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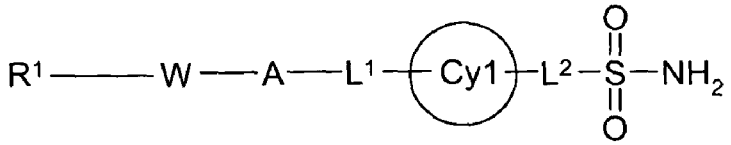
(54) Title: COMPOUNDS USEFUL AS CARBONIC ANHYDRASE MODULATORS AND USES THEREOF



I'

(57) Abstract: Compounds are disclosed that have formula (I'): wherein A, W, Cy1, Cy2, L^1, L^2, R^1 and R^2 are as defined herein. The compounds and pharmaceutical compositions thereof are useful as probes and imaging agents for identifying hypoxic tumors, and treatment of a variety of conditions such as cancers involving hypoxic tumors, in mammals including humans, including by way of non-limiting example, and others.

COMPOUNDS USEFUL AS CARBONIC ANHYDRASE MODULATORS AND USES THEREOF

PRIORITY APPLICATIONS

GOVERNMENT RIGHTS

[0001] This invention was made with government support under Grant Nos. **5PO1 CA33049** and **5P50 CA086438** awarded by the National Institutes of Health. Accordingly, the United States Government has certain rights in the invention.

FIELD OF THE INVENTION

[0002] This invention relates to novel compounds that are capable of modulating Carbonic Anhydrase activity, and to pharmaceutical compositions containing such compounds. The invention further relates to preparation of such compounds. This invention also relates to methods and use of these compounds or Carbonic anhydrase ligands as imaging agents for detection of tumors.

BACKGROUND OF THE INVENTION

[0003] Solid tumors which have regions of very low oxygen concentrations are said to be hypoxic. Hypoxia is a natural phenomenon of solid tumors and results from an insufficient vascular network. Tumour hypoxia results in resistance to ionizing radiation, resistance to chemotherapy and the magnification of mutated p53. In addition tissue hypoxia has been regarded as a key factor for tumour aggressiveness and metastasis by activation of signal transduction pathways and gene regulatory mechanisms. It is clear that hypoxia in solid tumors promotes a strong oncogenic phenotype and is a phenomenon that occurs in all solid tumors.

[0004] Tumor hypoxia usually occurs at a distance of 100–200μm from blood vessels [1,2] and seems to be strongly associated with tumor propagation, malignant progression and resistance to chemo- and radiotherapy [2] Hypoxia regulates the expression of several genes, including of Hypoxia-Inducible Factor 1α. (HIF-1α). HIF-1α can activate a large number of genes including many of those responsible for cell proliferation and apoptosis, glucose metabolism, pH regulation, erythropoiesis, iron metabolism, extracellular matrix metabolism, inflammation, angiogenesis and control of vascular tone [3]. However, carbonic anhydrase isoform CAIX is one of the most inducible and most uniformly HIF-1α induced genes [4]. Moreover because of its longer half-life (around 38 hours compared to minutes to HIF-1α [5]) and membrane location, it has become a reliable histological marker of hypoxia [6-8].

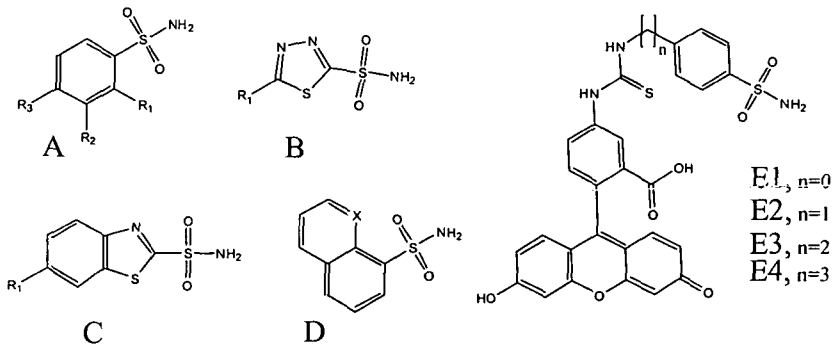
[0005] The expression of CAIX, as evaluated by immunohistochemical techniques in several human cancers, has revealed a prognostic significance in renal [9], breast [10], bladder [11] head and neck [12, 13], cervix carcinomas [14], soft tissue sarcoma [15] and in non-small cell lung carcinoma [16, 17]. In the gastrointestinal tract, its expression has been demonstrated in esophageal, gastric, colorectal, biliary, and pancreatic adenocarcinomas (range, 34%–80%) [18-20]. High CAIX expression has been

observed to correlate with poor prognosis in both esophageal and gastric adenocarcinoma [21]. Despite elevated expression in malignancies, it is generally absent from the normal tissues from which these tumors develop. Expression of CAIX in normal human tissues is restricted to epithelia of the gastrointestinal tract, namely those lining the stomach, small intestine and gallbladder [22].

[0006] Initial investigations using xenograft models demonstrated that the intratumoral expression of CAIX co-localized closely with the exogenous hypoxia marker pimonidazole, suggesting that expression of CAIX may act as an endogenous marker of tumor hypoxia [23]. Using immunohistochemical methods, the positive correlation of CAIX expression with uptake of exogenous hypoxia markers has been demonstrated in tumors of the cervix, nasophaynx and lung [24-26]. In addition, positive correlations have also been observed between CAIX expression and other indicators of tumor hypoxia, such as HIF [13], GLUT-1 [27] and pO_2 probe measurements[9, 28].

[0007] Fifteen different isoforms of Carbonic anhydrase are know to exist and the 12 catalytically active isoforms, which play important physiological functions are strongly inhibited by aromatic/heterocyclic sulfonamides, Only four of these isoforms (CAIV, CAIX, CAXII and CAXIV) exist as membrane bound forms. The catalytic site of these enzymes is a Zn(II) located at the bottom of a 15 Å deep active cleft and is coordinated with three histidine residues as well as a water molecule/hydroxide ion. Sulfonamide CA inhibitors work by binding to the Zn(II) ion in tetrahedral geometry via the nitrogen of the sulfonamide (31, 32).

[0008] Much of the early work on structure activity relationships has been performed with the isoform CAII and there are seven CA inhibitors in clinical use. A comparison of the inhibitory properties of a number of sulfonamides with CA I, CAII, CAIV and CAIX has been reported (Vullo et al., [33], cf Figure 1). The data show that aromatic and heterocyclic sulfonamides can be derivatised to show selectivity for CAIX over plasma membrane bound CAIV and the cytosolic CAI and CAII.



Vullo et al., Figure 1. Structure of aromatic and heterocyclic sulfonamide anlogs

[0009] Other data from the Supuran group ([34]-[36], cf Figure 2) has shown that various fluorescein-benzylsulfonamide conjugates have retained affinity for CAIX over CAI and that the spacer has little effect on these affinities (for compound E, Ki of 29, 26 and 24 nM ofr CAIX with n=0,1 and 2).

However the uptake of compound E3 by hypoxic cells showed intense staining in the cytoplasm whereas the CAIX is known to be membrane bound.

[0010] Since CAIX is an endogenous marker of hypoxia at the tumor level and HIF1 transcriptional activity at the cellular level, it is a good molecular target for imaging therapeutic interventions. The non-invasive assessment of CAIX expression has the potential to indicate disease prognosis, provide information relating to tumor biology at both the regional and molecular level, and also serve to indicate the efficacy of various radio- and chemotherapeutic strategies.

[0011] Since HIF-1α, has been shown to orchestrate a large number of molecular events required for the adaptation of tumor cells to hypoxia, it has become an attractive target for the development of anti-cancer drugs. Heat shock protein 90 (Hsp90) is a molecular chaperone whose association is required for stability and function of multiple mutated, chimeric, and over-expressed signaling proteins that promote cancer cell growth and/or survival [44]. Hsp90 client proteins include telomerase, mutated p53, Bcr-Abl, Raf-1, Akt, HER2/Neu (ErbB2), mutated B-Raf, mutated EGF receptor, and HIF-1α [44]. Treatment of a number of tumor types with HSP90 inhibitors has resulted in degradation of HIF 1α and CAIX [45-47]. In SiHa cervical carcinomas xenografts the proteasome inhibitor bortezomib has been shown to up regulate HIF-1α in non hypoxic tissue and a decrease CAIX levels [48]. In a clinical trial of bortezomib, the same groups were able to demonstrate a decrease in CAIX levels in colorectal tumors patients [48]. CAIX expression seems to be an important predictor of outcome in renal cell carcinoma patients receiving IL-2-based therapy and may enhance prognostic information obtained from pathology specimens [49]. HIV protease inhibitors such as Nelfinavir and amprenavir have been shown to decrease HIF-1α expression [50].

[0012] Histone deacetylase inhibitors (HDAIs) are among the promising anti -cancer compounds currently in clinical trials. In addition to inducing hyperacetylation of histones, HDAIs have been found to repress HIF function, which has been construed as an important pharmacological mechanism underlying the HDAI -mediated repression of tumor growth and angiogenesis. While HDAIs are potent inhibitors of HIF function and thus may be useful in the prevention and treatment of cancers, a major dilemma is that they may induce hyperacetylation of nonspecific targets thus causing side effects. A better understanding is now required of the molecular and biochemical mechanisms underlying the anti -HIF effects of these compounds [51].

[0013] Recently there has been a renewed interest in direct targeting of CA IX in cancer therapy [52]. Antiproliferative effects of sulfonamides are mediated by inhibition of CAIX [53, 54]. Indisulam is a sulfonamide derivative (originally called E7070, [55]) has demonstrated powerful anticancer activity and has recently been shown to have a nanomolar inhibitor of CA IX [56, 57] and has progressed to Phase I and Phase II clinical trials for treatment of solid tumors. Its mechanism of action is not clear, however, because the drug has a wide range of activity including: perturbation of the cell cycle in the G1 and/or G2 phases, down-regulation of cyclins, reduction of CDK2 activity, inhibition of phosphorylation of the retinoblastoma protein and in differential expression of molecules known to participate in cell adhesion, signaling and immune response, in addition to its inhibitory properties against CAIX. Indisulam shows *in vivo* efficacy against human tumor xenografts in nude mice, where it exhibits significant antitumor effects

[56]. Other CAIX inhibitors [58-60] strongly inhibit CAIX, with K_i values in the range 7.3–89 nM [59]. A broad-spectrum inhibitor acetazolamide, which can also inhibit intracellular carbonic anhydrases, has show synergy with several anti-cancer drugs in vivo [61].

[0014] Consequently, there are a number of drugs in preclinical and clinical development which directly and indirectly target CAIX, but other than invasive biopsy sampling, these is no effective method to determine the effect of the drug on its target and that is where non-invasive functional imaging methods such as Positron Emission Tomography (PET) could play a stronger role in drug development and clinical testing. PET is an emerging functional imaging technology, which is now broadly applied for imaging human tumors [62]. High resolution animal PET scanners are available for small animal imaging. An advantage of PET over conventional nuclear medicine imaging is that PET provides quantitative information about radiotracer accumulation.

[0015] As presented above, hypoxia is an important element of various tumor types and can impact on patient treatment and planning. Various tracers have been produced for non-invasive imaging of hypoxia, but they all rely on passive diffusion of the radiotracers into cells and their selective reduction and trapping in hypoxic cells as well as the release of the radiotracer from non hypoxic cells. Even with these small imaging agents the whole process can take a considerable amount of time before excess radioligand has cleared from the tissues and sufficient contrast between hypoxic and normal tumor allows for PET imaging. In addition conventional hypoxia tracers can redistribute over time and it is unclear if this is reflecting true hypoxic changes in the tumor microenvironment or some other effect. Since CAIX has a slow degradation rate *in vivo* ($t_{1/2}$ around 38 hours), this indicator of hypoxia will give a time averaged picture of the tumor hypoxia rather than a snapshot image of when the tumor is being imaged.

[0016] Conventional hypoxia tracers (i.e. ^{18}F-FMIZO, ^{64}Cu-ATSM and ^{124}I-IAZGP) can redistribute over short periods of time and it is unclear if this is reflecting true hypoxic changes in the tumor microenvironment or some other effect. Since CAIX has a slow degradation rate *in vivo* ($t_{1/2}$ around 38 hours), this indicator of hypoxia will enable an average picture of the tumor hypoxia over the preceding 24-48 hours to be imaged rather than a single frame in the movie showing the varying hypoxic status of the tumor.

[0017] A variety of new cancer therapies are based direct or indirect targeting of such cellular targets as HIF1α and CAIX. Currently the only way to asses the efficacy of these agents is wait lengthy follow up periods or to perform biopsies. In practice only a fraction of study patients have biopsies because they are invasive. Moreover, a majority of patients have tumors that cannot be sampled without significant risk to the patient.

[0018] Accordingly, a need therefore exists for the development of agents, i.e. compounds, that are effective to serve as monitors or tracers of Carbonic anhydrase activity in contemporary imaging testing systems and procedures, and it is toward the fulfillment of that need, that the present invention is directed.

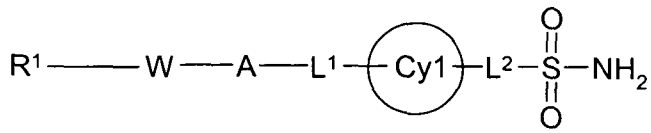
SUMMARY OF THE INVENTION

[0019] Compounds, and pharmaceutical compositions thereof, useful as probes and tracers for use in imaging systems, for indentifying hypoxic tumors are described herein.

[0020] In particular, compounds, pharmaceutical compositions and methods provided are used for indentifying hypoxic tumors in mammals.

[0021] In certain aspects, the present invention provides compounds useful as probes and racers for indentifying hypoxic tumors, wherein the the hypoxic tumor is Carbonic anhydrase IX-positive.

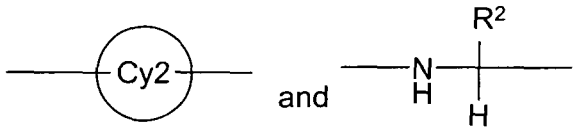
[0022] In one aspect, the present invention provides compounds according to formula I':



I'

wherein

W is a group selected from:



;

each Cy1 and Cy2 are independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

A is selectected from $-(CH_2)_n$-NH-C(=O)-, $-(CH_2)_n$-C(=O)NH-, $-(CH_2)_n$-NHC(=O)-NH-, and $-(CH_2)_n$–NH-C(=S)-NH-; n is 0, 1, or 2;

L^1 is a single bond, substituted or unsubstituted C_1-C_4 alkylene; or $-(CH_2)_m$-NH-C(=O)-; m is 2 or 3;

L^2 is a single bond, or substituted or unsubstituted C_1-C_4 alkylene;

R^1 is a metal chelator group or a fluorescent ligand; provided the metal chelator group or the fluorescent ligand contains at least 2 or more N; and each N atom is substituted with at least one CH_2COOH group; and

R^2 is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted CH_2-cycloalkyl, substituted or unsubstituted CH_2-heterocycloalkyl, substituted or unsubstituted CH_2-aryl, substituted or unsubstituted CH_2-heteroaryl, substituted or unsubstituted CH_2-SH;

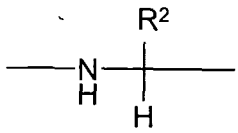
or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof;

provided that the compound is other than

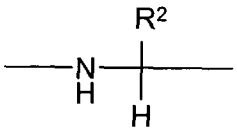
14-[4-(aminosulfonyl)phenyl]-3,6,9-tris(carboxymethyl)-11-oxo-3,6,9,12-tetraazatetradecanoic acid

[0023] In one particular embodiment of the invention, with respective to compounds of formula I', W is Cy2.

[0024] In another particular embodiment of the invention, with respective to compounds of formula I', W is



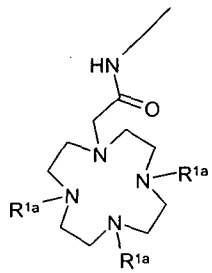
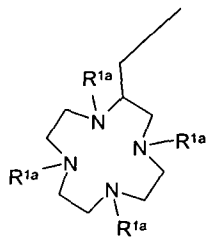
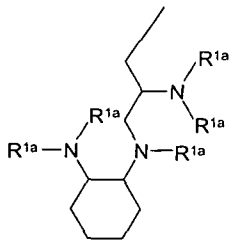
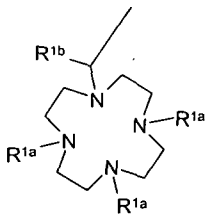
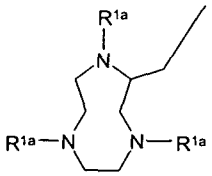
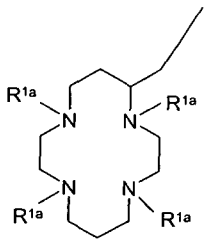
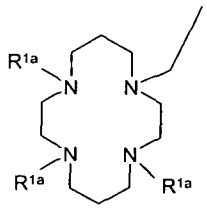
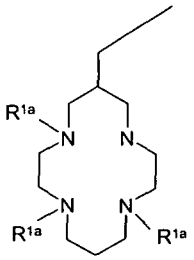
[0025] In one embodiment of the invention, with respective to compounds of formula I', W is



;

and L^2 is a single bond.

[0026] In one particular embodiment of the invention, with respective to compounds of formula I', R^1 is: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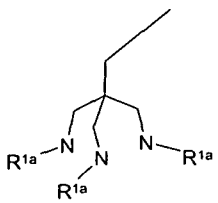


wherein R^{1a} is CH_2COOH and R^{1b} is COOH.

[0027] In another aspect, pharmaceutical compositions are provided comprising a compound of the invention, and a pharmaceutical carrier, excipient or diluent. The pharmaceutical composition can comprise one or more of the compounds described herein. In a further embodiment, the pharmaceutical

compositions of the invention can comprise a compound in combination with one or more other compounds and/or compositions having a like therapeutic effect.

[0028] It will be understood that compounds of the present invention useful in the pharmaceutical compositions and treatment methods disclosed herein, can be pharmaceutically acceptable as prepared and used.

[0029] In further aspect of the invention, the compounds of the invention may be generated and employed as e.g. specific positron emission tomography (PET) or single photon emission tomography (SPECT) radioligands against CAIX, which can be used repeatedly to determine the expression of this oncoprotein before and during therapy. As such, the invention extends to the use of the compounds and compositions of the invention as imaging agents to analyze and measure the status and activity of hypoxic tumors. More particularly, the invention includes a method for monitoring the progress and status of a cancer therapy, including the administration of medicaments or the performance of therapeutic procedures such as surgical procedures, the monitoring method comprising diagnostic imaging with the use and assistance of compounds of the invention, as well as the administration of therapeutic agents also comprising compounds of the invention, for the treatment of such hypoxic (solid) tumors.

[0030] With respect to the imaging technology useful in the present invention, positron emission tomography (PET) is an emerging functional imaging technology, which is now broadly applied for imaging human tumors. High resolution animal PET scanners are available for small animal imaging. An advantage of PET over conventional nuclear medicine imaging is that PET provides quantitative information about radiotracer accumulation. Consequently, the present invention extends to methods for the diagnosis and prognosis of the onset or presence of cancers associated with the presence and increased growth and malignancy of hypoxic tumors.

[0031] One of the advantages of combining such an imaging technique with a systemic administration of a radioligand is that it allows for the whole body to be analyzed at once for both the primary tumor as well as any metastases. Imaging also reports on the average expression of CAIX by whole tumors and not just that of a section which may or may not be representative of the whole tumor. As a result, this method is believed to facilitate very rapid and non invasive quantification of CAIX expression both before and during therapy, so that therapies that target these receptors could be individually optimized for a particular patient.

[0032] Sulfonamide ligands have been shown to bind to virtually all CA isoforms. Consequently, the present inventors hypothesized that the use of hydrophilic chelators and heavily sulfonated fluorophores (e.g. Alexa 680, Cy 5.5), would reduce the passive internalization of the ligand and preferentially target the CA isoforms expressed on the cell surface. Accordingly, the present invention includes the identification and production of first generation sulfonamide based agents which bind to CAIX *in vitro* and *in vivo*. More particularly, the invention includes the optimization of the binding to CAIX by probing the binding pocket with contains the active Zn(II). Certain of the compounds of the invention have been determined to have nM affinities to CAIX expressed by three different tumor models.

[0033] In further aspects, the invention extends to the identification of compounds having the activities sought herein, by measuring the binding of such compounds to CAIX to identify compounds having favorable binding affinities, and then further testing such compounds by contact with the CAIX Zn(II) binding pocket. The invention further extends to the structural optimization of active compounds, and may include various structural modifications to the molecule to enhance the uptake of the ligand as well as enhance desirable biodistribution. Those compounds identified and developed in accordance with these methods may then be used in accordance with the diagnostic and prognostic aspects of the invention, to monitor the effects of various drug therapies on CAIX upregulation and downregulation *in vivo*.

[0034] In another aspect, methods are provided for preventing, treating or ameliorating a condition from among those listed herein, and particularly, such condition as may be associated with, *e.g.*, hypoxic (solid) malignant tumors.

[0035] In yet another aspect, methods are provided for preventing, treating or ameliorating a variety of disease states, including the diseases associated with hypoxic (solid) malignant tumors by administration of a compound from among those provided herein.

[0036] In a further aspect, methods are provided for preventing, treating or ameliorating a disease or condition as may be associated with, *e.g.*, hypoxic (solid) malignant tumors in a mammal. Typically, the methods comprise administering an effective condition-treating or condition-preventing amount of one or more of the compounds as provided herein, or pharmaceutical composition thereof, to the mammal in need thereof.

[0037] In addition to the methods of treatment set forth above, the present invention extends to the use of any of the compounds of the invention for the preparation of medicaments that may be administered for such treatments, as well as to such compounds for the treatments disclosed and specified.

[0038] In additional aspects, methods are provided for synthesizing the compounds described herein, with representative synthetic protocols and pathways described below.

[0039] Accordingly, it is a principal object of the invention to provide a novel series of compounds, which can assist in the diagnostic imaging of hypoxic tumors, via the measurement of CAIX presence and expression.

[0040] A still further object of the invention is to provide pharmaceutical compositions that are effective in the diagnosis and/or prognosis or monitoring of disease states, including the diseases associated with the development, growth and malignancy of hypoxic tumors.

[0041] A still further object of the invention is to provide a method for the treatment of the disease states recited above, by the administration of a therapeutically effective amount of the compounds of the invention, and/or the pharmaceutical compositions of the invention, either alone, or in conjunction with known anti-tumor therapies and agents, to enhance or facilitate the therapeutic effectiveness of the latter.

[0042] A yet further object of the invention is to provide formulations for the treatment of the diseases as aforesaid, by the combination of at least one of the compounds of the invention, a

pharmaceutical composition of the invention, combinations thereof with other compounds and compositions having a like therapeutic effect.

[0043] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description, which proceeds with reference to the following illustrative drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0044] **FIGURE 1** is a preparative HPLC elution profile of ^{111}In-C14. ^{111}In-C14 elutes at 22.1 minutes.

[0045] **FIGURES 2A** and **2B** are graphs presenting the results of experiments with saturation binding ^{111}In-C15 and ^{131}I-cG250 to SKRC38 cells. The calculated B_{max} values are 930 000 sites/cell for In-C14 and 1 130 000 sites for ^{131}I-cG250.

[0046] **FIGURE 3** is a graph presenting the results of experiments with displacement binding of ^{111}In-C15 to SKRC38 cells.

