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(54) **Human protein-tyrosine phosphatase inhibitors and methods of use**

Hemmer der menschlichen Protein-Tyrosin-Phosphatase und Verfahren zur Verwendung

Inhibiteurs de la protéine-tyrosine phosphatase humaine et leurs procédés d'utilisation

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Description

FIELD

[0001] The present disclosure relates to compounds effective as human protein tyrosine phosphatase beta (HPTP-β) inhibitors thereby regulating angiogenesis. The present disclosure further relates to compositions comprising one or more human protein tyrosine phosphatase beta (HPTP-β) inhibitors, and to methods for regulating angiogenesis.

BACKGROUND

[0002] Angiogenesis, the sprouting of new blood vessels from the pre-existing vasculature, plays a crucial role in a wide range of physiological and pathological processes (Nguyen, L.L. et al., Int. Rev. Cytol., 204, 1-48, (2001)). Angiogenesis is a complex process, mediated by communication between the endothelial cells that line blood vessels and their surrounding environment. In the early stages of angiogenesis, tissue or tumor cells produce and secrete pro-angiogenic growth factors in response to environmental stimuli such as hypoxia. These factors diffuse to nearby endothelial cells and stimulate receptors that lead to the production and secretion of proteases that degrade the surrounding extracellular matrix. The activated endothelial cells begin to migrate and proliferate into the surrounding tissue toward the source of these growth factors (Bussolino, F., Trends Biochem. Sci., 22, 251-256, (1997)). Endothelial cells then stop proliferating and differentiate into tubular structures, which is the first step in the formation of stable, mature blood vessels. Subsequently, periendothelial cells, such as pericytes and smooth muscle cells, are recruited to the newly formed vessel in a further step toward vessel maturation.

[0003] Angiogenesis is regulated by a balance of naturally occurring pro- and anti-angiogenic factors. Vascular endothelial growth factor, fibroblast growth factor, and angiopoeitin represent a few of the many potential pro-angiogenic growth factors. These ligands bind to their respective receptor tyrosine kinases on the endothelial cell surface and transduce signals that promote cell migration and proliferation. Whereas many regulatory factors have been identified, the molecular mechanisms of this process are still not fully understood.

[0004] There are many disease states driven by persistent unregulated or improperly regulated angiogenesis. In such disease states, unregulated or improperly regulated angiogenesis may either cause a particular disease or exacerbate an existing pathological condition. For example, ocular neovascularization has been implicated as the most common cause of blindness and underlies the pathology of approximately 20 eye diseases. In certain previously existing conditions such as arthritis, newly formed capillary blood vessels invade the joints and destroy cartilage. In diabetes, new capillaries formed in the retina invade the vitreous humor, causing bleeding and blindness. Both the growth and metastasis of solid tumors are also angiogenesis-dependent (Folkman et al., "Tumor Angiogenesis," Chapter 10,206-32, in The Molecular Basis of Cancer, Mendelsohn et al., eds., W. B. Saunders, (1995)). It has been shown that tumors which enlarge to greater than 2 mm in diameter must obtain their own blood supply and do so by inducing the growth of new capillary blood vessels. After these new blood vessels become embedded in the tumor, they provide nutrients and growth factors essential for tumor growth as well as a means for tumor cells to enter the circulation and metastasize to distant sites, such as liver, lung or bone (Weidner, NewEng. J. Med., 324, 1, 1-8 (1991)). When used as drugs in tumor-bearing animals, natural inhibitors of angiogenesis may prevent the growth of small tumors (O'Reilly et al., Cell, 79, 315-28 (1994)). In some protocols, the application of such inhibitors leads to tumor regression and dormancy even after cessation of treatment (O'Reilly et al., Cell, 88, 277-85 (1997)). Moreover, supplying inhibitors of angiogenesis to certain tumors may potentiate their response to other therapeutic regimens (Teischer et al., Int J. Cancer, 57, 920-25 (1994)).

[0005] Although many disease states are driven by persistent unregulated or improperly regulated angiogenesis, some disease states could be treated by increased angiogenesis. Tissue growth and repair are biologic events wherein cellular proliferation and angiogenesis occur. Thus an important aspect of wound repair is the revascularization of damaged tissue by angiogenesis.

[0006] Chronic, non-healing wounds are a major cause of prolonged morbidity in the aged human population. This is especially the case in bedridden or diabetic patients who develop severe, non-healing skin ulcers. In many of these cases, the delay in healing is a result of inadequate blood supply either as a result of continuous pressure or of vascular blockage. Poor capillary circulation due to small artery atherosclerosis or venous stasis contributes to the failure to repair damaged tissue. Such tissues are often infected with microorganisms that proliferate unchallenged by the innate defense systems of the body which require well vascularized tissue to effectively eliminate pathogenic organisms. As a result, most therapeutic intervention centers on restoring blood flow to ischemic tissues thereby allowing nutrients and immunological factors access to the site of the wound.

[0007] Atherosclerotic lesions in large vessels may cause tissue ischemia that could be ameliorated by modulating blood vessel growth to the affected tissue. For example, atherosclerotic lesions in the coronary arteries may cause angina and myocardial infarction that could be prevented if one could restore blood flow by stimulating the growth of collateral arteries. Similarly, atherosclerotic lesions in the large arteries that supply the legs may cause ischemia in the

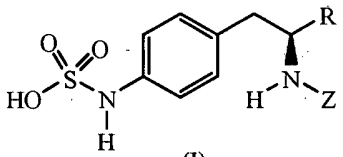
skeletal muscle that limits mobility and in some cases necessitates amputation, which may also be prevented by improving blood flow with angiogenic therapy.

[0008] Other diseases such as diabetes and hypertension are characterized by a decrease in the number and density of small blood vessels such as arterioles and capillaries. These small blood vessels are important for the delivery of oxygen and nutrients. A decrease in the number and density of these vessels contributes to the adverse consequences of hypertension and diabetes including claudication, ischemic ulcers, accelerated hypertension, and renal failure. These common disorders and many other less common ailments, such as Burgers disease, could be ameliorated by increasing the number and density of small blood vessels using angiogenic therapy.

[0009] It has been suggested that one means for regulating angiogenesis is to treat patients with a human protein tyrosine phosphatase beta (HPTP-β) inhibitor (Kruegar et al., EMBO J., 9, (1990)) and, therefore, to satisfy this need the compounds of the present disclosure have been prepared. US2004167183 discloses compounds that are effective in the treatment of protein tyrosine phosphatase (PTPase) mediated disorders such as diabetes. Those compounds differ from compounds of present formula I regarding Z and R.

SUMMARY

[0010] The present disclosure relates to compounds having Formula (I) as shown below:



(I)

or pharmaceutically acceptable salts thereof, wherein the R and Z groups are as defined in the claims. The compounds of Formula (I), and/or their pharmaceutically acceptable salts have been found to be inhibitors of human protein tyrosine phosphatase beta (HPTP-β), and hence are capable of regulating angiogenesis in humans, so as to treat various diseases that include but are not limited to diabetic retinopathy, macular degeneration, cancer, sickle cell anemia, sarcoid, syphilis, pseudoxanthoma elasticum, Paget's disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis/vitritis, mycobacterial infections, Lyme's disease, systemic lupus erythematosis, retinopathy of prematurity, Eales' disease, Behcet's disease, infections causing a retinitis or choroiditis, presumed ocular histoplasmosis, Best's disease, myopia, optic pits, Stargardt's disease, pars planitis, chronic retinal detachment, hyperviscosity syndrome, toxoplasmosis, trauma and post-laser complications, diseases associated with rubeosis, and proliferative vitreoretinopathy, Crohn's disease and ulcerative colitis, psoriasis, sarcoidosis, rheumatoid arthritis, hemangiomas, Osler-Weber-Rendu disease, hereditary hemorrhagic telangiectasia, solid or-blood borne tumors and acquired immune deficiency syndrome, skeletal muscle and myocardial ischemia, stroke, coronary artery disease, peripheral vascular disease, and coronary artery disease.

[0011] The present disclosure further relates to pharmaceutical compositions comprising one or more of the compounds of Formula (I), and pharmaceutically acceptable salts thereof.

[0012] The present disclosure also relates to methods for controlling angiogenesis, and thereby providing a treatment for diseases affected by angiogenesis, said methods comprising administering to a human an effective amount of one or more compounds having Formula (I), and pharmaceutically acceptable salts thereof, as disclosed herein.

DETAILED DESCRIPTION

[0013] In this specification and in the claims that follow, reference will be made to a number of terms, which shall be defined to have the following meanings:

All percentages, ratios and proportions herein are by weight, unless otherwise specifies. All temperatures are in degrees Celsius (° C) unless otherwise specified.

[0014] By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, i.e., the material can be administered to an individual along with the relevant active compound without causing clinically unacceptable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained.

[0015] Throughout the description and claims of this specification the word "comprise" and other forms of the word, such as "comprising" and "comprises," means including, for example, other additives, components, integers, or steps.

[0016] As used in the description and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a composition" includes mixtures of two or more such compositions, reference to "a phenylsulfamic acid" includes mixtures of two or more such phenylsulfamic acids, reference to "the compound" includes mixtures of two or more such compounds.

[0017] "Optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where the event or circumstance occurs and instances where it does not.

[0018] Ranges can be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that when a value is disclosed, then "less than or equal to" the value, "greater than or equal to the value," and possible ranges between values are also disclosed, as appropriately understood by the skilled artisan. For example, if the value "10" is disclosed, then "less than or equal to 10" as well as "greater than or equal to 10" is also disclosed. It is also understood that throughout the application data are provided in a number of different formats and that this data represent endpoints and starting points and ranges for any combination of the data points. For example, if a particular data point "10" and a particular data point "15" are disclosed, it is understood that greater than, greater than or equal to, less than, less than or equal to, and equal to 10 and 15 are considered disclosed as well as between 10 and 15. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0019] An organic unit can have, for example, 1-26 carbon atoms, 1-18 carbon atoms, 1-12 carbon atoms, 1-8 carbon atoms, or 1-4 carbon atoms. Organic radicals often have hydrogen bound to at least some of the carbon atoms of the organic radical. One example, of an organic radical that comprises no inorganic atoms is a 5, 6, 7, 8-tetrahydro-2-naphthyl radical. In some embodiments, an organic radical can contain 1-10 inorganic heteroatoms bound thereto or therein, including halogens, oxygen, sulfur, nitrogen, phosphorus. Examples of organic radicals include an alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, mono-substituted amino, di-substituted amino, acyloxy, cyano, carboxy, carboalkoxy, alkylcarboxamido, substituted alkylcarboxamido, dialkylcarboxamido, substituted dialkylcarboxamido, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy, haloalkyl, haloalkoxy, aryl, substituted aryl, heteroaryl, heterocyclic, or substituted heterocyclic radicals, wherein the terms are defined elsewhere herein. A few examples of organic radicals that include heteroatoms include alkoxy radicals, trifluoromethoxy radicals, acetoxy radicals, dimethylamino radicals.

[0020] Substituted and unsubstituted linear, branched, or cyclic alkyl units include the following examples: methyl (C_1), ethyl (C_2), n-propyl (C_3), *iso*-propyl (C_3), cyclopropyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), *tert*-butyl (C_4), cyclobutyl (C_4), cyclopentyl (C_5), cyclohexyl (C_6); whereas substituted linear, branched, or cyclic alkyl, examples of which includes, hydroxymethyl (C_1), chloromethyl (C_1), trifluoromethyl (C_1), aminomethyl (C_1), 1-chloroethyl (C_2), 2-hydroxyethyl (C_2), 1,2-difluoroethyl (C_2), 2,2,2-trifluoroethyl (C_3), 3-carboxypropyl (C_3), 2,3-dihydroxycyclobutyl (C_4).

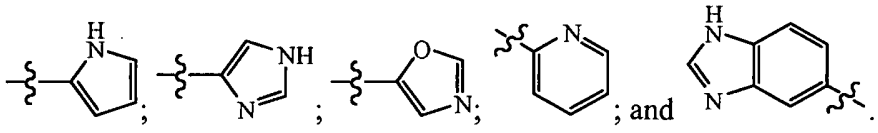
[0021] Substituted and unsubstituted linear, branched, or cyclic alkenyl include, ethenyl (C_2), 3-propenyl (C_3), 1-propenyl *(also* 2-methylethenyl) (C_3), isopropenyl *(also* 2-methylethen-2-yl) (C_3), buten-4-yl (C_4); substituted linear or branched alkenyl, examples of which include, 2-chloroethenyl (*also* 2-chlorovinyl) (C_2), 4-hydroxybuten-l-yl (C_4), 7-hydroxy-7-methyloct-4-en-2-yl (C_9), 7-hydroxy-7-methyloct-3,5-dien-2-yl (C_9).

[0022] Substituted and unsubstituted linear or branched alkynyl include, ethynyl (C_2), prop-2-ynyl *(also* propargyl) (C_3), propyn-1-yl (C_3), and 2-methyl-hex-4-yn-1-yl (C_7); substituted linear or branched alkynyl, examples of which include, 5-hydroxy-5-methylhex-3-ynyl (C_7), 6-hydroxy-6-methylhept-3-yn-2-yl (C_8), 5-hydroxy-5-ethylhept-3-ynyl (C_9).

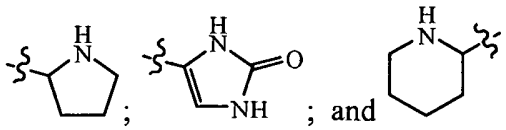
[0023] The term "aryl" as used herein denotes organic rings that consist only of a conjugated planar carbon ring system with delocalized pi electrons, examples of which include phenyl (C_6), naphthylen-1-yl (C_{10}), naphthylen-2-yl (C_{10}). Aryl rings can have one or more hydrogen atoms substituted by another organic or inorganic radical. Examples of substituted aryl rings include: 4-fluorophenyl (C_6), 2-hydroxyphenyl (C_6), 3-methylphenyl (C_6), 2-amino-4-fluorophenyl (C_6), 2-(*N,N*-diethylamino)phenyl (C_6), 2-cyanophenyl (C_6), 2,6-di-*tert*-butylphenyl (C_6), 3-methoxyphenyl (C_6), 8-hydroxynaphthylen-2-yl (C_{10}), 4,5-dimethoxynaphthylen-1-yl (C_{10}), and 6-cyanonaphthylen-1-yl (C_{10}).

[0024] The term "heteroaryl" denotes an aromatic ring system having from 5 to 10 atoms. The rings can be a single ring, for example, a ring having 5 or 6 atoms wherein at least one ring atom is a heteroatom to nitrogen, oxygen, or sulfur. Or "heteroaryl" can denote a fused ring system having 8 to 10 atoms wherein at least one of the rings is an aromatic ring and at least one atom of the aromatic ring is a heteroatom nitrogen, oxygen, or sulfur.

[0025] The following are examples of heteroaryl rings according to the present disclosure:

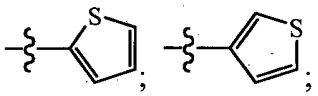


[0026] The term "heterocyclic" denotes a ring system having from 3 to 10 atoms wherein at least one of the ring atoms is a heteroatom to nitrogen, oxygen, or sulfur. The rings can be single rings, fused rings, or bicyclic rings. Examples of heterocyclic rings include:



[0027] All of the aforementioned heteroaryl or heterocyclic rings can be optionally substituted with one or more substitutes for hydrogen as described herein further.

[0028] Throughout the description of the present disclosure the terms having the spelling "thiophene-2-yl and thiophene-3-yl" are used to describe the heteroaryl units having the respective formulae:



whereas in naming the compounds of the present disclosure, the chemical nomenclature for these moieties are typically spelled "thiophen-2-yl and thiophen-3-yl" respectively. Herein the terms "thiophene-2-yl and thiophene-3-yl" are used when describing these rings as units or moieties which make up the compounds of the present disclosure solely to make it unambiguous to the artisan of ordinary skill which rings are referred to herein.

[0029] The term "substituted" is used throughout the specification. The term "substituted" is defined herein as "a hydrocarbyl moiety, whether acyclic or cyclic, which has one or more hydrogen atoms replaced by a substituent or several substituents as defined herein below." The units, when substituting for hydrogen atoms are capable of replacing one hydrogen atom, two hydrogen atoms, or three hydrogen atoms of a hydrocarbyl moiety at a time. In addition, these substituents can replace two hydrogen atoms on two adjacent carbons to form said substituent, new moiety, or unit. For example, a substituted unit that requires a single hydrogen atom replacement includes halogen, hydroxyl. A two hydrogen atom replacement includes carbonyl, oximino. A two hydrogen atom replacement from adjacent carbon atoms includes epoxy. A three hydrogen replacement includes cyano. The term substituted is used throughout the present specification to indicate that a hydrocarbyl moiety, *inter alia,* aromatic ring, alkyl chain; can have one or more of the hydrogen atoms replaced by a substituent. When a moiety is described as "substituted" any number of the hydrogen atoms may be replaced. For example, 4-hydroxyphenyl is a "substituted aromatic carbocyclic ring", (N,N-dimethyl-5-amino)octanyl is a "substituted C_8 alkyl unit, 3-guanidinopropyl is a "substituted C_3 alkyl unit," and 2-carboxypyridinyl is a "substituted heteroaryl unit."

[0030] The following are examples of units that can substitute for hydrogen atoms on a unit:

i) C_1-C_{12} linear, branched, or cyclic alkyl, alkenyl, and alkynyl; for example, methyl (C_1), ethyl (C_2), ethenyl (C_2), ethynyl (C_2), n-propyl (C_3), *iso*-propyl (C_3), cyclopropyl (C_3), 3-propenyl (C_3), 1-propenyl (*also* 2-methylethenyl) (C_3), isopropenyl *(also* 2-methylethen-2-yl) (C_3), prop-2-ynyl (*also* propargyl) (C_3), propyn-1-yl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), *tert*-butyl (C_4), cyclobutyl (C_4), buten-4-yl (C_4), cyclopentyl (C_5), cyclohexyl (C_6);

ii) substituted or unsubstituted C_6 or C_{10} aryl; for example, phenyl, naphthyl (also referred to herein as naphthylen-1-yl (C_{10}) or naphthylen-2-yl (C_{10});

iii) substituted or unsubstituted C_1-C_9 heterocyclic rings; as described herein below;

iv) substituted or unsubstituted C_1-C_9 heteroaryl rings; as described herein below;

v) $-(CR^{14a}R^{14b})_zOR^{13}$; for example, -OH, $-CH_2OH$, $-OCH_3$, $-CH_2OCH_3$, $-OCH_2CH_3$, $-CH_2OCH_2CH_3$, $-OCH_2CH_2CH_3$, and $-CH_2OCH_2CH_2CH_3$;

vi) $-(CR^{14a}R^{14b})_zC(O)R^{13}$; for example, $-COCH_3$, $-CH_2COCH_3$, $-OCH_2CH_3$, $-CH_2COCH_2CH_3$, $-COCH_2CH_2CH_3$, and $-CH_2COCH_2CH_2CH_3$;

vii) $-(CR^{14a}R^{14b})_zC(O)OR^{13}$; for example, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-CO_2CH_2CH_3$, $-CH_2CO_2CH_2CH_3$,

$-CO_2CH_2CH_2CH_3$, and - $CH_2CO_2CH_2CH_2CH_3$;
viii) $-(CR^{14a}R^{14b})_zC(O)N(R^{13})_2$; for example, $-CONH_2$, $-CH_2CONH_2$, - $CONHCH_3$, $-CH_2CONHCH_3$, $-CON(CH_3)_2$, and $-CH_2CON(CH_3)_2$;
ix) $-(CR^{14a}R^{14b})_zN(R^{13})_2$; ; for example, $-NH_2$, $-CH_2NH_2$, $-NHCH_3$, $-N(CH_3)_2$, - $NH(CH_2CH_3)$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, and $-CH_2NH(CH_2CH_3)$;
x) halogen; -F, -Cl, -Br, and -I;
xi) $-(CR^{11a}R^{14b})_zCN$;
xii) $-(CR^{14a}R^{14b})_zNO_2$;
xiii) $-CH_jX_k$; wherein X is halogen, j is from 0 to 2, j + k = 3; for example, - CH_2F, $-CHF_2$, $-CF_3$, $-CCl_3$, or $-CBr_3$;
xiv) $-(CR^{14a}R^{14b})_zSR^{13}$; -SH, $-CH_2SH$, $-SCH_3$, $-CH_2SCH_3$, $-SC_6H_5$, and - $CH_2SC_6H_5$;
xv) $-(CR^{14a}R^{14b})_zSO_2R^{13}$; $-SO_2H$, $-CH_2SO_2H$, $-SO_2CH_3$, $-CH_2SO_2CH_3$, - $SO_2C_6H_5$, and $-CH_2SO_2C_6H_5$; and
xiii) $-(CR^{14a}R^{14b})_zSO_3R^{13}$; for example, $-SO_3H$, $-CH_2SO_3H$, $-SO_3CH_3$, - $CH_2SO_3CH_3$, $-SO_3C_6H_5$, and $-CH_2SO_3C_6H_5$;

wherein each R^{13} is independently hydrogen, substituted or unsubstituted C_1-C_4 linear, branched, or cyclic alkyl, phenyl, benzyl; or two R^{13} units can be taken together to form a ring comprising 3-7 atoms; R^{14a} and R^{14b} are each independently hydrogen or C_1-C_4 linear or branched alkyl; the index p is from 0 to 4.

[0031] The present disclosure addresses several unmet medical needs, *inter alia;*

1) Providing compositions effective as human protein tyrosine phosphatase beta (HPTP-β) inhibitors; and thereby providing a method for regulating angiogenesis in a disorder, disease, malady, or condition wherein angiogenesis is elevated;

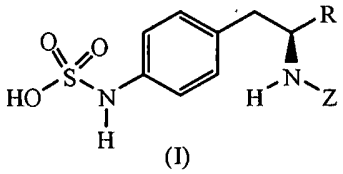
2) Providing compositions effective as human protein tyrosine phosphatase beta (HPTP-β) inhibitors; and thereby providing a method for regulating angiogenesis in a disorder, disease, malady, or condition; and

3) Providing compositions effective as human protein tyrosine phosphatase beta (HPTP-β) inhibitors; and thereby providing a method for regulating angiogenesis in a disorder, disease, malady, or condition wherein angiogenesis is decreased.

[0032] These and other unmet medical needs are resolved by the human protein tyrosine phosphatase beta (HPTP-β) inhibitors of the present disclosure, that are capable of regulating angiogenesis and thereby serving as a method for treating elevated or diminished angiogenesis in humans or in treating diseases that are caused by insufficient regulation of human protein tyrosine phosphatase beta (HPTP-β).

[0033] The compounds disclosed herein include all pharmaceutically acceptable salt forms, for example, salts of both basic groups, *inter alia,* amines, as well as salts of acidic groups, *inter alia,* sulfamic acids, and carboxylic acids. The following are examples of anions that can form salts with basic groups, such as amines: chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, citrate. The following are examples of cations that can form salts of acidic groups, such as carboxylic acid / carboxylate units: sodium, lithium, potassium, calcium, magnesium, bismuth.

[0034] The compounds of the present disclosure are ethyl-amino substituted phenylsulfamic acids, or their pharmaceutically acceptable salts, having the core structure of Compound (I) shown in the drawing below:



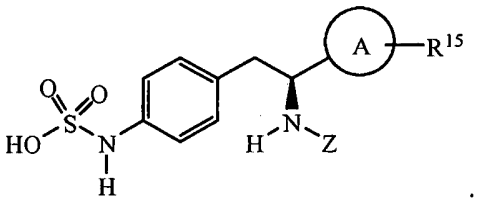
(I)

wherein the units R and Z can be any of the alternatives further defined and exemplified herein below. In such compounds of Formula (I), the carbon atom bearing the amino unit has the absolute stereochemistry(S) stereochemistry as indicated in the drawing above, which typically corresponds to an (S) configuration at the same amine-bearing carbon atom, but which could vary depending on the nature of the R substituent group and the resulting priority changes.

R Units

[0035] In some embodiments, the R units of the compounds of Formula (I) can be substituted or unsubstituted hete-

rocyclic or heteroaryl rings having from 3 to 15 ring atoms. The substituted or unsubstituted heterocyclic or heteroaryl rings of the R group of the compounds of Formula (I) can be represented below by the generic ring, A, in the drawing shown below:



These heterocyclic or heteroaryl "A" rings can be optionally substituted by one, two, or three independently chosen substituents represented in the generic formula by R^{15} units. Examples of R^{15} units include:

i) linear, branched, or cyclic alkyl, alkenyl, and alkynyl; for example, methyl (C_1), ethyl (C_2), n-propyl (C_3), *iso*-propyl (C_3), cyclopropyl (C_3), propylen-2-yl (C_3), propargyl (C_3), n-butyl (C_4), *iso*-butyl (C_4), *sec*-butyl (cm), *tert*-butyl (C_4), cyclobutyl (C_4), n-pentyl (C_5), cyclopentyl (C_5), n-hexyl (C_6), and cyclohexyl (C_6);
ii) substituted or unsubstituted aryl; for example, phenyl, 2-fluorophenyl, 3-chlorophenyl, 4-methylphenyl, 2-aminophenyl, 3-hydroxyphenyl, 4-trifluoromethylphenyl, and biphenyl-4-yl;
iii) substituted or unsubstituted heterocyclic; examples of which are provided herein below;
iv) substituted or unsubstituted heteroaryl; examples of which are provided herein below;
v) $-(CR^{17a}R^{17b})_qOR^{16}$; for example, $-OH$, $-CH_2OH$, $-OCH_3$, $-CH_2OCH_3$, $-OCH_2CH_3$, $-CH_2OCH_2CH_3$, $-OCH_2CH_2CH_3$, and $-CH_2OCH_2CH_2CH_3$;
vi) $-(CR^{17a}R^{17b})_qC(O)R^{16}$; for example, $-COCH_3$, $-CH_2COCH_3$, $-OCH_2CH_3$, $-CH_2COCH_2CH_3$, $-COCH_2CH_2CH_3$, and $-CH_2COCH_2CH_2CH_3$;
vii) $-(CR^{17a}R^{17b})_qC(O)OR^{16}$; for example, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-CO_2CH_2CH_3$, $-CH_2CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$, and $-*CH_2CO_2CH_2CH_2CH_3$;
viii) $-(CR^{17a}R^{17b})_qC(O)N(R^{16})_2$; for example, $-CONH_2$, $-CH_2CONH_2$, $-CONHCH_3$, $-CH_2CONHCH_3$, $-CON(CH_3)_2$, and $-CH_2CON(CH_3)_2$;
ix) $-(CR^{17a}R^{17b})_qOC(O)N(R^{16})_2$; for example, $-OC(O)NH_2$, $-CH_2OC(O)NH_2$, $-OC(O)NHCH_3$, $-CH_2OC(O)NHCH_3$, $-OC(O)N(CH_3)_2$, and $-CH_2OC(O)N(CH_3)_2$;
x) $-(CR^{17a}R^{17b})_qN(R^{16})_2$; for example, $-NH_2$, $-CH_2NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NH(CH_2CH_3)$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, and $-CH_2NH(CH_2CH_3)$;
xi) halogen: -F, -Cl, -Br, and -I;
xii) $-CH_mX_n$; wherein X is halogen, m is from 0 to 2, m+n =3; for example, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CCl_3$, or $-CBr_3$;
xiii) $-(CR^{17a}R^{17b})_qCN$; for example; -CN, $-CH_2CN$, and $-CH_2CH_2CN$;
xiv) $-(CR^{17a}R^{17b})_qNO_2$; for example; $-NO_2$, $-CH_2NO_2$, and $-CH_2CH_2NO_2$;
xv) $-(CR^{17a}R^{17b})_qSO^2R^{16}$; for example, $-SO_2H$, $-CH_2SO_2H$, $-SO_2CH_3$, $-CH_2SO_2CH_3$, $-SO_2C_6H_5$, and $-CH_2SO_2C_6H_5$; and
xvi) $-(CR^{17a}R^{17b})_qSO_3R^{16}$; for example, $-SO_{3H}$, $=CH_2SO_3H$, $-SO_3CH_3$, $-CH_2SO_3CH_3$, $-SO_3C_6H_5$, and $-CH_2SO_3C_6H_5$;

wherein each R^{16} is independently hydrogen, substituted or unsubstituted C_1-C_4 linear, branched, or cyclic alkyl; or two R^{16} units can be taken together to form a ring comprising 3-7 atoms; R^{17a} and R^{17b} are each independently hydrogen or C_1-C_a linear or branched alkyl,; the index q is from 0 to 4.

[0036] When R^{15} units comprise C_1-C_{12} linear, branched, or cyclic alkyl, alkenyl; substituted or unsubstituted C_6 or C_{10} aryl; substituted or unsubstituted C_1-C_9 heterocyclic; or substituted or unsubstituted C_1-C_9 heteroaryl; R^{15} units can further have one or more hydrogen atoms substituted by R^{18} units. Examples of R^{18} units include:

i) linear, branched, or cyclic alkyl, alkenyl, and alkynyl; for example, methyl (C_1), ethyl (C_2), n-propyl (C_3), *iso*-propyl (C_3), cyclopropyl (C_3), propylen-2-yl (C_3), propargyl (C_3), n-butyl (C_4), *iso*-butyl (C_4), *sec*-butyl (C_4), *tert*-butyl (C_4), cyclobutyl (C_4), n-pentyl (C_5), cyclopentyl (C_5), n-hexyl (C_6), and cyclohexyl (C_6);
ii) $-(CR^{20a}R^{20b})_qOR^{19}$; for example, $-OH$, $-CH_2OH$, $-OCH_3$, $-CH_2OCH_3$, $-OCH_2CH_3$, $-CH_2OCH_2CH_3$, $-OCH_2CH_2CH_3$, and $-CH_2OCH_2CH_2CH_3$;
iii) $-(CR^{20a}R^{20b})_qC(O)R^{19}$; for example, $-COCH_3$, $-CH_2COCH_3$, $-OCH_2CH_3$, $-CH_2COCH_2CH_3$, $-COCH_2CH_2CH_3$, and $-CH_2COCH_2CH_2CH_3$;
iv) $-(CR^{20a}R^{20b})_qC(O)OR^{19}$; for example, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-CO_2CH_2CH_3$, $-CH_2CO_2CH_2CH_3$,

$-CO_2CH_2CH_2CH_3$, and - $CH_2CO_2CH_2CH_2CH_3$;

v) $-(CR^{20a}R20^b)_qC(O)N(R^{19})_2$; for example, $-CONH_2$, $-CH_2CONH_2$, - $CONHCH_3$, $-CH_2CONHCH_3$, $-CON(CH_3)_2$, and $-CH_2CON(CH_3)_2$;

vi) $-(CR^{20a}R^{20b})_qOC(O)N(R^{19})_2$; for example, $-OC(O)NH_2$, $-CH_2OC(O)NH_2$, $-OC(O)NHCH_3$, $-CH_2OC(O)NHCH_3$, $-OC(O)N(CH_3)_2$, and - $CH_2OC(O)N(CH_3)_2$;

vii) $-(CR^{20a}R^{20b})_qN(R^{19})_2$; for example, $-NH_2$, $-CH_2NH_2$, $NHCH_3$, $-N(CH_3)_2$, - $NH(CH_2CH_3)$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, and $-CH_2NH(CH_2CH_3)$;

viii) halogen: -F, -Cl, -Br, and -I;

ix) $-CH_mX_n$; wherein X is halogen, m is from 0 to 2, m+n =3; for example, - CH_2F, $-CHF_2$, $-CF_3$, $-CCl_3$, or $-CBr_3$;

x) $-(CR^{20a}R^{20b})_qCN$; for example; -CN, $-CH_2CN$, and $-CH_2CH_2CN$;

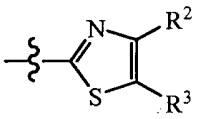
xi) $-(CR^{20a}R^{20b})qNO_2$; for example; $-NO_2$, $-CH_2NO_2$, and $-CH_2CH_2NO_2$;

xii) $-(CR^{20a}R^{20})_qSO_2R^{19}$; for example, $-SO_2H$, $-CH_2SO_2H$, $-SO_2CH_3$, - $CH_2SO_2CH_3$, $-SO_2C_6H_5$, and $-CH_2SO_2C_6H_5$; and

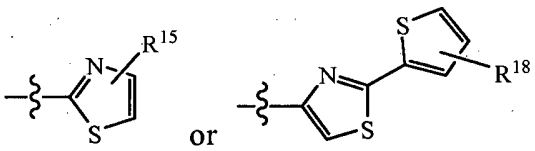
xiii) $-(CR^{20a}R^{20b})_qSO_3R^{19}$; for example, $-SO_3H$, $-CH_2SO_3H$, $-SO_3CH_3$, - $CH_2SO_3CH_3$, $-SO_3C_6H_5$, and $-CH_2SO_3C_6H_5$;

wherein each R^{19} is independently hydrogen, substituted or unsubstituted C_1-C_4 linear, branched, or cyclic alkyl; or two R^{19} units can be taken together to form a ring comprising 3-7 atoms; R^{20a} and R^{20b} are each independently hydrogen or C_1-C_4 linear or branched alkyl; the index p is from 0 to 4.

[0037] In the description that follows, R^{15} and R^{18} units may be represented by specific ring substitutions, for example, a ring encompassed within the definition of R can be depicted as either having the formula:



or as having the formula:



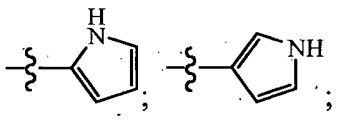
Both of the above formulae stand equally well for an optionally substituted thiazolyl ring.

R Units

[0038] R units comprise a ring having from 3 to 15 ring atoms.

[0039] R units can comprise 5-member heteroaryl rings. The following are Examples of 5-member heteroaryl rings:

i)



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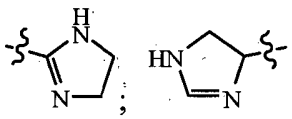
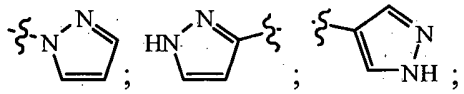
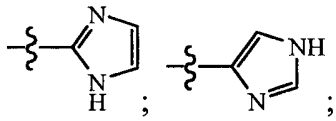


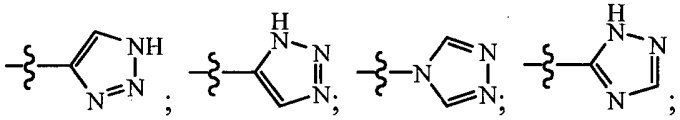
iii)



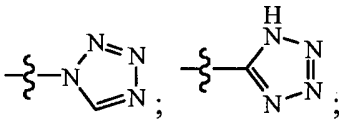
iv)



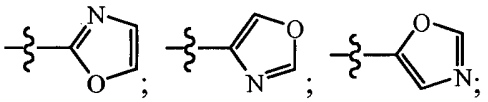
v)



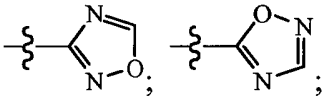
vi)



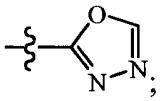
vii)



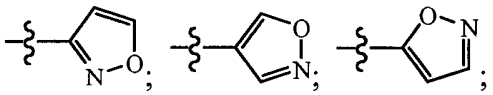
viii)



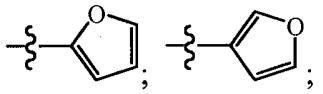
ix)



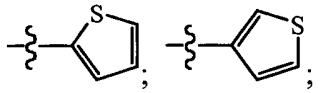
x)



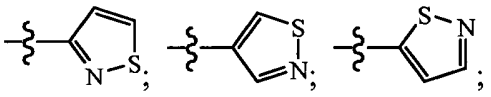
xi)



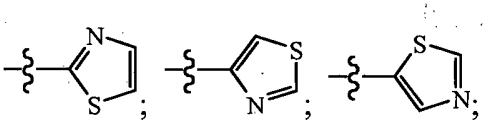
xii)



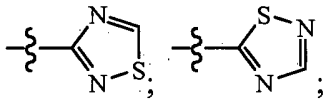
xiii)



xiv)

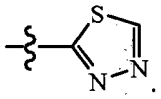


xv)

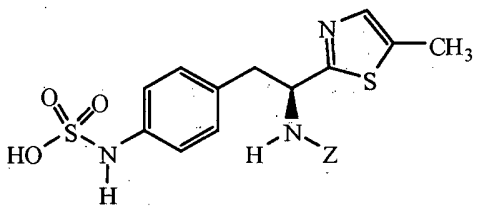


and

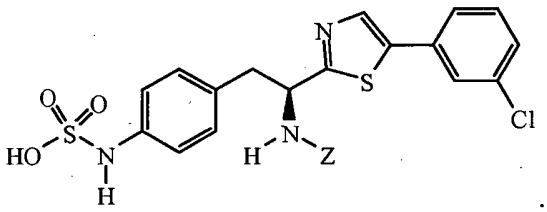
xvi)



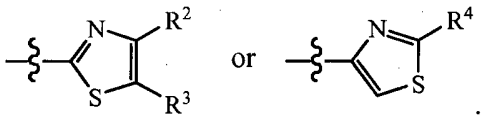
[0040] As described herein, the 5-member heteroaryl rings can be substituted with one or more substitutes for hydrogen, for example, with a methyl group:



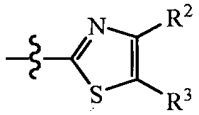
or with a substitute for hydrogen that itself is further substituted, for example:



[0041] Examples of 5-member ring R units includes thiazolyl units having the formula:



[0042] One example of a thiazolyl R unit includes thiazol-2-yl units having the formula:

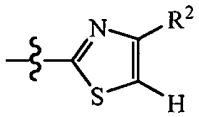


wherein R^2 and R^3 are each independently chosen from:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;
iii) substituted or unsubstituted phenyl;
iv) substituted or unsubstituted C_1-C_9 heteroaryl; or

R^2 and R^3 can be taken together to form a saturated or unsaturated ring having from 5 to 7 atoms.

[0043] One example of this R unit relates to units having the formula:



wherein R^3 is hydrogen and R^2 is a unit chosen from methyl (C_1), ethyl (C_2), n-propyl (C_3), iso-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), and *tert*-butyl (C_4).

[0044] Another example of this R unit relates to units wherein R^2 is a unit chosen from methyl (C_1), ethyl (C_2), n-propyl (C_3), iso-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), and *tert*-butyl (C_4); and R^3 is a unit chosen from methyl (C_1) or ethyl (C_2). Examples of this aspect of R includes 4,5-dimethylthiazol-2-yl, 4-ethyl-5-methylthiazol-2-yl, 4-methyl-5-ethylthiazol-2-yl, and 4,5-diethylthiazol-2-yl.

[0045] A further example of this R unit relates to units wherein R^3 is hydrogen and R^2 is a substituted alkyl unit, the substitutions chosen from:

i) halogen: -F, -Cl, -Br, and -I;
ii) $-N(R^{11})_2$; and
iii) $-OR^{11}$;

wherein each R^{11} is independently hydrogen or C_1-C_4 linear or branched alkyl. Examples of units comprising this embodiment of R includes: $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2Cl$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, and $-CH_2NH(CH_2CH_3)$.

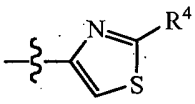
[0046] A yet further example of R units include units wherein R^3 is hydrogen and R^2 is phenyl.

[0047] A still further example of R units include units wherein R^3 is hydrogen and R^2 is a heteroaryl unit chosen from 1,2,3,4-tetrazol-1-yl,1,2,3,4-tetrazol-5-yl, [1,2,3]triazol-4-yl, [1,2,3]triazol-5-yl, [1,2,4]triazol-4-yl, [1,2,4]triazol-5-yl, imidazol-2-yl, imidazol-4-yl, pyrrol-2-yl, pyrrol-3-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, [1,2,4]oxadiazol-3-yl, [1,2,4]oxadiazol-5-yl, [1,3,4]oxadiazol-2-yl, furan-2-yl, furan-3-yl, thiophene-2-yl, thiophene-

3-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, [1,2,4]thiadiazol-3-yl, [1,2,4]thiadiazol-5-yl, and [1,3,4]thiadiazol-2-yl.

[0048] One example of R includes units wherein R^2 is thiophene-2-yl or thiophene-3-yl.

[0049] Another example of R units includes thiazol-4-yl units having the formula:



wherein R^4 is a unit chosen from:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;
iii) substituted or unsubstituted phenyl; or
iv) substituted or unsubstituted C_1-C_9 heteroaryl.

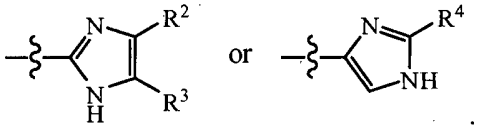
[0050] An example of R units includes compounds wherein R^4 is hydrogen.

[0051] Another example of R units includes compounds wherein R^4 is a unit chosen from methyl (C_1), ethyl (C_2), n-propyl (C_3), iso-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4); *iso*-butyl (C_4), and *tert*-butyl (C_4). Examples of this aspect of R includes 2-methylthiazol-4-yl, 2-ethylthiazol-4-yl, 2-(n-propyl)thiazol-4-yl, and 2-(*iso*-propyl)thiazol-4-yl.

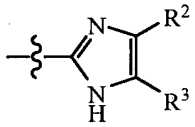
[0052] A further example of R units includes compounds wherein R^4 is substituted or unsubstituted phenyl, examples of which include phenyl, 2-fluorophenyl, 2-chlorophenyl, 2-methylphenyl, 2-methoxyphenyl, 3-fluorophenyl, 3-chlorophenyl, 3-methylphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methylphenyl, and 4-methoxyphenyl.

[0053] A yet further example of R units includes compounds wherein R^4 is substituted or unsubstituted heteroaryl, examples of which include thiophene-2-yl, thiophene-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, 2,5-dimethylthiazol-4-yl, 2,4-dimethylthiazol-5-yl, 4-ethylthiazol-2-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, and 3-methyl-1,2,4-oxadiazol-5-yl.

[0054] Another example of 5-member ring R units includes substituted or unsubstituted imidazolyl units having the formula:



[0055] One example of imidazolyl R units includes imidazol-2-yl units having the formula:

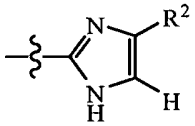


wherein R^2 and R^3 are each independently chosen from:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;
iii) substituted or unsubstituted phenyl;
iv) substituted or unsubstituted C_1-C_9 heteroaryl; or

R^2 and R^3 can be taken together to form a saturated or unsaturated ring having from 5 to 7 atoms.

[0056] One example of R units includes compounds wherein R units have the formula:



wherein R^3 is hydrogen and R^2 is a unit chosen from methyl (C_1), ethyl (C_2), n-propyl (C_3), iso-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), and *tert*-butyl (C_4).

[0057] Another example of R units includes compounds wherein R^2 is a unit chosen from methyl (C_1), ethyl (C_2), n-propyl (C_3), iso-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), and *tert*-butyl (C_4); and R^3 is a unit chosen from methyl (C_1) or ethyl (C_2). Examples of this aspect of R includes 4,5-dimethylimidazol-2-yl, 4-ethyl-5-methylimidazol-2-yl, 4-methyl-5-ethylimidazol-2-yl, and 4,5-diethylimidazol-2-yl.

[0058] An example of R units includes compounds wherein R^3 is hydrogen and R^2 is a substituted alkyl unit chosen, said substitutions chosen from:

i) halogen: -F, -Cl, -Br, and -I;
ii) $N(R^{11})_2$; and
iii) $-OR^{11}$;

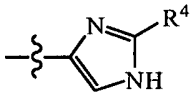
wherein each R^{11} is independently hydrogen or C_1-C_4 linear or branched alkyl. Examples of units comprising this embodiment of R includes: $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2Cl$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, and $-CH_2NH(CH_2CH_3)$.

[0059] A yet further example of units include units wherein R^3 is hydrogen and R^2 is phenyl.

[0060] A still further example of R units include units wherein R^3 is hydrogen and R^2 is a heteroaryl unit chosen from 1,2,3,4-tetrazol-1-yl,1,2,3,4-tetrazol-5-yl, [1,2,3]triazol-4-yl, [1,2,3]triazol-5-yl, [1,2,4]triazol-4-yl, [1,2,4]triazol-5-yl, imidazol-2-yl, imidazol-4-yl, pyrrol-2-yl, pyrrol-3-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, [1,2,4]oxadiazol-3-yl, [1,2,4]oxadiazol-5-yl, [1,3,4]oxadiazol-2-yl, furan-2-yl, furan-3-yl, thiophene-2-yl, thiophene-3-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, [1,2,4]thiadiazol-3-yl, [1,2,4]thiadiazol-5-y1, and [1,3,4]thiadiazol-2-yl.

[0061] One example of R includes units wherein R^2 is thiophene-2-yl or thiophene-3-yl.

[0062] Another example of R units includes imidazol-4-yl units having the formula:



wherein R^4 is a unit chosen from:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;
iii) substituted or unsubstituted phenyl; or
iv) substituted or unsubstituted C_1-C_9 heteroaryl.

[0063] One example of this embodiment of R units relates to compounds wherein R^4 is hydrogen.

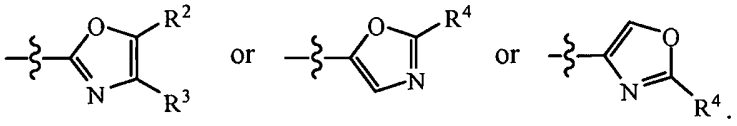
[0064] An example of R units includes compounds wherein R^4 is hydrogen.

[0065] Another example of R units includes compounds wherein R^4 is a unit chosen from methyl (C_1), ethyl (C_2), n-propyl (C_3), iso-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), and *tert*-butyl (C_4). Examples of this aspect of R includes 2-methylimidazol-4-yl, 2-ethylimidazol-4-yl, 2-(n-propyl)imidazol-4-yl, and 2-(*iso*-propyl)imidazol-4-yl.

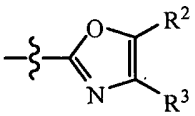
[0066] A further example of R units includes compounds wherein R^4 is substituted or unsubstituted phenyl, examples of which include phenyl, 2-fluorophenyl, 2-chlorophenyl, 2-methylphenyl, 2-methoxyphenyl, 3-fluorophenyl, 3-chlorophenyl, 3-methylphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methylphenyl, and 4-methoxyphenyl.

[0067] A yet further example of R units includes compounds wherein R^4 is substituted or unsubstituted heteroaryl, examples of which include thiophene-2-yl, thiophene-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, 2,5-dimethylthiazol-4-yl, 2,4-dimethylthiazol-5-yl, 4-ethylthiazol-2-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, and 3-methyl-1,2,4-oxadiazol-5-yl.

[0068] Further examples of 5-member ring R units are substituted or unsubstituted oxazolyl units having the formula:



[0069] One example of oxazolyl R units includes oxazol-2-yl units having the formula:

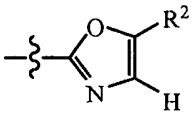


wherein R^2 and R^3 are each independently chosen from:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;
iii) substituted or unsubstituted phenyl;
iv) substituted or unsubstituted C_1-C_9 heteroaryl; or

R^2 and R^3 can be taken together to form a saturated or unsaturated ring having from 5 to 7 atoms.

[0070] One example of R units includes compounds wherein R units have the formula:



wherein R^3 is hydrogen and R^2 is a unit chosen from methyl (C_1), ethyl (C_2), n-propyl (C_3), iso-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), and *tert*-butyl (C_4).

[0071] Another example of R units includes units wherein R^2 is a unit chosen from methyl (C_1), ethyl (C_2), n-propyl (C_3), iso-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), iso-butyl (C_4), and *tert*-butyl (C_4); and R^3 is a unit chosen from methyl (C_1) or ethyl (C_2). Examples of this aspect of R includes 4,5-dimethyloxazol-2-yl, 4-ethyl-5-methyloxazol-2-yl, 4-methyl-5-ethyloxazol-2-yl, and 4,5-diethyloxazol-2-yl.

[0072] A further example of R units includes units wherein R^3 is hydrogen and R^2 is a substituted alkyl unit chosen, said substitutions chosen from:

i) halogen: -F, -Cl, -Br, and -I;
ii) $-N(R^{11})_2$; and
iii) $-OR^{11}$;

wherein each R^{11} is independently hydrogen or C_1-C_4 linear or branched alkyl.

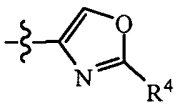
Examples of units comprising this embodiment of R includes: $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2Cl$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, and $-CH_2NH(CH_2CH_3)$.

[0073] A yet further example of R units include units wherein R^3 is hydrogen and R^2 is phenyl.

[0074] A still further example of R units include units wherein R^3 is hydrogen and R^2 is a heteroaryl unit chosen from 1,2,3,4-tetrazol-1-yl,1,2,3,4-tetrazol-5-yl, [1,2,3]triazol-4-yl, [1,2,3]triazol-5-yl, [1,2,4]triazol-4-yl, [1,2,4]triazol-5-yl, imidazol-2-yl, imidazol-4-yl, pyrrol-2-yl, pyrrol-3-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, [1,2,4]oxadiazol-3-yl, [1,2,4]oxadiazol-5-yl, [1,3,4]oxadiazol-2-yl, furan-2-yl, furan-3-yl, thiophene-2-yl, thiophene-3-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, [1,2,4]thiadiazol-3-yl, [1,2,4]thiadiazol-5-yl, and [1,3,4]thiadiazol-2-yl.

[0075] One example of R includes units wherein R^2 is thiopherie-2-yl or thiophene-3-yl.

[0076] Another example of R units includes oxazol-4-yl units having the formula:



wherein R^4 is a unit chosen from:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;
iii) substituted or unsubstituted phenyl; or
iv) substituted or unsubstituted C_1-C_9 heteroaryl.

wherein R^4 is a unit chosen from:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;
iii) substituted or unsubstituted phenyl; or
iv) substituted or unsubstituted C_1-C_9 heteroaryl.

[0077] One example of this embodiment of R units relates to compounds wherein R^4 is hydrogen.

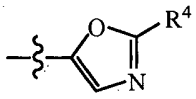
[0078] An example of R units includes compounds wherein R^4 is hydrogen.

[0079] Another example of R units includes compounds wherein R^4 is a unit chosen from methyl (C_1), ethyl (C_2), n-propyl (C_3), iso-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), and *tert*-butyl (C_4). Examples of this aspect of R includes 2-methyloxazol-4-yl, 2-ethyloxazol-4-yl, 2-(n-propyl)oxazol-4-yl, and 2-(*iso*-propyl)oxazol-4-yl.

[0080] A further example of R units includes compounds wherein R^4 is substituted or unsubstituted phenyl, examples of which include phenyl, 2-fluorophenyl, 2-chlorophenyl, 2-methylphenyl, 2-methoxyphenyl, 3-fluorophenyl, 3-chlorophenyl, 3-methylphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methylphenyl, and 4-methoxyphenyl.

[0081] A yet further example of R units includes compounds wherein R^4 is substituted or unsubstituted heteroaryl, examples of which include thiophene-2-yl, thiophene-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, 2,5-dimethylthiazol-4-yl, 2,4-dimethylthiazol-5-yl, 4-ethylthiazol-2-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, and 3-methyl-1,2,4-oxadiazol-5-yl.

[0082] A further example of R units relates to oxazol-5-yl units having the formula:



wherein R^4 is a unit chosen from:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;
iii) substituted or unsubstituted phenyl; or
iv) substituted or unsubstituted C_1-C_9 heteroaryl.

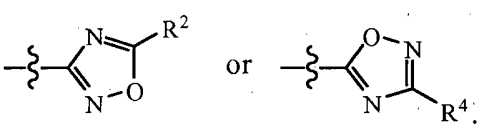
[0083] An example of R units includes compounds wherein R^4 is hydrogen.

[0084] Another example of R units includes compounds wherein R^4 is a unit chosen from methyl (C_1), ethyl (C_2), n-propyl (C_3), iso-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), and *tert*-butyl (C_4). Examples of this aspect of R includes 2-methyloxazol-4-yl, 2-etliyloxazol-4-yl, 2-(n-propyl)oxazol-4-yl, and 2-(*iso*-propyl)oxazol-4-yl.

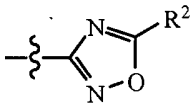
[0085] A further example of R units includes compounds wherein R^4 is substituted or unsubstituted phenyl, examples of which include phenyl, 2-fluorophenyl, 2-chlorophenyl, 2-methylphenyl, 2-methoxyphenyl, 3-fluorophenyl, 3-chlorophenyl, 3-methylphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methylphenyl, and 4-methoxyphenyl.

[0086] A yet further example of R units includes compounds wherein R^4 is substituted or unsubstituted heteroaryl, examples of which include thiophene-2-yl, thiophene-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, 2,5-dimethylthiazol-4-yl, 2,4-dimethylthiazol-5-yl, 4-ethylthiazol-2-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, and 3-methyl-1,2,4-oxadiazol-5-yl.

[0087] A yet further example of 5-member ring R units includes substituted or unsubstituted [1,2,4]oxadiazolyl units having the formula:



[0088] One example of [1,2,4]oxadiazolyl R units includes [1,2,4]oxadiazol-3-yl units having the formula:



wherein R^2 is chosen from:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;
iii) substituted or unsubstituted phenyl; or
iv) substituted or unsubstituted C_1-C_9 heteroaryl;

[0089] One example of R units includes units wherein R^2 is hydrogen.

[0090] Another example includes R units wherein R^2 is a unit chosen from methyl (C_1), ethyl (C_2), n-propyl (C_3), iso-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), and *tert*-butyl (C_4); and R^3 is a unit chosen from methyl (C_1) or ethyl (C_2). Examples of this aspect of R includes 5-methyl[1,2,4]oxadiazol-2-yl, 5-ethyl[1,2,4]-oxadiazol-2-yl, 5-propyl[1,2,4]oxadiazol-. 2-yl, and 5-cyclopropyl[1,2,4]oxadiazol-2-yl.

[0091] A further example of R units includes units wherein R^2 is a substituted alkyl unit chosen, said substitutions chosen from:

i) halogen: -F, -Cl, -Br, and -I;
ii) $-N(R^{11})_2$; and
iii) $-OR^{11}$;

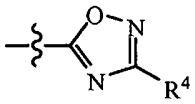
wherein each R^{11} is independently hydrogen or C_1-C_4 linear or branched alkyl. Examples of units comprising this embodiment of R includes: $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2Cl$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, and $-CH_2NH(CH_2CH_3)$.

[0092] A yet further example of R units includes units wherein R^2 is phenyl.

[0093] A still further example of R units includes units wherein R^2 is a heteroaryl unit chosen from 1,2,3,4-tetrazol-1-yl ,1,2,3,4-tetrazol-5-yl, [1,2,3]triazol-4-yl, [1,2,3]triazol-5-yl, [1,2,4]triazol-4-yl, [1,2,4]triazol-5-yl, imidazol-2-yl, imidazol-4-yl, pyrrol-2-yl, pyrrol-3-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, [1,2,4]oxadiazol-3-yl, [1,2,4]oxadiazol-5-yl, [1,3,4]oxadiazol-2-yl, furan-2-yl, furan-3-yl, thiophene-2-yl, thiophene-3-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, [1,2,4]thiadiazol-3-yl, [1,2,4]thiadiazol-5-yl, and [1,3,4]thiadiazol-2-yl.

[0094] Specific examples of R units include units wherein R^2 is thiophene-2-yl or thiophene-3-yl.

[0095] Another example of R units includes [1,2,4]oxadiazol-5-yl units having the formula:



wherein R^4 is a unit chosen from:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;
iii) substituted or unsubstituted phenyl; or
iv) substituted or unsubstituted C_1-C_9 heteroaryl.

[0096] One example of R units includes compounds wherein R^4 is hydrogen.

[0097] Another example of R units include compounds wherein R^4 is a unit chosen from methyl (C_1), ethyl2), n-propyl (C_3), iso-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), and *tert*-butyl (C_4). Examples of this aspect of R includes 3-methyl[1,2,4]oxadiazol-5-yl, 3- ethyl[1,2,4]oxadiazol-5-yl, 3-(n-propyl)[1,2,4]oxadiazol-5-yl, and *3-(iso*-propyl)[1,2,4]oxadiazol-5-yl.

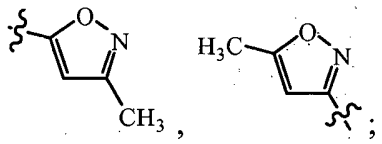
[0098] A further example of R units includes compounds wherein R^4 is substituted or unsubstituted phenyl, examples of which include phenyl, 2-fluorophenyl, 2-chlorophenyl, 2-methylphenyl, 2-methoxyphenyl, 3-fluorophenyl, 3-chlorophenyl, 3-methylphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methylphenyl, and 4-methoxyphenyl.

[0099] A yet further example of R units includes compounds wherein R^4 is substituted or unsubstituted heteroaryl,

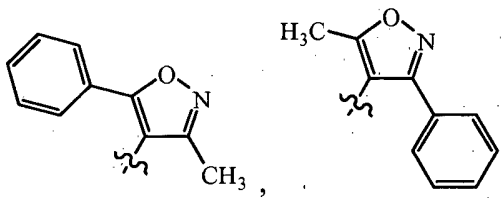
examples of which include thiophene-2-yl, thiophene-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, 2,5-dimethylthiazol-4-yl, 2,4-dimethylthiazol-5-yl, 4-ethylthiazol-2-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, and 3-methyl-1,2,4-oxadiazol-5-yl.

