalent arsenicals, 1,2-dithiole-3-thiones, hydroperoxides, vicinal dimercaptans, heavy metals, and polyenes. In general, Nrf2 Activators are chemically reactive in that they may be electrophiles, substrates for glutathione transferases, and/or can modify sulfhydryl groups by alkylation, oxidation, or reduction.

In another embodiment, the Nrf2 activators are bardoxolone methyl and dialkyl fumarate such as dimethyl fumarate and diethyl fumarate.

In another embodiment, Nrf2 activators are selected from: Chalcone derivatives such as 2-trifluoromethyl-2'-methoxychalcone, auranofin, ebselen, 1,2-naphthoquinone, cynnamic aldehyde, caffeic acid and its esters, curcumin, reservatrol, artesunate, tert-butylhydroquinone, and -quinone, (tBHQ, tBQ), vitamins K1, K2 and K3, menadione, fumaric acid esters, i.e. fumaric acid mono- and/or diester which may be selected from the group of monoalkyl hydrogen fumarate and dialkyl fumarate, such as monomethyl hydrogen fumarate, dimethyl fumarate (DMF), monoethyl hydrogen fumarate, and diethyl fumarate, 2-cyclopentenones, ethacrynic acid and its alkyl esters, bardoxolone methyl (methyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate) (CDDO-Me, RTA 402), ethyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oic acid (CDDO), 1[2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Im), (2-cyano-N-methyl-3,12-dioxooleana-1,9(11)-dien-28 amide (CDDO-methyl amide, CDDO-MA), isothiocyanate such as sulforaphane, 1,2-dithiole-3-thione such as oltipraz, 3,5-di-tert-butyl-4-hydroxytoluene, 3-hydroxycoumarin, 4-hydroxynonenal, 4-oxononenal, malondialdehyde, (E)-2-hexenal, capsaicin, allicin, allylisothiocyanate, 6-methylthiohexyl isothiocyanate, 7-methylthioheptyl isothiocyanate, sulforaphane, 8-methylthiooctyl isothiocyanate, corticosteroids, such as dexamethasone, 8-iso prostaglandin A2, alkyl pyruvate, such as methyl and ethyl pyruvate, diethyl or dimethyl oxaloproprionate, 2-acetamidoacrylate, methyl or

ethyl-2-acetamidoacrylate, hypoestoxide, parthenolide, eriodictyol, 4-hydroxy-2-nonenal, 4-oxo-2nonenal, geranial, zerumbone, aurone, isoliquiritigenin, xanthohumol, [10]-Shogaol, eugenol, 1'-acetoxychavicol acetate, allyl isothiocyanate, benzyl isothiocyanate, phenethyl isothiocyanate, 4-(methylthio)-3-butenyl isothiocyanate and 6-methylsulfinylhexyl isothiocyanate, ferulic acid and its esters, such as ferulic acid ethyl ester, and ferulic acid methyl ester, sofalcone, 4-methyl daphnetin, imperatorin, auraptene, poncimarin, bis[2-hydroxybenzylidene]acetones, alicylcurcuminoid, 4-bromo flavone, beta-naphthoflavone, sappanone A, aurones and its corresponding indole derivatives such as benzylidene-indolin-2-ones, perillaldehyde, quercetin, fisetin, koparin, genistein, tanshinone HA, BHA, BHT, PMX-290, AL-1, avicin D, gedunin, fisetin, andrographolide, and tricyclic bis(cyano enone) TBE-31 [(+/-)-(4bS,8aR,10aS)-10a-ethynyl-4-b,8,8-trimethyl-3,7-dioxo-3,4-b,7,8,- 8a,9,10,10a-octahydrophenanthrene-2,6-dicarbonitrile].

In another embodiment, Nrf2 activators are selected from: carnosic acid, 2-naphthoquinone, cynnamic aldehyde, caffeic acid and its esters, curcumin, reservatrol, artesunate, tert-butylhydroquinone, vitamins K1, K2 and K3, fumaric acid esters, i.e. fumaric acid mono- and/or diester which is preferably selected from the group of monoalkyl hydrogen fumarate and dialkyl fumarate, such as monomethyl hydrogen fumarate, dimethyl fumarate, monoethyl hydrogen fumarate, and diethyl fumarate, isothiocyanate such as sulforaphane, 1,2-dithiole-3-thione such as oltipraz, 3,5-di-tert-butyl-4-hydroxytoluene, 3-hydroxycoumarin, 4-hydroxynonenal, 4-oxononenal, malondialdehyde, (E)-2-hexenal, capsaicin, allicin, allylisothiocyanate, 6-methylthiohexyl isothiocyanate, 7-methylthioheptyl isothiocyanate, sulforaphane, 8-methylthiooctyl isothiocyanate, 8-iso prostaglandin A2, alkyl pyruvate, such as methyl and ethyl pyruvate, diethyl or dimethyl oxaloproprionate, 2-acetamidoacrylate, methyl or ethyl-2-acetamidoacrylate, hypoestoxide, parthenolide, eriodictyol, 4-Hydroxy-2-nonenal, 4-oxo-2nonenal, geranial, zerumbone, aurone, isoliquiritigenin, xanthohumol, [10]-Shogaol, eugenol, 1'-acetoxychavicol acetate, allyl isothiocyanate, benzyl isothiocyanate, phenethyl isothiocyanate, 4-(Methylthio)-3-butenyl isothiocyanate and 6-methylsulfinylhexyl

isothiocyanate and the respective quinone or hydroquinone forms of the aforementioned quinone and hydroquinone derivatives.

In another embodiment, Nrf2 Activators may be Michael reaction acceptors such as dimethylfumarate, monomethyl hydrogen fumarate isothiocyanates and 1,2-dithiole-3-thiones. In another embodiment, Nrf2 Activators are selected from monomethyl hydrogen fumarate, dimethyl fumarate, oltipraz, 1,2-naphthoquinone, tert-butylhydroquinone, methyl or ethyl pyruvate, 3,5-di-tert-butyl-4-hydroxytoluene, diethyl and dimethyl oxaloproprionate, hypoestoxide, parthenolide, eriodictyol, 4-Hydroxy-2-nonenal, 4-oxo-2nonenal, geranial, zerumbone, aurone, isoliquiritigenin, xanthohumol, [10]-Shogaol, eugenol, 1'-acetoxychavicol acetate, allyl isothiocyanate, benzyl isothiocyanate, phenethyl isothiocyanate, 4-(Methylthio)-3-butenyl isothiocyanate and 6-Methylsulfinylhexyl isothiocyanate.

Examples of the antioxidants include vitamin C, vitamin E, carotenoids, retinolds, polyphenols, flavonoids, lignan, selenium, butylated hydroxyanisole, ethylene diamine tetra-acetate, calcium disodium, acetylcysteine, probucol, and tempo.

Examples of the detoxification agents include dimethyl caprol, glutathione, acetylcysteine, methionine, sodium hydrogen carbonate, deferoxamine mesylate, calcium disodium edetate, trientine hydrochloride, penicillamine, and pharmaceutical charcoal.

The anti-inflammatory agents include steroidal anti-inflammatory agents and non-steroidal anti-inflammatory agents. Examples of the steroidal anti-inflammatory agents include cortisone acetate, hydrocortisone, paramethasone acetate, prednisolone, prednisolone, methylprednine, dexamethasone, triamcinolone, and betamethasone. Examples of the non-steroidal anti-inflammatory agents include salicylic acid non-steroidal anti-inflammatory agents such as aspirin, difiunisal, aspirin+ascorbic acid, and aspirin dialuminate; aryl acid non-steroidal anti-inflammatory agents such as diclofenac sodium, sulindac, fenbufen, indomethacin, indomethacin farnesyl, acemetacin, proglumetacin maleate, anfenac sodium, nabmeton, mofezolac, and etodorag; fenamic acid non-

steroidal anti-inflammatory agents such as mefenamic acid, flufenamic acid aluminum, tolfenamic acid, and floctafenine; propionic acid non-steroidal anti-inflammatory agents such as ibuprofen, flurbiprofen, ketoprofen, naproxen, pranoprofen, fenoprofen calcium, thiaprofen, oxaprozin, loxoprofen sodium, alminoprofen, and zaltoprofen; oxicam non-steroldal anti-inflammatory agents such as piroxicam, ampiroxicam, tenoxicam, lornoxicam, and meloxicam; and basic non-steroidal anti-inflammatory agents such as tiaramide hydrochloride, epirizole, and emorfazone.

An appropriate time course for sequential administration may be chosen by the physician, according to such factors as the nature of a patient's illness, and the patient's condition for administration of individual active agents. In certain embodiments, sequential administration includes the co-administration of one or more additional active agents within a period of one week, 72 hours, 48 hours, 24 hours, or 12 hours.

In some embodiments, the compositions disclosed herein are co-administered in combination with one or more additional active agents for treatment of sickle cell disease, beta-thalassemia, or a related disorder. Such additional active agents may include, but are not limited to, folic acid, penicillin or another antibiotics, preferably a quinolone or macrolide, antivirals, anti-malarial prophylactics, and analgesics to control pain crises.

In some embodiments, the compositions are co-administered with one or more additional agents that increase expression of HbF, for example, hydroxyurea (HU).