[0047] **FIGURES 4A** and **4B** graphically depict macroscopic biodistribution of ^{111}In-C15 in mice with SKRC38 tumors (LHS) and of either ^{111}In-C15 or ^{64}Cu/^{111}In-C15 in mice with HT29 tumors (RHS).

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0048] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

[0049] When describing the invention, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated, the term "substituted" is to be defined as set out below. It should be further understood that the terms "groups" and "radicals" can be considered interchangeable when used herein.

[0050] The articles "a" and "an" may be used herein to refer to one or to more than one (i.e. at least one) of the grammatical objects of the article. By way of example "an analogue" means one analogue or more than one analogue.

[0051] 'Acyl' or 'Alkanoyl' refers to a radical $-C(O)R^{20}$, where R^{20} is hydrogen, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylmethyl, 4-10 membered heterocycloalkyl, aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl as defined herein. Representative examples include, but are not limited to, formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl and benzylcarbonyl. Exemplary 'acyl' groups are $-C(O)H$, $-C(O)$-C_1-C_8 alkyl, $-C(O)$-$(CH_2)_t$(C_6-C_{10} aryl), $-C(O)$-$(CH_2)_t$(5-10 membered

heteroaryl), –C(O)-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and –C(O)-$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4.

[0052] 'Substituted Acyl' or 'Substituted Alkanoyl' refers to a radical -$C(O)R^{21}$, wherein R^{21} is independently

- C_1-C_8 alkyl, substituted with halo or hydroxy; or
- C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[0053] 'Acylamino' refers to a radical -$NR^{22}C(O)R^{23}$, where R^{22} is hydrogen, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, arylalkyl, 5-10 memberd heteroaryl or heteroarylalkyl and R^{23} is hydrogen, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, as defined herein. Exemplary 'acylamino' include, but are not limited to, formylamino, acetylamino, cyclohexylcarbonylamino, cyclohexylmethyl-carbonylamino, benzoylamino and benzylcarbonylamino. Particular exemplary 'acylamino' groups are –$NR^{24}C(O)$-C_1-C_8 alkyl, –$NR^{24}C(O)$-$(CH_2)_t$(C_6-C_{10} aryl), –$NR^{24}C(O)$-$(CH_2)_t$(5-10 membered heteroaryl), –$NR^{24}C(O)$-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and –$NR^{24}C(O)$-$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4, and each R^{24} independently represents H or C_1-C_8 alkyl.

[0054] 'Substituted Acylamino' refers to a radical -$NR^{25}C(O)R^{26}$, wherein:

R^{25} is independently

- H, C_1-C_8 alkyl, substituted with halo or hydroxy; or
- C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy; and

R^{26} is independently

- H, C_1-C_8 alkyl, substituted with halo or hydroxy; or
- C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxyl;

provided at least one of R^{25} and R^{26} is other than H.

[0055] 'Acyloxy' refers to a radical -$OC(O)R^{27}$, where R^{27} is hydrogen, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylmethyl, 4-10 membered heterocycloalkyl, aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl as defined herein. Representative examples include, but are not limited to,

formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl and benzylcarbonyl. Exemplary 'acyl' groups are –C(O)H, –C(O)-C_1-C_8 alkyl, –C(O)-$(CH_2)_t$(C_6-C_{10} aryl), –C(O)-$(CH_2)_t$(5-10 membered heteroaryl), –C(O)-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and –C(O)-$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4.

[0056] 'Substituted Acyloxy' refers to a radical -OC(O)R^{28}, wherein R^{28} is independently

- C_1-C_8 alkyl, substituted with halo or hydroxy; or
- C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[0057] 'Alkoxy' refers to the group –OR^{29} where R^{29} is C_1-C_8 alkyl. Particular alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy. Particular alkoxy groups are lower alkoxy, i.e. with between 1 and 6 carbon atoms. Further particular alkoxy groups have between 1 and 4 carbon atoms.

[0058] 'Substituted alkoxy' refers to an alkoxy group substituted with one or more of those groups recited in the definition of "substituted" herein, and particularly refers to an alkoxy group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, in particular 1 substituent, selected from the group consisting of amino, substituted amino, C_6-C_{10} aryl, aryloxy, carboxyl, cyano, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, halogen, 5-10 membered heteroaryl, hydroxyl, nitro, thioalkoxy, thioaryloxy, thiol, alkyl-S(O)-, aryl–S(O)-, alkyl–$S(O)_2$- and aryl-$S(O)_2$-. Exemplary 'substituted alkoxy' groups are –O-$(CH_2)_t$(C_6-C_{10} aryl), –O-$(CH_2)_t$(5-10 membered heteroaryl), –O-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and –O-$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy. Particular exemplary 'substituted alkoxy' groups are OCF_3, OCH_2CF_3, OCH_2Ph, OCH_2-cyclopropyl, OCH_2CH_2OH, and $OCH_2CH_2NMe_2$.

[0059] 'Alkoxycarbonyl' refers to a radical -C(O)-OR^{30} where R^{30} represents an C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, 4-10 membered heterocycloalkylalkyl, aralkyl, or 5-10 membered heteroarylalkyl as defined herein. Exemplary "alkoxycarbonyl" groups are C(O)O-C_1-C_8 alkyl, –C(O)O-$(CH_2)_t$(C_6-C_{10} aryl), –C(O)O-$(CH_2)_t$(5-10 membered heteroaryl), –C(O)O-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and –C(O)O-$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 1 to 4.

[0060] 'Substituted Alkoxycarbonyl' refers to a radical -C(O)-OR^{31} where R^{31} represents:

- C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, or 4-10 membered heterocycloalkylalkyl, each of which is substituted with halo, substituted or unsubstituted amino, or hydroxy; or

- C_6-C_{10} aralkyl, or 5-10 membered heteroarylalkyl, each of which is substituted with unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxyl.

[0061] 'Aryloxycarbonyl' refers to a radical -C(O)-OR^{32} where R^{32} represents an C_6-C_{10} aryl, as defined herein. Exemplary "aryloxycarbonyl" groups is –C(O)O-(C_6-C_{10} aryl).

[0062] 'Substituted Aryloxycarbonyl' refers to a radical -C(O)-OR^{33} where R^{33} represents

- C_6-C_{10} aryl, substituted with unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxyl.

[0063] 'Heteroaryloxycarbonyl' refers to a radical -C(O)-OR^{34} where R^{34} represents a 5-10 membered heteroaryl, as defined herein. An exemplary "aryloxycarbonyl" group is –C(O)O-(5-10 membered heteroaryl).

[0064] 'Substituted Heteroaryloxycarbonyl' refers to a radical -C(O)-OR^{35} where R^{35} represents:

- 5-10 membered heteroaryl, substituted with unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxyl.

[0065] 'Alkoxycarbonylamino' refers to the group -NR^{36}C(O)OR^{37}, where R^{36} is hydrogen, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylmethyl, 4-10 membered heterocycloalkyl, aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl as defined herein, and R^{37} is C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylmethyl, 4-10 membered heterocycloalkyl, aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl as defined herein.

[0066] 'Alkyl' means straight or branched aliphatic hydrocarbon having 1 to 20 carbon atoms. Particular alkyl has 1 to 12 carbon atoms. More particular is lower alkyl which has 1 to 6 carbon atoms. A further particular group has 1 to 4 carbon atoms. Exemplary straight chained groups include methyl, ethyl n-propyl, and n-butyl. Branched means that one or more lower alkyl groups such as methyl, ethyl, propyl or butyl is attached to a linear alkyl chain, exemplary branched chain groups include isopropyl, iso-butyl, t-butyl and isoamyl.

[0067] 'Substituted alkyl' refers to an alkyl group as defined above substituted with one or more of those groups recited in the definition of "substituted" herein, and particularly refers to an alkyl group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, in particular 1 substituent, selected from the group consisting of acyl, acylamino, acyloxy (-O-acyl or –OC(O)R^{20}), alkoxy, alkoxycarbonyl, alkoxycarbonylamino (-NR''-alkoxycarbonyl or -NH-C(O)-OR^{27}), amino, substituted amino, aminocarbonyl (carbamoyl or amido or –C(O)-NR''_2), aminocarbonylamino (-NR''-C(O)-NR''_2), aminocarbonyloxy (-O-C(O)-NR''_2), aminosulfonyl, sulfonylamino, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, halogen, hydroxy, heteroaryl, nitro, thiol, -S-alkyl, –S-aryl, -S(O)-alkyl,–S(O)-aryl, –$S(O)_2$-alkyl, and -$S(O)_2$-aryl. In a particular embodiment 'substituted alkyl' refers to a C_1-C_8 alkyl group substituted with halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -$NR'''SO_2R''$, -$SO_2NR''R'''$, -C(O)R'', -C(O)OR'', -OC(O)R'', -NR'''C(O)R'', -

C(O)NR''R''', -NR''R''', or -(CR'''R'''')$_m$OR'''; wherein each R'' is independently selected from H, C_1-C_8 alkyl, -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5-10 membered heteroaryl), -$(CH_2)_t$(C_3-C_{10} cycloalkyl), and -$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy. Each of R''' and R'''' independently represents H or C_1-C_8 alkyl.

[0068] 'Alkylene' refers to divalent saturated alkene radical groups having 1 to 11 carbon atoms and more particularly 1 to 6 carbon atoms which can be straight-chained or branched. This term is exemplified by groups such as methylene (-CH_2-), ethylene (-CH_2CH_2-), the propylene isomers (*e.g.*, -$CH_2CH_2CH_2$- and -$CH(CH_3)CH_2$-) and the like.

[0069] 'Substituted alkylene' refers to those groups recited in the definition of "substituted" herein, and particularly refers to an alkylene group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, aminocarbonyl, amino-carbonylamino, aminocarbonyloxy, aryl, aryloxy, azido, carboxyl, cyano, halogen, hydroxyl, keto, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioketo, thiol, alkyl-S(O)-, aryl–S(O)-, alkyl–$S(O)_2$- and aryl-$S(O)_2$-.

[0070] 'Alkenyl' refers to monovalent olefinically unsaturated hydrocarbyl groups preferably having 2 to 11 carbon atoms, particularly, from 2 to 8 carbon atoms, and more particularly, from 2 to 6 carbon atoms, which can be straight-chained or branched and having at least 1 and particularly from 1 to 2 sites of olefinic unsaturation. Particular alkenyl groups include ethenyl (-CH=CH_2), *n*-propenyl (-CH_2CH=CH_2), isopropenyl (-$C(CH_3)$=CH_2), vinyl and substituted vinyl, and the like.

[0071] 'Substituted alkenyl' refers to those groups recited in the definition of "substituted" herein, and particularly refers to an alkenyl group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, keto, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioketo, thiol, alkyl-S(O)-, aryl–S(O)-, alkyl–$S(O)_2$- and aryl-$S(O)_2$-.

[0072] 'Alkenylene' refers to divalent olefinically unsaturated hydrocarbyl groups particularly having up to about 11 carbon atoms and more particularly 2 to 6 carbon atoms which can be straight-chained or branched and having at least 1 and particularly from 1 to 2 sites of olefinic unsaturation. This term is exemplified by groups such as ethenylene (-CH=CH-), the propenylene isomers (*e.g.*, -CH=$CHCH_2$- and -$C(CH_3)$=CH- and -CH=$C(CH_3)$-) and the like.

[0073] 'Alkynyl' refers to acetylenically or alkynically unsaturated hydrocarbyl groups particularly having 2 to 11 carbon atoms, and more particularly 2 to 6 carbon atoms which can be straight-chained or branched and having at least 1 and particularly from 1 to 2 sites of alkynyl unsaturation.

Particular non-limiting examples of alkynyl groups include acetylenic, ethynyl (-C≡CH), propargyl (-$CH_2C{\equiv}CH$), and the like.

[0074] 'Substituted alkynyl' refers to those groups recited in the definition of "substituted" herein, and particularly refers to an alkynyl group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, keto, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioketo, thiol, alkyl-S(O)-, aryl–S(O)-, alkyl–$S(O)_2$- and aryl-$S(O)_2$-.

[0075] 'Amino' refers to the radical $-NH_2$.

[0076] 'Substituted amino' refers to an amino group substituted with one or more of those groups recited in the definition of 'substituted' herein, and particularly refers to the group $-N(R^{38})_2$ where each R^{38} is independently selected from:

- hydrogen, C_1-C_8 alkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, or C_3-C_{10} cycloalkyl; or
- C_1-C_8 alkyl, substituted with halo or hydroxy; or
- $-(CH_2)_t$(C_6-C_{10} aryl), $-(CH_2)_t$(5-10 membered heteroaryl), $-(CH_2)_t$(C_3-C_{10} cycloalkyl) or $-(CH_2)_t$(4-10 membered heterocycloalkyl) wherein t is an integer between 0 and 8, each of which is substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy; or
- both R^{38} groups are joined to form an alkylene group.

When both R^{38} groups are hydrogen, $-N(R^{38})_2$ is an amino group. Exemplary ' substituted amino' groups are $-NR^{39}$-C_1-C_8 alkyl, $-NR^{39}$-$(CH_2)_t$(C_6-C_{10} aryl), $-NR^{39}$-$(CH_2)_t$(5-10 membered heteroaryl), $-NR^{39}$-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and $-NR^{39}$-$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4, each R^{39} independently represents H or C_1-C_8 alkyl; and any alkyl groups present, may themselves be substituted by halo, substituted or unsubstituted amino, or hydroxy; and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy. For the avoidance of doubt the term "substituted amino" includes the groups alkylamino, substituted alkylamino, alkylarylamino, substituted alkylarylamino, arylamino, substituted arylamino, dialkylamino and substituted dialkylamino as defined below.

[0077] 'Alkylamino' refers to the group $-NHR^{40}$, wherein R^{40} is C_1-C_8 alkyl;

[0078] 'Substituted Alkylamino' refers to the group $-NHR^{41}$, wherein R^{41} is C_1-C_8 alkyl; and the alkyl group is substituted with halo, substituted or unsubstituted amino, hydroxy, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, aralkyl or heteroaralkyl; and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by

unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[0079] 'Alkylarylamino' refers to the group $-NR^{42}R^{43}$, wherein R^{42} is aryl and R^{43} is C_1-C_8 alkyl.

[0080] 'Substituted Alkylarylamino' refers to the group $-NR^{44}R^{45}$, wherein R^{44} is aryl and R^{45} is C_1-C_8 alkyl; and the alkyl group is substituted with halo, substituted or unsubstituted amino, hydroxy, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, aralkyl or heteroaralkyl; and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, cyano, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[0081] 'Arylamino' means a radical $-NHR^{46}$ where R^{46} is selected from C_6-C_{10} aryl and 5-10 membered heteroaryl as defined herein.

[0082] 'Substituted Arylamino' refers to the group $-NHR^{47}$, wherein R^{47} is independently selected from C_6-C_{10} aryl and 5-10 membered heteroaryl; and any aryl or heteroaryl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, cyano, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[0083] 'Dialkylamino' refers to the group $-NR^{48}R^{49}$, wherein each of R^{48} and R^{49} are independently selected from C_1-C_8 alkyl.

[0084] 'Substituted Dialkylamino' refers to the group $-NR^{50}R^{51}$, wherein each of R^{59} and R^{51} are independently selected from C_1-C_8 alkyl; and at least one of the alkyl groups is independently substituted with halo, hydroxy, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, aralkyl or heteroaralkyl; and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-$_4$ haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[0085] 'Diarylamino' refers to the group $-NR^{52}R^{53}$, wherein each of R^{52} and R^{53} are independently selected from C_6-C_{10} aryl.

[0086] 'Aminosulfonyl' or 'Sulfonamide' refers to the radical $-S(O_2)NH_2$.

[0087] 'Substituted aminosulfonyl' or 'substituted sulfonamide' refers to a radical such as $-S(O_2)N(R^{54})_2$ wherein each R^{548} is independently selected from:

- H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- C_1-C_8 alkyl substituted with halo or hydroxy; or
- C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy;

provided that at least one R^{54} is other than H.

[0088] Exemplary 'substituted aminosulfonyl' or 'substituted sulfonamide' groups are –$S(O_2)N(R^{55})$-C_1-C_8 alkyl, –$S(O_2)N(R^{55})$-$(CH_2)_t$(C_6-C_{10} aryl), –$S(O_2)N(R^{55})$-$(CH_2)_t$(5-10 membered heteroaryl), –$S(O_2)N(R^{55})$-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and –$S(O_2)N(R^{55})$-$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4; each R^{55} independently represents H or C_1-C_8 alkyl; and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

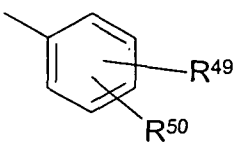
[0089] 'Aralkyl' or 'arylalkyl' refers to an alkyl group, as defined above, substituted with one or more aryl groups, as defined above. Particular aralkyl or arylalkyl groups are alkyl groups substituted with one aryl group.

[0090] 'Substituted Aralkyl' or 'substituted arylalkyl' refers to an alkyl group, as defined above, substituted with one or more aryl groups; and at least one of the aryl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, cyano, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[0091] 'Aryl' refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. In particular aryl refers to an aromatic ring structure, mono-cyclic or poly-cyclic that includes from 5 to 12 ring members, more usually 6 to 10. Where the aryl group is a monocyclic ring system it preferentially contains 6 carbon atoms. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, as-indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene and trinaphthalene. Particularly aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl.

[0092] 'Substituted Aryl' refers to an aryl group substituted with one or more of those groups recited in the definition of 'substituted' herein, and particularly refers to an aryl group that may optionally be substituted with 1 or more substituents, for instance from 1 to 5 substituents, particularly 1 to 3 substituents, in particular 1 substituent. Particularly, 'Substituted Aryl' refers to an aryl group substituted with one or more of groups selected from halo, C_1-C_8 alkyl, C_1-C_8 haloalkyl, cyano, hydroxy, C_1-C_8 alkoxy, and amino.

[0093] Examples of representative substituted aryls include the following



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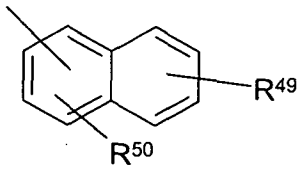

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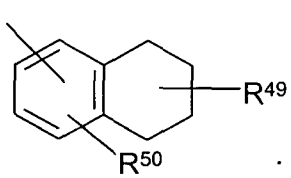

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[0094] In these formulae one of R^{56} and R^{57} may be hydrogen and at least one of R^{56} and R^{57} is each independently selected from C_1-C_8 alkyl, C_1-C_8 haloalkyl, 4-10 membered heterocycloalkyl, alkanoyl, C_1-C_8 alkoxy, heteroaryloxy, alkylamino, arylamino, heteroarylamino, $NR^{58}COR^{59}$, $NR^{58}SOR^{59}$

$NR^{58}SO_2R^{59}$, COOalkyl, COOaryl, $CONR^{58}R^{59}$, $CONR^{58}OR^{59}$, $NR^{58}R^{59}$, $SO_2NR^{58}R^{59}$, S-alkyl, SOalkyl, SO_2alkyl, Saryl, SOaryl, SO_2aryl; or R^{56} and R^{57} may be joined to form a cyclic ring (saturated or unsaturated) from 5 to 8 atoms, optionally containing one or more heteroatoms selected from the group N, O or S. R^{60}, and R^{61} are independently hydrogen, C_1-C_8 alkyl, C_1-C_4 haloalkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, substituted aryl, 5-10 membered heteroaryl.

[0095] 'Fused Aryl' refers to an aryl having two of its ring carbon in common with a second aryl ring or with an aliphatic ring.

[0096] 'Arylalkyloxy' refers to an -O-alkylaryl radical where alkylaryl is as defined herein.

[0097] 'Substituted Arylalkyloxy' refers to an -O-alkylaryl radical where alkylaryl is as defined herein; and any aryl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, cyano, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-$_4$ haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[0098] 'Azido' refers to the radical $-N_3$.

[0099] 'Carbamoyl or amido' refers to the radical $-C(O)NH_2$.

[00100] 'Substituted Carbamoyl or substituted amido' refers to the radical $-C(O)N(R^{62})_2$ wherein each R^{62} is independently

- H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- C_1-C_8 alkyl substituted with halo or hydroxy; or
- C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy;

provided that at least one R^{62} is other than H.

Exemplary 'Substituted Carbamoyl' groups are $-C(O)$ NR^{64}-C_1-C_8 alkyl, $-C(O)NR^{64}$-$(CH_2)_t$(C_6-C_{10} aryl), $-C(O)N^{64}$-$(CH_2)_t$(5-10 membered heteroaryl), $-C(O)NR^{64}$-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and $-C(O)NR^{64}$-$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4, each R^{64} independently represents H or C_1-C_8 alkyl and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[00101] 'Carboxy' refers to the radical -C(O)OH.

[00102] 'Cycloalkyl' refers to cyclic non-aromatic hydrocarbyl groups having from 3 to 10 carbon atoms. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclooctyl.

[00103] 'Substituted cycloalkyl' refers to a cycloalkyl group as defined above substituted with one or more of those groups recited in the definition of 'substituted' herein, and particularly refers to a cycloalkyl group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, in particular 1 substituent

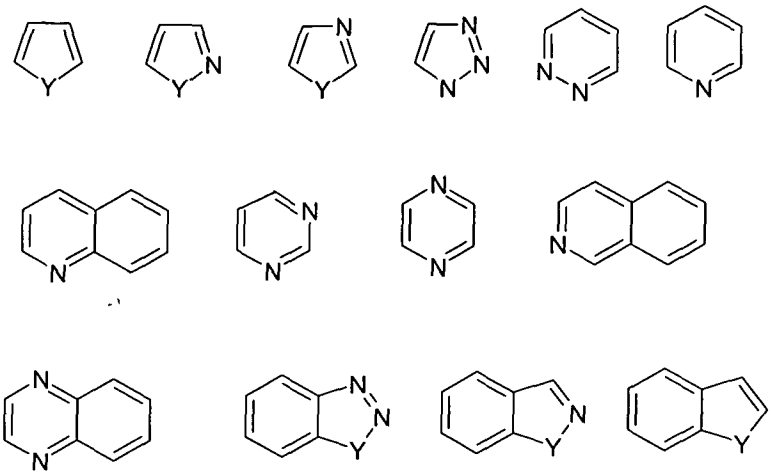
[00104] 'Cyano' refers to the radical -CN.

[00105] 'Halo' or 'halogen' refers to fluoro (F), chloro (Cl), bromo (Br) and iodo (I). Particular halo groups are either fluoro or chloro.

[00106] 'Hetero' when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, or sulfur heteroatom. Hetero may be applied to any of the hydrocarbyl groups described above such as alkyl, e.g. heteroalkyl, cycloalkyl, e.g. heterocycloalkyl, aryl, e.g. heteroaryl, cycloalkenyl, e.g. cycloheteroalkenyl, and the like having from 1 to 5, and particularly from 1 to 3 heteroatoms.