[0100] Further examples of 5-member heteroaryl rings include:

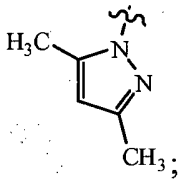
i)



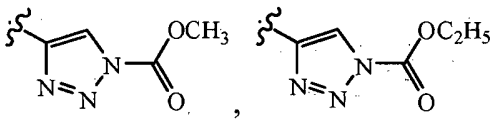
ii)



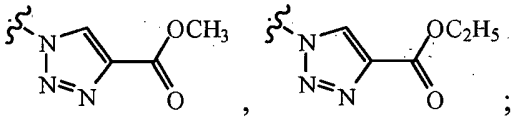
iii)



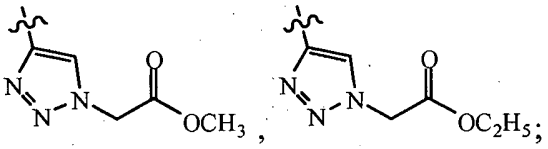
iv)



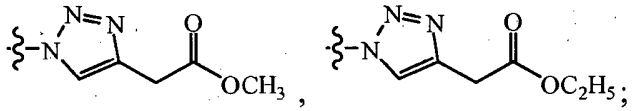
v)



vi)

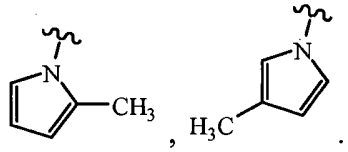


vii)



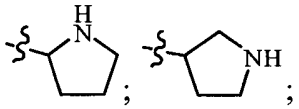
and

viii)



[0101] R units can comprise 5-member heterocyclic rings. Examples of 5-member heterocyclic rings include:

i)



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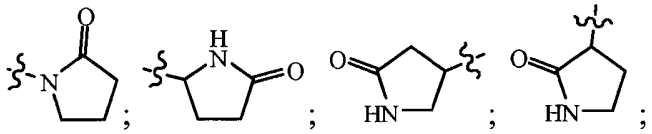

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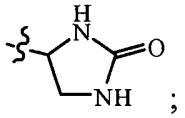

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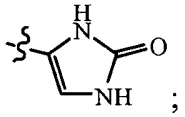

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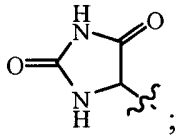

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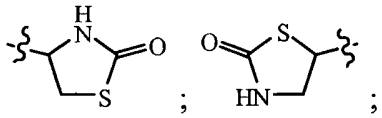
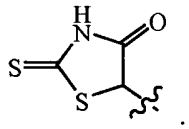


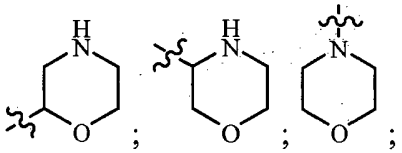
and.

vii)



[0102] R units can comprise 6-member heterocyclic rings. Examples of 6-member heterocyclic rings include:

i)



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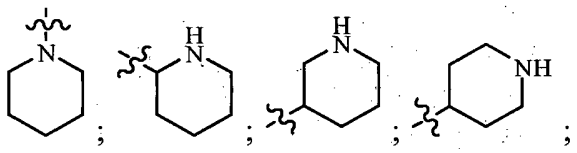

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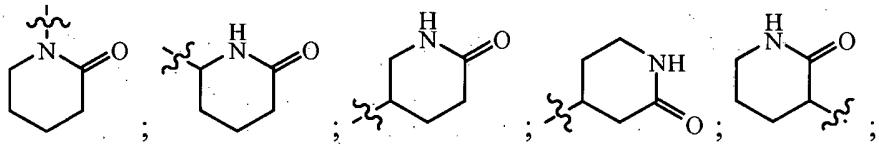
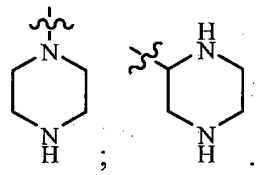


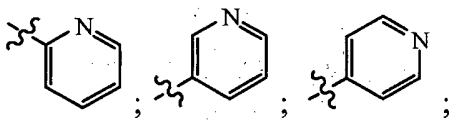
and

iv)



[0103] R units can comprise 6-member heteraryl rings. Examples of 6-member heteroaryl rings include:

i)



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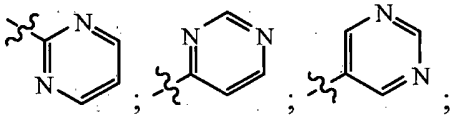
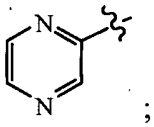
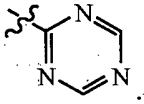


iii)

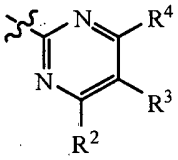


and

iv)



[0104] A example of 6-member heteroaryl rings includes pyrimidin-2-yl units having the formula:

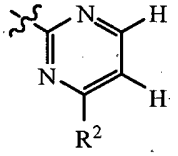


wherein R^2, R^3 and R^4 are each independently chosen from:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;
iii) substituted or unsubstituted phenyl;
iv) substituted or unsubstituted C_1-C_9 heteroaryl; or

R^2 and R^3 or R^3 and R^4 can be taken together to form a saturated or unsaturated ring having from 5 to 7 atoms.

[0105] Another example of R units includes units having the formula:



wherein R^3 and R^4 are both hydrogen and R^2 is a unit chosen from methyl (C_1), ethyl (C_2); n-propyl (C_3), iso-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), and *tert*-butyl (C_4).

[0106] Further examples of R units include units wherein R^2 and R^3 are chosen from methyl (C_1), ethyl (C_2), n-propyl (C_3), iso-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), and *tert*-butyl (C_4); and R^4 is hydrogen. Examples of

this aspect of R includes 4,5-dimethylpyrimidin-2-yl, 4,5-diethylpyrimidin-2-yl, 4-methyl-5-ethyl-pyrimidin-2-yl, and 4-ethyl-5-methyl-pyrimidin-2-yl.

[0107] A yet further example of R units include units wherein R^4 is hydrogen and R^2 and R^3 are chosen from:

i) halogen: -F, -Cl, -Br, and -I;
ii) $-N(R^{11})_2$; and
iii) $-OR^{11}$;

wherein each R^{11} is independently hydrogen or C_1-C_4 linear or branched alkyl. Examples of units comprising this embodiment of R includes: $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2Cl$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, and $-CH_2NH(CH_2CH_3)$.

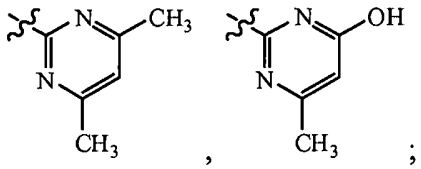
[0108] A yet further example of R units includes units wherein R^2 or R^3 is substituted phenyl and R^4 is hydrogen.

[0109] A still further example of R units includes units wherein R^4 is hydrogen and R^2 or R^3 is a heteroaryl unit chosen from 1,2,3,4-tetrazol-1-yl ,1,2,3,4-tetrazol-5-yl, [1,2,3]triazol-4-yl, [1,2,3]triazol-5-yl, [1,2,4]triazol-4-yl, [1,2,4]triazol-5-yl, imidazol-2-yl, imidazol-4-yl, pyrrol-2-yl, pyrrol-3-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, [1,2,4]oxadiazol-3-yl, [1,2,4]oxadiazol-5-yl, [1,3,4]oxadiazol-2-yl, furan-2-yl, furan-3-yl, thiophene-2-yl, thiophene-3-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, [1,2,4]thiadiazol-3-yl, [1,2,4]thiadiazol-5-yl, and [1,3,4]thiadiazol-2-yl.

[0110] The following are examples of R units wherein R^2 is thiophene-2-yl and wherein R^2 is thiophene-3-yl thereby providing R units that are 4-(thiophene-2-yl)pyrimidin-2-yl, 5-(thiophene-2-yl)pyrimidin-2-yl, 4-(thiophene-3-yl)pyrimidin-2-yl, and 5-(thiophene-2-yl)pyrimidin-3-yl.

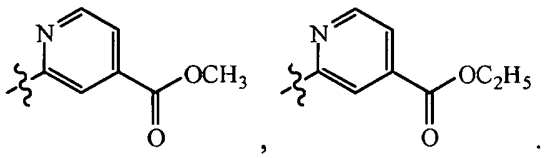
[0111] Examples of 6-member heteroaryl rings include:

i)



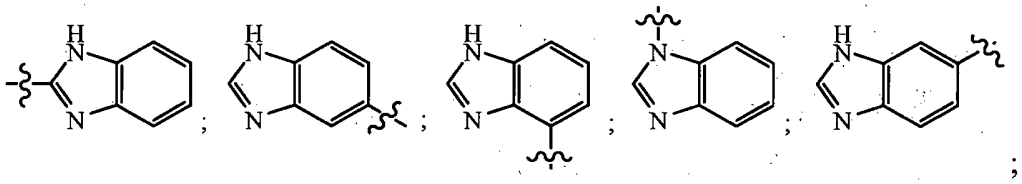
and

ii)

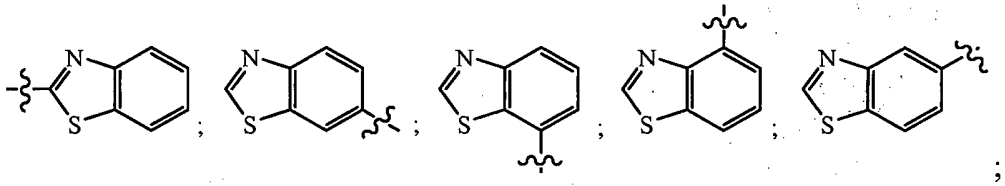


[0112] R units can also comprise fuse ring heteroaryl units. Examples of R units include:

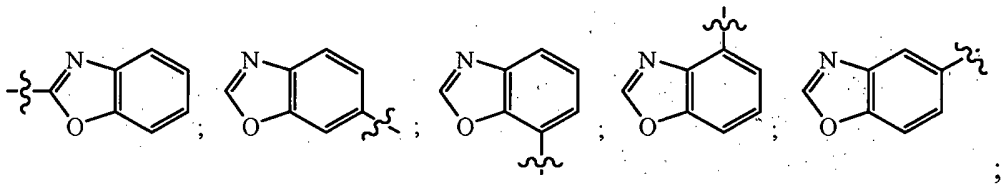
i)



ii)



iii)



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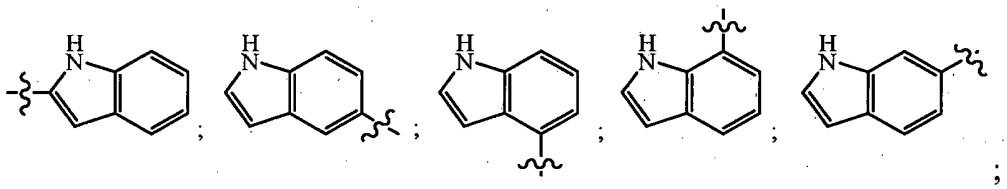
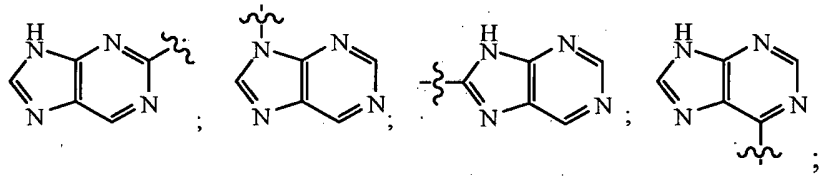
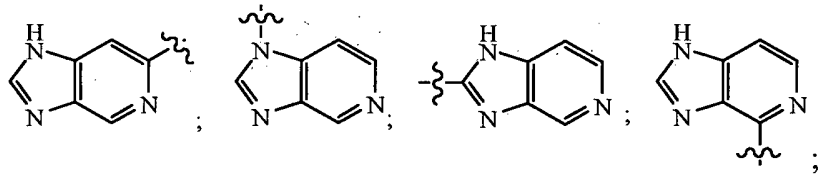


v)

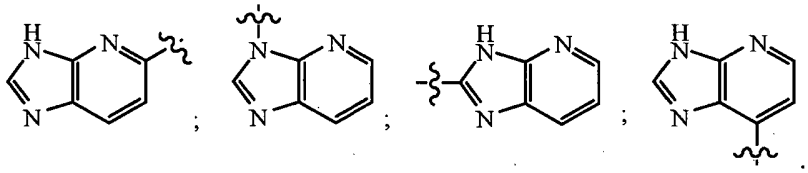


vi)



and

vii)



[0113] R units that are fused heteroaryl rings can be optionally substituted by one or more independently chosen substitutes for hydrogen as described herein above.

Z Units

[0114] Z is a unit having the formula:

$$—(L)_n—R^1$$

wherein R^1 is chosen from:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_6 linear, branched or cyclic alkyl;
iii) substituted or unsubstituted C_6 or C_{10} aryl;
iv) substituted or unsubstituted C_1-C_9 heterocyclic rings; or
v) substituted or unsubstituted C_1-C_9 heteroaryl rings.

[0115] One example of R^1 units includes substituted or unsubstituted phenyl (C_6 aryl) units, wherein each substitution is independently chosen from: halogen, C_1-C_4 linear, branched alkyl, or cyclic alkyl, $-OR^{11}$, -CN, $N(R^{11})_2$, $-CO_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NO_2$, and $-SO_2R^{11}$; each R^{11} is independently hydrogen; substituted or unsubstituted C_1-C_4 linear, branched, cyclic alkyl, alkenyl, or alkynyl; substituted or unsubstituted phenyl or benzyl; or two R^{11} units can be taken together to form a ring comprising from 3-7 atoms.

[0116] Another example of R^1 units includes substituted C_6 aryl units chosen from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 3,4-dimethoxyphenyl, and 3,5-dimethoxyphenyl.

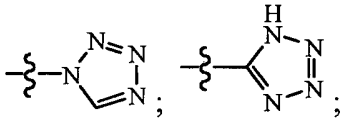
[0117] A further example of R^1 units includes substituted or unsubstituted C_6 aryl units chosen from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 2,3,4-trifluorophenyl, 2,3,5-trifluorophenyl, 2,3,6-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trifluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 2,3,4-trichlorophenyl, 2,3,5-trichlorophenyl, 2,3,6-trichlorophenyl, 2,4,5-trichlorophenyl, 3,4,5-trichlorophenyl, and 2,4,6-trichlorophenyl.

[0118] A yet further example of R^1 units includes substituted C_6 aryl units chosen from 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2,3-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethylphenyl, 3,4-dimethylphenyl, 2,3,4-trimethylphenyl, 2,3,5-trimethylphenyl, 2,3,6-trimethylphenyl, 2,4,5-trimethylphenyl, 2,4,6-trimethylphenyl, 2-ethylphenyl, 3-ethyl-phenyl, 4-ethylphenyl, 2,3-diethylphenyl, 2,4-diethylphenyl, 2,5-diethylphenyl, 2,6-diethylphenyl, 3,4-diethylphenyl, 2,3,4-triethylphenyl, 2,3,5-triethylphenyl, 2,3,6-triethylphenyl, 2,4,5-triethylphenyl, 2,4,6-triethylphenyl, 2-isopropylphenyl, 3-isopropylphenyl, and 4-isopropylphenyl.

[0119] Another still further example of R^1 units includes substituted C_6 aryl units chosen from 2-aminophenyl, 2-(*N*-methylamino)phenyl, 2-(*N,N*-dimethylamino)phenyl, 2-(*N*-ethylamino)phenyl, 2-(*N,N*-diethylamino)phenyl, 3-aminophenyl, 3-(*N*-methylamino)phenyl, 3-(*N,N*-dimethylamino)phenyl, 3-(*N*-ethylamino)phenyl, 3-(*N,N*-diethylamino)phenyl, 4-aminophenyl, 4-(*N*-methylamino)phenyl, 4-(*N,N*-dimethylamino)phenyl, 4-(*N*-ethylamino)phenyl, and 4-(*N,N*-diethylamino)phenyl.

[0120] R^1 can comprise heteroaryl units. Examples of heteroaryl units include:

i)



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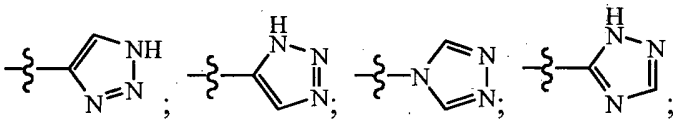

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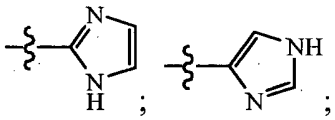

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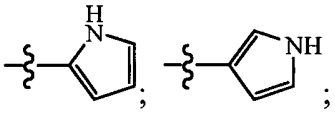

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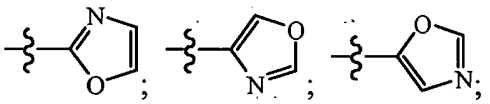

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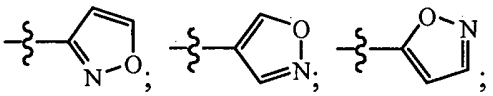
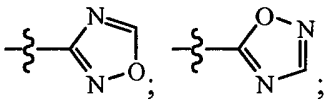
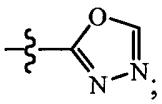


vii)



viii)



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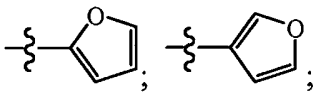
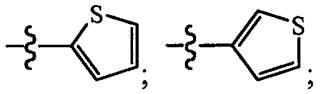


x)



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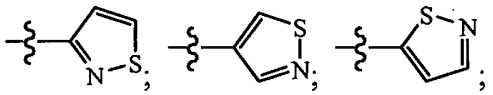
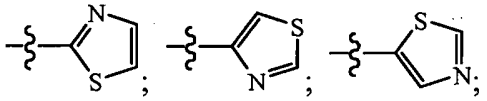


xii)



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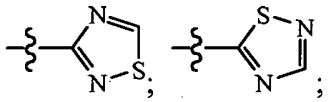
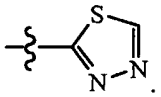


and
xiv)



[0121] R^1 heteroaryl units can be substituted or unsubstituted. Examples of units that can substitute for hydrogen include units chosen from:

i) C_1-C_6 linear, branched, and cyclic alkyl;
ii) substituted or unsubstituted phenyl and benzyl;
iii) substituted of unsubstituted C_1-C_9 heteroaryl;
iv) -C(O)R^9; and
v) -NHC(O)R^9;

wherein R^9 is C_1-C_6 linear and branched alkyl; C_1-C_6 linear and branched alkoxy; or - $NHCH_2C(O)R^{10}$; R^{10} is chosen from hydrogen, methyl, ethyl, and *tert*-butyl.

[0122] An example of R^1 relates to units substituted by an alkyl unit chosen from methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *iso*-butyl, *sec*-butyl, and *tert*-butyl.

[0123] Another example of R^1 includes units that are substituted by substituted or unsubstituted phenyl and benzyl, wherein the phenyl and benzyl substitutions are chosen from one or more:

i) halogen;
ii) C_1-C_3 alkyl;
iii) C_1-C_3 alkoxy;
iv) -CO_2R^{11}; and
v) -$NHCOR^{16}$;

wherein R^{11} and R^{16} are each independently hydrogen, methyl, or ethyl.

[0124] Another example of R^1 relates to phenyl and benzyl units substituted by a carboxy unit having the formula

-C(O)R^9; R^9 is chosen from methyl, methoxy, ethyl, and ethoxy.

[0125] A further example of R^1 includes phenyl and benzyl units substituted by an amide unit having the formula -NHC(O)R^9; R^9 is chosen from methyl, methoxy, ethyl, ethoxy, *tert*-butyl, and *tert*-butoxy.

[0126] A yet further example of R^1 includes phenyl and benzyl units substituted by one or more fluoro or chloro units.

[0127] L is a linking unit chosen from:

i) -C(O)NH[C($R^{5a}R^{5b}$)]$_w$-;
ii) -C(O)[C($R^{6a}R^{6b}$)]$_x$-;
iii) -C(O)[C($R^{7a}R^{7b}$)]$_y$C(O)-;
iv) -SO_2[C($R^{8a}R^{8b}$]$_z$-;

wherein R^{5a}, R^{5b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{8a}, and R^{8b} are each independently:

i) hydrogen;
ii) C_1-C_4 substituted or unsubstituted linear or branched alkyl;
iii) substituted or unsubstituted aryl;
iv) substituted or unsubstituted heterocyclic rings;
v) substituted or unsubstituted C_1-C_9 heteroaryl rings;

and the indices w, x, y, and z are each independently from 1 to 4. The linking group may be present, i.e. when the index n is equal to 1, or absent when the index n is equal to 0, for example, the linking unit is absent in Category V compounds further described herein below.

[0128] One example of L units includes linking units having the formula:

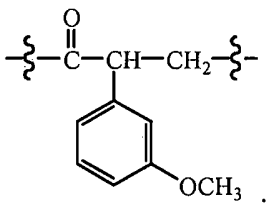
-C(O)[C($R^{6a}R^{6b}$)]$_x$-

wherein R^{6a} is hydrogen, substituted or unsubstituted phenyl, and substituted or unsubstituted heteroaryl, said substitutions for phenyl and heteroaryl are chosen from:

i) C_1-C_6 linear, branched, and cyclic alkyl;
ii) substituted or unsubstituted phenyl and benzyl;
iii) substituted of unsubstituted C_1-C_9 heteroaryl;
iv) -C(O)R^{16}; and
v) -NHC(O)R^{16};

wherein R^{16} is C_1-C_6 linear and branched alkyl; C_1-C_6 linear and branched alkoxy; or - $NHCH_2C(O)R^{17}$; R^{17} is chosen from hydrogen, methyl, ethyl, and *tert*-butyl; the index x is 1 or 2.

[0129] Another example of L units includes units wherein a first R^{6a} unit chosen from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 3,4-dimethoxyphenyl, and 3,5-dimethoxyphenyl; a second R^{6a} unit is hydrogen and R^{6b} units are hydrogen. For example a linking unit having the formula:



[0130] A further example of L includes a first R^{6a} unit as depicted herein above that is a substituted or unsubstituted heteroaryl unit as described herein above.

[0131] A yet further example of L includes units having the formula:

-C(O)[C($R^{6a}R^{6b}$)]$_x$-;

wherein R^{6a} and R^{6b} are hydrogen and the index x is equal to 1 or 2; said units chosen from:

i) $-C(O)CH_2-$; and
ii) $-C(O)CH_2CH_2-$.

[0132] Another example of L units includes units having the formula:

$$-C(O)[C(R^{7a}R^{7b})]_yC(O)-;$$

wherein R^{7a} and R^{7b} are hydrogen and the index x is equal to 1 or 2; said units chosen from:

i) $-C(O)CH_2C(O)-$; and
ii) $-C(O)CH_2CH_2C(O)-$.

[0133] A still further example of L units includes units having the formula:

$$-C(O)NH[C(R^{5a}R^{5b})]_w-;$$

wherein R^{5a} and R^{5b} are hydrogen and the index w is equal to 0, 1 or 2; said units chosen from:

ii) $-C(O)NH-$;
ii) $-C(O)NHCH_2-$; and
iii) $-C(O)NHCH_2CH_2-$.

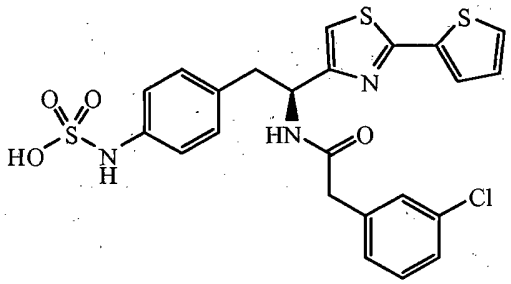
[0134] A yet still further example of L units includes units having the formula:

$$-SO_2[C(R^{8a}R^{8b})]_z-;$$

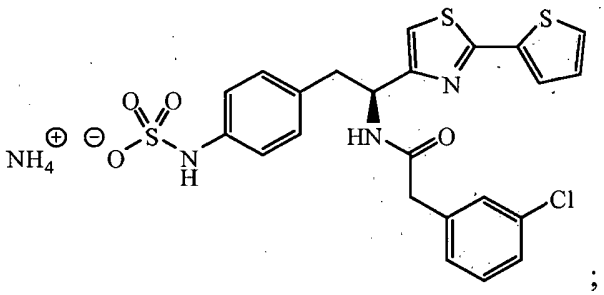
wherein R^{8a} and R^{8b} are hydrogen and the index z is equal to 0, 1 or 2; said units chosen from:

ii) $-SO_2-$;
ii) $-SO_2CH_2-$; and
iii) $-SO_2CH_2CH_2-$.

[0135] A described herein above the compounds of the present invention includes all pharmaceutically acceptable salt forms. A compound having the formula:

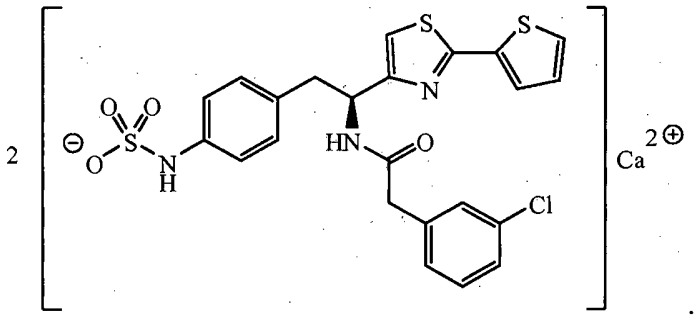


can form salts, for example, a salt of the sulfonic acid:



;

and



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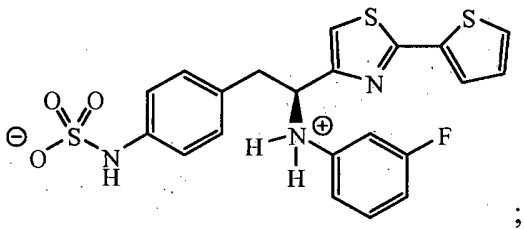
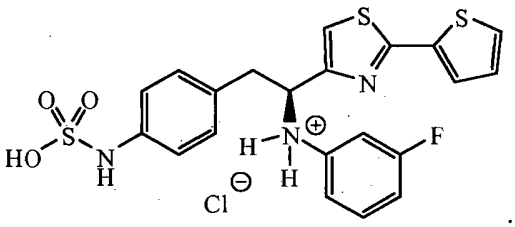
[0136] The compounds can also exist in a zwitterionic form, for example:



;

or as a salt of a strong acid, for example:



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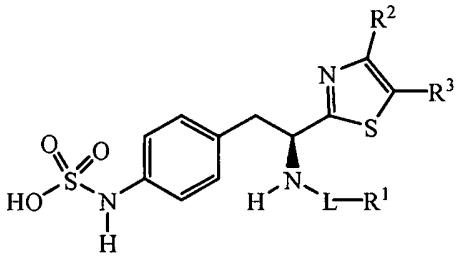
[0137] The analogs (compounds) of the present disclosure are arranged into several Categories to assist the formulator in applying a rational synthetic strategy for the preparation of analogs which are not expressly exampled herein. The arrangement into categories does not imply increased or decreased efficacy for any of the compositions of matter described herein.

[0138] The first aspect of Category I of the present disclosure relates to 2-(thiazol-2-yl) compounds having the formula:



wherein R^1, R^2, R^3, and L are further defined herein in Table I herein below.

TABLE I

No.	L	R^1	R^2	R^3
1	-C(O)CH_2-	phenyl	-CH_3	-H
2	-C(O)CH_2-	2-fluorophenyl	-CH_3	-H
3	-C(O)CH_2-	3-fluorophenyl	-CH_3	-H
4	-C(O)CH_2-	4-fluorophenyl	-CH_3	-H
5	-C(O)CH_2-	2,3-difluorophenyl	-CH_3	-H
6	-C(O)CH_2-	3,4-difluorophenyl	-CH_3	-H
7	-C(O)CH_2-	3,5-difluorophenyl	-CH_3	-H
8	-C(O)CH_2-	2-chlorophenyl	-CH_3	-H
9	-C(O)CH_2-	3-chlorophenyl	-CH_3	-H
10	-C(O)CH_2-	4-chlorophenyl	-CH_3	-H
11	-C(O)CH_2-	2,3-dichlorophenyl	-CH_3	-H
12	-C(O)CH_2-	3,4-dichlorophenyl	-CH_3	-H
13	-C(O)CH_2-	3,5-dichlorophenyl	-CH_3	-H
14	-C(O)CH_2-	2-hydroxyphenyl	-CH_3	-H
15	-C(O)CH_2-	3-hydroxyphenyl	-CH_3	-H
16	-C(O)CH_2-	4-hydroxyphenyl	-CH_3	-H
17	-C(O)CH_2-	2-methoxyphenyl	-CH_3	-H
18	-C(O)CH_2-	3-methoxyphenyl	-CH_3	-H
19	-C(O)CH_2-	4-methoxyphenyl	-CH_3	-H
20	-C(O)CH_2-	2,3-dimethoxyphenyl	-CH_3	-H
21	-C(O)CH_2-	3,4-dimethoxyphenyl	-CH_3	-H
22	-C(O)CH_2-	3,5-dimethoxyphenyl	-CH_3	-H
23	-C(O)CH_2-	phenyl	-CH_2CH_3	-H
24	-C(O)CH_2-	2-fluorophenyl	-CH_2CH_3	-H
25	-C(O)CH_2-	3-fluorophenyl	-CH_2CH_3	-H
26	-C(O)CH_2-	4-fluorophenyl	-CH_2CH_3	-H
27	-C(O)CH_2-	2,3-difluorophenyl	-CH_2CH_3	-H
28	-C(O)CH_2-	3,4-difluorophenyl	-CH_2CH_3	-H
29	-C(O)CH_2-	3,5-difluorophenyl	-CH_2CH_3	-H
30	-C(O)CH_2-	2-chlorophenyl	-CH_2CH_3	-H

(continued)

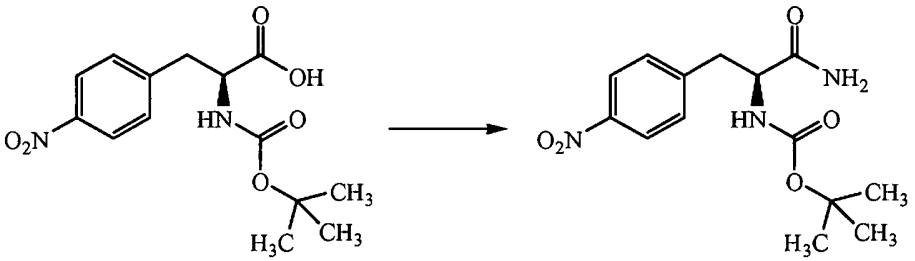
No.	L	R^1	R^2	R^3
31	$-C(O)CH_2-$	3-chlorophenyl	$-CH_2CH_3$	-H
32	$-C(O)CH_2-$	4-chlorophenyl	$-CH_2CH_3$	-H
33	$-C(O)CH_2-$	2,3-dichlorophenyl	$-CH_2CH_3$	-H
34	$-C(O)CH_2-$	3,4-dichlorophenyl	$-CH_2CH_3$	-H
35	$-C(O)CH_2-$	3,5-dichlorophenyl	$-CH_2CH_3$	-H
36	$-C(O)CH_2-$	2-hydroxyphenyl	$-CH_2CH_3$	-H
37	$-C(O)CH_2-$	3-hydroxyphenyl	$-CH_2CH_3$	-H
38	$-C(O)CH_2-$	4-hydroxyphenyl	$-CH_2CH_3$	-H
39	$-C(O)CH_2-$	2-methoxyphenyl	$-CH_2CH_3$	-H
40	$-C(O)CH_2-$	3-methoxyphenyl	$-CH_2CH_3$	-H
41	$-C(O)CH_2-$	4-methoxyphenyl	$-CH_2CH_3$	-H
42	$-C(O)CH_2-$	2,3-dimethoxyphenyl	$-CH_2CH_3$	-H
43	$-C(O)CH_2-$	3,4-dimethoxyphenyl	$-CH_2CH_3$	-H
44	$-C(O)CH_2-$	3,5-dimethoxyphenyl	$-CH_2CH_3$	-H
45	$-C(O)CH_2CH_2-$	phenyl	$-CH_3$	-H
46	$-C(O)CH_2CH_2-$	2-fluorophenyl	$-CH_3$	-H
47	$-C(O)CH_2CH_2-$	3-fluorophenyl	$-CH_3$	-H
48	$-C(O)CH_2CH_2-$	4-fluorophenyl	$-CH_3$	-H
49	$-C(O)CH_2CH_2-$	2,3-difluorophenyl	$-CH_3$	-H
50	$-C(O)CH_2CH_2-$	3,4-difluorophenyl	$-CH_3$	-H
51	$-C(O)CH_2CH_2-$	3,5-difluorophenyl	$-CH_3$	-H
52	$-C(O)CH_2CH_2-$	2-chlorophenyl	$-CH_3$	-H
53	$-C(O)CH_2CH_2-$	3-chlorophenyl	$-CH_3$	-H
54	$-C(O)CH_2CH_2-$	4-chlorophenyl	$-CH_3$	-H
55	$-C(O)CH_2CH_2-$	2,3-dichlorophenyl	$-CH_3$	-H
56	$-C(O)CH_2CH_2-$	3,4-dichlorophenyl	$-CH_3$	-H
57	$-C(O)CH_2CH_2-$	3,5-dichlorophenyl	$-CH_3$	-H
58	$-C(O)CH_2CH_2-$	2-hydroxyphenyl	$-CH_3$	-H
59	$-C(O)CH_2CH_2-$	3-hydroxyphenyl	$-CH_3$	-H
60	$-C(O)CH_2CH_2-$	4-hydroxyphenyl	$-CH_3$	-H
61	$-C(O)CH_2CH_2-$	2-methoxyphenyl	$-CH_3$	-H
62	$-C(O)CH_2CH_2-$	3-methoxyphenyl	$-CH_3$	-H
63	$-C(O)CH_2CH_2-$	4-methoxyphenyl	$-CH_3$	-H
64	$-C(O)CH_2CH_2-$	2,3-dimethoxyphenyl	$-CH_3$	-H
65	$-C(O)CH_2CH_2-$	3,4-dimethoxyphenyl	$-CH_3$	-H
66	$-C(O)CH_2CH_2-$	3,5-dimethoxyphenyl	$-CH_3$	-H
67	$-C(O)CH_2CH_2-$	phenyl	$-CH_2CH_3$	-H
68	$-C(O)CH_2CH_2-$	2-fluorophenyl	$-CH_2CH_3$	-H

(continued)

No.	L	R^1	R^2	R^3
69	$-C(O)CH_2CH_2-$	3-fluorophenyl	$-CH_2CH_3$	-H
70	$-C(O)CH_2CH_2-$	4-fluorophenyl	$-CH_2CH_3$	-H
71	$-C(O)CH_2CH_2-$	2,3-difluorophenyl	$-CH_2CH_3$	-H
72	$-C(O)CH_2CH_2-$	3,4-difluorophenyl	$-CH_2CH_3$	-H
73	$-C(O)CH_2CH_2-$	3,5-difluorophenyl	$-CH_2CH_3$	-H
74	$-C(O)CH_2CH_2-$	2-chlorophenyl	$-CH_2CH_3$	-H
75	$-C(O)CH_2CH_2-$	3-chlorophenyl	$-CH_2CH_3$	-H
76	$-C(O)CH_2CH_2-$	4-chlorophenyl	$-CH_2CH_3$	-H
77	$-C(O)CH_2CH_2-$	2,3-dichlorophenyl	$-CH_2CH_3$	-H
78	$-C(O)CH_2CH_2-$	3,4-dichlorophenyl	$-CH_2CH_3$	-H
79	$-C(O)CH_2CH_2-$	3,5-dichlorophenyl	$-CH_2CH_3$	-H
80	$-C(O)CH_2CH_2-$	2-hydroxyphenyl	$-CH_2CH_3$	-H
81	$-C(O)CH_2CH_2-$	3-hydroxyphenyl	$-CH_2CH_3$	-H
82	$-C(O)CH_2CH_2-$	4-hydroxyphenyl	$-CH_2CH_3$	-H
83	$-C(O)CH_2CH_2-$	2-methoxyphenyl	$-CH_2CH_3$	-H
84	$-C(O)CH_2CH_2-$	3-methoxyphenyl	$-CH_2CH_3$	-H
85	$-C(O)CH_2CH_2-$	4-methoxyphenyl	$-CH_2CH_3$	-H
86	$-C(O)CH_2CH_2-$	2,3-dimethoxyphenyl	$-CH_2CH_3$	-H
87	$-C(O)CH_2CH_2-$	3,4-dimethoxyphenyl	$-CH_2CH_3$	-H
88	$-C(O)CH_2CH_2-$	3,5-dimethoxyphenyl	$-CH_2CH_3$	-H

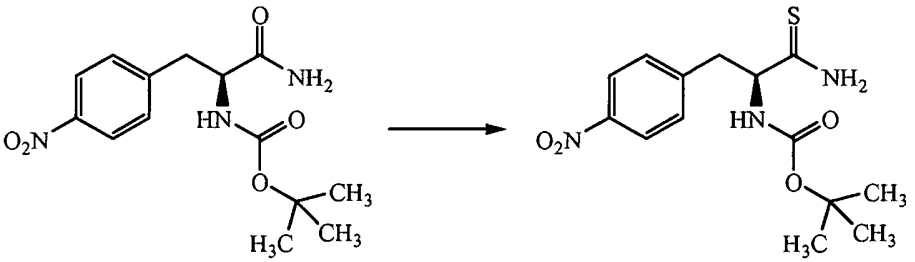
[0139] The compounds encompassed within the first aspect of Category I of the present disclosure can be prepared by the procedure outlined in Scheme I and described in Example 1 herein below.

Scheme I



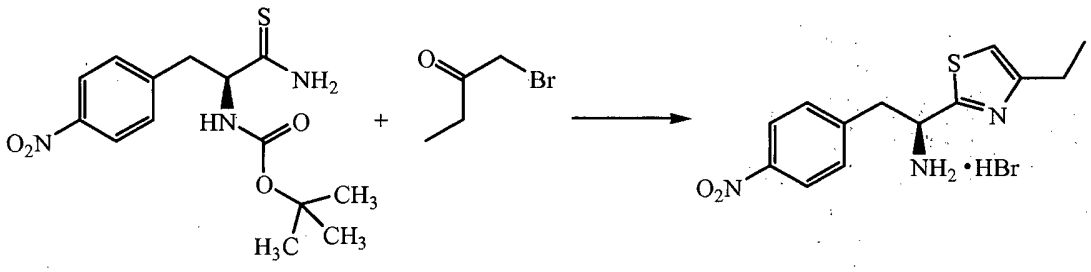
1

Reagents and conditions: (a)(i) (*iso*-butyl)OCOCl, NMM, DMF; 0 °C, 20 min.
(ii) NH_3; 0 °C for 30 min.



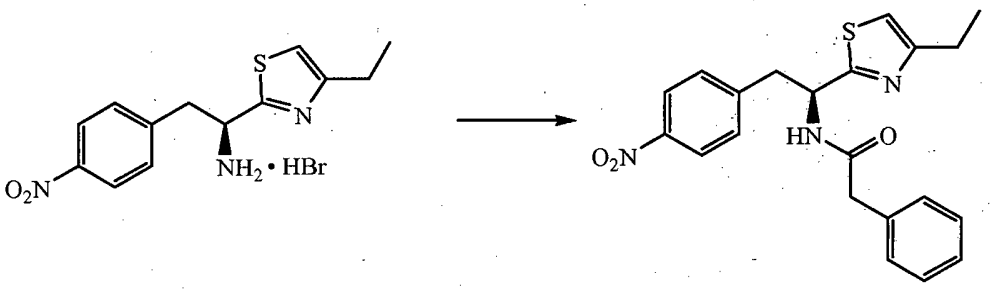
1 2

Reagents and conditions: (b) Lawesson's reagent, THF; rt, 3 hr.



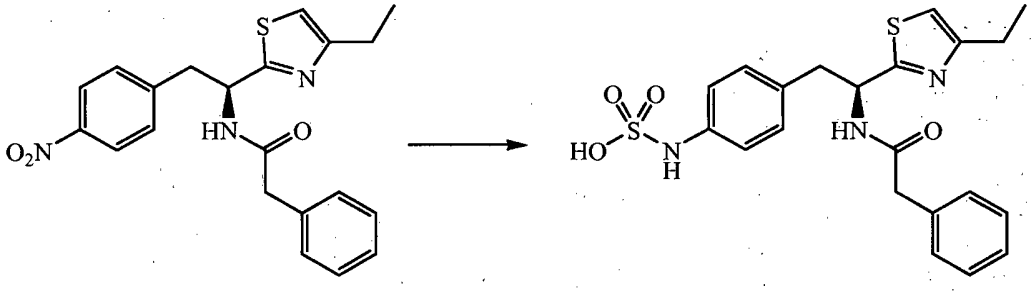
2 3

Reagents and conditions: (c) CH_3CN; reflux, 2hr.



3 4

Reagents and conditions: (d) $C_6H_4CO_2H$, EDCI, HOBt, DIPEA, DMF; rt, 18 hr.



4 5

Reagents and conditions: (e) (i) H_2:Pd/C, MeOH; (ii) SO_3-pyridine, NH_4OH, rt, 18 hr.

EXAMPLE 1

{4-[2-(*S*)-(4-Ethylthiazol-2-yl)-2-(2-phenylacetylamido)ethyl]phenyl}sulfamic acid (5) (*S*)-*tert*-butyl 1-amino-3-(4-nitrophenyl)-1-oxopropan-2-ylcarbamate

[0140] Preparation of *(S)-tert*-butyl 1-amino-3-(4-nitrophenyl)-1-oxopropan-2-ylcarbamate (1): To a 0 °C solution of 2-(*S*)-*tert*-butoxycarbonylamino-3-(4-nitrophenyl)-propionic acid and *N*-methylmorpholine (1.1 mL, 9.65 mmol) in DMF (10 mL) is added dropwise *iso*-butyl chloroformate (1.25 mL, 9.65 mmol). The mixture is stirred at 0 °C for 20 minutes, after which NH_3 (g) is passed through the reaction mixture for 30 minutes at 0 °C. The reaction mixture is concentrated and the residue dissolved in EtOAc, washed successively with 5% citric acid, water, 5% $NaHCO_3$, water and brine, dried (Na_2SO_4), filtered and concentrated in vacuo to a residue that is triturated with a mixture of EtOAc/petroleum ether to provide 2.2 g (74% yield) of the desired product as a white solid.

[0141] Preparation of [2-(4-nitrophenyl)-1-(*S*)-thiocarbamoylethyl]carbamic acid *tert*-butyl ester (2): To a solution of *(S)-tert*-butyl 1-amino-3-(4-nitrophenyl)-1-oxopropan-2-ylcarbamate, 1, (0.400 g, 1.29 mmol) in THF (10 mL) is added

Lawesson's reagent (0.262 g. 0.65 mmol). The reaction mixture is stirred for 3 hours and concentrated to a residue that is purified over silica to provide 0.350 g (83% yield) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.10 (d. *J* = 8.4 Hz, 2H), 8.01 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 5.70 (d, *J* = 7.2 Hz, 1H), 4.85 (d, *J*= 7.2 Hz, 1H), 3.11-3.30 (m, 1H), 1.21 (s, 9H).

[0142] Preparation of 1-(S)-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethyl amine hydrobromide (3): A mixture of [2-(4-nitrophenyl)-1-(*S*)-thiocarbamoylethyl]-carbamic acid *tert*-butyl ester, 2, (10g, 30.7mmol) and 1-bromo-2-butanone (90%, 3.8mL, 33.8mmol) in CH_3CN (500 mL) is refluxed for 18 hours. The reaction mixture is cooled to room temperature and diethyl ether is added to the solution and the precipitate which forms is removed by filtration to afford 7.47g of the desired product. ESI+ MS 278 (M+1).

[0143] Preparation of *N*-[1-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethyl]-2-phenyl-acetamide (4): To a solution of 1-(S)-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethyl amine hydrobromide, 3, (0.393 g, 1.1 mmol), phenylacetic acid (0.190 g, 1.4 mmol) and 1-hydroxybenzotriazole (HOBt) (0.094 g, 0.70 mmol) in DMF (10 mL) at 0°, is added 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide (EDCI) (0.268g, 1.4 mmol) followed by triethylamine (0.60 mL, 4.2mmol). The mixture is stirred at 0 °C for 30 minutes then at room temperature overnight. The reaction mixture is diluted with water and extracted with EtOAc. The combined organic phase is washed with 1 N aqueous HCl, 5 % aqueous $NaHCO_3$, water and brine, and dried over Na_2SO_4. The solvent is removed *in vacuo* to afford 0.260 g (60 % yield) of the desired product which is used without further purification. ESI+ MS 396 (M+1).

[0144] Preparation of {4-[2-(*S*)-(4-ethylthiazol-2-yl)-2-(2-phenylacetylamido)ethyl]-phenyl}sulfamic acid (5): *N*-[1-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethyl]-2-phenyl-acetamide, 4, (0.260 g) is dissolved in MeOH (4 mL). A catalytic amount of Pd/C (10% w/w) is added and the mixture is stirred under a hydrogen atmosphere 18 hours. The reaction mixture is filtered through a bed of CELITE™ and the solvent is removed under reduced pressure. The crude product is dissolved in pyridine (12 mL) and treated with SO_3-pyridine (0.177 g, 1.23). The reaction is stirred at room temperature for 5 minutes after which a 7% solution of NH_4OH (10 mL) is added. The mixture is then concentrated and the resulting residue is purified by reverse phase chromatography to afford 0.136 g of the desired product as the ammonium salt. ^{1}H NMR (CD_3OD) δ 8.60 (d, 1H, J = 8.1Hz), 7.33-7.23 (m, 3H), 7.16-7.00 (m, 6H), 5.44-5.41 (m, 1H), 3.28 (1H, A of ABX, obscured by solvent), 3.03 (1H, B of ABX, J = 14.1, 9.6Hz), 2.80 (q, 2H, J = 10.5, 7.8Hz) 1.31 (t, 3H, J = 4.6Hz).

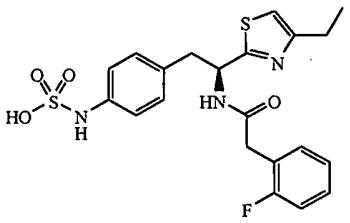
[0145] The following is a general procedure for isolating the final compound as a free acid.

[0146] Reduction of the aryl nitro group to free a amine:

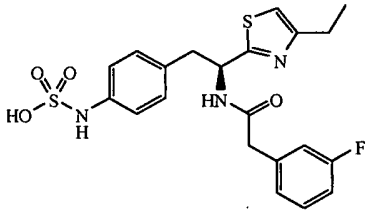
> To a Parr hydrogenation vessel is charged the nitro compound [for example, intermediate 4] (1.0 eq) and Pd/C (10 % Pd on C, 50 % wet, Degussa-type E101 NE/W, 2.68 g, 15 wt %) as solids. MeOH (15 mL/g) is added to provide a suspension. The vessel is put on a Parr hydrogenation apparatus. The vessel is submitted to a fill/vacuum evacuate process with N_2 (3 x 20 psi) to inert, followed by the same procedure with H_2 (3 x 40 psi). The vessel is filled with H_2 and the vessel is shaken under 40 psi H_2 for ~40 hr. The vessel is evacuated and the atmosphere is purged with N_2 (5 x 20 psi). An aliquot is filtered and analyzed by HPLC to insure complete conversion. The suspension is filtered through a pad of CELITE™ to remove the catalyst, and the homogeneous yellow filtrate is concentrated by rotary evaporation to afford the desired product which is used without further purification.

[0147] Preparation of free sulfamic acid: A 100 mL RBF is charged with the free amine (1.0 eq) prepared in the step described herein above. Acetonitrile (5 mL/g) is added and the yellow suspension which is typically yellow to orange in color is stirred at room temperature. A second 3-necked 500 mL RBF is charged with SO_3· pyr (1.4 eq) and acetonitrile (5 mL/g) and the suspension is stirred at room temperature. Both suspensions are gently heated until the reaction solution containing the amine becomes orange to red-orange in color (typically at about 40-45 °C). This substrate containing solution is poured in one portion into the stirring suspension of SO_3· pyr at 35 °C. The resulting opaque mixture is stirred vigorously while allowed to slowly cool to room temperature. After stirring for 45 min, or once the reaction is determined to be complete by HPLC, water (20 mL/g) is added to the colored suspension to provide a homogeneous solution having a pH of approximately 2.4. Concentrated H_3PO_4 is added slowly to lower the pH to approximately 1.4. During this pH adjustment, an off-white precipitate typically forms and the solution is stirred at room temperature for an additional hour. The suspension is filtered and the filter cake is washed with the filtrate. The filter cake is air-dried overnight to afford the desired product as the free acid.

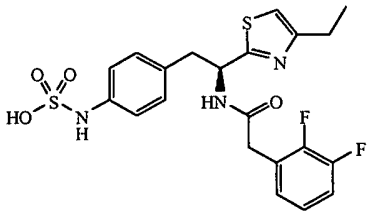
[0148] The following are examples of the first aspect of Category I of the present disclosure.



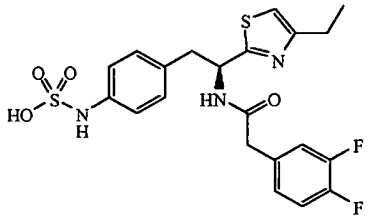
[0149] (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(2-fluorophenyl)acetamido)ethyl)phenyl-sulfamic acid: ^{1}H NMR (CD_3OD) δ 8.65(d, 1H, J = 8.4Hz), 7.29-7.15 (m, 1H), 7.13-7.03 (m, 7H), 5.46-5.42 (m, 1H), 3.64-3.51 (m, 2H), 3.29 (1H), 3.04 (1H, B of ABX, J = 13.8, 9.6Hz), 2.81 (q, 2H, J = 15.6, 3.9Hz), 1.31 (t, 3H, J = 7.8Hz). ^{19}F NMR (CD_3OD) δ 43.64. (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(2-fluorophenyl)acetamido)ethyl)phenyl-sulfamic acid



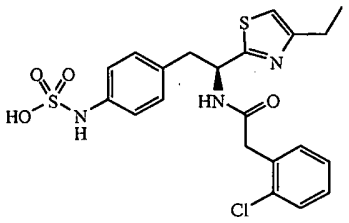
[0150] (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(3-fluorophenyl)acetamido)ethyl)phenyl-sulfamic acid: ^{1}H NMR (CD30D) δ 8.74 (d, 1H, J = 8.4Hz), 7.32 (q, 1H, J = 6.6, 14.2Hz), 7.10-6.91 (m, 8H), 5.47-5.40 (m, 1H), 3.53 (s, 2H), 3.30 (1H), 3.11 (1H, B of ABX, J = 9.6, 14.1Hz), 2.80 (q, 2H, J = 6.6, 15.1Hz), 1.31 (t, 3H, J = 7.8Hz). 19F NMR δ 47.42.



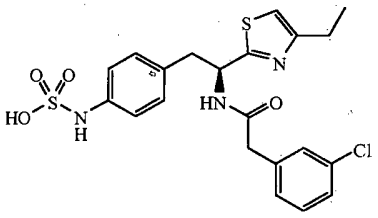
[0151] (*S*)-4-(2-(2-(2,3-Difluorophenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid: ^{1}H NMR (CD_3OD) δ 7.16-7.05 (m, 5H), 6.85-6.80 (m, 1H), 5.48-5.43 (m, 1H), 3.63 (s, 2H), 3.38 (1H, A of ABX, obscured by solvent), 3.03 (1H), 2.80 (q, H, J = 15.1, 7.8Hz), 1.31 (t, 3H, J = 7.5Hz).



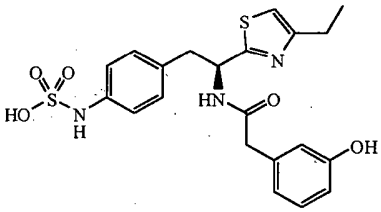
[0152] (*S*)-4-(2-(2-(3,4-Difluorophenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid: ^{1}H NMR (CD_3OD) δ 8.75 (d, 1H, J = 7.8Hz), 7.23-7.04 (m, 6H), 6.88-6.84 (m, 1H), 5.44-5.40 (m, 1H), 3.49 (s, 2H), 3.34 (1H), 3.02 (1H, B of ABX, J = 14.1, 9.9Hz), 2.80 (q, 2H, J = 15.1, 7.8Hz), 1.31 (t, 1H, J = 7.5Hz). 19F NMR (CD3OD) δ 22.18, 19.45.



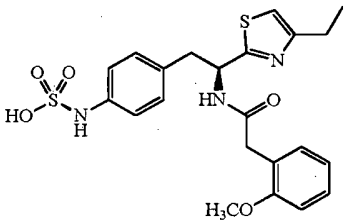
[0153] (*S*)-4-(2-(2-(2-Chlorophenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid: ^{1}H NMR (CD30D) δ 7.39-7.36 (m, 1H), 7.27-7.21 (m, 2H), 7.15-6.98 (m, 5H), 5.49-5.44 (m, 1H), 3.69 (d, 2H, J = 11.7Hz), 3.32 (1H), 3.04 (1H, B of ABX, J = 9.3, 13.9Hz), 2.80 (q, 2H, J = 7.8, 15.3Hz), 1.31 (t, 3H, J = 7.5Hz).



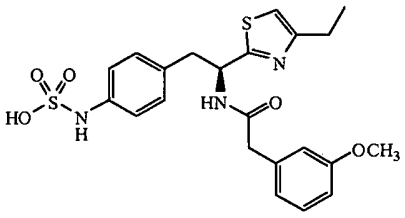
[0154] (*S*)-4-(2-(2-(3-Chlorophenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid: ^{1}H NMR (CD3OD) δ 7.33-7.23 (m, 3H), 7.13-7.03 (m, 5H), 5.43 (q, 1H, J = 5.1, 9.6Hz), 3.51 (s, 2H), 3.29 (1H), 3.03 (1H, B of ABX, J = 9.9, 14.1Hz), 2.80 (q, 2H, J = 7.5, 15Hz), 1.31 (t, 3H, J = 7.8Hz).



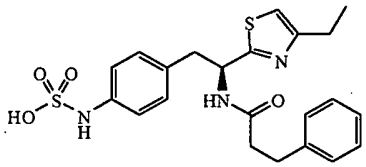
[0155] (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(3-hydroxyphenyl)acetamido)ethyl)phenyl-sulfamic acid: ^{1}H NMR (CD_3OD) δ 7.16-7.08 (m, 3H), 7.03-7.00 (m, 3H), 6.70-6.63 (m, 2H), 5.42-5.40 (m, 1H), 3.44 (s, 2H), 3.28 (1H, A of ABX, obscured by solvent), 3.04 (B of ABX, J = 14.1, 9.6Hz), 2.89 (q, 2H, J = 15, 7.5Hz), 1.31 (t, 3H, J = 7.5Hz).



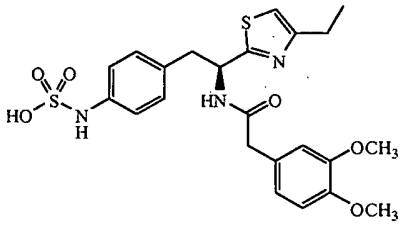
[0156] (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(2-methoxyphenyl)acetamido)ethyl)phenyl-sulfamic acid: ^{1}H NMR (CD_3OD) δ 8.00 (d, 1H, J = 7.8Hz), 7.26 (t, 1H, J = 13.2Hz), 7.09-7.05 (m, 4H), 7.01 (s, 1H), 6.91-6.89 (m, 4H), 5.44-5.39 (m, 1H), 3.71 (s, 3H), 3.52 (s, 2H), 3.26 (1H, A of ABX, J = 14.1, 5.1Hz), 3.06 (1H B of ABX, J = 13.8, 8.4Hz), 2.80 (q, 2H, J = 8.1, 15.6Hz), 1.31 (t, 3H, J = 1.2Hz).



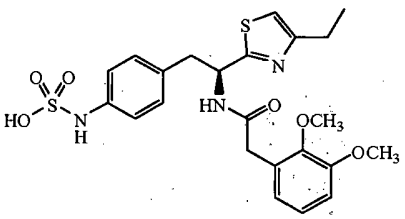
[0157] (*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(3-methoxyphenyl)acetamido]ethyl}phenyl-sulfamic acid: ^{1}H NMR (CD_3OD) δ 8.58 (d, 1H, J = 8.1 Hz), 7.21 (t, 1H, J = 7.8Hz), 7.12-7.02 (m, 4H), 6.81 (s, 2H), 6.72 (d, 1H, J = 7.5Hz), 5.45-5.40 (m, 1H), 3.79 (s, 3H), 3.50 (s, 2H), 3.29 (1H, A of ABX, obscured by solvent), 3.08 (1H, B of ABX, J = 11.8, 5.1Hz), 2.80 (q, 2H, J = 15, 7.5Hz), 1.31 (t, 3H, J = 6.6Hz).



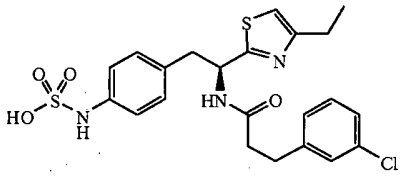
[0158] (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-phenylpropanamido)ethyl)phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 8.56 (d, 1H, J = 8.4Hz), 7.25-6.98 (m, 9H), 5.43-5.38 (m, 1H), 3.26 (1H, A of ABX, J = 14.1, 9.6Hz), 2.97 (1H, B of ABX, J = 10.9, 3Hz), 2.58-2.76 (m, 3H), 2.98 (q, 2H, J = 13.8, 7.2Hz), 1.29 (t, 3H, J = 8.7Hz).



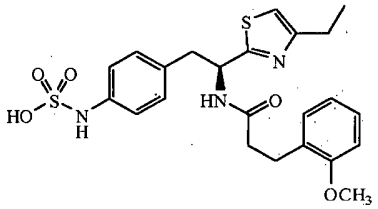
[0159] (*S*)-4-(2-(2-(3,4-Dimethoxyphenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)-phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 7.12-7.03 (m, 3H), 6.91 (d, 1H, J = 8.4Hz), 6.82 (s, 1H), 6.66 (d, 1H, J = 2.1Hz), 6.63 (d, 1H, J = 2.1Hz), 5.43 (m, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.45 (s, 2H), 3.30 (1H), 3.03 (1H, B of ABX, J = 14.1, 9.6Hz), 2.79 (q, 2H, J = 15.1, 7.2Hz), 1.30 (t, 3H, J = 7.2Hz).



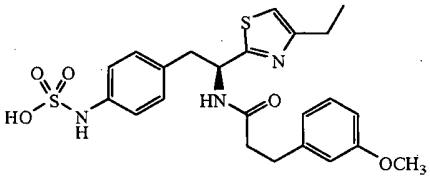
[0160] (*S*)-4-(2-(2-(2,3-Dimethoxyphenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)-phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 8.31 (d, 1H, J = 7.8Hz), 7.11-6.93 (m, 6H), 6.68 (d, 1H, J = 7.5Hz), 5.49-5.40 (m, 1H), 3.87 (s, 3H), 3.70 (s, 3H), 3.55 (s, 2H), 3.26 (1H, A of ABX, obscured by solvent), 3.06 (1H, B of ABX, J = 13.9, 9Hz), 2.80 (q, 2H, J = 14.8, 7.5Hz), 1.31 (t, 3H, J = 7.5Hz,).



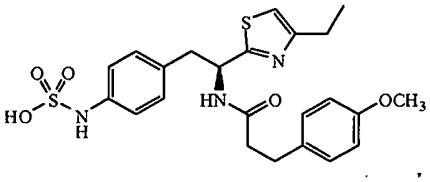
[0161] (S)-4-(2-(3-(3-Chlorophenyl)propanamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid: ^{1}H NMR (CD3OD) δ 7.27-7.18 (m, 3H), 7.13-7.08 (m, 5H), 7.01 (s, 1H), 5.39 (q, 1H, J = 5.1, 9.4Hz), 3.28 (1H, A of ABX, J = 5.1, 14.1Hz), 2.97 (1H, B of ABX, J = 9.3, 13.9Hz), 2.88-2.76 (m, 4H), 2.50 (t, 2H, J = 8.1Hz), 1.31 (t, 3H, J = 7.8Hz).



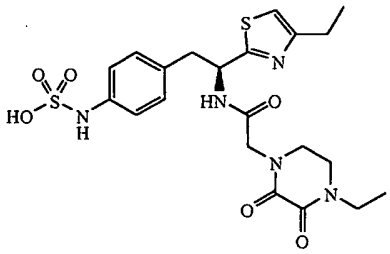
[0162] (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-(2-methoxyphenyl)propanamido)ethyl)phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 7.18-7.08 (m, 6H), 6.92 (d, 1H, J = 8.1Hz), 6.82 (t, 1H, J = 7.5Hz), 5.40-5.35 (m, 1H), 3.25 (1H, A of ABX, J = 15, 5.4Hz), 3.00 (1H, B of ABX, J = 10.5, 7.5Hz), 2.88-2.76 (m, 4H), 2.47 (q, 2H, J = 9.1, 6Hz), 1.31 (t, 3H, J = 7.8Hz).



[0163] (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-(3-methoxyphenyl)propanamido)ethyl)phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 7.19-7.00 (m, 5H), 6.75 (s, 1H), 6.73 (s, 1H), 5.42-5.37 (m, 1H), 3.76 (s, 3H), 3.25 (1H, A of ABX, J = 13.9, 5.4Hz), 2.98 (1H, B of ABX, J = 14.1, 9.6Hz), 2.86-2.75 (m, 4H), 2.48 (q, 2H, J = 11.7, 1.2Hz), 1.31 (t, 3H, J = 7.5Hz).