In some embodiments, the compositions are co-administered with one or more additional treatment protocols, for example, transfusion therapy, stem cell therapy, gene therapy, bone marrow transplants, dialysis or kidney transplant for kidney disease, gallbladder removal in people with gallstone disease, hip replacement for avascular necrosis of the hip, surgery for eye problems, and wound care for leg ulcers.

C. Effective Amounts

In some embodiments, the compositions are administered in an amount effective to induce a pharmacological, physiological, or molecular effect compared to a control that is not administered the composition. In some embodiments, the compositions are administered to a subject in need thereof to increase expression of HbF in the subject.

Suitable controls are known in the art and can be determined based on the disease to be treated. Suitable controls include, but are not limited to a subject, or subjects without sickle cell disease, a beta-thalassemia, or a sickle cell related disorder; or a condition or status of a subject with the disease or disorder prior to initiation of the treatment.

D. Dosages and Dosage Regimes

The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment desired. Generally dosage levels of 0.001 to 100 mg/kg of body weight daily are administered to mammals. Generally, for intravenous injection or infusion, dosage may be lower.

An appropriate dose of a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in the present invention, may be determined according to any one of several well-established protocols. For example, animal studies such as studies using mice, rats, dogs, and/or monkeys may be used to determine an appropriate dose of a pharmaceutical compound. Results from animal studies may be extrapolated to determine doses for use in other species, such as for example, humans.

A compound of Formula (I) or a pharmaceutically acceptable salt thereof may be administered in a daily dosage of between 0.1 mg and 15 mg per kg. In another embodiment, where the subject is a human the daily dose may be between 1 mg and 1000 mg. In another embodiment, a compound of Formula (I) or a pharmaceutically acceptable salt thereof is administered in an amount from 10 mg/day to 1000 mg/day, or from 25 mg/day to 800 mg/day, or from 37 mg/day to 750 mg/day, or from

75 mg/day to 700 mg/day, or from 100 mg/day to 600 mg/day, or from 150 mg/day to 500 mg/day, or from 200 mg/day to 400 mg/day. In other embodiments, the previous daily periods of administration of an amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof may be changed to a period of every 6 hours, 12 hours, 48 hours, 72 hours, 96 hours, 1 week, or 2 weeks.

In some embodiments, the compositions comprising a fumaric acid ester, such as DMF, MMF, or a combination thereof, daily dosages for fumaric acid esters in a human can range from about 1 mg to about 5,000 mg, from about 10 mg to about 2,500 grams, or from about 50 mg to about 2,000 grams of a fumaric acid ester, or a pharmacologically active salt thereof. In another embodiment, an effective dose of DMF or MMF to be administered to a subject, for example orally, can be from about 0.1 g to about 1 g or more than 1 g per day; from about 200 mg to about 800 mg per day; from about 240 mg to about 720 mg per day; from about 480 mg to about 720 mg per day; or about 720 mg per day. The daily dose can be administered in separate administrations of 2, 3, 4, or 6 equal doses. In some embodiments of the one or more fumaric acid esters, or pharmacologically active salts, derivatives, analogues or prodrugs thereof are present in a pharmaceutical preparation. In some embodiments the composition is administered to the patient three times per day (TID). In some embodiments the pharmaceutical preparation is administered to the patient two times per day (BID). In some embodiments, the composition is administered at least one hour before or after food is consumed by the patient.

In some embodiments, the composition is administered as part of a dosing regimen. For example, the patient can be administered a first dose of the composition for a first dosing period; and a second dose of the composition for a second dosing period, optionally followed by one or more additional doses for one or more additional dosing periods. The first dosing period can be less than one week, one week, or more than one week.

In some embodiments the dosage regime is a dose escalating dosage regime. The first dose can be a low dose, followed by measurement of levels of HbF expression, and then the step of decreasing, maintaining, or increasing the dose.

The current labeled dosing of hydroxyurea for sickle cell disease calls for the administration of an initial dose of 15 mg/kg/day in the form of a single dose, with monitoring of the patient's blood count every 2 weeks. If the blood counts are in an acceptable range, the dose may be increased by 5 mg/kg/day every 12 weeks until the MTD of 35 mg/kg/day is reached. Pharmaceutical compositions can contain 1 mg/kg to 50 mg/kg of a fumaric acid ester, such as MMF, in combination with 1 mg/kg to 35 mg/kg of HU. The combination formulation can contain 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 mg/kg of HU.

E. Formulations

Pharmaceutical compositions comprising a compound of the invention are disclosed. The pharmaceutical compositions may be for administration by oral, parenteral (intramuscular, intraperitoneal, intravenous (IV) or subcutaneous injection), transdermal (either passively or using iontophoresis or electroporation), or transmucosal (nasal, vaginal, rectal, or sublingual) routes of administration or using bioerodible inserts and can be formulated in unit dosage forms appropriate for each route of administration.

Red blood cells, which are cells of erythroid lineage, are the primary producers of hemoglobin. Therefore, in an embodiment a compound of the invention or a pharmaceutical composition is administered to a subject in an effective amount to induce HbF in hematopoietic stems cells. Therefore, in some embodiments, a compound of the invention or a pharmaceutical composition is administered in an effective amount to induce HbF expression in cells of erythroid lineage in the bone marrow (i.e., the red bone marrow), the liver, the spleen, or combinations thereof.

In a further embodiment, a compound of the invention or a pharmaceutical composition induces HbF in cells synthesizing or committed to synthesize hemoglobin. For example, in preferred embodiments, a compound of the invention induces HbF in basophilic normoblast/early normoblast also commonly called erythroblast, polychromatophilic normoblast/intermediate normoblast, orthochromatic normoblast/late normoblast, or a combination thereof.

In some embodiments, a compound of the invention or a pharmaceutical composition is administered locally, to the site in need of therapy. Although red blood cells are the primary producers of hemoglobin, other, non-hematopoietic cells, including macrophage, retinal pigment cells, and alveolar epithelial cells such as alveolar type II (ATII) cells and Clara cells may also synthesize hemoglobin. Therefore, in some embodiments, a compound of the invention or a pharmaceutical composition is administered locally to interfaces where oxygen-carbon dioxide diffusion occurs, including but not limited, to the eye or lungs.

In some embodiments, a compound of the invention or a pharmaceutical composition is administered locally to the eye to treat a retinopathy, or another ocular manifestation associated with sickle cell disease or a related disorder.

In an embodiment, the pharmaceutical compositions are formulated for oral delivery. Oral solid dosage forms are described generally in Remington's Pharmaceutical Sciences, 21th Ed. 2005 at Chapter 45. Solid dosage forms include tablets, capsules, pills, troches or lozenges, cachets, pellets, powders, or granules or incorporation of the material into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc., or into liposomes. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the disclosed. The compositions may be prepared in liquid form, or may be in dried powder (e.g., lyophilized) form. Another embodiment provides liquid dosage forms for oral administration, including pharmaceutically acceptable emulsions, solutions, suspensions, and syrups, which may contain other components including inert diluents; adjuvants such as wetting agents, emulsifying and suspending agents; and sweetening, flavoring, and perfuming agents.

Controlled release oral formulations may be desirable. Compounds of the invention can be incorporated into an inert matrix which permits release by either diffusion or leaching mechanisms, e.g., gums. Slowly degenerating matrices may also be incorporated into the formulation.

For oral formulations, the location of release may be the stomach, the small intestine (the duodenum, the jejunem, or the ileum), or the large intestine.

IV. Methods of Diagnosis

The methods of treatment disclosed herein can include a first step of selecting a subject for treatment. In some embodiments, the subject is selected for treatment when the subject exhibits one or more of the clinical symptoms of sickle cell disease, beta-thalassemia, or a related disorder such as those discussed above. In some embodiments, the subject is selected for treatment when the subject exhibits a genetic or biochemical indicator of sickle cell disease, beta-thalassemia, or a related disorder. For example, the subject can be selected for treatment based on identification of a genetic alteration, defect, or mutation in the beta-globin gene or an expression control sequence thereof, by biochemical or morphological alterations in hemoglobin or hemoglobin synthesizing cells, or combinations thereof.

In some embodiments, the subject is selected when a combination of clinical symptoms and genetic or biochemical alterations are identified. In some embodiments, the subject is selected based on one or more clinical symptoms, or one or more genetic or biochemical alterations. For example, subjects can be selected for treatment based on the identification of a genetic alteration, a biochemical or morphological alteration, or a combination thereof, before the subject exhibits clinical symptoms of sickle cell disease, beta-thalassemia, or a related disorder.

In some embodiments, the methods of treatment may further comprise the step of determining whether a subject is at risk for or has sickle cell disease, beta-thalassemia, or a related disorder by obtaining or having obtained a biological sample from the subject and performing or having performed a bodily fluid test on the biological sample to determine if the subject has one or more biomarkers or a genetic mutation associated with sickle cell disease, beta-thalassemia, or a related disorder. If the subject is determined to be at risk for or has sickle cell disease, beta-thalassemia, or a related disorder, the method further comprises administering to the subject a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

In any of the preceding methods, the method may further comprise obtaining or having obtained biological samples over a period of time from the subject and performing or having performed a bodily fluid test on the biological samples to determine whether the level of one or more biochemical markers are increasing or decreasing, and if the level of one or more biochemical markers are not trending in the desired direction then administering a greater dose of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. For example, the ratio of HbF to HbS in a sample may be measured and a pronounced increase in the amount of HbF to HbS in a second sample relative to a first sample from a subject indicates that the dosage of a Formula (I) or a pharmaceutically acceptable salt thereof is a therapeutically effective dosage. Conversely, no change or no significant change in the amount of HbF to HbS in a second sample relative to a first sample from a subject may indicate that the dosage of a Formula (I) or a pharmaceutically acceptable salt thereof is not a therapeutically effective dosage and that the dosage may need to be increased.