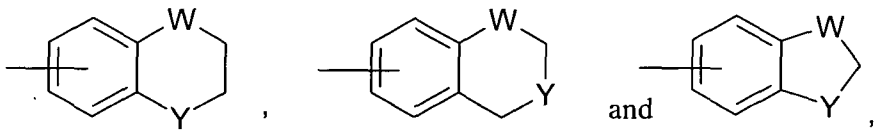
[00107] 'Heteroaryl' means an aromatic ring structure, mono-cyclic or polycyclic, that includes one or more heteroatoms and 5 to 12 ring members, more usually 5 to 10 ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings or, by way of a further example, two fused five membered rings. Each ring may contain up to four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five. Examples of five membered monocyclic heteroaryl groups include but are not limited to pyrrole, furan, thiophene, imidazole, furazan, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, isothiazole, pyrazole, triazole and tetrazole groups. Examples of six membered monocyclic heteroaryl groups include but are not limited to pyridine, pyrazine, pyridazine, pyrimidine and triazine. Particular examples of bicyclic heteroaryl groups containing a five membered ring fused to another five membered ring include but are not limited to imidazothiazole and imidazoimidazole. Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzfuran, benzthiophene, benzimidazole, benzoxazole, isobenzoxazole, benzisoxazole, benzthiazole, benzisothiazole, isobenzofuran, indole, isoindole, isoindolone, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, pyrazolopyrimidine, triazolopyrimidine, benzodioxole and pyrazolopyridine groups. Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoline, isoquinoline, chroman, thiochroman, chromene, isochromene, chroman, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine groups. Particular heteroaryl groups are those derived from thiophene, pyrrole, benzothiophene, benzofuran, indole, pyridine, quinoline, imidazole, oxazole and pyrazine.

[00108] Examples of representative heteroaryls include the following:



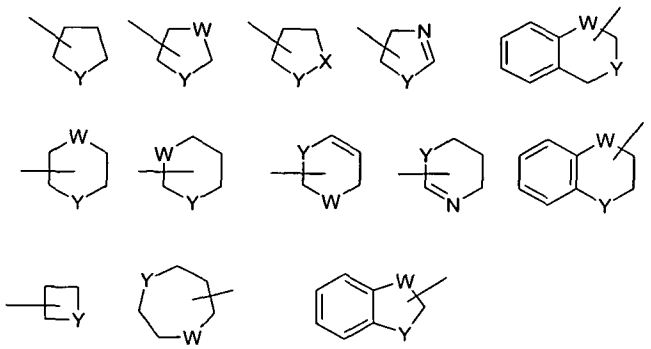
wherein each Y is selected from carbonyl, N, NR^{65}, O and S; and R^{65} is independently hydrogen, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, and 5-10 membered heteroaryl.

[00109] Examples of representative aryl having hetero atoms containing substitution include the following:



wherein each W is selected from $C(R^{66})_2$, NR^{66}, O and S; and each Y is selected from carbonyl, NR^{66}, O and S; and R^{66} is independently hydrogen, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, and 5-10 membered heteroaryl.

[00110] As used herein, the term 'heterocycloalkyl' refers to a 4-10 membered, stable heterocyclic non-aromatic ring and/or including rings containing one or more heteroatoms independently selected from N, O and S, fused thereto. A fused heterocyclic ring system may include carbocyclic rings and need only include one heterocyclic ring. Examples of heterocyclic rings include, but are not limited to, morpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. 4-tetrahydro pyranyl), imidazoline, imidazolidinone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine. Further examples include thiomorpholine and its S-oxide and S,S-dioxide (particularly thiomorpholine). Still further examples include azetidine, piperidone, piperazone, and N-alkyl piperidines such as N-methyl piperidine. Particular examples of heterocycloalkyl groups are shown in the following illustrative examples:



wherein each W is selected from CR^{67}, $C(R^{67})_2$, NR^{67}, O and S; and each Y is selected from NR^{67}, O and S; and R^{67} is independently hydrogen, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, These heterocycloalkyl rings may be optionally substituted with one or more groups selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, aminocarbonyl (carbamoyl or amido), aminocarbonylamino, aminosulfonyl, sulfonylamino, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, halogen, hydroxy, keto, nitro, thiol, -S-alkyl, –S-aryl, -S(O)-alkyl,–S(O)-aryl, $–S(O)_2$-alkyl, and $-S(O)_2$-aryl. Substituting groups include carbonyl or thiocarbonyl which provide, for example, lactam and urea derivatives.

[00111] 'Hydroxy' refers to the radical -OH.

[00112] 'Nitro' refers to the radical $–NO_2$.

[00113] 'Substituted' refers to a group in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s). Typical substituents may be selected from the group consisting of:

halogen, $-R^{68}$, $-O^-$, =O, $-OR^{68}$, $-SR^{68}$, $-S^-$, =S, $-NR^{68}R^{69}$, $=NR^{68}$, $-CCl_3$, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)_2O^-$, $-S(O)_2OH$, $-S(O)_2R^{68}$, $-OS(O_2)O^-$, $-OS(O)_2R^{68}$, $-P(O)(O^-)_2$, $-P(O)(OR^{68})(O^-)$, $-OP(O)(OR^{68})(OR^{69})$, $-C(O)R^{68}$, $-C(S)R^{68}$, $-C(O)OR^{68}$, $-C(O)NR^{68}R^{69}$, $-C(O)O^-$, $-C(S)OR^{68}$, $-NR^{70}C(O)NR^{68}R^{69}$, $-NR^{70}C(S)NR^{68}R^{69}$, $-NR^{71}C(NR^{70})NR^{68}R^{69}$ and $-C(NR^{70})NR^{68}R^{69}$;

wherein each R^{68}, R^{69}, R^{70} and R^{71} are independently:

- hydrogen, C_1-C_8 alkyl, C_6-C_{10} aryl, arylalkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, heteroarylalkyl; or
- C_1-C_8 alkyl substituted with halo or hydroxy; or
- C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} cycloalkyl or 4-10 membered heterocycloalkyl each of which is substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

In a particular embodiment, substituted groups are substituted with one or more substituents, particularly with 1 to 3 substituents, in particular with one substituent group.

In a further particular embodiment the substituent group or groups are selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{72}SO_2R^{73}$, $-SO_2NR^{73}R^{72}$, $-C(O)R^{73}$, $-C(O)OR^{73}$, $-OC(O)R^{73}$, $-NR^{72}C(O)R^{73}$, $-C(O)NR^{73}R^{72}$, $-NR^{73}R^{72}$, $-(CR^{72}R^{72})_mOR^{72}$, wherein, each R^{73} is independently selected

from H, C_1-C_8 alkyl, -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5-10 membered heteroaryl), -$(CH_2)_t$(C_3-C_{10} cycloalkyl), and -$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4; and

- any alkyl groups present, may themselves be substituted by halo or hydroxy; and
- any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy. Each R'' independently represents H or C_1-C_6alkyl.

[00114] 'Substituted sulfanyl' refers to the group $-SR^{74}$, wherein R^{74} is selected from:

- C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- C_1-C_8 alkyl substituted with halo, substituted or unsubstituted amino, or hydroxy; or
- C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[00115] Exemplary 'substituted sulfanyl' groups are $-S$-(C_1-C_8 alkyl) and $-S$-(C_3-C_{10} cycloalkyl), $-S$-$(CH_2)_t$(C_6-C_{10} aryl), $-S$-$(CH_2)_t$(5-10 membered heteroaryl), $-S$-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and $-S$-$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy. The term 'substituted sulfanyl' includes the groups 'alkylsulfanyl' or 'alkylthio', 'substituted alkylthio' or 'substituted alkylsulfanyl', 'cycloalkylsulfanyl' or 'cycloalkylthio', 'substituted cycloalkylsulfanyl' or 'substituted cycloalkylthio', 'arylsulfanyl' or 'arylthio' and 'heteroarylsulfanyl' or 'heteroarylthio' as defined below.

[00116] 'Alkylthio' or 'Alkylsulfanyl' refers to a radical $-SR^{75}$ where R^{75} is a C_1-C_8 alkyl or group as defined herein. Representative examples include, but are not limited to, methylthio, ethylthio, propylthio and butylthio.

[00117] 'Substituted Alkylthio'or 'substituted alkylsulfanyl' refers to the group $-SR^{76}$ where R^{76} is a C_1-C_8 alkyl, substituted with halo, substituted or unsubstituted amino, or hydroxy.

[00118] 'Cycloalkylthio' or 'Cycloalkylsulfanyl' refers to a radical $-SR^{77}$ where R^{77} is a C_3-C_{10} cycloalkyl or group as defined herein. Representative examples include, but are not limited to, cyclopropylthio, cyclohexylthio, and cyclopentylthio.

[00119] 'Substituted cycloalkylthio' or 'substituted cycloalkylsulfanyl' refers to the group $-SR^{78}$ where R^{78} is a C_3-C_{10} cycloalkyl, substituted with halo, substituted or unsubstituted amino, or hydroxy.

[00120] 'Arylthio' or 'Arylsulfanyl' refers to a radical $-SR^{79}$ where R^{79} is a C_6-C_{10} aryl group as defined herein.

[00121] 'Heteroarylthio' or 'Heteroarylsulfanyl' refers to a radical $-SR^{80}$ where R^{80} is a 5-10 membered heteroaryl group as defined herein.

[00122] 'Substituted sulfinyl' refers to the group $-S(O)R^{81}$, wherein R^{81} is selected from:

- C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- C_1-C_8 alkyl substituted with halo, substituted or unsubstituted amino, or hydroxy; or
- C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[00123] Exemplary 'substituted sulfinyl' groups are $-S(O)-(C_1$-C_8 alkyl) and $-S(O)-(C_3$-C_{10} cycloalkyl), $-S(O)-(CH_2)_t(C_6$-C_{10} aryl), $-S(O)-(CH_2)_t$(5-10 membered heteroaryl), $-S(O)-(CH_2)_t(C_3$-C_{10} cycloalkyl), and $-S(O)-(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy. The term substituted sulfinyl includes the groups 'alkylsulfinyl', 'substituted alkylsulfinyl', 'cycloalkylsulfinyl', 'substituted cycloalkylsulfinyl', 'arylsulfinyl' and 'heteroarylsulfinyl' as defined herein.

[00124] 'Alkylsulfinyl' refers to a radical $-S(O)R^{82}$ where R^{82} is a C_1-C_8 alkyl group as defined herein. Representative examples include, but are not limited to, methylsulfinyl, ethylsulfinyl, propylsulfinyl and butylsulfinyl.

[00125] 'Substituted Alkylsulfinyl' refers to a radical $-S(O)R^{83}$ where R^{83} is a C_1-C_8 alkyl group as defined herein, substituted with halo, substituted or unsubstituted amino, or hydroxy.

[00126] 'Cycloalkylsulfinyl' refers to a radical $-S(O)R^{84}$ where R^{84} is a C_3-C_{10} cycloalkyl or group as defined herein. Representative examples include, but are not limited to, cyclopropylsulfinyl, cyclohexylsulfinyl, and cyclopentylsulfinyl. Exemplary 'cycloalkylsulfinyl' groups are $S(O)-C_3$-C_{10} cycloalkyl.

[00127] 'Substituted cycloalkylsulfinyl' refers to the group $-S(O)R^{85}$ where R^{85} is a C_3-C_{10} cycloalkyl, substituted with halo, substituted or unsubstituted amino, or hydroxy.

[00128] 'Arylsulfinyl' refers to a radical $-S(O)R^{86}$ where R^{86} is a C_6-C_{10} aryl group as defined herein.

[00129] 'Heteroarylsulfinyl' refers to a radical $-S(O)R^{87}$ where R^{87} is a 5-10 membered heteroaryl group as defined herein.

[00130] 'Substituted sulfonyl' refers to the group $-S(O)_2R^{88}$, wherein R^{88} is selected from:

- C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- C_1-C_8 alkyl substituted with halo, substituted or unsubstituted amino, or hydroxy; or
- C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted C_1-C_4 alkyl, halo,

unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[00131] Exemplary 'substituted sulfonyl' groups are $-S(O)_2$-(C_1-C_8 alkyl) and $-S(O)_2$-(C_3-C_{10} cycloalkyl), $-S(O)_2$-$(CH_2)_t$(C_6-C_{10} aryl), $-S(O)_2$-$(CH_2)_t$(5-10 membered heteroaryl), $-S(O)_2$-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and $-S(O)_2$-$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy. The term substituted sulfonyl includes the groups alkylsulfonyl, substituted alkylsulfonyl, cycloalkylsulfonyl, substituted cycloalkylsulfonyl, arylsulfonyl and heteroarylsulfonyl.

[00132] 'Alkylsulfonyl' refers to a radical $-S(O)_2R^{89}$ where R^{89} is an C_1-C_8 alkyl group as defined herein. Representative examples include, but are not limited to, methylsulfonyl, ethylsulfonyl, propylsulfonyl and butylsulfonyl.

[00133] 'Substituted Alkylsulfonyl' refers to a radical $-S(O)_2R^{90}$ where R^{90} is an C_1-C_8 alkyl group as defined herein, substituted with halo, substituted or unsubstituted amino, or hydroxy.

[00134] 'Cycloalkylsulfonyl' refers to a radical $-S(O)_2R^{91}$ where R^{91} is a C_3-C_{10} cycloalkyl or group as defined herein. Representative examples include, but are not limited to, cyclopropylsulfonyl, cyclohexylsulfonyl, and cyclopentylsulfonyl.

[00135] 'Substituted cycloalkylsulfonyl' refers to the group $-S(O)_2R^{92}$ where R^{92} is a C_3-C_{10} cycloalkyl, substituted with halo, substituted or unsubstituted amino, or hydroxy.

[00136] 'Arylsulfonyl' refers to a radical $-S(O)_2R^{93}$ where R^{93} is an C_6-C_{10} aryl group as defined herein.

[00137] 'Heteroarylsulfonyl' refers to a radical $-S(O)_2R^{94}$ where R^{94} is an 5-10 membered heteroaryl group as defined herein.

[00138] 'Sulfo' or 'sulfonic acid' refers to a radical such as $-SO_3H$.

[00139] 'Substituted sulfo' or 'sulfonic acid ester' refers to the group $-S(O)_2OR^{95}$, wherein R^{95} is selected from:

- C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- C_1-C_8 alkyl substituted with halo, substituted or unsubstituted amino, or hydroxy; or
- C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[00140] Exemplary 'Substituted sulfo' or 'sulfonic acid ester' groups are $-S(O)_2$-O-(C_1-C_8 alkyl) and $-S(O)_2$-O-(C_3-C_{10} cycloalkyl), $-S(O)_2$-O-$(CH_2)_t$(C_6-C_{10} aryl), $-S(O)_2$-O-$(CH_2)_t$(5-10 membered heteroaryl), $-S(O)_2$-O-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and $-S(O)_2$-O-$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present,

may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[00141] 'Thiol' refers to the group -SH.

[00142] 'Aminocarbonylamino' refers to the group $-NR^{96}C(O)NR^{96}R^{96}$ where each R^{96} is independently hydrogen C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl, as defined herein; or where two R^{96} groups, when attached to the same N, are joined to form an alkylene group.

[00143] 'Bicycloaryl' refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent bicycloaromatic ring system. Typical bicycloaryl groups include, but are not limited to, groups derived from indane, indene, naphthalene, tetrahydronaphthalene, and the like. Particularly, an aryl group comprises from 8 to 11 carbon atoms.

[00144] 'Bicycloheteroaryl' refers to a monovalent bicycloheteroaromatic group derived by the removal of one hydrogen atom from a single atom of a parent bicycloheteroaromatic ring system. Typical bicycloheteroaryl groups include, but are not limited to, groups derived from benzofuran, benzimidazole, benzindazole, benzdioxane, chromene, chromane, cinnoline, phthalazine, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, benzothiazole, benzoxazole, naphthyridine, benzoxadiazole, pteridine, purine, benzopyran, benzpyrazine, pyridopyrimidine, quinazoline, quinoline, quinolizine, quinoxaline, benzomorphan, tetrahydroisoquinoline, tetrahydroquinoline, and the like. Preferably, the bicycloheteroaryl group is between 9-11 membered bicycloheteroaryl, with 5-10 membered heteroaryl being particularly preferred. Particular bicycloheteroaryl groups are those derived from benzothiophene, benzofuran, benzothiazole, indole, quinoline, isoquinoline, benzimidazole, benzoxazole and benzdioxane.

[00145] 'Compounds of the present invention', and equivalent expressions, are meant to embrace the compounds as hereinbefore described, in particular compounds according to any of the formulae herein recited and/or described, which expression includes the prodrugs, the pharmaceutically acceptable salts, and the solvates, e.g., hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

[00146] 'Cycloalkylalkyl' refers to a radical in which a cycloalkyl group is substituted for a hydrogen atom of an alkyl group. Typical cycloalkylalkyl groups include, but are not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclooctylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopentylethyl, cyclohexylethyl, cycloheptylethyl, and cyclooctylethyl, and the like.

[00147] 'Heterocycloalkylalkyl' refers to a radical in which a heterocycloalkyl group is substituted for a hydrogen atom of an alkyl group. Typical heterocycloalkylalkyl groups include, but are not limited to, pyrrolidinylmethyl, piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, pyrrolidinylethyl, piperidinylethyl, piperazinylethyl, morpholinylethyl, and the like.

[00148] 'Cycloalkenyl' refers to cyclic hydrocarbyl groups having from 3 to 10 carbon atoms and having a single cyclic ring or multiple condensed rings, including fused and bridged ring systems and having at least one and particularly from 1 to 2 sites of olefinic unsaturation. Such cycloalkenyl groups include, by way of example, single ring structures such as cyclohexenyl, cyclopentenyl, cyclopropenyl, and the like.

[00149] 'Substituted cycloalkenyl' refers to those groups recited in the definition of "substituted" herein, and particularly refers to a cycloalkenyl group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, keto, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioketo, thiol, alkyl-S(O)-, aryl–S(O)-, alkyl–$S(O)_2$- and aryl-$S(O)_2$-.

[00150] 'Fused Cycloalkenyl' refers to a cycloalkenyl having two of its ring carbon atoms in common with a second aliphatic or aromatic ring and having its olefinic unsaturation located to impart aromaticity to the cycloalkenyl ring.

[00151] 'Ethenyl' refers to substituted or unsubstituted –(C=C)-.

[00152] 'Ethylene' refers to substituted or unsubstituted –(C-C)-.

[00153] 'Ethynyl' refers to –(C≡C)-.

[00154] 'Hydrogen bond donor' group refers to a group containg O-H, or N-H functionality. Examples of 'hydrogen bond donor' groups include –OH, $-NH_2$, and $-NH-R^{97}$ and wherein R^{97} is alkyl, acyl, cycloalkyl, aryl, or heteroaryl.

[00155] 'Dihydroxyphosphoryl' refers to the radical $-PO(OH)_2$.

[00156] 'Substituted dihydroxyphosphoryl' refers to those groups recited in the definition of "substituted" herein, and particularly refers to a dihydroxyphosphoryl radical wherein one or both of the hydroxyl groups are substituted. Suitable substituents are described in detail below.

[00157] 'Aminohydroxyphosphoryl' refers to the radical $-PO(OH)NH_2$.

[00158] 'Substituted aminohydroxyphosphoryl' refers to those groups recited in the definition of "substituted" herein, and particularly refers to an aminohydroxyphosphoryl wherein the amino group is substituted with one or two substituents. Suitable substituents are described in detail below. In certain embodiments, the hydroxyl group can also be substituted.

[00159] 'Nitrogen-Containing Heterocycloalkyl' group means a 4 to 7 membered non-aromatic cyclic group containing at least one nitrogen atom, for example, but without limitation, morpholine, piperidine (e.g. 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (e.g. 2-pyrrolidinyl and 3-pyrrolidinyl), azetidine, pyrrolidone, imidazoline, imidazolidinone, 2-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine. Particular examples include azetidine, piperidone and piperazone.

[00160] 'Thioketo' refers to the group =S.

[00161] One having ordinary skill in the art of organic synthesis will recognize that the maximum number of heteroatoms in a stable, chemically feasible heterocyclic ring, whether it is aromatic or non

aromatic, is determined by the size of the ring, the degree of unsaturation and the valence of the heteroatoms. In general, a heterocyclic ring may have one to four heteroatoms so long as the heteroaromatic ring is chemically feasible and stable.

[00162] 'Pharmaceutically acceptable' means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

[00163] 'Pharmaceutically acceptable salt' refers to a salt of a compound of the invention that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like. The term "pharmaceutically acceptable cation" refers to an acceptable cationic counter-ion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium cations, and the like.

[00164] 'Pharmaceutically acceptable vehicle' refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered.

[00165] 'Prodrugs' refers to compounds, including derivatives of the compounds of the invention,which have cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.

[00166] 'Solvate' refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association includes hydrogen bonding. Conventional solvents include water, ethanol, acetic acid and the like. The compounds of the invention may be prepared e.g. in crystalline form and may be solvated or hydrated. Suitable solvates include pharmaceutically acceptable

solvates, such as hydrates, and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. 'Solvate' encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates and methanolates.

[00167] 'Subject' includes humans. The terms 'human', 'patient' and 'subject' are used interchangeably herein.

[00168] 'Therapeutically effective amount' means the amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" can vary depending on the compound, the disease and its severity, and the age, weight, etc., of the subject to be treated.

[00169] 'Preventing' or 'prevention' refers to a reduction in risk of acquiring or developing a disease or disorder (i.e., causing at least one of the clinical symptoms of the disease not to develop in a subject that may be exposed to a disease-causing agent, or predisposed to the disease in advance of disease onset.

[00170] The term 'prophylaxis' is related to 'prevention', and refers to a measure or procedure the purpose of which is to prevent, rather than to treat or cure a disease. Non-limiting examples of prophylactic measures may include the administration of vaccines; the administration of low molecular weight heparin to hospital patients at risk for thrombosis due, for example, to immobilization; and the administration of an anti-malarial agent such as chloroquine, in advance of a visit to a geographical region where malaria is endemic or the risk of contracting malaria is high.

[00171] 'Treating' or 'treatment' of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (i.e., arresting the disease or reducing the manifestation, extent or severity of at least one of the clinical symptoms thereof). In another embodiment 'treating' or 'treatment' refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, 'treating' or 'treatment' refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In a further embodiment, "treating" or "treatment" relates to slowing the progression of the disease.

[00172] 'Compounds of the present invention', and equivalent expressions, are meant to embrace compounds of the Formula(e) as hereinbefore described, which expression includes the prodrugs, the pharmaceutically acceptable salts, and the solvates, e.g., hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

[00173] When ranges are referred to herein, for example but without limitation, C_1-C_8 alkyl, the citation of a range should be considered a representation of each member of said range.

[00174] Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but in the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., Design of Prodrugs, pp.

7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well know to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups pendant on the compounds of this invention are particular prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. Particularly the C_1 to C_8 alkyl, C_2-C_8 alkenyl, aryl, C_7-C_{12} substituted aryl, and C_7-C_{12} arylalkyl esters of the compounds of the invention.

[00175] As used herein, the term 'isotopic variant' refers to a compound that contains unnatural proportions of isotopes at one or more of the atoms that constitute such compound. For example, an 'isotopic variant' of a compound can contain one or more non-radioactive isotopes, such as for example, deuterium (^{2}H or D), carbon-13 (^{13}C), nitrogen-15 (^{15}N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be ^{2}H/D, any carbon may be ^{13}C, or any nitrogen may be ^{15}N, and that the presence and placement of such atoms may be determined within the skill of the art. Likewise, the invention may include the preparation of isotopic variants with radioisotopes, in the instance for example, where the resulting compounds may be used for drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Further, compounds may be prepared that are substituted with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, and would be useful in Positron Emission Topography (PET) studies, or Single Photon Emission Tomography (SPECT), for examining substrate receptor occupancy.