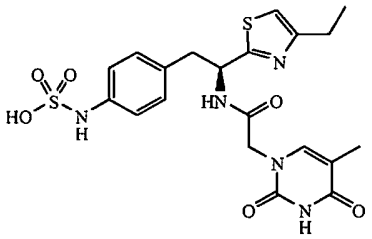


[0164] (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-(4-methoxyphenyl)propanamido)ethyl)phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 7.13-6.99 (m, 7H), 6.82-6.78 (m, 2H), 5.42-5.37 (m, 1H), 3.33 (s, 3H), 3.23 (1H), 2.97 (1H, B of ABX, J = 13.3, 11.4Hz), 2.83-2.75 (m, 4H), 2.49 (q, 2H, J = 6.4, 3.3Hz), 1.31 (t, 3H, J = 7.5Hz).

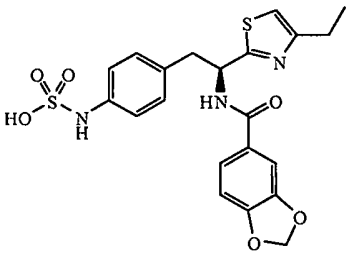


[0165] (*S*)-4-{2-[2-(4-Ethyl-2,3-dioxopiperazin-1-yl)acetamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 7.14 (s, 4H), 7.08 (s, 1H), 5.56-5.51 (m, 1H), 4.34 (d, 2H, J = 16.2Hz), 3.88 (d, 2H, J = 17.6Hz), 3.59-3.40 (m, 3H), 3.26-3.14 (m, 3H), 2.98 (1H, B of ABX, J = 10.8, 13.9Hz), 2.82 (q, 2H, J = 6.9, 15Hz), 1.32 (t, 3H, J = 7.5Hz),

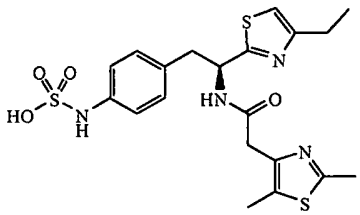
1.21 (t, 3H, J = 7.2Hz).



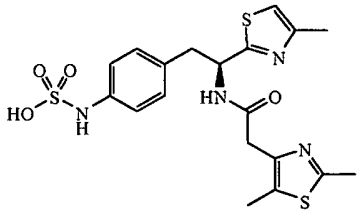
[0166] (*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1-(2H)-yl)acetamido]ethyl}phenylsulfamic acid: ^{1}H (CD_3OD): δ 7.13 (s, 1H), 7.06-7.02 (m, 4H), 6.95 (s, 1H), 5.42-5.31 (m, 1H), 4.43-4.18 (dd, 2H, *J*=16.5 Hz), 3.24-2.93 (m, 2H), 2.74-2.69 (q, 2H, *J*=7.3 Hz), 1.79 (s, 3H), 1.22 (t, 3H, *J*=1.5 Hz).



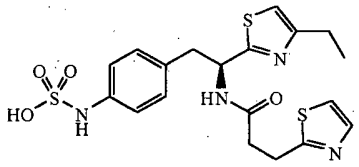
[0167] (*S*)-4-[2-(benzo[d][1,3]dioxole-5-carboxamido)-2-(4-ethylthiazol-2-yl)ethyl]-phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 7.25 (d, 1H, J=6.5 Hz), 7.13 (s, 1H), 7.06 (d, 2H, J=8.5 Hz), 7.00 (d, 2H, J=8.5 Hz), 6.91 (s, 1H), 6.76 (d, 1H, J=8.1 Hz), 5.90 (s, 2H), 5.48 (q, 1H, J=5.0 Hz), 3.32-3.24 (m, 2H), 3.07-2.99 (m, 2H), 2.72 (q, 2H, J=7.5 Hz), 1.21 (t, 3H, J=7.5 Hz).



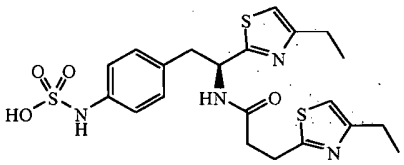
[0168] (*S*)-4-{2-[2-(2,5-Dimethylthiazol-4-yl)acetamido]-2-(4-ethylthiazol-2-yl)ethyl}-phenylsulfamic acid: ^{1}H (CD_3OD): δ 7.10-7.01 (m, 5H), 5.41 (t, 1H, *J*=6.9 Hz), 3.58 (s, 2H), 3.33-3.01 (m, 2H), 2.82-2.75 (q, 2H, *J*=7.5 Hz), 2.59 (s, 3H), 2.23 (s, 3H), 1.30 (t, 3H, *J*=7.5 Hz).



[0169] (*S*)-4-{2-[2-(2,4-Dimethylthiazol-5-yl)acetamido]-2-(4-methylthiazol-2-yl)ethyl}phenylsulfamic acid: ^{1}H (CD_3OD): δ 8.71-8.68 (d, 1H, J=8.4 Hz), 7.10-7.03 (m, 4H), 7.01 (s, 1H), 5.41 (m, 1H), 3.59 (s, 1H), 3.34-2.96 (m, 2H), 2.59 (s, 3H), 2.40 (s, 3H), 2.23 (s, 3H).

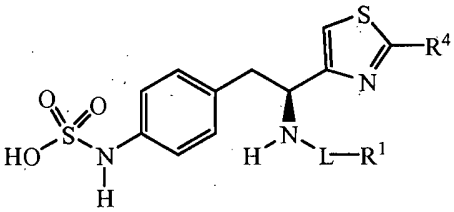


[0170] (*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[3-(thiazol-2-yl)propanamido]ethyl}phenyl-sulfamic acid: ^{1}H (CD_3OD): δ 7.67-7.65 (m, 1H), 7.49-7.47 (m, 1H), 7.14-7.08 (m, 4H), 7.04 (s, 1H), 5.46-5.41 (q, 1H, *J*=5.1 Hz), 3.58 (s, 2H), 3.30-3.25 (m, 3H), 3.02-2.67 (m, 5H), 1.31 (t, 3H, *J*=7.5 Hz).



[0171] (*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(4-ethylthiazol-2-yl)acetamido]ethyl}phenyl-sulfamic acid: ^{1}H(CD_3OD): δ 7.04-6.91 (m, 6H), 5.32 (t, 1H, *J*=5.4 Hz), 3.25-2.90 (m, 2H), 2.71-2.61 (m, 4H) 1.93 (s, 2H) 1.22-1.14 (m, 6H).

[0172] The second aspect of Category I of the present disclosure relates to 2-(thiazol-4-yl) compounds having the formula:



wherein R^1, R^4, and L are further defined herein in Table II herein below.

TABLE II

No.	L	R^1	R^4
89	-C(O)CH_2-	phenyl	methyl
90	-C(O)CH_2-	phenyl	ethyl
91	-C(O)CH_2-	phenyl	phenyl
92	-C(O)CH_2-	phenyl	thiophene-2-yl
93	-C(O)CH_2-	phenyl	thiazol-2-yl
94	-C(O)CH_2-	phenyl	oxazol-2-yl
95	-C(O)CH_2-	phenyl	isoxazol-3-yl
96	-C(O)CH_2-	3-chlorophenyl	methyl
97	-C(O)CH_2-	3-chlorophenyl	ethyl
98	-C(O)CH_2-	3-chlorophenyl	phenyl
99	-C(O)CH_2-	3-chlorophenyl	thiophene-2-yl
100	-C(O)CH_2-	3-chlorophenyl	thiazol-2-yl
101	-C(O)CH_2-	3-chlorophenyl	oxazol-2-yl
102	-C(O)CH_2-	3-chlorophenyl	isoxazol-3-yl
103	-C(O)CH_2-	3-methoxyphenyl	methyl

(continued)

No.	L	R^1	R^4
104	$-C(O)CH_2-$	3-methoxyphenyl	ethyl
105	$-C(O)CH_2-$	3-methoxyphenyl	phenyl
106	$-C(O)CH_2-$	3-methoxyphenyl	thiophene-2-yl
107	$-C(O)CH_2-$	3-methoxyphenyl	thiazol-2-yl
108	$-C(O)CH_2-$	3-methoxyphenyl	oxazol-2-yl
109	$-C(O)CH_2-$	3-methoxyphenyl	isoxazol-3-yl
110	$-C(O)CH_2-$	3-fluorophenyl	methyl
111	$-C(O)CH_2-$	3-fluorophenyl	ethyl
112	$-C(O)CH_2-$	3-fluorophenyl	phenyl
113	$-C(O)CH_2-$	3-fluorophenyl	thiophene-2-yl
114	$-C(O)CH_2-$	3-fluorophenyl	thiazol-2-yl
115	$-C(O)CH_2-$	3-fluorophenyl	oxazol-2-yl
116	$-C(O)CH_2-$	3-fluorophenyl	isoxazol-3-yl
117	$-C(O)CH_2-$	2,5-dimethylthiazol-4-yl	methyl
118	$-C(O)CH_2-$	2,5-dimethylthiazol-4-yl	ethyl
119	$-C(O)CH_2-$	2,5-dimethylthiazol-4-yl	phenyl
120	$-C(O)CH_2-$	2,5-dimethylthiazol-4-yl	thiophene-2-yl
121	$-C(O)CH_2-$	2,5-dimethylthiazol-4-yl	thiazol-2-yl
122	$-C(O)CH_2-$	2,5-dimethylthiazol-4-yl	oxazol-2-yl
123	$-C(O)CH_2-$	2,5-dimethylthiazol-4-yl	isoxazol-3-yl
124	$-C(O)CH_2-$	2,4-dimethylthiazol-5-yl	methyl
125	$-C(O)CH_2-$	2,4-dimethylthiazol-5-yl	ethyl
126	$-C(O)CH_2-$	2,4-dimethylthiazol-5-yl	phenyl
127	$-C(O)CH_2-$	2,4-dimethylthiazol-5-yl	thiophene-2-yl
128	$-C(O)CH_2-$	2,4-dimethylthiazol-5-yl	thiazol-2-yl
129	$-C(O)CH_2-$	2,4-dimethylthiazol-5-yl	oxazol-2-yl
130	$-C(O)CH_2-$	2,4-dimethylthiazol-5-yl	isoxazol-3-yl
131	$-C(O)CH_2-$	4-ethylthiazol-2-yl	methyl
132	$-C(O)CH_2-$	4-ethylthiazol-2-yl	ethyl
133	$-C(O)CH_2-$	4-ethylthiazol-2-yl	phenyl
134	$-C(O)CH_2-$	4-ethylthiazol-2-yl	thiophene-2-yl
135	$-C(O)CH_2-$	4-ethylthiazol-2-yl	thiazol-2-yl
136	$-C(O)CH_2-$	4-ethylthiazol-2-yl	oxazol-2-yl
137	$-C(O)CH_2-$	4-ethylthiazol-2-yl	isoxazol-3-yl
138	$-C(O)CH_2-$	3-methyl-1,2,4-oxadiazol-5-yl	methyl
139	$-C(O)CH_2-$	3-methyl-1,2,4-oxadiazol-5-yl	ethyl
140	$-C(O)CH_2-$	3-methyl-1,2,4-oxadiazol-5-yl	phenyl
141	$-C(O)CH_2-$	3-methyl-1,2,4-oxadiazol-5-yl	thiophene-2-yl

(continued)

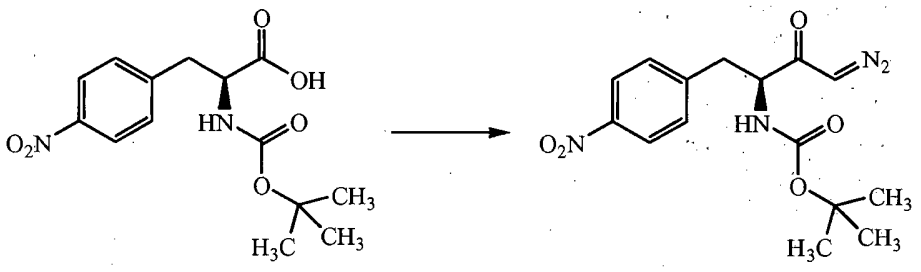
No.	L	R^1	R^4
142	$-C(O)CH_2-$	3-methyl-1,2,4-oxadiazol-5-yl	thiazol-2-yl
143	$-C(O)CH_2-$	3-methyl-1,2,4-oxadiazol-5-yl	oxazol-2-yl
144	$-C(O)CH_2-$	3-methyl-1,2,4-oxadiazol-5-yl	isoxazol-3-yl
145	$-C(O)CH_2CH_2-$	phenyl	methyl
146	$-C(O)CH_2CH_2-$	phenyl	ethyl
147	$-C(O)CH_2CH_2-$	phenyl	phenyl
148	$-C(O)CH_2CH_2-$	phenyl	thiophene-2-yl
149	$-C(O)CH_2CH_2-$	phenyl	thiazol-2-yl
150	$-C(O)CH_2CH_2-$	phenyl	oxazol-2-yl
151	$-C(O)CH_2CH_2-$	phenyl	isoxazol-3-yl
152	$-C(O)CH_2CH_2-$	3-chlorophenyl	methyl
153	$-C(O)CH_2CH_2-$	3-chlorophenyl	ethyl
154	$-C(O)CH_2CH_2-$	3-chlorophenyl	phenyl
155	$-C(O)CH_2CH_2-$	3-chlorophenyl	thiophene-2-yl
156	$-C(O)CH_2CH_2-$	3-chlorophenyl	thiazol-2-yl
157	$-C(O)CH_2CH_2-$	3-chlorophenyl	oxazol-2-yl
158	$-C(O)CH_2CH_2-$	3-chlorophenyl	isoxazol-3-yl
159	$-C(O)CH_2CH_2-$	3-methoxyphenyl	methyl
160	$-C(O)CH_2CH_2-$	3-methoxyphenyl	ethyl
161	$-C(O)CH_2CH_2-$	3-methoxyphenyl	phenyl
162	$-C(O)CH_2CH_2-$	3-methoxyphenyl	thiophene-2-yl
163	$-C(O)CH_2CH_2-$	3-methoxyphenyl	thiazol-2-yl
164	$-C(O)CH_2CH_2-$	3-methoxyphenyl	oxazol-2-yl
165	$-C(O)CH_2CH_2-$	3-methoxyphenyl	isoxazol-3-yl
166	$-C(O)CH_2CH_2-$	3-fluorophenyl	methyl
167	$-C(O)CH_2CH_2-$	3-fluorophenyl	ethyl
168	$-C(O)CH_2CH_2-$	3-fluorophenyl	phenyl
169	$-C(O)CH_2CH_2-$	3-fluorophenyl	thiophene-2-yl
170	$-C(O)CH_2CH_2-$	3-fluorophenyl	thiazol-2-yl
171	$-C(O)CH_2CH_2-$	3-fluorophenyl	oxazol-2-yl
172	$-C(O)CH_2CH_2-$	3-fluorophenyl	isoxazol-3-yl
173	$-C(O)CH_2CH_2-$	2,5-dimethylthiazol-4-yl	methyl
174	$-C(O)CH_2CH_2-$	2,5 5-dimethylthiazol-4-yl	ethyl
175	$-C(O)CH_2CH_2-$	2,5-dimethylthiazol-4-yl	phenyl
176	$-C(O)CH_2CH_2-$	2,5-dimethylthiazol-4-yl	thiophene-2-yl
177	$-C(O)CH_2CH_2-$	2,5-dimethylthiazol-4-yl	thiazol-2-yl
178	$-C(O)CH_2CH_2-$	2,5-dimethylthiazol-4-yl	oxazol-2-yl
179	$-C(O)CH_2CH_2-$	2,5-dimethylthiazol-4-yl	isoxazol-3-yl

(continued)

No.	L	R^1	R^4
180	$-C(O)CH_2CH_2-$	2,4-dimethylthiazol-5-yl	methyl
181	$-C(O)CH_2CH_2-$	2,4-dimethylthiazol-5-yl	ethyl
182	$-C(O)CH_2CH_2-$	2,4-dimethylthiazol-5-yl	phenyl
183	$-C(O)CH_2CH_2-$	2,4-dimethylthiazol-5-yl	thiophene-2-yl
184	$-C(O)CH_2CH_2-$	2,4-dimethylthiazol-5-yl	thiazol-2-yl
185	$-C(O)CH_2CH_2-$	2,4-dimethylthiazol-5-yl	oxazol-2-yl
186	$-C(O)CH_2CH_2-$	2,4-dimethylthiazol-5-yl	isoxazol-3-yl
187	$-C(O)CH_2CH_2-$	4-ethylthiazol-2-yl	methyl
188	$-C(O)CH_2CH_2-$	4-ethylthiazol-2-yl	ethyl
189	$-C(O)CH_2CH_2-$	4-ethylthiazol-2-yl	phenyl
190	$-C(O)CH_2CH_2-$	4-ethylthiazol-2-yl	thiophene-2-yl
191	$-C(O)CH_2CH_2-$	4-ethylthiazol-2-yl	thiazol-2-yl
192	$-C(O)CH_2CH_2-$	4-ethylthiazol-2-yl	oxazol-2-yl
193	$-C(O)CH_2CH_2-$	4-ethylthiazol-2-yl	isoxazol-3-yl
194	$-C(O)CH_2CH_2-$	3-methyl-1,2,4-oxadiazol-5-yl	methyl
195	$-C(O)CH_2CH_2-$	3-methyl-1,2,4-oxadiazol-5-yl	ethyl
196	$-C(O)CH_2CH_2-$	3-methyl-1,2,4-oxadiazol-5-yl	phenyl
197	$-C(O)CH_2CH_2-$	3-methyl-1,2,4-oxadiazol-5-yl	thiophene-2-yl
198	$-C(O)CH_2CH_2-$	3-methyl-1,2,4-oxadiazol-5-yl	thiazol-2-yl
199	$-C(O)CH_2CH_2-$	3-methyl-1,2,4-oxadiazol-5-yl	oxazol-2-yl
200	$-C(O)CH_2CH_2-$	3-methyl-1,2,4-oxadiazol-5-yl	isoxazol-3-yl

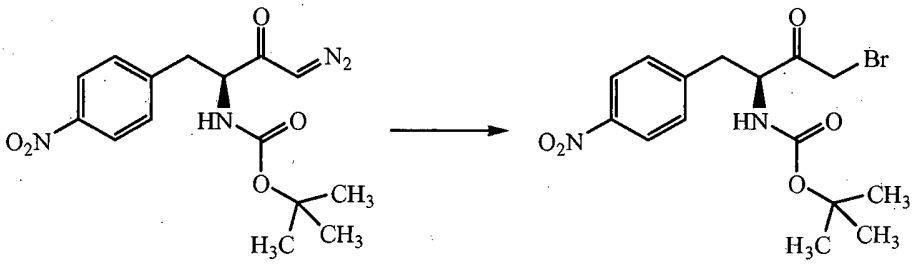
[0173] The compounds encompassed within the second aspect of Category I of the present disclosure can be prepared by the procedure outlined in Scheme II and described in Example 2 herein below.

Scheme II



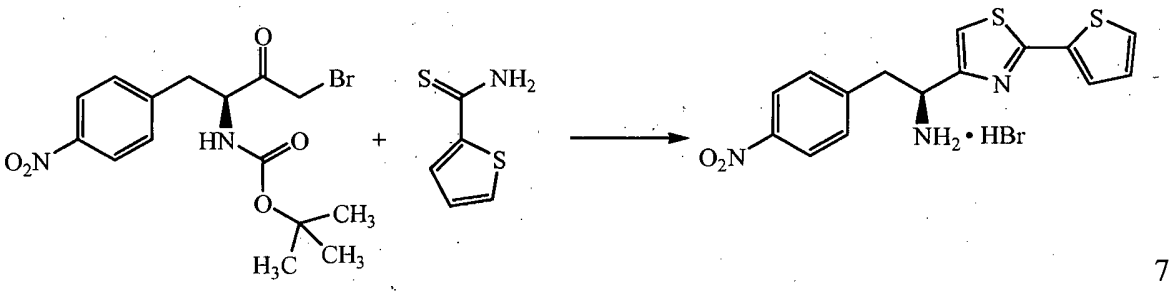
6

Reagents and conditions: (a)(i) (*iso*-butyl)OCOCl, Et_3N, THF; 0 °C, 20 min.
(ii) CH_2N_2; room temp for 3 hours.



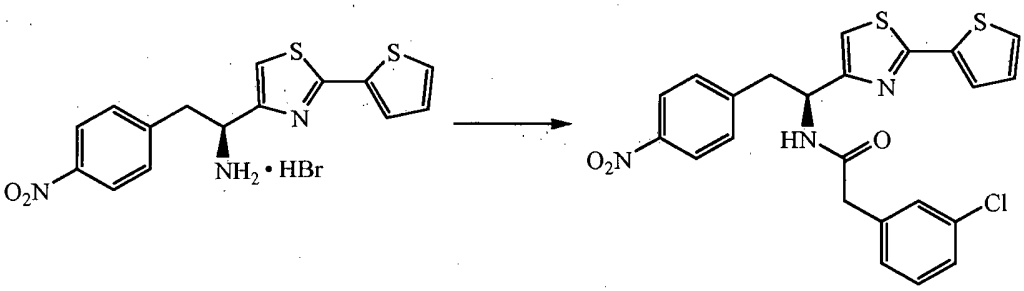
6 7

Reagents and conditions: (b) 48% HBr, THF; 0 °C, 1.5 hr.



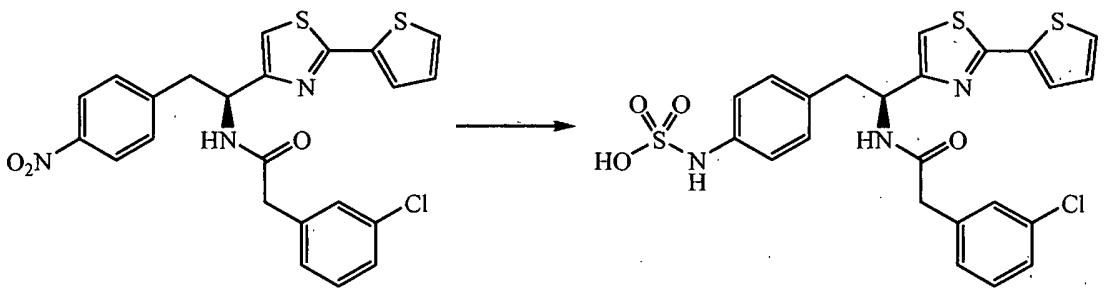
8 7

Reagents and conditions: (c) CH_3CN; reflux 5 hr.



8 9

Reagents and conditions: (d) (3-Cl)$C_6H_4CO_2H$, EDCI, HOBt, DIPEA, DMF; rt, 18 hr.



9 10

Reagents and conditions: (e) (i) H_2:Pd/C, MeOH; (ii) SO_3-pyridine, NH_4OH, rt, 18 hr.

EXAMPLE 2

4-((*S*)-2-(2-(3-chlorophenyl)acetamido)-2-(2-(thiophene-2-yl)thiazol-4-yl)ethyl)phenylsulfamic acid (10)

[0174] Preparation of (S)-[3-diazo-1-(4-nitrobenzyl)-2-oxo-propyl]-carbamic acid *tert*-butyl ester (6): To a 0 °C solution of 2-(*S*)-*tert*-butoxycarbonylamino-3-(4-nitrophenyl)-propionic acid (1.20 g, 4.0 mmol) in THF (20 mL) is added dropwise triethylamine (0.61 mL, 4.4 mmol) followed by *iso*-butyl chloroformate (0.57 mL, 4.4 mmol). The reaction mixture is stirred at 0 °C for 20 minutes and filtered. The filtrate is treated with an ether solution of diazomethane (~16 mmol) at 0 °C. The reaction mixture is stirred at room temperature for 3 hours then concentrated *in vacuo*. The resulting residue is dissolved in EtOAc and washed successively with water and brine, dried (Na_2SO_4), filtered and concentrated. The residue is purified over silica (hexane/EtOAc 2:1) to afford 1.1 g (82% yield) of the desired product as a slightly yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 8.7 Hz, 2H), 7.39 (d, J= 8.7 Hz, 2H), 5.39 (s, 1H), 5.16 (d, J = 6.3 Hz, 1H), 4.49 (s, 1H), 3.25 (dd, J = 13.8 and 6.6, 1 H), 3.06 (dd, J = 13.5 and 6.9 Hz, 1H), 1.41 (s, 9H).

[0175] Preparation of (*S*)-*tert*-butyl 4-bromo-1-(4-nitrophenyl)-3-oxobutan-2-ylcarbamate (7): To a 0 °C solution of (*S*)-[3-diazo-1-(4-nitrobenzyl)-2-oxo-propyl]-carbamic acid *tert*-butyl ester, 6, (0.350 g, 1.04 mmol) in THF (5 mL) is added dropwise 48% aq. HBr (0.14 mL, 1.25 mmol). The reaction mixture is stirred at 0 °C for 1.5 hours then the reaction is quenched at 0 °C with sat. Na_2CO_3. The mixture is extracted with EtOAc (3x 25 mL) and the combined organic extracts are washed with brine, dried (Na_2SO_4), filtered and concentrated to obtain 0.400 g of the product which is used in the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 5.06 (d, J= 7.8 Hz, 1H), 4.80 (q, J = 6.3 Hz, 1H), 4.04 (s, 2H), 1.42 (s, 9H).

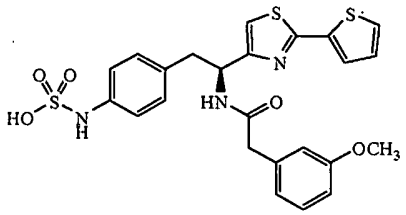
[0176] Preparation of (*S*)-2-(4-nitrophenyl)-1-[(thiophene-2-yl)thiazol-4-yl]ethanamine hydrobromide salt (8): A mixture of (*S*)-tert-butyl 4-bromo-1-(4-nitrophenyl)-3-oxobutan-2-ylcarbamate, 7, (7.74g, 20mmol), and thiophene-2-carbothioic acid amide (3.14g, 22mmol) in CH_3CN (200 mL) is refluxed for 5 hours. The reaction mixture is cooled to room temperature and diethyl ether (50 mL) is added to the solution. The precipitate which forms is collected by filtration. The solid is dried under vacuum to afford 7.14 g (87 % yield) of the desired product. ESI+ MS 332 (M+1).

[0177] Preparation of 2-(3-chlorophenyl)-*N*-{(*S*)-2-(4-nitrophenyl)-1-[2-(thiophene-2-yl)thiazol-4-yl]ethyl]acetamide (9): To a solution of 2-(4-nitrophenyl)-1-(2-thiophene2-ylthiazol-4-yl)ethylamine, 8, (0.41 g, 1mmol) 3-chlorophenylacetic acid (0.170g, 1mmol) and 1-hydroxybenzotriazole (HOBt) (0.070g, 0.50mmol) in DMF (5 mL) at 0°, is added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) (0.190g, 1mmol) followed by triethylamine (0.42mL, 3mmol). The mixture is stirred at 0 °C for 30 minutes then at room temperature overnight. The reaction mixture is diluted with water and extracted with EtOAc. The combined organic phase is washed with 1 N aqueous HCl, 5 % aqueous $NaHCO_3$, water and brine, and dried over Na_2SO_4. The solvent is removed *in vacuo* to afford 0.290 g (60 % yield) of the desired product which is used without further purification. ESI- MS 482 (M-1).

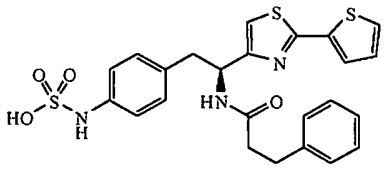
[0178] Preparation of {4-[2-(3-chlorophenyl)acetylamino]-2-(2-thiophen-2-ylthiazol-4-yl)ethyl]phenyl}sulfamic acid

(10): 2-(3-chlorophenyl)-*N*-{(*S*)-2-(4-nitrophenyl)-1-[2-(thiophene2-yl)thiazol-4-yl]ethyl}acetamide, 9, (0.290 g) is dissolved in MeOH (4 mL). A catalytic amount of Pd/C (10% w/w) is added and the mixture is stirred under a hydrogen atmosphere 18 hours. The reaction mixture is filtered through a bed of CELITE™ and the solvent is removed under reduced pressure. The crude product is dissolved in pyridine (12 mL) and treated with SO_3-pyridine (0.157 g). The reaction is stirred at room temperature for 5 minutes after which a 7% solution of NH_4OH is added. The mixture is then concentrated and the resulting residue is purified by reverse phase chromatography to afford 0.078 g of the desired product as the ammonium salt. ^{1}H NMR (CD_3OD) δ 7.61 (d, 1H, J = 3.6Hz), 7.58 (d, 1H, J = 5.1Hz), 7.41-7.35 (m, 1H), 7.28-7.22 (m, 2H), 7.18-6.98 (m, 6H), 5.33 (t, 1H, J = 6.6Hz), 3.70 (d, 2H, J = 3.9Hz), 3.23 (1H, A of ABX, J = 6.6, 13.8Hz), 3.07 (1H, B of ABX, J = 8.1, 13.5Hz).

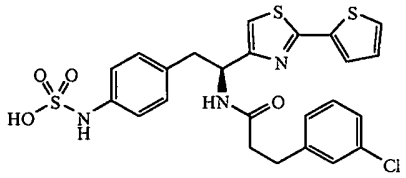
[0179] The following are examples of compounds encompassed within the second aspect of Category I of the present disclosure.



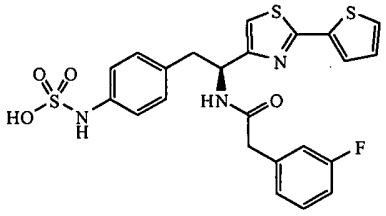
[0180] 4-((*S*)-2-(2-(3-Methoxyphenyl)acetamido)-2-(2-(thiophen-2-yl)thiazol-4-yl)ethyl)-phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 8.35 (d, 1H, J = 8.7Hz), 7.61-7.57 (m, 2H), 7.25-7.20 (m, 2H), 7.25-7.20 (m, 2H), 7.09 (s, 1H), 7.05 (d, 2H, J = 4.2Hz), 6.99 (d, 1H, J = 8.7Hz), 6.81 (d, 1H, J = 7.8Hz), 6.77 (s, 1H), 5.30-5.28 (m, 1H), 3.76 (s, 3H), 3.51 (s, 2H), 3.20 (1H, A of ABX, J = 6.3, 13.6Hz), 3.06 (1H, B ofABX, J = 8.1, 13.8Hz).



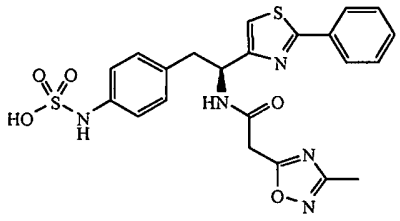
[0181] 4-{(*S*)-2-(3-Phenylpropanamido)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenyl-sulfamic acid: ^{1}H NMR (CD_3OD) δ 8.30 (d, 1H, J = 9Hz), 7.61-7.56 (m, 2H), 7.26-7.14 (m, 7H), 7.12 (d, 1H, J = 1.5Hz), 7.09 (d, 1H, J = 2.1Hz), 6.89 (s, 1H), 5.28-5.26 (m, 1H), 3.18 (1H, A of ABX, J = 6.2, 13.8Hz), 2.96 (1H, B of ABX, J = 8.4, 13.6Hz).



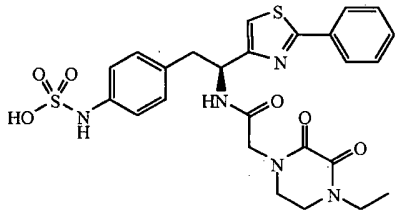
[0182] 4-{(*S*)-2-(3-(3-Chlorophenyl)propanamido)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 7.61-7.56 (m, 3H), 7.22-7.14 (m, 6H), 7.08 (d, 1H), 7.00 (d, 1H, J = 77.5Hz), 6.870 (s, 1H), 5.25 (t, 1H, J = 7.8Hz), 3.18 (1H, A of ABX, J = 6.6, 13.8Hz), 2.97 (1H, B of ABX, J = 7.8, 13.8Hz), 2.87 (t, 2H, J = 7.5Hz), 2.51 (t, 2H, J = 7.2Hz).



[0183] 4-{(*S*)-2-[2-(3-Fluorophenyl)acetamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 7.61-7.57 (m, 2H), 7.32-7.28 (m, 1H), 7.19-7.16 (m, 2H), 7.08 (t, 1H, J = 4.5Hz), 7.02-6.95 (m, 6H), 5.29 (t, 1H, J = 8.1Hz), 3.53 (s, 2H), 3.22 (1H, A of ABX, J = 6.6, 13.9Hz), 3.06 (1H, B of ABX, J = 8.4, 13.6Hz).

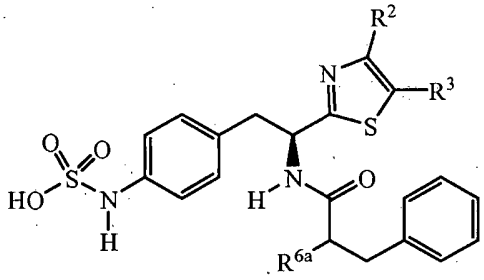


[0184] (*S*)-4-{2-[2-(3-Methyl-1,2,4-oxadiazol-5-yl)acetamido]-2-(2-phenylthiazol-4-yl)ethyl}phenylsulfamic acid: ^{1}H (CD_3OD): δ 7.98-7.95 (m, 2H), 7.48-7.46 (m, 3H), 7.23 (s, 1H), 7.09-7.05 (m, 4H), 5.33 (t, 1H, *J*=7.2 Hz), 3.33-3.06 (m, 2H), 2.35 (s, 3H).



[0185] 4-{(*S*)-2-[2-(4-ethyl-2,3-dioxopiperazin-1-yl)acetamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 7.62 (d, 1H, J = 3Hz), 7.58 (d, 1H, J = 15.6Hz), 7.27 (s, 1H), 7.16 (t, 1H, J = 1.5Hz), 5.42-5.32 (m, 1H), 4.31 (d, 1H, J = 15.6Hz), 3.91 (d, 1H, J = 15.9Hz), 3.60-3.50 (m, 4H), 3.30-3.23 (m, 2H), 2.98 (1H, B of ABX, J = 9.9, 13.8Hz), 1.21 (t, 3H, J = 6.9Hz).

[0186] The third aspect of Category I of the present disclosure relates to compounds having the formula:



wherein the linking unit L comprises a phenyl unit, said linking group having the formula:

$$-C(O)[(CR^{6a}H)][(CH_2)]-$$

R^{5a} is phenyl or substituted phenyl and examples of the units R^2, R^3, and R^{6a} are further exemplified herein below in Table III.

TABLE III

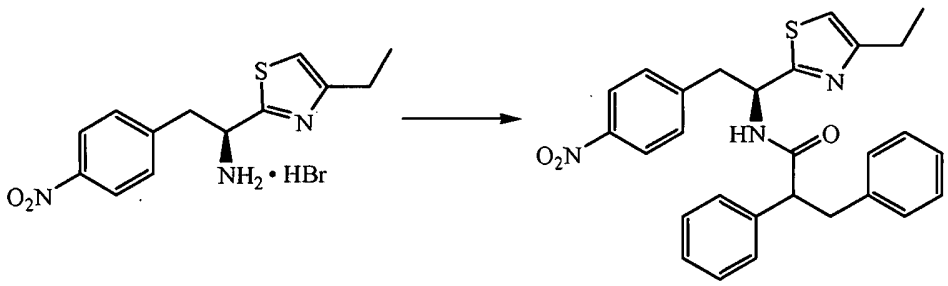
No.	R^2	R^3	R^{6a}
201	methyl	hydrogen	phenyl
202	methyl	hydrogen	2-fluorophenyl
203	methyl	hydrogen	3-fluorophenyl

(continued)

No.	R^2	R^3	R^{6a}
204	methyl	hydrogen	4-fluorophenyl
205	methyl	hydrogen	3,4-difluorophenyl
206	methyl	hydrogen	2-chlorophenyl
207	methyl	hydrogen	3-chlorophenyl
208	methyl	hydrogen	4-chlorophenyl
209	methyl	hydrogen	3,4-dichlorophenyl
210	methyl	hydrogen	2-methoxyphenyl
211	methyl	hydrogen	3-methoxyphenyl
212	methyl	hydrogen	4-methoxyphenyl
213	ethyl	hydrogen	phenyl
214	ethyl	hydrogen	2-fluorophenyl
215	ethyl	hydrogen	3-fluorophenyl
216	ethyl	hydrogen	4-fluorophenyl
217	ethyl	hydrogen	3,4-difluorophenyl
218	ethyl	hydrogen	2-chlorophenyl
219	ethyl	hydrogen	3-chlorophenyl
220	ethyl	hydrogen	4-chlorophenyl
221	ethyl	hydrogen	3,4-dichlorophenyl
222	ethyl	hydrogen	2-methoxyphenyl
223	ethyl	hydrogen	3-methoxyphenyl
224	ethyl	hydrogen	4-methoxyphenyl

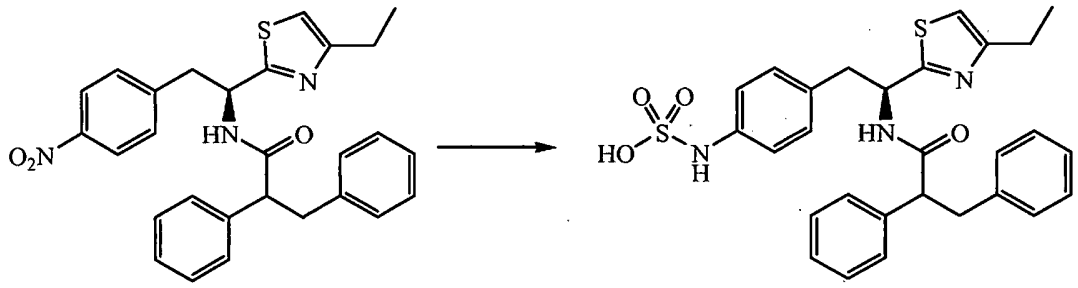
[0187] The compounds encompassed within the third aspect of Category I of the present disclosure can be prepared by the procedure outlined in Scheme III and described in Example 3 herein below.

Scheme III



3 11

Reagents and conditions: (a) diphenylpropionic acid, EDCI, HOBt, TEA, DMF; 0 °C to rt, 18 hr.



11 12

Reagents and conditions: (b) (i) H_2:Pd/C, MeOH; (ii) SO_3-pyridine, NH_4OH; rt, 18 hr.

EXAMPLE 3

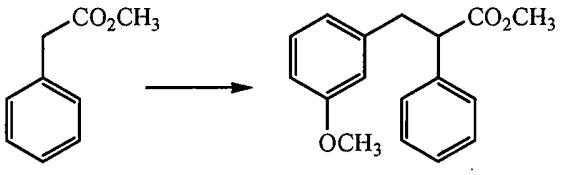
(*S*)-4-(2-(2,3-Diphenylpropanamido)-2-(4-ethylthiazol-2-yl)ethyl)-phenylsulfamic acid (12)

[0188] Preparation of (*S*)-*N*-[1-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethyl]-2,3-diphenyl-propanamide (11): To a solution of 1-(*S*)-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethyl amine hydrobromide, 3, (0.95 g, 2.65 mmol), diphenylpropionic acid (0.60 g, 2.65 mmol) and 1-hydroxybenzotriazole (HOBt) (0.180 g, 1.33 mmol) in DMF (10 mL) at 0°, is added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) (0.502 g, 2.62 mmol) followed by triethylamine (1.1 mL, 7.95 mmol). The mixture is stirred at 0 °C for 30 minutes then at room temperature overnight. The reaction mixture is diluted with water and extracted with EtOAc. The combined organic phase is washed with 1 N aqueous HCl, 5 % aqueous $NaHCO_3$, water and brine, and dried over Na_2SO_4. The solvent is removed *in vacuo* to afford 0.903 g (70% yield) of the desired product which is used without further purification.

[0189] Preparation of (*S*)-4-(2-(2,3-diphenylpropanamido)-2-(4-ethylthiazol-2-yl)ethyl)phenylsulfamic acid (12) (*S*)-*N*-[1-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethyl]-2,3-diphenyl-propanamide, 11, (0.903 g) is dissolved in MeOH (10 mL). A catalytic amount of Pd/C (10% w/w) is added and the mixture is stirred under a hydrogen atmosphere 18 hours. The reaction mixture is filtered through a bed of CELITE™ and the solvent is removed under reduced pressure. The crude product is dissolved in pyridine (30 mL) and treated with SO_3-pyridine (0.621 g). The reaction is stirred at room temperature for 5 minutes after which a 7% solution of NH_4OH is added. The mixture is then concentrated and the resulting residue is purified by reverse phase chromatography to afford 0.415 g of the desired product as the ammonium salt. ^1H NMR (CD30D) δ 8.59-8.52 (m, 1H), 7.37-7.04 (m, 9H), 6.97-6.93 (m, 1H), 6.89-6.85 (m, 2H), 5.36-5.32 (m, 1H), 3.91-3.83 (m, 1H), 3.29 (1H, A of ABX, obscured by solvent), 3.15 (1H, B of ABX, J = 5.4, 33.8Hz), 2.99-2.88 (m, 2H), 2.81-2.69 (m, 2H), 1.32-1.25 (m, 3H).

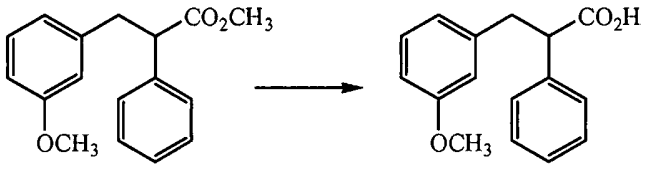
[0190] The precursors of many of the Z units which comprise the third aspect of Category I are not readily available. The following procedure illustrates an example of the procedure which can be used to provide different R^{6a} units according to the present disclosure. Using the procedure outlined in Scheme IV and described in Example 4 the artisan can make modifications without undue experimentation to achieve the R^{5a} units encompassed by the present disclosure.

Scheme IV



13

Reagents and conditions: (a) methyl 2-(2-methoxyphenyl)acetate, LDA, THF; 0 °C to rt 18 hr.



13 14

Reagents and conditions: (b)

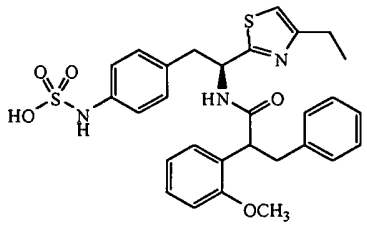
EXAMPLE 4

2-(2-Methoxyphenyl)-3-phenylpropanoic acid (14)

[0191] Preparation of methyl 2-(2-methoxyphenyl)-3-phenylpropanoate (13): A 500mL roundbottom flask is charged with methyl 2-(2-methoxyphenyl)acetate (8.496 g, 47 mmol, 1eq) and THF (200mL). The homogeneous mixture is cooled to 0 °C in an ice bath. Lithium diisopropyl amide (23.5mL of a 2.0M solution in heptane/THF) is added, maintaining a temperature less than 3°C. The reaction is stirred 45 minutes at this reduced temperature. Benzyl bromide (5.6mL, 47mmol, 1eq) is added dropwise. The reaction is allowed to gradually warm to room temperature and is stirred for 18 hours. The reaction is quenched with 1N HCl and extracted 3 times with equal portions of EtOAc. The combined extracts are washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated. The residue is purified over silica to afford 4.433g (35%) of the desired compound. ESI+ MS 293 (M+Na).

[0192] Preparation of 2-(2-methoxyphenyl)-3-phenylpropanoic acid (14): Methyl 2-(2-methoxyphenyl)-3-phenylpropanoate (4.433g, 16mmol, 1eq) is dissolved in 100mL of a 1:1 (v:v) mixture of THF and methanol. Sodium hydroxide (3.28g, 82mmol, 5eq) is added and the reaction mixture is stirred 18 hours at room temperature. The reaction is then poured into H_2O and the pH is adjusted to 2 via addition of 1N HCl. A white precipitate forms which is removed by filtration. The resulting solution is extracted with 3 portion of diethyl ether. The extracts are pooled, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue is purified over silica to afford 2.107g (51%) of the desired compound. ESI- MS 255 (M-1), 211 (M-CO_2H).

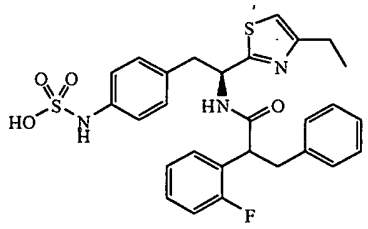
[0193] Intermediate 14 can be carried forward according to the procedure outlined in Scheme III and described in Example 3 to produce the following compound according to the third aspect of Category I.



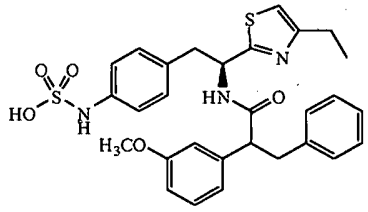
[0194] (*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(2-methoxyphenyl)-3-phenylpropanamido]-ethyl}phenylsulfamic acid: ^1H NMR (CD_3OD) δ 7.32-7.12 (m, 7H), 7.05-7.02 (m, 1H), 6.99-6.83 (m, 4H), 6.80-6.75 (m, 2H), 5.35-5.31 (m, 1H), 4.31-4.26

(m, 1H), 3.75 (s, 3H), 3.20-2.90 (m, 4H), 2.79-2.74 (m, 2H), 1.32-1.25 (m, 3H).

[0195] The following are further examples of compounds according to the third aspect of Category I of the present disclosure.

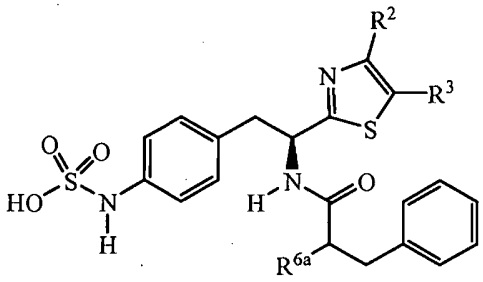


[0196] (*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(2-fluorophenyl)-3-phenylpropanamido]-ethyl}phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 7.33-6.87 (m, 14H), 5.39-5.25 (m, 1H), 3.95-3.83 (m, 1H), 3.31-3.10 (m, 1H), 3.05-2.88 (m, 2H), 2.80-2.70 (m, 2H), 1.32-1.23 (m, 3H). ^{19}F NMR δ 47.59.



[0197] (*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(3-methoxyphenyl)-3-phenylpropanamido]-ethyl}phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 7.85 (d, 1H, J = 8.4Hz), 7.25-7.20 (m, 1H), 7.11-7.02 (m, 4H), 7.01 (s, 1H), 6.90-6.79 (m, 2H), 5.45-5.40 (m, 1H), 4.09 (s, 2H), 3.79 (s, 3H), 3.12-3.08 (m, 2H), 1.10 (s, 9H).

[0198] The fourth aspect of Category I of the present disclosure relates to compounds having the formula:



wherein the linking unit L comprises a phenyl unit, said linking group having the formula:

$$-C(O)[(CR^{6a}H)][(CH_2]-$$

R^{5a} is substituted or unsubstituted heteroaryl and the units R^2, R^3, and R^{5a} are further exemplified herein below in Table IV.

TABLE IV

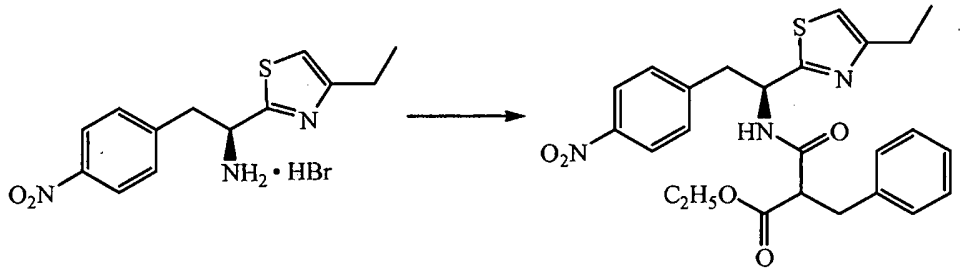
No.	R^2	R^3	R^{6a}
225	methyl	hydrogen	3-methyl-1,2,4-oxadiazol-5-yl
226	methyl	hydrogen	thiophene-2-yl
227	methyl	hydrogen	thiazol-2-yl
228	methyl	hydrogen	oxazol-2-yl
229	methyl	hydrogen	isoxazol-3-yl

(continued)

No.	R^2	R^3	R^{6a}
230	ethyl	hydrogen	3-methyl-1,2,4-oxadiazol-5-yl
231	ethyl	hydrogen	thiophene-2-yl
232	ethyl	hydrogen	thiazol-2-yl
233	ethyl	hydrogen	oxazol-2-yl
234	ethyl	hydrogen	isoxazol-3-yl
235	ethyl	methyl	3-methyl-1,2,4-oxadiazol-5-yl
236	ethyl	methyl	thiophene-2-yl
237	ethyl	methyl	thiazol-2-yl
238	ethyl	methyl	oxazol-2-yl
239	ethyl	methyl	isoxazol-3-yl
240	thiophene-2-yl	hydrogen	3-methyl-1,2,4-oxadiazol-5-yl
241	thiophene-2-yl	hydrogen	thiophene-2-yl
242	thiophene-2-yl	hydrogen	thiazol-2-yl
243	thiophene-2-yl	hydrogen	oxazol-2-yl
244	thiophene-2-yl	hydrogen	isoxazol-3-yl
245	isoxazol-3-yl	hydrogen	3-methyl-1,2,4-oxadiazol-5-yl
246	isoxazol-3-yl	hydrogen	thiophene-2-yl
247	isoxazol-3-yl	hydrogen	thiazol-2-yl
248	isoxazol-3-yl	hydrogen	oxazol-2-yl
249	isoxazol-3-yl	hydrogen	isoxazol-3-yl

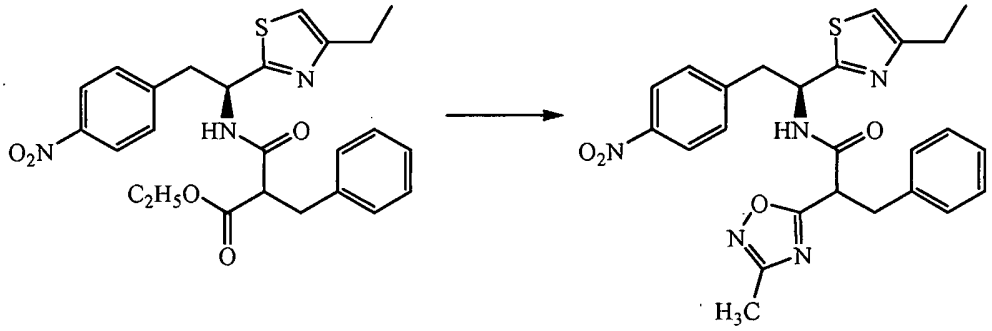
[0199] The compounds encompassed within the fourth aspect of Category I of the present disclosure can be prepared by the procedure outlined in Scheme V and described in Example 5 herein below.

Scheme V



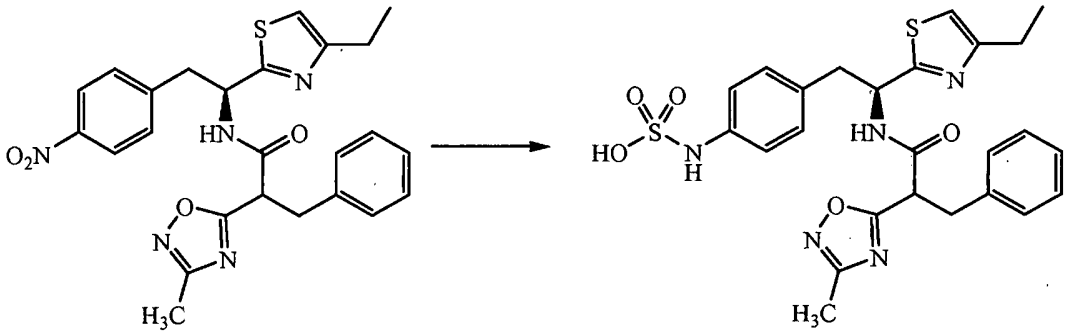
3 15

Reagents and conditions: (a) 2-benzyl-3-ethoxy-3-oxopropanoic acid, EDCI, HOBt, DIPEA, DMF; rt, 18 hr.



15 16

Reagents and conditions: (b) $CH_3C(=NOH)NH_2$, K_2CO_3, toluene; reflux, 18 hr



16 17

Reagents and conditions: (c) (i) H_2:Pd/C, MeOH; (ii) SO_3-pyridine, NH_4OH; rt, 18 hr.

EXAMPLE 5

4-{(*S*)-2-(4-Ethylthiazol-2-yl)-2-[2-(3-methyl-1,2,4-oxadiazol-5-yl)-3-phenylpropanamido]ethyl}phenylsulfamic acid (17):

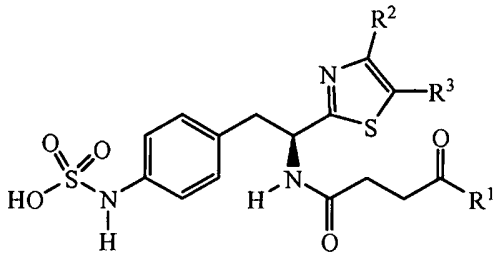
[0200] Preparation of ethyl-2-benzyl-3-[(*S*)-1-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)-ethylamino]-3-oxopropanoate (15): To a solution of 1-(S)-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethyl amine hydrobromide, 3, (0.406 g, 1.13 mmol), 2-benzyl-3-ethoxy-3-oxopropanoic acid (0.277 g) and 1-hydroxybenzotriazole (HOBt) (0.191 g, 1.41 mmol) in DMF (10 mL) at 0°, is added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) (0.240 g, 1.25 mmol) followed by diisopro-

pylethylamine (DIPEA) (0.306 g). The mixture is stirred at 0 °C for 30 minutes then at room temperature overnight. The reaction mixture is diluted with water and extracted with EtOAc. The combined organic phase is washed with 1 N aqueous HCl, 5 % aqueous $NaHCO_3$, water and brine, and dried over Na_2SO_4. The solvent is removed *in vacuo* to afford 0.169 g (31 % yield) of the desired product which is used without further purification.

[0201] Preparation of *N*-[(*S*)-1-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethyl]-2-(3-methyl-1,2,4-oxadiazol-5-yl)-3-phenylpropanamide (16): Ethyl 2-benzyl-3-((S)-1-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethylamino)-3-oxopropanoate is dissolved in toluene (5 mL) and heated to reflux. Potassium carbonate (80 mg) and acetamide oxime (43 mg) are added. and treated with 80 mg potassium carbonate and 43 mg acetamide oxime at reflux. The reaction mixture is cooled to room temperature, filtered and concentrated. The residue is chromatographed over silica to afford 0.221 g (94%) of the desired product as a yellow oil.

[0202] Preparation of 4- {(*S*)-2-(4-ethylthiazol-2-yl)-2-[2-(3-methyl-1,2,4-oxadiazol-5-yl)-3-phenylpropanamido]ethyl}phenylsulfamic acid (17): *N*-[(*S*)-1-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethyl]-2-(3-methyl-1,2,4-oxadiazol-5-yl)-3-phenylpropanamide, 16, (0. 221 g) and tin (II) chloride (507 mg, 2.2 mmol) are dissolved in EtOH (25 mL) and the solution is brought to reflux 4 hours. The solvent is removed in vacuo and the resulting residue is dissolved in EtOAc. A saturated solution of $NaHCO_3$ (50 mL) is added and the solution is stirred 1 hour. The organic layer is separated and the aqueous layer extracted twice with EtOAc. The combined organic layers are dried (Na_2SO_4), filtered and concentrated to a residue which is dissolved in pyridine (0.143 g) and treated with SO_3-pyridine (0.143 g). The reaction is stirred at room temperature for 5 minutes after which a 7% solution of NH_4OH is added. The mixture is then concentrated and the resulting residue is purified by reverse phase chromatography to afford 0.071g of the desired product as the ammonium salt. ^1H (CD_3OD): δ 7.29-6.87 (m, 10H), 5.38-5.30 (m, 1H), 4.37-4.30 (m, 1H), 3.42-2.74 (m, 6H), 2.38-2.33 (m, 3H), 1.34-1.28 (m, 3H).

[0203] Category II of the present disclosure relates to 2-(thiazol-2-yl) compounds having the formula:



wherein R^1, R^2, R^3, and L are further defined herein in Table V herein below.

TABLE V

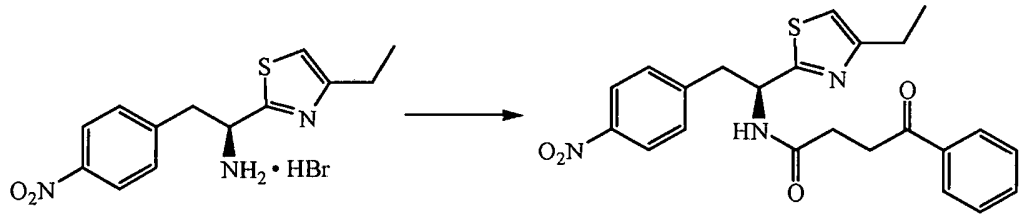
No.	R^2	R^3	R^1
250	ethyl	hydrogen	thiophene-2-yl
251	ethyl	hydrogen	thiazol-2-yl
252	ethyl	hydrogen	oxazol-2-yl
253	ethyl	hydrogen	isoxazol-3-yl
254	ethyl	hydrogen	thiophene-2-yl
255	ethyl	hydrogen	thiazol-2-yl
256	ethyl	hydrogen	oxazol-2-yl
257	ethyl	hydrogen	isoxazol-3-yl
258	ethyl	hydrogen	thiophene-2-yl
259	ethyl	hydrogen	thiazol-2-yl
260	ethyl	methyl	methyl
261	ethyl	methyl	ethyl
262	ethyl	methyl	propyl
263	ethyl	methyl	*iso*-propyl

(continued)

No.	R^2	R^3	R^1
264	ethyl	methyl	butyl
265	ethyl	methyl	phenyl
266	ethyl	methyl	benzyl
267	ethyl	methyl	2-fluorophenyl
268	ethyl	methyl	3-fluorophenyl
269	ethyl	methyl	4-fluorophenyl
270	phenyl	hydrogen	methyl
271	phenyl	hydrogen	ethyl
272	phenyl	hydrogen	propyl
273	phenyl	hydrogen	*iso*-propyl
274	phenyl	hydrogen	butyl
275	phenyl	hydrogen	phenyl
276	phenyl	hydrogen	benzyl
277	phenyl	hydrogen	2-fluorophenyl
278	phenyl	hydrogen	3-fluorophenyl
279	phenyl	hydrogen	4-fluorophenyl
280	thiophene-2-yl	hydrogen	methyl
281	thiophene-2-yl	hydrogen	ethyl
282	thiophene-2-yl	hydrogen	propyl
283	thiophene-2-yl	hydrogen	*iso*-propyl
284	thiophene-2-yl	hydrogen	butyl
285	thiophene-2-yl	hydrogen	phenyl
286	thiophene-2-yl	hydrogen	benzyl
287	thiophene-2-yl	hydrogen	2-fluorophenyl
288	thiophene-2-yl	hydrogen	3-fluorophenyl
289	thiophene-2-yl	hydrogen	4-fluorophenyl

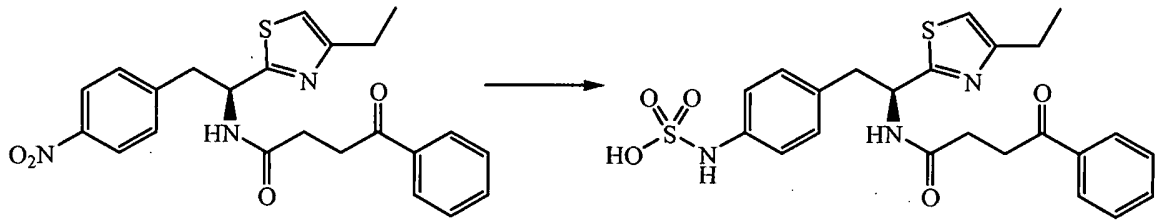
[0204] The compounds encompassed within Category II of the present disclosure can be prepared by the procedure outlined in Scheme VI and described in Example 6 herein below.