In some embodiments, a compound of Formula (I) or a pharmaceutically acceptable salt thereof is administered to a subject in need thereof in an amount to decrease the level of one or more biomarker markers such as CRP or ROS.

The period between collection of biological samples may be 1 week, 2 weeks, 3 weeks, 4 weeks, 2 months, 3 months, 6 months, 9 months, or 12 months and the compound of Formula (I) or a pharmaceutically acceptable salt thereof may be administered during this period.

A. Identification of Genetic Alterations

In some embodiments, the subject is selected for treatment based on identification of one or more genetic alterations in one or more alleles of the human beta-globin gene or expression control sequence thereof. Genetic alterations indicative of sickle cell disease, beta-thalassemia, or related disorders include the exemplary mutations discussed above, or other mutations that lead to a reduction in the synthesis, structure, or function of human beta-globin protein.

Methods of selecting a subject having one or more genetic alterations in one or more alleles of the beta-globin gene or expression control sequences thereof include the steps of obtaining a biological sample and detecting the presence or absence one or more genetic alterations. In an embodiment, the biological sample obtained contains nucleic acid from the subject and the step of detecting detects the presence or absence one or more genetic alterations in one or more alleles of the beta-globin gene or expression control sequences thereof in the biological sample. Any biological sample that contains the DNA of the subject to be diagnosed can be employed, including tissue samples and blood samples, with nucleated blood cells being a particularly convenient source. The DNA may be isolated from the biological sample prior to testing the DNA for the presence or absence of the genetic alterations.

The detecting step can include determining whether the subject is heterozygous or homozygous for a genetic alteration. The step of detecting the presence or absence of the genetic alteration can include the step of detecting the presence or absence of the alteration in both chromosomes of the subject (i.e., detecting the presence or absence of one or two alleles containing the marker or functional polymorphism). More than one copy of a genetic alterations (i.e., subjects homozygous for the genetic marker) can indicate a greater risk of developing sickle cell disease, beta-thalassemia, or related disorder. In some embodiments, the subject is heterozygous for two or more genetic alterations in the beta-globin gene (also referred to herein as double heterozygotes, triple heterozygotes, etc.). One copy of two or more genetic alterations in the beta-globin gene can indicate a greater risk of developing sickle cell disease, beta-thalassemia, or related disorder.

The process of determining the genetic sequence of human beta-globin gene is referred to as genotyping. In some embodiments, the human beta-globin gene is sequenced. Methods for amplifying DNA fragments and sequencing them are well known in the art. For example, automated sequencing procedures that can be utilized to sequence the beta-globin gene, include, but not limited to, sequencing by mass spectrometry single-molecule real-time sequencing, ion semiconductor (ion

torrent sequencing), pyrosequencing (454), sequencing by synthesis, sequencing by ligation, chain termination (Sanger sequencing).

In some embodiments, the genotype of the subject is determined by identifying the presence of one or more single nucleotide polymorphisms (SNP) associated with sickle cell disease, beta-thalassemia, or a related disorder. Methods for SNP genotyping are generally known in the art. SNP genotyping can include the steps of collecting a biological sample from a subject (e.g., sample of tissues, cells, fluids, secretions, etc.), isolating genomic DNA from the cells of the sample, contacting the nucleic acids with one or more primers which specifically hybridize to a region of the isolated nucleic acid containing a target SNP under conditions such that hybridization and amplification of the target nucleic acid region occurs, and determining the nucleotide present at the SNP position of interest, or, in some assays, detecting the presence or absence of an amplification product (assays can be designed so that hybridization and/or amplification will only occur if a particular SNP allele is present or absent). In some assays, the size of the amplification product is detected and compared to the length of a control sample; for example, deletions and insertions can be detected by a change in size of the amplified product compared to a normal genotype.

The neighboring sequence can be used to design SNP detection reagents such as oligonucleotide probes and primers. Common SNP genotyping methods include, but are not limited to, TaqMan assays, molecular beacon assays, nucleic acid arrays, allele-specific primer extension, allele-specific PCR, arrayed primer extension, homogeneous primer extension assays, primer extension with detection by mass spectrometry, pyrosequencing, multiplex primer extension sorted on genetic arrays, ligation with rolling circle amplification, homogeneous ligation, multiplex ligation reaction sorted on genetic arrays, restriction-fragment length polymorphism, single base extension-tag assays, and the Invader assay. Such methods may be used in combination with detection mechanisms such as, for example, luminescence or chemiluminescence detection, fluorescence detection,

time-resolved fluorescence detection, fluorescence resonance energy transfer, fluorescence polarization, mass spectrometry, and electrical detection.

Other suitable methods for detecting polymorphisms include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA duplexes, comparison of the electrophoretic mobility of variant and wild type nucleic acid molecules, and assaying the movement of polymorphic or wild-type fragments in polyacrylamide gels containing a gradient of denaturant using denaturing gradient gel electrophoresis (DGGE). Sequence variations at specific locations can also be assessed by nuclease protection assays such as Rnase and S1 protection or chemical cleavage methods.

Another method for genotyping SNPs is the use of two oligonucleotide probes in an oligonucleotide ligation assay (OLA). Other methods that can be used to genotype the SNPs include single-strand conformational polymorphism (SSCP).

B. Identification of Biochemical and Morphological Alterations

In some embodiments, subjects are selected for treatment based on identification of biochemical or morphological alterations or abnormalities in hemoglobin, or hemoglobin synthesizing cells such as hematopoietic stem cells, erythrocyte progenitor cells, erythrocytes, macrophage, retinal pigment epithelial cells, alveolar type II (ATII) cells, and others. The methods typically include identifying one or more biochemical or morphological alterations that is/are associated with a genetic alteration in the human beta-globin gene, or otherwise diagnostic of sickle cell disease, a beta-thalassemia, or a related disorder. Methods of diagnosing sickle cell disease, beta-thalassemia, or a related disorder according to biochemical or morphological alterations in the hemoglobin or hemoglobin synthesizing cells are known in the art, and include but are not limited to, analysis of erythrocyte morphology, osmotic fragility, hemoglobin composition, globin synthesis rates, and red blood cell indices.

In some embodiments, the method includes first testing a subject's blood for HbS, and selecting the subject for treatment if HbS is present. Methods for testing a

subject's blood for the presence of HbS include solubility tests (e.g., SICKLEDEX) and sickling test. With the SICKLEDEX test, if HbS is present in a sample, it becomes insoluble and forms a cloudy suspension. Other hemoglobins are more soluble and will form a transparent solution. A sickling test can be used to determine if a red blood cell changes into a sickle shape after a blood sample is mixed with a reducing agent and identifying morphological changes to shape of red blood cells (i.e., "sickling") by microscopy. Shape change of red blood cells may also be analyzed for shape change using a flow cytometer such as the Amnis ImageStreamX Mark II Imaging Flow Cytometer (MilliporeSigma). Shape change of red blood cells may be quantitated using a software program such as IDEAS application software (MilliporeSigma) using a modified protocol as described in "Imaging flow cytometry for automated detection of hypoxia-induced erythrocyte shape change in sickle cell disease." van Beers EJ, et al. Am J Hematol. 2014;89(6):598–603; or as described in "Sickle Cell Imaging Flow Cytometry Assay (SIFCA)." Fertrin KY, et al. Methods Mol Biol. 2016;1389:279–292.

Other suitable tests include, hemoglobin electrophoresis, which employs gel electrophoretic techniques to separate out the various types of hemoglobin from a blood sample obtained from the subject. The test can detect abnormal levels of HbS, as well as other abnormal hemoglobins, such as hemoglobin C. It can also be used to determine whether there is a deficiency of any normal form of hemoglobin, as in various thalassemias. Alternatives to electrophoretic techniques include isoelectric focusing and chromatographic techniques. Other tests that can be used to select a subject for treatment with the compositions and methods disclosed herein include tests typically employed as part of a hemoglobinopathy screen, for example, a complete blood count (CBC) or iron study (ferritin). For example, a blood count can be used to detect anemia, and a blood smear and be used to identify sickled cells.

EXAMPLES

General Procedure A: Ipso substitution of 6-chloro-5-nitro-nicotinic acid methyl ester

To a DMF or THF solution of a 6-chloro-5-nitro-nicotinic acid methyl ester is added 2 M methylamine in THF and the reaction mixture stirred at room temperature for 16 h. The resulting mixture is poured into water to precipitate the product. The precipitate may be filtered and dried to give the product, which may not be purified further before use in the next step.

General Procedure B: Reduction of nitro group to amine

10% Pd/C is added to a solution of the nitro compound in methanol. The resulting mixture is stirred at room temperature under a H_2 atmosphere for 16 h. The contents may then be filtered through a pad of Celite or silica gel and the solid washed with portions of methanol. The filtrate and washings are combined and evaporated to afford the corresponding diamine, which may not be purified further before use in the next step.