[00176] Known radionuclides useful in the imaging systems and procedures of the present invention may include the isotopes ^{3}H, ^{14}C, ^{18}F, ^{32}P, ^{35}S, ^{36}Cl, ^{51}Cr, ^{57}Co, ^{58}Co, ^{59}Fe, ^{81m}Kr, ^{82}Rb, ^{86}Y, ^{89}Zr, ^{90}Y, ^{99m}Tc, ^{125}I, ^{131}I, ^{61}Cu, ^{64}Cu, ^{67}Ga, ^{68}Ga, ^{86}Y, ^{89}Zr, ^{111}In, ^{123}I, ^{131}I, ^{133}Xe, ^{186}Re and ^{201}Tl. It should also be noted and included herein, that certain radionuclides may be used for therapeutic purposes, and these include, for example, ^{90}Y and ^{131}I.

[00177] All isotopic variants of the compounds provided herein, radioactive or not, are intended to be encompassed within the scope of the invention.

[00178] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed 'isomers'. Isomers that differ in the arrangement of their atoms in space are termed 'stereoisomers'.

[00179] Stereoisomers that are not mirror images of one another are termed 'diastereomers' and those that are non-superimposable mirror images of each other are termed 'enantiomers'. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or

levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a 'racemic mixture'.

[00180] 'Tautomers' refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro- forms of phenylnitromethane, that are likewise formed by treatment with acid or base.

[00181] Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[00182] As used herein a pure enantiomeric compound is substantially free from other enantiomers or stereoisomers of the compound (*i.e.*, in enantiomeric excess). In other words, an "S" form of the compound is substantially free from the "R" form of the compound and is, thus, in enantiomeric excess of the "R" form. The term "enantiomerically pure" or "pure enantiomer" denotes that the compound comprises more than 75% by weight, more than 80% by weight, more than 85% by weight, more than 90% by weight, more than 91% by weight, more than 92% by weight, more than 93% by weight, more than 94% by weight, more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 98.5% by weight, more than 99% by weight, more than 99.2% by weight, more than 99.5% by weight, more than 99.6% by weight, more than 99.7% by weight, more than 99.8% by weight or more than 99.9% by weight, of the enantiomer. In certain embodiments, the weights are based upon total weight of all enantiomers or stereoisomers of the compound.

[00183] As used herein and unless otherwise indicated, the term "enantiomerically pure R-compound" refers to at least about 80% by weight R-compound and at most about 20% by weight S-compound, at least about 90% by weight R-compound and at most about 10% by weight S-compound, at least about 95% by weight R-compound and at most about 5% by weight S-compound, at least about 99% by weight R-compound and at most about 1% by weight S-compound, at least about 99.9% by weight R-compound or at most about 0.1% by weight S-compound. In certain embodiments, the weights are based upon total weight of compound.

[00184] As used herein and unless otherwise indicated, the term "enantiomerically pure S-compound" or "S-compound" refers to at least about 80% by weight S-compound and at most about 20% by weight R-compound, at least about 90% by weight S-compound and at most about 10% by weight R-compound, at least about 95% by weight S-compound and at most about 5% by weight R-compound, at least about 99% by weight S-compound and at most about 1% by weight R-compound or at least about 99.9% by weight S-compound and at most about 0.1% by weight R-compound. In certain embodiments, the weights are based upon total weight of compound.

[00185] In the compositions provided herein, an enantiomerically pure compound or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof can be present with other active or inactive ingredients. For example, a pharmaceutical composition comprising enantiomerically pure R-

compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure R-compound. In certain embodiments, the enantiomerically pure R-compound in such compositions can, for example, comprise, at least about 95% by weight R-compound and at most about 5% by weight S-compound, by total weight of the compound. For example, a pharmaceutical composition comprising enantiomerically pure S-compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure S-compound. In certain embodiments, the enantiomerically pure S-compound in such compositions can, for example, comprise, at least about 95% by weight S-compound and at most about 5% by weight R-compound, by total weight of the compound. In certain embodiments, the active ingredient can be formulated with little or no excipient or carrier.

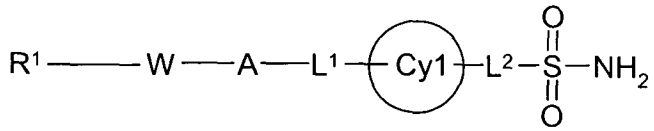
[00186] The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)- stereoisomers or as mixtures thereof.

[00187] Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

THE COMPOUNDS

[00188] In certain aspects, the present invention provides compounds useful as probes and imaging agents, for indentifying and assisting with the monitoring and measurement of the growth and movement of hypoxic tumors.

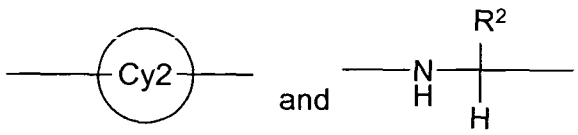
[00189] In one aspect, the present invention provides compounds according to formula I':



I'

wherein

W is a group selected from:



;

each Cy1 and Cy2 are independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

A is selectected from $-(CH_2)_n$-NH-C(=O)-, $-(CH_2)_n$-C(=O)NH-, $-(CH_2)_n$-NHC(=O)-NH-, and $-(CH_2)_n$-NH-C(=S)-NH-; n is 0, 1, or 2;

L^1 is a single bond, substituted or unsubstituted C_1-C_4 alkylene; or $-(CH_2)_m$-NH-C(=O)-; m is 2 or 3;

L^2 is a single bond, or substituted or unsubstituted C_1-C_4 alkylene;

R^1 is a metal chelator group or a fluorescent ligand; provided the metal chelator group or the fluorescent ligand contains at least 2 or more N; and each N atom is substituted with at least one CH_2COOH group; and

R^2 is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted CH_2-cycloalkyl, substituted or unsubstituted CH_2-heterocycloalkyl, substituted or unsubstituted CH_2-aryl, substituted or unsubstituted CH_2-heteroaryl, substituted or unsubstituted CH_2-SH;

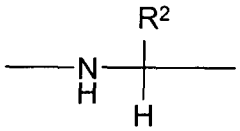
or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof;

provided that the compound is other than

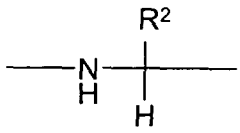
14-[4-(aminosulfonyl)phenyl]-3,6,9-tris(carboxymethyl)-11-oxo-3,6,9,12-tetraazatetradecanoic acid

[00190] In one particular embodiment of the invention, with respective to compounds of formula I', W is Cy2.

[00191] In another particular embodiment of the invention, with respective to compounds of formula I', W is



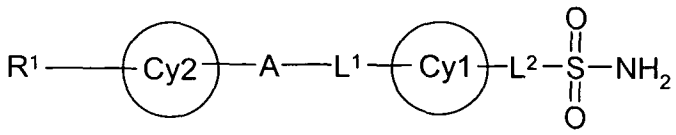
[00192] In one embodiment of the invention, with respective to compounds of formula I', W is



;

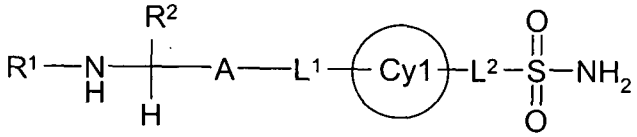
and L^2 is a single bond.

[00193] In one embodiment of the invention, with respective to compounds of formula I', the compound is according to formula Ia or Ib:



Ia

or



Ib

and wherein A, Cy1, Cy2, L^1, L^2, R^1, and R^2 are as described for formula I';

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof;

provided that the compound is other than

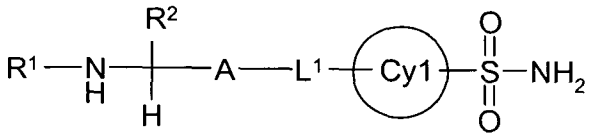
14-[4-(aminosulfonyl)phenyl]-3,6,9-tris(carboxymethyl)-11-oxo-3,6,9,12-tetraazatetradecanoic acid.

[00194] In one embodiment, with respect to compounds of formula I', the compound is according to formula Ia.

[00195] In another embodiment, with respect to compounds of formula I', the compound is according to formula Ib.

[00196] In another embodiment, with respect to compounds of formula I', the compound is according to formula Ib; and L^2 is a single bond.

[00197] In another embodiment, with respect to compounds of formula I', the compound is according to formula Ic:



Ic

;

and wherein A, Cy1, L^1, R^1, and R^2 are as described for formula I';

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof;

provided that the compound is other than

14-[4-(aminosulfonyl)phenyl]-3,6,9-tris(carboxymethyl)-11-oxo-3,6,9,12-tetraazatetradecanoic acid.

[00198] In one embodiment, with respect to compounds of formulae I', Ia-Ic, A is selectected from $-(CH_2)_n$-NH-C(=O)-, $-(CH_2)_n$-C(=O)NH-, $-(CH_2)_n$-NHC(=O)-NH-, and $-(CH_2)_n$-NH-C(=S)-NH-; and n is 0. In another embodiment, A is 1 or 2..

[00199] In one particular embodiment, with respect to compounds of formula I, A is $-(CH_2)_n$-NH-C(=O)-; and n is 0.

[00200] In one particular embodiment, with respect to compounds of formulae I', Ia-Ic, A is–$(CH_2)_n$-C(=O)NH-; and n is 0.

[00201] In one particular embodiment, with respect to compounds of formulae I', Ia-Ic, A is –$(CH_2)_n$-NHC(=O)-NH-; and n is 0.

[00202] In one particular embodiment, with respect to compounds of formulae I', Ia-Ic, A is –$(CH_2)_n$–NH-C(=S)-NH-; and n is 0.

[00203] In one particular embodiment, with respect to compounds of formulae I', Ia-Ic, A is –$(CH_2)_n$-NH-C(=O)-; and n is 1.

[00204] In one particular embodiment, with respect to compounds of formulae I', Ia-Ic, A is–$(CH_2)_n$-C(=O)NH-; and n is 1.

[00205] In one particular embodiment, with respect to compounds of formulae I', Ia-Ic, A is –$(CH_2)_n$-NHC(=O)-NH-; and n is 1.

[00206] In one particular embodiment, with respect to compounds of formulae I', Ia-Ic, A is –$(CH_2)_n$–NH-C(=S)-NH-; and n is 1.

[00207] In one particular embodiment, with respect to compounds of formulae I', Ia-Ic, n is 0.

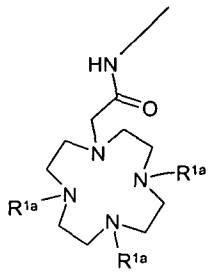
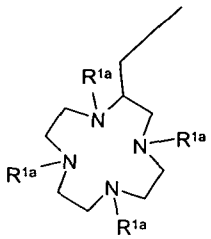
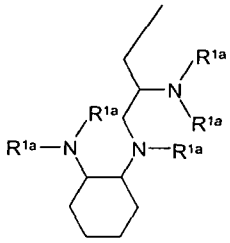
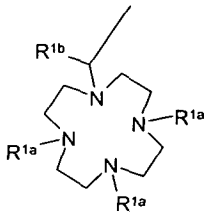
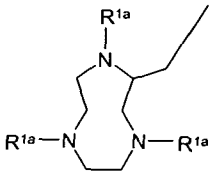
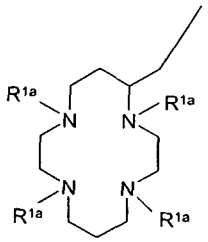
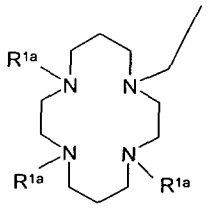
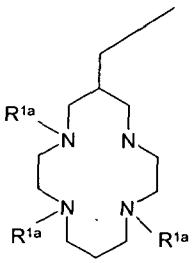
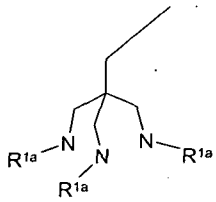
[00208] In one particular embodiment, with respect to compounds of formulae I', Ia-Ic, R^1 is a metal chelator group containing at least 2 or more N; and each N atom is substituted with a CH_2COOH group.

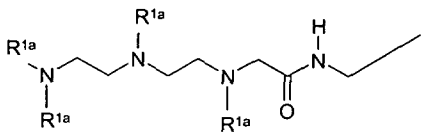
[00209] In one particular embodiment, with respect to compounds of formulae I', Ia-Ic, R^1 is a heterocycloalkylmethyl group; and the heterocycle contains 2 or more N atoms.

[00210] In one particular embodiment, with respect to compounds of formulae I', Ia-Ic, R^1 is as described above; and each N atom is substituted with a CH_2COOH group.

[00211] In one particular embodiment, with respect to compounds of formulae I', Ia-Ic, R^1 is triazacyclononanemethyl, tetrazacyclododecanemethyl, or tetraazacyclotetradecanemethyl; and each N atom is substituted with CH_2COOH.

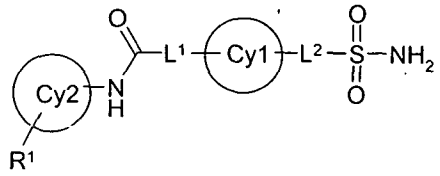
[00212] In a more particular embodiment, with respect to compounds of formulae I', the compound is according to formula Ia-Ic; and R^1 is










or

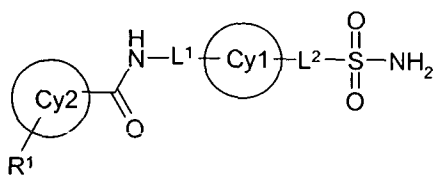


and each R^{1a} is CH_2CO_2H; and R^{1b} is CO_2H.

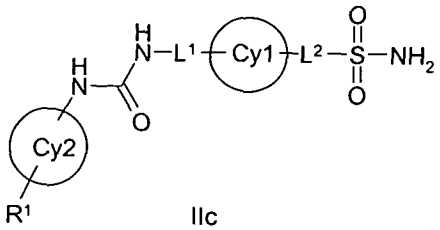
[00213] In one particular embodiment, with respect to compounds of formula I', the compound is according to formula IIa, IIb, IIc, IId, IIe, IIf, IIg, or IIh:



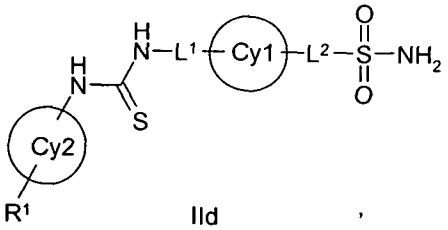
IIa



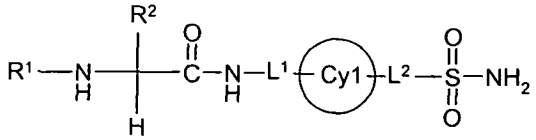
IIb



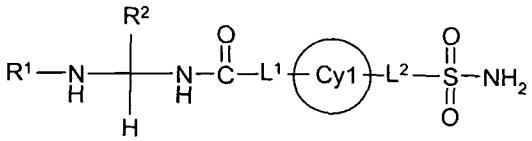
IIc



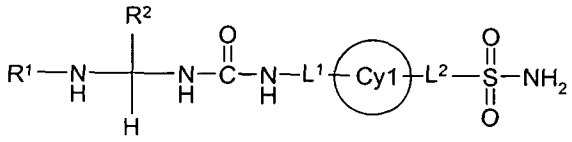
IId



IIe

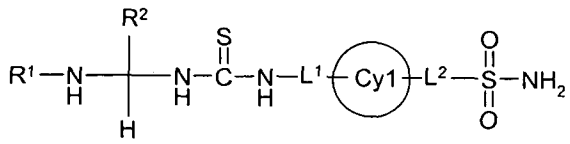


IIf



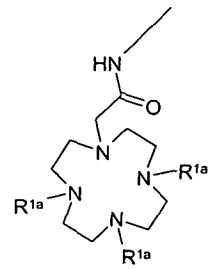
IIg

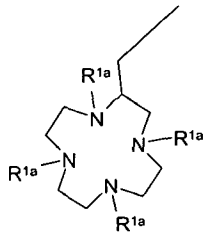
or

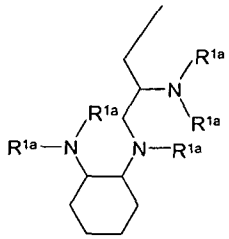


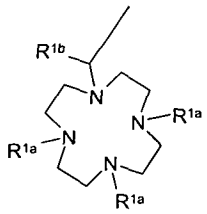
IIh

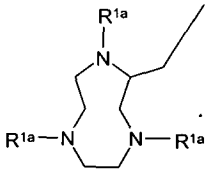
wherein Cy1, Cy2, L^1, L^2 and R^2 are as described for formula I'; and R^1 is selected from substituted or unsubstituted

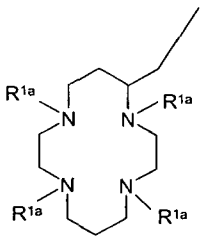


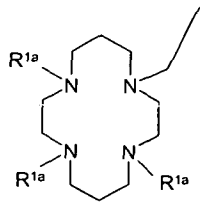


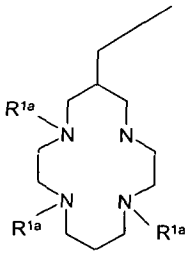


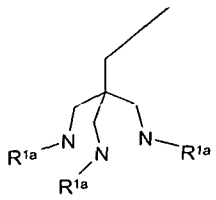












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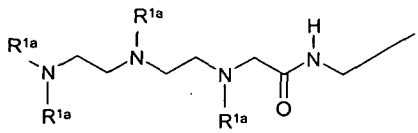
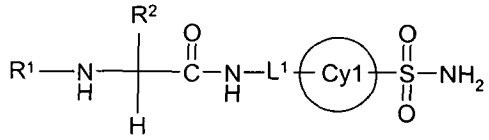


and each R^{1a} is CH_2CO_2H; and R^{1b} is CO_2H.

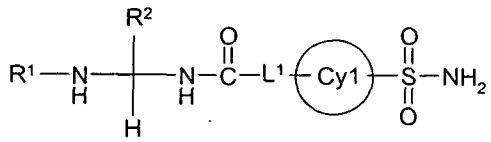
[00214] In one embodiment, with respect to compounds of formula I', the compound is according to formula IIa, IIb, IIc, or IId. In another embodiment, the compound is according to formula IIe, IIf, IIg, or IIh.

[00215] In one particular embodiment, with respect to compounds of formula IIe-IIh, L^2 is a single bond.

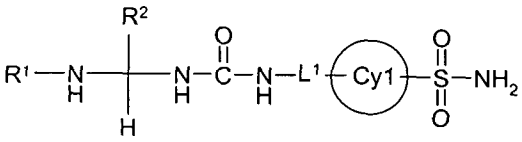
[00216] In one particular embodiment, with respect to compounds of formula I' the compound is according to formula IIe', IIf', IIg', or IIh':



IIe'

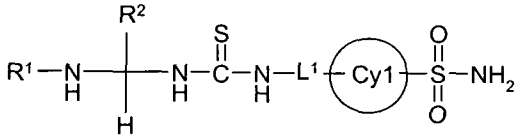


IIf'



IIg'

or

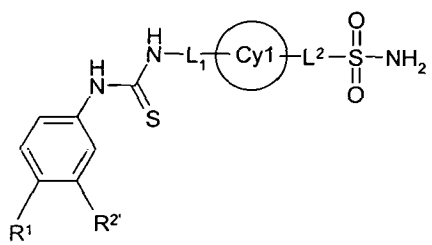


IIh'

[00217] In one particular embodiment, with respect to compounds of formula I', Ia, or IIa-IId, Cy2 is substituted or unsubstituted phenyl.

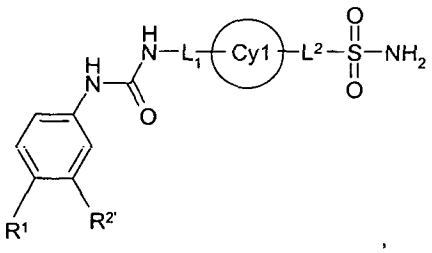
[00218] In one particular embodiment, with respect to compounds of formula I', Ia, or IIa-IId, Cy2 is phenyl, unsubstituted or substituted with one or more groups selected from halo, alkyl, alkoxy, and trihaloalkyl.

[00219] In one particular embodiment, with respect to compounds of formula I', the compound is according to formula IIIa or IIIb:



IIIa

or



IIIb

and wherein Cy1 is independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; each L^1 and L^2 is a single bond or substituted or unsubstituted C_1-C_4 alkylene;

R^1 is as described for formula IIa-d; $R^{2'}$ is H, alkyl, halo, haloalkyl, or alkoxy. .

[00220] In one particular embodiment, with respect to compounds of formula IIIa-IIIb, R^2 is H or alkoxy.

[00221] In one particular embodiment, with respect to compounds of formula I', Ia-Ib, IIa-IIh, IIe'-IIh', or IIIa-IIIb, L^1 is a single bond.

[00222] In one particular embodiment, with respect to compounds of formula I', Ia-Ib, IIa-IIh, IIe'-IIh', or IIIa-IIIb, L^1 is $-CH_2-$, $-CH_2-CH_2-$, or $-CH_2CH_2CH_2-$.

[00223] In one particular embodiment, with respect to compounds of formula I', Ia-Ib, IIa-IIh, IIe'-IIh', or IIIa-IIIb, L^1 is $-CH_2-CH_2-$.

[00224] In one particular embodiment, with respect to compounds of formula I', Ia-Ib, IIa-IIh, IIe'-IIh', or IIIa-IIIb, L^1 is $-CH_2-$.

[00225] In one particular embodiment, with respect to compounds of formula I', Ia-Ib, IIa-IIh, IIe'-IIh', or IIIa-IIIb, L^1 is $-CH_2-CH_2-NH-C(=O)-$.

[00226] In one particular embodiment, with respect to compounds of formula I', Ia-Ib, IIa-IIh, IIe'-IIh', or IIIa-IIIb, L^2 is $-CH_2-$.

[00227] In one particular embodiment, with respect to compounds of formula I', Ia-Ib, IIa-IIh, IIe'-IIh', or IIIa-IIIb, L^2 is a single bond.

[00228] In one particular embodiment, with respect to compounds of formula I', Ia-Ib, IIa-IIh, IIe'-IIh', or IIIa-IIIb, Cy1 is substituted or unsubstituted phenyl.

[00229] In one particular embodiment, with respect to compounds of formula I', Ia-Ib, IIa-IIh, IIe'-IIh', or IIIa-IIIb, Cy1 is phenyl, unsubstituted or substituted with one or more groups selected from halo, alkyl, alkoxy, sulfonamido, and trihaloalkyl.

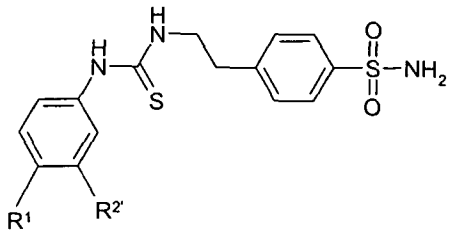
[00230] In one particular embodiment, with respect to compounds of formula I', Ia-Ib, IIa-IIh, IIe'-IIh', or IIIa-IIIb, Cy1 is phenyl, unsubstituted or substituted with one or more groups selected from Cl, F, Br, I, CF_3, SO_2NH_2, and Me.