Scheme VI



3 18

Reagents and conditions: (a) 3-benzoylpropionic acid, TsCl, *N*-methyl imidazole, CH_2Cl_2; rt, 18 hr.



18 19

Reagents and conditions: (b) (i) H_2:Pd/C, MeOH; (ii) SO_3-pyridine, NH_4OH.

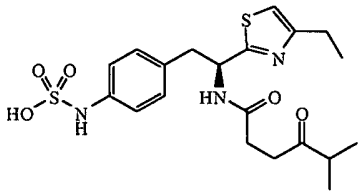
EXAMPLE 6

(*S*)-4-[2-(4-Ethylthiazol-2-yl)-2-(4-oxo-4-phenylbutanamido)ethyl]-phenylsulfamic acid (19)

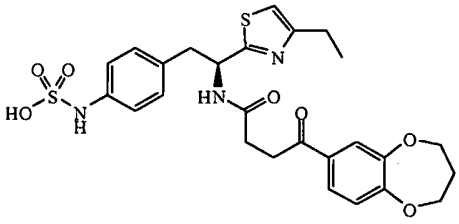
[0205] Preparation of (*S*)-N-[1-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethyl]-4-oxo-4-phenylbutanamide (18): 3-Benzoylpropionic acid (0.250 g) is dissolved in CH_2Cl_2 (5 mL), *N*-methyl imidazole (0.333 mL) is added and the resulting solution is cooled to 0 °C after which a solution of *p*-toluenesulfonyl chloride (0.320 g) in CH_2Cl_2 (2 mL) is added dropwise. After 0.5 hours (*S*)-1-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethanamine, 3, (0.388 g) is added. The reaction is stirred for 18 hours at room temperature and then concentrated in vacuo. The resulting residue is dissolved in EtOAc and washed with 1N HCl and brine. The solution is dried over Na_2SO_4, filtered, and concentrated and the crude material purified over silica to afford 0.415 g of the desired product.

[0206] Preparation of (*S*)-4-[2-(4-ethylthiazol-2-yl)-2-(4-oxo-4-phenylbutanamido)-ethyl]phenylsulfamic acid (19): (*S*)-*N*-[1-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethyl]-2,3-diphenyl-propanamide, 18, (0.2 g) is dissolved in MeOH (15 mL). A catalytic amount of Pd/C (10% w/w) is added and the mixture is stirred under a hydrogen atmosphere 18 hours. The reaction mixture is filtered through a bed of CELITE™ and the solvent is removed under reduced pressure. The crude product is dissolved in pyridine (5 mL) and treated with SO_3-pyridine (0.153 g). The reaction is stirred at room temperature for 5 minutes after which a 7% solution of NH_4OH is added. The mixture is then concentrated and the resulting residue is purified by reverse phase chromatography to afford 0.090 g of the desired product as the ammonium salt. ^1H NMR (CD_3OD) δ 8.68 (d, 1H, J=8.2 Hz), 8.00 (d, 2H, J=7.2 Hz), 7.80-7.50 (m, 3H), 7.12 (s, 4H), 7.03 (s, 1H), 5.46-5.38 (m, 1H), 3.29-3.14 (m, 2H), 3.06-2.99 (m, 2H), 2.83 (q, 2H, J=7.5 Hz), 2.69-2.54 (m, 2H), 1.33 (t, 3H, J=7.5 Hz).

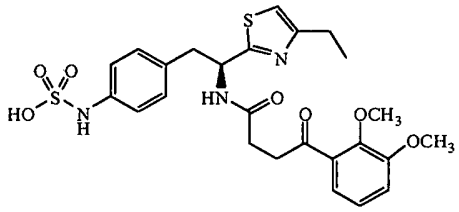
[0207] The following are examples of compounds encompassed within Category II of the present disclosure. The intermediate nitro compounds of the following can be prepared by coupling the appropriate 4-oxo-carboxcylic acid with intermediate 3 under the conditions described herein above for the formation of intermediate 4 of scheme I.



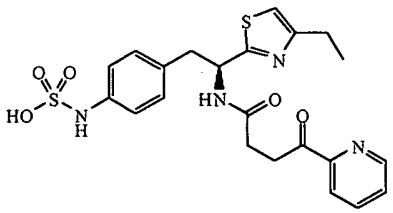
[0208] (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(5-methyl-4-oxohexanamido)ethyl)phenyl-sulfamic acid: ^{1}H NMR (CD_3OD) δ 8.59 (d, 1H, J=8.1 Hz), 7.14 (s, 4H), 7.08 (t, 1H, J=13.0 Hz), 5.40-5.35 (m, 1H), 3.37-3.27 (m, 2H), 3.04-2.97 (m, 1H), 2.83-2.61 (m, 4H), 2.54-2.36 (m, 3H), 1.33 (t, 2H, J=7.3 Hz), 1.09 (dd, 6H, J=7.0, 2.2 Hz).



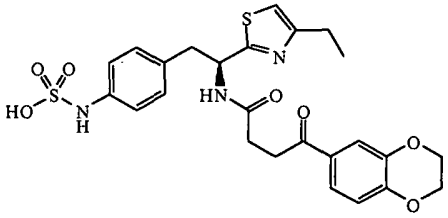
[0209] (*S*)-4-{2-[4-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-4-oxobutanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenyl-sulfamic acid: ^{1}H NMR(CD_3OD) δ 8.64 (d, 1H, J=8.4 Hz), 7.60 (d, 2H, J=10.6 Hz), 7.11 (s, 3H), 7.04 (d, 2H, J=5.5 Hz), 5.42-5.40 (m, 1H), 4.30-4.22 (m, 4H), 3.20-2.98 (m, 4H), 2.82 (q, 2H, J=7.3 Hz), 2.67-2.48 (m, 2H), 2.23 (t, 2H, J=5.5 Hz), 1.32 (t, 3H, J=7.3 Hz).



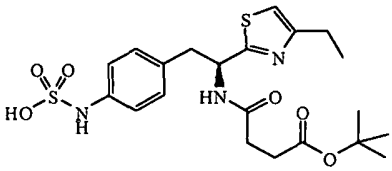
[0210] (*S*)-4-{2-[4-(2,3-Dimethoxyphenyl)-4-oxobutanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid: ^{1}H NMR (CD_3OD), δ 8.64 (□d, 1H, J=8.1 Hz), 7.21-7.11 (m, 7H), 7.02 (s, 1H),□ 5.42 (q, 1H, J=5.9 Hz), 3.90 (d, 3H, J=3.3 Hz), 3.88 (d, 3H, J=2.9 Hz), 3.22-3.18 (m, 2H), 3.07-2.99 (m, 2H), 2.83 (q, 2H, J=7.3 Hz), 2.63-2.54 (m, 2H), 1.34 (t, 3H, J=7.69 Hz).



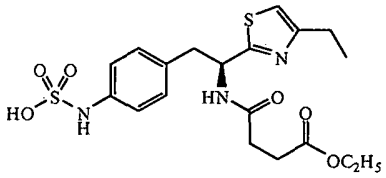
[0211] (*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[4-oxo-4-(pyridin-2-yl)butanamido]ethyl}-phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 8.60 (d, 1H, J=12.8 Hz), 7.91-7.81 (m, 2H), 7.48-7.44 (m, 1H), 7.22-7.21 (m, 1H), 6.99 (s, 3H), 6.91 (s, 1H), 5.30 (q, 1H, J=5.4 Hz), 3.36 (q, 2H, J=7.0 Hz), 3.21-3.15 (m, 1H), 2.91-2.85 (m, 1H), 2.74 (q, 2H, J=10.4 Hz), 2.57-2.50 (m, 2H), 1.20 (t, 3H, J=7.5 Hz).



[0212] (S)-4-{2-[4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4-oxobutanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid: ^{1}H NMR (CD_3□OD) δ 7.52-7.47 (m,2 H), 7.11(s,4H), 7.03 (s,1H), 6.95 (d, 1H, J=8.4 Hz), 5.41 (q, 1H, J=3.7 Hz), 4.31 (d, 4H, J=5.5 Hz), 3.24-3.12 (m, 2H), 3.06-2.98 (m, 2H), 2.83 (q, 2H, J=7.3 Hz), 2.62-2.53 (m, 2H), 1.33 (t, 3H, J=7.3 Hz).

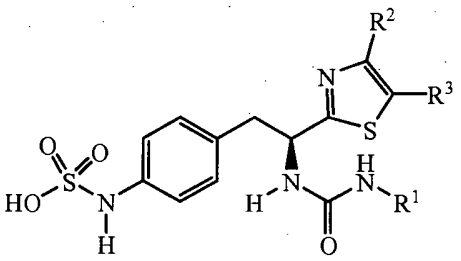


[0213] (*S*)-4-[2-(4-tert-butoxy-4-oxobutanamido)-2-(4-ethylthiazol-2-yl)ethyl]phenyl-sulfamic acid: ^{1}H NMR (CD_3OD), δ 7.10 (s 4H), 7.02 (s, 1H), 5.41 (q, 1H, J=3.7 Hz), 3.30-3.25 (m, 1H), 3.06-2.99 (m, 1H), 2.83 (q, 2H, J=7.3 Hz), 2.52-2.40 (m, 4H), 1.42 (s, 9H), 1.33 (t, 3H, J=7.3 Hz).



[0214] (*S*)-4-[2-(4-ethoxy-4-oxobutanamido)-2-(4-ethylthiazol-2-yl)ethyl]phenylsulfamic acid: ^{1}H NMR (CD30D) δ 8.62 (d, 1H, J=8.4 Hz), 7.10 (s, 4H), 7.02 (s, 1H), 5.40 (q, 1H, 3.7 Hz), 4.15 (q, 2H, J=7.3 Hz), 3.28-3.25 (m, 1H), 3.05-3.02 (m, 1H), 2.82 (q, 2H, J=4.4 Hz), 2.54-2.48 (m, 2H), 1.33 (t, 3H, J=7.3 Hz), 1.24 (t, 3H, J=7.0 Hz).

[0215] The first aspect of Category III of the present disclosure relates to 2-(thiazol-2-yl) compounds having the formula:



wherein examples of R^1, R^2, and R^3 are further described herein below in Table VI.

TABLE VI

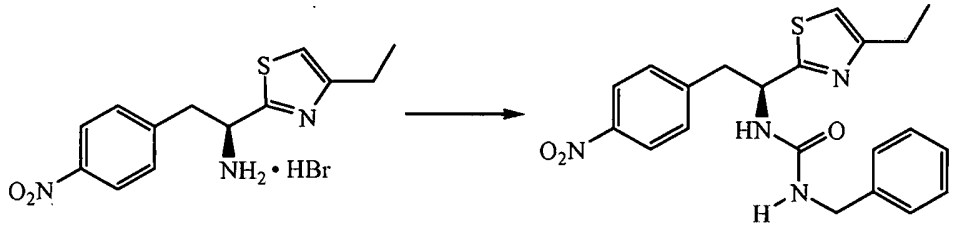
No.	R^2	R^3	R^1
290	methyl	hydrogen	phenyl
291	methyl	hydrogen	benzyl
292	methyl	hydrogen	2-fluorophenyl
293	methyl	hydrogen	3-fluorophenyl

(continued)

No.	R^2	R^3	R^1
294	methyl	hydrogen	4-fluorophenyl
295	methyl	hydrogen	2-chlorophenyl
296	methyl	hydrogen	3-chlorophenyl
297	methyl	hydrogen	4-chlorophenyl
298	ethyl	hydrogen	phenyl
299	ethyl	hydrogen	benzyl
300	ethyl	hydrogen	2-fluorophenyl
301	ethyl	hydrogen	3-fluorophenyl
302	ethyl	hydrogen	4-fluorophenyl
303	ethyl	hydrogen	2-chlorophenyl
304	ethyl	hydrogen	3-chlorophenyl
305	ethyl	hydrogen	4-chlorophenyl
306	thiene-2-yl	hydrogen	phenyl
307	thiene-2-yl	hydrogen	benzyl
308	thiene-2-yl	hydrogen	2-fluorophenyl
309	thiene-2-yl	hydrogen	3-fluorophenyl
310	thiene-2-yl	hydrogen	4-fluorophenyl
311	thiene-2-yl	hydrogen	2-chlorophenyl
312	thiene-2-yl	hydrogen	3-chlorophenyl
313	thiene-2-yl	hydrogen	4-chlorophenyl

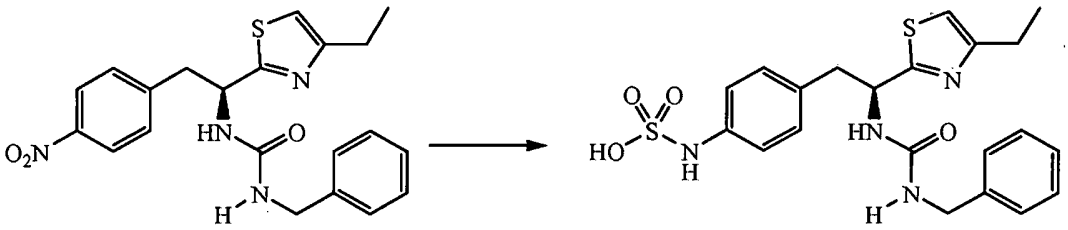
[0216] The compounds encompassed within Category III of the present disclosure can be prepared by the procedure outlined in Scheme VIII and described in Example 7 herein below.

Scheme VII



3 20

Reagents and conditions: (a) benzyl isocyanate, TEA, CH_2Cl_2; rt, 18 hr.



20 21

Reagents and conditions: (b) (i) H_2:Pd/C, MeOH; (ii) SO_3-pyridine, NH_4OH.

EXAMPLE 7

(S)-4-(2-(3-Benzylureido)-2-(4-ethylthiazol-2-yl)ethyl)phenylsulfamic acid (21)

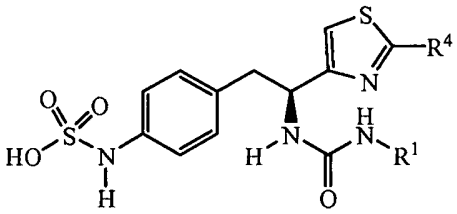
[0217] Preparation of (*S*)-1-benzyl-3-[1-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethyl]urea (20): To a solution of 1-(*S*)-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethyl amine hydrobromide, 3, (0.360 g, 1 mmol) and Et_3N (0.42 mL, 3mmol) in 10 mL CH_2Cl_2 is added benzyl isocyanate (0.12 mL, 1 mmol). The mixture is stirred at room temperature for 18 hours: The product is isolated by filtration to afford 0.425 g (96% yield) of the desired product which is used without further purification.

[0218] Preparation of (S)-4-(2-(3-benzylureido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid (21): (*S*)-1-benzyl-3-[1-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethyl]urea, 20, (0.425 g) is dissolved in MeOH (4 mL). A catalytic amount of Pd/C (10% w/w) is added and the mixture is stirred under a hydrogen atmosphere 18 hours. The reaction mixture is filtered through a bed of CELITE™ and the solvent is removed under reduced pressure. The crude product is dissolved in pyridine (12 mL) and treated with SO_3-pyridine (0.220 g). The reaction is stirred at room temperature for 5 minutes after which a 7% solution of NH_4OH is added. The mixture is then concentrated and the resulting residue is purified by reverse phase chromatography to afford 0.143 g of the desired product as the ammonium salt. ^1H NMR (CD30D) δ 7.32-7.30 (m, 2H), 7.29-7.22 (m, 3H), 7.12-7.00 (m, 4H), 6.84 (d, 1H, J = 8.1Hz), 5.35-5.30 (m, 1H), 4.29 (s, 2H), 3.27-3.22 (m, 3H), 3.11-3.04 (m, 3H), 2.81 (q, 2H, J = 10.2, 13.0Hz), 1.31 (t, 3H, J = 4.5Hz).

[0219] The following is a examples of compounds encompassed within the first aspect of Category III of the present disclosure.

[0220] 4-{[(*S*)-2-(2-Ethylthiazol-4-yl)-2-(3-(*R*)-methoxy-1-oxo-3-phenylpropan-2-yl)ureido]ethyl}phenylsulfamic acid: ^1H NMR (CD30D) δ 7.36-7.26 (m, 3H), 7.19-7.17 (m, 2H), 7.10-7.06 (m, 2H), 6.90-6.86 (m, 3H), 5.12-5.06 (m, 1H), 4.60-4.55 (m, 1H), 3.69 (s, 3H) 3.12-2.98 (m, 6H), 1.44-1.38 (m, 3H).

[0221] The second aspect of Category III of the present disclosure relates to 2-(thiazol-4-yl) compounds having the formula:



wherein non-limiting examples of R^1 and R^4 are further described herein below in Table VII.

TABLE VII

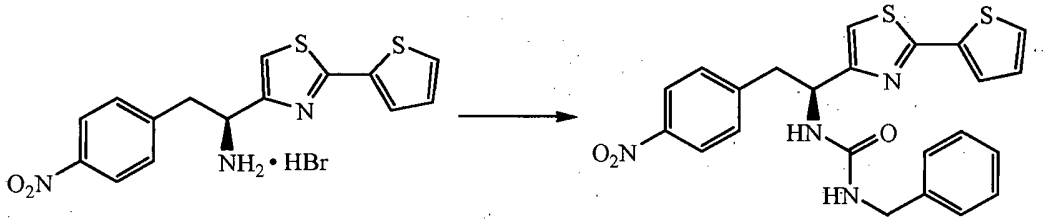
No.	R^1	R^4
314	methyl	methyl
315	ethyl	methyl
316	n-propyl	methyl
317	*iso*-propyl	methyl
318	phenyl	methyl
319	benzyl	methyl
320	2-fluorophenyl	methyl
321	2-chlorophenyl	methyl
322	thiophene-2-yl	methyl
323	thiazol-2-yl	methyl
324	oxazol-2-yl	methyl
325	isoxazol-3-yl	methyl
326	methyl	ethyl
327	ethyl	ethyl
328	n-propyl	ethyl
329	*iso*-propyl	ethyl
330	phenyl	ethyl
331	benzyl	ethyl
332	2-fluorophenyl	ethyl
333	2-chlorophenyl	ethyl
334	thiophene-2-yl	ethyl
335	thiazol-2-yl	ethyl
336	oxazol-2-yl	ethyl
337	isoxazol-3-yl	ethyl
338	methyl	thiophene-2-yl
339	ethyl	thiophene-2-yl
340	n-propyl	thiophene-2-yl
341	*iso*-propyl	thiophene-2-yl
342	phenyl	thiophene-2-yl
343	benzyl	thiophene-2-yl
344	2-fluorophenyl	thiophene-2-yl

(continued)

No.	R^1	R^4
345	2-chlorophenyl	thiophene-2-yl
346	thiophene-2-yl	thiophene-2-yl
347	thiazol-2-yl	thiophene-2-yl
348	oxazol-2-yl	thiophene-2-yl
349	isoxazol-3-yl	thiophene-2-yl
350	methyl	thiazol-2-yl
351	ethyl	thiazol-2-yl
352	n-propyl	thiazol-2-yl
353	*iso*-propyl	thiazol-2-yl
354	phenyl	thiazol-2-yl
355	benzyl	thiazol-2-yl
356	2-fluorophenyl	thiazol-2-yl
357	2-chlorophenyl	thiazol-2-yl
358	thiophene-2-yl	thiazol-2-yl
359	thiazol-2-yl	thiazol-2-yl
360	oxazol-2-yl	thiazol-2-yl
361	isoxazol-3-yl	thiazol-2-yl
362	methyl	oxazol-2-yl
363	ethyl	oxazol-2-yl
364	n-propyl	oxazol-2-yl
365	*iso*-propyl	oxazol-2-yl
366	phenyl	oxazol-2-yl
367	benzyl	oxazol-2-yl
368	2-fluorophenyl	oxazol-2-yl
369	2-chlorophenyl	oxazol-2-yl
370	thiophene-2-yl	oxazol-2-yl
371	thiazol-2-yl	oxazol-2-yl
372	oxazol-2-yl	oxazol-2-yl
373	isoxazol-3-yl	oxazol-2-yl

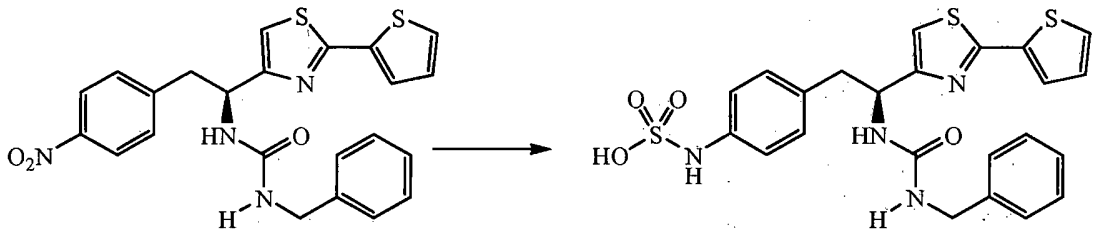
[0222] The compounds encompassed within the second aspect of Category III of the present disclosure can be prepared by the procedure outlined in Scheme VIII and described in Example 8 herein below.

Scheme VIII



9 22

Reagents and conditions (a) benzyl isocyanate, TEA, CH_2Cl_2; rt, 18 hr.



22 23

Reagents and conditions: (b) (i) H_2:Pd/C, MeOH; (ii) SO_3-pyridine, NH_4OH.

EXAMPLE 8

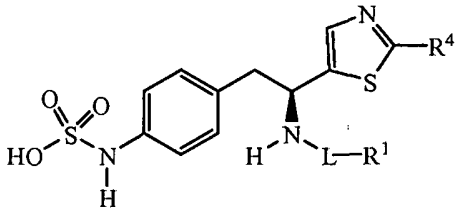
4-{(*S*)-2-(3-Benzylureido)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}-phenylsulfamic acid (23)

[0223] Preparation of 1-benzyl-3-{(*S*)-2-(4-nitrophenyl)-1-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}urea (22): To a solution of (*S*)-2-(4-nitrophenyl)-1-[(2-thiophene-2-yl)thiazol-4-yl)ethan-amine hydrobromide salt, 8, and Et_3N (0.42mL, 3mmol) in 10 mL DCM is added benzyl isocyanate (0.12mL, 1mmol). The mixture is stirred at room temperature for 18 hours. The product is isolated by filtration to afford 0.445 g (96% yield) of the desired product which is used without further purification.

[0224] Preparation of 4-{(*S*)-2-(3-benzylureido)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid (23): 1-Benzyl-3-{(*S*)-2-(4-nitrophenyl)-1-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}urea, 22, (0.445g) is dissolved in MeOH (10 mL) and CH_2Cl_2 (5 mL). A catalytic amount of Pd/C (10% w/w) is added and the mixture is stirred under a hydrogen atmosphere 18 hours. The reaction mixture is filtered through a bed of CELITE™ and the solvent is removed under reduced pressure. The crude product is dissolved in pyridine (12 mL) and treated with SO_3-pyridine (0.110 g). The reaction is stirred at room temperature for 5 minutes after which a 7% solution of NH_4OH is added. The mixture is then concentrated and the resulting residue is purified by reverse phase chromatography to afford 0.080 g of the desired product as the ammonium salt.

^1H NMR (CD30D) δ 7.61 (d, 1H, J = 2.1 Hz), 7.58 (d, 1H, J = 6Hz), 7.33-7.22 (m, 4H), 7.17-7.14 (m, 1H), 7.09-6.94 (m, 6H), 5.16 (t, 1H, J = 6.6Hz), 4.13 (s, 2H), 3.14-3.11 (m, 2H).

[0225] Category IV of the present disclosure relates to 2-(thiazol-4-yl) compounds having the formula:



wherein R^1, R^4, and L are further defined herein in Table VIII herein below.

TABLE VIII

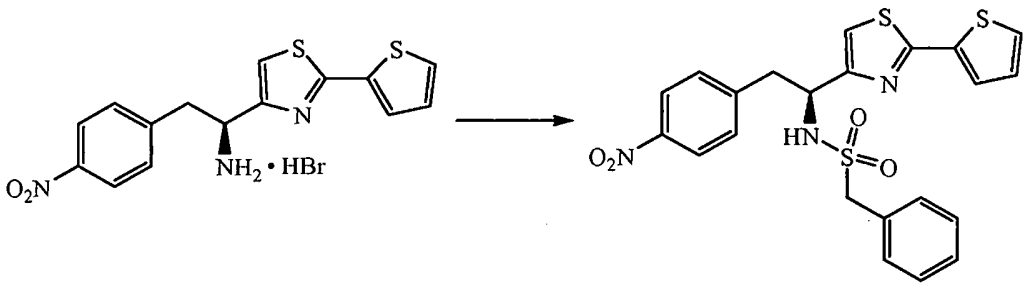
No.	R^4	L	R^1
374	methyl	$-SO_2-$	methyl
375	ethyl	$-SO_2-$	methyl
376	phenyl	$-SO_2-$	methyl
377	thiophene-2-yl	$-SO_2-$	methyl
378	methyl	$-SO_2-$	trifluoromethyl
379	ethyl	$-SO_2-$	trifluoromethyl
380	phenyl	$-SO_2-$	trifluoromethyl
381	thiophene-2-yl	$-SO_2-$	trifluoromethyl
382	methyl	$-SO_2-$	ethyl
383	ethyl	$-SO_2-$	ethyl
384	phenyl	$-SO_2-$	ethyl
385	thiophene-2-yl	$-SO_2-$	ethyl
386	methyl	$-SO_2-$	2,2,2-trifluoroethyl
387	ethyl	$-SO_2-$	2,2,2-trifluoroethyl
388	phenyl	$-SO_2-$	2,2,2-trifluoroethyl
389	thiophene-2-yl	$-SO_2-$	2,2,2-trifluoroethyl
390	methyl	$-SO_2-$	phenyl
391	ethyl	$-SO_2-$	phenyl
392	phenyl	$-SO_2-$	phenyl
393	thiophene-2-yl	$-SO_2-$	phenyl
394	methyl	$-SO_2-$	4-fluorophenyl
395	ethyl	$-SO_2-$	4-fluorophenyl
396	phenyl	$-SO_2-$	4-fluorophenyl
397	thiophene-2-yl	$-SO_2-$	4-fluorophenyl
398	methyl	$-SO_2-$	3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl
399	ethyl	$-SO_2-$	3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl
400	phenyl	$-SO_2-$	3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl
401	thiophene-2-yl	$-SO_2-$	3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl
402	methyl	$-SO_2-$	1-methyl-1*H*-imidazol-4-yl
403	ethyl	$-SO_2-$	1-methyl-1*H*-imidazol-4-yl
404	phenyl	$-SO_2-$	1-methyl-1*H*-imidazol-4-yl
405	thiophene-2-yl	$-SO_2-$	1-methyl-1*H*-imidazol-4-yl
406	methyl	$-SO_2-$	4-acetamidophenyl
407	ethyl	$-SO_2-$	4-acetamidophenyl
408	phenyl	$-SO_2-$	4-acetamidophenyl
409	thiophene-2-yl	$-SO_2-$	4-acetamidophenyl
410	methyl	$-SO_2CH_2-$	phenyl

(continued)

No.	R^4	L	R^1
411	ethyl	$-SO_2CH_2-$	phenyl
412	phenyl	$-SO_2CH_2-$	phenyl
413	thiophene-2-yl	$-SO_2CH_2-$	phenyl
414	methyl	$-SO_2CH_2-$	(4-methylcarboxyphenyl)methyl
415	ethyl	$-SO_2CH_2-$	(4-methylcarboxyphenyl)methyl
416	phenyl	$-SO_2CH_2-$	(4-methylcarboxyphenyl)methyl
417	thiophene-2-yl	$-SO_2CH_2-$	(4-methylcarboxyphenyl)methyl
418	methyl	$-SO_2CH_2-$	(2-methylthiazol-4-yl)methyl
419	ethyl	$-SO_2CH_2-$	(2-methylthiazol-4-yl)methyl
420	phenyl	$-SO_2CH_2-$	(2-methylthiazol-4-yl)methyl
421	thiophene-2-yl	$-SO_2CH_2-$	(2-methylthiazol-4-yl)methyl
422	methyl	$-SO_2CH_2CH_2-$	phenyl
423	ethyl	$-SO_2CH_2CH_2-$	phenyl
424	phenyl	$-SO_2CH_2CH_2-$	phenyl
425	thiophene-2-yl	$-SO_2CH_2CH_2-$	phenyl

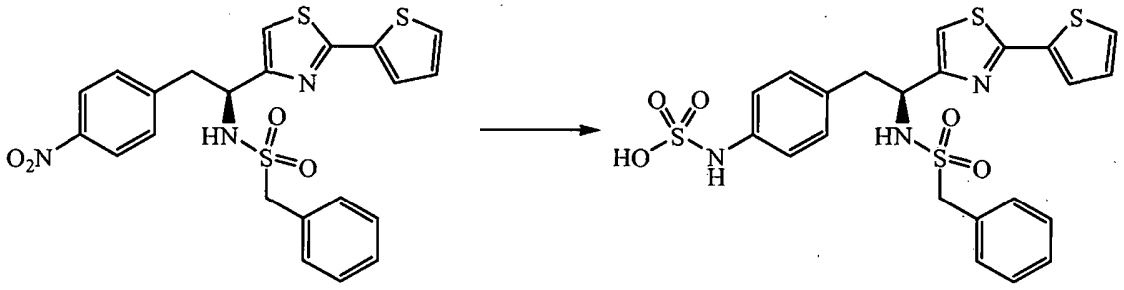
[0226] The compounds encompassed within Category IV of the present disclosure can be prepared by the procedure outlined in Scheme IX and described in Example 9 herein below.

Scheme IX



8 24

Reagents and conditions: (a) $C_6H_4CH_2SO_2Cl$, DIPEA, CH_2Cl_2; 0 °C to rt, 14 hr.



24 25

Reagents and conditions: (b) (i) H_2:Pd/C, MeOH; (ii) SO_3-pyridine, NH_4OH.

EXAMPLE 9

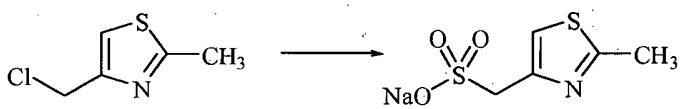
{4-(*S*)-[2-Phenylmethanesulfonylamino-2-(2-thiophen-2-ylthiazol-4-yl)ethyl]phenyl}sulfamic acid (25)

[0227] Preparation of (S)- *N*-{2-(4-nitrophenyl)-1-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}-1-phenylmethanesulfonamide (24): To a suspension of 2-(4-nitrophenyl)-1-(2-thiophene2-ylthiazol-4-yl)ethylamine, 8, (330 mg, 0.80 mmol) in CH_2Cl_2 (6 mL) at 0 °C is added diisopropylethylamine (0.30 mL, 1.6 mmol) followed by phenylmethanesulfonyl chloride (167 mg, 0.88 mmol). The reaction mixture is stirred at room temperature for 14 hours. The mixture is diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$ followed by brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The resulting residue is purified over silica to afford 210 mg of the desired product as a white solid.

[0228] Preparation of {4-(S)-[2-phenylmethanesulfonylamino-2-(2-thiophen-2-ylthiazol-4-yl)ethyl]phenyl}sulfamic acid (25): (*S*)-*N*-{2-(4-nitrophenyl)-1-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}-1-phenylmethanesulfonamide, 24, (210 mg, 0.41 mmol) is dissolved in MeOH (4 mL). A catalytic amount of Pd/C (10% w/w) is added and the mixture is stirred under a hydrogen atmosphere 18 hours. The reaction mixture is filtered through a bed of CELITE™ and the solvent is removed under reduced pressure. The crude product is dissolved in pyridine (12 mL) and treated with SO_3-pyridine (197 mg, 1.23 mmol). The reaction is stirred at room temperature for 5 minutes after which a 7% solution of NH_4OH is added. The mixture is then concentrated and the resulting residue is purified by reverse phase chromatography to afford 0.060 g of the desired product as the ammonium salt. ^1H NMR (300 MHz, MeOH-d_4) δ 7.52-7.6 (m, 6.70-7.28 (m, 11H), 4.75 (t, *J* = 7.2 Hz, 1H), 3.95-4.09 (m, 2H), 3.20 (dd, *J* = 13.5 and 7.8 Hz, 1H), 3.05 (dd, *J* = 13.5 and 7.8 Hz, 1H). 1013770

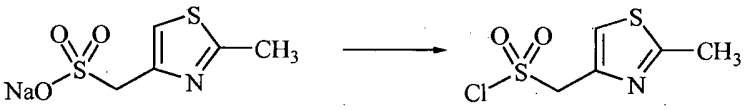
[0229] Intermediates for use in Step (a) of Scheme IX can be conveniently prepared by the procedure outlined herein below in Scheme X and described in Example 10.

Scheme X



26

Reagents and conditions: (a) Na_2SO_3, H_2O; microwave @ 200°C, 20 min.



26 27

Reagents and conditions: (b) PCl_5, $POCl_3$; 50 °C, 3 hrs.

EXAMPLE 10

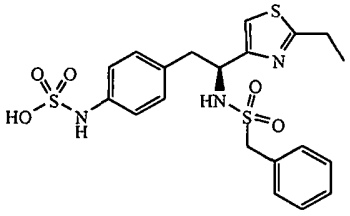
(2-Methylthiazol-4-yl)methanesulfonyl chloride (27)

[0230] Preparation of sodium (2-methylthiazol-4-yl)methanesulfonate (26): 4-Chloromethyl-2-methylthiazole (250 mg, 1.69 mmol) is dissolved in H_2O (2 mL) and treated with sodium sulfite (224 mg, 1.78 mmol). The reaction mixture is subjected to microwave irradiation for 20 minutes at 200°C. The reaction mixture is diluted with H_2O (30 mL) and washed with EtOAc (2 x 25 mL). The aqueous layer is concentrated to afford 0.368g of the desired product as a yellow solid. LC/MS ESI+ 194 (M+1, free acid).

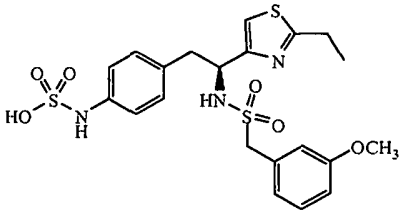
[0231] Preparation of (2-methylthiazol-4-yl)methanesulfonyl chloride (27): Sodium (2-methylthiazol-4-yl)methanesulfonate (357 mg, 1.66 mmol) is dissolved in phosphorous oxychloride (6 mL) and is treated with phosphorous pentachloride (345 mg, 1.66 mmol). The reaction mixture is stirred at 50 °C for 3hours, then allowed to cool to room temperature. The solvent is removed under reduced pressure and the residue is re-dissolved in CH_2Cl_2 (40 mL) and is washed with sat. $NaHCO_3$ and brine. The organic layer is dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* to afford 0.095 g of the desired product as a brown oil. LC/MS ESI+ 211 (M+1). Intermediates are obtained in sufficient purity to be carried forward according to Scheme IX without the need for further purification.

[0232] (*S*)-{4-[2-(2-Ethylthiazol-4-yl)-2-(2-methylthiazole-4-sulfonamido)ethyl]phenyl} sulfamic acid: ^1H (CD_3OD): δ 7.71-7.6 (m, 2H), 7.27-7.10 (m, 7H), 4.87 (t, 1H, *J*=7.3 Hz), 4.30-4.16 (q, 2H, *J*=13.2 Hz), 3.34-3.13 (m, 2H), 2.70 (s, 3H).

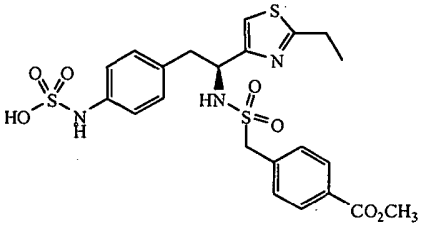
[0233] The following are examples of compounds encompassed within Category IV of the present disclosure.



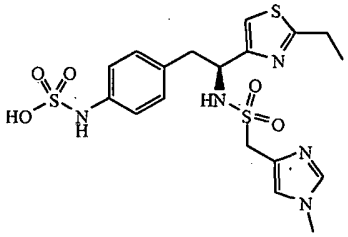
[0234] {4-(*S*)-[2-Phenylmethanesulfonylamino-2-(2-ethylthiazol-4-yl)ethyl]phenyl}-sulfamic acid: ^1H NMR (300 MHz, MeOH-d_4) δ 7.27-7.32 (m, 3H), 7.16-7.20 (m, 3H), 7.05-7.6 (m, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 4.70 (t, *J* = 9.0 Hz, 1H), 3.91-4.02 (m, 2H), 2.95-3.18 (m, 4H), 1.41 (t, *J* = 7.5 Hz, 3H).



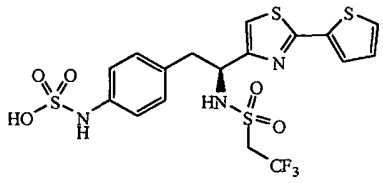
[0235] (*S*)-(4-(2-(2-Ethylthiazol-4-yl)-2-((3-methoxyphenyl)methylsulfonamido)-ethyl)phenyl)sulfamic acid: ^1H NMR (300 MHz, MeOH-d_4) δ 7.20 (t, *J* = 8.1 Hz. 1H), 6.94-7.08 (m,4H), 6.88-6.94 (m, 3H), 6.75-6.80 (m, 1H), 4.67 (t, *J* = 7.2 Hz, 1H), 3.90-4.0 (m, 2H), 3.76 (s, 3H), 2.95-3.16 (m, 4H), 1.40 (t, *J* = 7.5 HZ, 3H).



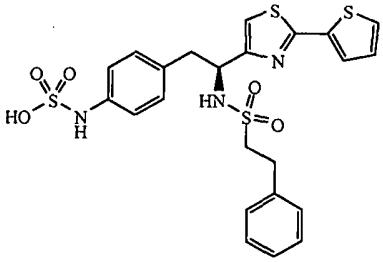
[0236] (*S*)-4-{[1-(2-Ethylthiazol-4-yl)-2-(4-sulfoaminophenyl)ethylsulfamoyl]methyl} -benzoic acid methyl ester: ^1H NMR (300 MHz, MeOH-d_4) δ 7.90-7.94- (m, 2H), 7.27-7.30 (m, 2H), 7.06-7.11 (m, 3H), 6.97-7.00 (m, 2H), 4.71 (t, *J* = 7.2 Hz, 1H), 3.95-4.08 (4, 2H), 3.92 (s, 3H), 2.80-3.50 (m, 4H), 1.38-1.44 (m, 3H).



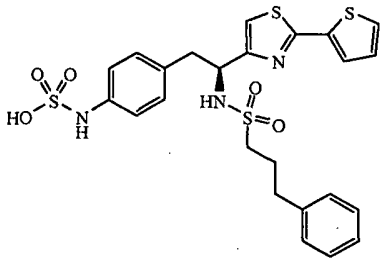
[0237] (*S*)-4-[2-(2-Ethylthiazol-4-yl)-2-((1-methyl-1*H*-imidazol-4-methylsulfonamido)ethyl]-phenylsulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.54 (s, 1H, 7.20 (s, 1H), 7.09 (s, 1H), 6.92-7.00 (m, 4H), 4.62 (t, *J* = 5.4 Hz, 1H), 3.70 (s, 3H), 2.98-3.14 (m,3H), 2.79 (dd, *J* = 9.3 and 15.0 Hz, 1H), 1.39 (q, *J* = 7.5 Hz, 3H).



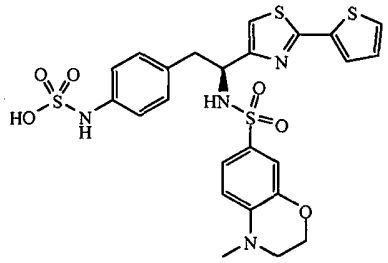
[0238] 4-{(*S*)-2-[2-(Thiophen-2-yl)thiazol-4-yl]-2-(2,2,2-trifluoroethylsulfonamido)-ethyl}phenylsulfamic acid: ^{1}H (CD_3OD): δ 7.62-7.56 (m, 2H), 7.22 (s, 1H), 7.16-7.06 (m, 5H), 4.84 (t, 1H, *J*=7.6 Hz), 3.71-3.62 (m, 2H), 3.32-3.03 (m, 2H).



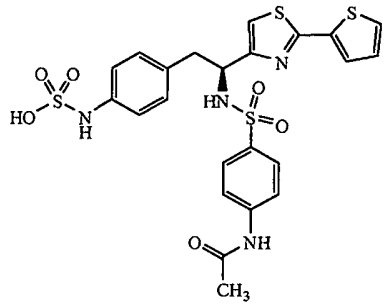
[0239] {4-(*S*)-[2-(Phenylethanesulfonylamino)-2-(thiophen-2-ylthiazol-4-yl)ethyl]-phenyl}sulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.56-7.62 (m, 2H), 7.04-7.19(m, 9H), 6.94-6.97 (m, 2H), 4.78 (t, *J* = 7.8 Hz, 1H), 3.22-3.30 (m, 2H)), 3.11 (dd, *J* = 13.5 and 7.8 Hz, 1H), 2.78-2.87 (m, 4H).



[0240] (*S*)-(4-{2-(3-Phenylpropylsulfonamido)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenyl)sulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.56-7.62 (m, 2H), 6.99-7.17 (m, 10H), 4.72 (t, *J* = 7.8 Hz, 1H), 3.21 (dd, *J* = 13.5 and 7.2 Hz, 1H), 3.02 (dd, *J* = 13.5 and 7.2 Hz, 1H), 2.39-2.64 (m, 4H), 1.65-1.86 (m, 2H).

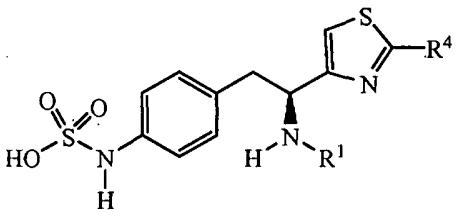


[0241] (*S*)-{4-[2-(4-Methyl-3,4-dihydro-2*H*-benzo[1,4]oxazine-7-sulfonylamino)-2-(2-thiophen-2-ylthiazol-4-yl)ethyl]phenyl}sulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.53 (d, *J*= 5.1 Hz, 1H) 7.48 (d, J=5.1 Hz, 1H), 7.13-7.10 (m, 1H), 7.04 (d, J = 8.4 Hz, 2H), 6.93-6.88 (m, 3H), 6.75 (d, J = 8.1 Hz, 1H), 6.54 (d, J= 8.1 Hz, 1H), 4.61 (t, J = 7.5 Hz, 1H), 4.20-4.08 (m, 2H), 3.14-3.00 (m, 4H), 2.69 (s, 3H).



[0242] 4-{(*S*)-2-(4-acetamidophenylsulfonamido)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid: ^{1}H (CD_3OD): δ 7.67-7.52 (m, 6H), 7.24-7.23 (m, 1H), 7.12-7.09 (m, 3H), 7.02-6.99 (m, 2H), 4.70 (t, 1H, *J*=7.3 Hz), 3.25-3.00 (m, 2H), 2.24 (s, 3H).

[0243] The first aspect of Category V of the present disclosure relates to compounds having the formula:



wherein R^1 is a substituted or unsubstituted heteroaryl and R^4 is C_1-C_6 linear, branched, or cyclic alkyl as further described herein below in Table IX.

TABLE IX

No.	R^4	R^1
426	$-CH_3$	4-(methoxycarbonyl)thiazol-5-yl
427	$-CH_3$	4-[(2-methoxy-2-oxoethyl)carbamoyl]thiazol-5-yl
428	$-CH_3$	5-[1-*N*-(2-methoxy-2-oxoethyl)-1-*H*-indol-3-yl]oxazol-2-yl
429	$-CH_3$	5-(2-methoxyphenyl)oxazol-2-yl
430	$-CH_3$	5-[(*S*)-1-(*tert*-butoxycarbonyl)-2-phenylethyl]oxazol-2-yl
431	$-CH_3$	5-[4-(methylcarboxy)phenyl]oxazol-2-yl
432	$-CH_3$	5-(3-methoxybenzyl)oxazol-2-yl
433	$-CH_3$	5-(4-phenyl)oxazol-2-yl
434	$-CH_3$	5-(2-methoxyphenyl)thiazol-2-yl

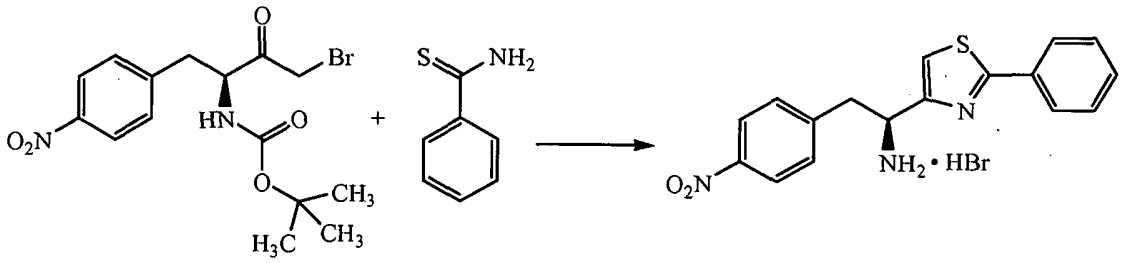
(continued)

No.	R^4	R^1
435	$-CH_3$	5-(3-methoxyphenyl)thiazol-2-yl
436	$-CH_3$	5-(4-fluorophenyl)thiazol-2-yl
437	$-CH_3$	5-(2,4-difluorophenyl)thiazol-2-yl
438	$-CH_3$	5-(3-methoxybenzyl)thiazol-2-yl
439	$-CH_3$	4-(3-methoxyphenyl)thiazol-2-yl
440	$-CH_3$	4-(4-fluorophenyl)thiazol-2-yl
441	$-CH_2CH_3$	4-(methoxycarbonyl)thiazol-5-yl
442	$-CH_2CH_3$	4-[(2-methoxy-2-oxoethyl)carbamoyl]thiazol-5-yl
443	$-CH_2CH_3$	5-[1-*N*-(2-methoxy-2-oxoethyl)-1-*H*-indol-3-yl]oxazol-2-yl
444	$-CH_2CH_3$	5-(2-methoxyphenyl)oxazol-2-yl
445	$-CH_2CH_3$	5-[(*S*)-1-(*tert*-butoxycarbonyl)-2-phenylethyl]oxazol-2-yl
446	$-CH_2CH_3$	5-[4-(methylcarboxy)phenyl]oxazol-2-yl
447	$-CH_2CH_3$	5-(3-methoxybenzyl)oxazol-2-yl
448	$-CH_2CH_3$	5-(4-phenyl)oxazol-2-yl
449	$-CH_2CH_3$	5-(2-methoxyphenyl)thiazol-2-yl
450	$-CH_2CH_3$	5-(3-methoxyphenyl)thiazol-2-yl
451	$-CH_2CH_3$	5-(4-fluorophenyl)thiazol-2-yl
452	$-CH_2CH_3$	5-(2,4-difluorophenyl)thiazol-2-yl
453	$-CH_2CH_3$	5-(3-methoxybenzyl)thiazol-2-yl
454	$-CH_2CH_3$	4-(3-methoxyphenyl)thiazol-2-yl
455	$-CH_2CH_3$	4-(4-fluorophenyl)thiazol-2-yl
456	cyclopropyl	4-(methoxycarbonyl)thiazol-5-yl
457	cyclopropyl	4-[(2-methoxy-2-oxoethyl)carbamoyl]thiazol-5-yl
458	cyclopropyl	5-[1-*N*-(2-methoxy-2-oxoethyl)-1-*H*-indol-3-yl]oxazol-2-yl
459	cyclopropyl	5-(2-methoxyphenyl)oxazol-2-yl
460	cyclopropyl	5-[(*S*)-1-(*tert*-butoxycarbonyl)-2-phenylethyl]oxazol-2-yl
461	cyclopropyl	5-[4-(methylcarboxy)phenyl]oxazol-2-yl
462	cyclopropyl	5-(3-methoxybenzyl)oxazol-2-yl
463	cyclopropyl	5-(4-phenyl)oxazol-2-yl
464	cyclopropyl	5-(2-methoxyphenyl)thiazol-2-yl
465	cyclopropyl	5-(3-methoxyphenyl)thiazol-2-yl
466	cyclopropyl	5-(4-fluorophenyl)thiazol-2-yl
467	cyclopropyl	5-(2,4-difluorophenyl)thiazol-2-yl
468	cyclopropyl	5-(3-methoxybenzyl)thiazol-2-yl
469	cyclopropyl	4-(3-methoxyphenyl)thiazol-2-yl
470	cyclopropyl	4-(4-fluorophenyl)thiazol-2-yl

[0244] Compounds according to the first aspect of Category V which comprise a substituted or unsubstituted thiazol-

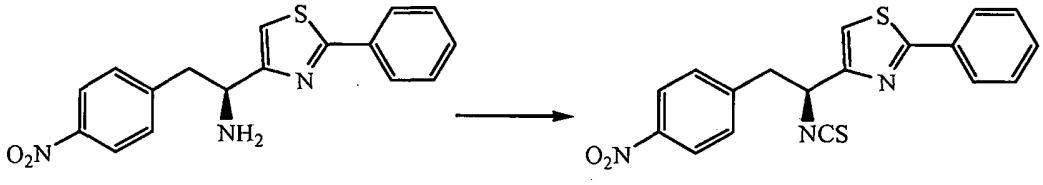
4-yl unit for R^1 can be prepared by the procedure outlined in Scheme XI and described herein below in Example 11.

Scheme XI



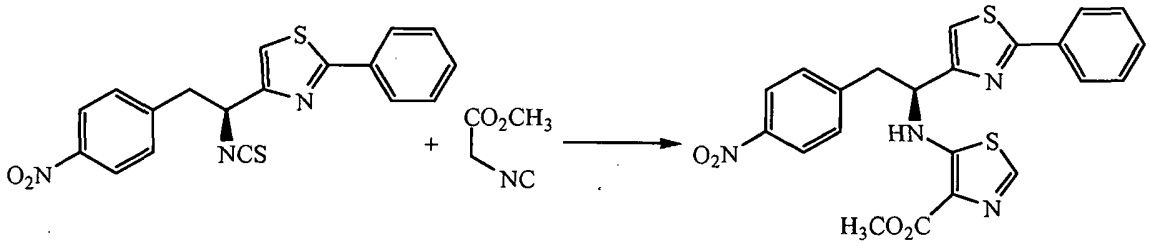
7 28

Reagents and conditions: (a) CH_3CN, reflux; 24 hr.



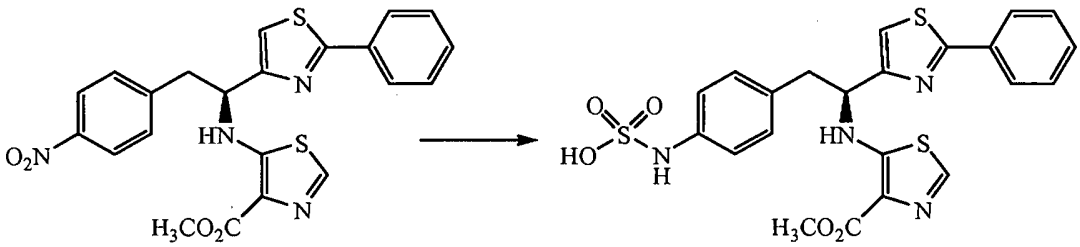
28 29

Reagents and conditions: (b) thiophosgene, $CaCO_3$, CCl_4, H_2O; rt, 18 hr.



29 30

Reagents and conditions: (c) KOtBu, THF; rt, 2hr.



30 31

Reagents and conditions: (d) (i) $SnCl_2$-$2H_2O$, EtOH; reflux, 4 hours (ii) SO_3-pyridine, NH_4OH.

EXAMPLE 11

(*S*)-4-(2-(2-Phenylthiazol-4-yl)-2-(4-(methoxycarbonyl)thiazol-5-ylamino)ethyl)phenylsulfamic acid (31)

[0245] Preparation of (*S*)-2-(4-nitrophenyl)-1-(2-phenylthiazol-4-yl)ethanamine hydrobromide salt (28): A mixture of (*S*)-*tert*-butyl 4-bromo-1-(4-nitrophenyl)-3-oxobutan-2-ylcarbamate, 7, (1.62 g, 4.17 mmol) and thiobenzamide (0.63 g, 4.60 mmol) in CH_3CN (5 mL) is refluxed for 24 hours. The reaction mixture is cooled to room temperature and diethyl ether (50 mL) is added to the solution. The precipitate which forms is collected by filtration. The solid is dried under vacuum to afford 1.2 g (67 % yield) of the desired product. LC/MS ESI+ 326 (M+1).

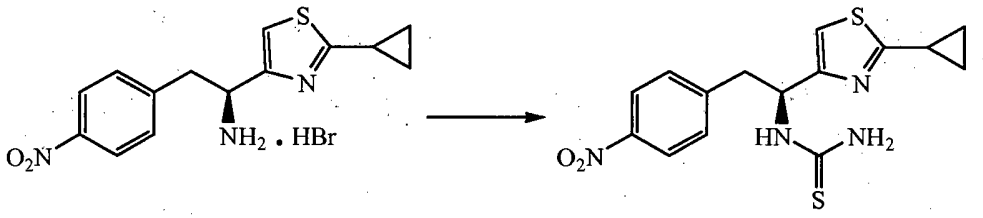
[0246] Preparation of (*S*)-4-(1-isothiocyanato-2-(4-nitrophenyl)ethyl)-2-phenylthiazole (29): To a solution of (*S*)-2-(4-nitrophenyl)-1-(2-phenylthiazol-4-yl)ethanamine hydrobromide salt, 29, (726 mg, 1.79 mmol) and $CaCO_3$ (716 mg, 7.16 mmol) in H_2O (2 mL) is added CCl_4 (3 mL) followed by thiophosgene (0.28 mL, 3.58 mmol). The reaction is stirred at room temperature for 18 hours then diluted with CH_2Cl_2 and water. The layers are separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers are washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to a residue which is purified over silica (CH_2Cl_2) to afford 480 mg (73 %) of the desired product as a yellow solid. ^{1}H NMR (300 MHz, CDCl3) δ 8.15 (d, *J* = 8.7 Hz, 2H), 7.97-7.99 (m, 2H), 7.43-7.50 (m, 3H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 0.9 Hz, 1H), 5.40-5.95 (m, 1H), 3.60 (dd, *J* = 13.8 and 6.0 Hz, 1H), 3.46 (dd, *J* = 13.8 and 6.0 Hz).

[0247] Preparation of (*S*)-methyl 5-[1-(2-phenylthiazol-4-yl)-2-(4-nitrophenyl)-ethylamino]thiazole-4-carboxylate (30): To a suspension of potassium *tert*-butoxide (89 mg, 0.75 mmol) in THF (3 mL) is added methyl isocyanoacetate (65 μL, 0.68 mmol) followed by (*S*)-2-phenyl-4-(1-isothiocyanato-2-(4-nitrophenyl)ethyl)thiazole, 29, (250 mg, 0.68 mmol). The reaction mixture is stirred at room temperature for 2 hours then poured into sat. $NaHCO_3$. The mixture is extracted with EtOAc (3x 25 mL) and the combined organic layers are washed with brine and dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue is purified over silica to afford 323 mg (~ 100% yield) of the desired product as a slightly yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09-8.13 (m, 2H), 7.95-7 98 (m, 3H), 7.84 (d, *J*= 1.2 Hz, 1H), 7.44-7.50 (m, 3H), 7.28-7.31 (m, 2H), 7.96 (d, *J* = 0.6 Hz, 1H), 4.71-4.78(m, 1H), 3.92 (s, 3H), 3.60 (dd, *J* = 13.8 and 6.0 Hz, 1H), 3.45 (dd, *J* = 13.8 and 6.0 Hz, 1H).

[0248] Preparation of (*S*)-4-(2-(2-phenylthiazol-4-yl)-2-(4-(methoxycarbonyl)thiazol-5-ylamino)ethyl)phenylsulfamic acid (31): (*S*)-methyl 5-[1-(2-phenylthiazol-4-yl)-2-(4-nitrophenyl)-ethylamino]thiazole-4-carboxylate, 30, (323 mg, 0.68 mmol) and tin (II) chloride (612 mg, 2.72 mmol) are dissolved in EtOH and the solution is brought to reflux. The solvent is removed *in vacuo* and the resulting residue is dissolved in EtOAc. A saturated solution of $NaHCO_3$ is added and the solution is stirred 1 hour. The organic layer is separated and the aqueous layer extracted twice with EtOAc. The combined organic layers are dried (Na_2SO_4), filtered and concentrated to a residue which is dissolved in pyridine (10 mL) and treated with SO_3-pyridine (130 mg, 0.82 mmol). The reaction is stirred at room temperature for 5 minutes after which a 7% solution of NH_4OH is added. The mixture is then concentrated and the resulting residue is purified by reverse phase chromatography to afford 0.071g of the desired product as the ammonium salt ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.97-8.00 (m, 3H), 7.48-7.52 (m, 3H), 7.22 (s, 1H), 7.03-7.13 (m, 4H), 4.74 (t, *J* = 6.6 Hz, 1H), 3.88 (s, 3H), 3.28-3.42 (m, 2H).

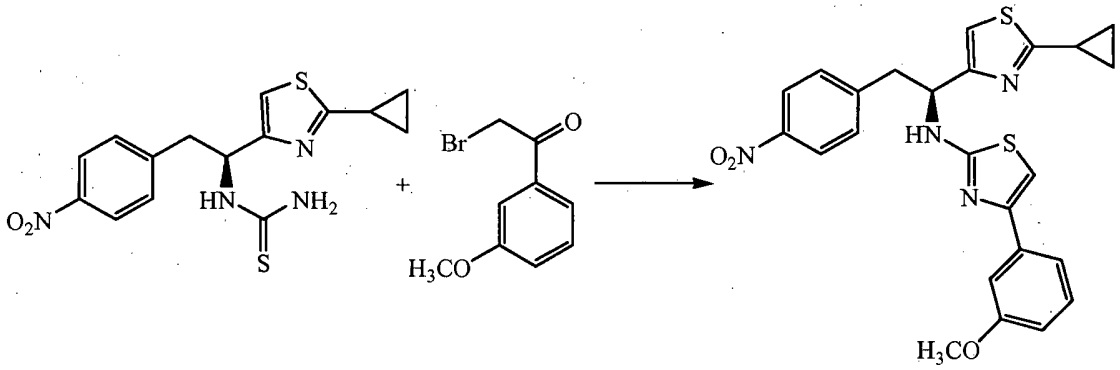
[0249] Compounds according to the first aspect of Category V which comprise a substituted or unsubstituted thiazol-2-yl unit for R^1 can be prepared by the procedure outlined in Scheme XII and described herein below in Example 12. Intermediate 32 can be prepared according to Scheme II and Example 2 by substituting cyclopropane-carbothioic acid amide for thiophene-2-carbothioic acid amide.

Scheme XII



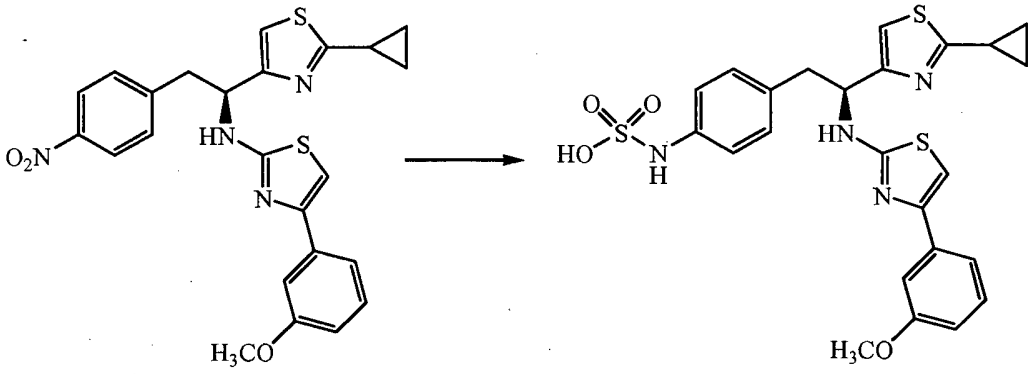
32 33

Reagents and conditions: (a) thiophosgene ,$CaCO_3$, CCl_4/H_2O; rt, 18 hr.