General Procedure C: Thiourea formation and its conversion to 2-amino-imidazopyridine

1,1'-Thiocarbonylimidazole is added to a solution of an amine with triethylamine (1 eq.) in acetonitrile (10 mL). The reaction mixture is stirred at room temperature (1-24 h). The solvent is then evaporated, and the product suspended in acetonitrile. The solvent is then evaporated to produce the product as a precipitate. The precipitate is filtered and washed with acetonitrile and dried. The product may be used directly in the next step without further purification.

To the product obtained immediately above is added EDAC at room temperature followed by a substituted diaminopyridine, and the reaction mixture is stirred at 90 ^{o}C for 16 h. The reaction mixture is then cooled to room temperature, poured into cold water, and the solid collected by filtration. The crude product thus obtained may be purified by trituration with methanol.

General Procedure D: Hydrolysis of ester

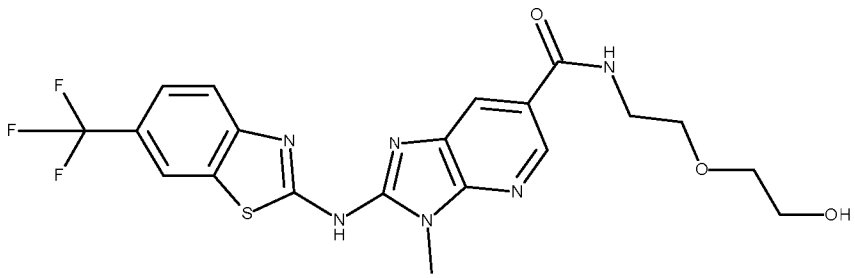
A solution of NaOH in water is added to a solution of an ester in 1:1 THF/MeOH, and the resulting mixture is stirred at 60 °C for 16 h. After completion of the reaction, the mixture is concentrated under vacuum. The pH of the resulting suspension may be adjusted by the dropwise addition of 6 N HCl to pH ~3, and the precipitate collected by filtration, washed with water and dried under vacuum. The desired carboxylic acid may be used without purification.

General Procedure E: Amide formation using HBTU as coupling reagent

To a solution of a carboxylic acid in dry DMF is added DIEA followed by HBTU, and the reaction mixture is stirred at room temperature for 30 min. An appropriate amine is then added, and the reaction stirred at room temperature for 16 h. The contents may be diluted with ice-water, and the product precipitated. The product may be isolated after filtration either with subsequent washings with water and DCM/methanol or through silica gel chromatography using hexanes/ethyl acetate (from 80:20 to 60:40) as an eluent system.

Compound 473

N-[2-(2-Hydroxyethoxy)ethyl]-3-methyl-2-[[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino]imidazo[4,5-b]pyridine-6-carboxamide



6-Methylamino-5-nitro-nicotinic acid methyl ester (5.0 g) was prepared by following General Procedure A starting from 6-chloro-5-nitro-nicotinic acid methyl ester

(5.0 g) and methylamine (33% in EtOH, 24 mL) in THF (150 mL). The crude product was used in the next step without further purification.

5-Amino-6-methylamino-nicotinic acid methyl ester (4.8 g) was prepared by following General Procedure B starting from 6-methylamino-5-nitro-nicotinic acid methyl ester (5.0 g) and Pd/C (20% by weight, 1.0 g) in methanol:THF (1:1, 50 mL). The crude product was used in the next step without further purification.

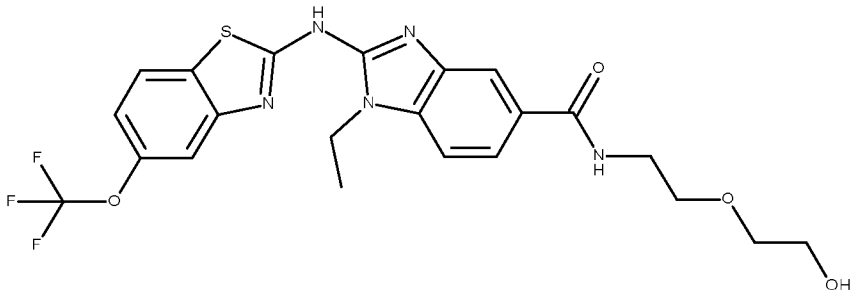
Methyl 3-methyl-2-[[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino]imidazo[4,5-b]pyridine-6-carboxylate (5.0 g) was prepared by following General Procedure C starting from 6-(trifluoromethyl)-1,3-benzothiazol-2-amine (5.0 g), 5-amino-6-methylamino-nicotinic acid methyl ester (5.0 g), 1,1'-thiocarbonyl-diimidazole (5.0 g), and EDAC (4.5 g) . The crude product was used in next step without further purification.

3-Methyl-2-[[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino]imidazo[4,5-b]pyridine-6-carboxylic acid (4.2 g) was prepared by following General Procedure D starting from methyl 3-methyl-2-[[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino]imidazo[4,5-b]pyridine-6-carboxylate (5.0 g) and NaOH (2N, 25 mL) in methanol:THF (2:1, 50 mL). The crude product was used in next step without further purification.

N-[2-(2-Hydroxyethoxy)ethyl]-3-methyl-2-[[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino]imidazo[4,5-b]pyridine-6-carboxamide (40 mg) was prepared by following General Procedure E starting from 3-methyl-2-[[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino]imidazo[4,5-b]pyridine-6-carboxylic acid (100 mg), 2-(2-aminoethoxy)ethanol (100 mg), HBTU (200 mg) and DIEA (0.2 mL) in DMF (2.0 mL). LC/MS: m/z 481.7. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.67-8.59 (m, 2H), 8.29-8.23 (d, 2H), 7.71-7.69 (d, 1H), 4.61 (s, 1H), 3.68 (br s, 3H), 3.57-3.44 (m, 8H), 3.32 (br s, 2H).

Compound 474

1-Ethyl-N-[2-(2-hydroxyethoxy)ethyl]-2-[[5-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino]benzimidazole-5-carboxamide



1-Ethyl-N-[2-(2-hydroxyethoxy)ethyl]-2-[[5-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino]benzimidazole-5-carboxamide (40 mg) was prepared by following General Procedure E starting from 3-ethyl-2-[[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino]imidazo[4,5-b]pyridine-6-carboxylic acid (100 mg) (See WO '018), 2-(2-aminoethoxy)ethanol (100 mg), HBTU (200 mg) and DIEA (0.2 mL) in DMF (2.0 mL). LC/MS: m/z 510.7.

General Assay Methods

Western blot assay

About 20-50 µg of protein is separated by SDS-polyacrylamide gel electrophoresis, and transferred to nitrocellulose membranes. Membranes are blocked in 5% dry milk containing TBS-T for 30 minutes followed by one hour and incubated with HbF or actin antibodies. After several washes, membranes are incubated with 1:10000 diluted HRP-conjugated secondary antibody (Thermo Scientific), developed with ECL Prime reagent (GE Healthcare Bio-sciences). Images may be captured on a Bio-Rad Chemi-Doc MP Imaging System and protein bands quantified by densitometry.

Flow cytometry assay

About 5 x 105 cells are harvested after treatment with compound, washed twice with ice cold phosphate buffered saline and resuspended in 4% paraformaldehyde for 40 minutes at 37 °C. Fixed cells are permeabilized with ice-cold acetone/methanol (4:1) and washed with phosphate buffered saline followed

by incubation with FITC-conjugated anti-HbF antibody (1:1000, Abcam) for 20 minutes. The labeled cells may be analyzed using a Becton Dickerson LSR-II flow cytometer (BD Bioscience, San Jose, CA, USA) and FlowJo v0.9 software.

Example 1

KU812, a human leukemic cell line that expresses the fetal gamma-globin and adult beta-globin genes, was used as a system for screening. KU812 cells have comparable globin gene response patterns as primary erythroid cells after treatments with potential HbF inducers. (See Zein S, Lou RF, Sivanand S, Ramakrishnan V, Mackie A, Li W, Pace BS. KU812 Cell Line: model for identifying fetal hemoglobin inducing drugs. Exp Biol Med (Maywood) 235:1385-94, 2010.) KU812 cells were grown in Iscove's Modified Dulbecco Media (IMDM) and 10% fetal bovine serum until in log phase growth.

KU812 cells in log growth phase were treated with compounds 73, 134, 473 and 236 (See Table A) at a doses of 0.5, 2.5, 5.0 and 20 μM for 48 hours. At harvest, cell counts and viability were measured by 0.4% Trypan blue exclusion. See Figures 1A-1D. Compounds 134 and 473 had minimal effects on cell growth rates and viability remained >90% at the widest range of drug concentrations (See Figures 1B and 1C, respectively).

Western blot analysis was also conducted to determine level of induction of HbF in KU812 cells by Compounds 73, 134, 473, and 236. Hydroxyurea and hemin were used as positive controls, and ß-actin was used as a protein loading control. Compounds 73, 134 and 473 each showed HbF induction, and compounds 134 and 473 increased HbF at concentrations between 0.5 to 5 μM (Figure 1E). Compound 236 did not show significant induction of HbF by Western blot analysis at the tested concentrations.

Flow cytometry was conducted for KU812 cells following treatment with Compounds 473 and 236 at various concentrations (0.5, 2.5, 5, 10, and 20 μM). An increase in the number of HbF positive cells (F-cells) and increased mean fluorescence intensity (MFI) was observed for Compound 473 (Figure 2). By

contrast, Compound 236 did not significantly increase F-cells at these concentrations, but some increase in MFI was observed (data not shown). Compounds 73 and 134 were not analyzed by flow cytometry.