[00231] In one particular embodiment, with respect to compounds of formula I', Ia-Ib, IIa-IIh, IIe'-IIh', or IIIa-IIIb, Cy1 is substituted or unsubstituted thiadiazolyl.

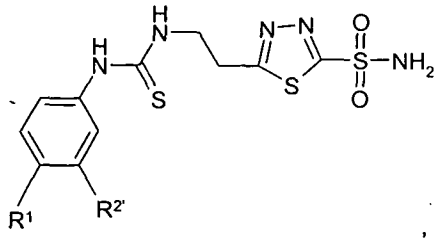
[00232] In one particular embodiment, with respect to compounds of formula II', Ia-Ib, IIa-IIh, IIe'-IIh', or IIIa-IIIb, Cy1 is substituted or unsubstituted pyrimidinyl.

[00233] In one particular embodiment, with respect to compounds of formula II', Ia-Ib, IIa-IIh, IIe'-IIh', or IIIa-IIIb, Cy1 is substituted or unsubstituted benzothiazolyl.

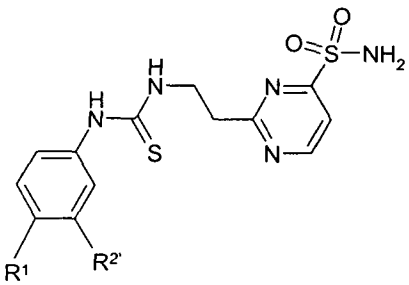
[00234] In one particular embodiment, with respect to compounds of formula I', the compound is according to formula IVa, IVb, IVc, IVd, IVe, IVf, IVg or IVh:



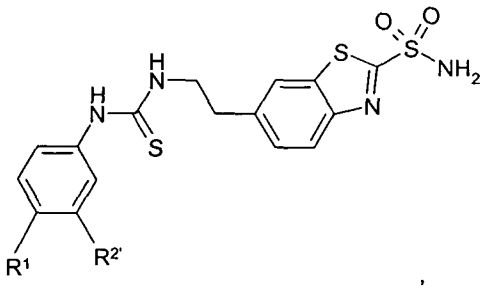
IVa



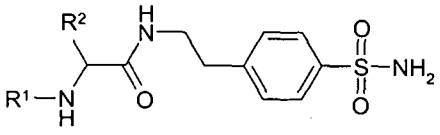
IVb



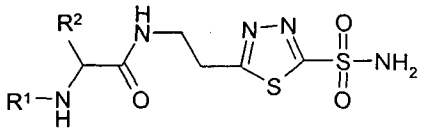
IVc



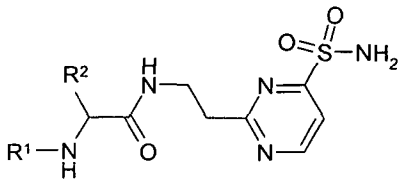
IVd



IVe

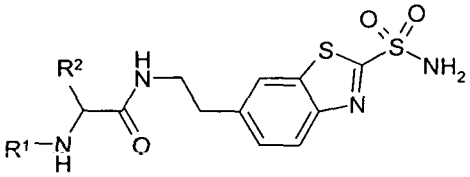


IVf



IVg

or



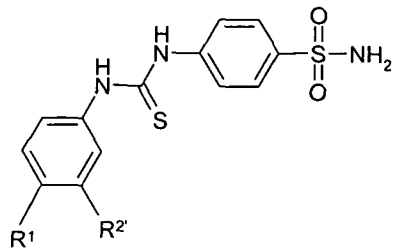
IVh

and wherein R^1 and R^2 are as described for formulae I', Ia, Ib, or IIa-IIh; and $R^{2'}$ is H, alkyl, halo, haloalkyl, or alkoxy.

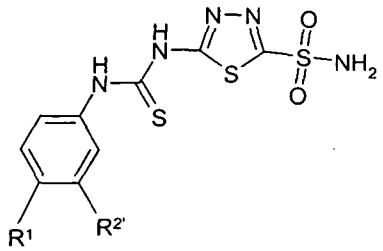
[00235] In one particular embodiment, with respect to compounds of formula I', the compound is according to formula IVa, IVb, IVc, or IVd.

[00236] In one particular embodiment, with respect to compounds of formula I', the compound is according to formula IVe, IVf, IVg or IVh.

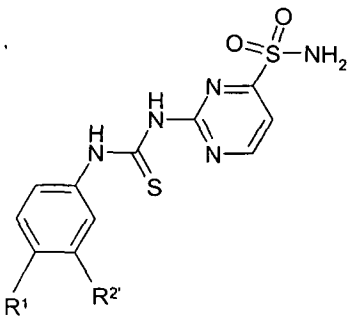
[00237] In one particular embodiment, with respect to compounds of formula I, the compound is according to formula Va, Vb, Vc Vd, Ve, Vf, Vg or Vh:



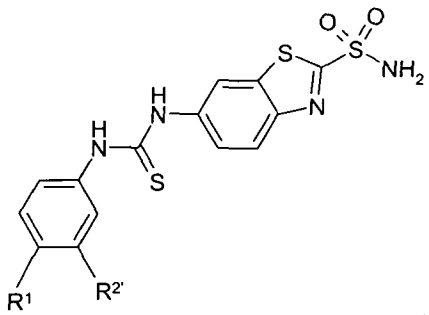
Va



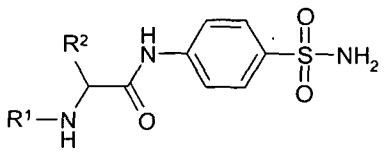
Vb



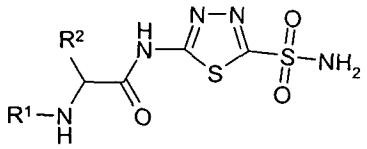
Vc



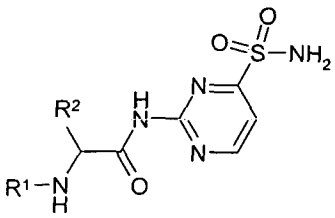
Vd



Ve

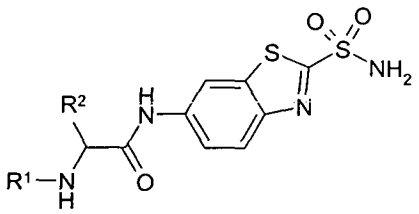


Vf



Vg

or



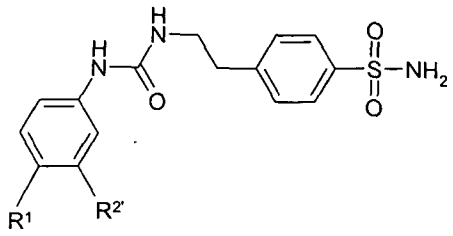
Vh

and wherein R^1 and R^2 are as described for formulae I', Ia, Ib, or IIa-IIh; and $R^{2'}$ is H, alkyl, halo, haloalkyl, or alkoxy.

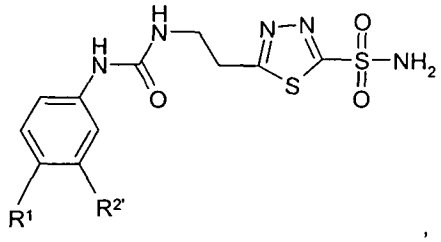
[00238] In one particular embodiment, with respect to compounds of formula I', the compound is according to formula Va, Vb, Vc, or Vd.

[00239] In one particular embodiment, with respect to compounds of formula I', the compound is according to formula Ve, Vf, Vg or Vh.

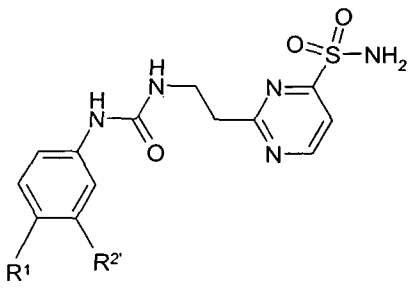
[00240] In one particular embodiment, with respect to compounds of formula I, the compound is according to formula VIa, VIb, VIc or VId:



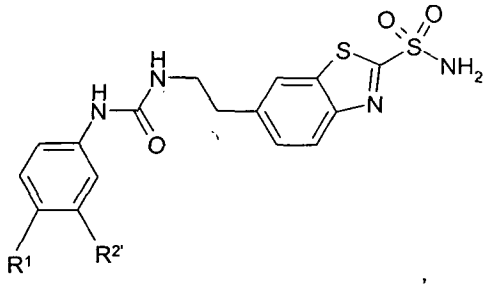
VIa



VIb



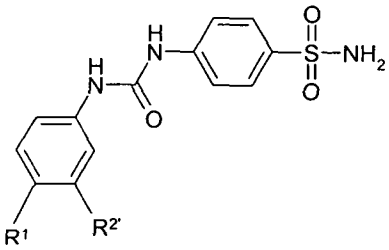
VIc or



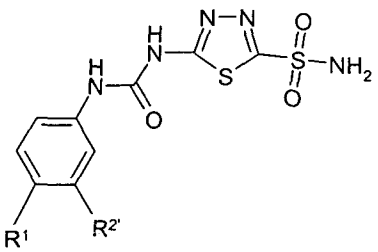
VId

and wherein R^1 is as described for formula I', Ia, Ib, or IIa-IIh; and $R^{2'}$ is H, alkyl, halo, haloalkyl, or alkoxy.

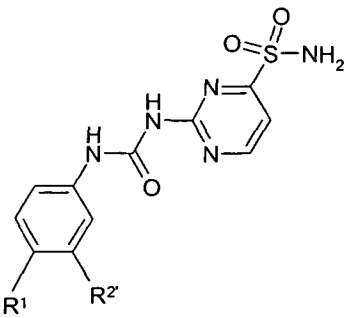
[00241] In one particular embodiment, with respect to compounds of formula I, the compound is according to formula VIIa, VIIb, VIIc or VIId:



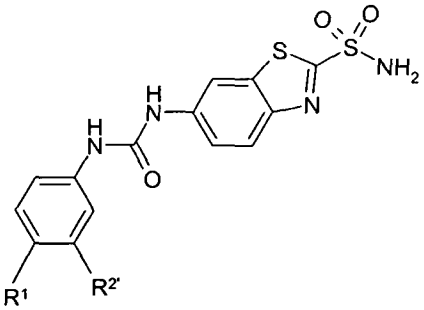
VIIa



VIIb



VIIc or



VIId

and wherein R^1 is as described for formula I', Ia, Ib, or IIa-IIh; and $R^{2'}$ is H, alkyl, halo, haloalkyl, or alkoxy.

[00242] In one embodiment, with respect to compounds of formula IIIa-IIIb, IVa-IVd, Va-Vd, or VIa-VIId, $R^{2'}$ is H, Me, CF_3, Cl, F, or OMe.

[00243] In one embodiment, with respect to compounds of formula I', the compound is according to formula IVe, IVf, IVg, IVh, Ve, Vf, Vg, or Vh.

[00244] In another embodiment, with respect to compounds of formula I', the compound is according to formula IVe, IVf, IVg, IVh, Ve, Vf, Vg, or Vh; and the group –[NH-C(R^2)-C(O)-]- represents an amino acid residue.

[00245] In another embodiment, with respect to compounds of formula I', the compound is according to formula IVe, IVf, IVg, IVh, Ve, Vf, Vg, or Vh; wherein the group –[NH-C(R^2)-C(O)-]- represents an amino acid residue; and the amino acid residue is selected from –Ala-, -Arg-, -Asn-, -Asp-, -Cis-, -Glu-, -Gln-, -Gly-, -His-, -Ile-, -Leu-, -Lys-, -Met-, -Phe-, -Ser-, -Thr-, -Trp-, -Tyr-, and -Val-.

[00246] In another embodiment, with respect to compounds of formula I', the compound is according to formula IVe, IVf, IVg, IVh, Ve, Vf, Vg, or Vh; wherein the group –[NH-C(R^2)-C(O)-]- represents an amino acid residue; and the amino acid residue is selected from –Phe-, -Trp-, and -Tyr-.

[00247] In one embodiment, with respect to compounds of formula I', Ib, IIe-IIf, IIe'-IIf', IVe-IVh, or Ve-Vh, R^2 is H, CH_2Ph, CH_2-naphthyl, CH_2-dihydronaphthyl, CH_2-indol-3-yl, CH_2-imidazolyl, CH_2-(4-hydroxy)phenyl, CH_2-cyclohexyl, or CH_2-[4-$(CO_2H)_2$-CH-O-]phenyl;

[00248] In one embodiment, with respect to compounds of formula I', Ib, IIe-IIf, IIe'-IIf', IVe-IVh, or Ve-Vh, R^2 is H.

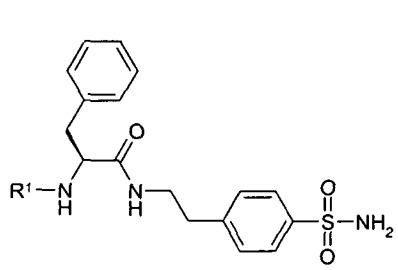
[00249] In one embodiment, with respect to compounds of formula I', Ib, IIe-IIf, IIe'-IIf', IVe-IVh, or Ve-Vh, R^2 is substituted or unsubstituted alkyl.

[00250] In one embodiment, with respect to compounds of formula I', Ib, IIe-IIf, IIe'-IIf', IVe-IVh, or Ve-Vh, R^2 is Me, i-Pr, i-Bu, or sec-Bu.

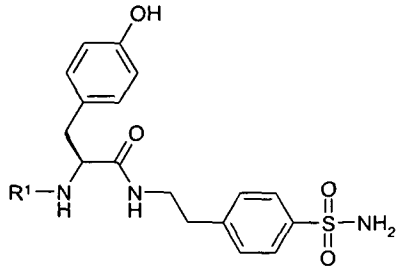
[00251] In one embodiment, with respect to compounds of formula I', Ib, IIe-IIf, IIe'-IIf', IVe-IVh, or Ve-Vh, R^2 is alkyl substituted with SH, or amino.

[00252] In one embodiment, with respect to compounds of formula I', Ib, IIe-IIf, IIe'-IIf', IVe-IVh, or Ve-Vh, R^2 is CH_2Ph, CH_2-naphthyl, CH_2-indol-3-yl, or CH_2-(4-hydroxy)phenyl.

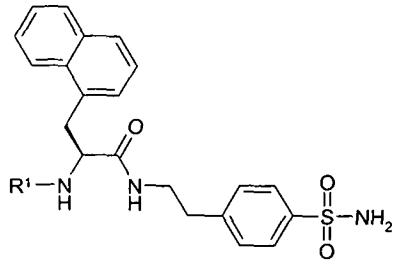
[00253] In one embodiment, with respect to compounds of formula I', the compound is according to formula VIIIa, VIIIb, VIIIc, VIIId or VIIIe:



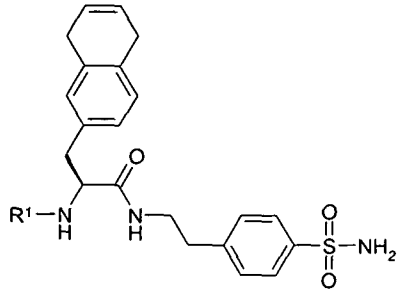
VIIIa



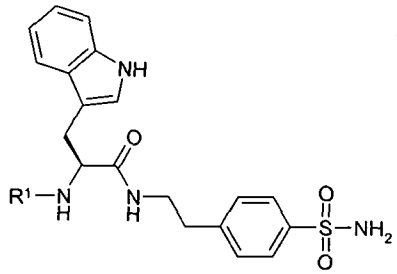
VIIIb



VIIIc



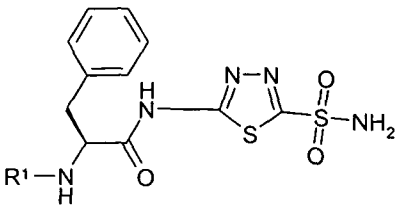
VIIId



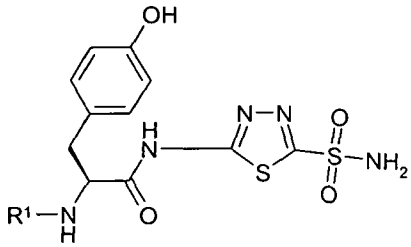
VIIIe

and wherein R^1 is as for formula I', Ia-Ib, or IIa-IIh.

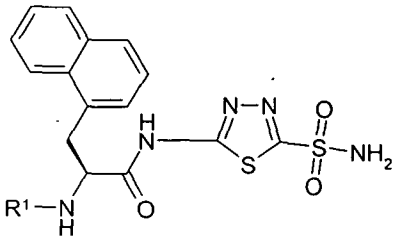
[00254] In one embodiment, with respect to compounds of formula I', the compound is according to formula IXa, IXb, IXc, IXd, or IXe:



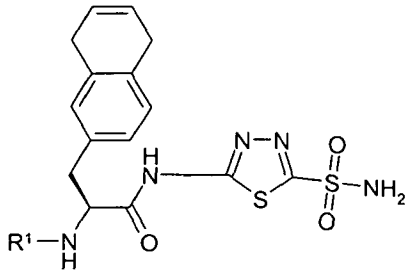
IXa ,



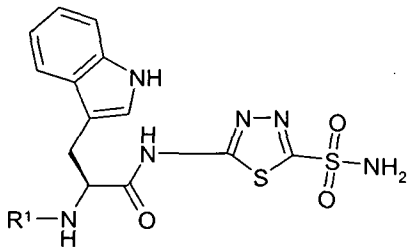
IXb ,



IXc ,



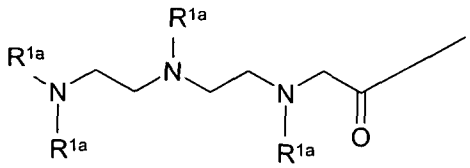
IXd ,



IXe ,

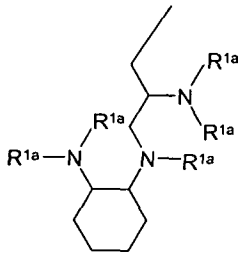
and wherein R^1 is as for formula I', Ia-Ib, or IIa-IIh.

[00255] In one particular embodiment, with respect to compounds of formula I-IXe, R^1 is



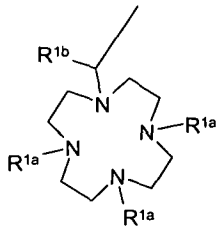
and wherein R^{1a} is as described for formula IIa-IIh.

[00256] In one particular embodiment, with respect to compounds of formula I-IXe, R^1 is



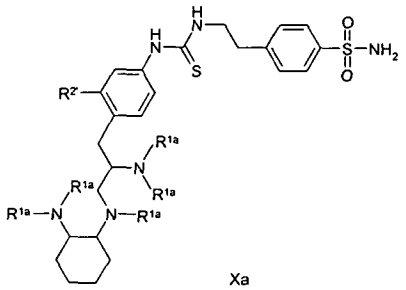
and wherein R^{1a} is as described for formula IIa-IIh.

[00257] In one particular embodiment, with respect to compounds of formula I-IXe, R^1 is

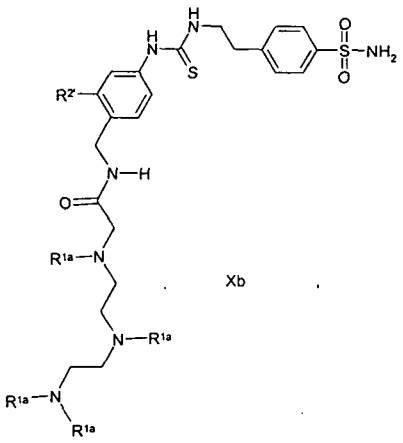


and wherein R^{1a} and R^{1b} are as described for formula IIa-IIh.

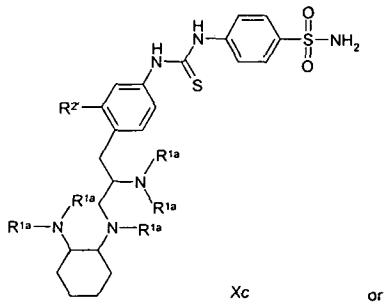
[00258] In one particular embodiment, with respect to compounds of formula I', the compound is according to formula Xa, Xb, Xc or Xd:



Xa

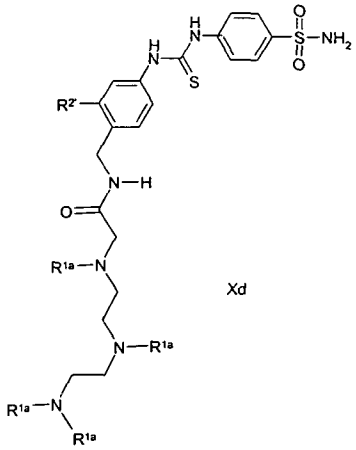


Xb



Xc

or

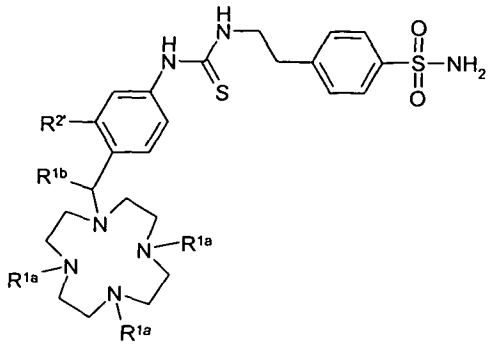


Xd

and wherein R^{1a} is as in formula IIa-IIh; and R^2 is H or alkoxy.

[00259] In one particular embodiment, with respect to compounds of formula I, the compound is according to formula Xa. In another particular embodiment, the compound is according to formula Xb. In a further particular embodiment, the compound is according to formula Xc. In a yet further particular embodiment the compound is according to formula Xd.

[00260] In one particular embodiment, with respect to compounds of formula I, the compound is according to formula XI:



XI

and wherein R^{1a} and R^{1b} are as in formula 1; and R^2 is H or alkoxy.

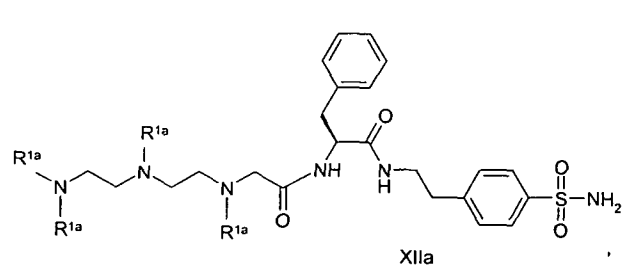
[00261] In one particular embodiment, with respect to compounds of the invention, $R^{2'}$, when present, is H.

[00262] In one particular embodiment, with respect to compounds of the invention, $R^{2'}$, when present, is methoxy.

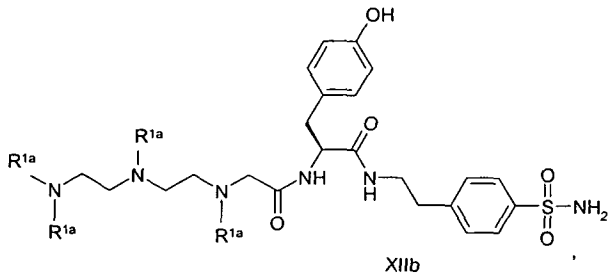
[00263] In one particular embodiment, with respect to compounds of formula IIa-XI, R^{1a} when present, is CH_2COOH.

[00264] In one particular embodiment, with respect to compounds of formula IIa-XI, R^{1b} when present, is COOH.