33 34

Reagents and conditions: (b)



34 35

Reagents and conditions: (c) (i) H_2:Pd/C, MeOH; (ii) SO_3-pyridine, NH_4OH.

EXAMPLE 12

4-{(*S*)-2-(2-Cyclopropylthiazol-4-yl)-2-[4-(3-methoxyphenyl)thiazol-2-ylamino]ethyl}phenylsulfamic acid (35)

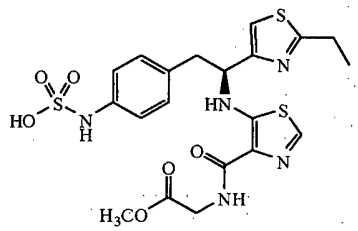
[0250] Preparation of (*S*)-1-(1-(2-cyclopropylthiazol-4-yl)-2-(4-nitrophenyl)ethyl)-thiourea (33): To a solution of (*S*)-1-(2-cyclopropylthiazol-4-yl)-2-(4-nitrophenyl)ethan-amine hydrobromide hydrobromide salt, 32, (4.04 g, 10.9 mmol) and $CaCO_3$ (2.18 g, 21.8 mmol) in CCl_4/water (25 mL/20 mL) is added thiophosgene (1.5 g, 13.1 mmol). The reaction is

stirred at room temperature for 18 hours then diluted with CH_2Cl_2 and water. The layers are separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers are washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to a residue which is subsequently treated with ammonia (0.5M in 1,4-dioxane, 120 mL) which is purified over silica to afford 2.90 g of the desired product as a red-brown solid. LC/MS ESI- 347 (M-1).

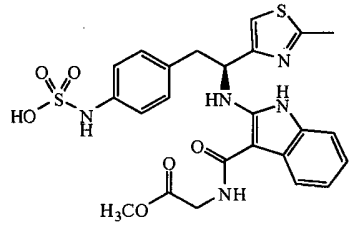
[0251] Preparation of (*S*)-4-(3-methoxybenzyl)-*N*-(1-(2-cyclopropylthiazol-4-yl)-2-(4-nitrophenyl)ethyl)thiazol-2-amine (34): (*S*)-1-(1-(2-Cyclopropylthiazol-4-yl)-2-(4-nitrophenyl)ethyl)-thiourea, 32, (350 mg, 1.00 mmol) and 2-bromo-3'-methoxy-acetophenone (253 mg, 1.10 mmol) are combined in 3 mL CH_3CN and heated to reflux for 24 hours. The mixture is concentrated and chromatographed to afford 0.172 g of the product as a yellow solid. LC/MS ESI+ 479 (M+1).

[0252] Preparation of 4-{(S)-2-(2-cyclopropylthiazol-4-yl)-2-[4-(3-methoxyphenyl)-thiazol-2-ylamino]ethyl}phenylsulfamic acid: (35): (*S*)-4-(3-methoxybenzyl)-*N*-(1-(2-cyclopropylthiazol-4-yl)-2-(4-nitrophenyl)ethyl)thiazol-2-amine, 34, (0.172 g) is dissolved in 10 mL MeOH. A catalytic amount of Pd/C (10% w/w) is added and the mixture is stirred under a hydrogen atmosphere for 18 hours. The reaction mixture is filtered through a bed of CELITE™ and the solvent is removed under reduced pressure. The crude product is dissolved in 5 mL pyridine and treated with SO_3-pyridine (114 mg). The reaction is stirred at room temperature for 5 minutes after which 10 mL of a 7% solution of NH_4OH is added. The mixture is then concentrated and the resulting residue is purified by reverse-phase chromatography to afford 0.033 g of the desired product as the ammonium salt. ^1H (CD_3OD): δ 7.33-7.22 (m, 3H), 7.10-6.97 (m, 5H), 6.84-6.80 (m, 2H), 5.02 (t, 1H, *J*=6.9 Hz), 3.82 (s, 1H), 3.18 (q, 2H, *J*=7.1 Hz), 2.36 (q, 1H, *J*=4.6 Hz), 1.20-1.13 (m, 2H), 1.04-0.99 (m, 2H).

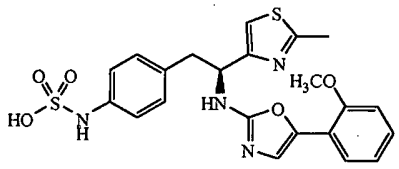
[0253] The following are examples of compounds encompassed within the first aspect of Category V.



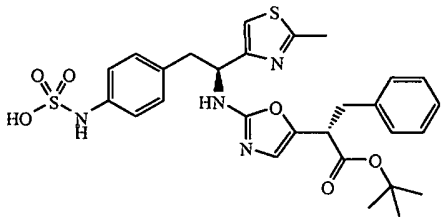
[0254] (*S*)-4-(2-(4-((2-Methoxy-2-oxoethyl)carbamoyl)thiazole-5-ylamino)2-(2-ethylthiazole-4-yl)ethyl)phenylsulfamic acid: ^1H NMR (300 MHz, MeOH-d_4) δ 7.91 (s, 1H), 7.08-7.10 (m, 3H), 6.99 (d, *J* = 8.7 Hz, 2H), 4.58 (t, *J*= 6.9 Hz, 1H), 4.11 (d, *J*= 2.7 Hz, 2H), 3.78 (s, 3H), 3.14-3.28 (m, 2H), 3.06 (q, *J* = 7.5 Hz, 2H), 1.41 (t, *J* = 7.5 Hz, 3H).



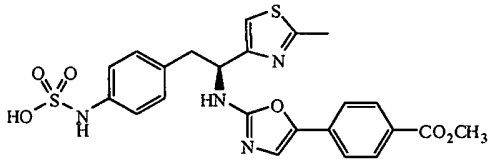
[0255] (*S*)-4-(2-(3-((2-Methoxy-2-oxoethyl)carbamoyl)-1*H*-indol-2-ylamino)-2-(2-methylthiazol-4-yl)ethyl)phenylsulfamic acid: ^1H NMR (300 MHz, MeOH-d_4) δ 7.63 (d, *J* = 7.8 Hz, 1H), 7.37 (s, 1H), 7.18-7.29 (m, 4H), 7.02-7.16 (m, 4H), 6.85 (s, 1H), 5.04-5.09 (m, 1H), 4.85 (s, 3H), 3.27 (dd, *J* = 13.5 and 8.1 Hz, 1H), 3.10 (m, *J* = 13.5 and 8.1 Hz, 1H), 2.69 (s, 3H).



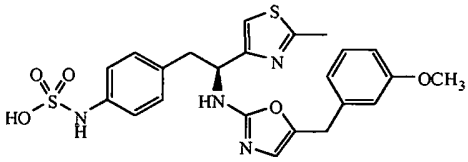
[0256] 4-((S)-2-(5-(2-Methoxyphenyl)oxazol-2-ylamino)-2-(2-methylthiazol-4-yl)ethyl)phenylsulfamic acid: ^1H NMR (300 MHz, MeOH-d_4) δ 7.52 (dd, *J* = 7.5 and 1.2 Hz, 1H), 6.95-7.24 (m, 10H), 5.04-5.09 (m, 1H), 3.92 (s, 3H), 3.26 (dd, *J* = 13.8 and 8.4 Hz, 1H), 3.10 (dd, *J* = 13.8 and 8.4 Hz, 1H), 2.72 (s, 3H).



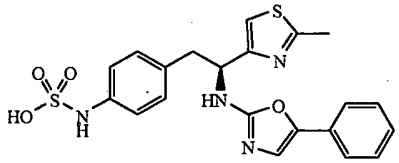
[0257] 4-((*S*)-2-(5-((*S*)-1-(*tert*-Butoxycarbonyl)-2-phenylethyl)oxazole-2-ylamino)-2-(2-methylthiazole-4-yl)ethyl)phenylsulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.03-7.27 (m, 10 H), 6.50 (s, 1H), 4.95-5.00 (m, 1H), 4.76 (t, *J* = 6.9 Hz, 1H), 3.22 (dd, *J* = 14.1 and 6.9 Hz, 1H), 3.00-3.10 (m, 2H), 2.90 (dd, *J* = 14.1 and 6.9 Hz, 1H), 2.72 (s, 3H), 1.37 (s, 9H).



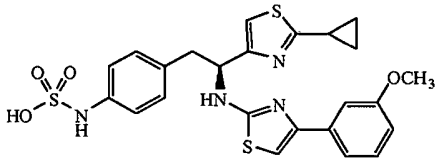
[0258] (*S*)-{4-{2-[5-(4-Methoxycarbonyl)phenyl]oxazol-2-ylamino} -2-(2-methylthiazol-4-yl)ethyl}phenylsulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.99 (d, *J* = 7.5 Hz, 2H), 7.56-7.59 (m, 2H), 7.23-7.24 (m, 1H), 7.08-7.14 (m, 4H), 6.83 (d, *J* = 10.2 Hz, 1H), 5.08 (t, J = 6.0 Hz, 1H), 3.91 (s, 3H), 3.25-3.35 (m, 1H), 3.09-3.13 (m, 1H), 2.73 (s, 3H).



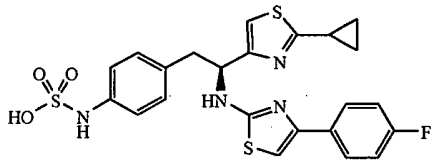
[0259] (*S*)-4-(2-(5-(3-Methoxybenzyl)oxazole-2-ylamino)-2-(2-methylthiazole-4-yl)ethyl)phenylsulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.03-7.28 (m, 8H), 6.79-6.83 (m, 1H), 5.70 (s, 1H), 4.99-5.06 (m, 2H), 4.41 (d, *J* = 2.1 Hz, 2H), 3.80 (s, 3H), 3.27-3.37 (m, 1H), 3.03-3.15 (m, 1H), 2.71 (s, 3H).



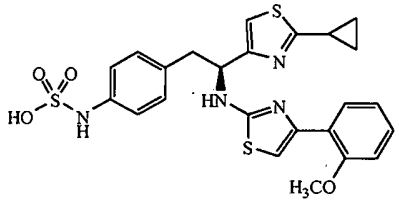
[0260] (*S*)-4-(2-(2-Methylthiazole-4-yl)2-(5-phenyloxazole-2-ylamino)ethyl)phenyl-sulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.45 (d, J = 8.7 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.18-7.22 (m, 1H), 7.10-7.14 (m, 6H), 7.04 (s, 1H), 5.04-5.09 (m, 1H), 3.26 (dd, J = 13.8 and 6.3 Hz, 1H), 3.10 (dd, *J* = 13.8 and 6.3 Hz, 1H), 2.70 (s, 3H).



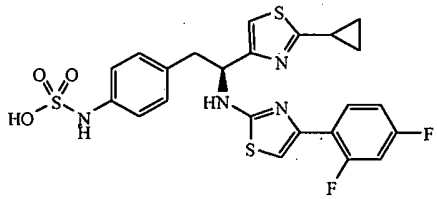
[0261] 4-((S)-2-(2-Cyclopropylthiazol-4-yl)-2-(4-(3-methoxyphenyl)thiazol-2-ylamino)ethyl)phenylsulfamic acid: ^{1}H (CD_3OD): δ 7.33-7.2 (m, 3H), 7.10-6.97 (m, 5H), 6.84-6.80 (m, 2H), 5.02 (t, 1H, *J*=6.9 Hz), 3.82 (s, 1H), 3.18 (q, 2H, *J*=7.1 Hz), 2.36 (q, 1H, *J*=4.6 Hz), 1.20-1.13 (m, 2H), 1.04-0.99 (m, 2H).



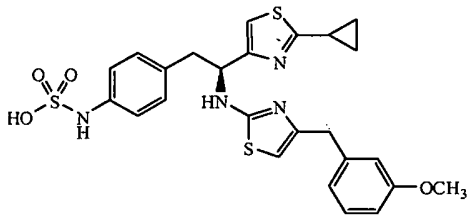
[0262] (*S*)-4-(2-(2-cyclopropylthiazol-4-yl)-2-(4-(4-fluorophenyl)thiazol-2-ylamino)ethyl)phenylsulfamic acid: ^{1}H (CD_3OD): δ 7.79-7.7 (m, 2H), 7.14-7.03 (m, 7H), 7.21 (s, 1H), 6.79 (s, 1H), 5.08 (t, 1H, *J*=6.6 Hz), 3.29-3.12 (m, 2H), 2.40 (q, 2.40, *J*=5.1 Hz), 1.23-1.18 (m, 2H), 1.08-1.02 (m, 2H).



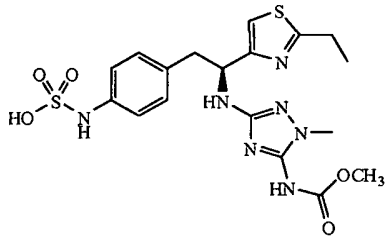
[0263] 4-((*S*)-2-(2-cyclopropylthiazol-4-yl)-2-(4-(2-methoxyphenyl)thiazol-2-ylamino)ethyl)phenylsulfamic acid: ^{1}H (CD_3OD): δ 7.89-7.87 (d, 1H, *J*=7.6 Hz), 7.28 (t, 1H, *J*=7.0 Hz), 7.10-6.96 (m, 8H), 5.03 (t, 1H, *J*=6.9 Hz), 3.90 (s, 1H), 3.19 (q, 2H, *J*=6.6 Hz), 2.38 (q, 1H, *J*=4.8 Hz), 1.21-1.14 (m, 2H), 1.06-1.00 (m, 2H).



[0264] 4-((*S*)-2-(2-cyclopropylthiazol-4-yl)-2-(4-(2,4-difluorophenyl)thiazol-2-ylamino)ethyl)phenylsulfamic acid: ^{1}H (CD_3OD): δ 8.06-8.02 (q, 2H, *J*=6.9 Hz), 7.12-6.95 (m, 7H), 6.88 (s, 1H), 5.11 (t, 1H, *J*=6.9 Hz), 3.22-3.15 (m, 2H), 2.38 (q, 1H, *J*=4.8 Hz), 1.22-1.15 (m, 2H), 1.06-1.02 (m, 2H).



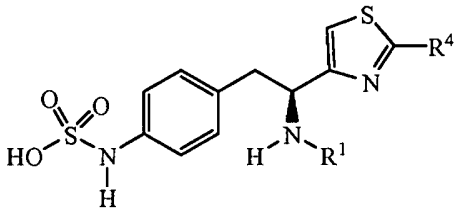
[0265] (*S*)-4-(2-(4-(3-methoxybenzyl)thiazol-2-ylamino)-2-(2-cyclopropylthiazol-4-yl)ethyl)phenylsulfamic acid: ^{1}H (CD_3OD): δ 7.22-7.17 (m, 3H), 7.09-6.97 (m, 5H), 6.78-6.66 (m, 3H), 3.77 (s, 2H), 3.75 (s, 3H), 3.20-3.07 (m, 2H), 2.35 (q, 1H, *J*=4.8 Hz), 1.19-1.13 (m, 2H), 1.03-1.00 (m, 2H).



[0266] (*S*)-{5-[1-(2-Ethylthiazol-4-yl)-2-(4-sulfoaminophenyl)ethylamino]-2-methyl-2H-[1,2,4]triazole-3-yl}carbamic

acid methyl ester: ^{1}H NMR (300 MHz, MeOH-d_4) δ 6.97-7.08 (m, 5H), 3.71 (s, 3H), 3.51 (s, 3H), 3.15 (dd, *J* = 13.5 and 6.3 Hz, 1H), 3.02-3.07 (m, 3H), 1.40 (t, *J* = 6.6 Hz, 3H).

[0267] The second aspect of Category V of the present disclosure relates to compounds having the formula:



wherein R^1 is a substituted or unsubstituted heteroaryl and R^4 is substituted or unsubstituted phenyl and substituted or unsubstituted heteroaryl as further described herein below in Table X.

TABLE X

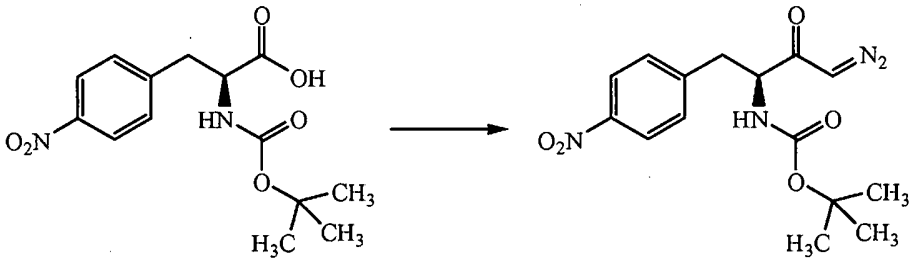
No.	R^4	R^1
471	phenyl	4-(methoxycarbonyl)thiazol-5-yl
472	phenyl	4-[(2-methoxy-2-oxoethyl)carbamoyl]thiazol-5-yl
473	phenyl	5-[1-*N*-(2-methoxy-2-oxoethyl)-1-*H*-indol-3-yl]oxazol-2-yl
474	phenyl	5-(2-methoxyphenyl)oxazol-2-yl
475	phenyl	5-[(*S*)-1-(*tert*-butoxycarbonyl)-2-phenylethyl]oxazol-2-yl
476	phenyl	5-[4-(methylcarboxy)phenyl]oxazol-2-yl
477	phenyl	5-(3-methoxybenzyl)oxazol-2-yl
478	phenyl	5-(4-phenyl)oxazol-2-yl
479	phenyl	5-(2-methoxyphenyl)thiazol-2-yl
480	phenyl	5-(3-methoxyphenyl)thiazol-2-yl
481	phenyl	5-(4-fluorophenyl)thiazol-2-yl
482	phenyl	5-(2,4-difluorophenyl)thiazol-2-yl
483	phenyl	5-(3-methoxybenzyl)thiazol-2-yl
484	phenyl	4-(3-methoxyphenyl)thiazol-2-yl
485	phenyl	4-(4-fluorophenyl)thiazol-2-yl
486	thiophene-2-yl	4-(methoxycarbonyl)thiazol-5-yl
487	thiophene-2-yl	4-[(2-methoxy-2-oxoethyl)carbamoyl]thiazol-5-yl
488	thiophene-2-yl	5-[1-*N*-(2-methoxy-2-oxoethyl)-1-*H*-indol-3-yl]oxazol-2-yl
489	thiophene-2-yl	5-(2-methoxyphenyl)oxazol-2-yl
490	thiophene-2-yl	5-[(*S*)-1-(*tert*-butoxycarbonyl)-2-phenylethyl]oxazol-2-yl
491	thiophene-2-yl	5-[4-(methylcarboxy)phenyl]oxazol-2-yl
492	thiophene-2-yl	5-(3-methoxybenzyl)oxazol-2-yl
493	thiophene-2-yl	5-(4-phenyl)oxazol-2-yl
494	thiophene-2-yl	5-(2-methoxyphenyl)thiazol-2-yl
495	thiophene-2-yl	5-(3-methoxyphenyl)thiazol-2-yl
496	thiophene-2-yl	5-(4-fluorophenyl)thiazol-2-yl
497	thiophene-2-yl	5-(2,4-difluorophenyl)thiazol-2-yl
498	thiophene-2-yl	5-(3-methoxybenzyl)thiazol-2-yl

(continued)

No.	R^4	R^1
499	thiophene-2-yl	4-(3-methoxyphenyl)thiazol-2-yl
500	thiophene-2-yl	4-(4-fluorophenyl)thiazol-2-yl
501	cyclopropyl	4-(methoxycarbonyl)thiazol-5-yl
502	cyclopropyl	4-[(2-methoxy-2-oxoethyl)carbamoyl]thiazol-5-yl
503	cyclopropyl	5-[1-*N*-(2-methoxy-2-oxoethyl)-1-*H*-indol-3-yl]oxazol-2-yl
504	cyclopropyl	5-(2-methoxyphenyl)oxazol-2-yl
505	cyclopropyl	5-[(*S*)-1-(*tert*-butoxycarbonyl)-2-phenylethyl]oxazol-2-yl
506	cyclopropyl	5-[4-(methylcarboxy)phenyl]oxazol-2-yl
507	cyclopropyl	5-(3-methoxybenzyl)oxazol-2-yl
508	cyclopropyl	5-(4-phenyl)oxazol-2-yl
509	cyclopropyl	5-(2-methoxyphenyl)thiazol-2-yl
510	cyclopropyl	5-(3-methoxyphenyl)thiazol-2-yl
511	cyclopropyl	5-(4-fluorophenyl)thiazol-2-yl
512	cyclopropyl	5-(2,4-difluorophenyl)thiazol-2-yl
513	cyclopropyl	5-(3-methoxybenzyl)thiazol-2-yl
514	cyclopropyl	4-(3-methoxyphenyl)thiazol-2-yl
515	cyclopropyl	4-(4-fluorophenyl)thiazol-2-yl

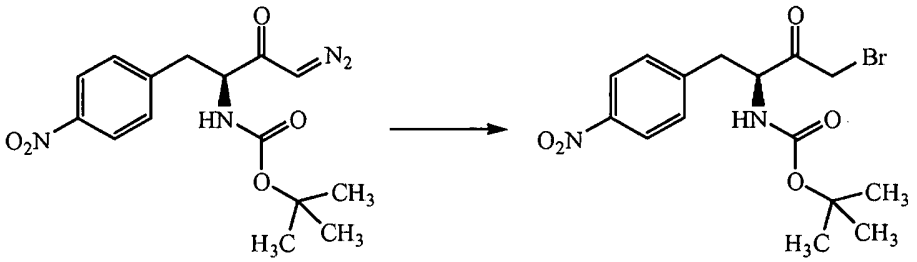
[0268] Compounds according to the second aspect of Category V which comprise a substituted or unsubstituted thiazol-4-yl unit for R^1 can be prepared by the procedure outlined in Schemes XIII, XIV, and XV and described herein below in Examples 13, 14, and 15.

Scheme XIII



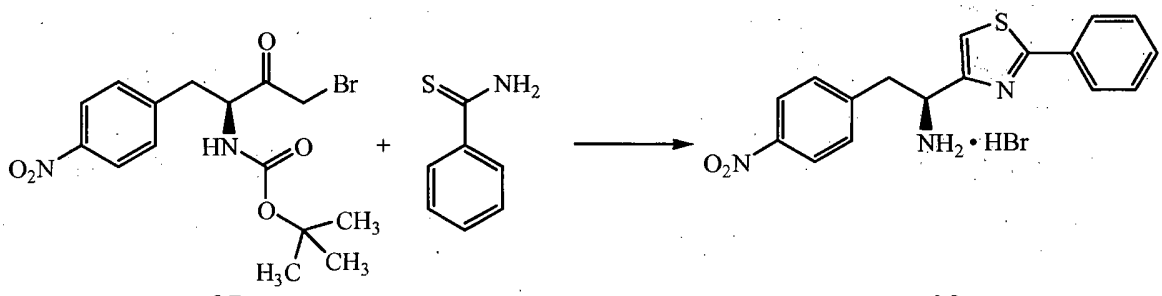
36

Reagents and conditions: (a)(i) (*iso*-butyl)OCOCl, Et_3N, THF; 0 °C, 20 min.
(ii) CH_2N_2; 0 °C to room temp for 3 hours.



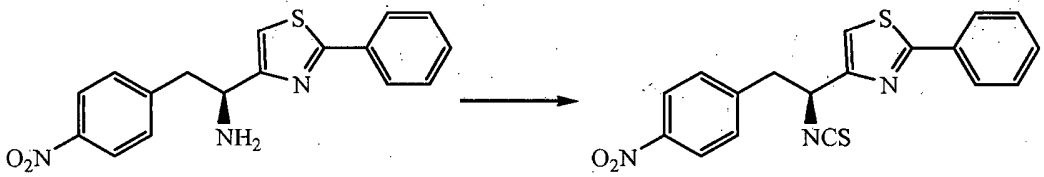
36 37

Reagents and conditions: (b) 48% HBr, THF; 0 °C, 1.5 hr.



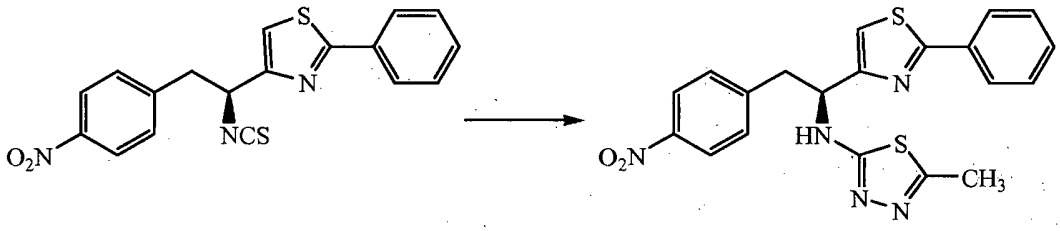
37 38

Reagents and conditions: (c) CH_3CN; reflux 2hr.



38 39

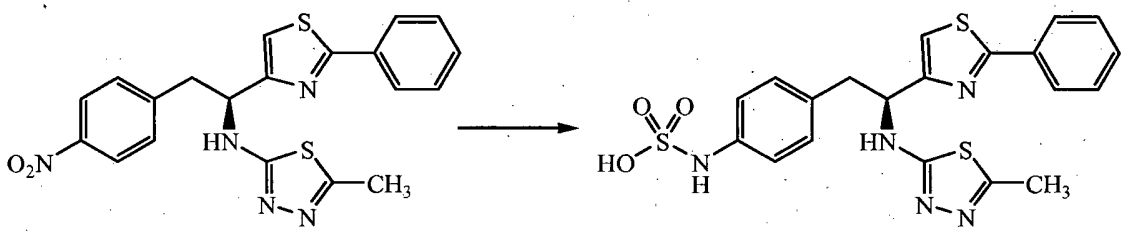
Reagents and conditions: (d) thiophosgene, $CaCO_3$, CCl_4, H_2O; rt, 18 hr.



39 40

Reagents and conditions: (e)(i) $CH_3C(O)NHNH_2$, EtOH; reflux, 2 hr.

(ii) $POCl_3$, rt 18 hr; 50 °C 2 hr.



40 41

Reagents and conditions: (f) (i) H_2:Pd/C, MeOH; (ii) SO_3-pyridine, NH_4OH.

EXAMPLE 13

(*S*)-4-(2-((5-Methyl-1,3,4-thiadiazol-2-yl)amino)-2-(2-phenylthiazol-4-yl)ethyl)phenylsulfamic acid (41)

[0269] Preparation of [3-diazo-1-(4-nitrobenzyl)-2-oxo-propyl]-carbamic acid *tert*-butyl ester (36): To a 0 °C solution of 2-(*S*)-*tert*-butoxycarbonylamino-3-(4-nitrophenyl)-propionic acid (1.20 g, 4.0 mmol) in THF (20 mL) is added dropwise triethylamine (0.61 mL, 4.4 mmol) followed by *iso*-butyl chloroformate (0.57 mL, 4.4 mmol). The reaction mixture is stirred at 0 °C for 20 minutes then filtered. The filtrate is treated with an ether solution of diazomethane (~16 mmol) at 0 °C. The reaction mixture is stirred at room temperature for 3 hours and concentrated. The residue is dissolved in EtOAc and washed successively with water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resulting residue is purified over silica (hexane/EtOAc 2:1) to afford 1.1 g (82% yield) of the desired product as a slightly yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 5.39 (s, 1H), 5.16 (d, *J* = 6.3 Hz, 1H), 4.49 (s, 1H), 3.25 (dd, *J* = 13.8 and 6.6, 1H), 3.06 (dd, *J* = 13.5 and 6.9 Hz, 1H), 1.41 (s, 9H).

[0270] Preparation of [3-bromo-1-(4-nitro-benzyl)-2-oxo-propyl]-carbamic acid *tert*-butyl ester (37): To a 0 °C solution of [3-diazo-1-(4-nitrobenzyl)-2-oxo-propyl]-carbamic acid *tert*-butyl ester, 36, (0.350 g, 1.04 mmol) in THF (5 mL) is added dropwise 48% aq. HBr (0.14 mL, 1.25 mmol). The reaction mixture is stirred at 0 °C for 1.5 hours and quenched at 0 °C with saturated aqueous Na_2CO_3. The mixture is extracted with EtOAc (3 x 25 mL) and the combined organic extracts are washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 0.400 g of the desired product that is used in the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 5.06 (d, *J* = 7.8 Hz, 1H), 4.80 (q, *J* = 6.3 Hz, 1H), 4.04 (s, 2H), 1.42 (s, 9H).

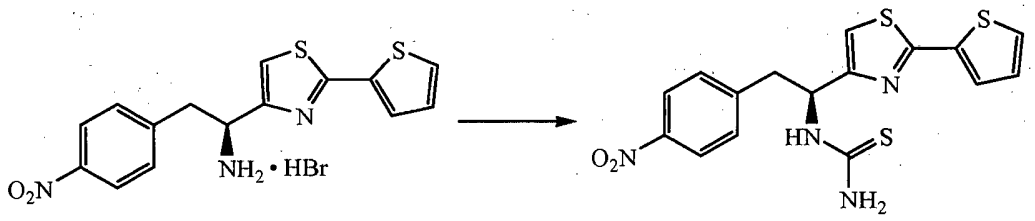
[0271] Preparation of (*S*)-2-(4-nitrophenyl)-1-(2-phenylthiazol-4-yl)ethanamine hydrobromide salt (38): A mixture of [3-bromo-1-(4-nitro-benzyl)-2-oxo-propyl]-carbamic acid *tert*-butyl ester, 37, (1.62 g, 4.17 mmol) and benzothioamide (0.630 g, 4.59 mmol), in CH_3CN (5 mL) is refluxed for 24 hours. The reaction mixture is cooled to room temperature and diethyl ether (50 mL) is added to the solution and the precipitate that forms is collected by filtration. The solid is dried under vacuum to afford 1.059 g (63%) of the desired product. ESI+MS 326 (M+1).

[0272] Preparation of (*S*)-4-[1-isothiocyanato-2-(4-nitrophenyl)-ethyl]-2-phenylthiazole (39): To a solution of (*S*)-2-(4-nitrophenyl)-1-(2-phenylthiazol-4-yl)ethanamine hydrobromide salt, 38, (2.03g, 5 mmol) and $CaCO_3$ (1 g, 10 mmol) in CCl_4/water (10:7.5 mL) is added thiophosgene (0.46 mL, 6 mmol). The reaction is stirred at room temperature for 18 hours then diluted with CH_2Cl_2 and water. The layers are separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers are washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to a residue that is purified over silica (CH_2Cl_2) to afford 1.71g (93% yield) of the desired product. ESI+ MS 368 (M+1).

[0273] Preparation of (*S*)-5-methyl-*N*-[2-(4-nitrophenyl)-1-(2-phenylthiazol-4-yl)ethyl]-1,3,4-thiadiazol-2-amine (40): A solution of (*S*)-4-[1-isothiocyanato-2-(4-nitrophenyl)-ethyl]-2-phenylthiazole, 39, (332 mg, 0.876 mmol) and acetic hydrazide (65 mg, 0.876 mmol) in EtOH (5 mL) is refluxed for 2 hours. The solvent is removed under reduced pressure, the residue is dissolved in $POCl_3$ (3 mL) and the resulting solution is stirred at room temperature for 18 hours after which the solution is heated to 50 °C for 2 hours. The solvent is removed *in vacuo* and the residue is dissolved in EtOAc (40 mL) and the resulting solution is treated with 1N NaOH until the pH remains approximately 8. The solution is extracted with EtOAc. The combined aqueous layers are washed with EtOAc, the organic layers combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford 0.345 g (93% yield) of the desired product as a yellow solid. ^1H NMR ($CDCl_3$) 8.09 (d, J = 8.4 Hz, 2H), 7.91 (m, 2H), 7.46 (m, 4H), 7.44 (s, 1H), 5.23 (m, 1H), 3.59 (m, 2H), 2.49 (s, 3H). ESI+ MS 424 (M+1).

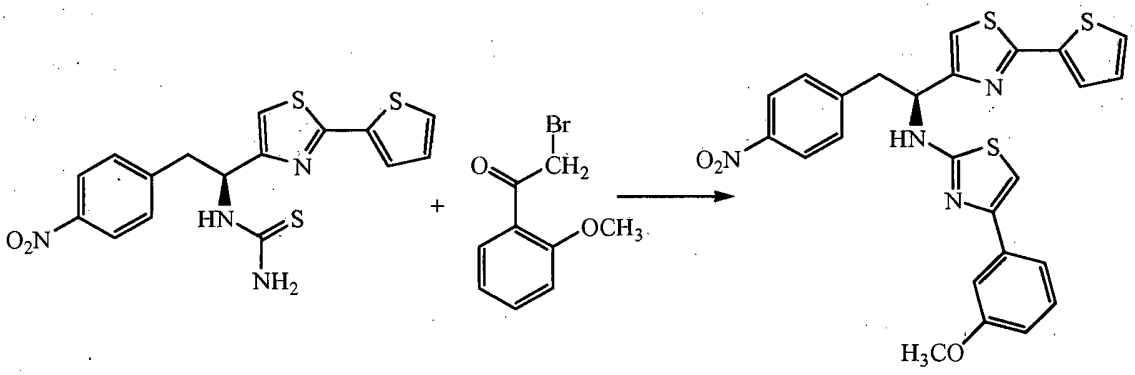
[0274] Preparation of (*S*)-4-(2-((5-Methyl-1,3,4-thiadiazol-2-yl)amino)-2-(2-phenylthiazol-4-yl)ethyl)phenylsulfamic acid (41): (*S*)-5-Methyl-N-[2-(4-nitrophenyl)-1-(2-phenylthiazol-4-yl)ethyl]-1,3,4-thiadiazol-2-amine, 40, (0.404 g, 0.954 mmol) is dissolved in MeOH (5 mL). Pd/C (50 mg, 10% w/w) is added and the mixture is stirred under a hydrogen atmosphere until the reaction is judged to be complete. The reaction mixture is filtered through a bed of CELITE™ and the solvent removed under reduced pressure. The crude product is dissolved in pyridine (4 mL) and treated with SO_3-pyridine (0.304 g, 1.91 mmol). The reaction is stirred at room temperature for 5 minutes after which a 7% solution of NH_4OH (50 mL) is added. The mixture is then concentrated and the resulting residue is purified by reverse phase preparative HPLC to afford 0.052 g (11% yield) of the desired product as the ammonium salt. ^1H (CD_3OD): δ 8.00-7.97 (m, 2H), 7.51-7.47 (m, 3H), 7.23 (s, 1H), 7.11-7.04 (q, 4H, *J*=9.0 Hz), 5.18 (t, 1H, *J*=7.2 Hz), 3.34-3.22 (m, 2H), 2.50 (s, 3H). ESI-MS 472 (M-1).

Scheme XIV



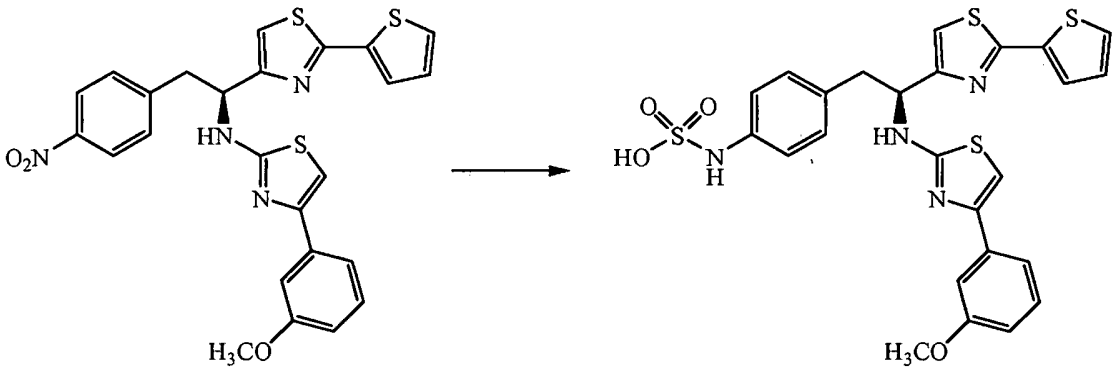
8 42

Reagents and conditions: (a) thiophosgene ,$CaCO_3$, CCl_4/H_2O; rt, 18 hr.



42 43

Reagents and conditions: (b) CH_3CN, reflux, 5 hours



43 44

Reagents and conditions: (c) (i) H_2:Pd/C, MeOH; (ii) SO_3-pyridine, NH_4OH; rt, 18 hr.

EXAMPLE 14

(*S*)-[4-(2-{[4-(3-Methoxyphenyl)thiazol-2-yl]amino}-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl)phenyl]sulfamic acid (44)

[0275] Preparation of (*S*)-1-[1-(thiophen-2-ylthiazol-4-yl)-2-(4-nitrophenyl)ethyl]-thiourea (42): To a solution of (*S*)-2-(4-nitrophenyl)-1-(thiophen-2-ylthiazol-4-yl)ethanamine hydrobromide salt, 8, (1.23 g, 2.98 mmol) and $CaCO_3$ (0.597 g, 5.96 mmol) in CCl_4/water (10 mL/5 mL) is added thiophosgene (0.412g, 3.58 mmol). The reaction is stirred at room temperature for 18 hours then diluted with CH_2Cl_2 and water. The layers are separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers are washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to a residue which is subsequently treated with ammonia (0.5M in 1,4-dioxane, 29.4 mL, 14.7 mmol) which is purified over silica to

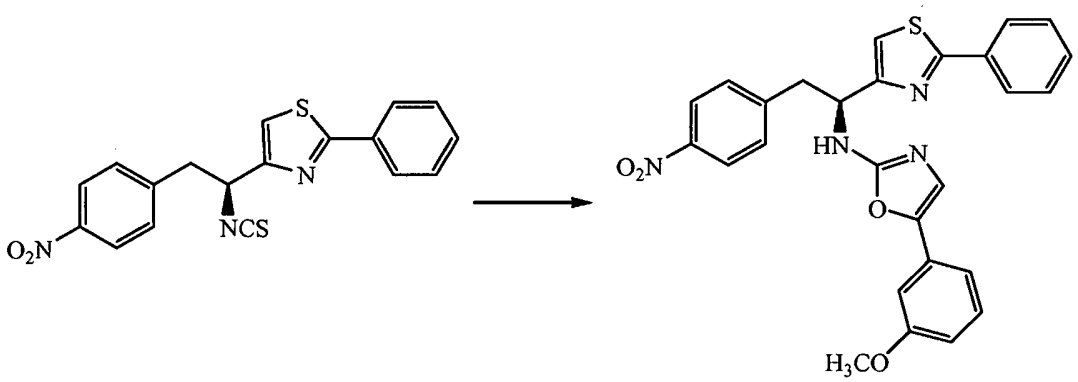
afford 0.490 g of the desired product as a red-brown solid. ESI+ MS 399 (M+1).

[0276] Preparation of 4-(2-methoxyphenyl)-*N*-{(S)-2-(4-nitrophenyl)-1-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}thiazol-2-amine (43): (*S*)-1-[1-(thiophen-2-ylthiazol-4-yl)-2-(4-nitrophenyl)ethyl]-thiourea, 42, (265 mg, 0.679 mmol) is treated with bromo-2'-methoxyacetophenone (171 mg, 0.746 mmol) to afford 0.221 g of the product as a yellow solid. ESI+ MS 521 (M+1).

[0277] Preparation of *(S)*-[4-(2-{[4-(3-Methoxyphenyl)thiazol-2-yl]amino}-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl)phenyl]sulfamic acid (44): 4-(2-methoxyphenyl)-*N*-{(*S*)-2-(4-nitrophenyl)-1-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}thiazol-2-amine, 43, (0.229 g) is dissolved in 12 mL MeOH. A catalytic amount of Pd/C (10% w/w) is added and the mixture is stirred under a hydrogen atmosphere for 18 hours. The reaction mixture is filtered through a bed of CELITE™ and the solvent is removed under reduced pressure. The crude product is dissolved in 6 mL pyridine and treated with SO_3-pyridine (140 mg). The reaction is stirred at room temperature for 5 minutes after which 10 mL of a 7% solution of NH_4OH is added. The mixture is then concentrated and the resulting residue is purified by reverse-phase chromatography to afford 0.033g of the desired product as the ammonium salt. ^1H (CD_3OD): δ 7.96-7.93 (m, 1H), 7.60-7.55 (m, 2H), 7.29-7.23 (m, 1H), 7.18-6.95 (m, 9H), 5.15 (t, 1H, *J*=6.9 Hz), 3.90 (s, 3H), 3.35-3.24 (m, 2H).

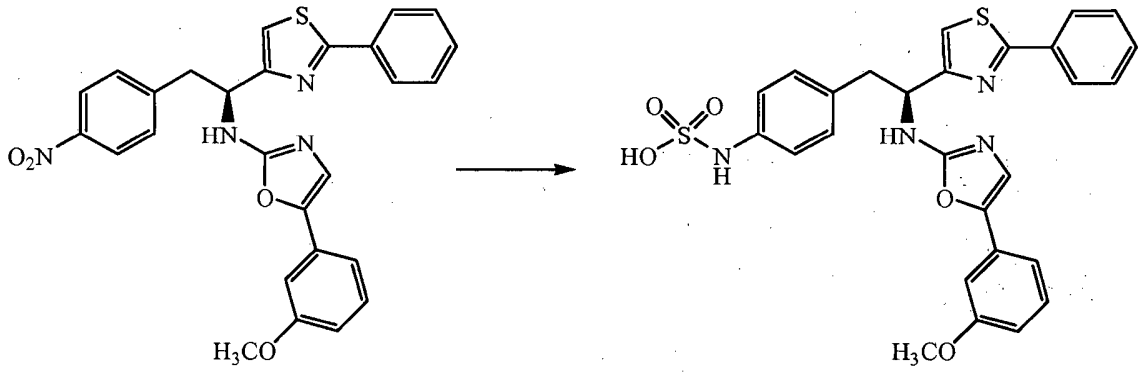
[0278] Compounds according to the second aspect of Category V which comprise a substituted or unsubstituted oxazol-2-yl unit for R^1 can be prepared by the procedure outlined in Scheme XV and described herein below in Example 15. Intermediate 39 can be prepared according to Scheme XIII and Example 13.

Scheme XV



39 45

Reagents and conditions: (a) 1-azido-1-(3-methoxyphenyl)ethanone, PPh_3, dioxane, 90 °C 20 minutes.



45 46

Reagents and conditions: (b) (i) H_2:Pd/C, MeOH; (ii) SO_3-pyridine, NH_4OH; rt, 18 hr.

EXAMPLE 15

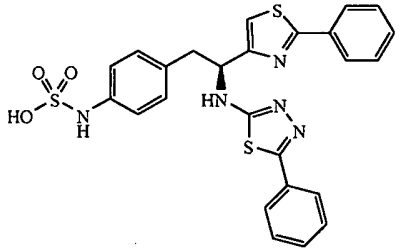
4-{(*S*)-2-[5-(3-Methoxyphenyl)oxazole-2-ylamino]-2-(2-phenylthiazole-4-yl)ethyl}phenylsulfamic acid (46)

[0279] Preparation of [5-(3-methoxyphenyl)oxazol-2-yl]-[2-(4-nitrophenyl)-1-(2-phenylthiazole-4-yl) ethyl]amine (45): A mixture of (*S*)-4-(isothiocyanato-2-(4-nitrophenyl)ethyl)-2-phenylthiazole, 39, (300 mg, 0.81 mmol), 1-azido-1-(3-methoxyphenyl)ethanone (382 mg, 2.0 mmol) and PPh_3 (0.8 g, polymer bound, ~3 mmol/g) in dioxane (6 mL) is heated at 90 °C for 20 minutes. The reaction solution is cooled to room temperature and the solvent removed in vacuo and the resulting residue is purified over silica to afford 300 mg (74% yield) of the desired product as a yellow solid. ^{1}H NMR (300 MHz, MeOH-d_4) δ 8.02 (d, J = 7.2 Hz, 2H), 7.92-7.99 (m, 2H), 7.42-7.47 (m, 3H), 7.22-7.27 (m, 3H), 6.69-7.03 (m, 4H), 6.75-6.78 (m, 1H), 5.26 (t, J = 6.3 Hz, 1H), 3.83 (s, 4H), 3.42-3.45 (m, 2H).

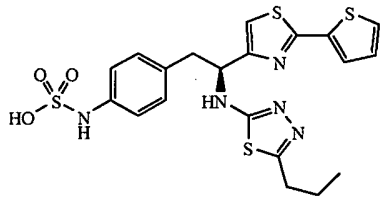
[0280] Preparation of 4-{(*S*)-2-[5-(3-methoxyphenyl)oxazole-2-ylamino]-2-(2-phenylthiazole-4-yl)ethyl}phenylsulfamic acid (46): [5-(3-methoxyphenyl)oxazol-2-yl]-[2-(4-nitrophenyl)-1-(2-phenylthiazole-4-yl) ethyl]amine, 45, (300 mg, 0.60 mmol) is dissolved in MeOH (15 mL). A catalytic amount of Pd/C (10% w/w) is added and the mixture is stirred under a hydrogen atmosphere 18 hours. The reaction mixture is filtered through a bed of CELITE™ and the solvent is removed under reduced pressure. The crude product is dissolved in pyridine (10 mL) and treated with SO_3-pyridine (190 mg, 1.2 mmol). The reaction is stirred at room temperature for 5 minutes after which a 7% solution of NH_4OH is added. The mixture is then concentrated and the resulting residue is purified by reverse-phase chromatography to afford 0.042 g of the desired product as the ammonium salt. ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.99 (d, *J* = 7.5 Hz, 2H), 7.46-7.50 (m, 3H),7.23-7.29 (m, 3H), 7.04-7.12 (m, 6H), 6.78 (dd, *J* = 8.4 and 2.4 Hz, 1H), 5.16 (t, *J* = 6.6 Hz, 1H), 3.81 (s, 3H), 3.29-3.39 (m, 1H), 3.17 (dd, *J* = 13.8 and 8.1 Hz, 1H).

[0281] Further to the preparation of compounds which encompass Category V of the present disclosure, compounds of the present disclosure comprising R^1 units having non-exemplified units can be prepared by modifying the procedures described herein above. For example, compounds of Category V comprising substituted or unsubstituted [1,2,4]triazole-3-yl units can be prepared.

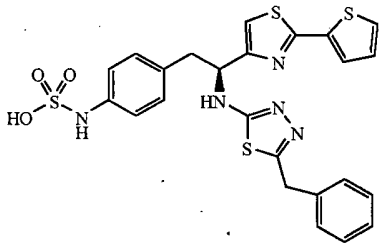
[0282] The following are examples of the second aspect of Category V of the present disclosure.



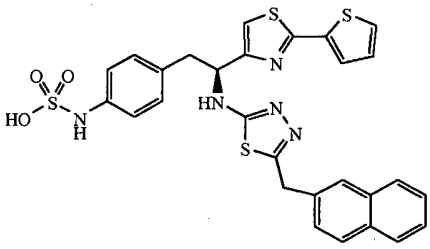
[0283] (*S*)-4-(2-(5-Phenyl-1,3,4-thiadiazol-2-ylamino)-2-(2-phenylthiazol-4-yl)ethyl)-phenylsulfamic acid: ^{1}H (CD_3OD): δ 7.97-7.94 (m, 2H), 7.73-7.70 (m, 2H), 7.44-7.39 (m, 6H), 7.25 (s, 1H), 7.12 (s, 4H), 5.29 (t, 1H, *J*=6.9 Hz), 3.35-3.26 (m, 2H).



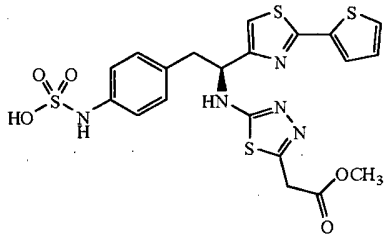
[0284] 4-((*S*)-2-(5-Propyl-1,3,4-thiadiazol-2-ylamino)-2-(2-(thiophen-2-yl)thiazol-4-yl)ethyl)phenylsulfamic acid: ^{1}H (CD_3OD): δ 7.59-7.54 (m, 2H), 7.17-7.03 (m, 6H), 5.13 (t, 1H, *J*=7.2 Hz), 3.32-3.13 (m, 2H), 2.81 (t, 2H, *J*=7.4 Hz), 1.76-1.63 (h, 6H, *J*=7.4 Hz), 0.97 (t, 3H, *J*=7.3 Hz).



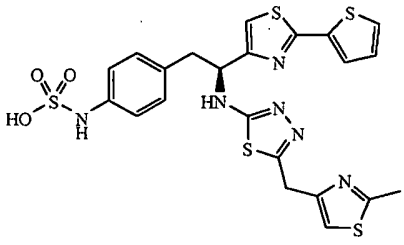
[0285] 4-((*S*)-2-(5-Benzyl-1,3,4-thiadiazol-2-ylamino)-2-(2-(thiophen-2-yl)thiazol-4-yl)ethyl)phenylsulfamic acid: ^{1}H (CD_3OD): δ (m, 2H), 7.49-7.45 (m, 2H), 7.26-7.16 (m, 5H), 7.05-6.94 (m, 6H), 5.04 (t, 1H, *J*=7.1 Hz), 4.07 (s, 2H), 3.22-3.04 (m, 2H).



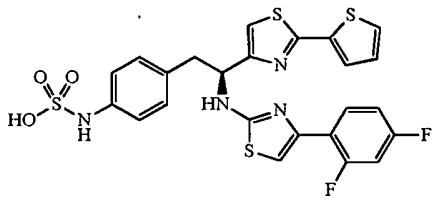
[0286] 4-((*S*)-2-(5-(Naphthalen-1-ylmethyl)-1,3,4-thiadiazol-2-ylamino)-2-(2-(thiophen-2-yl)thiazol-4-yl)ethyl)phenylsulfamic acid: ^{1}H (CD_3OD): δ 8.08-8.05 (m, 1H), 7.89-7.80 (m, 2H), 7.55-7.43 (m, 6H), 7.11-7.00 (m, 6H), 5.08 (t, 1H, *J*=7.1 Hz), 4.63 (s, 2H), 3.26-3.08 (m, 2H).



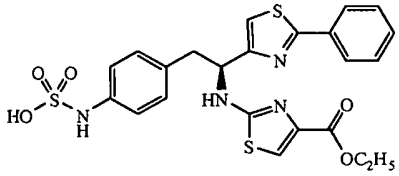
[0287] 4-((*S*)-2-(5-((Methoxycarbonyl)methyl)-1,3,4-thiadiazol-2-ylamino)-2-(2-(thiophen-2-yl)thiazol-4-yl)ethyl)phenylsulfamic acid: ^{1}H(CD_3OD): δ 7.48-7.44 (m, 2H), 7.03-6.92 (m, 6H), 5.02 (t, 1H, *J*=7.2 Hz), 4.30 (s, 2H), 3.55 (s, 3H), 3.22-3.02 (m, 2H).



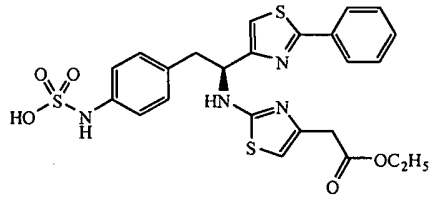
[0288] 4-((*S*)-2-(5-((2-Methylthiazol-4-yl)methyl)-1,3,4-thiadiazol-2-ylamino)-2-(2-(thiophen-2-yl)thiazol-4-yl)ethyl)phenylsulfamic acid: ^{1}H(CD_3OD): δ 7.60-7.56 (m, 2H), 7.19 (s, 1H), 7.15-7.12 (m, 2H), 7.09-7.03 (q, 4H, *J*=8.7 Hz), 5.14 (t, 1H, *J*=7.2 Hz), 4.28 (s, 2H), 3.33-3.14 (m, 2H), 2.67 (s, 3H).



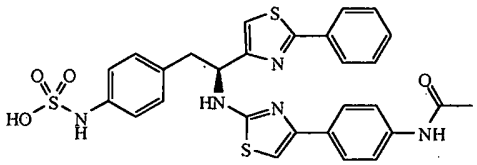
[0289] 4-{(*S*)-2-[4-(2,4-Difluorophenyl)thiazol-2-ylamino]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid: ^{1}H(CD_3OD): δ 8.06-8.02 (q, 1H, *J*=6.8 Hz), 7.59-7.54 (m, 2H), 7.16-7.08 (m, 6H), 7.01-6.88 (m, 4H), 5.20 (t, 1H, *J*=7.0 Hz), 3.36-3.17 (m, 2H).



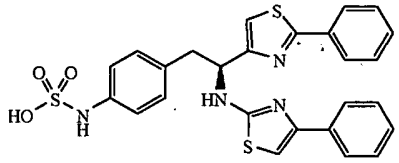
[0290] (*S*)-4-{2-[4-(Ethoxycarbonyl)thiazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylsulfamic acid: ^{1}H (CD_3OD): δ 8.02-7.99 (m, 2H), 7.54-7.45 (m, 4H), 7.26 (s, 1H), 7.08 (s, 4H), 5.26 (t, 1H, *J*=6.9 Hz), 4.35-4.28 (q, 2H, *J*=6.9 Hz), 3.38-3.18 (m, 2H), 1.36 (t, 3H, *J*=7.2 Hz).



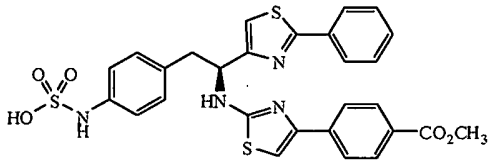
[0291] (*S*)-4-{2-[4-(2-Ethoxy-2-oxoethyl)thiazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylsulfamic acid: ^{1}H (CD_3OD): δ 7.96 (m, 2H), 7.50-7.46 (m, 3H), 7.21 (s, 1H), 7.10-7.04 (m, 4H), 6.37 (s, 1H), 5.09 (t, 1H, *J*=6.9 Hz), 4.17-4.10 (q, 2H, *J*=7.1 Hz), 3.54 (s, 2H), 3.35-3.14 (m, 2H), 1.22 (t, 3H, *J*=7.1 Hz).



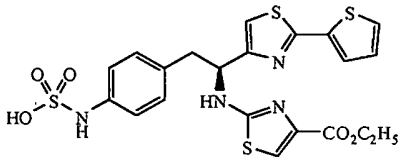
[0292] (*S*)-4-{2-[4-(4-acetamidophenyl)thiazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylsulfamic acid: ^{1}H (CD_3OD): δ 8.11 (m, 2H), 7.82-7.80 (m, 2H), 7.71-7.61 (m, 6H), 7.40 (s, 1H), 7.23 (s, 4H), 5.32 (t, 1H, J=7.0 Hz), 3.51-3.35 (m, 2H), 2.28 (s, 3H).



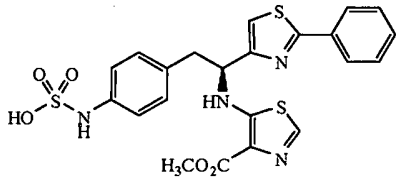
[0293] (S)-4-[2-(4-phenylthiazol-2-ylamino)-2-(2-phenylthiazol-4-yl)ethyl]phenyl-sulfamic acid: ^{1}H (CD_3OD): δ 8.03-7.99 (m, 2H), 7.75-7.72 (d, 2H, *J*=8.4 Hz), 7.53-7.48 (m, 3H), 7.42 (m, 4H), 7.12 (s, 4H), 6.86 (s, 1H), 5.23 (t, 1H, *J*=7.2 Hz), 3.40-3.27 (m, 2H).



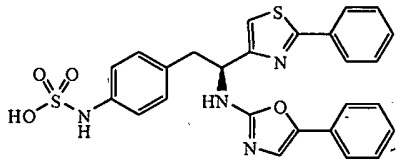
[0294] (*S*)-4-{2-[4-(4-(methoxycarbonyl)phenyl)thiazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylsulfamic acid: ^{1}H (CD_3OD): δ 8.04-8.00 (m, 4H), 7.92-7.89 (d, 2H, *J*=9.0 Hz), 7.53-7.49 (m, 3H), 7.30 (s, 1H), 7.15 (s, 4H), 7.05 (s, 1H), 5.28 (t, 1H, *J*=6.9 Hz), 3.93 (s, 3H), 3.35-3.24 (m, 2H).



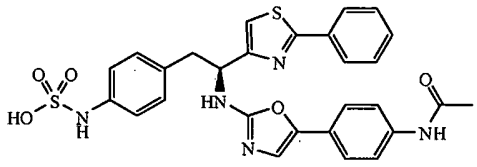
[0295] 4-{(*S*)-2-[4-(Ethoxycarbonyl)thiazol-2-ylamino]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid: ^{1}H (CD_3OD): δ 7.43-7.38 (m, 2H), 7.26 (s, 1H), 7.00-6.94 (m, 3H), 6.89 (s, 4H), 5.02 (t, 1H, *J*=7.0 Hz), 4.16-4.09 (q, 2H, *J*=7.1 Hz), 3.14-2.94 (m, 2H), 1.17 (t, 3H, *J*=7.1 Hz).



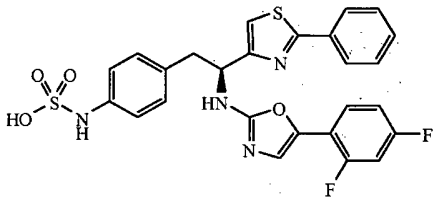
[0296] (*S*)-4-[2-(4-(Methoxycarbonyl)thiazol-5-ylamino)-2-(2-phenylthiazole-4-yl)ethyl]phenylsulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_d) δ 7.97-8.00 (m, 3H), 7.48-7.52 (m, 3H), 7.22 (s, 1H), 7.03-7.13 (m, 4H), 4.74 (t, *J*= 6.6 Hz, 1H), 3.88 (s, 3H), 3.28-3.42 (m, 2H).



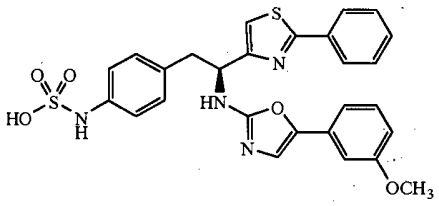
[0297] (*S*)-4-[2-(5-Phenyloxazol-2-ylamino)-2-(2-phenylthiazol-4-yl)ethyl]-phenylsulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.94-7.96 (m, 2H), 7.45-7.49 (m, 5H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.12 (s, 1H), 7.19 (t, *J* = 7.2 Hz, 1 H), 7.12 (s, 4H), 7.05 (s, 1H), 5.15 (t, *J* = 6.4 Hz, 1H), 3.34 (dd, *J* = 14.1 and 8.4 Hz, 1H), 3.18 (dd, *J* = 14.1 and 8.4 Hz, 1H).



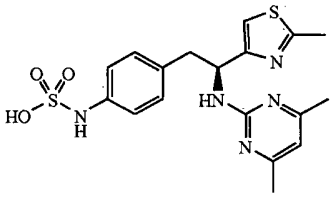
[0298] (*S*)-4-{2-[5-(4-Acetamidophenyl)oxazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylsulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.92-7.94 (m, 2H), 7.55-7.58 (m, 2H), 7.39-7.50 (m, 5H), 7.26 (s, 1H), 7.12 (s, 4H), 7.02 (s, 1H0), 5.14 (t, *J* = 7.8 Hz, 1H), 3.13-3.38 (m, 2H), 2.11 (s, 3H).