Example 2

To test compounds under conditions more closely modeling physiological conditions for one with a SCD, sickle erythroid progenitor cells were cultured for 10 days and then treated with Compound 473 for 48 hours at concentrations of 0.5 μM and 2.5 μM. Treated cells were analyzed by western blot for levels of expression of HbF, HbS, and β-actin relative to cells treated with DMSO, hemin, or HU. The same treated cells were also analyzed by flow cytometry for γ-globin gene expression relative to cells treated with DMSO, hemin, or HU. Compound 473 (0.5 μM and 2.5 μM) induced γ-globin gene expression by 1.6 and 1.9 fold, respectively, without affecting HbS protein levels. See Figure 3A. Increased F-cell levels were observed by flow cytometry. See Figure 3B.

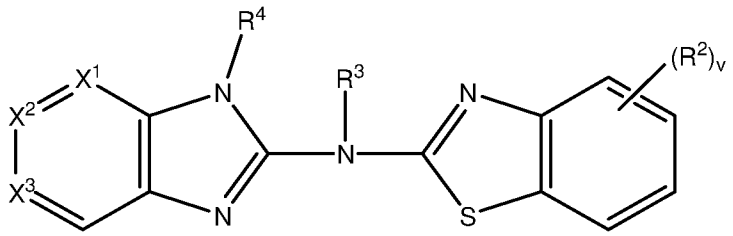
Anti-sickling activity was observed in treated cells under hypoxia conditions. As described above, sickle erythroid progenitor cells were cultured for 10 days and then treated with Compound 473 for 48 hours at concentrations of 0.5 μM and 2.5 μM or with hemin (about 50 μM) or with HU (about 100 μM). Treated cells were then subjected to hypoxia conditions (1% O_2 and 5% CO_2). Cells treated with Compound 473 at concentrations of 0.5 μM and 2.5 μM significantly decreased the percent of sickled cells compared to DMSO control. See Figures 4A and 4B.

CLAIMS

I claim:

1. A method of treating a sickle cell disorder or complication thereof in a subject comprising:

administering to the subject a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein a compound of Formula (I) has the structure shown below

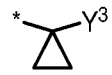


(I)

wherein

X^1 is =N- or =CH-;

X^2 is =C(R^1)- and X^3 is =C(-L-G)-; or X^2 is =C(-L-G)- and X^3 is =C(R^1)-;

G is hydrogen, -C_{1-8} alkyl, -C_{3-10} cycloalkyl, -C_{1-6} alkylene-C_{3-10} cycloaklyl, heterocyclyl, -C_{1-6} alkylene-C_{3-10} heterocyclyl, phenyl, heteroaryl, or $NR^h R^k$, where the alkyl, alkylene, cycloalkyl, heterocyclyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^c; or G is -CH_2Y^3, -$CH_2CH_2Y^3$, -$CH_2CH_2CH_2Y^3$, -$CH(CH_3)CH_2Y^3$, -$CH_2CH(Y^3)CH_3$, -$CH(Y^3)CH_3$, -$CH_2C(Y^3)(CH_3)_2$, -$C(Y^3)(CH_3)_2$, or  , where Y^3 is cyclopropyl, -CF_3, -OCF_3, -OCH_3, -OCH_2CH_3, -F, -Cl, -OH, -$O(CH_2)_2$-OH, -$O(CH_2)_2$-F, -SCH_3, -$S(O)_2$-CH_3, -SCH_2CH_3, -$S(O)_2CH_2CH_3$, -NH-CH_3, -NH-CH_2CH_3, -$N(CH_3)_2$, tetrahydropyran-4-yl, tetrahydrofuran-2-yl, morpholin-2-yl, morpholin-4-yl, piperidin-1-yl, 4-hydroxy-piperidin-

1-yl, 3-hydroxy-piperidin-1-yl, -NH-C(O)-CH_3, -NH-C(O)-CH_2CH_3, tetrahydrofuran-2-yl-methyloxy, or -C(O)-Y^4, where Y^4 is -OH, -OCH_3, -OCH_2CH_3, -$OC(CH_3)_3$, -NH_2, -NH-CH_3, -NH-CH_2CH_3, -$N(CH_3)_2$, -$N(CH_2CH_3)_2$, morpholin-4-yl, 4-methyl-piperazin-1-yl, pyrrolidin-1-yl, or piperazin-1-yl;

L is -CH_2-C(O)N(R^6)-, -C(O)N(R^6)-, -C(O)-O-, -SO_2-, -C(O)-, heteroarylene optionally substituted one or more times with substituents independently selected from R^x, or heterocyclylene optionally substituted one or more times with substituents independently selected from R^x; or the group -L-G is -cyano;

R^1 is hydrogen, R^a, phenyl, or heteroaryl, where the phenyl and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^x;

R^2 is R^b;

R^3 is hydrogen, -C_{1-6} alkyl, or -C_{1-6} alkylene-C_{3-10} cycloaklyl, where the alkyl, alkylene, and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^z;

R^4 is -C_{1-6} alkyl or -C_{1-6} alkylene-C_{3-10} cycloaklyl, where the alkyl, alkylene, and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^y;

R^6 is hydrogen, -C_{1-6} alkyl, -C_{1-6} alkylene-C_{3-10} cycloaklyl, where the alkyl, alkylene, and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^x;

R^a is

a) -halogen,

b) -C_{1-6} alkyl,

c) -C_{3-10} cycloalkyl,

d) -heterocyclyl,

e) -cyano,

f) -CF_3,

g) -OCF_3,
h) -O-R^d,
i) -$S(O)_w$-R^d,
j) -$S(O)_2O$-R^d,
k) -NR^dR^e,
l) -C(O)-R^d,
m) -C(O)-O-R^d,
n) -OC(O)-R^d,
o) -$C(O)NR^d$ R^e,
p) -C(O)-heterocyclyl,
q) -NR^d C(O)R^e,
r) -$OC(O)NR^d$ R^e,
s) -NR^d $C(O)OR^d$, or
t) -NR^d $C(O)NR^d$ R^e,

where the alkyl, cycloalkyl, and heterocyclyl groups are optionally substituted one or more times with substituents independently selected from R^y;

R^b is

a) -halogen,
b) -C_{1-6} alkyl,
c) -C_{3-10} cycloalkyl,
d) -heterocyclyl,
e) -phenyl,
f) -heteroaryl,
g) -cyano,
h) -CF_3,
i) -OCF_3,
j) -O-R^f,
k) -$S(O)_w$-R^f,
l) -$S(O)_2O$-R^f,

m) –NR^fR^g,
n) -C(O)-R^f,
o) -C(O)-O-R^f,
p) -OC(O)-R^f,
q) -$C(O)NR^f R^g$,
r) -C(O)-heterocyclyl,
s) -$NR^f C(O)R^g$,
t) -$OC(O)NR^f R^g$,
u) -$NR^f C(O)OR^f$, or
v) -$NR^f C(O)NR^f R^g$,

where the alkyl, cycloalkyl, heterocyclyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^z;

R^c is

a) -halogen,
b) -C_{1-6} alkyl,
c) -C_{3-10} cycloalkyl,
d) -heterocyclyl,
e) -cyano,
f) -CF_3,
g) -OCF_3,
h) -O-R^h,
i) -$S(O)_w$-R^h,
j) -$S(O)_2O$-R^h,
k) -NR^hR^k,
l) -C(O)-R^h,
m) -C(O)-O-R^h,
n) -OC(O)-R^h,
o) -$C(O)NR^h R^k$,
p) -C(O)-heterocyclyl,

q) $-NR^h C(O)R^k$,

r) $-OC(O)NR^h R^k$,

s) $-NR^h C(O)OR^k$,

t) $-NR^h C(O)NR^h R^k$,

u) $-NR^h S(O)_wR^k$,

v) -phenyl,

w) -heteroaryl, or

x) $-O-(C_{1-4}$ alkylene)$-O-(C_{1-4}$ alkylene)$-N(R^h)C(O)-OR^k$,

where the alkylene, alkyl, cycloalkyl, heterocyclyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^x;

R^d and R^e are independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl, where the alkyl and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^y; or, if R^d and R^e are both attached to the same nitrogen atom, together with that nitrogen atom may optionally form a heterocyclic ring selected from the group consisting of azetidino, pyrrolidino, pyrazolidino, imidazolidino, oxazolidino, isoxazolidino, thiazolidino, isothiazolidino, piperidino, piperazino, morpholino, thiomorpholino, and azepano, where each ring is optionally substituted one or more times with substituents independently selected from R^y;

R^f and R^g are independently hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, phenyl, or heteroaryl, where the alkyl, cycloalkyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^z; or, if R^f and R^g are both attached to the same nitrogen atom, together with that nitrogen atom may optionally form a heterocyclic ring selected from the group consisting of azetidino, pyrrolidino, pyrazolidino, imidazolidino, oxazolidino, isoxazolidino, thiazolidino, isothiazolidino, piperidino, piperazino, morpholino,

thiomorpholino, and azepano, where each ring is optionally substituted one or more times with substituents independently selected from R^z;