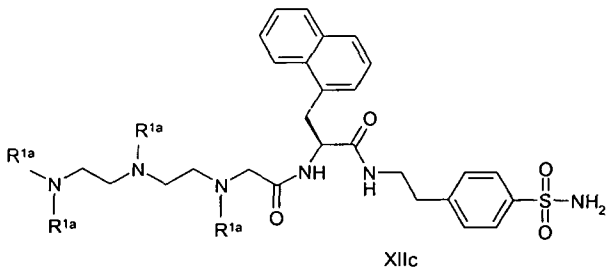
[00265] In one particular embodiment, with respect to compounds of formula I', the compound is according to formula XIIa, XIIb, XIIc, XIId or XIIe:



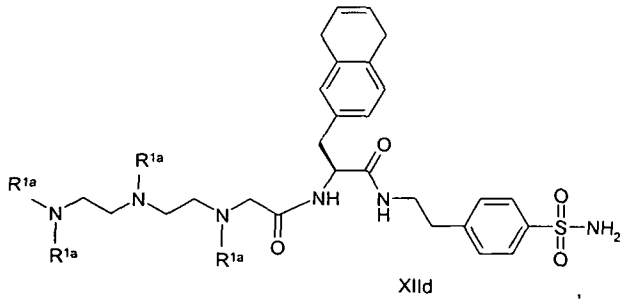
XIIa



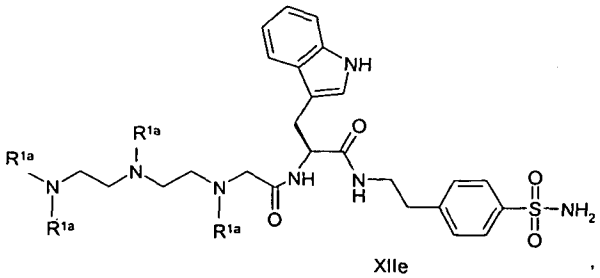
XIIb



XIIc



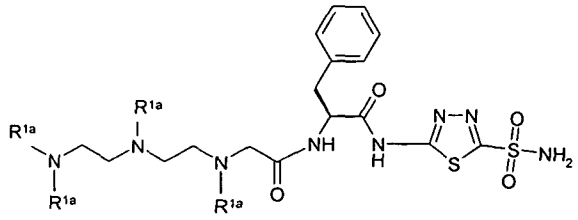
XIId



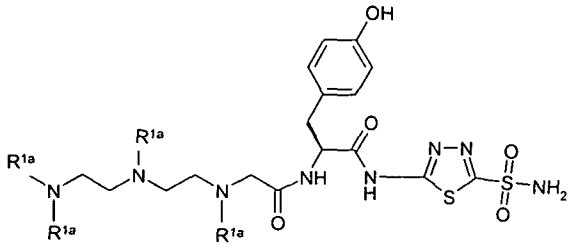
XIIe

each R^{1a} is CH_2CO_2H.

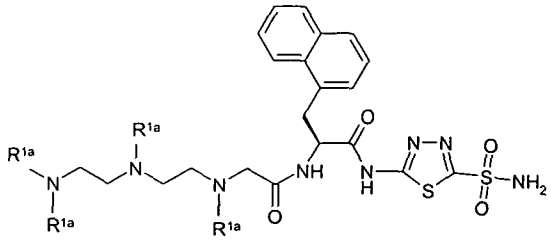
[00266] In one particular embodiment, with respect to compounds of formula I', the compound is according to formula XIIIa, XIIIb, XIIIc, XIIId or XIIIe:



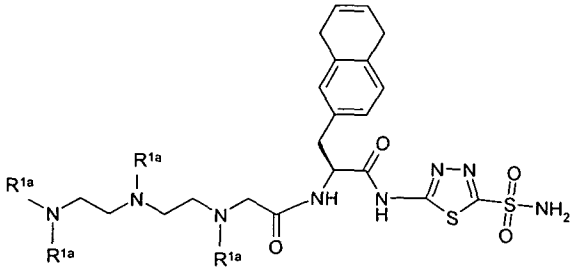
XIIIa



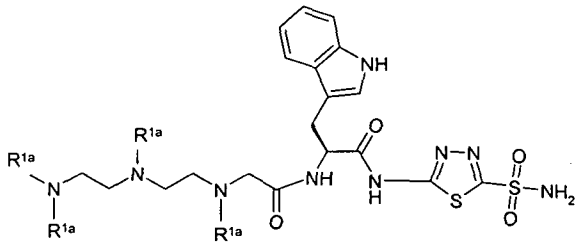
XIIIb



XIIIc



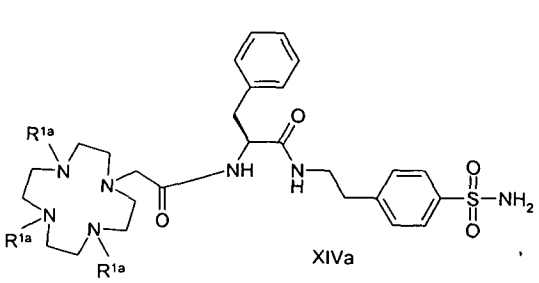
XIIId



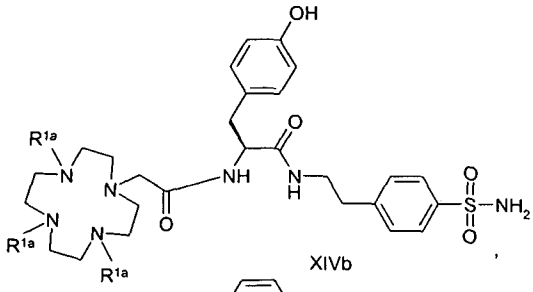
XIIIe

each R^{1a} is CH_2CO_2H.

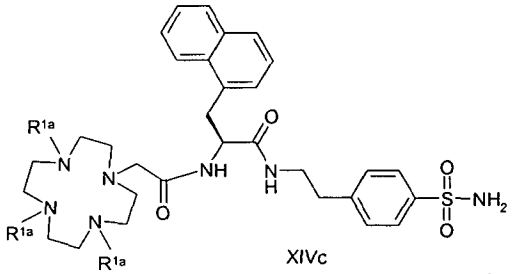
[00267] In one particular embodiment, with respect to compounds of formula I', the compound is according to formula XIVa, XIVb, XIVc, XIVd or XIVe:



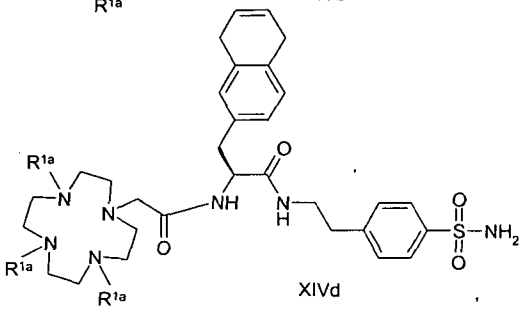
XIVa



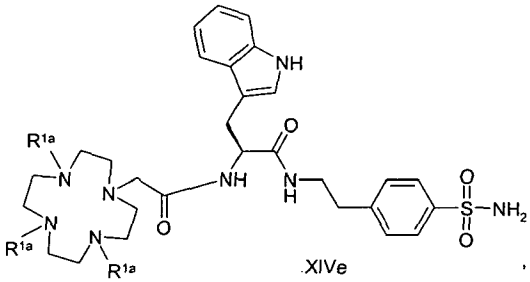
XIVb



XIVc



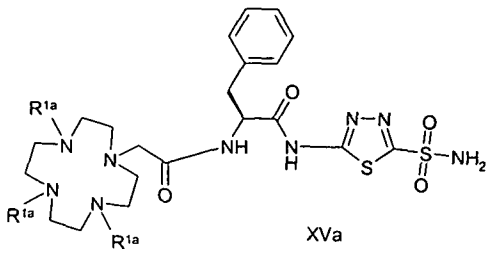
XIVd



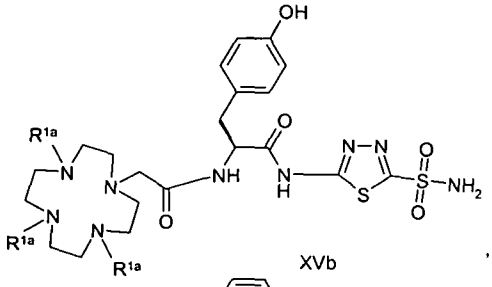
XIVe

each R^{1a} is CH_2CO_2H.

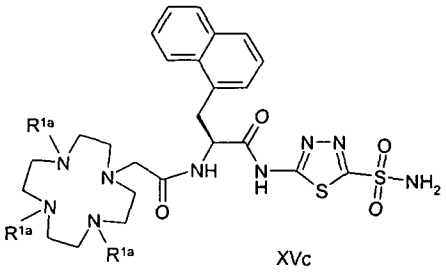
[00268] In one particular embodiment, with respect to compounds of formula I', the compound is according to formula XVa, XVb, XVc, XVd or XVe:



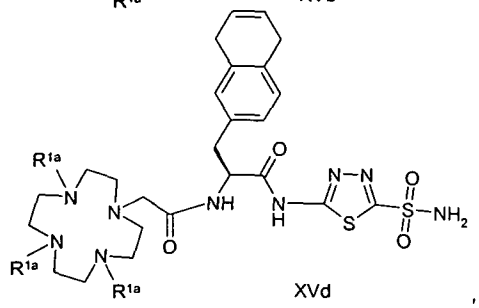
XVa



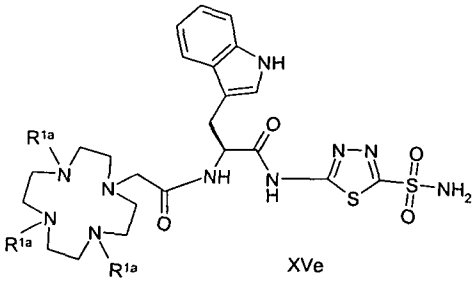
XVb



XVc



XVd



XVe

each R^{1a} is CH_2CO_2H.

[00269] In one particular embodiment, with respect to compounds of formula I', the compound is selected from the compounds exemplified in Table 1;

or a pharmaceutically acceptable salt, solvate or prodrug thereof;

and stereoisomers, isotopic variants and tautomers thereof.

[00270] In another particular embodiment, with respect to compounds of formula I', the compound is selected from the compounds exemplified in Table 2;

or a pharmaceutically acceptable salt, solvate or prodrug thereof;

and stereoisomers, isotopic variants and tautomers thereof.

[00271] In one particular embodiment, with respect to compounds of formula I', the compound is selected from the compounds exemplified in Table 3;

or a pharmaceutically acceptable salt, solvate or prodrug thereof;

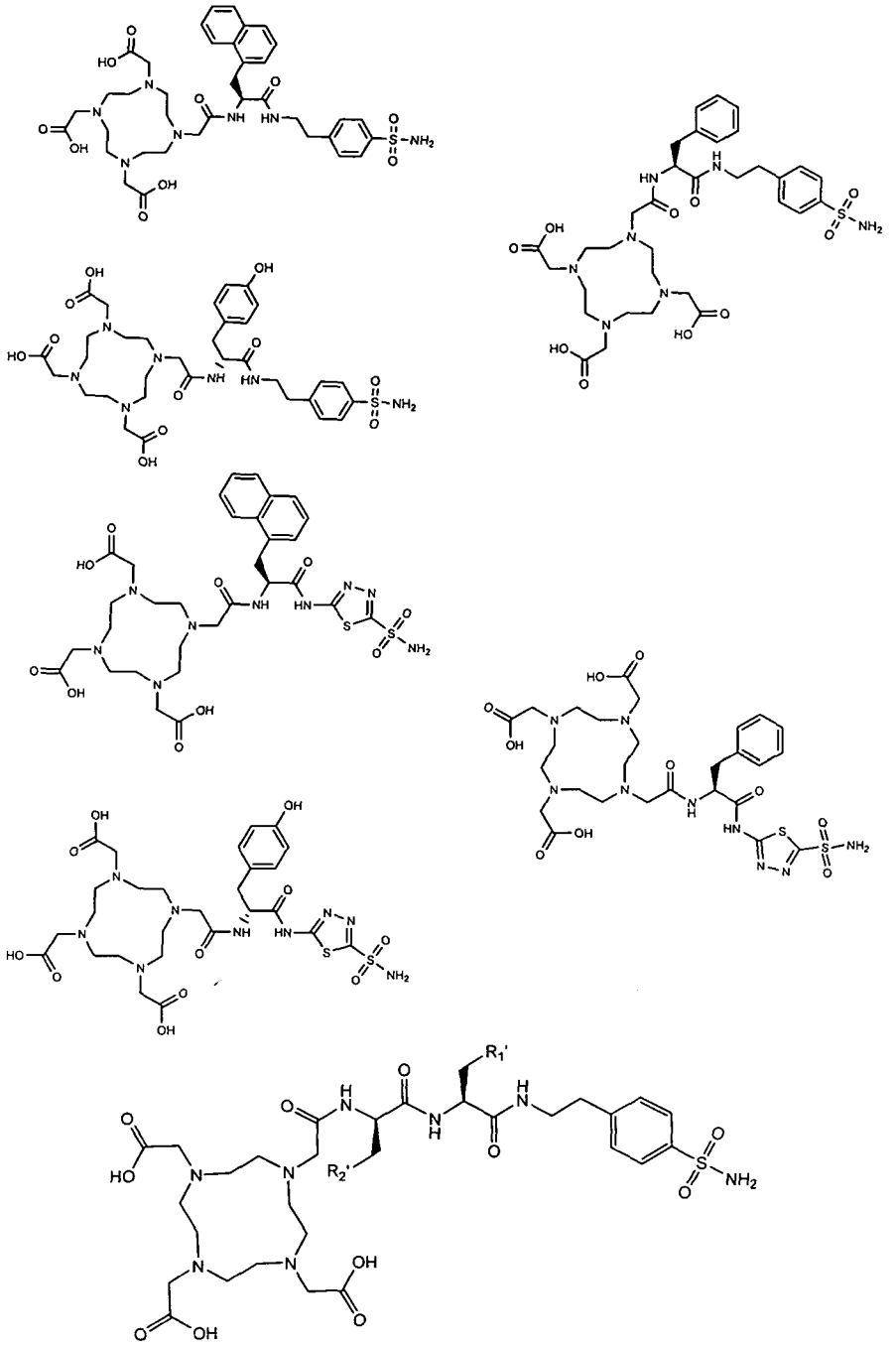
and stereoisomers, isotopic variants and tautomers thereof.

[00272] In another particular embodiment, with respect to compounds of formula I', the compound is selected from the compounds exemplified in Table 4;

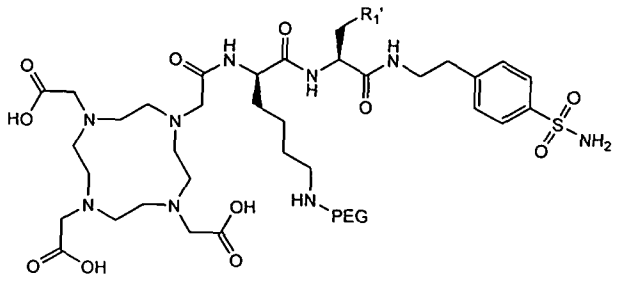
or a pharmaceutically acceptable salt, solvate or prodrug thereof;

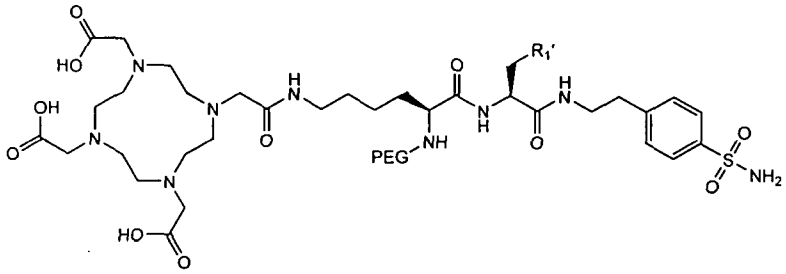
and stereoisomers, isotopic variants and tautomers thereof.

[00273] In another particular embodiment, with respect to compounds of formula I', the compound is:



R_1' = alkyl, aminoalkyl, hydroxyalkyl, benzyl, phenyl, napthyl, or other amino acid side chain; R_2' = alkyl, aminoalkyl, hydroxyalkyl, benzyl, phenyl napthyl, or other amino acid side chain.





R_1' = alkyl, aminoalkyl, hydroxyalkyl, benzyl, phenyl, napthyl, or other amino acid side chain;
PEG – polyethyleneglycol;
or a pharmaceutically acceptable salt, solvate or prodrug thereof;
and stereoisomers, isotopic variants and tautomers thereof.

[00274] In one particular embodiment, the invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of formula I, for use as a diagnostic and/ or therapeutic agent.

[00275] In another particular embodiment, the compounds of the invention function as imaging agents and the invention extends to a method for identifying or detecting hypoxic tumors in a subject or patient, which comprises administering to the subject or patient an effective amount of a compound of formula I, for example, as an imaging agent and in conjunction with the performance of an imaging protocol.

[00276] In another particular embodiment, the invention provides a compound according to formula I, for use as a probe for the identification of hypoxic tumors.

[00277] In one embodiment, the hypoxic tumor is Carbonic anhydrase IX-positive.

[00278] In one embodiment, the method for the measurement or examination of the subject for the presence or activity of a hypoxic tumor, may be carried out by radiographic imaging with one of many radionuclides known for this purpose. Suitable radionuclides may be selected from ^{3}H, ^{14}C, ^{18}F, ^{32}P, ^{35}S, ^{36}Cl, ^{51}Cr, ^{57}Co, ^{58}Co, ^{59}Fe, ^{61}Cu, ^{64}Cu, ^{67}Ga, ^{68}Ga, ^{81m}Kr, ^{82}Rb, ^{86}Y, ^{89}Zr, ^{90}Y, ^{99m}Tc, ^{111}In, ^{123}I, ^{125}I, ^{131}I, ^{131}I, ^{133}Xe, ^{186}Re and ^{201}Tl, with particular radionuclides including ^{111}In, ^{68}Ga or ^{64}Cu. Exemplary diagnostic doses may range from about 2-20mCi of e.g. ^{61}Cu, ^{64}Cu, ^{67}Ga, ^{68}Ga, ^{86}Y, ^{89}Zr or ^{111}In, per patient. A particular dose would range from 5-10mCi of ^{64}Cu, ^{68}Ga or ^{111}In. Further, the mass of the substance may be approximately 0.01-1 mg per patient, and the time period within which imaging is generally performed can range from 1 hour to about 24 hours following injection with the imaging agent. The imaging methods useful in the invention are as recited above, and include positron-emission tomography (PET) and single photon emission tomography (SPECT).

[00279] In one embodiment, the method for the measurement or examination of the subject for the presence or activity of a hypoxic tumor is carried out by positron-emission tomography, and the radionuclides that are used may comprise ^{64}Cu and ^{68}Ga.

[00280] In one embodiment, the method for the measurement or examination of the subject for the presence or activity of a hypoxic tumor is carried out by single photon emission tomography, and the radionuclides that are used may comprise ^{111}In.

[00281] In one embodiment, the method for the measurement or examination of the subject for the presence or activity of a hypoxic tumor is carried out by gamma scintigraphy.

[00282] In another particular embodiment, the invention provides a method for defining CAIX positive tumors which comprises administering to the mammal an effective amount of a compound according to formula I.

[00283] In another particular embodiment, the invention provides a method for defining tumor hypoxia for dose painting in radiation planning which comprises administering to the mammal an effective amount of a compound according to formula I.

[00284] In one embodiment, the tumor is selected from: head, breast, neck, kidney, gliomas, mesotheliomas; and stomach, colon, pancreatic, biliary, cervix, endometrial, and squamal or basal cell carcinomas.

[00285] In one particular embodiment, the tumor is a head tumor.

[00286] In another particular embodiment, the tumor is a breast tumor.

[00287] In another particular embodiment, the tumor is a colon tumor.

[00288] In another particular embodiment, the tumor is a kidney tumor.

[00289] In another particular embodiment, the invention provides a compound according to formula I, for use as a pharmaceutical.

[00290] In another particular embodiment, the invention provides a compound according to formula I, use as a pharmaceutical or medicament.

[00291] In another particular embodiment, the invention provides a use of a compound according to formula I, in the manufacture of a medicament for the use in combination therapy.

[00292] In one embodiment, the therapy is antitumor therapy, wherein the tumors are hypoxic.

[00293] Additional embodiments within the scope of the present invention are set forth in non-limiting fashion elsewhere herein and in the examples. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

[00294] In certain aspects, the present invention provides prodrugs and derivatives of the compounds according to the formulae above. Prodrugs are derivatives of the compounds of the invention, which have metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention, which are pharmaceutically active, *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholinyl esters and the like.

[00295] Certain compounds of this invention have activity in both their acid and acid derivative forms, but the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier,

Amsterdam 1985). Prodrugs include acid derivatives well know to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups pendant on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. Preferred are the C_1 to C_8 or C_1-C_6alkyl, C_2-C_8 alkenyl, aryl, substituted aryl, and arylalkyl esters of the compounds of the invention.

PHARMACEUTICAL COMPOSITIONS

[00296] When employed as pharmaceuticals, the compounds of this invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. In certain embodiments, the pharmaceutical composition may comprise a compound of the invention in combination with one or more compounds or compositions of like therapeutic utility and effect.

[00297] Generally, the compounds of this invention are administered in a pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[00298] The pharmaceutical compositions of this invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Depending on the intended route of delivery, the compounds of this invention are preferably formulated as either injectable or oral compositions or as salves, as lotions or as patches all for transdermal administration.

[00299] The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the furansulfonic acid compound is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

[00300] Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose,

a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00301] Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As before, the active compound in such compositions is typically a minor component, often being from about 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

[00302] Transdermal compositions are typically formulated as a topical ointment or cream containing the active ingredient(s), generally in an amount ranging from about 0.01 to about 20% by weight, preferably from about 0.1 to about 20% by weight, preferably from about 0.1 to about 10% by weight, and more preferably from about 0.5 to about 15% by weight. When formulated as a ointment, the active ingredients will typically be combined with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal formulations are well-known in the art and generally include additional ingredients to enhance the dermal penetration of stability of the active ingredients or the formulation. All such known transdermal formulations and ingredients are included within the scope of this invention.

[00303] The compounds of this invention can also be administered by a transdermal device. Accordingly, transdermal administration can be accomplished using a patch either of the reservoir or porous membrane type, or of a solid matrix variety.

[00304] The above-described components for orally administrable, injectable or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of Remington's The Science and Practice of Pharmacy, 21st edition, 2005, Publisher: Lippincott Williams & Wilkins, which is incorporated herein by reference.

[00305] The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in Remington's Pharmaceutical Sciences.

[00306] The following formulation examples illustrate representative pharmaceutical compositions that may be prepared in accordance with this invention. The present invention, however, is not limited to the following pharmaceutical compositions.

Formulation 1 - Tablets

[00307] A compound of the invention may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 240-270 mg tablets (80-90 mg of active compound per tablet) in a tablet press.

Formulation 2 - Capsules

[00308] A compound of the invention may be admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture is filled into 250 mg capsules (125 mg of active compound per capsule).

Formulation 3 - Liquid

[00309] A compound of the invention (125 mg) may be admixed with sucrose (1.75 g) and xanthan gum (4 mg) and the resultant mixture may be blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color are diluted with water and added with stirring. Sufficient water may then be added to produce a total volume of 5 mL.