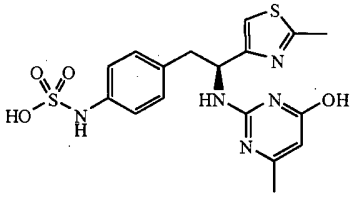
[0299] 4-((*S*)-2-(5-(2,4-Difluorophenyl)oxazole-2-ylamino)-2-(2-phenylthiazole-4-yl)ethyl)phenylsulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.97-7.99 (m, 2H), 7.54-7.62 (m, 1H), 7.45-7.50 (m, 3H), 7.28 (s, 1H), 7.12 (s, 4H), 6.97-7.06 (m, 3H), 5.15-5.20 (m, 1H), 3.28-3.40 (m, 1H), 3.20 (dd, *J* = 13.8 and 8.4 Hz, 1H).



[0300] 4-{(*S*)-2-[5-(3-Methoxyphenyl)oxazol-2-ylamino]-2-[(2-thiophen-2-yl)thiazole-4-yl]ethyl}phenylsulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.55-7.60 (m, 2H), 7.26 (t, *J* = 8.1 Hz, 1H), 7.21 (s, 1H), 7.04-7.15 (m, 8H), 6.77-6.81 (m, 1H), 5.10 (t, *J* = 6.3 Hz, 1H), 3.81 (s, 3H), 3.29-3.36(m, 1H), 3.15 (dd, *J*= 14.1 and 8.4 Hz, 1H).

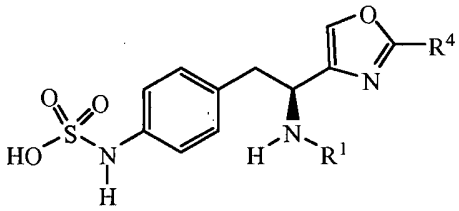


[0301] (*S*)-4-[2-(4,6-Dimethylpyrimidin-2-ylamino)-2-(2-methylthiazole-4-yl)ethyl]phenylsulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.00-7.10 (m, 5H), 6.44 (s, 1H), 5.50 (t, *J*= 7.2 Hz, 1H), 3.04-3.22 (m, 2H), 2.73 (s, 3H), 2.27 (s, 6H).



[0302] (*S*)-4-[2-(4-Hydroxy-6-methylpyrimidine-2-ylamino)-2-(2-methylthiazole-4-yl)ethyl]phenylsulfamic acid: ^{1}H NMR (300 MHz, MeOH-d4) δ 7.44 (d, *J* = 8.4Hz,2H), 6.97-7.10 (m, 4H), 5.61 (s, 1H), 5.40-5.49 (m, 1H), 3.10-3.22 (m, 2H), 2.73 (s, 3 H), 2.13 (s, 3H).

[0303] The first aspect of Category VI of the present disclosure relates to compounds having the formula:



wherein R^1 is heteroaryl and R^4 is further described herein below in Table XI.

TABLE XI

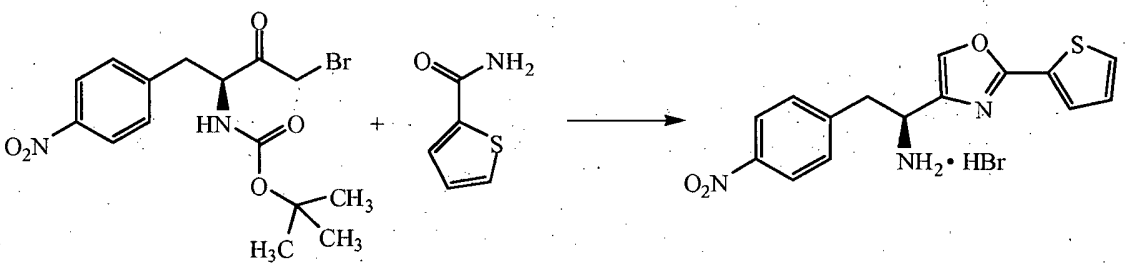
No.	R^4	R^1
516	phenyl	4-(methoxycarbonyl)thiazol-5-yl
517	phenyl	4-[(2-methoxy-2-oxoethyl)carbamoyl]thiazol-5-yl
518	phenyl	5-[1-*N*-(2-methoxy-2-oxoethyl)-1-*H*-indol-3-yl]oxazol-2-yl
519	phenyl	5-(2-methoxyphenyl)oxazol-2-yl
520	phenyl	5-[(*S*)-1-(*tert*-butoxycarbonyl)-2-phenylethyl]oxazol-2-yl
521	phenyl	5-[4-(methylcarboxy)phenyl]oxazol-2-yl
522	phenyl	5-(3-methoxybenzyl)oxazol-2-yl
523	phenyl	5-(4-phenyl)oxazol-2-yl
524	phenyl	5-(2-methoxyphenyl)thiazol-2-yl
525	phenyl	5-(3-methoxyphenyl)thiazol-2-yl
526	phenyl	5-(4-fluorophenyl)thiazol-2-yl
527	phenyl	5-(2,4-difluorophenyl)thiazol-2-yl
528	phenyl	5-(3-methoxybenzyl)thiazol-2-yl
529	phenyl	4-(3-methoxyphenyl)thiazol-2-yl
530	phenyl	4-(4-fluorophenyl)thiazol-2-yl
531	thiophene-2-yl	4-(methoxycarbonyl)thiazol-5-yl
532	thiophene-2-yl	4-[(2-methoxy-2-oxoethyl)carbamoyl]thiazol-5-yl
533	thiophene-2-yl	5-[1-*N*-(2-methoxy-2-oxoethyl)-1-*H*-indol-3-yl]oxazol-2-yl
534	thiophene-2-yl	5-(2-methoxyphenyl)oxazol-2-yl
535	thiophene-2-yl	5-[(*S*)-1-(*tert*-butoxycarbonyl)-2-phenylethyl]oxazol-2-yl
536	thiophene-2-yl	5-[4-(methylcarboxy)phenyl]oxazol-2-yl
537	thiophene-2-yl	5-(3-methoxybenzyl)oxazol-2-yl
538	thiophene-2-yl	5-(4-phenyl)oxazol-2-yl
539	thiophene-2-yl	5-(2-methoxyphenyl)thiazol-2-yl
540	thiophene-2-yl	5-(3-methoxyphenyl)thiazol-2-yl
541	thiophene-2-yl	5-(4-fluorophenyl)thiazol-2-yl
542	thiophene-2-yl	5-(2,4-difluorophenyl)thiazol-2-yl
543	thiophene-2-yl	5-(3-methoxybenzyl)thiazol-2-yl
544	thiophene-2-yl	4-(3-methoxyphenyl)thiazol-2-yl
545	thiophene-2-yl	4-(4-fluorophenyl)thiazol-2-yl
546	cyclopropyl	4-(methoxycarbonyl)thiazol-5-yl
547	cyclopropyl	4-[(2-methoxy-2-oxoethyl)carbamoyl]thiazol-5-yl
548	cyclopropyl	5-[1-*N*-(2-methoxy-2-oxoethyl)-1-*H*-indol-3-yl]oxazol-2-yl
549	cyclopropyl	5-(2-methoxyphenyl)oxazol-2-yl
550	cyclopropyl	5-[(*S*)-1-(*tert*-butoxycarbonyl)-2-phenylethyl]oxazol-2-yl
551	cyclopropyl	5-[4-(methylcarboxy)phenyl]oxazol-2-yl
552	cyclopropyl	5-(3-methoxybenzyl)oxazol-2-yl

(continued)

No.	R^4	R^1
553	cyclopropyl	5-(4-phenyl)oxazol-2-yl
554	cyclopropyl	5-(2-methoxyphenyl)thiazol-2-yl
555	cyclopropyl	5-(3-methoxyphenyl)thiazol-2-yl
556	cyclopropyl	5-(4-fluorophenyl)thiazol-2-yl
557	cyclopropyl	5-(2,4-difluorophenyl)thiazol-2-yl
558	cyclopropyl	5-(3-methoxybenzyl)thiazol-2-yl
559	cyclopropyl	4-(3-methoxyphenyl)thiazol-2-yl
560	cyclopropyl	4-(4-fluorophenyl)thiazol-2-yl

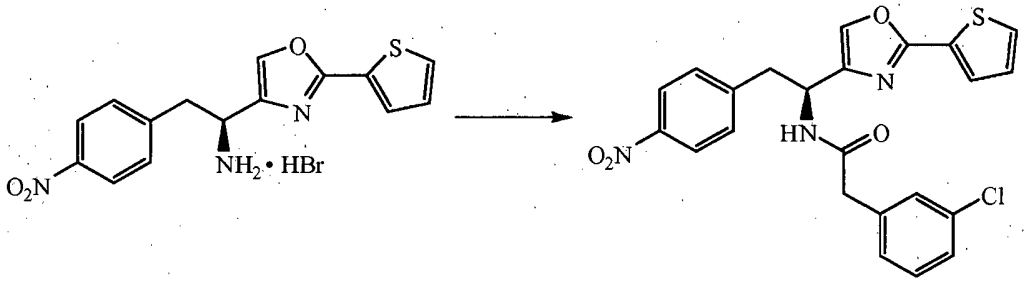
[0304] Compounds according to the first aspect of Category VI can be prepared by the procedure outlined in Scheme XVI and described herein below in Example 16.

Scheme XVI



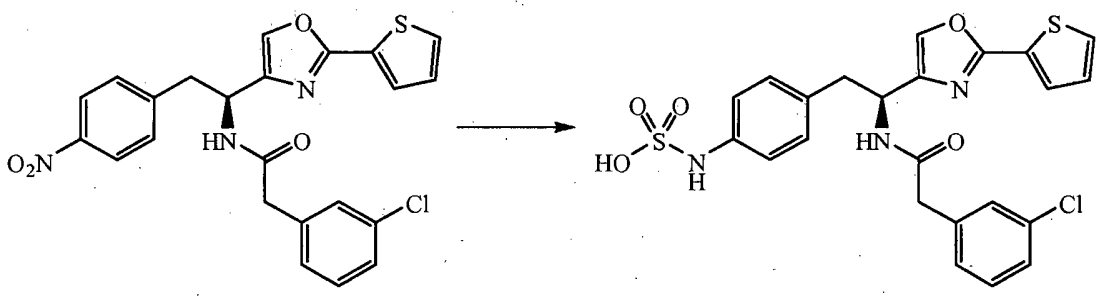
7 47

Reagents and conditions: (a) CH_3CN; reflux 2hr.



47 48

Reagents and conditions: (b) $(3\text{-Cl})C_6H_4CO_2H$, EDCI, HOBt, DIPEA, DMF; rt, 18 hr.



48 49

Reagents and conditions: (c) (i) H_2:Pd/C, MeOH; (ii) SO_3-pyridine, NH_4OH, rt, 18 hr.

EXAMPLE 16

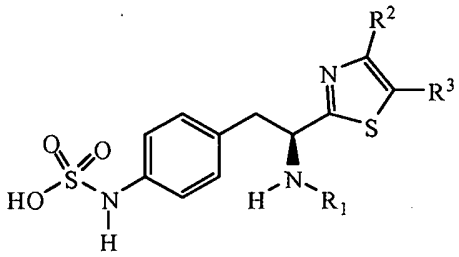
4-((*S*)-2-(2-(3-Chlorophenyl)acetamido)-2-(2-(thiophene-2-yl)oxazol-4-yl)ethyl)phenylsulfamic acid (49)

[0305] Preparation of (*S*)-2-(4-nitrophenyl)-1-[(thiophene-2-yl)oxazol-4-yl]ethanamine hydrobromide salt (47): A mixture of (*S*)-tert-butyl 4-bromo-1-(4-nitrophenyl)-3-oxobutan-2-ylcarbamate, 7, (38.7 g, 100 mmol), and thiophene-2-carboxamide (14 g, 110 mmol) (available from Alfa Aesar) in CH_3CN (500 mL) is refluxed for 5 hours. The reaction mixture is cooled to room temperature and diethyl ether (200 mL) is added to the solution. The precipitate which forms is collected by filtration. The solid is dried under vacuum to afford the desired product which can be used for the next step without purification.

[0306] Preparation of 2-(3-chlorophenyl)-*N*-{(*S*)-2-(4-nitrophenyl)-1-[2-(thiophene-2-yl)oxazol-4-yl]ethyl}acetamide (48): To a solution of (*S*)-2-(4-nitrophenyl)-1-[(thiophene-2-yl)oxazol-4-yl]ethanamine HBr, 47, (3.15 g, 10 mmol) 3-chlorophenyl-acetic acid (1.70 g, 10 mmol) and 1-hydroxybenzotriazole (HOBt) (0.70g, 5.0 mmol) in DMF (50 mL) at 0 °C, is added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) (1.90 g, 10 mmol) followed by triethylamine (4.2 mL, 30 mmol). The mixture is stirred at 0 °C for 30 minutes then at room temperature overnight. The reaction mixture is diluted with water and extracted with EtOAc. The combined organic phase is washed with 1 N aqueous HCl, 5 % aqueous $NaHCO_3$, water and brine, and dried over Na_2SO_4. The solvent is removed *in vacuo* to afford the desired product which is used without further purification.

[0307] Preparation of -((*S*)-2-(2-(3-chlorophenyl)acetamido)-2-(2-(thiophene-2-yl)oxazol-4-yl)ethyl)phenylsulfamic acid (49): 2-(3-chlorophenyl)-*N*-{(*S*)-2-(4-nitrophenyl)-1-[2-(thiophene-2-yl)oxazol-4-yl]ethyl}acetamide, 48, (3 g) is dissolved in MeOH (4 mL). A catalytic amount of Pd/C (10% w/w) is added and the mixture is stirred under a hydrogen atmosphere 18 hours. The reaction mixture is filtered through a bed of CELITE™ and the solvent is removed under reduced pressure. The crude product is dissolved in pyridine (12 mL) and treated with SO_3-pyridine (0.157 g). The reaction is stirred at room temperature for 5 minutes after which a 7% solution of NH_4OH is added. The mixture is then concentrated and the resulting residue can be purified by reverse phase chromatography to afford the desired product as the ammonium salt.

[0308] The second aspect of Category VI of the present disclosure relates to compounds having the formula:



wherein R^1 is aryl and R^2 and R^3 are further described herein below in Table XII.

TABLE XII

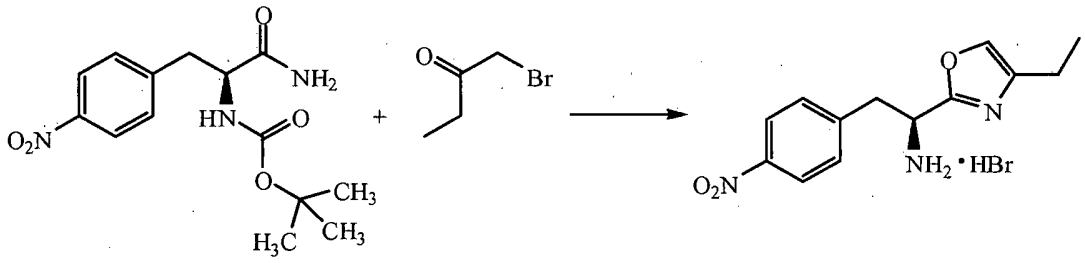
No.	R^2	R^3	R^1
561	methyl	hydrogen	phenyl
562	methyl	hydrogen	benzyl
563	methyl	hydrogen	2-fluorophenyl
564	methyl	hydrogen	3-fluorophenyl
565	methyl	hydrogen	4-fluorophenyl
566	methyl	hydrogen	2-chlorophenyl
567	methyl	hydrogen	3-chlorophenyl
568	methyl	hydrogen	4-chlorophenyl
569	ethyl	hydrogen	phenyl
570	ethyl	hydrogen	benzyl
571	ethyl	hydrogen	2-fluorophenyl
572	ethyl	hydrogen	3-fluorophenyl
573	ethyl	hydrogen	4-fluorophenyl
574	ethyl	hydrogen	2-chlorophenyl
575	ethyl	hydrogen	3-chlorophenyl
576	ethyl	hydrogen	4-chlorophenyl
577	thiene-2-yl	hydrogen	phenyl

(continued)

No.	R^2	R^3	R^1
578	thiene-2-yl	hydrogen	benzyl
579	thiene-2-yl	hydrogen	2-fluorophenyl
580	thiene-2-yl	hydrogen	3-fluorophenyl
581	thiene-2-yl	hydrogen	4-fluorophenyl
582	thiene-2-yl	hydrogen	2-chlorophenyl
583	thiene-2-yl	hydrogen	3-chlorophenyl
584	thiene-2-yl	hydrogen	4-chlorophenyl

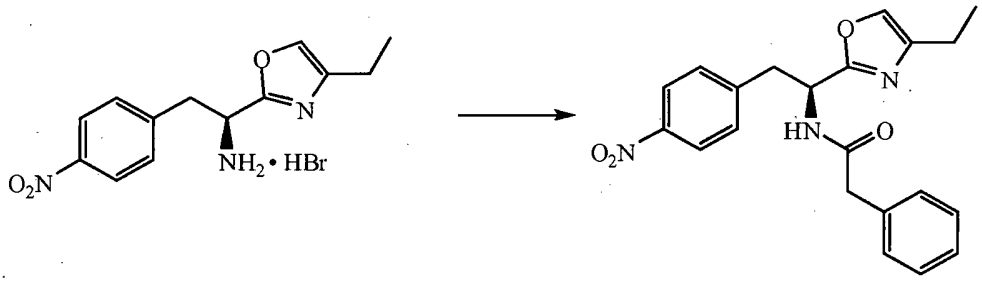
[0309] Compounds according to the second aspect of Category VI .can be prepared by the procedure outlined in Scheme XVII and described herein below in Example 17.

Scheme XVII



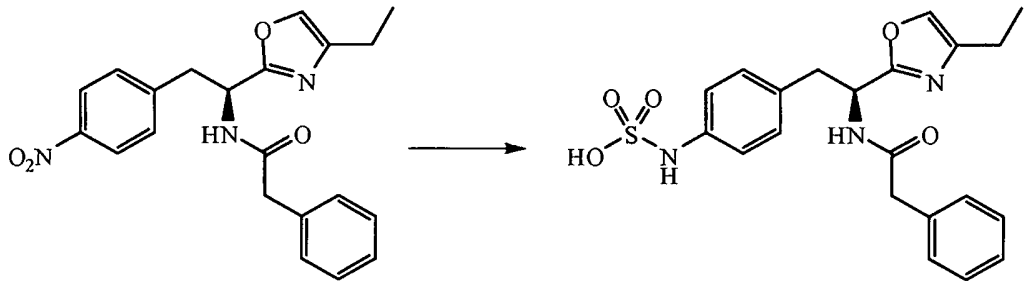
1 50

Reagents and conditions: (a) CH_3CN; reflux, 2 hr.



50 51

Reagents and conditions: (b) $C_6H_4CO_2H$, EDCI, HOBt, DIPEA, DMF; rt, 18 hr.



51 52

Reagents and conditions: (c) (i) H_2:Pd/C, MeOH; (ii) SO_3-pyridine, NH_4OH, rt, 18 hr.

EXAMPLE 17

{4-[2-(*S*)-(4-Ethyloxazol-2-yl)-2-phenylacetylaminoethyl] -phenyl}sulfamic acid (52)

[0310] Preparation of (*S*)-1-(4-ethyloxazol-2-yl)-2-(4-nitrophenyl)ethanamine (50): A mixture of [1-(S)-carbamoyl-2-(4-nitrophenyl)ethyl-carbamic acid *tert*-butyl ester, 1, (10 g, 32.3mmol) and 1-bromo-2-butanone (90%, 4.1 mL, 36 mmol) in CH_3CN (500 mL) is refluxed for 18 hours. The reaction mixture is cooled to room temperature and diethyl ether is added to the solution and the precipitate which forms is removed by filtration and is used without further purification.

[0311] Preparation of *N*-[1-(4-ethyloxazol-2-yl)-2-(4-nitrophenyl)ethyl]-2-phenyl-acetamide (51): To a solution of (*S*)-1-(4-ethyloxazol-2-yl)-2-(4-nitrophenyl)ethanamine, 50, (2.9 g, 11 mmol), phenylacetic acid (1.90 g, 14 mmol) and 1-hydroxybenzotriazole (HOBt) (0.94 g, 7.0 mmol) in DMF (100 mL) at 0 °C, is added 1-(3-dirnethylamino-propyl)-3-ethylcarbodiimide (EDCI) (2.68g, 14 mmol) followed by triethylamine (6.0 mL, 42mmol). The mixture is stirred at 0 °C for 30 minutes then at room temperature overnight. The reaction mixture is diluted with water and extracted with EtOAc. The combined organic phase is washed with 1 N aqueous HCl, 5 % aqueous $NaHCO_3$, water and brine, and dried over Na_2SO_4. The solvent is removed *in vacuo* to afford the desired product which is used without further purification.

[0312] Preparation of {4-[2-(*S*)-(4-ethyloxazol-2-yl)-2-phenylacetylaminoethyl]-phenyl}sulfamic acid (52): *N*-[1-(4-ethyloxazol-2-yl)-2-(4-nitrophenyl)ethyl]-2-phenyl-acetamide, 51, (0.260 g) is dissolved in MeOH (4 mL). A catalytic amount of Pd/C (10% w/w) is added and the mixture is stirred under a hydrogen atmosphere 18 hours. The reaction mixture is filtered through a bed of CELITE™ and the solvent is removed under reduced pressure. The crude product is dissolved in pyridine (12 mL) and treated with SO_3-pyridine (0.177 g, 1.23). The reaction is stirred at room temperature for 5 minutes after which a 7% solution of NH_4OH (10 mL) is added. The mixture is then concentrated and the resulting residue is purified by reverse phase chromatography to afford the desired product as the ammonium salt.

[0313] Regulation of HPTP-β provides a method for modulating the activity of angiopoietin receptor-type tyrosine kinase Tie-2, and thereby mediate, affect, or otherwise control disease states related to angiogenesis wherein angiogenesis is improperly regulated by the human body. The compounds of the present disclosure serve as a method for providing regulation of angiogenesis. As such the present disclosure addresses several unmet medical needs, *inter alia*;

1) Providing compositions effective as human protein tyrosine phosphatase beta (HPTP-β) inhibitors; and thereby providing a method for regulating angiogenesis in a disorder wherein angiogenesis is elevated;

2) Providing compositions effective as human protein tyrosine phosphatase beta (HPTP-β) inhibitors; and thereby providing a method for regulating angiogenesis in a disorder; and

3) Providing compositions effective human protein tyrosine phosphatase beta (HPTP-β) inhibitors; and thereby providing a method for regulating angiogenesis in a disorder wherein angiogenesis is decreased.

[0314] For purposes of the present disclosure the term "regulate" is defined as including, up-regulate or down-regulate, to fix, to bring order or uniformity, to govern, or to direct by various means. In one aspect, an antibody may be used in a method for the treatment of an "angiogenesis elevated disorder" or "angiogenesis reduced disorder". As used herein, an "angiogenesis elevated disorder" is one that involves unwanted or elevated angiogenesis in the biological manifestation of the disease, disorder, and/or condition; in the biological cascade leading to the disorder; or as a symptom of the disorder. Similarly, the "angiogenesis reduced disorder" is one that involves wanted or reduced angiogenesis in the biological manifestations. This "involvement" of angiogenesis in an angiogenesis elevated/reduced disorder includes the following:

1. The angiogenesis as a "cause" of the disorder or biological manifestation, whether the level of angiogenesis is elevated or reduced genetically, by infection, by autoimmunity, trauma, biomechanical causes, lifestyle, or by some other causes.

2. The angiogenesis as part of the observable manifestation of the disease or disorder. That is, the disease or disorder is measurable in terms of the increased or reduced angiogenesis. From a clinical standpoint, angiogenesis indicates the disease; however, angiogenesis need not be the "hallmark" of the disease or disorder.

3. The angiogenesis is part of the biochemical or cellular cascade that results in the disease or disorder. In this respect, regulation of angiogenesis may interrupt the cascade, and may control the disease. Examples of angiogenesis regulated disorders that may be treated by the present disclosure are herein described below.

FORMULATIONS

[0315] The present disclosure also relates to compositions or formulations that comprise one or more human protein tyrosine phosphatase beta (HPTP-β) inhibitors as disclosed herein. In general, the disclosed compositions comprise:

a) an effective amount of one or more phenylsufamic acids or salts thereof according to the present disclosure that are effective as human protein tyrosine phosphatase beta (HPTP-β) inhibitors; and
b) one or more excipients.

[0316] For the purposes of the present disclosure the term "excipient" and "carrier" are used interchangeably throughout the description of the present disclosure and said terms are defined herein as, "ingredients which are used in the practice of formulating a safe and effective pharmaceutical composition."

[0317] The formulator will understand that excipients are used primarily to serve in delivering a safe, stable, and functional pharmaceutical, serving not only as part of the overall vehicle for delivery but also as a means for achieving effective absorption by the recipient of the active ingredient. An excipient may fill a role as simple and direct as being an inert filler, or an excipient as used herein may be part of a pH stabilizing system or coating to insure delivery of the ingredients safely to the stomach. The formulator can also take advantage of the fact the compounds of the present disclosure have improved cellular potency, pharmacokinetic properties, as well as improved oral bioavailability.

[0318] Examples of disclosed compositions include:

a) from about 0.001 mg to about 1000 mg of one or more phenylsulfamic acids or salts thereof according to the present disclosure; and
b) one or more excipients.

[0319] Another example of disclosed compositions includes:

a) from about 0.01 mg to about 100 mg of one or more phenylsulfamic acids or salts thereof according to the present disclosure; and
b) one or more excipients.

[0320] A further example of disclosed compositions includes:

a) from about 0.1 mg to about 10 mg of one or more phenylsulfamic acids or salts thereof according to the present disclosure; and
b) one or more excipients.

[0321] The term "effective amount" as used herein means "an amount of one or more phenylsulfamic acids, effective at dosages and for periods of time necessary to achieve the desired or therapeutic result." An effective amount may vary according to factors known in the art, such as the disease state, age, sex, and weight of the human or animal being treated. Although particular dosage regimes may be described in examples herein, a person skilled in the art would appreciated that the dosage regime may be altered to provide optimum therapeutic response. Thus, it is not possible to specify an exact "effective amount." For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. In addition, the compositions of the present disclosure can be administered as frequently as necessary to achieve a therapeutic amount.

METHOD OF USE

[0322] The present disclosure relates to methods for regulating angiogenesis in a human comprising administering to a human one or more of the disclosed compounds.

[0323] One example of the disclosed methods includes a method for treating an angiogenesis regulated disorder in a subject, wherein the angiogenesis regulated disorder is an angiogenesis elevated disorder, and said disorder is chosen from diabetic retinopathy, macular degeneration, cancer, sickle cell anemia, sarcoid, syphilis, pseudoxanthoma elasticum, Paget's disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis/vitritis, mycobacterial infections, Lyme's disease, systemic lupus erythematosis, retinopathy of prematurity, Eales' disease, Behcet's disease, infections causing a retinitis or choroiditis, presumed ocular histoplasmosis, Best's disease, myopia, optic pits, Stargardt's disease, pars planitis, chronic retinal detachment, hyperviscosity syndrome, toxoplasmosis, trauma and post-laser complications, diseases associated with rubeosis, and proliferative vitreoretinopathy.

[0324] Another example of the disclosed methods includes a method for treating an angiogenesis regulated disorder in a subject, wherein the angiogenesis regulated disorder is an angiogenesis elevated disorder, and said disorder is chosen from inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, psoriasis, sarcoidosis, rheumatoid arthritis, hemangiomas, Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia, solid or blood borne tumors and acquired immune deficiency syndrome.

[0325] A further example of the disclosed methods includes a method for treating an angiogenesis regulated disorder in a subject wherein the angiogenesis regulated disorder is an angiogenesis reduced disorder and chosen from skeletal muscle and myocardial ischemia, stroke, coronary artery disease, peripheral vascular disease, coronary artery disease.

[0326] A yet further example of the disclosed methods includes a method of vascularizing ischemic tissue. As used herein, "ischemic tissue," means tissue that is deprived of adequate blood flow. Examples of ischemic tissue include tissue that lack adequate blood supply resulting from myocardial and cerebral infarctions, mesenteric or limb ischemia, or the result of a vascular occlusion or stenosis. In one example, the interruption of the supply of oxygenated blood may be caused by a vascular occlusion. Such vascular occlusion may be caused by arteriosclerosis, trauma, surgical procedures, disease, and/or other etiologies. Also included within the methods of treatment of the present disclosure is the treatment of skeletal muscle and myocardial ischemia, stroke, coronary artery disease, peripheral vascular disease, coronary artery disease.

[0327] A still further example of the disclosed methods includes a method of repairing tissue. As used herein, "repairing tissue" means promoting tissue repair, regeneration, growth, and/or maintenance including, wound repair or tissue engineering. One skilled in the art appreciates that new blood vessel formation is required for tissue repair. In turn, tissue may be damaged by, including traumatic injuries or conditions including arthritis, osteoporosis and other skeletal disorders, and burns. Tissue may also be damaged by injuries due to surgical procedures, irradiation, laceration, toxic chemicals, viral infection or bacterial infections, or bums. Tissue in need of repair also includes non-healing wounds. Examples of non-healing wounds include non-healing skin ulcers resulting from diabetic pathology; or fractures that do not heal readily.

[0328] The disclosed compounds are also suitable for use in effecting tissue repair in the context of guided tissue regeneration (GTR) procedures. Such procedures are currently used by those skilled in the arts to accelerate wound healing following invasive surgical procedures.

[0329] A yet still further example of the disclosed methods includes a method of promoting tissue repair characterized by enhanced tissue growth during the process of tissue engineering. As used herein, "tissue engineering" is defined as the creation, design, and fabrication of biological prosthetic devices, in combination with synthetic or natural materials, for the augmentation or replacement of body tissues and organs. Thus, the present methods may be used to augment the design and growth of human tissues outside the body for later implantation in the repair or replacement of diseased tissues. For example, antibodies may be useful in promoting the growth of skin graft replacements that are used as a therapy in the treatment of bums.

[0330] Other examples of the tissue engineering example of the disclosed methods includes in cell-containing or cell-free devices that induce the regeneration of functional human tissues when implanted at a site that requires regeneration. As discussed herein, biomaterial-guided tissue regeneration may be used to promote bone re-growth in, for example, periodontal disease. Thus, antibodies may be used to promote the growth of reconstituted tissues assembled into three-dimensional configurations at the site of a wound or other tissue in need of such repair.

[0331] A yet further example of the tissue engineering example of the disclosed methods, the compounds disclosed herein can be included in external or internal devices containing human tissues designed to replace the function of diseased internal tissues. This approach involves isolating cells from the body, placing them with structural matrices, and implanting the new system inside the body or using the system outside the body. For example, antibodies may be included in a cell-lined vascular graft to promote the growth of the cells contained in the graft. It is envisioned that the methods of the disclosure may be used to augment tissue repair, regeneration and engineering in products such as cartilage and bone, central nervous system tissues, muscle, liver, and pancreatic islet (insulin-producing) cells.

[0332] The present disclosure also relates to the use of the disclosed phenylsulfamic acids in the manufacture of a medicament for promoting the growth of skin graft replacements.

[0333] The present disclosure also relates to the use of the disclosed phenylsulfamic acids according to the present disclosure in the manufacture of a medicament for use in effecting tissue repair in the context of guided tissue regeneration (GTR) procedures.

[0334] The disclosed compounds can be used in the manufacture of one or more medicaments, examples of these medicaments are:

Medicaments for the treatment an angiogenesis regulated disorder in a subject, wherein the angiogenesis regulated disorder is an angiogenesis elevated disorder.

Medicaments for the treatment an angiogenesis regulated disorder in a subject, wherein the angiogenesis regulated disorder is an angiogenesis elevated disorder chosen from Crohn's disease and ulcerative colitis, psoriasis, sarcoidosis, rheumatoid arthritis, hemangiomas, Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia, solid or blood borne tumors and acquired immune deficiency syndrome.

Medicaments useful for the purposes of tissue engineering thereby inducing enhanced tissue growth.

Medicaments for the treatment an angiogenesis regulated disorder in a subject, wherein the angiogenesis regulated disorder is an angiogenesis reduced disorder.

PROCEDURES

Screening Assays using *in vitro* and *in vivo* models of angiogenesis

[0335] Antibodies of the disclosed compounds may be screened in angiogenesis assays that are known in the art. Such assays include *in vitro* assays that measure surrogates of blood vessel growth in cultured cells or formation of vascular structures from tissue explants and *in vivo* assays that measure blood vessel growth directly or indirectly (Auerbach,R., et al. (2003). Clin Chem 49, 32-40, Vailhe,B., et al. (2001). Lab Invest 81, 439-452).

1. *In vitro* models of angiogenesis

[0336] The *in vitro* models which are suitable for use in the present disclosure employ cultured endothelial cells or tissue explants and measure the effect of agents on "angiogenic" cell responses or on the formation of blood capillary-like structures. Examples of *in vitro* angiogenesis assays include endothelial cell migration and proliferation, capillary tube formation, endothelial sprouting, the aortic ring explant assay and the chick aortic arch assay.

2. *In vivo* models of angiogenesis

[0337] The *in vivo* agents or antibodies which are suitable for use in the present disclosure are administered locally or systemically in the presence or absence of growth factors (i.e. VEGF or angiopoietin 1) and new blood vessel growth is measured by direct observation or by measuring a surrogate marker such as hemoglobin content or a fluorescent indicator. Examples of *in vitro* angiogenesis assays include chick chorioallantoic membrane assay, the corneal angiogenesis assay, and the MATRIGEL™ plug assay.

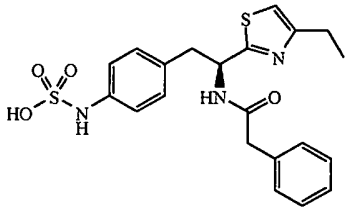
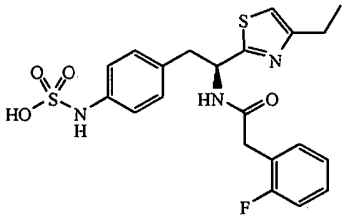
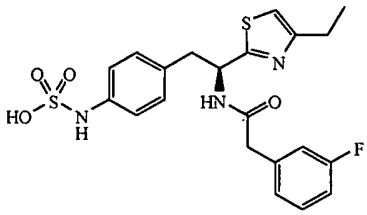
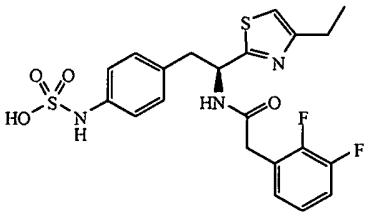
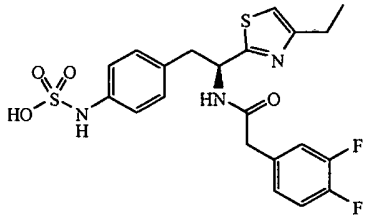
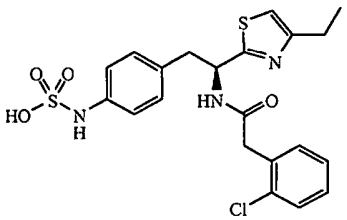
3. Procedures for Determining Vascularization of Ischemic Tissue.

[0338] Standard routine techniques are available to determine if a tissue is at risk of suffering ischemic damage from undesirable vascular occlusion. For example, in myocardial disease these methods include a variety of imaging techniques (e.g., radiotracer methodologies, x-ray, and MRI) and physiological tests. Therefore, induction of angiogenesis as an effective means of preventing or attenuating ischemia in tissues affected by or at risk of being affected by a vascular occlusion can be readily determined.

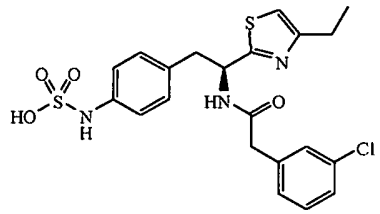
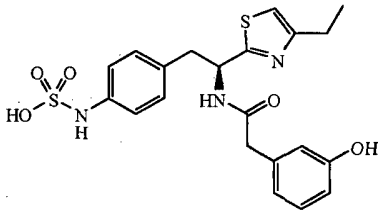
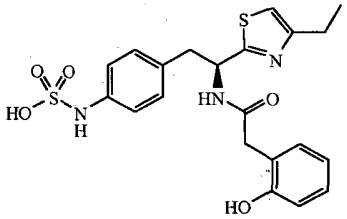
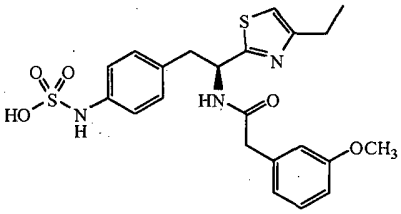
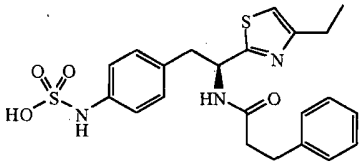
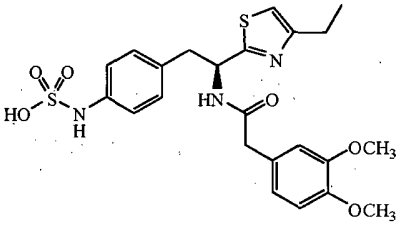
[0339] A person skilled in the art of using standard techniques can measure the vascularization of tissue. Examples of measuring vascularization in a subject include SPECT (single photon emission computed tomography); PET (positron emission tomography); MRI (magnetic resonance imaging); and combination thereof, by measuring blood flow to tissue before and after treatment. Angiography may be used as an assessment of macroscopic vascularity. Histologic evaluation may be used to quantify vascularity at the small vessel level. These and other techniques are discussed in Simons, et al., "Clinical trials in coronary angiogenesis," Circulation, 102, 73-86 (2000).

[0340] The following are examples of HPTPβ (IC_{50} μM) and PTP1B (IC_{50} μM) activity is listed herein below in Table A.

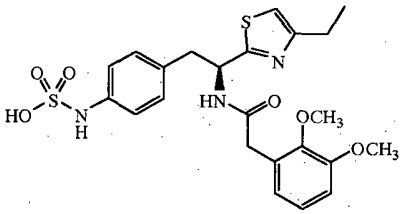
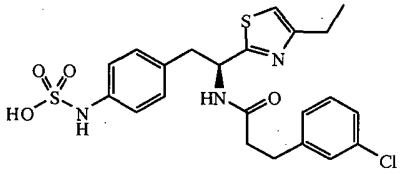
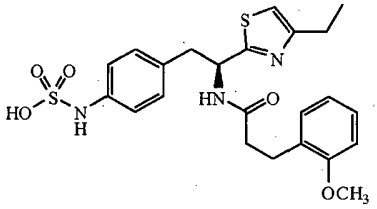
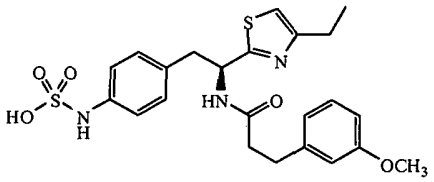
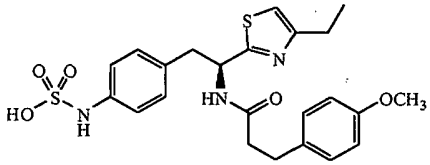
TABLE A

Compound	HPTPβ IC_{50} μM	PTP1B IC_{50} μM
 (*S*)-{4-[2-(4-Ethylthiazol-2-yl)-2-(phenylacetylamido)ethyl]-phenyl}sulfamic acid	0.05	22.9
 (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(2-fluorophenyl)acetamido)ethyl)phenyl-sulfamic acid	0.012	5.36
 (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(3-fluorophenyl)acetamido)ethyl)phenyl-sulfamic acid	0.0003	2.85
 (*S*)-4-(2-(2-(2,3-Difluorophenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid	0.028	5.36
 (*S*)-4-(2-(2-(3,4-Difluorophenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid	0.075	23.9
 (*S*)-4-(2-(2-(2-Chlorophenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid	0.056	22.8

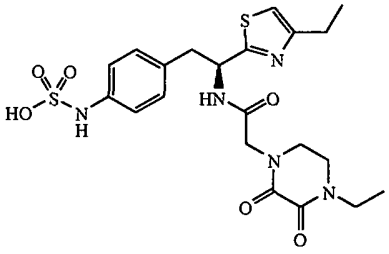
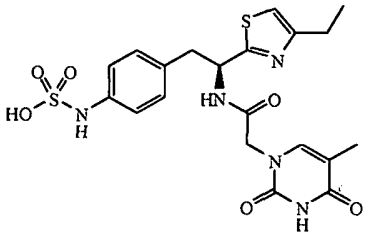
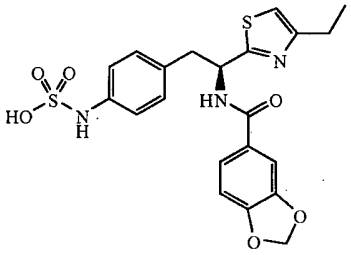
(continued)

Compound	HPTPβ IC_{50} μM	PTP1B IC_{50} μM
 (*S*)-4-(2-(2-(3-Chlorophenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid	0.033	13.6
 (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(3-hydroxyphenyl)acetamido)ethyl)phenyl-sulfamic acid	0.04	6.57
 (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(2-methoxyphenyl)acetamido)ethyl)phenyl-sulfamic acid	0.014	11.7
 (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(3-methoxyphenyl)acetamido)ethyl)phenyl-sulfamic acid	0.008	4.05
 (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-phenylpropanamido)ethyl)phenylsulfamic acid	0.002	10.4
 (*S*)-4-(2-(2-(3,4-Dimethoxyphenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)-phenylsulfamic acid	0.028	15.5

(continued)

Compound	HPTPβ IC_{50} μM	PTP1B IC_{50} μM
 (*S*)-4-(2-(2-(2,3-Dimethoxyphenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)-phenylsulfamic acid	0.037	25.4
 (*S*)-4-(2-(3-(3-Chlorophenyl)propanamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid	0.0002	15.3
 (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-(2-methoxyphenyl)propanamido)ethyl)phenyl-sulfamic acid	0.003	16.9
 (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-(3-methoxyphenyl)propanamido)ethyl)phenyl-sulfamic acid	0.01	20.6
 (*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-(4-methoxyphenyl)propanamido)ethyl)phenyl-sulfamic acid	0.006	16.0

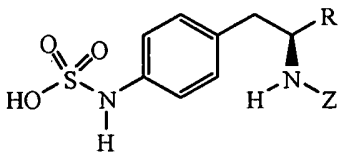
(continued)

Compound	HPTPβ IC_{50} μM	PTP1B IC_{50} μM
 (*S*)-4-{2-[2-(4-Ethyl-2,3-dioxopiperazin-1-yl)acetamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid	0.002	0.53
 (*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetamido]ethyl}phenylsulfamic acid	0.002	0.254
 (*S*)-4-[2-(Benzo[*d*][1,3]dioxole-5-carboxamido)-2-(4-ethylthiazol-2-yl)ethyl]phenylsulfamic acid	0.042	19

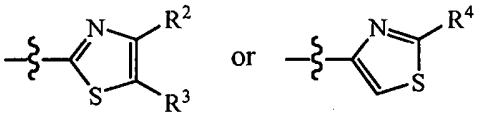
[0341] While particular embodiments of the present disclosure have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made.

Claims

1. A compound having the formula:



wherein R is a substituted or unsubstituted thiazolyl unit having the formula:



R^2 and R^3 are each independently chosen from:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;
iii) substituted or unsubstituted phenyl; or
iv) substituted or unsubstituted 5-member or 6-member heteroaryl ring, wherein at least one ring atom is a heteroatom chosen from nitrogen, oxygen, and sulfur;

or
R^2 and R^3 can be taken together to form a saturated or unsaturated ring having from 5 to 7 atoms;
R^4 is a unit chosen from:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;
iii) substituted or unsubstituted phenyl; or
iv) substituted or unsubstituted 5-member or 6-member heteroaryl ring, wherein at least one ring atom is a heteroatom chosen from nitrogen, oxygen, and sulfur;

said substitutions for R, R^2, R^3, and R^4 are independently chosen from one or more C_1-C_6 linear, branched, or cyclic alkyl, $-N(R^{16})_2$, $-OR^{16}$, halogen, or
cyano units; each R^{16} is independently hydrogen, C_1-C_4 linear, branched, or cyclic alkyl;
Z is a unit having the formula:

$$—(L)_n—R^1$$

R^1 is chosen from:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;
iii) substituted or unsubstituted C_6 aryl, wherein each substitution is independently chosen from halogen, C_1-C_4 linear, branched, or cyclic alkyl, $-OR^{11}$, -CN, $-N(R^{11})_2$, $-CO_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NO_2$, and $-SO_2R^{11}$, each R^{11} is independently hydrogen, substituted or unsubstituted C_1-C_4 linear, branched, or cyclic alkyl, alkenyl, or alkynyl; substituted or unsubstituted phenyl or benzyl; or two R^{11} units can be taken together to form a ring comprising from 3-7 atoms;
iv) substituted or unsubstituted C1-C_9 heterocyclic rings, wherein the heteroatoms are chosen from nitrogen, oxygen, and sulfur; or
v) substituted or unsubstituted C_1-C_9 heteroaryl rings, wherein at least one ring atom is a heteroatom selected from nitrogen, oxygen or sulfur;

L is a linking unit chosen from:

i) $-C(O)NH[C(R^{5a}R^{5b})]_w-$;
ii) $-C(O)[C(R^{6a}R^{6b})])_x-$;
iii) $-C(O)[C(R^{7a}R^{7b})]_yC(O)-$;
iv) $-SO_2[C(R^{8a}R^{8b})]_z-$;

R^{5a}, R^{5b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{8a}, and R^{8b} are each independently:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_4 linear or branched alkyl;

iii) substituted or unsubstituted aryl;
iv) substituted or unsubstituted heterocyclic rings; or
v) substituted or unsubstituted C_1-C_9 heteroaryl;

said substitutions for R^1, R^{5a}, R^{5b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{8a}, and R^{8b} are independently chosen from C_1-C_6 linear, branched, or cyclic alkyl, phenyl and benzyl, C_1-C_9 heteroaryl, -C(O)R^9, and -NHC(O)R^9; R^9 is C_1-C_6 linear and branched alkyl; C_1-C_6 linear and branched alkoxy; or -NHCH$_2$C(O)R^{10}; R^{10} is chosen from hydrogen, methyl, ethyl, and *tert*-butyl;
the index n is 0 or 1; the indices w, x, y, and z are each independently from 1 to 4;
or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, wherein R^2 and R^3 are each hydrogen or substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl.

3. A compound according to Claim 1, wherein R^2 is substituted or unsubstituted phenyl and R^3 is hydrogen, or wherein R^2 is substituted or unsubstituted heteroaryl and R^3 is hydrogen.

4. A compound according to Claim 1, wherein R^4 is hydrogen or substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl, or wherein R^4 is substituted or unsubstituted phenyl and R^3 is hydrogen.

5. A compound according to Claim 1, wherein R^4 is substituted or unsubstituted heteroaryl.

6. A compound according to any of Claims 1 to 5, wherein L has the formula:

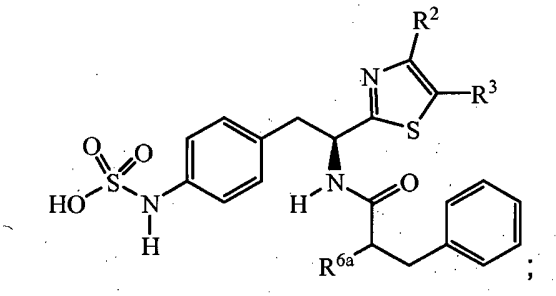
$$-C(O)[C(R^{6a}R^{6b})_x-$$

R^{6a} is hydrogen, substituted or unsubstituted phenyl, and substituted or unsubstituted heteroaryl; the index x is 1 or 2.

7. A compound according to Claim 6, wherein R^1 is chosen from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 3,4-dimethoxyphenyl, and 3,5-dimethoxyphenyl.

8. A compound according to Claim 1, having the formula:

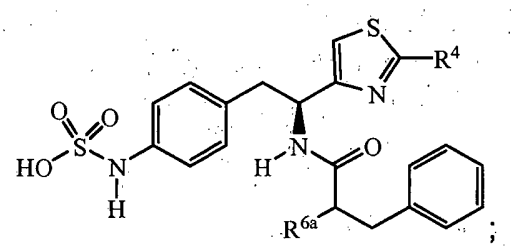
i)



;

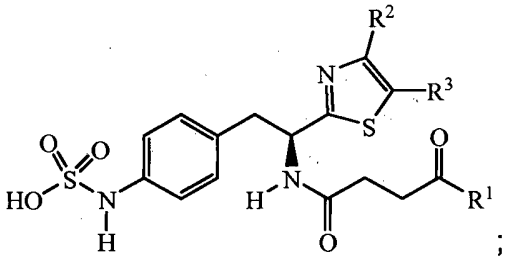
wherein R^2 is methyl or ethyl, R^3 is hydrogen, R^{6a} is chosen from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 3,4-dimethoxyphenyl, and 3,5-dimethoxyphenyl;

ii)



wherein R^4 is methyl, ethyl, phenyl, or thiophene-2-yl, R^{6a} is chosen from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl,3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 3,4-dimethoxyphenyl, and 3,5-dimethoxyphenyl;

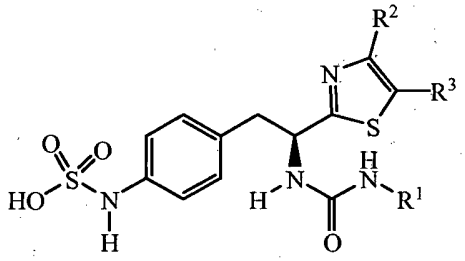
iii)



wherein R^2 is chosen from methyl, ethyl, phenyl, and thiophene-2-yl, R^3 is hydrogen or methyl; R^1 is chosen from phenyl, thiophene-2-yl, thiophene-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, and isoxazol-3-yl;

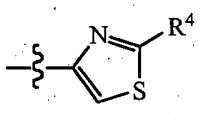
or

iv)



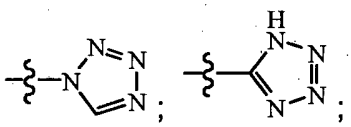
wherein R^2 and R^3 are each independently hydrogen, methyl or ethyl; R^1 is chosen from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 3,4-dimethoxyphenyl, and 3,5-dimethoxyphenyl.

9. The compound according to Claim 1, wherein R is:

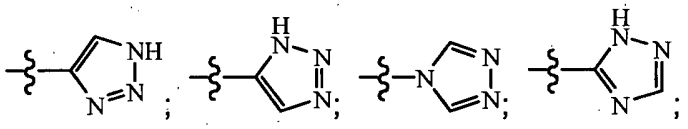


and wherein in the Z units R^1 is a substituted or unsubstituted heteroaryl unit chosen from:

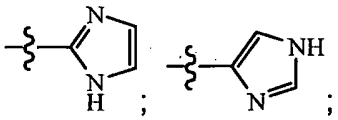
i) 1,2,3,4-tetrazol-1-yl and 1,2,3,4-tetrazol-5-yl having the respective formulae:



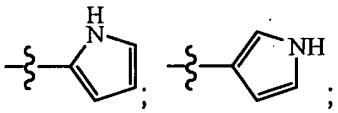
ii) [1,2,3]triazol-4-yl, [1,2,3]triazol-5-yl, [1,2,4]triazol-4-yl, and [1,2,4]triazol-5-yl having the respective formulae:



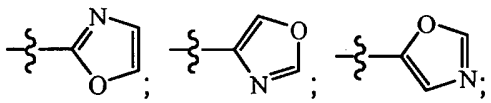
iii) imidazol-2-yl and imidazol-4-yl having the respective formulae:



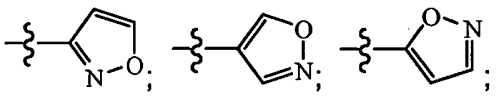
iv) pyrrol-2-yl and pyrrol-3-yl having the respective formulae:



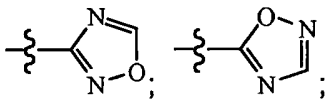
v) oxazol-2-yl, oxazol-4-yl, and oxazol-5-yl having the respective formulae:



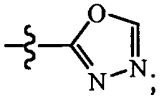
vi) isoxazol-3-yl, isoxazol-4-yl, and isoxazol-5-yl having the respective formulae:



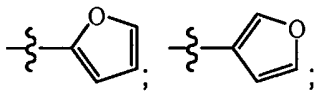
vii) [1,2,4]oxadiazol-3-yl and [1,2,4]oxadiazol-5-yl having the respective formulae:



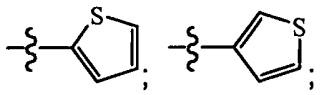
viii) [1,3,4]oxadiazol-2-yl having the formula:



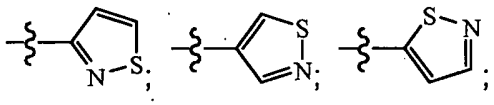
ix) furan-2-yl and furan-3-yl having the respective formulae:



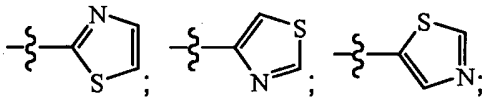
x) thiophen-2-yl and thiophen-3-yl having the respective formulae:



xi) isothiazol-3-yl, isothiazol-4-yl and isothiazol-5-yl having the respective formulae:

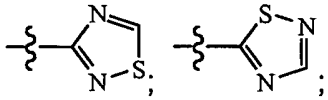


xii) thiazol-2-yl, thiazol-4-yl and thiazol-5-yl having the respective formulae:



and

xiii) [1,2,4]thiadiazol-3-yl and [1,2,4]thiadiazol-5-yl having the respective formulae:



wherein said heteroaryl unit substitutions are chosen from C_1-C_6 linear, branched, and cyclic alkyl, substituted or unsubstituted phenyl and benzyl, substituted or unsubstituted C_1-C_9 heteroaryl, -C(O)R^9, and -NHC(O)R^9; R^9 is chosen from C_1-C_6 linear and branched alkyl; C_1-C_6 linear and branched alkoxy; or -$NHCH_2C(O)R^{10}$; R^{10} is chosen from hydrogen, methyl, ethyl, and *tert*-butyl ;

R^4 is a unit chosen from:

i) hydrogen;
ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;
iii) substituted or unsubstituted phenyl; and
iv) substituted or unsubstituted 5-member or 6-member heteroaryl, wherein at least one ring atom is a heteroatom chosen from nitrogen, oxygen, or sulfur.

10. A compound according to Claim 9, wherein Z is chosen from 4-(methoxy-carbonyl)thiazol-5-yl, 4-[(2-methoxy-2-oxoethyl)carbamoyl]thiazol-5-yl, 5-[1-*N*-(2-methoxy-2-oxoethyl)-1-*H*-indol-3-yl]oxazol-2-yl, 5-(2-methoxyphenyl)oxazol-2-yl, 5-[(*S*)-1-(*tert*-butoxycarbonyl)-2-phenylethyl]oxazol-2-yl, 5-[4-(methyl-carboxy)phenyl]oxazol-2-yl, 5-(3-methoxybenzyl)oxazol-2-yl, 5-(4-phenyl)-oxazol-2-yl, 5-(2-methoxyphenyl)thiazol-2-yl, 5-(3-methoxyphenyl)thiazol-2-yl, 5-(4-fluorophenyl)thiazol-2-yl, 5-(2,4-difluorophenyl)thiazol-2-yl, 5-(3-methoxy-benzyl)thiazol-2-yl, 4-(3-methoxyphenyl)thiazol-2-yl, and 4-(4-fluorophenyl)-thiazol-2-yl.