R^h and R^k are independently hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, heterocyclyl, phenyl, or heteroaryl, where the alkyl, cycloalkyl, heterocyclyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^x; or, if R^h and R^k are both attached to the same nitrogen atom, together with that nitrogen atom may optionally form a heterocyclic ring selected from the group consisting of azetidino, pyrrolidino, pyrazolidino, imidazolidino, oxazolidino, isoxazolidino, thiazolidino, isothiazolidino, piperidino, piperazino, morpholino, thiomorpholino, and azepano, where each ring is optionally substituted one or more times with substituents independently selected from R^x;

R^y is

a) -halogen,

b) $-NH_2$,

c) -cyano,

d) -carboxy,

e) -hydroxy,

f) -thiol,

g) $-CF_3$,

h) $-OCF_3$,

i) $-C(O)-NH_2$,

j) $-S(O)_2-NH_2$,

k) oxo,

l) $-C_{1-6}$ alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}\text{ alkyl})_2$,

m) -heterocyclyl optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

n) -C_{3-10} cycloalkyl optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

o) -O-C_{1-6} alkyl optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

p) -O-C_{3-10} cycloalkyl optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

q) -NH-C_{1-6} alkyl optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

r) -N(C_{1-6} alkyl)$_2$ optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

s) -C(O)-C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

t) -C(O)-O-C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of

halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

u) -S-C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

v) -$S(O)_2$-C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

w) -C(O)-NH-C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

x) -C(O)-N(C_{1-6} alkyl)$_2$, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

y) -$S(O)_2$-NH-C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

z) -$S(O)_2$-N(C_{1-6} alkyl)$_2$, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

aa) -NH-C(O)-C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, $-NH_2$, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$, or

bb) -NH-S(O)$_2$-C$_{1-6}$ alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C$_{1-6}$ alkyl, -NH$_2$, -NH-C$_{1-6}$ alkyl, and -N(C$_{1-6}$ alkyl)$_2$;

R^x is

a) -R^y

b) -phenyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C$_{1-6}$ alkyl, -NH$_2$, -NH-C$_{1-6}$ alkyl, and -N(C$_{1-6}$ alkyl)$_2$,

c) -heteroaryl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, -OH, -O-C$_{1-6}$ alkyl, -NH$_2$, -NH-C$_{1-6}$ alkyl, and -N(C$_{1-6}$ alkyl)$_2$,

d) -O-phenyl,

e) -O-heteroaryl,

f) -C(O)-phenyl,

g) -C(O)-heteroaryl,

h) -C(O)-O-phenyl, or

i) -C(O)-O-heteroaryl;

R^z is

a) -R^y

b) -phenyl,

c) -heteroaryl;

d) -O-phenyl,

e) -O-heteroaryl,

f) -C(O)-phenyl,

g) -C(O)-heteroaryl,

h) -C(O)-O-phenyl, or

i) -C(O)-O-heteroaryl;

v is an integer from 0 to 4, and

w is an integer from 0 to 2.

2. The method of claim 1, wherein

a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof is an amount sufficient to increase expression of fetal hemoglobin expression (HbF) in the subject.

3. The method of claim 1, wherein

a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof is an amount sufficient to inhibit polymerization of HbS, increase dissolved oxygen levels in a subject's blood, or reduce levels of reactive oxygen species (ROS).

4. The method of claim 1, wherein

a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof is an amount sufficient to reduce blood cell sickling in response to reduced air pressure, reduced barometric pressure, reduced partial pressure of oxygen, or hypoxia.

5. The method of claim 1, wherein

a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof is an amount sufficient to reduce incidences or rate of painful crises, reduce incidences or rate of painful crises requiring hospitalization, reduce incidences of chest syndrome, reduce the number of transfusion events, or reduce the number of units of blood transfused per event.

6. The method of claim 1, wherein

a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof is an amount sufficient to treat hemolytic anemia; a vaso-occlusive crisis; or multiple organ damage from microinfarcts.

7. The method of any of the previous claims, wherein further comprising the step of selecting the subject for treatment.

8. The method of claim 7, wherein the subject is selected for treatment when the subject exhibits one or more of the clinical symptoms of sickle cell disease, beta-thalassemia, or a related disorder.

9. The method of claim 7, wherein the subject is selected for treatment when the subject exhibits a genetic or biochemical indicator of sickle cell disease, beta-thalassemia, or a related disorder.

10. The method of claim 7, wherein the method further comprises the step of determining whether a subject is at risk for or has sickle cell disease, beta-thalassemia, or a related disorder by
obtaining or having obtained a biological sample from the subject and
performing or having performed a bodily fluid test on the biological sample to determine if the subject has a biomarker or genetic mutation associated with sickle cell disease, beta-thalassemia, or a related disorder.

11. The method of any of the preceding claims, wherein the method further comprises the steps of
obtaining or having obtained biological samples over a period of time from the subject, and

performing or having performed a bodily fluid test on the biological samples to determine whether the level of one or more biochemical markers are increasing or decreasing, and

if the level of one or more biochemical markers are not trending in the desired direction then administering a greater dose of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

12. The method of any of the previous claims, wherein a compound of Formula (I) or a pharmaceutically acceptable salt thereof is administered in combination with another active compound.

13. The method of claim 10, wherein the another active compound is selected from the group consisting of hydroxyurea, dimethyl fumarate, monomethyl fumarate, and bardoxolone methyl.

14. A compound, wherein the compound is N-[2-(2-Hydroxyethoxy)ethyl]-3-methyl-2-[[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino]imidazo[4,5-b]pyridine-6-carboxamide or a pharmaceutically acceptable salt thereof.

15. 1-Ethyl-N-[2-(2-hydroxyethoxy)ethyl]-2-[[5-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino]benzimidazole-5-carboxamide or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a compound of claim 14 and a pharmaceutically acceptable carrier.

17. A pharmaceutical composition comprising a compound of claim 15 and a pharmaceutically acceptable carrier.

Fig. 1A

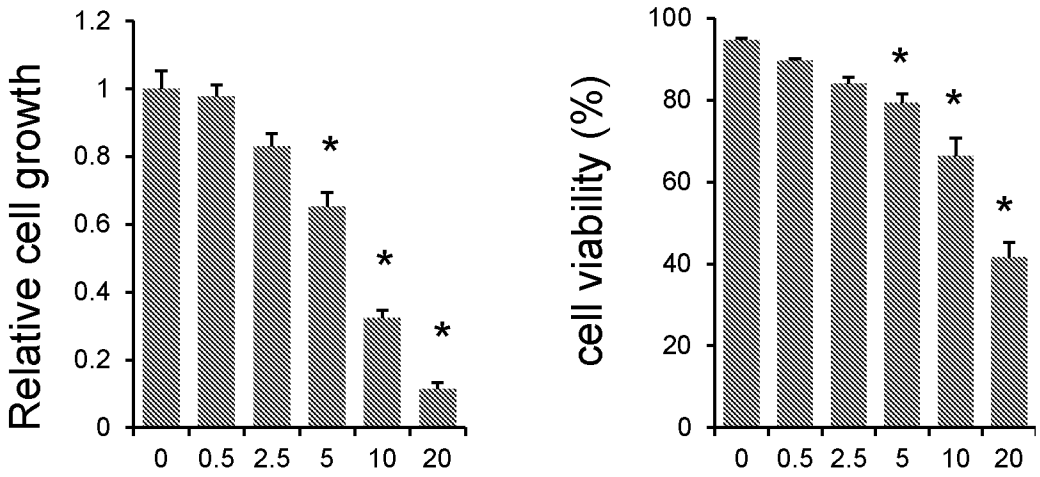

Compound 73
Relative cell growth
1.2
1
0.8
0.6
0.4
0.2
0
0 0.5 2.5 5 10 20
*
cell viability (%)
100
80
60
40
20
0
0 0.5 2.5 5 10 20
*

Fig. 1B

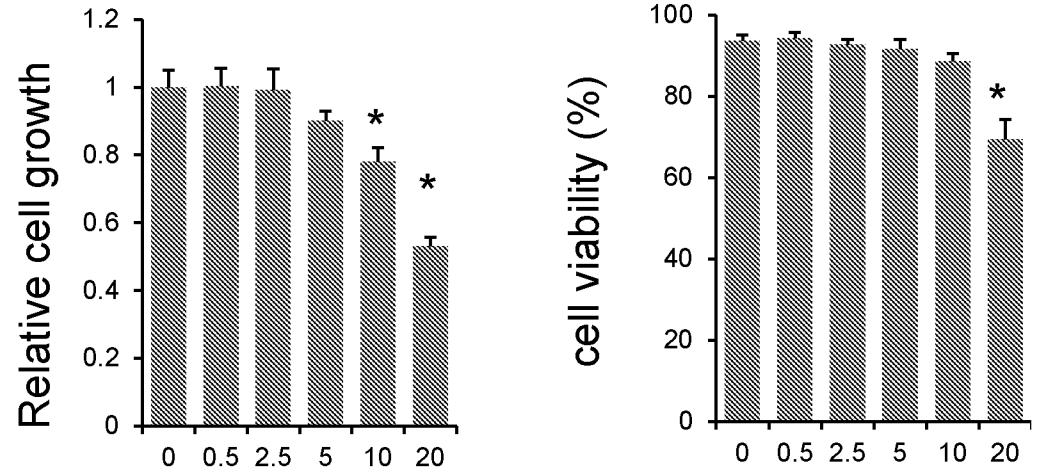

Compound 134
Relative cell growth
1.2
1
0.8
0.6
0.4
0.2
0
0 0.5 2.5 5 10 20
*
cell viability (%)
100
80
60
40
20
0
0 0.5 2.5 5 10 20
*