Formulation 4 - Tablets

[00310] A compound of the invention may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of active compound) in a tablet press.

Formulation 5 - Injection

[00311] A compound of the invention may be dissolved or suspended in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/mL.

Formulation 6 - Topical

[00312] Stearyl alcohol (250 g) and a white petrolatum (250 g) may be melted at about 75°C and then a mixture of a compound of the invention (50 g) methylparaben (0.25 g), propylparaben (0.15 g), sodium lauryl sulfate (10 g), and propylene glycol (120 g) dissolved in water (about 370 g) is added and the resulting mixture is stirred until it congeals.

METHODS OF TREATMENT

[00313] The present compounds may be used as therapeutic agents for the treatment of conditions in mammals characterized by aberrant activity associated with carbonic anhydrase, as described herein. Accordingly, the compounds and pharmaceutical compositions of this invention find use as therapeutics for diagnosing, monitoring, preventing and/or treating cancer conditions in mammals including humans, which conditions exist or result from the growth and malignancy of hypoxic tumors. Thus, and as stated earlier, the present invention includes within its scope, and extends tothe use of the compounds for the recited methods of diagnosis, prognosis, monitoring or treatment, as well as to the compounds for such methods, and for the preparation of medicaments useful for such methods.

[00314] In a method of treatment aspect, this invention provides a method of treating a mammal susceptible to or afflicted with a condition associated with cancer resulting from or associated with the growth and presence of a hypoxic tumor, which method comprises administering an effective amount of one or more of the pharmaceutical compositions just described.

[00315] In additional method of treatment aspects, this invention provides methods of treating a mammal susceptible to or afflicted with cancer resulting from or associated with the growth and presence of a hypoxic tumor, which method comprises administering an effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions just described.

[00316] As a further aspect of the invention there is provided the present compounds for use as a pharmaceutical especially in the treatment or prevention of the aforementioned conditions and diseases. We also provide the use of the present compounds in the manufacture of a medicament for the treatment or prevention of one of the aforementioned conditions and diseases.

[00317] Injection dose levels range from about 0.1 mg/kg/hour to at least 10 mg/kg/hour, all for from about 1 to about 120 hours and especially 24 to 96 hours. A preloading bolus of from about 0.1 mg/kg to about 10 mg/kg or more may also be administered to achieve adequate steady state levels. The maximum total dose is not expected to exceed about 2 g/day for a 40 to 80 kg human patient.

[00318] For the prevention and/or treatment of long-term conditions, the regimen for treatment usually stretches over many months or years so oral dosing is preferred for patient convenience and tolerance. With oral dosing, one to five and especially two to four and typically three oral doses per day are representative regimens. Using these dosing patterns, each dose provides from about 0.01 to about 20 mg/kg of the compound of the invention, with preferred doses each providing from about 0.1 to about 10 mg/kg and especially about 1 to about 5 mg/kg.

[00319] Transdermal doses are generally selected to provide similar or lower blood levels than are achieved using injection doses.

[00320] When used to prevent or treat conditions contemplated herein, the compounds of this invention will be administered to a patient at risk for developing the condition, typically on the advice and under the supervision of a physician, at the dosage levels described above. Patients at risk for developing a particular condition generally include those that have a family history of the condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition.

[00321] The compounds of this invention can be administered as the sole active agent or they can be administered in combination with other agents, including other active amines and derivatives.

GENERAL SYNTHETIC PROCEDURES

[00322] The compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. *See, e.g.*, Synthetic Scheme, below. It will be appreciated that where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

[00323] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

[00324] The compounds of this invention, for example, may be prepared by the reaction of a chloro derivative with an appropriately substituted amine and the product isolated and purified by known standard procedures. Such procedures include (but are not limited to) recrystallization, column chromatography or HPLC. The following schemes are presented with details as to the preparation of representative fused heterocyclics that have been listed hereinabove. The compounds of the invention

may be prepared from known or commercially available starting materials and reagents by one skilled in the art of organic synthesis.

[00325] The compounds of the present invention may be prepared by a variety of processes well known for the preparation of compounds of this type, for example reaction schemes, and general procedures as described below.

[00326] The syntheses of representative compounds of this invention are carried out in accordance with the methods set forth above and using the appropriate reagents, starting materials, and purification methods known to those skilled in the art. All starting materials in the following general syntheses may be commercially available or obtained by conventional methods known to those skilled in the art.

[00327] In this specification, especially in "Representative Synthetic Methods", the following abbreviations can be used:

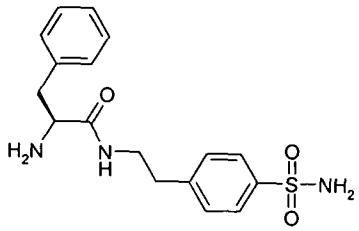
BEP	2-bromo-1-ethylpyridinium tetrafluoroborate
BOP	benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
CDI	2-chloro-1,3-dimethylimidazolinium chloride
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DME	1,2-dimethoxyethane, dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
EDC	1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrogen chloride
EtOAc	ethyl acetate
EtOH	ethanol
HOBt	1-hydroxybenzotriazole
MBq	megabecquerels
MeOH	methanol
mCi	millicuries
NMP	N-methyl-2-pyrroliidone
THF	tetrahydrofuran
TFA	trifluoroacetic acid
uM	μM
uL	μL

[00328] Synthesized compounds are characterized with Waters LC-MS system (Waters system fluidics organizer, photodiode array detector 2298, mass detector 3100 and binary gradient module 2545) using XBridge™ C_{18} 5μm column (4.6×150mm, Waters, USA) (eluents: A=0.05% TFA in water and B=0.05% TFA in acetonitrile; flow rate: 1.2mL/min; gradient: 0-2 min, 2% A; 2-10 min, 2% A-30% A, 10-14min100% B; 14-15 min, 2% A)

SYNTHESIS OF INTERMEDIATES

Intermediate 1

(S)-2-Amino-3-phenyl-N-[2-(4-sulfamoyl-phenyl)-ethyl]-propionamide



Method A (General Procedure)

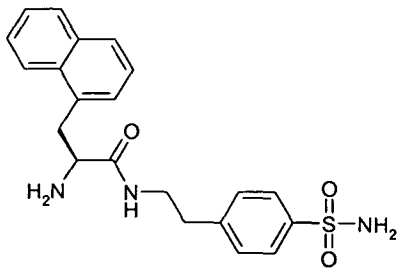
[00329] Boc-Phe-OH (300mg, 1.13mmol) and HATU (1.2mmol) were weighted and dissolved in 5mL anhydrous DMF for 15min; then 4-(2-aminoethyl)benzenesulfonamide (1.13mmol, 226mg) and DIPEA (3.4mmol) were added subsequently. After the mixture was stirring for 2 hour under room temperature, it was extracted with ethylacetate/saturated NaCl solution three times. The crude Boc-protected intermediate was purified with normal phase column, and then deprotected using TFA/H_2O (5ml, 95%TFA). After evaporation of solvents gave the intermediate (S)-2-amino-3-phenyl-N-[2-(4-sulfamoyl-phenyl)-ethyl]-propionamide,which was characterized with LC-MS and [^{1}H]NMR for its purity and molecular weight, and was used for the next step without further purification.

Method B (Alternate General Procedure)

[00330] The appropriate Boc- protected amino acid (1.0 mmol), EDC (1.1 mmol) and HoBt (1.1 mmol) were weighted and dissolved in 3 mL anhydrous DMF for 15min; then 4-(2-aminoethyl)benzenesulfonamide (1.0 mmol, 200 mg) and DIPEA (1.0 mmol) were added subsequently. After the mixture was stirring for 2.5 hours under room temperature, it was extracted with ethylacetate/saturated NaCl solution three times. Crude Boc-protected product was purified with normal phase column (DCM/MeOH), then pure Boc-protected intermediate was obtained after evaporation of solvents, which was characterized with LC-MS system and [1H]NMR for its purity and molecular weight. After 30 min incubation with TFA/H2O (3 ml, 95%TFA) for removal of Boc, pure amino compound was obtained after evaporation without further purification.

Intermediate 2

(S)-2-Amino-3-naphthalen-1-yl-N-[2-(4-sulfamoyl-phenyl)-ethyl]-propionamide

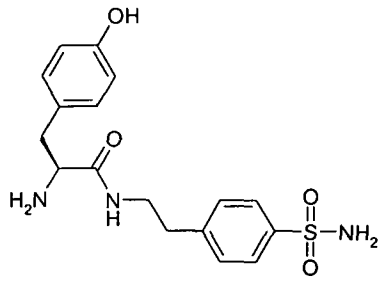


[00331] This intermediate was prepared following the method described for Intermediate 1 and using Boc protected (S)-2-Amino-3-naphthalen-1-yl-propionic acid. The intermediate 2 was characterized

with LC-MS and [^{1}H]NMR for its purity and molecular weight, and was used for the next step without further purification.

Intermediate 3

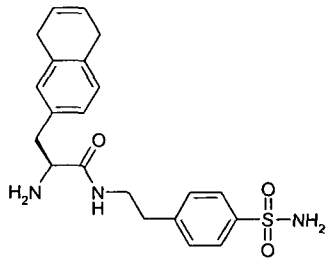
(S)-2-Amino-3-(4-hydroxyphenyl)-N-[2-(4-sulfamoyl-phenyl)-ethyl]-propionamide



[00332] This intermediate was prepared following the method described for Intermediate 1 and using Boc protected Tyr-OH. The intermediate 3 was characterized with LC-MS and [^{1}H]NMR for its purity and molecular weight, and was used for the next step without further purification.

Intermediate 4

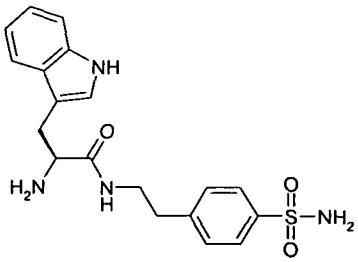
(S)-2-Amino-3-(5,8-dihydro-naphthalen-2-yl)-N-[2-(4-sulfamoyl-phenyl)-ethyl]-propionamide



[00333] This intermediate was prepared following the method described for Intermediate 1 and using Boc protected (S)-2-Amino-3-(5,8-dihydro-naphthalen-2-yl)-propionic acid. The intermediate 4 was characterized with LC-MS and [^{1}H]NMR for its purity and molecular weight, and was used for the next step without further purification.

Intermediate 5

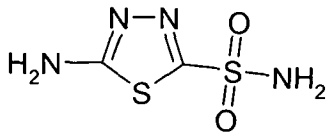
(S)-2-Amino-3-(1H-indol-3-yl)-N-[2-(4-sulfamoyl-phenyl)-ethyl]-propionamide



[00334] This intermediate was prepared following the method described for Intermediate 1 and using Boc Trp-OH. The intermediate 5 was characterized with LC-MS and [^{1}H]NMR for its purity and molecular weight, and was used for the next step without further purification.

Intermediate 6

5-amino-1,3,4-thiadiazol-2-sulfonamide

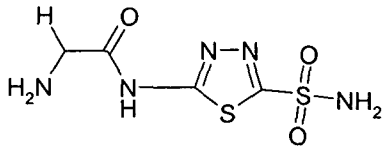


[00335] N-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide (0.78g, 3.5mmol) is added to a solution of HCl/EtOH (v/v=0.85mL/3.0mL), and sealed into microwave-reaction vial. Then reaction mixture is maintained for 1 hour under 150°C. After the reaction, solvents are evaporated away under vacuum, the residue is dissolved into 3-5mL of MeOH/DCM (v/v=1/9) and purified with silica gel column to afford 5-amino-1,3,4-thiadiazole-2-sulfonamide.

Calculated MW: 180.2, MS-ES(+): 180.8 $[M+H]^+$, 361.5 $[2M+H]^+$; purity: >98% (UV=254nm

Intermediate 7

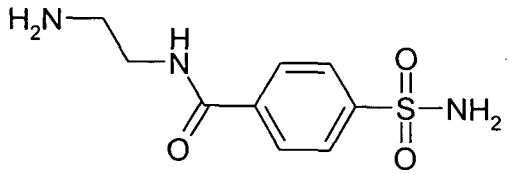
2-Amino-N-(5-sulfamoyl-[1,3,4]thiadiazol-2-yl)-acetamide



[00336] This intermediate was prepared following the method described for Intermediate 1 and using Boc protected Trp-OH and 5-amino-1,3,4-thiadiazol-2-sulfonamide. The intermediate 7 was characterized with LC-MS and [^{1}H]NMR for its purity and molecular weight, and was used for the next step without further purification.

Intermediate 8

N-(2-Aminoethyl)-4-sulfamoylbenzamide (C2)



[00337] 4-Carboxybenzenesulfonamide (1.16g, 5.76mmol) and *N,N'*-diisopropylcarbodiimide (2.9mmol, 0.45mL) are dissolved in 12 mL anhydrous DMF. Fifteen minutes later, *N*-Boc-ethylenediamine (0.35g, 2.2mmol) is added together with a traceable amount of DMAP. The reaction mixture is stirred for 3 hours. The volatiles are evaporated under reduced pressure, and the residue is

dissolved into 3-5mL of MeOH/DCM (v/v=1/9). The crude product is purified with normal phase column to afford 0.56 g of pure *N*-(2-(Boc-amino)ethyl)-4-sulfamoylbenzamide.

Calculated MW: 343.4, MS-ES(+): 344.3 $[M+H]^+$, 366.1 $[M+Na]^+$, 709.4 $[2M+Na]^+$; purity: >98% (UV=254nm).

[^{1}H]NMR [MeOD]: δ 1.41 (s, 9H, $C(CH_3)_3$); 3.45-3.47(t, 2H, $CH_2\underline{CH_2}NHCO$); 3.29-3.31(t, 2H, $BocNH\underline{CH_2}CH_2NHCO$); 7.96 (s, 4H, C_6H_4);

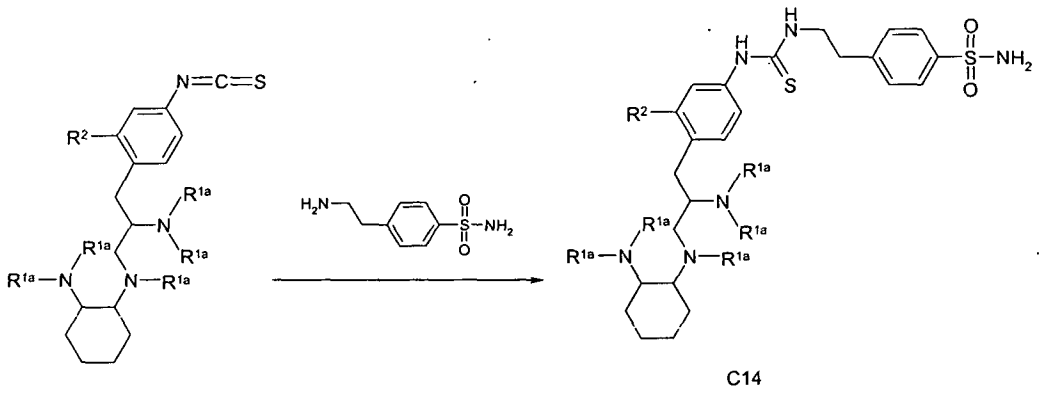
[^{13}C]NMR [MeOD]: δ 28.78 ($C(\underline{CH_3})_3$); 80.25 (s, $\underline{C}(CH_3)_3$); 40.77($CH_2\underline{CH_2}NHCO$); 41.63($BocNH\underline{CH_2}CH_2NHCO$); 127.3, 129.1 ($C_4H_4$); 147.7 ($CSO_2NH_2$); 139.0 ($NHCO\underline{C}$); 169.0 ($NH\underline{C}OC$); 158.8 ($tBuO\underline{C}NH$).

[00338] The Boc protected *N*-(2-aminoethyl)-4-sulfamoylbenzamide (0.50g, 5.76mmol) is dissolved in HCl/EtOH (v/v=0.85mL/3.0mL) and sealed in a microwave-reaction vial. The reaction mixture is reacted for 0.5 hour in microwave under 100°C. After the reaction, solvents are evaporated away under reduced pressure, the residue is dissolved into 3-5mL of MeOH/DCM (v/v=1/9) and the mixture purified with normal phase column to afford pure desired *N*-(2-aminoethyl)-4-sulfamoylbenzamide.

Calculated MW: 243.3, MS-ES(+): 244.2 $[M+H]^+$, 487.5 $[2M+H]^+$; purity: >98% (UV=254nm).

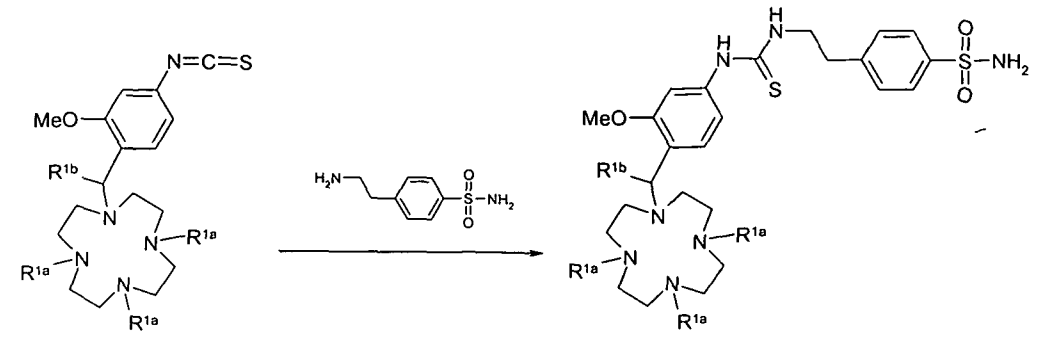
Bifunctional DTPA/DOTA-conjugated sulfonamides

Scheme 1



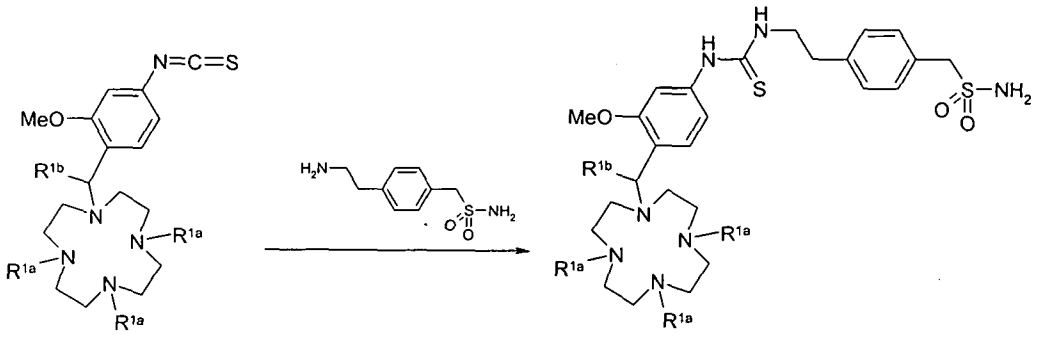
C14

Scheme 2



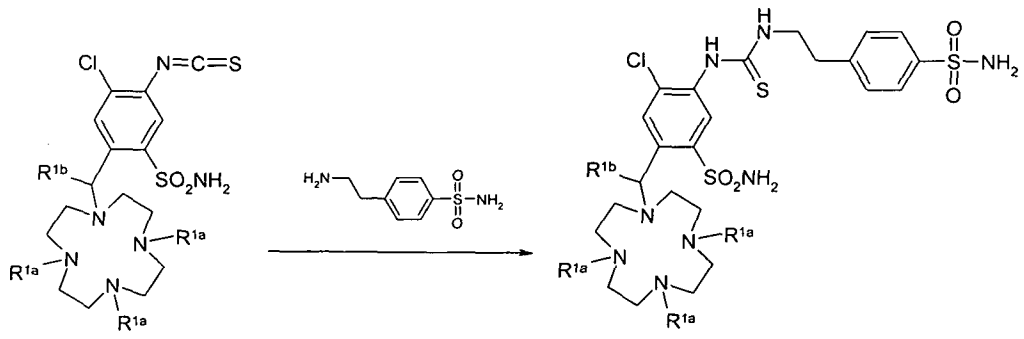
C15

Scheme 3



C16

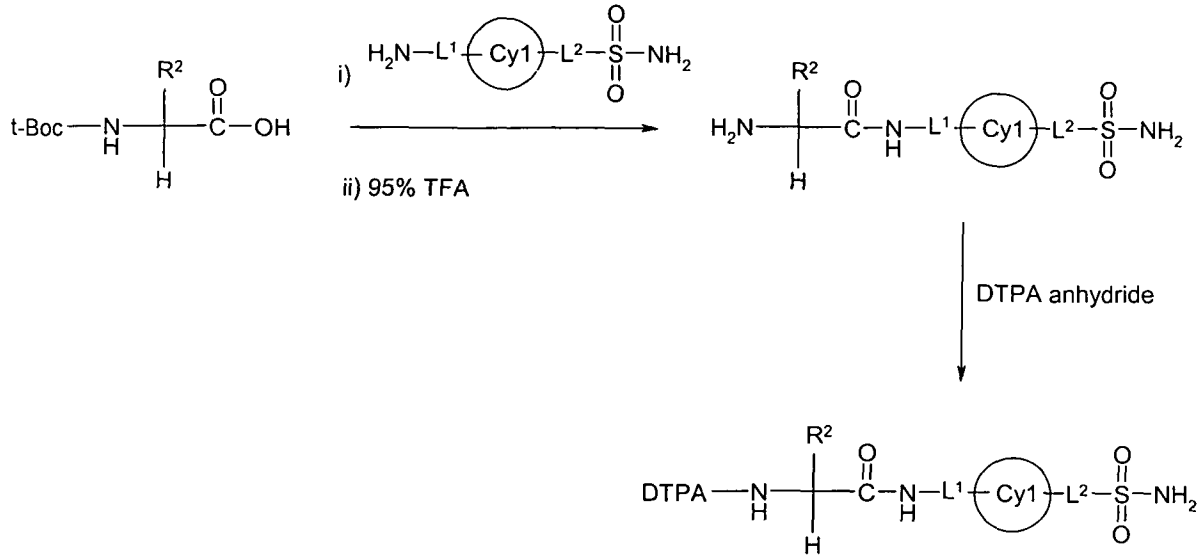
Scheme 4



C17

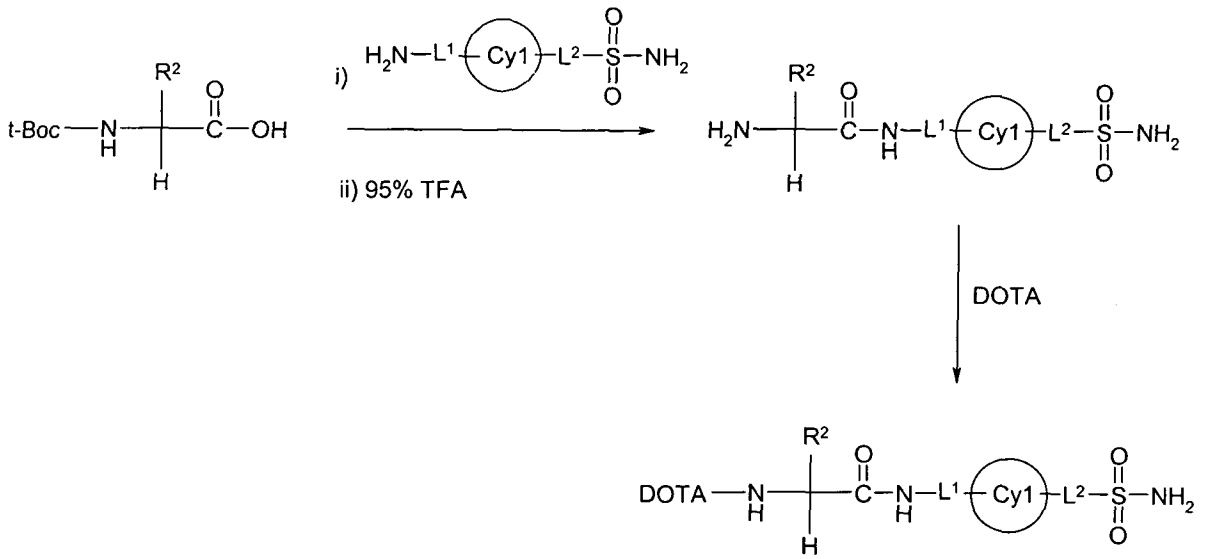
wherein in Schemes 1-4 above, R^{1a} is CH_2COOH; and R^{1b} is COOH.