11. A compound according to Claim 1, chosen from:

(*S*)-{4-[2-(4-Ethylthiazol-2-yl)-2-phenylacetylaminoethyl]-phenyl}sulfamic acid;

(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(2-fluorophenyl)acetamido)ethyl)phenyl-sulfamic acid;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(3-fluorophenyl)acetamido)ethyl)phenyl-sulfamic acid;
(*S*)-4-(2-(2-(2,3-Difluorophenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid;
(*S*)-4-(2-(2-(3,4-Difluorophenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid;
(*S*)-4-(2-(2-(2-Chlorophenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid;
(*S*)-4-(2-(2-(3-Chlorophenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(3-hydroxyphenyl)acetamido)ethyl)phenyl-sulfamic acid;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(2-methoxyphenyl)acetamido)ethyl)phenyl-sulfamic acid;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(3-methoxyphenyl)acetamido)ethyl)phenyl-sulfamic acid;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-phenylpropanamido)ethyl)phenylsulfamic acid;
(*S*)-4-(2-(2-(3,4-Dimethoxyphenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)-phenylsulfamic acid;
(*S*)-4-(2-(2-(2,3-Dimethoxyphenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)-phenylsulfamic acid;
(*S*)-4-(2-(3-(3-Chlorophenyl)propanamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-(2-methoxyphenyl)propanamido)ethyl)phenyl-sulfamic acid;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-(3-methoxyphenyl)propanamido)ethyl)phenyl-sulfamic acid;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-(4-methoxyphenyl)propanamido)ethyl)phenyl-sulfamic acid;
(*S*)-4-{2-[2-(4-Ethyl-2,3-dioxopiperazin-1-yl)acetamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid;
(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetamido]ethyl}phenyl-sulfamic acid;
(*S*)-4-[2-(Benzo[*d*][1,3]dioxole-5-carboxamido)-2-(4-ethylthiazol-2-yl)ethyl]-phenylsulfamic acid;
4-((*S*)-2-(2-(2-Chlorophenyl)acetamido)-2-(2-(thiophene2-yl)thiazol-4-yl)ethyl)phenylsulfamic acid;
4-((*S*)-2-(2-(3-Methoxyphenyl)acetamido)-2-(2-(thiophene2-yl)thiazol-4-yl)ethyl)-phenylsulfamic acid;
4-{(*S*)-2-(3-Phenylpropanamido)-2-[2-(thiophene2-yl)thiazol-4-yl]ethyl}phenyl-sulfamic acid;
4-{(*S*)-2-(3-(3-Chlorophenyl)propanamido)-2-[2-(thiophene2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;
4-{(*S*)-2-[2-(3-Fluorophenyl)acetamido]-2-[2-(thiophene2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;
(*S*)-4-{2-[2-(2,5-Dimethylthiazol-4-yl)acetamido]-2-(4-ethylthiazol-2-yl]ethyl}-phenylsulfamic acid;
(*S*)-4-{2-[2-(2,4-Dimethylthiazol-5-yl)acetamido]-2-(4-methylthiazol-2-ylethyl}phenylsulfamic acid;
(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[3-(thiazol-2-yl)propanamido]ethyl}phenyl-sulfamic acid;
(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(4-ethylthiazol-2-yl)acetamido]ethyl}-phenyl-sulfamic acid;
(*S*)-4-{2-[2-(3-Methyl-1,2,4-oxadiazol-5-yl)acetamido]-2-(2-phenylthiazol-4-yl)ethyl}phenylsulfamic acid;
4-{(*S*)-2-[2-(4-Ethyl-2,3-dioxopiperazin-1-yl)acetamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;
(*S*)-4-(2-(2,3-Diphenylpropanamido)-2-(4-ethylthiazol-2-yl)ethyl)phenylsulfamic acid;
(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(2-methoxyphenyl)-3-phenylpropanamido]-ethyl)phenylsulfamic acid;
(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(3-fluorophenyl)-3-phenylpropanamido]-ethyl}phenylsulfamic acid;
(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(3-methoxyphenyl)-3-phenylpropanamido]-ethyl}phenylsulfamic acid;
4-{(*S*)-2-(4-Ethylthiazol-2-yl)-2-[2-(3-methyl-1,2,4-oxadiazol-5-yl)-3-phenylpropanamido]ethyl}phenylsulfamic acid;
(*S*)-4-[2-(4-Ethylthiazol-2-yl)-2-(4-oxo-4-phenylbutanamido)-ethyl]phenylsulfamic acid;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(5-methyl-4-oxohexanamido)ethyl)phenyl-sulfamic acid;
(*S*)-4-{2-[4-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-4-oxobutanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenyl-sulfamic acid;
(*S*)-4-{2-[4-(2,3-Dimethoxyphenyl)-4-oxobutanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid;
(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[4-oxo-4-(pyridin-2-yl)butanamido]ethyl}-phenylsulfamic acid;
(*S*)-4-{2-[4-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-4-oxobutanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid;
(*S*)-4-[2-(4-*tert*-Butoxy-4-oxobutanamido)-2-(4-ethylthiazol-2-yl)ethyl]phenyl-sulfamic acid;
(*S*)-4-[2-(4-Ethoxy-4-oxobutanamido)-2-(4-ethylthiazol-2-yl)ethyl]phenylsulfamic acid;
(*S*)-4-(2-(3-Benzylureido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid;
4-{(*S*)-2-(3-Benzylureido)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenyl-sulfamic acid;
{4-(*S*)-[2-Phenylmethanesulfonylamino-2-(2-thiophen-2-ylthiazol-4-yl)ethyl]phenyl}sulfamic acid;
4-{(*S*)-2-[(2-Methylthiazol-4-yl)methylsulfonamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;
{4-(*S*)-[2-Phenylmethanesulfonylamino-2-(2-ethylthiazol-4-yl)ethyl]phenyl}-sulfamic acid;
{4-(*S*)-[2-(3-Methoxyphenyl)methanesulfonylamino-2-(2-ethylthiazol-4-yl)ethyl]phenyl}sulfamic acid;
(*S*)-4-{[1-(2-Ethylthiazol-4-yl)-2-(4-sulfoaminophenyl)ethylsulfamoyl]methyl}-benzoic acid methyl ester;
(*S*)-4-[2-(2-Ethylthiazol-4-yl)-2-(1-methyl-1*H*-imidazol-4-sulfonamido)ethyl]-phenylsulfamic acid;
4-{(*S*)-2-[2-(Thiophen-2-yl)thiazol-4-yl]-2-(2,2,2-trifluoroethylsulfonamido)-ethyl}phenylsulfamic acid;
{4-(*S*)-[2-(Phenylethanesulfonylamino)-2-(2thiophen-2-ylthiazol-4-yl)ethyl]-phenyl}sulfamic acid;

{4-(*S*)-[3-(Phenylpropanesulfonylamino)-2-(2thiophen-2-ylthiazol-4-yl)ethyl]-phenyl}sulfamic acid;
(*S*)-{4-[2-(4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-sulfonylamino)-2-(2-thiophen-2-ylthiazol-4-yl)ethyl]phenyl}sulfamic acid;
4-{(*S*)-2-(4-Acetamidophenylsulfonamido)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;
4-{(*S*)-2-(2-cyclopropylthiazol-4-yl)-2-[4-(3-methoxyphenyl)-thiazol-2-ylamino]ethyl}phenylsulfamic acid;
(*S*)-4-(2-(4-((2-Methoxy-2-oxoethyl)carbamoyl)thiazole-5-ylamino)2-(2-ethylthiazole-4-yl)ethyl)phenylsulfamic acid;
4-((*S*)-2-(5-(1-*N*-(2-Methoxy-2-oxoethyl)-1-*H*-indol-3-yl)oxazole-2-ylamino)-2-(2-methylthiazol-4-yl)ethyl))phenylsulfamic acid;
4-((*S*)-2-(5-(2-Methoxyphenyl)oxazol-2-ylamino)-2-(2-methylthiazol-4-yl)ethyl)phenylsulfamic acid;
4-((*S*)-2-(5-((*S*)-1-(tert-Butoxycarbonyl)-2-phenylethyl)oxazole-2-ylamino)-2-(2-methylthiazole-4-yl)ethyl)phenylsulfamic acid;
(*S*)-4-(2-(5-(4-Methoxycarbonyl)phenyl)oxazole-2-ylamino)2-(2-methylthiazole-4-yl)ethyl)phenylsulfamic acid;
(*S*)-4-(2-(5-(3-Methoxybenzyl)oxazole-2-ylamino)-2-(2-methylthiazole-4-yl)ethyl)phenylsulfamic acid;
(*S*)-4-(2-(2-Methylthiazole-4-yl)2-(5-phenyloxazole-2-ylamino)ethyl)phenyl-sulfamic acid;
4-((*S*)-2-(2-Cyclopropylthiazol-4-yl)-2-(4-(3-methoxyphenyl)thiazol-2-ylamino)ethyl)phenylsulfamic acid;
(*S*)-4-(2-(2-cyclopropylthiazol-4-yl)-2-(4-(4-fluorophenyl)thiazol-2-ylamino)ethyl)phenylsulfamic acid;
4-((*S*)-2-(2-cyclopropylthiazol-4-yl)-2-(4-(2-methoxyphenyl)thiazol-2-ylamino)ethyl)phenylsulfamic acid;
4-((*S*)-2-(2-cyclopropylthiazol-4-yl)-2-(4-(2,4-difluorophenyl)thiazol-2-ylamino)ethyl)phenylsulfamic acid;
(*S*)-4-(2-(4-(3-methoxybenzyl)thiazol-2-ylamino)-2-(2-cyclopropylthiazol-4-yl)ethyl)phenylsulfamic acid;
(*S*)-{5-[1-(2-Ethylthiazol-4-yl)-2-(4-sulfoaminophenyl)ethylamino]-2-methyl-2H-[1,2,4]triazole-3-yl}carbamic acid methyl ester;
4-{(S)-2-[4-(2-Methoxyphenyl)thiazol-2-ylamino)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;
4-{(S)-2-[5-(3-Methoxyphenyl)oxazole-2-ylamino]-2-(2-phenylthiazole-4-yl)ethyl}phenylsulfamic acid;
4-{(S)-2-[4-(2,4-Difluorophenyl)thiazol-2-ylamino]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;
(S)-4-{2-[4-(Ethoxycarbonyl)thiazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylsulfamic acid;
(S)-4-{2-[4-(2-Ethoxy-2-oxoethyl)thiazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylsulfamic acid;
(*S*)-4-{2-[4-(4-Acetamidophenyl)thiazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylsulfamic acid;
(S)-4-[2-(4-Phenylthiazol-2-ylamino)-2-(2-phenylthiazol-4-yl)ethyl]phenyl-sulfamic acid;
(*S*)-4-{2-[4-(4-(Methoxycarbonyl)phenyl)thiazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylsulfamic acid;
4-{(S)-2-[4-(Ethoxycarbonyl)thiazol-2-ylamino]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;
(*S*)-4-[2-(4-(Methoxycarbonyl)thiazol-5-ylamino)-2-(2-phenylthiazole-4-yl)ethyl]phenylsulfamic acid;
(*S*)-4-[2-(5-Phenyloxazole-2-ylamino)]-2-(2-phenylthiazole-4-yl)phenylsulfamic acid;
(*S*)-4-{2-[5-(4-Acetamidophenyl)oxazole-2-ylamino]-2-(2-phenylthiazole-4-yl)ethyl}phenylsufamic acid;
4-((*S*)-2-(5-(2,4-Difluorophenyl)oxazole-2-ylamino)-2-(2-phenylthiazole-4-yl)ethyl)phenylsulfamic acid;
4-{(*S*)-2-[5-(3-Methoxyphenyl)oxazol-2-ylamino]-2-[(2-thiophen-2-yl)thiazole-4-yl]ethyl}phenylsulfamic acid;
(*S*)-4-[2-(4,6-Dimethylpyrimidene-2-ylamino)-2-(2-methylthiazole-4-yl)ethyl]phenylsulfamic acid; and
(*S*)-4-[2-(4-Hydroxy-6-methylpyrimidine-2-ylamino)-2-(2-methylthiazole-4-yl)ethyl]phenylsulfamic acid.

12. The compound according to any of Claims 1-11, wherein the compounds are salts comprising anions chosen from chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, and citrate, or cations chosen from sodium, lithium, potassium, calcium, magnesium, and bismuth.

13. The use of a compound according to any of Claims 1-12, for making a medicament for treating a disease chosen from sickle cell anemia, sarcoid, syphilis, pseudoxanthoma elasticum, Paget's disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis/vitritis, mycobacterial infections, Lyme's disease, systemic lupus erythematosis, retinopathy of prematurity, Eales' disease, Behcet's disease, infections causing a retinitis or choroiditis, presumed ocular histoplasmosis, Best's disease, myopia, optic pits, Stargardt's disease, pars planitis, chronic retinal detachment, hyperviscosity syndrome, toxoplasmosis, trauma and post-laser complications, diseases associated with rubeosis, psoriasis, sarcoidosis, rheumatoid arthritis, hemangiomas, Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia, solid or blood borne tumors, acquired immune deficiency syndrome, skeletal muscle and myocardial ischemia, stroke, coronary artery disease, peripheral vascular disease.

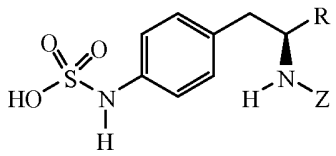
14. The use of a compound according to any of Claims 1-12, for making a medicament for regulating angiogenesis, vascularizing ischemic tissue, promoting the growth of skin graft replacements, or promoting tissue repair in the context of guided tissue regeneration (GTR) process.

15. Compound according to any of Claims 1-12 for use for treating a condition chosen from sickle cell anemia, sarcoid, syphilis, pseudoxanthoma elasticum, Paget's disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis/vitritis, mycobacterial infections, Lyme's disease, systemic lupus erythematosis, retinopathy of prematurity, Eales' disease, Behcet's disease, infections causing a retinitis or choroiditis, presumed ocular histoplasmosis, Best's disease, myopia, optic pits, Stargardt's disease, pars planitis, chronic retinal detachment, hyperviscosity syndrome, toxoplasmosis, trauma and post-laser complications, diseases associated with rubeosis, and proliferative vitreoretinopathy, proliferative vitroeretinopathy, psoriasis, sarcoidosis, rheumatoid arthritis, hemangiomas, Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia, solid or blood borne tumors, acquired immune deficiency syndrome, skeletal muscle and myocardial ischemia, stroke, coronary artery disease, peripheral vascular disease

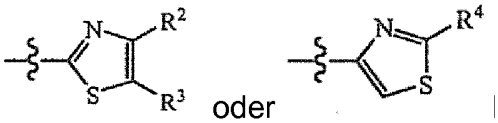
16. Compound according to any of Claims 1-12 for use for regulating angiogenesis, vascularizing ischemic tissue, promoting the growth of skin graft replacements, or promoting tissue repair in the context of guided tissue regeneration (GTR) process.

Patentansprüche

1. Verbindung mit der Formel:



wobei R eine substituierte oder unsubstituierte Thiazolyl-Einheit ist, die die Formel:



hat;
R^2 und R^3 jeweils unabhängig ausgewählt sind aus:

i) Wasserstoff;
ii) substituiertem oder unsubstituiertem linearem, verzweigtem oder zyklischem C_1-C_6 Alkyl;
iii) substituiertem oder unsubstituiertem Phenyl; oder
iv) substituiertem oder unsubstituiertem Heteroarylring mit 5 oder 6 Ringatomen, wobei mindestens ein Ringatom ein Heteroatom ist, das ausgewählt ist aus Stickstoff, Sauerstoff, und Schwefel;

oder
R^2 und R^3 zusammen genommen werden können, um einen gesättigten oder ungesättigten Ring zu bilden, der 5 bis 7 Atome hat;
R^4 eine Einheit ist, die ausgewählt ist aus:

i) Wasserstoff;
ii) substituiertem oder unsubstituiertem linearem, verzweigtem, oder zyklischem C_1-C_6 Alkyl;
iii) substituiertem oder unsubstituiertem Phenyl; oder
iv) substituiertem oder unsubstituiertem Heteroarylring mit 5 oder 6 Ringatomen, wobei mindestens ein Ringatom ein Heteroatom ist, das ausgewählt ist aus Stickstoff, Sauerstoff, und Schwefel;

wobei die Substitutionen für R, R^2, R^3, und R^4 unabhängig ausgewählt sind aus einem oder mehreren aus linearem, verzweigtem, oder zyklischem C_1-C_6 Alkyl, -$N(R^{16})_2$, -OR^{16}, Halogen, oder Cyano-Einheiten; jedes R^{16} unabhängig Wasserstoff, lineares, verzweigtes, oder zyklisches C_1-C_4 Alkyl ist;

Z eine Einheit mit der Formel

$$—(L)_n—R^1$$

ist
R^1 ausgewählt ist aus:

i) Wasserstoff;
ii) substituiertem oder unsubstituiertem linearem, verzweigtem oder zyklischem C_1-C_6 Alkyl;
iii) substituiertem oder unsubstituiertem C_6 Aryl, wobei jede Substitution unabhängig ausgewählt ist aus Halogen, linearem, verzweigtem, oder zyklischem C_1-C_4 Alkyl, -OR^{11}, -CN, -$N(R^{11})_2$, -CO_2R^{11}, -$C(O)N(R^{11})_2$, -$NR^{11}C(O)R^{11}$, -NO_2, und -SO_2R^{11}, jedes R^{11} unabhängig Wasserstoff, substituiertes oder unsubstituiertes lineares, verzweigtes, oder zyklisches C_1-C_4 Alkyl, Alkenyl, oder Alkynyl; substituiertes oder unsubstituiertes Phenyl oder Benzyl ist; oder zwei R^{11}-Einheiten zusammen genommen werden können, um einen Ring zu bilden, der 3 - 7 Atome aufweist;
iv) substituierten oder unsubstituierten heterozyklischen C_1-C_9 Ringen, wobei die Heteroatome ausgewählt sind aus Stickstoff, Sauerstoff, und Schwefel; oder
v) substituierten oder unsubstituierten C_1-C_9 Heteroarylringen, wobei mindestens ein Ringatom eine Heteroatom ist, das ausgewählt ist aus Stickstoff, Sauerstoff, oder Schwefel;

L eine Verbindungseinheit ist, die ausgewählt ist aus:

i) -$C(O)NH[C(R^{5a}R^{5b})]_w$-;
ii) -$C(O)[C(R^{6a}R^{6b})]_x$-;
iii) -$C(O)[C(R^{7a}R^{7b})]_yC(O)$-;
iv) -$SO_2[C(R^{8a}R^{8b})]_z$-;

R^{5a}, R^{5b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{8a}, und R^{8b} alle jeweils unabhängig:

i) Wasserstoff;
ii) substituiertes oder unsubstituiertes lineares oder verzweigtes C_1-C_4 Alkyl;
iii) substituiertes oder unsubstituiertes Aryl;
iv) substituierte oder unsubstituierte heterozyklische Ringe; oder
v) substituiertes oder unsubstituiertes C_1-C_9 Heteroaryl sind;

wobei die Substitutionen für R^1, R^{5a}, R^{5b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{8a}, und R^{8b} unabhängig ausgewählt sind aus linearem, verzweigtem, oder zyklischem C_1-C_6 Alkyl, Phenyl und Benzyl, C_1-C_9 Heteroaryl, -$C(O)R^9$, und -$NHC(O)R^9$; R^9 lineares und verzweigtes C_1-C_6Alkyl; lineares und verzweigtes C_1-C_6Alkoxy; oder -$NHCH_2C(O)R^{10}$ ist; R^{10} ausgewählt ist aus Wasserstoff, Methyl, Ethyl, und *tert*-Butyl;
der Index n 0 oder 1 ist; die Indizes w, x, y, und z alle unabhängig von 1 bis 4 sind;
oder ein pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1, wobei R^2 und R^3 jeweils Wasserstoff oder substituiertes oder unsubstituiertes lineares, verzweigtes oder zyklisches C_1-C_6 Alkyl sind.

3. Verbindung nach Anspruch 1, wobei R^2 substituiertes oder unsubstituiertes Phenyl und R^3 Wasserstoff ist, oder wobei R^2 substituiertes oder unsubstituiertes Heteroaryl und R^3 Wasserstoff ist.

4. Verbindung nach Anspruch 1, wobei R^4 Wasserstoff oder substituiertes oder unsubstituiertes lineares, verzweigtes oder zyklisches C_1-C_6 Alkyl ist, oder wobei R^4 substituiertes oder unsubstituiertes Phenyl und R^3 Wasserstoff ist.

5. Verbindung nach Anspruch 1, wobei R^4 substituiertes oder unsubstituiertes Heteroaryl ist.

6. Verbindung nach einem der Ansprüche 1 bis 5, wobei L die Formel:

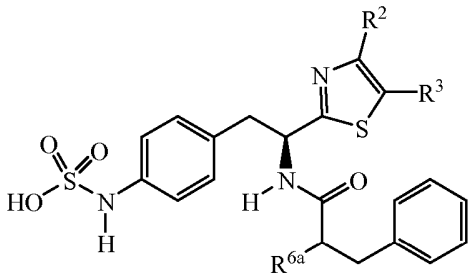
-$C(O)[C(R^{6a}R^{6b})]_x$- hat

R^{6a} Wasserstoff, substituiertes oder unsubstituiertes Phenyl, und substituiertes oder unsubstituiertes Heteroaryl ist; der Index x 1 oder 2 ist.

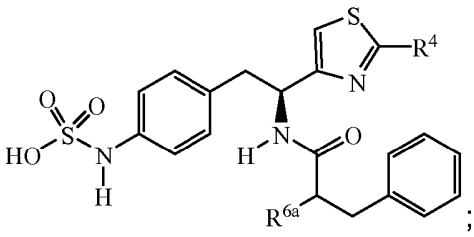
7. Verbindung nach Anspruch 6, wobei R^1 ausgewählt ist aus Phenyl, 2-Fluorphenyl, 3-Fluorphenyl, 4-Fluorphenyl, 2,3-Difluorphenyl, 3,4-Difluorphenyl, 3,5-Difluorphenyl, 2-Chlorphenyl, 3-Chlorphenyl, 4-Chlorphenyl, 2,3-Dichlorphenyl, 3,4-Dichlorphenyl, 3,5-Dichlorphenyl, 2-Hydroxyphenyl, 3-Hydroxyphenyl, 4-Hydroxyphenyl, 2-Methoxyphenyl, 3-Methoxyphenyl, 4-Methoxyphenyl, 2,3-Dimethoxyphenyl, 3,4-Dimethoxyphenyl, und 3,5-Dimethoxyphenyl.

8. Verbindung nach Anspruch 1, welche die Formel:

i)

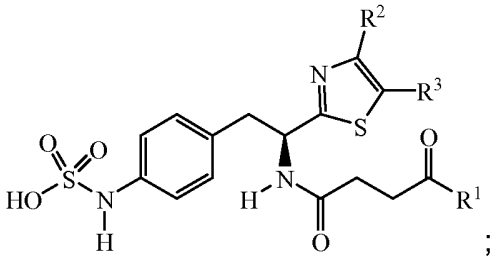


hat;
wobei R^2 Methyl oder Ethyl ist, R^3 Wasserstoff ist, R^{6a} ausgewählt ist aus Phenyl, 2-Fluorphenyl, 3-Fluorphenyl, 4-Fluorphenyl, 2,3-Difluorphenyl, 3,4-Difluorphenyl, 3,5-Difluorphenyl, 2-Chlorphenyl, 3-Chlorphenyl, 4-Chlorphenyl, 2,3-Dichlorphenyl, 3,4-Dichlorphenyl, 3,5-Dichlorphenyl, 2-Hydroxyphenyl, 3-Hydroxyphenyl, 4-Hydroxyphenyl, 2-Methoxyphenyl, 3-Methoxyphenyl, 4-Methoxyphenyl, 2,3-Dimethoxyphenyl, 3,4-Dimethoxyphenyl, und 3,5-Dimethoxyphenyl;
ii)



;

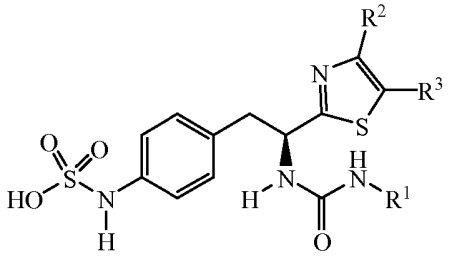
wobei R^4 Methyl, Ethyl, Phenyl, oder Thiophen-2-yl ist, R^{6a} ausgewählt ist aus Phenyl, 2-Fluorphenyl, 3-Fluorphenyl, 4-Fluorphenyl, 2,3-Difluorphenyl, 3,4-Difluorphenyl, 3,5-Difluorphenyl, 2-Chlorphenyl, 3-Chlorphenyl, 4-Chlorphenyl, 2,3-Dichlorphenyl, 3,4-Dichlorphenyl, 3,5-Dichlorphenyl, 2-Hydroxyphenyl, 3-Hydroxyphenyl, 4-Hydroxyphenyl, 2-Methoxyphenyl, 3-Methoxyphenyl, 4-Methoxyphenyl, 2,3-Dimethoxyphenyl, 3,4-Dimethoxyphenyl, und 3,5-Dimethoxyphenyl;
iii)



;

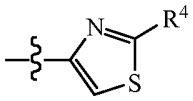
wobei R^2 ausgewählt ist aus Methyl, Ethyl, Phenyl, und Thiophen-2-yl, R^3 Wasserstoff oder Methyl ist; R^1 ausgewählt ist aus Phenyl, Thiophen-2-yl, Thiophen-3-yl, Thiazol-2-yl, Thiazol-4-yl, Thiazol-5-yl, Oxazol-2-yl, Oxazol-4-yl, Oxazol-5-yl, und Isoxazol-3-yl;
oder

iv)



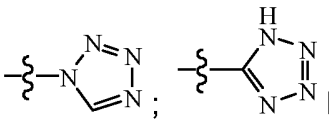
wobei R^2 und R^3 jeweils unabhängig Wasserstoff, Methyl oder Ethyl sind; R^1 ausgewählt ist aus Phenyl, 2-Fluorphenyl, 3-Fluorphenyl, 4-Fluorphenyl, 2,3-Difluorphenyl, 3,4-Difluorphenyl, 3,5-Difluorphenyl, 2-Chlorphenyl, 3-Chlorphenyl, 4-Chlorphenyl, 2,3-Dichlorphenyl, 3,4-Dichlorphenyl, 3,5-Dichlorphenyl, 2-Hydroxyphenyl, 3-Hydroxyphenyl, 4-Hydroxyphenyl, 2-Methoxyphenyl, 3-Methoxyphenyl, 4-Methoxyphenyl, 2,3-Dimethoxyphenyl, 3,4-Dimethoxyphenyl, und 3,5-Dimethoxyphenyl.

9. Verbindung nach Anspruch 1, wobei R:

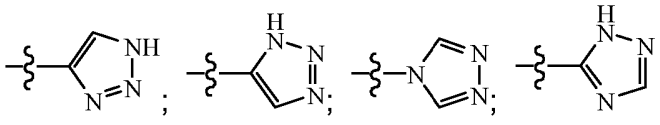


ist und wobei in den Z-Einheiten R^1 eine substituierte oder unsubstituierte Heteroaryl-Einheit ist, ausgewählt ist aus:

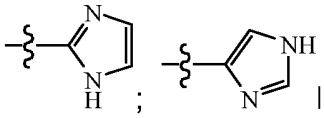
i) 1,2,3,4-Tetrazol-1-yl und 1,2,3,4-Tetrazol-5-yl, welche die jeweiligen Formeln:



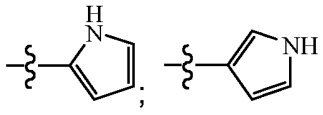
haben;
ii) [1,2,3]Triazol-4-yl, [1,2,3]Triazol-5-yl, [1,2,4]Triazol-4-yl, und [1,2,4]Triazol-5-yl, welche die jeweiligen Formeln:



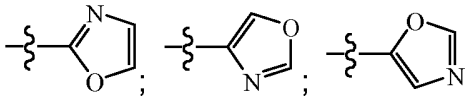
haben;
iii) Imidazol-2-yl und Imidazol-4-yl, welche die jeweiligen Formeln:



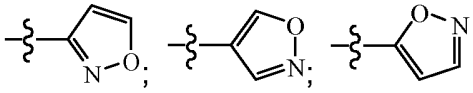
haben;
iv) Pyrrol-2-yl und Pyrrol-3-yl, welche die jeweiligen Formeln:



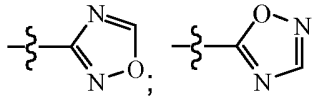
haben;
v) Oxazol-2-yl, Oxazol-4-yl, und Oxazol-5-yl, welche die jeweiligen Formeln:



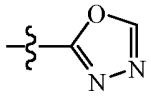
haben;
vi) Isoxazol-3-yl, Isoxazol-4-yl, und Isoxazol-5-yl, welche die jeweiligen Formeln:



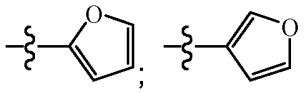
haben;
vii) [1,2,4]Oxadiazol-3-yl und [1,2,4]Oxadiazol-5-yl, welche die jeweiligen Formeln:



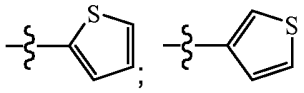
haben;
viii) [1,3,4]Oxadiazol-2-yl, welches die Formel:



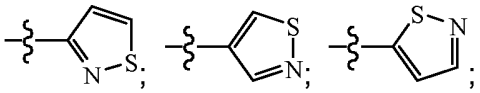
hat;
ix) Furan-2-yl und Furan-3-yl, welche die jeweiligen Formeln:



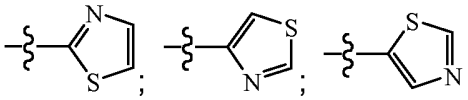
haben;
x) Thiophen-2-yl und Thiophen-3-yl, welche die jeweiligen Formeln:



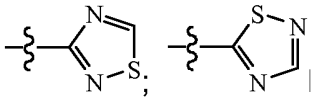
haben;
xi) Isothiazol-3-yl, Isothiazol-4-yl und Isothiazol-5-yl, welche die jeweiligen Formeln:



xii) Thiazol-2-yl, Thiazol-4-yl und Thiazol-5-yl, welche die jeweiligen Formeln:



haben; und xiii) [1,2,4]Thiadiazol-3-yl und [1,2,4]Thiadiazol-5-yl, welche die jeweiligen Formeln:



haben;

wobei die Heteroaryleinheitsubstitutionen ausgewählt sind aus linearem, verzweigtem und zyklischem C_1-C_6 Alkyl, substituiertem oder unsubstituiertem Phenyl und Benzyl, substituiertem oder unsubstituiertem C_1-C_9 Heteroaryl, -C(O)R^9, und -NHC(O)R^9; R^9 ausgewählt ist aus linearem und verzweigtem C_1-C_6 Alkyl; linearem und verzweigtem C_1-C_6 Alkoxy; oder -NHCH$_2$C(O)R^{10}; R^{10} ausgewählt ist aus Wasserstoff, Methyl, Ethyl, und *tert*-Butyl;
R^4 eine Einheit ist, ausgewählt aus:

i) Wasserstoff;
ii) substituiertem oder unsubstituiertem linearem, verzweigtem, oder zyklischem C_1-C_6 Alkyl;
iii) substituiertem oder unsubstituiertem Phenyl; und
iv) substituiertem oder unsubstituiertem Heteroaryl mit 5 oder 6 Ringatomen, wobei mindestens ein Ringatom ein Heteroatom ist, das ausgewählt ist aus Stickstoff, Sauerstoff, oder Schwefel.

10. Verbindung nach Anspruch 9, wobei Z ausgewählt ist aus 4-(Methoxy-carbonyl)thiazol-5-yl, 4-[(2-Methoxy-2-oxo-ethyl)carbamoyl]thiazol-5-yl, 5-[1-*N*-(2-Methoxy-2-oxoethyl)-1-*H*-indol-3-yl]oxazol-2-yl, 5-(2-Methoxyphenyl)oxazol-2-yl, 5-[(*S*)-1-(*tert*-Butoxycarbonyl)-2-phenylethyl]oxazol-2-yl, 5-[4-(Methyl-carboxy)phenyl]oxazol-2-yl, 5-(3-Methoxybenzyl)oxazol-2-yl, 5-(4-Phenyl)-oxazol-2-yl, 5-(2-Methoxyphenyl)thiazol-2-yl, 5-(3-Methoxyphenyl)thiazol-2-yl, 5-(4-Fluorphenyl)thiazol-2-yl, 5-(2,4-Difluorphenyl)thiazol-2-yl, 5-(3-Methoxy-benzyl)thiazol-2-yl, 4-(3-Methoxyphenyl)thiazol-2-yl, und 4-(4-Fluorphenyl)-thiazol-2-yl.

11. Verbindung nach Anspruch 1, ausgewählt aus:

(*S*)-{4-[2-(4-Ethylthiazol-2-yl)-2-phenylacetylaminoethyl]-phenyl}amido-sulfonsäure;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(2-fluorphenyl)acetamido)ethyl)phenyl-amidosulfonsäure;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(3-fluorphenyl)acetamido)ethyl)phenyl-amidosulfonsäure;
(*S*)-4-(2-(2-(2,3-Difluorphenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-amidosulfonsäure;
(*S*)-4-(2-(2-(3,4-Difluorphenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-amidosulfonsäure;
(*S*)-4-(2-(2-(2-Chlorphenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-amidosulfonsäure;
(*S*)-4-(2-(2-(3-Chlorphenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-amidosulfonsäure;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(3-hydroxyphenyl)acetamido)ethyl)phenyl-amidosulfonsäure;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(2-methoxyphenyl)acetamido)ethyl)phenyl-amidosulfonsäure;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(3-methoxyphenyl)acetamido)ethyl)phenyl-amidosulfonsäure;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-phenylpropanamido)ethyl)phenyl-amidosulfonsäure;
(*S*)-4-(2-(2-(3,4-Dimethoxyphenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)-phenylamidosulfonsäure;
(*S*)-4-(2-(2-(2,3-Dimethoxyphenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)-phenylamidosulfonsäure;
(*S*)-4-(2-(3-(3-Chlorphenyl)propanamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-amidosulfonsäure;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-(2-methoxyphenyl)propanamido)ethyl)phenylamidosulfonsäure;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-(3-methoxyphenyl)propanamido)ethyl)phenylamidosulfonsäure;

(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-(4-methoxyphenyl)propanamido)ethyl)phenylamidosulfonsäure;
(*S*)-4-{2-[2-(4-Ethyl-2,3-dioxopiperazin-1-yl)acetamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylamidosulfonsäure;
(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetamido]ethyl}phenylamidosulfonsäure;
(*S*)-4-[2-(Benzo[*d*][1,3]dioxol-5-carboxamido)-2-(4-ethylthiazol-2-yl)ethyl]-phenylamidosulfonsäure;
4-((*S*)-2-(2-(2-Chlorphenyl)acetamido)-2-(2-(thiophen-2-yl)thiazol-4-yl)ethyl)phenylamidosulfonsäure;
4-((*S*)-2-(2-(3-Methoxyphenyl)acetamido)-2-(2-(thiophen-2-yl)thiazol-4-yl)ethyl)-phenylamidosulfonsäure;
4-{(*S*)-2-(3-Phenylpropanamido)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenyl-amidosulfonsäure;
4-{(*S*)-2-(3-(3-Chlorphenyl)propanamido)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylamidosulfonsäure;
4-{(*S*)-2-[2-(3-Fluorphenyl)acetamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylamidosulfonsäure;
(*S*)-4-{2-[2-(2,5-Dimethylthiazol-4-yl)acetamido]-2-(4-ethylthiazol-2-yl]ethyl}-phenylamidosulfonsäure;
(*S*)-4-{2-[2-(2,4-Dimethylthiazol-5-yl)acetamido]-2-(4-methylthiazol-2-ylethyl}phenylamidosulfonsäure;
(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[3-(thiazol-2-yl)propanamido]ethyl}phenyl-amidosulfonsäure;
(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(4-ethylthiazol-2-yl)acetamido]ethyl}-phenyl-amidosulfonsäure;
(*S*)-4-{2-[2-(3-Methyl-1,2,4-oxadiazol-5-yl)acetamido]-2-(2-phenylthiazol-4-yl)ethyl}phenylamidosulfonsäure;
4-{(*S*)-2-[2-(4-Ethyl-2,3-dioxopiperazin-1-yl)acetamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylamidosulfonsäure;
(*S*)-4-(2-(2,3-Diphenylpropanamido)-2-(4-ethylthiazol-2-yl)ethyl)phenylamidosulfonsäure;
(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(2-methoxyphenyl)-3-phenylpropanamido]-ethyl)phenylamidosulfonsäure;
(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(3-fluorphenyl)-3-phenylpropanamido]-ethyl}phenylamidosulfonsäure;
(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(3-methoxyphenyl)-3-phenylpropanamido]-ethyl}phenylamidosulfonsäure;
4-{(*S*)-2-(4-Ethylthiazol-2-yl)-2-[2-(3-methyl-1,2,4-oxadiazol-5-yl)-3-phenylpropanamido]ethyl}phenylamidosulfonsäure;
(*S*)-4-[2-(4-Ethylthiazol-2-yl)-2-(4-oxo-4-phenylbutanamido)-ethyl]phenylamidosulfonsäure;
(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(5-methyl-4-oxohexanamido)ethyl)phenyl-amidosulfonsäure;
(*S*)-4-{2-[4-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-4-oxobutanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylamidosulfonsäure;
(*S*)-4-{2-[4-(2,3-Dimethoxyphenyl)-4-oxobutanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylamidosulfonsäure;
(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[4-oxo-4-(pyridin-2-yl)butanamido]ethyl}-phenylamidosulfonsäure;
(*S*)-4-{2-[4-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-4-oxobutanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylamidosulfonsäure;
(*S*)-4-[2-(4-*tert*-Butoxy-4-oxobutanamido)-2-(4-ethylthiazol-2-yl)ethyl]phenyl-amidosulfonsäure;
(*S*)-4-[2-(4-Ethoxy-4-oxobutanamido)-2-(4-ethylthiazol-2-yl)ethyl]phenylamidosulfonsäure;
(*S*)-4-(2-(3-Benzylureido)-2-(4-ethylthiazol-2-yl)ethyl)phenylamidosulfonsäure;
4-{(*S*)-2-(3-Benzylureido)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenyl-amidosulfonsäure;
{4-(*S*)-[2-Phenylmethansulfonylamino-2-(2-thiophen-2-ylthiazol-4-yl)ethyl]phenyl}amidosulfonsäure;
4-{(*S*)-2-[(2-Methylthiazol-4-yl)methylsulfonamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylamidosulfonsäure;
{4-(*S*)-[2-Phenylmethansulfonylamino-2-(2-ethylthiazol-4-yl)ethyl]phenyl}-amidosulfonsäure;
{4-(*S*)-[2-(3-Methoxyphenyl)methansulfonylamino-2-(2-ethylthiazol-4-yl)ethyl]phenyl}amidosulfonsäure;
(*S*)-4-{[1-(2-Ethylthiazol-4-yl)-2-(4-sulfoaminophenyl)ethylsulfamoyl]methyl}-benzoesäuremethylester;
(*S*)-4-[2-(2-Ethylthiazol-4-yl)-2-(1-methyl-1*H*-imidazol-4-sulfonamido)ethyl]-phenylamidosulfonsäure;
4-{(*S*)-2-[2-(Thiophen-2-yl)thiazol-4-yl]-2-(2,2,2-trifluorethylsulfonamido)-ethyl}phenylamidosulfonsäure;
{4-(*S*)-[2-(Phenylethansulfonylamino)-2-(2thiophen-2-ylthiazol-4-yl)ethyl]-phenyl}amidosulfonsäure;
{4-(*S*)-[3-(Phenylpropansulfonylamino)-2-(2thiophen-2-ylthiazol-4-yl)ethyl]-phenyl}amidosulfonsäure;
(*S*)-{4-[2-(4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-sulfonylamino)-2-(2-thiophen-2-ylthiazol-4-yl)ethyl]phenyl}amidosulfonsäure;
4-{(*S*)-2-(4-Acetamidophenylsulfonamido)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylamidosulfonsäure;
4-{(*S*)-2-(2-Cyclopropylthiazol-4-yl)-2-[4-(3-methoxyphenyl)-thiazol-2-ylamino]ethyl}phenylamidosulfonsäure;
(*S*)-4-(2-(4-((2-Methoxy-2-oxoethyl)carbamoyl)thiazol-5-ylamino)2-(2-ethylthiazol-4-yl)ethyl)phenylamidosulfonsäure;
4-((*S*)-2-(5-(1-*N*-(2-Methoxy-2-oxoethyl)-1-*H*-indol-3-yl)oxazol-2-ylamino)-2-(2-methylthiazol-4-yl)ethyl))phenylamidosulfonsäure;
4-((*S*)-2-(5-(2-Methoxyphenyl)oxazol-2-ylamino)-2-(2-methylthiazol-4-yl)ethyl)phenylamidosulfonsäure;
4-((*S*)-2-(5-((*S*)-1-(*tert*-Butoxycarbonyl)-2-phenylethyl)oxazol-2-ylamino)-2-(2-methylthiazol-4-yl)ethyl)phenylamidosulfonsäure;
(*S*)-4-(2-(5-(4-Methoxycarbonyl)phenyl)oxazol-2-ylamino)2-(2-methylthiazol-4-yl)ethyl)phenylamidosulfonsäure;

(*S*)-4-(2-(5-(3-Methoxybenzyl)oxazol-2-ylamino)-2-(2-methylthiazol-4-yl)ethyl)phenylamidosulfonsäure;
(*S*)-4-(2-(2-Methylthiazol-4-yl)2-(5-phenyloxazol-2-ylamino)ethyl)phenyl-amidosulfonsäure;
4-((S)-2-(2-Cyclopropylthiazol-4-yl)-2-(4-(3-methoxyphenyl)thiazol-2-ylamino)ethyl)phenylamidosulfonsäure;
(*S*)-4-(2-(2-Cyclopropylthiazol-4-yl)-2-(4-(4-fluorphenyl)thiazol-2-ylamino)ethyl)phenylamidosulfonsäure;
4-((*S*)-2-(2-Cyclopropylthiazol-4-yl)-2-(4-(2-methoxyphenyl)thiazol-2-ylamino)ethyl)phenylamidosulfonsäure;
4-((*S*)-2-(2-Cyclopropylthiazol-4-yl)-2-(4-(2,4-difluorphenyl)thiazol-2-ylamino)ethyl)phenylamidosulfonsäure;
(*S*)-4-(2-(4-(3-Methoxybenzyl)thiazol-2-ylamino)-2-(2-cyclopropylthiazol-4-yl)ethyl)phenylamidosulfonsäure;
(*S*)-{5-[1-(2-Ethylthiazol-4-yl)-2-(4-sulfoaminophenyl)ethylamino]-2-methyl-2H-[1,2,4]triazol-3-yl}carbaminsäuremethylester;
4-{(S)-2-[4-(2-Methoxyphenyl)thiazol-2-ylamino)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylamidosulfonsäure;
4-{(*S*)-2-[5-(3-Methoxyphenyl)oxazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylamidosulfonsäure;
4-{(*S*)-2-[4-(2,4-Difluorphenyl)thiazol-2-ylamino]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylamidosulfonsäure;
(*S*)-4-{2-[4-(Ethoxycarbonyl)thiazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylamidosulfonsäure;
(*S*)-4-{2-[4-(2-Ethoxy-2-oxoethyl)thiazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylamidosulfonsäure;
(*S*)-4-{2-[4-(4-Acetamidophenyl)thiazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylamidosulfonsäure;
(S)-4-[2-(4-Phenylthiazol-2-ylamino)-2-(2-phenylthiazol-4-yl)ethyl]phenyl-amidosulfonsäure;
(*S*)-4-{2-[4-(4-(Methoxycarbonyl)phenyl)thiazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylamidosulfonsäure;
4-{(S)-2-[4-(Ethoxycarbonyl)thiazol-2-ylamino]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylamidosulfonsäure;
(*S*)-4-[2-(4-(Methoxycarbonyl)thiazol-5-ylamino)-2-(2-phenylthiazol-4-yl)ethyl]phenylamidosulfonsäure;
(*S*)-4-[2-(5-Phenyloxazol-2-ylamino)]-2-(2-phenylthiazol-4-yl)phenylamidosulfonsäure;
(*S*)-4-{2-[5-(4-Acetamidophenyl)oxazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylamidosulfonsäure;
4-((*S*)-2-(5-(2,4-Difluorphenyl)oxazol-2-ylamino)-2-(2-phenylthiazol-4-yl)ethyl)phenylamidosulfonsäure;
4-{(*S*)-2-[5-(3-Methoxyphenyl)oxazol-2-ylamino]-2-[(2-thiophen-2-yl)thiazol-4-yl]ethyl}phenylamidosulfonsäure;
(*S*)-4-[2-(4,6-Dimethylpyrimiden-2-ylamino)-2-(2-methylthiazol-4-yl)ethyl]phenylamidosulfonsäure; und
(*S*)-4-[2-(4-Hydroxy-6-methylpyrimidin-2-ylamino)-2-(2-methylthiazol-4-yl)ethyl]phenylamidosulfonsäure.

12. Verbindung nach irgendeinem der Ansprüche 1-11, wobei die Verbindungen Salze sind, die Anionen aufweisen, die ausgewählt sind aus Chlorid, Bromid, Iodid, Sulfat, Bisulfat, Carbonat, Bicarbonat, Phosphat, Formiat, Acetat, Propionat, Butyrat, Pyruvat, Lactat, Oxalat, Malonat, Maleat, Succinat, Tartrat, Fumarat, und Citrat, oder Kationen aufweisen, die ausgewählt sind aus Natrium, Lithium, Kalium, Calcium, Magnesium, und Wismut.

13. Verwendung einer Verbindung nach irgendeinem der Ansprüche 1-12 zur Herstellung eines Medikaments zur Behandlung einer Krankheit ausgewählt aus Sichelzellanämie, Sarkoid, Syphilis, Pseudoxanthoma elasticum, Morbus Paget, Venenverschluss, Arterienverschluss, Carotis-Verschlusskrankheit, chronischer Uveitis/Vitritis, mykobakteriellen Infektionen, Lyme-Borreliose, systemischem Lupus erythematodes, Frühgeborenenretinopathie, Morbus Eales, Morbus Behçet, Infektionen, die eine Retinitis oder Choroiditis hervorrufen, einer vermuteten okulären Histoplasmose, Morbus Best, Kurzsichtigkeit, Grubenpapillen, Morbus Stargardt, Pars planitis, chronischer Retinaablösung, Hyperviskositätssyndrom, Toxoplasmose, Trauma und Komplikationen nach Laserbehandlung, Krankheiten, die mit Rubeosis zusammenhängen, Psoriasis, Sarkoidosis, Rheumatoid-Arthritis, Hämangiomen, Morbus Osler, oder Teleangiectasia haemorrhagica hereditaria, soliden oder im Blut vorhandenen Tumoren, AIDS, Skelettmuskel- und Myokardischämie, Schlaganfall, Erkrankung der Koronararterie, peripheren Gefäßerkrankungen.

14. Verwendung einer Verbindung nach irgendeinem der Ansprüche 1-12 zur Herstellung eines Medikaments zur Regulierung der Angiogenese, zur Vaskularisierung ischämischen Gewebes, zum Fördern des Wachstums von Hauttransplantatersatz, oder zur Förderung der Gewebereparatur im Kontext der gesteuerten Geweberegenerations(GTR)-Verfahren.

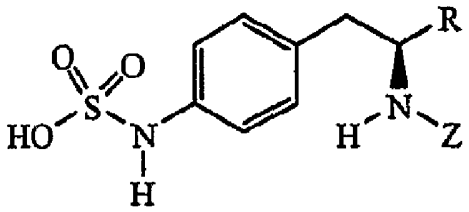
15. Verbindung nach irgendeinem der Ansprüche 1-12 zur Verwendung zur Behandlung eines Zustands ausgewählt aus Sichelzellanämie, Sarkoid, Syphilis, Pseudoxanthoma elasticum, Morbus Paget, Venenverschluss, Arterienverschluss, Carotis-Verschlusskrankheit, chronischer Uveitis/Vitritis, mykobakteriellen Infektionen, Lyme-Borreliose, systemischem Lupus erythematodes, Frühgeborenenretinopathie, Morbus Eales, Morbus Behçet, Infektionen, die eine Retinitis oder Choroiditis hervorrufen, einer vermuteten okulären Histoplasmose, Morbus Best, Kurzsichtigkeit, Grubenpapillen, Morbus Stargardt, Pars planitis, chronischer Retinaablösung, Hyperviskositätssyndrom, Toxoplasmose, Trauma und Komplikationen nach Laserbehandlung, Krankheiten, die mit Rubeosis zusammen-

hängen, Psoriasis, Sarkoidosis, Rheumatoid-Arthritis, Hämangiomen, Morbus Osler, oder Teleangiectasia haemorrhagica hereditaria, soliden oder im Blut vorhandenen Tumoren, AIDS, Skelettmuskel- und Myokardischämie, Schlaganfall, Erkrankung der Koronararterie, peripheren Gefäßerkrankungen.

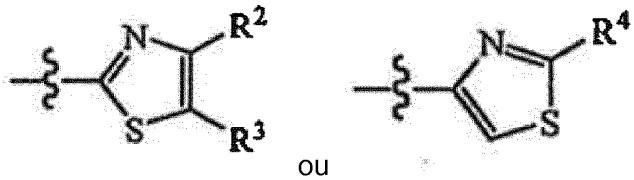
16. Verbindung nach irgendeinem der Ansprüche 1-12 zur Verwendung zur Regulierung der Angiogenese, zur Vaskularisierung ischämischen Gewebes, zum Fördern des Wachstums von Hauttransplantatersatz, oder zur Förderung der Gewebereparatur im Kontext der gesteuerten Geweberegenerations(GTR)-Verfahren.

Revendications

1. Composé de formule :



dans lequel R est un motif thiazolyle substitué ou non substitué de formule :



ou

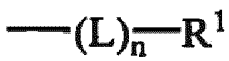
R^2 et R^3 sont chacun indépendamment choisis parmi :

i) un groupe hydrogène ;
ii) un groupe alkyle linéaire, ramifié ou cyclique en C_1 à C_6 substitué ou non substitué ;
iii) un groupe phényle substitué ou non substitué ; ou
iv) un cycle hétéroaryle à 5 ou 6 chaînons substitué ou non substitué,

où au moins un atome du cycle est un hétéroatome choisi parmi l'azote, l'oxygène et le soufre ;
ou
R^2 et R^3 peuvent être regroupés pour former un cycle saturé ou insaturé ayant de 5 à 7 atomes ;
R^4 est un motif choisi parmi :

i) l'hydrogène ;
ii) un groupe alkyle linéaire, ramifié ou cyclique en C_1 à C_6 substitué ou non substitué ;
iii) un groupe phényle substitué ou non substitué ; ou
iv) un cycle hétéroaryle à 5 ou 6 chaînons substitué ou non substitué,

dans lequel au moins un atome du cycle est un hétéroatome choisi parmi l'azote, l'oxygène et le soufre ;
lesdites substitutions pour R, R^2, R^3 et R^4 sont indépendamment choisies parmi un ou plusieurs des motifs alkyle linéaire, ramifié ou cyclique en C_1 à C_6, $-N(R^{16})_2$, $-OR^{16}$, halogène ou cyano ; chaque R^{16} est indépendamment un groupe hydrogène, un groupe alkyle linéaire, ramifié ou cyclique en C_1 à C_4 ;
Z est un motif de formule :



R^1 est choisi parmi :

i) l'hydrogène ;
ii) un groupe alkyle linéaire, ramifié ou cyclique en C_1 à C_6 substitué ou non substitué ;
iii) un groupe aryle en C_6 substitué ou non substitué, où chaque substitution est indépendamment choisie parmi un groupe halogène, un groupe alkyle linéaire, ramifié ou cyclique en C_1 à C_4, $-OR^{11}$, -CN, $-N(R^{11})_2$, $-CO_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NO_2$ et $-SO_2R^{11}$, chaque R^{11} est indépendamment un hydrogène, un groupe alkyle, un groupe alcényle ou un groupe alcynyle linéaire, ramifié ou cyclique en C_1 à C_4 substitué ou non substitué ; un groupe phényle ou un groupe benzyle substitué ou non substitué ; ou deux motifs R^{11} peuvent être regroupés pour former un cycle de 3 à 7 atomes ;
iv) des cycles hétérocycliques en C_1 à C_9 substitués ou non substitués, où les hétéroatomes sont choisis parmi l'azote, l'oxygène et le soufre ; ou
v) des cycles hétéroaryles en C_1 à C_9 substitués ou non substitués, où au moins un atome du cycle est un hétéroatome choisi parmi l'azote, l'oxygène et le soufre ;

L est un motif de liaison choisi parmi :

i) $-C(O)NH[C(R^{5a}R^{5b})]_w-$;
ii) $-C(O)[C(R^{6a}R^{6b})_x$;
iii) $-C(O)[C(R^{7a}R^{7b})]_yC(O)-$;
iv) $-SO_2[C(R^{8a}R^{8b})]/_z-$;

R^{5a}, R^{5b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{8a} et R^{8b} sont chacun indépendamment :

i) l'hydrogène ;
ii) un groupe alkyle linéaire ou ramifié en C_1 à C_4 substitué ou non substitué ;
iii) un groupe aryle substitué ou non substitué ;
iv) des cycles hétérocycliques substitués ou non substitués ; ou
v) un groupe hétéroaryle en C_1 à C_9 substitué ou non substitué ;

lesdites substitutions pour R^1, R^{5a}, R^{5b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{8a} et R^{8b} sont indépendamment choisies parmi les groupes alkyle linéaire, ramifié ou cyclique en C_1 à C_6, phényle ou benzyle, hétéroaryle en C_1 à C_9, $-C(O)R^9$ et $-NHC(O)R^9$; R^9 est un groupe alkyle linéaire ou ramifié en C_1 à C_6, un groupe alcoxy linéaire ou ramifié en C_1 à C_6 ou $-NHCH_2C(O)R^{10}$; R^{10} est choisi parmi les groupes hydrogène, méthyle, éthyle et *tert*-butyle ;
l'indice n est égal à 0 ou 1 ; les indices w, x, y et z vont chacun indépendamment de 1 à 4 ; ou son sel pharmaceutiquement acceptable.

2. Composé selon la revendication 1, dans lequel R^2 et R^3 sont chacun un groupe hydrogène ou un groupe alkyle linéaire, ramifié ou cyclique en C_1 à C_6 substitué ou non substitué.

3. Composé selon la revendication 1, dans lequel R^2 est un groupe phényle substitué ou non substitué et R^3 est un groupe hydrogène, ou dans lequel R^2 est un groupe hétéroaryle substitué ou non substitué et R^3 est un hydrogène.

4. Composé selon la revendication 1, dans lequel R^4 est un groupe alkyle linéaire, ramifié ou cyclique en C_1 à C_6 substitué ou non substitué, ou dans lequel R^4 est un groupe phényle substitué ou non substitué et R^3 est un hydrogène.

5. Composé selon la revendication 1, dans lequel R^4 est un groupe hétéroaryle substitué ou non substitué.

6. Composé selon l'une quelconque des revendications 1 à 5, dans lequel L est de formule :

$$\mathbf{-C(O)[C(R^{6a}R^{6b})]_x-}$$

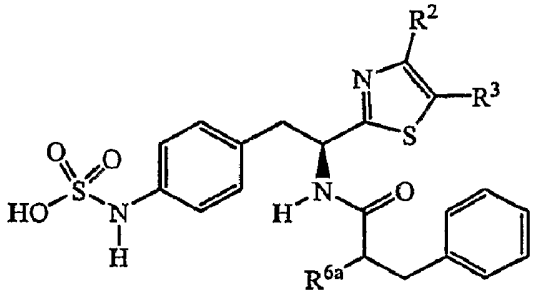
R^{8a} est un groupe hydrogène, un groupe phényle substitué ou non substitué et un groupe hétéroaryle substitué ou non substitué ; l'indice x est égal à 1 ou 2.

7. Composé selon la revendication 6, dans lequel R^1 est choisi parmi les groupes phényle, 2-fluorophényle, 3-fluorophényle, 4-fluorophényle, 2,3-difluorophényle, 3,4-difluorophényle, 3,5-difluorophényle, 2-chlorophényle, 3-chloro-

phényle, 4-chlorophényle, 2,3-dichlorophényle, 3,4-dichlorophényle, 3,5-dichlorophényle, 2-hydroxyphényle, 3-hydroxyphényle, 4-hydroxyphényle, 2-méthoxyphényle, 3-méthoxyphényle, 4-méthoxyphényle, 2,3-diméthoxyphényle, 3,4-diméthoxyphényle et 3,5-diméthoxyphényle.

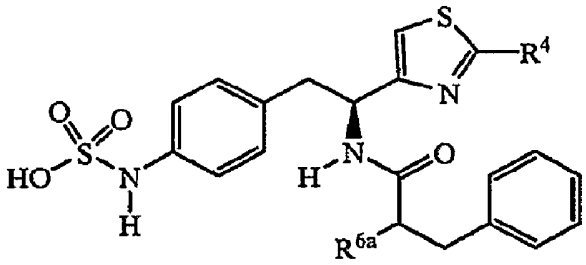
8. Composé selon la revendication 1, de formule :

i)



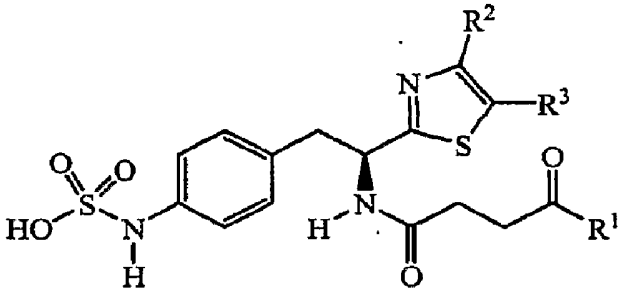
dans lequel R^2 est un groupe méthyle ou éthyle ; R^3 est un hydrogène ; R^{6a} est choisi parmi les groupes phényle, 2-fluorophényle, 3-fluorophényle, 4-fluorophényle, 2,3-difluorophényle, 3,4-difluorophényle, 3,5-difluorophényle, 2-chlorophényle, 3-chlorophényle, 4-chlorophényle, 2,3-dichlorophényle, 3,4-dichlorophényle, 3,5-dichlorophényle, 2-hydroxyphényle, 3-hydroxyphényle, 4-hydroxyphényle, 2-méthoxyphényle, 3-méthoxyphényle, 4-méthoxyphényle, 2,3-diméthoxyphényle, 3,4-diméthoxyphényle et 3,5-diméthoxyphényle ;

ii)



dans lequel R^4 est un groupe méthyle, éthyle, phényle ou thiophén-2-yle ; R^{6a} est choisi parmi les groupes phényle, 2-fluorophényle, 3-fluorophényle, 4-fluorophényle, 2,3-difluorophényle, 3,4-difluorophényle, 3,5-difluorophényle, 2-chlorophényle, 3-chlorophényle, 4-chlorophényle, 2,3-dichlorophényle, 3,4-dichlorophényle, 3,5-dichlorophényle, 2-hydroxyphényle, 3-hydroxyphényle, 4-hydroxyphényle, 2-méthoxyphényle, 3-méthoxyphényle, 4-méthoxyphényle, 2,3-diméthoxyphényle, 3,4-diméthoxyphényle et 3,5-diméthoxyphényle ;

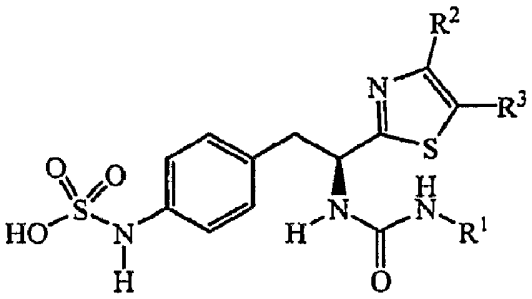
iii)



dans lequel R^2 est choisi parmi les groupes méthyle, éthyle, phényle et thiophén-2-yle ; R^3 est un hydrogène ou un groupe méthyle ; R^1 est choisi parmi les groupes phényle, thiophén-2-yle, thiophén-3-yle, thiazol-2-yle, thiazol-4-yle, thiazol-5-yle, oxazol-2-yle, oxazol-4-yle, oxazol-5-yle et isoxazol-3-yle ;

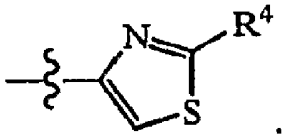
ou

iv)



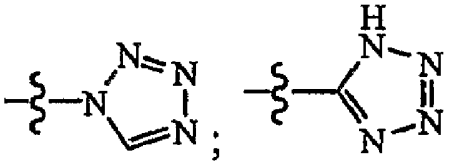
dans lequel R^2 et R^3 sont chacun indépendamment un hydrogène, un groupe méthyle ou éthyle ; R^1 est choisi parmi les groupes phényle, 2-fluorophényle, 3-fluorophényle, 4-fluorophényle, 2,3-difluorophényle, 3,4-difluorophényle, 3,5-difluorophényle, 2-chlorophényle, 3-chlorophényle, 4-chlorophényle, 2,3-dichlorophényle, 3,4-dichlorophényle, 3,5-dichlorophényle, 2-hydroxyphényle, 3-hydroxyphényle, 4-hydroxyphényle, 2-méthoxyphényle, 3-méthoxyphényle, 4-méthoxyphényle, 2,3-diméthoxyphényle, 3,4-diméthoxyphényle et 3,5-diméthoxyphényle.