Fig. 1C Compound 473

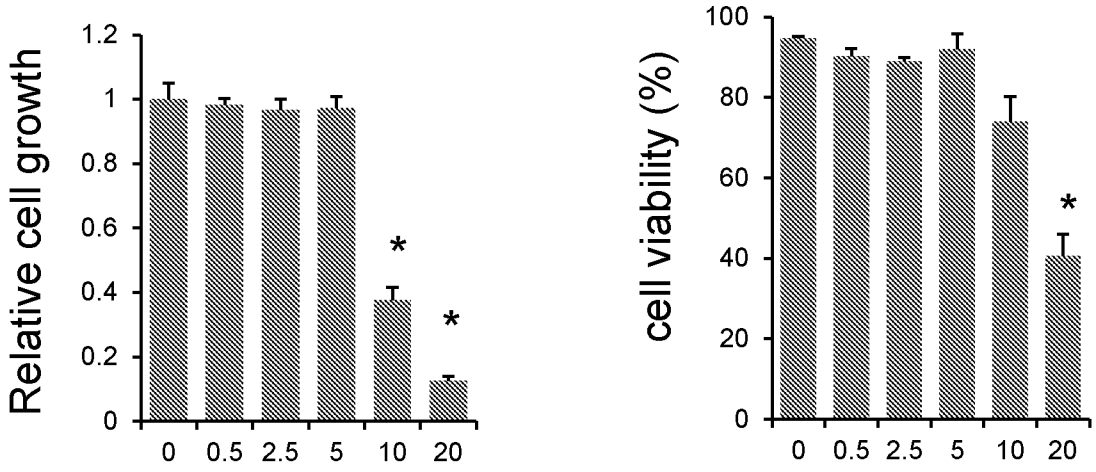
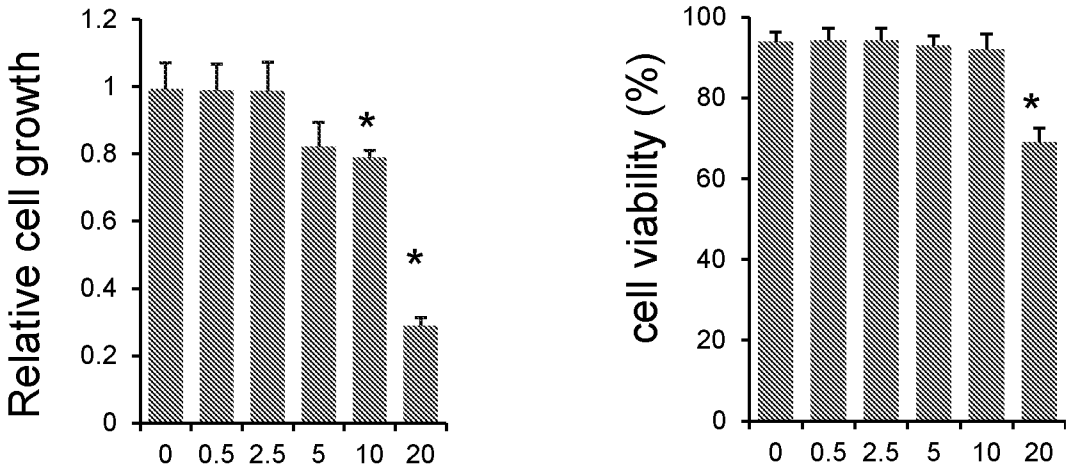


Fig. 1D Compound 236



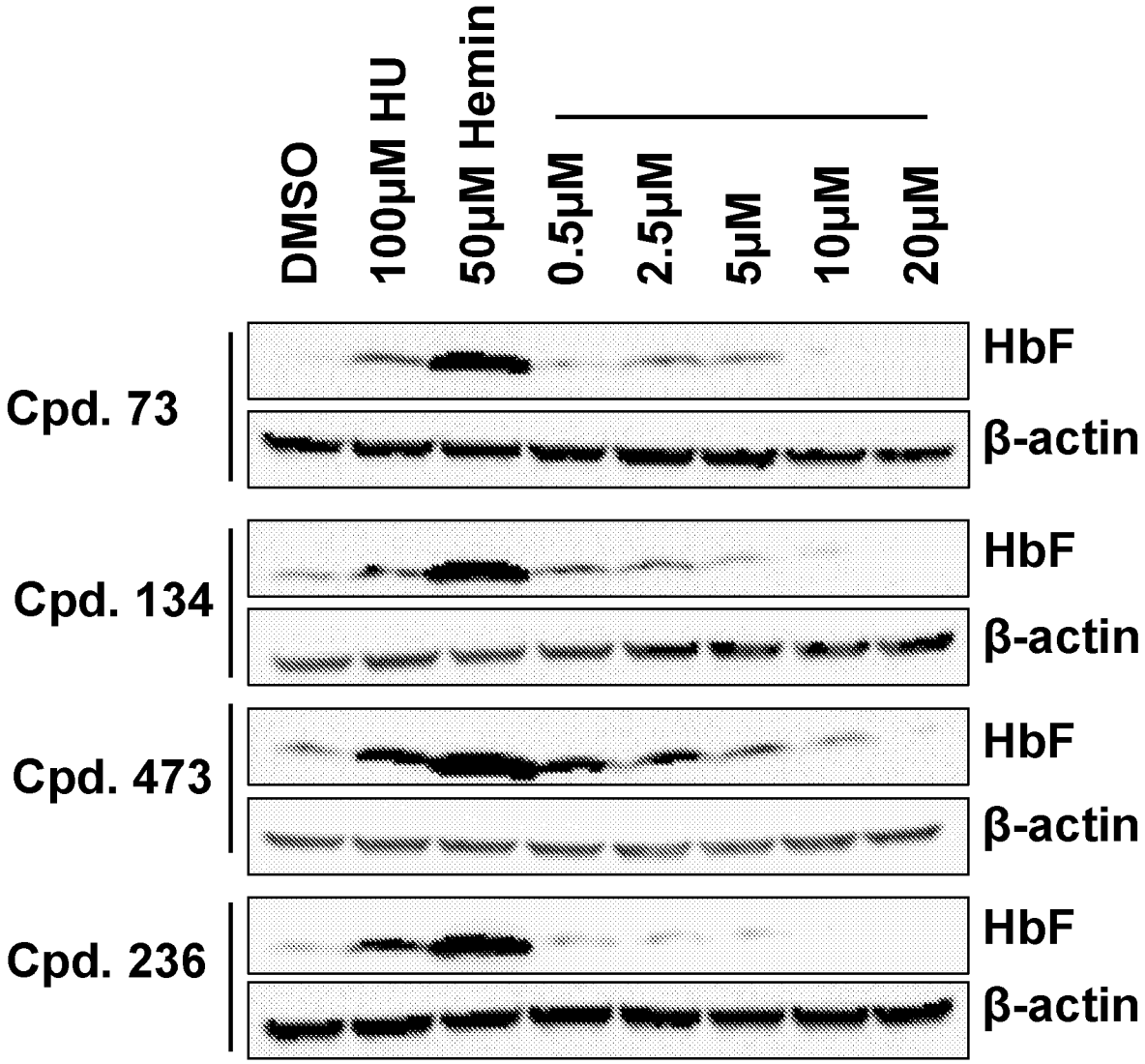

DMSO
100μM HU
50μM Hemin
0.5μM
2.5μM
5μM
10μM
20μM
Cpd. 73
HbF
β-actin
Cpd. 134
HbF
β-actin
Cpd. 473
HbF
β-actin
Cpd. 236
HbF
β-actin