9. Composé selon la revendication 1, dans lequel R est :

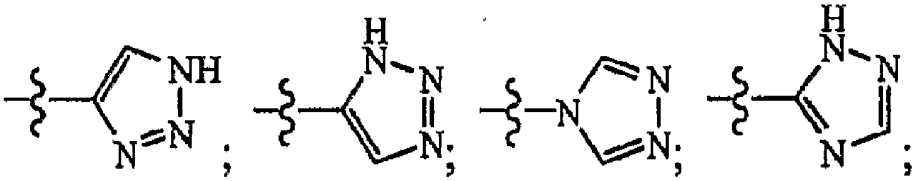


et dans lequel, dans les motifs Z, R^1 est un motif hétéroaryle substitué ou non substitué choisi parmi :

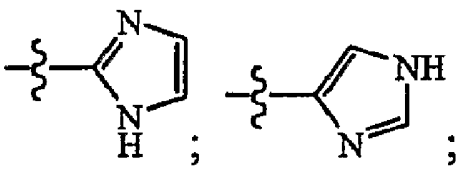
i) les groupes 1,2,3,4-tétrazol-1-yle et 1,2,3,4-tétrazol-5-yle de formules respectives :



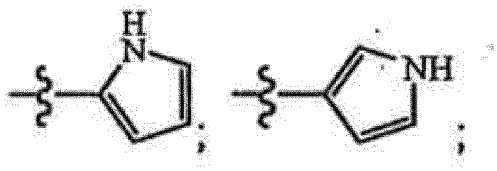
ii) les groupes [1,2,3]triazol-4-yle, [1,2,3]triazol-5-yle, [1,2,4]triazol-4-yle et [1,2,4]triazol-5-yle de formules respectives :



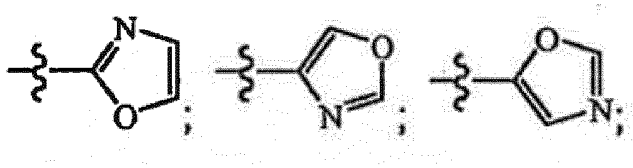
iii) les groupes imidazol-2-yle et imidazol-4-yle de formules respectives :



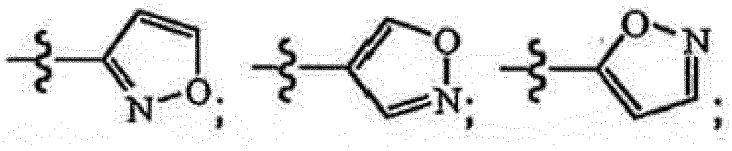
iv) les groupes pyrrol-2-yle et pyrrol-3-yle de formules respectives :



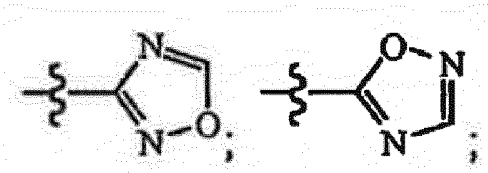
v) les groupes oxazol-2-yle, oxazol-4-yle et oxazol-5-yle de formules respectives :



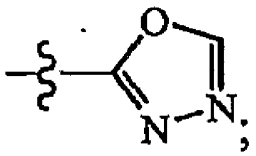
vi) les groupes isoxazol-3-yle, isoxazol-4-yle et isoxazol-5-yle de formules respectives :



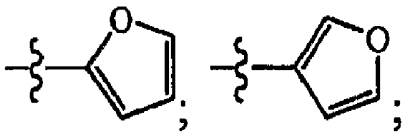
vii) les groupes [1,2,4]oxadiazol-3-yle et [1,2,4]oxadiazol-5-yle de formules respectives :



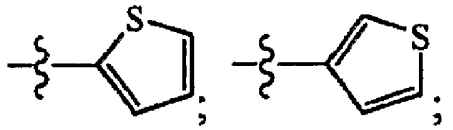
viii) le groupe [1,3,4]oxadiazol-2-yle de formule :



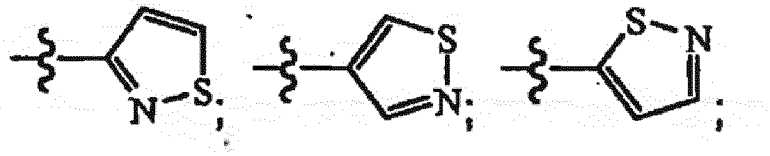
ix) les groupes furan-2-yle et furan-3-yle de formules respectives :



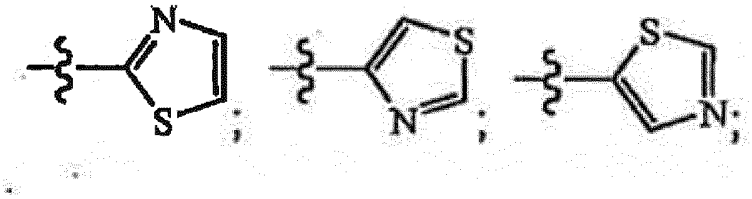
x) les groupes thiophén-2-yle et thiophén-3-yle de formules respectives :



xi) les groupes isothiazol-3-yle, isothiazol-4-yle et isothiazol-5-yle de formules respectives :

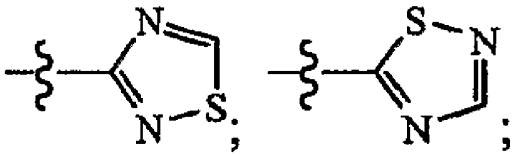


xii) les groupes thiazol-2-yle, thiazol-4-yle et thiazol-5-yle de formules respectives :



et

xiii) les groupes [1,2,4]thiadiazol-3-yle et [1,2,4]thiadiazol-5-yle de formules respectives :



dans lequel lesdites substitutions de motif hétéroaryle sont choisies parmi les groupes alkyle linéaire, ramifié ou cyclique en C_1 à C_6, phényle et benzyle substitué ou non substitué, hétéroaryle en C_1 à C_9 substitué ou non substitué, -C(O)R^9 et -NHC(O)R^9 ; R^9 est choisi parmi les groupes alkyle linéaire ou ramifié en C_1 à C_6, alcoxy linéaire ou ramifié en C_1 à C_6; ou -NHCH$_2$C(O)R^{10} ; R^{10} est choisi parmi l'hydrogène, les groupes méthyle, éthyle et *tert*-butyle ; R^4 est un motif choisi parmi :

i) l'hydrogène ;
ii) un groupe alkyle linéaire, ramifié ou cyclique en C_1 à C_6 substitué ou non substitué ;
iii) un groupe phényle substitué ou non substitué ; et
iv) un groupe hétéroaryle à 5 ou 6 chaînons substitué ou non substitué,

où au moins un atome du cycle est un hétéroatome choisi parmi l'azote, l'oxygène et le soufre.

10. Composé selon la revendication 9, dans lequel Z est choisi parmi les groupes 4-(méthoxycarbonyl)thiazol-5-yle, 4-[(2-méthoxy-2-oxoéthyl)carbamoyl]thiazol-5-yle, 5-[1-*N*-(2-méthoxy-2-oxoéthyl)-1-*H*-indol-3-yl]oxazol-2-yle, 5-(2-méthoxyphényl)oxazol-2-yle, 5-[(*S*)-1-(*tert*-butoxycarbonyl)-2-phényléthyl]oxazol-2-yle, 5-[4-(méthylcarboxy)phényl]oxazol-2-yle, 5-(3-méthoxybenzyl)oxazol-2-yle, 5-(4-phényl)-oxazol-2-yle, 5-(2-méthoxyphényl)thiazol-2-yle, 5-(3-méthoxyphényl)thiazol-2-yle, 5-(4-fluorophényl)thiazol-2-yle, 5-(2,4-difluorophényl)thiazol-2-yle, 5-(3-méthoxybenzyl)thiazol-2-yle, 4-(3-méthoxyphényl)thiazol-2-yle et 4-(4-fluorophényl)-thiazol-2-yle.

11. Composé selon la revendication 1, choisi parmi :

l'acide (*S*)-{4-[2-(4-éthylthiazol-2-yl)-2-phénylacétylaminoéthyl]-phényl}sulfamique ;

l'acide (*S*)-4-(2-(4-éthylthiazol-2-yl)-2-(2-(2-fluorophényl)acétamido)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(4-éthylthiazol-2-yl)-2-(2-(3-fluorophényl)acétamido)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(2-(2,3-difluorophényl)acétamido)-2-(4-éthylthiazol-2-yl)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(2-(3,4-difluorophényl)acétamido)-2-(4-éthylthiazol-2-yl)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(2-(2-chlorophényl)acétamido)-2-(4-éthylthiazol-2-yl)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(2-(3-chlorophényl)acétamido)-2-(4-éthylthiazol-2-yl)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(4-éthylthiazol-2-yl)-2-(2-(3-hydroxyphényl)acétamido)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(4-éthylthiazol-2-yl)-2-(2-(2-méthoxyphényl)acétamido)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(4-éthylthiazol-2-yl)-2-(2-(3-méthoxyphényl)acétamido)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(4-éthylthiazol-2-yl)-2-(3-phénylpropanamido)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(2-(3,4-diméthoxyphényl)acétamido)-2-(4-éthylthiazol-2-yl)éthyl)-phénylsulfamique ;
l'acide (*S*)-4-(2-(2-(2,3-diméthoxyphényl)acétamido)-2-(4-éthylthiazol-2-yl)éthyl)-phénylsulfamique ;
l'acide (*S*)-4-(2-(3-(3-chlorophényl)propanamido)-2-(4-éthylthiazol-2-yl)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(4-éthylthiazol-2-yl)-2-(3-(2-méthoxyphényl)propanamido)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(4-éthylthiazol-2-yl)-2-(3-(3-méthoxyphényl)propanamido)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(4-éthylthiazol-2-yl)-2-(3-(4-méthoxyphényl)propanamido)éthyl)phénylsulfamique ;
l'acide (*S*)-4-{2-[2-(4-éthyl-2,3-dioxopipérazin-1-yl)acétamido]-2-(4-éthylthiazol-2-yl)éthyl}phénylsulfamique ;
l'acide (*S*)-4-{2-(4-éthylthiazol-2-yl)-2-[2-(5-méthyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acétamido]éthyl}-phénylsulfamique ;
l'acide (*S*)-4-[2-(benzo[*d*][1,3]dioxole-5-carboxamido)-2-(4-éthylthiazol-2-yl)éthyl]-phénylsulfamique ;
l'acide 4-((*S*)-2-(2-(2-chlorophényl)acétamido)-2-(2-(thiophén-2-yl)thiazol-4-yl)éthyl)phénylsulfamique ;
l'acide 4-((*S*)-2-(2-(3-méthoxyphényl)acétamido)-2-(2-(thiophén-2-yl)thiazol-4-yl)éthyl)-phénylsulfamique ;
l'acide 4-{(*S*)-2-(3-phénylpropanamido)-2-[2-(thiophén-2-yl)thiazol-4-yl]éthyl}phénylsulfamique ;
l'acide 4-{(*S*)-2-(3-(3-chlorophényl)propanamido)-2-[2-(thiophén-2-yl)thiazol-4-yl]éthyl}phénylsulfamique ;
l'acide 4-{(*S*)-2-[2-(3-fluorophényl)acétamido]-2-[2-(thiophén-2-yl)thiazol-4-yl]éthyl}phénylsulfamique ;
l'acide (*S*)-4-{2-[2-(2,5-diméthylthiazol-4-yl)acétamido]-2-(4-éthylthiazol-2-yl]éthyl}-phénylsulfamique ;
l'acide (*S*)-4-{2-[2-(2,4-diméthylthiazol-5-yl)acétamido]-2-(4-méthylthiazol-2-yléthyl}phénylsulfamique ;
l'acide (*S*)-4-{2-(4-éthylthiazol-2-yl)-2-[3-(thiazol-2-yl)propanamido]éthyl}phénylsulfamique ;
l'acide (*S*)-4-{2-(4-éthylthiazol-2-yl)-2-[2-(4-éthylthiazol-2-yl) acétamido]éthyl}phénylsulfamique ;
l'acide (*S*)-4-{2-[2-(3-méthyl-1,2,4-oxadiazol-5-yl) acétamido]-2-(2-phénylthiazol-4-yl)éthyl}phénylsulfamique ;
l'acide 4-{(*S*)-2-[2-(4-éthyl-2,3-dioxopipérazin-1-yl) acétamido]-2-[2-(thiophén-2-yl)thiazol-4-yl]éthyl}phenyl-sulfamique ;
l'acide (*S*)-4-(2-(2,3-diphénylpropanamido)-2-(4-éthylthiazol-2-yl)éthyl)phénylsulfamique ;
l'acide (*S*)-4-{2-(4-éthylthiazol-2-yl)-2-[2-(2-méthoxyphényl)-3-phénylpropanamido]-éthyl)phénylsulfamique ;
l'acide (*S*)-4-{2-(4-éthylthiazol-2-yl)-2-[2-(3-fluorophényl)-3-phénylpropanamido]-éthyl}phénylsulfamique ;
l'acide (*S*)-4-{2-(4-éthylthiazol-2-yl)-2-[2-(3-méthoxyphényl)-3-phénylpropanamido]-éthyl}phenylsulfamique ;
l'acide 4-{(*S*)-2-(4-éthylthiazol-2-yl)-2-[2-(3-méthyl-1,2,4-oxadiazol-5-yl)-3-phénylpropanamido]éthyl}phényl-sulfamique ;
l'acide (*S*)-4-[2-(4-éthylthiazol-2-yl)-2-(4-oxo-4-phénylbutanamido)-éthyl]phénylsulfamique ;
l'acide (*S*)-4-(2-(4-éthylthiazol-2-yl)-2-(5-méthyl-4-oxohexanamido)éthyl)phényl-sulfamique ;
l'acide (*S*)-4-{2-[4-(3,4-dihydro-2H-benzo[b][1,4]dioxépin-7-yl)-4-oxobutanamido]-2-(4-éthylthiazol-2-yl)éthyl}-phénylsulfamique ;
l'acide (*S*)-4-{2-[4-(2,3-diméthoxyphényl)-4-oxobutanamido]-2-(4-éthylthiazol-2-yl)éthyl}phénylsulfamique ;
l'acide (*S*)-4-{2-(4-éthylthiazol-2-yl)-2-[4-oxo-4-(pyridin-2-yl)butanamido]éthyl}-phénylsulfamique ;
l'acide (*S*)-4-{2-[4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4-oxobutanamido]-2-(4-éthylthiazol-2-yl)éthyl}phényl-sulfamique ;
l'acide (*S*)-4-[2-(4-*tert*-butoxy-4-oxobutanamido)-2-(4-éthylthiazol-2-yl)éthyl]phénylsulfamique ;
l'acide (*S*)-4-[2-(4-éthoxy-4-oxobutanamido)-2-(4-éthylthiazol-2-yl)éthyl]phénylsulfamique ;
l'acide (*S*)-4-(2-(3-benzyluréido)-2-(4-éthylthiazol-2-yl)éthyl)phénylsulfamique ;
l'acide 4-{[(*S*)-2-(3-benzyluréido)-2-[2-(thiophén-2-yl)thiazol-4-yl]éthyl}phénylsulfamique;
l'acide {4-(*S*)-[2-phénylméthanesulfonylamino-2-(2-thiophén-2-ylthiazol-4-yl)éthyl]phényl}sulfamique ;
l'acide 4-{(*S*)-2-[(2-méthylthiazol-4-yl)méthylsulfonamido]-2-[2-(thiophén-2-yl)thiazol-4-yl]éthyl}phénylsulfa-mique ;
l'acide {4-(*S*)-[2-phénylméthanesulfonylamino-2-(2-éthylthiazol-4-yl)éthyl]phényl}-sulfamique ;
l'acide {4-(*S*)-[2-(3-méthoxyphényl)méthanesulfonylamino-2-(2-éthylthiazol-4-yl)éthyl]phényl}sulfamique ;
l'ester méthylique d'acide (*S*)-4-{[1-(2-éthylthiazol-4-yl)-2-(4-sulfoaminophényl)éthylsulfamoyl]méthyl}-benzoïque ;
l'acide (*S*)-4-[2-(2-éthylthiazol-4-yl)-2-(1-méthyl-1*H*-imidazol-4-sulfonamido)éthyl]-phénylsulfamique ;

l'acide 4-{(*S*)-2-[2-(thiophén-2-yl)thiazol-4-yl]-2-(2,2,2-trifluoroéthylsulfonamido)-éthyl}phénylsulfamique ;
l'acide {4-(*S*)-[2-(phényléthanesulfonylamino)-2-(2-thiophén-2-ylthiazol-4-yl)éthyl]-phényl}sulfamique ;
l'acide {4-(*S*)-[3-(phénylpropanesulfonylamino)-2-(2-thiophén-2-ylthiazol-4-yl)éthyl]-phényl}sulfamique ;
l'acide (*S*)-{4-[2-(4-méthyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-sulfonylamino)-2-(2-thiophén-2-ylthiazol-4-yl)-éthyl]phényl}sulfamique ;
l'acide 4-{(*S*)-2-(4-acétamidophénylsulfonamido)-2-[2-(thiophén-2-yl)thiazol-4-yl]éthyl}phénylsulfamique ;
l'acide 4-{(*S*)-2-(2-cyclopropylthiazol-4-yl)-2-[4-(3-méthoxyphényl)-thiazol-2-ylamino]éthyl}phénylsulfamique ;
l'acide (*S*)-4-(2-(4-((2-méthoxy-2-oxoéthyl)carbamoyl)thiazol-5-ylamino)2-(2-éthylthiazol-4-yl)éthyl)phénylsulfamique ;
l'acide 4-((*S*)-2-(5-(1-*N*-(2-méthoxy-2-oxoéthyl)-1*H*-indol-3-yl)oxazol-2-ylamino)-2-(2-méthylthiazol-4-yl)-éthyl))phénylsulfamique ;
l'acide 4-((*S*)-2-(5-(2-méthoxyphényl)oxazol-2-ylamino)-2-(2-méthylthiazol-4-yl)éthyl)phénylsulfamique ;
l'acide 4-((*S*)-2-(5-((S)-1-(*tert*-butoxycarbonyl)-2-phényléthyl)oxazol-2-ylamino)-2-(2-méthylthiazol-4-yl)-éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(5-(4-méthoxycarbonyl)phényl)oxazol-2-ylamino)2-(2-méthylthiazol-4-yl)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(5-(3-méthoxybenzyl)oxazol-2-ylamino)-2-(2-méthylthiazol-4-yl)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(2-méthylthiazol-4-yl)2-(5-phényloxazol-2-ylamino)éthyl)phénylsulfamique ;
l'acide 4-((*S*)-2-(2-cyclopropylthiazol-4-yl)-2-(4-(3-méthoxyphényl)thiazol-2-ylamino)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(2-cyclopropylthiazol-4-yl)-2-(4-(4-fluorophényl)thiazol-2-ylamino)éthyl)phénylsulfamique ;
l'acide 4-((*S*)-2-(2-cyclopropylthiazol-4-yl)-2-(4-(2-méthoxyphényl)thiazol-2-ylamino)éthyl)phénylsulfamique ;
l'acide 4-((*S*)-2-(2-cyclopropylthiazol-4-yl)-2-(4-(2,4-difluorophényl)thiazol-2-ylamino)éthyl)phénylsulfamique ;
l'acide (*S*)-4-(2-(4-(3-méthoxybenzyl)thiazol-2-ylamino)-2-(2-cyclopropylthiazol-4-yl)éthyl)phénylsulfamique ;
l'ester méthylique d'acide (*S*)-{5-[1-(2-éthylthiazol-4-yl)-2-(4-sulfoaminophényl)éthylamino]-2-méthyl-2H-[1,2,4]triazol-3-yl}carbamique ;
l'acide 4-{(*S*)-2-[4-(2-méthoxyphényl)thiazol-2-ylamino)-2-[2-(thiophén-2-yl)thiazol-4-yl]éthyl}phénylsulfamique ;
l'acide 4-{(*S*)-2-[5-(3-méthoxyphényl)oxazol-2-ylamino]-2-(2-phénylthiazol-4-yl)éthyl}phénylsulfamique ;
l'acide 4-{(*S*)-2-[4-(2,4-difluorophényl)thiazol-2-ylamino]-2-[2-(thiophén-2-yl)thiazol-4-yl]éthyl}phénylsulfamique ;
l'acide (*S*)-4-{2-[4-(éthoxycarbonyl)thiazol-2-ylamino]-2-(2-phénylthiazol-4-yl)éthyl}phénylsulfamique ;
l'acide (*S*)-4-{2-[4-(2-éthoxy-2-oxoéthyl)thiazol-2-ylamino]-2-(2-phénylthiazol-4-yl)éthyl}phénylsulfamique ;
l'acide (*S*)-4-{2-[4-(4-acétamidophényl)thiazol-2-ylamino]-2-(2-phénylthiazol-4-yl)éthyl}phénylsulfamique ;
l'acide (*S*)-4-[2-(4-phénylthiazol-2-ylamino)-2-(2-phénylthiazol-4-yl)éthyl]phénylsulfamique ;
l'acide (*S*)-4-{2-[4-(4-(méthoxycarbonyl)phényl)thiazol-2-ylamino]-2-(2-phénylthiazol-4-yl)éthyl}phénylsulfamique ;
l'acide 4-{(*S*)-2-[4-(éthoxycarbonyl)thiazol-2-ylamino]-2-[2-(thiophén-2-yl)thiazol-4-yl]éthyl}phénylsulfamique ;
l'acide (*S*)-4-[2-(4-(méthoxycarbonyl)thiazol-5-ylamino)-2-(2-phénylthiazol-4-yl)éthyl]phénylsulfamique ;
l'acide (*S*)-4-[2-(5-phényloxazol-2-ylamino)]-2-(2-phénylthiazol-4-yl)phénylsulfamique ;
l'acide (*S*)-4-{2-[5-(4-acétamidophényl)oxazol-2-ylamino]-2-(2-phénylthiazol-4-yl)éthyl}phénylsulfamique ;
l'acide 4-((*S*)-2-(5-(2,4-difluorophényl)oxazol-2-ylamino)-2-(2-phénylthiazol-4-yl)éthyl)phénylsulfamique ;
l'acide 4-{(*S*)-2-[5-(3-méthoxyphényl)oxazol-2-ylamino]-2-[(2-thiophén-2-yl)thiazol-4-yl]éthyl}phénylsulfamique ;
l'acide (*S*)-4-[2-(4,6-diméthylpyrimidine-2-ylamino)-2-(2-méthylthiazol-4-yl)éthyl]phénylsulfamique ; et
l'acide (*S*)-4-[2-(4-hydroxy-6-méthylpyrimidine-2-ylamino)-2-(2-méthylthiazol-4-yl)éthyl]phénylsulfamique.

12. Composé selon l'une quelconque des revendications 1 à 11, dans lequel les composés sont des sels comprenant des anions choisis parmi le chlorure, le bromure, l'iodure, le sulfate, le bisulfate, le carbonate, le bicarbonate, le phosphate, le formiate, l'acétate, le propionate, le butyrate, le pyruvate, le lactate, l'oxalate, le malonate, le maléate, le succinate, le tartrate, le fumarate et le citrate, ou des cations choisis parmi le sodium, le lithium, le potassium, le calcium, le magnésium et le bismuth.

13. Utilisation d'un composé selon l'une quelconque des revendications 1 à 12, pour fabriquer un médicament pour le traitement d'une maladie choisie parmi la drépanocytose, la sarcoïdose, la syphilis, l'élastorrhexie systématisée, la maladie de Paget, l'occlusion veineuse, l'occlusion artérielle, l'obstruction de l'artère carotide, l'uvéite/vitrite chronique, les infections par des mycobactéries, la maladie de Lyme, le lupus érythémateux systémique, la rétinopathie des prématurés, la maladie d'Eales, la maladie de Behçet, les infections causant une rétinite ou une choroïdite, l'histoplasmose oculaire présumée, la maladie de Best, la myopie, les fossettes optiques, la maladie de Stargardt,

la pars planite, le décollement rétinien chronique, le syndrome d'hyperviscosité, la toxoplasmose, les complications traumatiques et post-laser, les maladies associées à la rubéose, le psoriasis, la sarcoïdose, la polyarthrite rhumatoïde, les hémangiomes, la maladie d'Osler-Weber-Rendu, ou télangiectasie hémorragique héréditaire, les tumeurs solides ou hématogènes, le syndrome d'immunodéficience acquise, l'ischémie du muscle squelettique et du myocarde, l'accident vasculaire cérébral, la coronopathie et l'acrosyndrome.

14. Utilisation d'un composé selon l'une quelconque des revendications 1 à 12, pour fabriquer un médicament pour la régulation de l'angiogenèse, la vascularisation du tissu ischémique, la stimulation de la croissance des substituts de greffe de peau ou la stimulation de la réparation du tissu dans le cadre d'un processus de régénération tissulaire guidée (RTG).

15. Composé selon l'une quelconque des revendications 1 à 12, pour une utilisation dans le traitement d'une pathologie choisie parmi la drépanocytose, la sarcoïdose, la syphilis, l'élastorrhexie systématisée, la maladie de Paget, l'occlusion veineuse, l'occlusion artérielle, l'obstruction de l'artère carotide, l'uvéite/vitrite chronique, les infections par des mycobactéries, la maladie de Lyme, le lupus érythémateux systémique, la rétinopathie des prématurés, la maladie d'Eales, la maladie de Behçet, les infections causant une rétinite ou une choroïdite, l'histoplasmose oculaire présumée, la maladie de Best, la myopie, les fossettes optiques, la maladie de Stargardt, la pars planite, le décollement rétinien chronique, le syndrome d'hyperviscosité, la toxoplasmose, les complications traumatiques et post-laser, les maladies associées à la rubéose et à la vitréorétinopathie prolifératives, le psoriasis, la sarcoïdose, la polyarthrite rhumatoïde, les hémangiomes, la maladie d'Osler-Weber-Rendu, ou télangiectasie hémorragique héréditaire, les tumeurs solides ou hématogènes, le syndrome d'immunodéficience acquise, l'ischémie du muscle squelettique et du myocarde, l'accident vasculaire cérébral, la coronopathie et l'acrosyndrome.

16. Composé selon l'une quelconque des revendications 1 à 12, pour une utilisation dans la régulation de l'angiogenèse, la vascularisation du tissu ischémique, la stimulation de la croissance des substituts de greffe de peau ou la stimulation de la réparation du tissu dans le cadre d'un processus de régénération tissulaire guidée (RTG).

REFERENCES CITED IN THE DESCRIPTION

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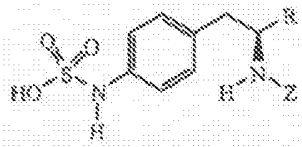
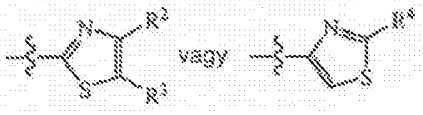
Szabadalmi igénypontok

1.



képletű vegyület – ahol a képletben R jelentése adott esetben helyettesített,



képletű tiazolil-egység;

R^2 és R^3 jelentése egymástól függetlenül az alábbiak közül van megválasztva:

i) hidrogénatom;

ii) adott esetben helyettesített, C_1-C_6 egyenes vagy elágazó láncú vagy gyűrűs alkilcsoport;

iii) adott esetben helyettesített fenilcsoport; vagy

iv) adott esetben helyettesített, 5-tagú vagy 6-tagú heteroarilgyűrű, ahol legalább egy gyűrűbeli atom nitrogén-, oxigén- és kénatom közül van megválasztva;

vagy

R^2 és R^3 együtt telített vagy telítetlen, 5 - 7 atomot tartalmazó gyűrűt alkothat;

R^4 jelentése az alábbiak közül van megválasztva:

i) hidrogénatom;

ii) adott esetben helyettesített, C_1-C_6 egyenes vagy elágazó láncú vagy gyűrűs alkilcsoport;

iii) adott esetben helyettesített fenilcsoport; vagy

iv) adott esetben helyettesített, 5-tagú vagy 6-tagú heteroarilgyűrű, ahol legalább egy gyűrűbeli atom nitrogén-, oxigén- és kénatom közül van megválasztva;

R, R^2, R^3 és R^4 esetén a helyettesítők egymástól függetlenül vannak megválasztva egy vagy több C_1-C_6 egyenes vagy elágazó láncú vagy gyűrűs alkilcsoport, $-N(R^{16})_2$, $-OR^{16}$, halogénatom vagy cianocsoport közül; mindegyik R^{16} jelentése egymástól függetlenül hidrogénatom vagy C_1-C_4 egyenes vagy elágazó láncú vagy gyűrűs alkilcsoport;

Z jelentése

$$—(L)_g—R^1$$

képletű csoport;

R^1 jelentése az alábbiak közül van megválasztva:

i) hidrogénatom;

ii) adott esetben helyettesített, C_1-C_6 egyenes vagy elágazó láncú vagy gyűrűs alkilcsoport;

iii) adott esetben helyettesített C_6 arilcsoport, ahol mindegyik helyettesítő egymástól függetlenül halogénatom, C_1-C_4 egyenes vagy elágazó láncú vagy gyűrűs alkilcsoport, $-OR^{11}$, -CN, $-N(R^{11})_2$, $-CO_2R^{11}$,

$-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NO_2$ és $-SO_2R^{11}$ csoport közül van megválasztva, mindegyik R^{11} jelentése egymástól függetlenül megválasztva hidrogénatom, adott esetben helyettesített C_1-C_4 egyenes vagy elágazó láncú vagy gyűrűs alkil-, alkenil- vagy alkinilcsoport vagy adott esetben helyettesített fenil- vagy benzilcsoport; vagy két R^{11} egység együtt 3 - 7 atomot tartalmazó gyűrűt képezhet;

iv) adott esetben helyettesített C_1-C_9 heterociklusos gyűrűk, ahol a heteroatomok nitrogén-, oxigén- és kénatomok közül vannak megválasztva; vagy

v) adott esetben helyettesített C_1-C_9 heteroarilgyűrűk, ahol legalább egy heteroatom nitrogén-, oxigén- és kénatomok közül megválasztott heteroatom;

L jelentése az alábbiak közül megválasztott kapcsoló csoport:

i) $-C(O)NH[C(R^{5a}R^{5b})]_w-$;

ii) $-C(O)[C(R^{6a}R^{6b})]_x-$;

iii) $-C(O)[C(R^{7a}R^{7b})]_yC(O)-$,

iv) $-SO_2[C(R^{8a}R^{8b})]_z-$;

R^{5a}, R^{5b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{8a} és R^{8b} jelentése egymástól függetlenül az alábbi:

i) hidrogénatom;

ii) adott esetben helyettesített, C_1-C_4 egyenes vagy elágazó láncú alkilcsoport;

iii) adott esetben helyettesített arilcsoport;

iv) adott esetben helyettesített heterociklusos gyűrűk; vagy

v) adott esetben helyettesített C_1-C_9 heteroarilcsoport;

R^1, R^{5a}, R^{5b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{8a} és R^{8b} esetén a helyettesítők egymástól függetlenül vannak megválasztva egy vagy több C_1-C_6 egyenes vagy elágazó láncú vagy gyűrűs alkilcsoport, fenilcsoport, benzilcsoport, C_1-C_9 heteroarilcsoport, $-C(O)R^9$ és $-NHC(O)R^9$ csoport közül; R^9 jelentése C_1-C_6 egyenes vagy elágazó láncú alkilcsoport, C_1-C_6 egyenes vagy elágazó láncú alkoxicsoport vagy $-NHCH_2C(O)R^{10}$ képletű csoport; R^{10} jelentése hidrogénatom, metil-, etil- és *terc*-butilcsoport közül van megválasztva;

n értéke 0 vagy 1; w, x, y és z értéke egymástól függetlenül 1, 2, 3 vagy 4 -

vagy egy gyógyászatilag elfogadható sója.

2. Az 1. igénypont szerinti vegyület, ahol R^2 és R^3 mindegyike hidrogénatomot vagy adott esetben helyettesített, C_1-C_6 egyenes vagy elágazó láncú vagy gyűrűs alkilcsoportot jelent.

3. Az 1. igénypont szerinti vegyület, ahol R^2 jelentése adott esetben helyettesített fenilcsoport és R^3 jelentése hidrogénatom, vagy R^2 jelentése adott esetben helyettesített heteroarilcsoport és R^3 jelentése hidrogénatom.

4. Az 1. igénypont szerinti vegyület, ahol R^4 jelentése hidrogénatom vagy adott esetben helyettesített, C_1-C_6 egyenes vagy elágazó láncú vagy gyűrűs alkilcsoport, vagy R^4 jelentése adott esetben helyettesített fenilcsoport és R^3 jelentése hidrogénatom.

5. Az 1. igénypont szerinti vegyület, ahol R^4 jelentése adott esetben helyettesített heteroarilcsoport.

6. Az 1 - 5. igénypontok bármelyike szerinti vegyület, ahol L jelentése

$$-C(O)[C(R^{6a}R^{6b})]_x-$$

képletű csoport, és ebben a képletben

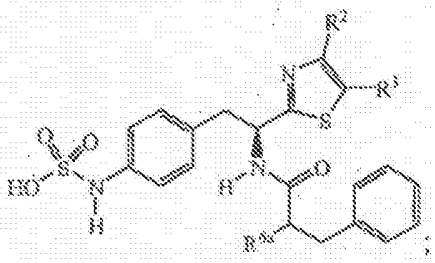
R^{6a} jelentése hidrogénatom, adott esetben helyettesített fenilcsoport vagy adott esetben helyettesített heteroarilcsoport, és

x értéke 1 vagy 2.

7. A 6. igénypont szerinti vegyület, ahol R^1 jelentése fenil-, 2-fluorfenil-, 3-fluorfenil-, 4-fluorfenil-, 2,3-difluorfenil-, 3,4-difluorfenil-, 3,5-difluorfenil-, 2-klórfenil-, 3-klórfenil-, 4-klórfenil-, 2,3-diklórfenil-, 3,4-diklórfenil-, 3,5-diklórfenil-, 2-hidroxifenil-, 3-hidroxifenil-, 4-hidroxifenil-, 2-metoxifenil-, 3-metoxifenil-, 4-metoxifenil-, 2,3-dimetoxifenil-, 3,4-dimetoxifenil- és 3,5-dimetoxifenilcsoport közül van megválasztva.

8. Az 1. igénypont szerinti vegyületek közül az alábbi képletű vegyületek:

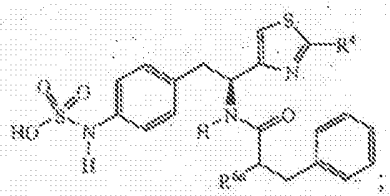
i)



;

- ahol a képletben R^2 jelentése metil- vagy etilcsoport, R^3 jelentése hidrogénatom, és R^{6a} jelentése fenil-, 2-fluorfenil-, 3-fluorfenil-, 4-fluorfenil-, 2,3-difluorfenil-, 3,4-difluorfenil-, 3,5-difluorfenil-, 2-klórfenil-, 3-klórfenil-, 4-klórfenil-, 2,3-diklórfenil-, 3,4-diklórfenil-, 3,5-diklórfenil-, 2-hidroxifenil-, 3-hidroxifenil-, 4-hidroxifenil-, 2-metoxifenil-, 3-metoxifenil-, 4-metoxifenil-, 2,3-dimetoxifenil-, 3,4-dimetoxifenil- és 3,5-dimetoxifenilcsoport közül van megválasztva -;

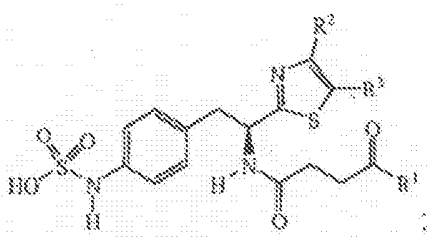
ii)



;

- ahol a képletben R^4 jelentése metil-, etil-, fenil- vagy tiofén-2-il-csoport, és R^{6a} jelentése fenil-, 2-fluorfenil-, 3-fluorfenil-, 4-fluorfenil-, 2,3-difluorfenil-, 3,4-difluorfenil-, 3,5-difluorfenil-, 2-klórfenil-, 3-klórfenil-, 4-klórfenil-, 2,3-diklórfenil-, 3,4-diklórfenil-, 3,5-diklórfenil-, 2-hidroxifenil-, 3-hidroxifenil-, 4-hidroxifenil-, 2-metoxifenil-, 3-metoxifenil-, 4-metoxifenil-, 2,3-dimetoxifenil-, 3,4-dimetoxifenil- és 3,5-dimetoxifenilcsoport közül van megválasztva -;

iii)

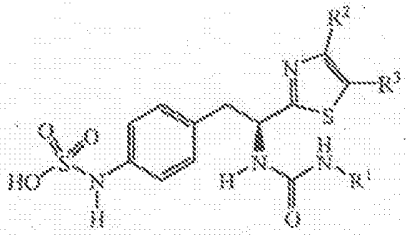


;

- ahol a képletben R^2 jelentése metil-, etil-, fenil- és tiofén-2-il-csoport közül van megválasztva, R^3 jelentése hidrogénatom vagy metilcsoport; és R^1 jelentése fenil-, tiofén-2-il-, tiofén-3-il-, tiazol-2-il-, tiazol-4-il-, tiazol-5-il-, oxazol-2-il-, oxazol-4-il-, oxazol-5-il- és izoxazol-3-il-csoport közül van megválasztva -;

vagy

iv)

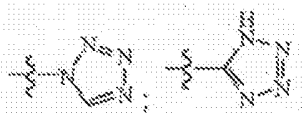


- ahol a képletben R^2 és R^3 jelentése egymástól függetlenül hidrogénatom, metilcsoport vagy etilcsoport, és R^1 jelentése fenil-, 2-fluorfenil-, 3-fluorfenil-, 4-fluorfenil-, 2,3-difluorfenil-, 3,4-difluorfenil-, 3,5-difluorfenil-, 2-klórfenil-, 3-klórfenil-, 4-klórfenil-, 2,3-diklórfenil-, 3,4-diklórfenil-, 3,5-diklórfenil-, 2-hidroxifenil-, 3-hidroxifenil-, 4-hidroxifenil-, 2-metoxifenil-, 3-metoxifenil-, 4-metoxifenil-, 2,3-dimetoxifenil-, 3,4-dimetoxifenil- és 3,5-dimetoxifenilcsoport közül van megválasztva -.

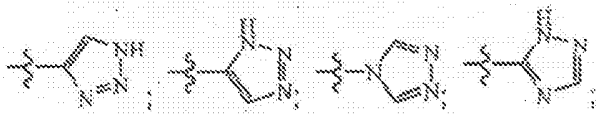
9. Az 1. igénypont szerinti vegyület, ahol R jelentése

képletű csoport, és a Z helyettesítő képletében R^1 jelentése az alábbiak közül megválasztott, adott esetben helyettesített heteroarilcsoport:

i) rendre az alábbi képletek valamelyikével bíró 1,2,3,4-tetrazol-1-il- és 1,2,3,4-tetrazol-5-il-csoport:

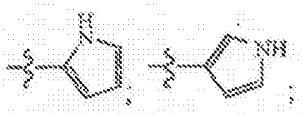


ii) rendre az alábbi képletek valamelyikével bíró [1,2,3]triazol-4-il-, [1,2,3]triazol-5-il-, [1,2,4]triazol-4-il- és [1,2,4]triazol-5-il-csoport:



iii) rendre az alábbi képletek valamelyikével bíró imidazol-2-il- és imidazol-4-il-csoport:

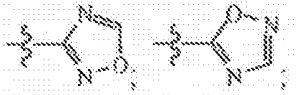
iv) rendre az alábbi képletek valamelyikével bíró pirrol-2-il- és pirrol-3-il-csoport:



v) rendre az alábbi képletek valamelyikével bíró oxazol-2-il-, oxazol-4-il- és oxazol-5-il-csoport:

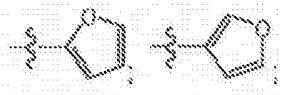
vi) rendre az alábbi képletek valamelyikével bíró izoxazol-3-il-, izoxazol-4-il- és izoxazol-5-il-csoport:

vii) rendre az alábbi képletek valamelyikével bíró [1,2,4]oxadiazol-3-il- és [1,2,4]oxadiazol-5-il-csoport:



viii) az alábbi képletű [1,3,4]oxadiazol-2-il-csoport:

ix) rendre az alábbi képletek valamelyikével bíró furán-2-il- és furán-3-il-csoport:



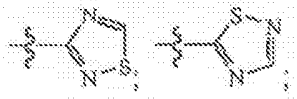
x) rendre az alábbi képletek valamelyikével bíró tiofén-2-il- és tiofén-3-il-csoport:

xi) rendre az alábbi képletek valamelyikével bíró izotiazol-3-il-, izotiazol-4-il- és izotiazol-5-il-csoport:

xii) rendre az alábbi képletek valamelyikével bíró tiazol-2-il-, tiazol-4-il- és tiazol-5-il-csoport:

és

xiii) rendre az alábbi képletek valamelyikével bíró [1,2,4]tiadiazol-3-il- és [1,2,4]tiadiazol-5-il-csoport:



ahol az említett heteroarilcsoportok helyettesítői C_1-C_6 egyenes vagy elágazó láncú vagy gyűrűs alkilcsoport, adott esetben helyettesített fenil- és benzilcsoport, adott esetben helyettesített C_1-C_3 heteroarilcsoport, -C(O)R^7 és -NHC(O)R^8 csoport közül vannak megválasztva; R^7 jelentése C_1-C_6 egyenes vagy elágazó láncú alkilcsoport, C_1-C_6 egyenes vagy elágazó láncú alkoxicsoport vagy -$NHCH_2C(O)R^{10}$ csoport; és R^{10} jelentése hidrogénatom, metilcsoport, etilcsoport és *terc*-butilcsoport közül van megválasztva; és

R^4 jelentése az alábbiak közül van megválasztva:

i) hidrogénatom;

ii) adott esetben helyettesített, C_1-C_6 egyenes vagy elágazó láncú vagy gyűrűs alkilcsoport;

iii) adott esetben helyettesített fenilcsoport; vagy

iv) adott esetben helyettesített, 5-tagú vagy 6-tagú heteroarilgyűrű, ahol legalább egy gyűrűbeli atom nitrogén-, oxigén- és kénatom közül van megválasztva.

10. A 9. igénypont szerinti vegyület, ahol Z jelentése 4-(metoxi-karbonil)-tiazol-5-il-, 4-[(2-metoxi-2-oxoetil)-karbamoil]-tiazol-5-il-, 5-[1-*N*-(2-metoxi-2-oxoetil)-1-*H*-indol-3-il]-oxazol-2-il-, 5-(2-metoxifenil)-oxazol-2-il-, 5-[(*S*)-1-(*terc*-butoxikarbonil)-2-feniletil]-oxazol-2-il-, 5-[4-(metil-karboxi)-fenil]-oxazol-2-il-, 5-(3-metoxibenzil)-oxazol-2-il-, 5-(4-fenil)-oxazol-2-il-, 5-(2-metoxifenil)-tiazol-2-il-, 5-(3-metoxifenil)-tiazol-2-il-, 5-(4-fluorfenil)-tiazol-2-il-, 5-(2,4-difluorfenil)-tiazol-2-il-, 5-(3-metoxi-benzil)-tiazol-2-il-, 4-(3-metoxi-fenil)-tiazol-2-il- és 4-(4-fluorfenil)-tiazol-2-ilcsoport közül van megválasztva.

11. Az 1. igénypont szerinti vegyületek közül az alábbiak valamelyike:

(*S*)-{4-[2-(4-etiltiazol-2-il)-2-fenilacetilaminoetil]-fenil}szulfaminsav;

(*S*)-4-(2-(4-etiltiazol-2-il)-2-(2-(2-fluorfenil)acetamido)etil)fenil-szulfaminsav;

(*S*)-4-(2-(4-etiltiazol-2-il)-2-(2-(3-fluorfenil)acetamido)etil)fenil-szulfaminsav;

(*S*)-4-(2-(2-(2,3-difluorfenil)acetamido)-2-(4-etiltiazol-2-il)etil)fenil-szulfaminsav;

(*S*)-4-(2-(2-(3,4-difluorfenil)acetamido)-2-(4-etiltiazol-2-il)etil)fenil-szulfaminsav;

(*S*)-4-(2-(2-(2-klórfenil)acetamido)-2-(4-etiltiazol-2-il)etil)fenil-szulfaminsav;

(*S*)-4-(2-(2-(3-klórfenil)acetamido)-2-(4-etiltiazol-2-il)etil)fenil-szulfaminsav;

(*S*)-4-(2-(4-etiltiazol-2-il)-2-(2-(3-hidroxifenil)acetamido)etil)fenil-szulfaminsav;

(*S*)-4-(2-(4-etiltiazol-2-il)-2-(2-(2-metoxifenil)acetamido)etil)fenil-szulfaminsav;

(*S*)-4-(2-(4-etiltiazol-2-il)-2-(2-(3-metoxifenil)acetamido)etil)fenil-szulfaminsav;

(*S*)-4-(2-(4-etiltiazol-2-il)-2-(3-fenilpropánamido)etil)fenilszulfaminsav;

(*S*)-4-(2-(2-(3,4-dimetoxifenil)acetamido)-2-(4-etiltiazol-2-il)etil)-fenilszulfaminsav;

(*S*)-4-(2-(2-(2,3-dimetoxifenil)acetamido)-2-(4-etiltiazol-2-il)etil)-fenilszulfaminsav;

(*S*)-4-(2-(3-(3-klórfenil)propánamido)-2-(4-etiltiazol-2-il)etil)fenil-szulfaminsav;

(*S*)-4-(2-(4-etiltiazol-2-il)-2-(3-(2-metoxifenil)propánamido)etil)fenil-szulfaminsav;

(*S*)-4-(2-(4-etiltiazol-2-il)-2-(3-(3-metoxifenil)propánamido)etil)fenil-szulfaminsav;

(*S*)-4-(2-(4-etiltiazol-2-il)-2-(3-(4-metoxifenil)propánamido)etil)fenil-szulfaminsav;

(*S*)-4-{2-[2-(4-etil-2,3-dioxopiperazin-1-il)acetamido]-2-(4-etiltiazol-2-il)etil}fenilszulfaminsav;

(*S*)-4-{2-(4-etiltiazol-2-il)-2-[2-(5-metil-2,4-dioxo-3,4-dihidropirimidin-1(2*H*)-il)acetamido]etil}-fenilszulfaminsav;

(*S*)-4-[2-(benzo[*d*][1,3]dioxol-5-karboxamido)-2-(4-etiltiazol-2-il)etil]-fenilszulfaminsav;

4-((*S*)-2-(2-(2-klórfenil)acetamido)-2-(2-(tiofén-2-il)tiazol-4-il)etil)fenilszulfaminsav;

4-((*S*)-2-(2-(3-metoxifenil)acetamido)-2-(2-(tiofén-2-il)tiazol-4-il)etil)-fenilszulfaminsav;

4-{(*S*)-2-(3-fenilpropánamido)-2-[2-(tiofén-2-il)tiazol-4-il]etil}fenil-szulfaminsav;

4-{(*S*)-2-(3-(3-klórfenil)propánamido)-2-[2-(tiofén-2-il)tiazol-4-il]etil}fenilszulfaminsav;

4-{(*S*)-2-[2-(3-fluorfenil)acetamido]-2-[2-(tiofén-2-il)tiazol-4-il]etil}fenilszulfaminsav,

(*S*)-4-{2-[2-(2,5-dimetiltiazol-4-il)acetamido]-2-(4-etiltiazol-2-il]etil}-fenilszulfaminsav;

(*S*)-4-{2-[2-(2,4-dimetiltiazol-5-il)acetamido]-2-(4-metiltiazol-2-iletil}fenilszulfaminsav;

(*S*)-4-{2-(4-etiltiazol-2-il)-2-[3-(tiazol-2-il)propánamido]etil}fenil-szulfaminsav;

(*S*)-4-{2-(4-etiltiazol-2-il)-2-[2-(4-etiltiazol-2-il)acetamido]etil}-fenil-szulfaminsav;

(*S*)-4-{2-[2-(3-metil-1,2,4-oxadiazol-5-il)acetamido]-2-(2-feniltiazol-4-il)etil}fenilszulfaminsav;

4-{(*S*)-2-[2-(4-etil-2,3-dioxopiperazin-1-il)acetamido]-2-[2-(tiofén-2-il)tiazol-4-il]etil}fenilszulfaminsav;

(*S*)-4-(2-(2,3-difenilpropánamido)-2-(4-etiltiazol-2-il)etil)fenilszulfaminsav;

(*S*)-4-{2-(4-etiltiazol-2-il)-2-[2-(2-metoxifenil)-3-fenilpropánamido]-etil}fenilszulfaminsav;

(*S*)-4-{2-(4-etiltiazol-2-il)-2-[2-(3-fluorfenil)-3-fenilpropánamido]-etil}fenilszulfaminsav;

(*S*)-4-{2-(4-etiltiazol-2-il)-2-[2-(3-metoxifenil)-3-fenilpropánamido]-etil}fenilszulfaminsav;

4-{(*S*)-2-(4-etiltiazol-2-il)-2-[2-(3-metil-1,2,4-oxadiazol-5-il)-3-fenilpropánamido]etil}fenilszulfaminsav;

(*S*)-4-[2-(4-etiltiazol-2-il)-2-(4-oxo-4-fenilbutánamido)-etil]fenilszulfaminsav;

(*S*)-4-(2-(4-etiltiazol-2-il)-2-(5-metil-4-oxohexánamido)etil)fenil-szulfaminsav;

(*S*)-4-{2-[4-(3,4-dihidro-2H-benzo[b][1,4]dioxepin-7-il)-4-oxobutánamido]-2-(4-etiltiazol-2-il)etil}fenil-szulfaminsav;

(*S*)-4-{2-[4-(2,3-dimetoxifenil)-4-oxobutánamido]-2-(4-etiltiazol-2-il)etil}fenilszulfaminsav;

(*S*)-4-{2-(4-etiltiazol-2-il)-2-[4-oxo-4-(piridin-2-il)butánamido]etil}-fenilszulfaminsav;

(*S*)-4-{2-[4-(2,3-dihidrobenzo[b][1,4]dioxin-6-il)-4-oxobutánamido]-2-(4-etiltiazol-2-il)etil}fenilszulfaminsav;

(*S*)-4-[2-(4-*terc*-butoxi-4-oxobutánamido)-2-(4-etiltiazol-2-il)etil]fenil-szulfaminsav;

(*S*)-4-[2-(4-etoxi-4-oxobutánamido)-2-(4-etiltiazol-2-il)etil]fenilszulfaminsav;

(*S*)-4-(2-(3-benzilureido)-2-(4-etiltiazol-2-il)etil)fenil-szulfaminsav;

4-{(*S*)-2-(3-benzilureido)-2-[2-(tiofén-2-il)tiazol-4-il]etil}fenil-szulfaminsav;

{4-(*S*)-[2-fenilmetánszulfonilamino-2-(2-tiofén-2-il-tiazol-4-il)etil]fenil}szulfaminsav;

4-{(*S*)-2-[(2-metiltiazol-4-il)metilszulfonamido]-2-[2-(tiofén-2-il)tiazol-4-il]etil}fenilszulfaminsav;

{4-(*S*)-[2-fenilmetánszulfonilamino-2-(2-etiltiazol-4-il)etil]fenil}-szulfaminsav;

{4-(*S*)-[2-(3-metoxifenil)metánszulfonilamino-2-(2-etiltiazol-4-il)etil]fenil}szulfaminsav;

(*S*)-4-{[1-(2-etiltiazol-4-il)-2-(4-szulfoaminofenil)etilszulfamoil]metil}-benzoesav-metilészter;

(*S*)-4-[2-(2-etiltiazol-4-il)-2-(1-metil-1*H*-imidazol-4-szulfonamido)etil]-fenilszulfaminsav;

4-{(*S*)-2-[2-(tiofén-2-il)tiazol-4-il]-2-(2,2,2-trifluoretilszulfonamido)-etil}fenilszulfaminsav;

{4-(*S*)-[2-(feniletánszulfonilamino)-2-(2-tiofén-2-il-tiazol-4-il)etil]-fenil}szulfaminsav;

{4-(*S*)-[3-(fenilpropánszulfonilamino)-2-(2-tiofén-2-il-tiazol-4-il)etil]-fenil}szulfaminsav;

(*S*)-{4-[2-(4-metil-3,4-dihidro-2H-benzo[1,4]oxazin-7-szulfonilamino)-2-(2-tiofén-2-il-tiazol-4-il)etil]fenil}-szulfaminsav;

4-{(*S*)-2-(4-acetamidofenilszulfonamido)-2-[2-(tiofén-2-il)tiazol-4-il]etil}fenilszulfaminsav;

4-{(*S*)-2-(2-ciklopropiltiazol-4-il)-2-[4-(3-metoxifenil)-tiazol-2-ilamino]etil}fenilszulfaminsav;

(*S*)-4-(2-(4-((2-metoxi-2-oxoetil)karbamoil)tiazol-5-ilamino)2-(2-etiltiazol-4-il)etil)fenilszulfaminsav;

4-((*S*)-2-(5-(1-*N*-(2-metoxi-2-oxoetil)-1-*H*-indol-3-il)oxazol-2-ilamino)-2-(2-metiltiazol-4-il)etil))-fenilszulfaminsav;

4-((*S*)-2-(5-(2-metoxifenil)oxazol-2-ilamino)-2-(2-metiltiazol-4-il)etil)fenilszulfaminsav;

4-((*S*)-2-(5-((*S*)-1-(terc-butoxikarbonil)-2-feniletil)oxazol-2-ilamino)-2-(2-metiltiazol-4-il)etil)-fenilszulfaminsav;

(*S*)-4-(2-(5-(4-metoxikarbonil)fenil)oxazol-2-ilamino)2-(2-metiltiazol-4-il)etil)fenilszulfaminsav;

(*S*)-4-(2-(5-(3-metoxibenzil)oxazol-2-ilamino)-2-(2-metiltiazol-4-il)etil)fenilszulfaminsav;

(*S*)-4-(2-(2-metiltiazol-4-il)2-(5-feniloxazol-2-ilamino)etil)fenil-szulfaminsav;

4-((*S*)-2-(2-ciklopropiltiazol-4-il)-2-(4-(3-metoxifenil)tiazol-2-ilamino)etil)fenilszulfaminsav;

(*S*)-4-(2-(2-ciklopropiltiazol-4-il)-2-(4-(4-fluorfenil)tiazol-2-ilamino)etil)fenilszulfaminsav;
4-((*S*)-2-(2-ciklopropiltiazol-4-il)-2-(4-(2-metoxifenil)tiazol-2-ilamino)etil)fenilszulfaminsav;
4-((*S*)-2-(2-ciklopropiltiazol-4-il)-2-(4-(2,4-difluorfenil)tiazol-2-ilamino)etil)fenilszulfaminsav;
(*S*)-4-(2-(4-(3-metoxibenzil)tiazol-2-ilamino)-2-(2-ciklopropiltiazol-4-il)etil)fenilszulfaminsav;
(*S*)-{5-[1-(2-etiltiazol-4-il)-2-(4-szulfoaminofenil)etilamino]-2-metil-2H-[1,2,4]triazol-3-il}karbaminsav-metilészter;
4-{(*S*)-2-[4-(2-metoxifenil)tiazol-2-ilamino)-2-[2-(tiofén-2-il)tiazol-4-il]etil}fenilszulfaminsav;
4-{(*S*)-2-[5-(3-metoxifenil)oxazol-2-ilamino]-2-(2-feniltiazol-4-il)etil}fenilszulfaminsav;
4-{(*S*)-2-[4-(2,4-difluorfenil)tiazol-2-ilamino]-2-[2-(tiofén-2-il)tiazol-4-il]etil}fenilszulfaminsav;
(*S*)-4-{2-[4-(etoxikarbonil)tiazol-2-ilamino]-2-(2-feniltiazol-4-il)etil}fenilszulfaminsav;
(*S*)-4-{2-[4-(2-etoxi-2-oxoetil)tiazol-2-ilamino]-2-(2-feniltiazol-4-il)etil}fenilszulfaminsav;
(*S*)-4-{2-[4-(4-acetamidofenil)tiazol-2-ilamino]-2-(2-feniltiazol-4-il)etil}fenilszulfaminsav;
(*S*)-4-[2-(4-feniltiazol-2-ilamino)-2-(2-feniltiazol-4-il)etil]fenil-szulfaminsav;
(*S*)-4-{2-[4-(4-(metoxikarbonil)fenil)tiazol-2-ilamino]-2-(2-feniltiazol-4-il)etil}fenilszulfaminsav;
4-{(*S*)-2-[4-(etoxikarbonil)tiazol-2-ilamino]-2-[2-(tiofén-2-il)tiazol-4-il]etil}fenilszulfaminsav;
(*S*)-4-[2-(4-(metoxikarbonil)tiazol-5-ilamino)-2-(2-feniltiazol-4-il)etil]fenilszulfaminsav;
(*S*)-4-[2-(5-feniloxazol-2-ilamino)]-2-(2-feniltiazol-4-il)fenilszulfaminsav;
(*S*)-4-{2-[5-(4-acetamidofenil)oxazol-2-ilamino]-2-(2-feniltiazol-4-il)etil}fenilszulfaminsav;
4-((*S*)-2-(5-(2,4-difluorfenil)oxazol-2-ilamino)-2-(2-feniltiazol-4-il)etil)fenilszulfaminsav;
4-{(*S*)-2-[5-(3-metoxifenil)oxazol-2-ilamino]-2-[(2-tiofén-2-il)tiazol-4-il]etil}fenilszulfaminsav;
(*S*)-4-[2-(4,6-dimetilpirimidén-2-ilamino)-2-(2-metiltiazol-4-il)etil]fenilszulfaminsav; és
(*S*)-4-[2-(4-hidroxi-6-metilpirimidin-2-ilamino)-2-(2-metiltiazol-4-il)etil]fenilszulfaminsav.

12. Az 1 – 11. igénypontok bármelyike szerinti vegyület, ahol a vegyületek klorid, bromid, jodid, szulfát, biszulfát, karbonát, bikarbonát, foszfát, formiát, acetát, propionát, butirát, piruvát, laktát, oxalát, malonát, maleát, szukcinát, tartarát, fumarát és citrát közül megválasztott anionokat vagy nátrium, lítium, kálium, kalcium, magnézium és bizmut közül megválasztott kationokat tartalmazó sók.

13. Az 1 – 12. igénypontok bármelyike szerinti vegyület alkalmazása olyan gyógyszer előállítására, amely alkalmas a következőkben felsorolt betegségek valamelyikének kezelésére: sarlósejtes vérszegénység, sarcoid (daganat), vérbaj, pseudoxantoma elasticum, Paget-kór, véna-elzáródás, artéria-elzáródás, nyaki verőér elzáródásos megbetegedése, krónikus uveagyulladás/üvegtest gyulladásos megbetegedése, mikobakteriális fertőzések, Lyme-kór, egész szervezetre kiterjedő bőrtuberkulózis, koraszülöttségkor jelentkező recehártya-betegség, Eales-kór, Behcet-kór, recehártyagyulladást vagy érhártyagyulladást okozó fertőzések, vélt szembéli hisztoplazma-fertőzés, Best-kór, rövidlátás, optikai ideglyukak, Stargardt-kór, pars planitis, krónikus retinaleválás, hiperviszkozitás szindróma, toxoplazma-fertőzés, sérülés és lézer-kezelés utáni szövődmények, kanyaróval kapcsolatos megbetegedések, pikkelysömör, sarcoidosis, reumás ízületi gyulladás, a belhámsejtek jóindulatú duzzadásai, Osler-Weber-Rendu-kór, vagy öröklődő vérzéses hajszálértágulat, szilárd vagy vérben képződő tumorok, szerzett immunhiányos szindróma, vázizom- és miokardiális helyi vérelégtelenség, sztrók, koszorúér-artériabetegség, perifériális érbetegség.

14. Az 1 – 12. igénypontok bármelyike szerinti vegyület alkalmazása érképződés szabályozására, helyi vérelégtelenségben szenvedő szövet ereződésére, bőrbetültetésnél a betültetett bőr növekedésének elősegítésére

vagy szabályozott szövetregenerálás (guided tissue regeneration - GTR) vonatkozásában a szövetreparáció elősegítésére alkalmas gyógyszer előállítására.

15. Az 1 – 12. igénypontok bármelyike szerinti vegyület sarlósejtes vérszegénység, sarcoid (daganat), vérbaj, pseudoxantoma elasticum, Paget-kór, véna-elzáródás, artéria-elzáródás, nyaki verőér elzáródásos megbetegedése, krónikus uveagyulladás/üvegtest gyulladásos megbetegedése, mikobakteriális fertőzések, Lyme-kór, egész szervezetre kiterjedő bőrtuberkulózis, koraszülöttségkor jelentkező recehártya-betegség, Eales-kór, Behcet-kór, recehártyagyulladást vagy érhártyagyulladást okozó fertőzések, vélt szembéli hisztoplazma-fertőzés, Best-kór, rövidlátás, optikai ideglyukak, Stargardt-kór, pars planitis, krónikus retinaleválás, hipervizkozitás szindróma, toxoplazma-fertőzés, sérülés és lézer-kezelés utáni szövődmények, kanyaróval kapcsolatos megbetegedések, pikkelysömör, sarcoidosis, reumás ízületi gyulladás, a belhámsejtek jóindulatú duzzadásai, Osler-Weber-Rendu-kór, vagy öröklődő vérzéses hajszálértágulat, szilárd vagy vérben képződő tumorok, szerzett immunhiányos szindróma, vázizom- és miokardiális helyi vérelégtelenség, sztrók, koszorúér-artéria-betegség és perifériális érbetegség közül megválasztott állapot kezelésére való alkalmazásra.

16. Az 1 – 12. igénypontok bármelyike szerinti vegyület érképződés szabályozására, helyi vérelégtelenségben szenvedő szövet ereződésére, bőrbeültetésnél a beültetett bőr növekedésének elősegítésére vagy szabályozott szövetregenerálás (guided tissue regeneration - GTR) vonatkozásában a szövetreparáció elősegítésére való alkalmazására.