Fig. 1E

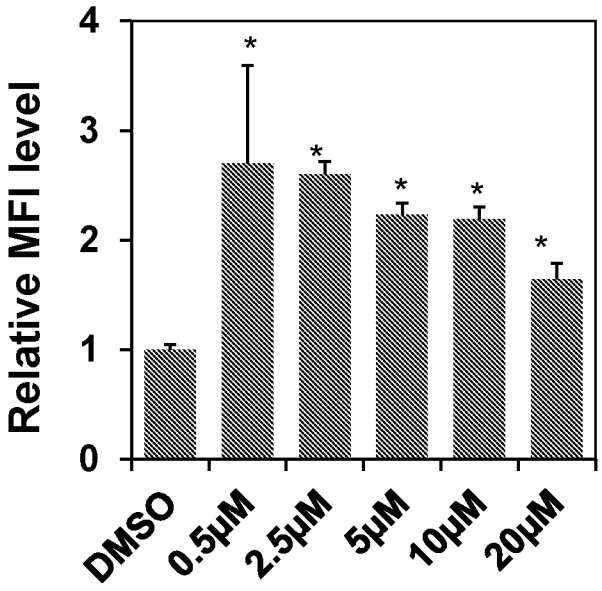


Fig. 2

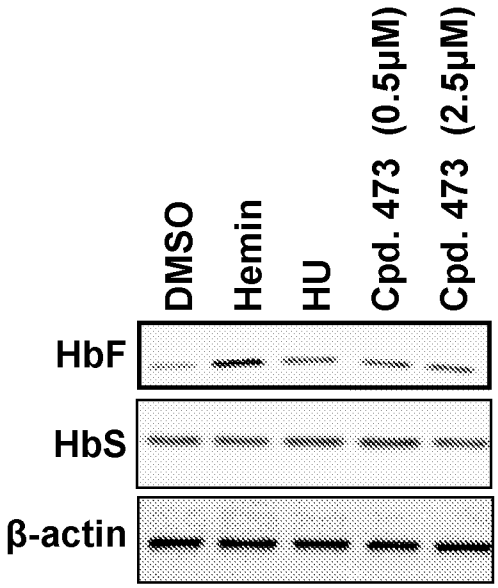


Fig. 3A

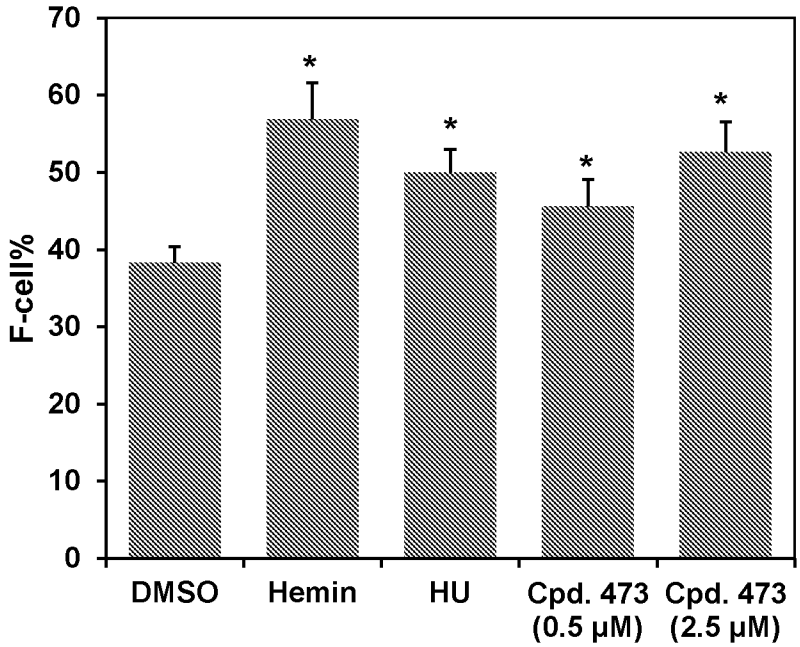

70
60
50
40
30
20
10
0
F-cell%
*
*
*
*
DMSO
Hemin
HU
Cpd. 473 (0.5 μM)
Cpd. 473 (2.5 μM)

Fig. 3B

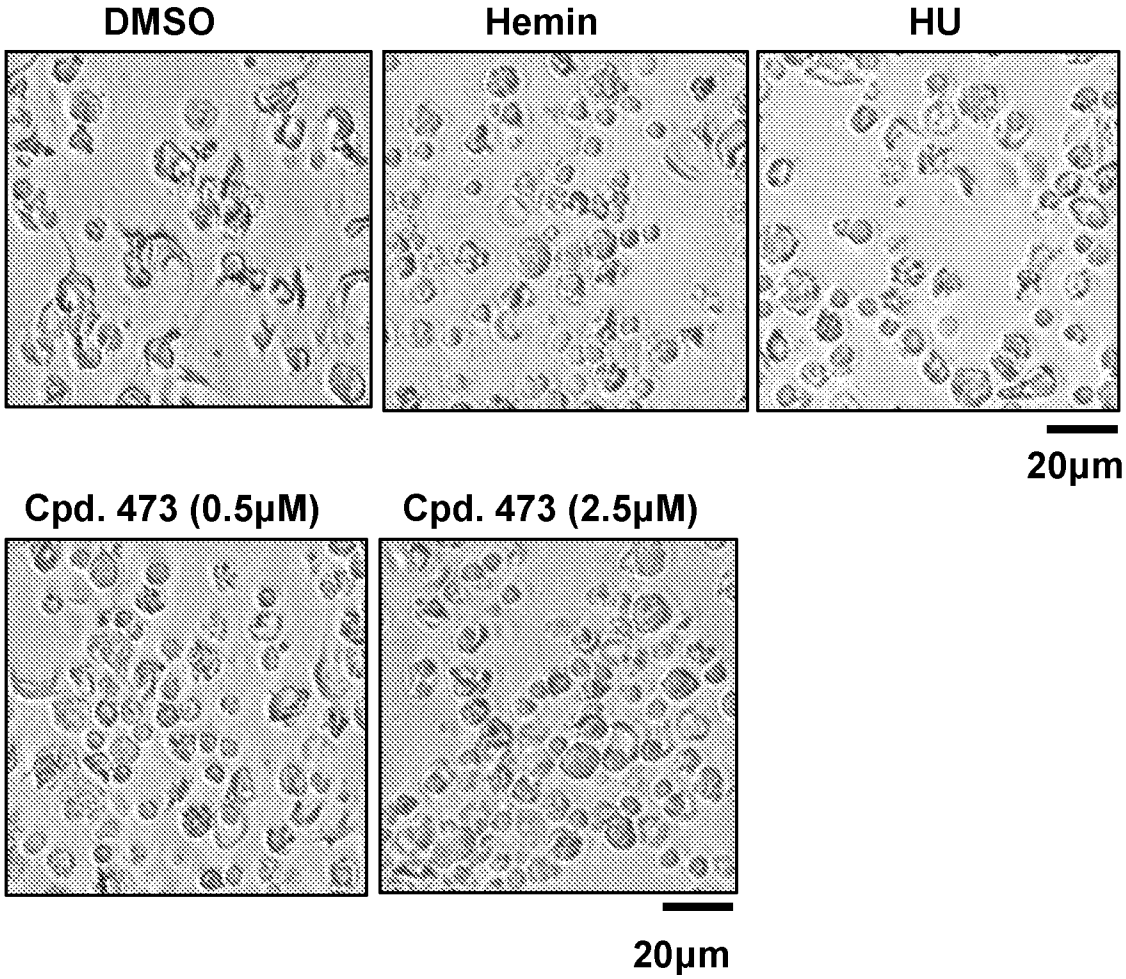


Fig. 4A

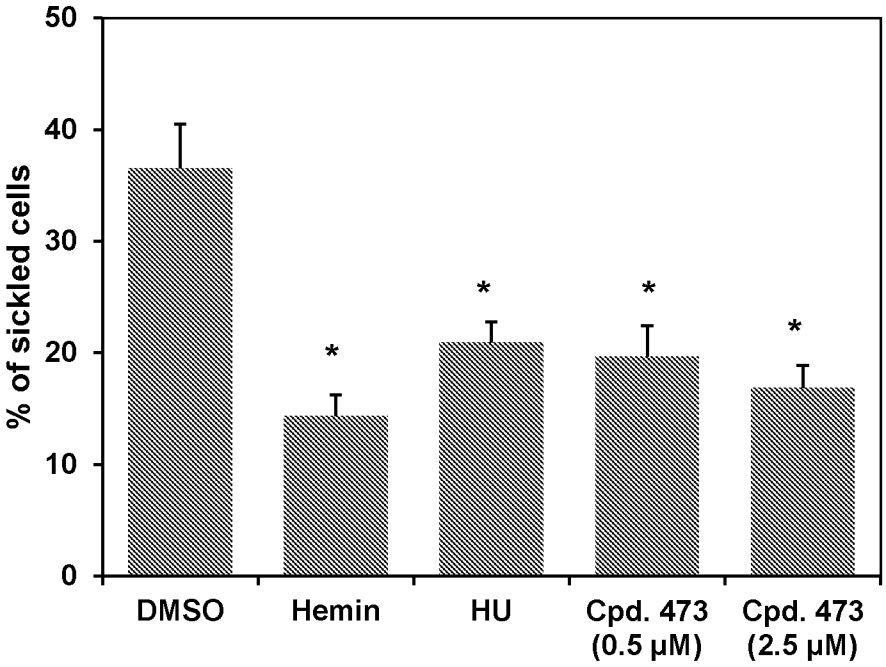

50
40
30
20
10
0
% of sickled cells
*
*
*
*
DMSO
Hemin
HU
Cpd. 473 (0.5 µM)
Cpd. 473 (2.5 µM)

Fig. 4B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/13616

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/428; A61K 31/437; A61K 31/4188 (2020.01)

CPC - C07D 235/30; C07D 417/12; C07D 513/04

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)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	US 8,759,535 B2 (MJALLI et al.) 24 June 2014 (24.06.2014) col 2, ln 57 to col 3, ln 7; col 7, ln 11-26; Table 1; Table 2	14-17 ---------- 1-10
Y	BELCHER et al. 'Control of Oxidative Stress and Inflammation in Sickle Cell Disease with the Nrf2 Activator Dimethyl Fumarate', ANTIOXIDANTS & REDOX SIGNALING, 2017, Volume 26, Number 14, pp. 748-762. DOI: 10.1089/ars.2015.6571. abstract; pg 749, col 2, para 4; pg 750, Fig 1; pg 753, col 2, para 1; pg 756, Table 3	1-10
A	US 2017/0174716 A1 (UNIVERSITE PARIS EST CRETEIL VAL DE MARNE et al.) 22 June 2017 (22.06.2017) Entire Document	1-10, 14-17
A	US 2017/0056413 A1 (VTV THERAPEUTICS LLC) 02 March 2017 (02.03.2017) Entire Document	1-10, 14-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"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
16 April 2020	15 MAY 2020
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/13616

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:

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

3. ☒ Claims Nos.: 11-13
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.