Scheme 5



wherein Cy1, L^1, L^2, and R^2 are as described herein.

Scheme 6



wherein Cy1, L^1, L^2, and R^2 are as described herein.

Representative Synthetic Method for Preparation of the Compounds of Invention

[00339] 2,2'-(2-((2-(Bis(carboxymethyl)amino)-3-(4-isothiocyanatophenyl)propyl)-(carboxymethyl)amino)cyclohexylazanediyl)diacetic acid (CHXA'-DTPA benzylisothiocyanate, 0.1 mmole) or 2,2',2"-(10-(carboxy(4-isothiocyanato-2-methoxyphenyl)methyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (DOTA-benzyl isothiocyanate, 0.1 mmole) and the appropriate sulfonamide (0.1 mmol) are dissolved in 1.0 mL water, and then a traceable amount of sodium carbonate is used to adjust pH value to 9. The mixture is stirring for 18 hour under room temperature. After the reaction, the solution is diluted with 3.0 mL water and purified with LC-MS system (all are same

with analytical LC-MS system except that flow rate for purification is 20.0 mL/min and column is 19×150mm, Xbridge PreC_{18} OBD^{TM}) to afford pure desired compounds.

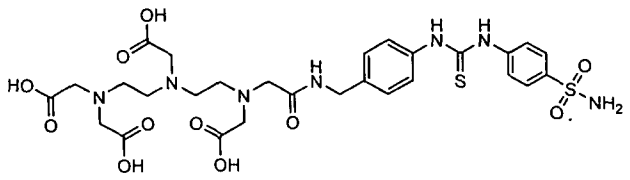
C14 calculated MW: 794.9, MS-ES(+): 795.9 $[M+H]^+$; purity: >98% (UV=254nm).

C15 calculated MW: 767.9, MS-ES(+): 767.9 $[M+H]^+$; purity: >98% (UV=254nm).

C16 calculated MW: 753.8, MS-ES(+): 754.9 $[M+H]^+$; purity: >98% (UV=254nm).

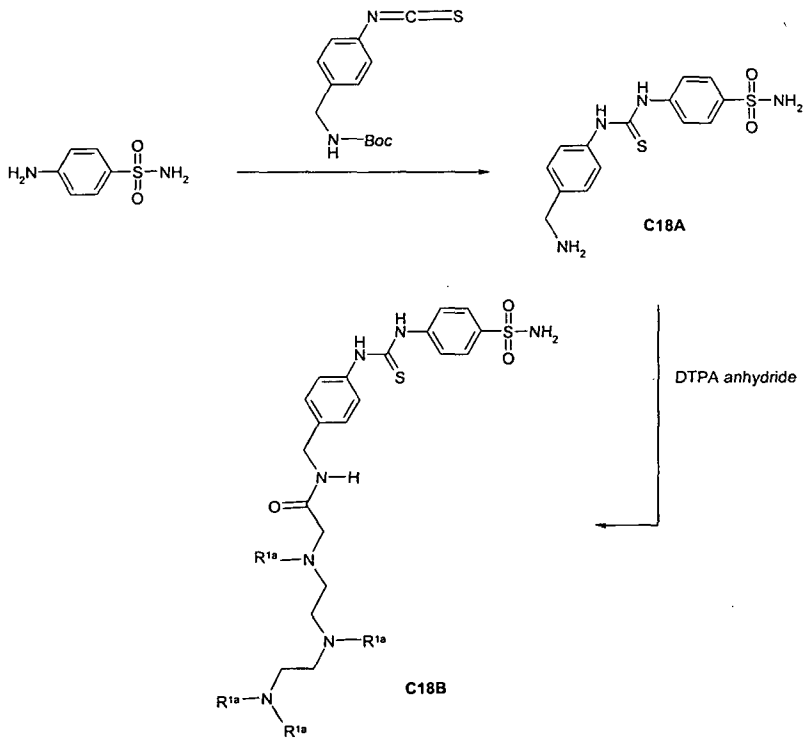
C17 calculated MW: 853.8, MS-ES(+): 854.9 $[M+H]^+$; purity: >98% (UV=254nm).

C18B



C18B

Scheme 7



R^{1a} is CH_2COOH

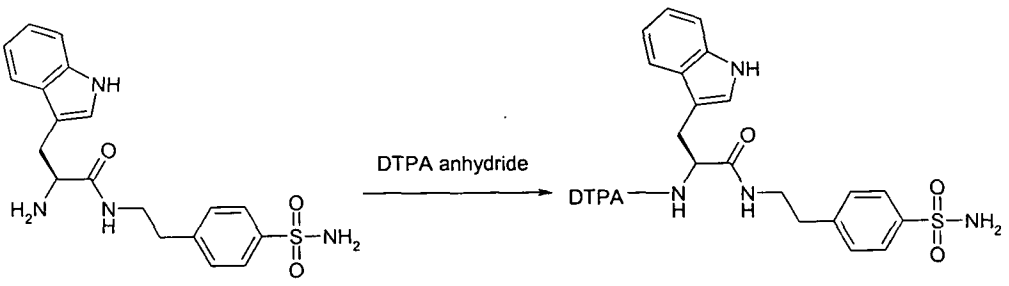
[00340] 4-(Boc-aminomethyl)phenyl isothiocyanate (400mg, 1.51mmol) and sulfanilamide (1.51mmol) were weighted and dissolved in 5mL anhydrous DMF, and a traceable amount of TEA was added till pH value was greater than 9. The mixture was stirred for 3 hour under room temperature. The volatiles were evaporated away under reduced pressure, the residue was dissolved into 2-3mL of MeOH/DCM (v/v=1/9) and purified with normal phase column to afford the pure desired compound,

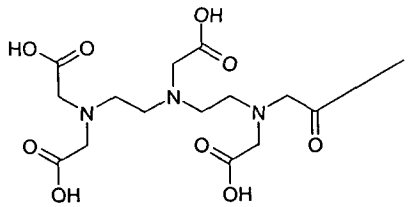
which was characterized with same LC-MS system (same as first section) for its purity and molecular weight. Then TFA/H_2O (5ml, 95%TFA) was used for removal of Boc, pure **C18A** was obtained after evaporation without further purification, which was characterized with LC-MS system and [^{1}H]NMR.

[00341] DTPA anhydride (0.60mmol) and **C18A** (0.15mmol, 50mg) were weighted and dissolved in 1.0mL water, and then a traceable amount of sodium carbonate was used to adjust pH value to 9. The mixture was stirred for 2-4 hour at room temperature. The reaction solution was diluted with 3.0 mL acidic water and purified with LC-MS system (all are same with analytical LC-MS system except that flow rate for purification is 20.0 mL/min and column is 19×150mm, Xbridge PreC_{18} OBD^{TM}) to afford pure **C18B**, which was characterized with LC-MS system for its purity and molecular weight after lyophilization.

Compound 6

[(2-{[2-(Bis-carboxymethyl-amino)-ethyl]-carboxymethyl-amino}-ethyl)-({(S)-2-(1H-indol-3-yl)-1-[2-(4-sulfamoyl-phenyl)-ethylcarbamoyl]-ethylcarbamoyl}-methyl)-amino]-acetic acid





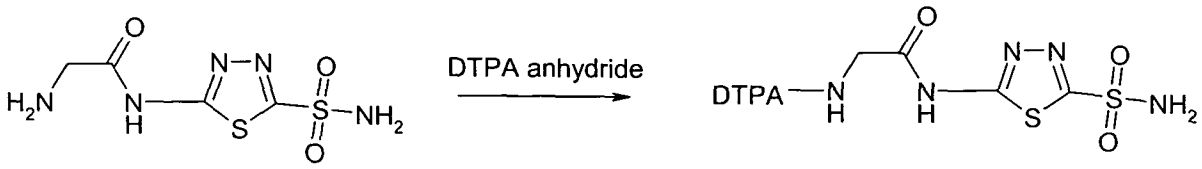
DTPA

[00342] DTPA anhydride (0.60mmol) and (S)-2-amino-3-(1H-indol-3-yl)-N-[2-(4-sulfamoyl-phenyl)-ethyl]-propionamide (Intermediate 5, 0.15mmol) were weighted and dissolved in 1.0mL water, and then a traceable amount of sodium carbonate was used to adjust pH value to 9. The mixture was stirring for 2-4 hour under room temperature. After the reaction solution was diluted with 3.0 mL acidic water and purified with LC-MS system (all are same with analytical LC-MS system except that flow rate for purification is 20.0 mL/min and column is 19×150mm, Xbridge PreC_{18} OBD^{TM}) to afford pure title compound, which were characterized with LC-MS system for its purity and molecular weight after lyophilization.

Calculated MW: 761.8, MS-ES(+): 762.7 $[M+H]^+$; purity: >98% (UV=254nm).

Compound 7

{Carboxymethyl-[2-(carboxymethyl-{2-[carboxymethyl-({[(5-sulfamoyl-[1,3,4]thiadiazol-2-ylcarbamoyl)-methyl]-carbamoyl}-methyl)-amino]-ethyl}-amino)-ethyl]-amino}-acetic acid



[00343] DTPA anhydride (0.60mmol) and 2-amino-N-(5-sulfamoyl-[1,3,4]thiadiazol-2-yl)-acetamide (Intermediate 7, 0.15mmol) were weighted and dissolved in 1.0mL water, and then a traceable amount of sodium carbonate was used to adjust pH value to 9. The mixture was stirring for 2-4 hour under room temperature. After the reaction solution was diluted with 3.0 mL acidic water and purified with LC-MS system (all are same with analytical LC-MS system except that flow rate for purification is 20.0 mL/min and column is 19×150mm, Xbridge PreC_{18} OBD^{TM}) to afford pure title compound, which were characterized with LC-MS system for its purity and molecular weight after lyophilization.

Radiolabeling

[00344] Ten microliters of a solution of C14 or C15 is dissolved in 1 M NH_4OAc (1 mg/mL) and added to 1 mCi of ^{111}In. After incubating for 1 hour at 60°C, the reactions are quenched with 50 uL of 20 mM DTPA and the mixture purified with HPLC (Shimadzu LC10 system, Partisil 10 ODS-2 4.6 x 250 mm column, 1 mL/min 0-90% acetonitrile 50 mM NH_4OAc, over 30 mins). Retention times 22.1 and 18.5 mins. Radioactive peak fraction is evaporated to dryness under nitrogen and redissolved in 1% BSA/PBS.

ASSAYS

Biological Testing

Example 1

Saturation binding

[00345] SKRC38 cells are grown in RPMI media supplemented with, 1% glutamine, 50 units/ml penicillin, 50 units/ml streptomycin, and 10% heat-inactivated fetal bovine serum a temperature of 37°C in an environment containing 5% CO_2. The cells are trypsinized, washed and resuspended in phosphate buffered saline. A suspension fo 200,000 cells, and increasing concentrations of ^{111}In-C15, either with or without 1000 nM C15 are shaken at room temperature for one hour. The cells are then isolated and washed with ice cold Tris buffered saline using a Brandel cell harvester (Gaithersburg, MD). The specific uptake of ^{111}In-C15 is determined by counting all the isolated cell samples, appropriate standards of total activity and blank controls with a gamma counter. Saturation binding curves are plotted and the K_d and B_{max} values are determined using a one site model and a least squares curve fitting routine (Origin,

OriginLab, Northampton, MA). The number of CAIX sites expressed by this cell line is also determined using ^{131}I-cG250, an antibody specific for CAIX.

Example 2

Displacement binding – screening studies

[00346] A suspension of 200 000 cells, 20 000 cpm of ^{111}In-C15, and increasing concentrations of cold competitor (1 pM to 1μM), are shaken at room temperature for one hour. The cells are then isolated and washed with ice cold Tris buffered saline using a Brandel cell harvester (Gaithersburg, MD). The specific uptake of ^{111}In-C15 is determined by counting all the isolated cell samples, appropriate standards of total activity and blank controls with a gamma counter. Displacement binding curves are plotted and the IC_{50} values are determined using a one site model and a least squares curve fitting routine (Origin, OriginLab, Northampton, MA).

Example 3

Biological testing

[00347] Prior to use, SKRC 38 or HT29 cells are trypsinized, counted and suspended in with 50% Matrigel for tumor implantation. Six- to eight-week old *nu/nu* athymic male mice are maintained in ventilated cages and fed/watered *ad libitum*. The experiments are be carried out under an IACUC approved protocol as well as following institutional guidelines for the proper and humane use of animals in research. 5 x 10^6 tumor cells are injected sc into the flanks of the animals and after 14-21 days tumors (200-500 mg) are present.

[00348] Within 24 h of birth, Ntv-a/Ink4a$^{-/-}$Arf$^{-/-}$ mice are injected intracranially with 10^4 DF-1 cells infected with and producing RCAS-PDGF retroviral vectors. Mice are monitored daily for symptoms of tumor development. All imaging experiments are performed on mice at 4–6 wk of age. Non–tumor-bearing mice serve as controls.

[00349] The tumor bearing mice are injected, via the tail vein, with either 1.6 MBq of ^{111}In-C14, 1.6 MBq ^{111}In-C15, or 14 MBq of ^{64}Cu –C15 in 200 μL of PBS (pH 7.4, 0.2% BSA). Animals injected with ^{64}Cu-C15 are imaged with a MicroPET camera (Concorde) up to 24 hours post injection. Coincident data are collected for the 511 KeV gamma rays with a 250-750 KeV window for ten minutes. The images are reconstructed and ROIs drawn around the tumors and major organs.

[00350] Selected animals are also injected with Pimomidazole (60 mg/kg) one hour pre sacrifice to assess tumor hypoxia, and Hoechst 33342 (40 mg/kg) at 5 minutes pre sacrifice to assess tumor perfusion. At either 1 or 24 hours post injection, CO_2 euthanasia is used to kill groups of animals.

[00351] Radioactive, tumor and tissue samples are collected, weighed and counted, with appropriate standards, in an automatic NaI(Tl) counter. These measured relative activity data (cpm) are background corrected and expressed as a percentage of the injected dose per gram (%ID/g). These data are also fitted with a least squares regression analysis to determine the biological clearance of the different

forms of antibody. The tumors are immediately frozen at -80°C and sections processed for immunohistochemistry and / or digital autoradiography.

[00352] For CAIX staining, tumor sections are fixed for 20 min in 4% paraformaldehyde solution, air-dried and blocked (Superblock blocking buffer in PBS, Pierce) at room temperature for 1hr. Sections are then incubated with primary antibody (cG250, a murine Fv grafted human IgG1K - kindly supplied by Ludwig Institute of Cancer Research) applied in blocking solution at a concentration of 25μg/ml. Slides are incubated for 1hr at room temperature, washed X3 with PBS and incubated with secondary fluorescent Alex-568 goat anti-human antibody in blocking solution at a concentration of 40μg/ml. Negative controls consisted of tumor sections exposed to fluorescent anti-human antibody alone.

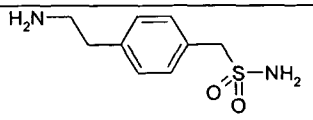
[00353] Tumor sections are imaged with a Zeiss Axioplan2 fluorescence microscope connected to a CCD camera in RGB mode. Fluorescence images are obtained using appropriate filter cubes for each fluorochrome. DAB-stained sections are imaged using standard bright field illumination settings. The microscope has a computer controlled motorized stage that enables images of whole sections to be generated as a mosaic at any given magnification with identical exposure time per frame.

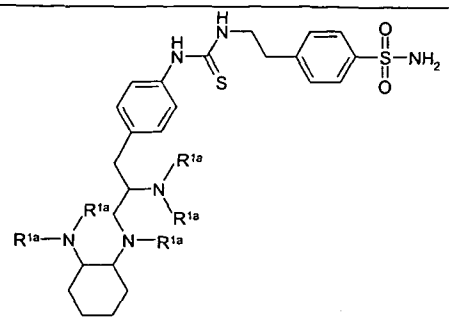
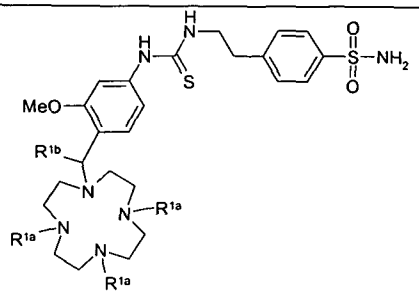
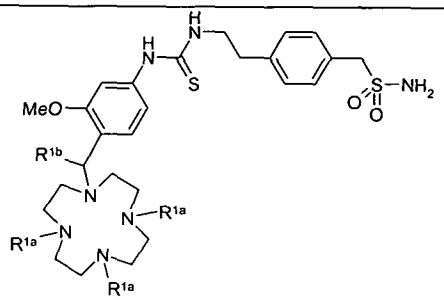
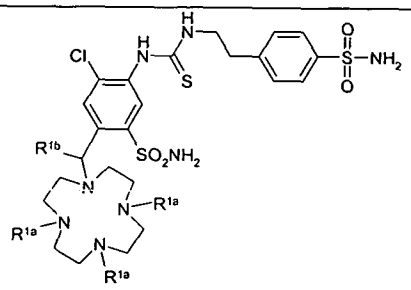
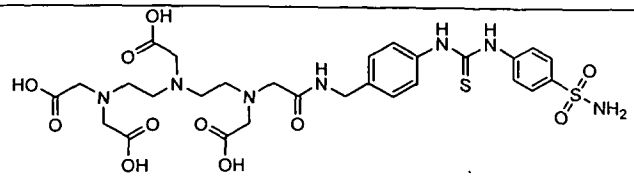
[00354] Tumor sections are placed on a phosphor-imaging plate (Fujifilm BAS-MS2325, Fuji Photo Film, Japan) for an appropriate length of time at -20°C. Upon the completion of an exposure, the imaging plates are removed from the cassette and placed in a BAS-1800II Bio-Imaging Analyzer (Fujifilm Medical Systems, USA) to readout the image. The image reader creates 16-bit grayscale digital images with pixel size of 50μm. These images are then converted to .tiff image format files for subsequent analysis.

Activity of Exemplary Compounds of the Invention

[00355] The following compounds (Tables 1-4) have been or can be prepared according to the methods of the invention. An displacement binding assay is performed as described above in Example 2. The IC_{50} data for some of the representative compounds are given in Tables 1 and 3 below.

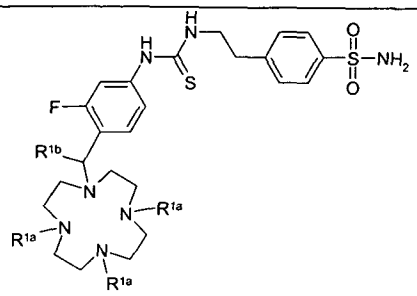
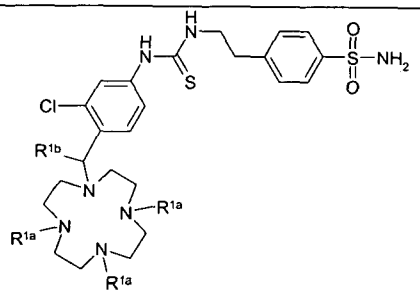
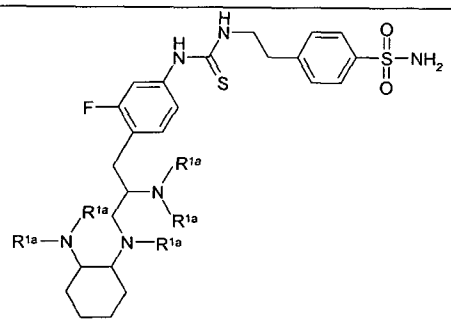
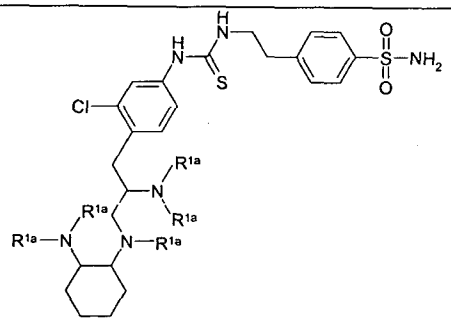
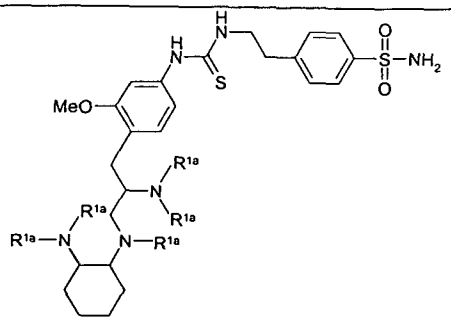
[00356] **Table 1: IC_{50} values for the displacement of ^{111}In-C15 binding to SKRC38 cells**

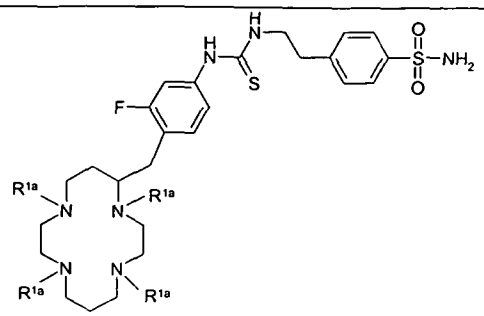
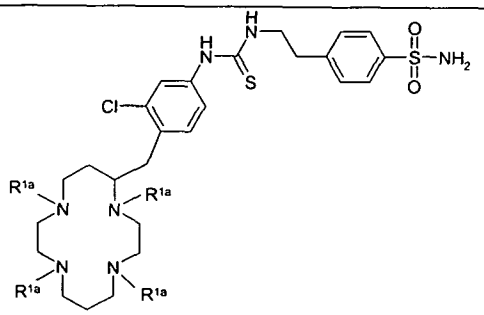
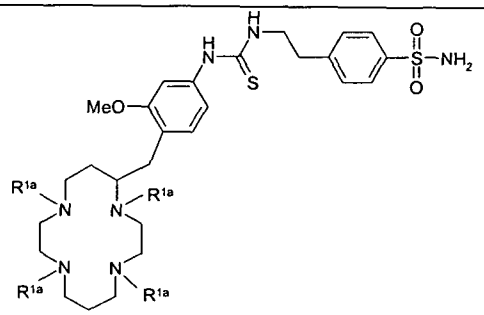
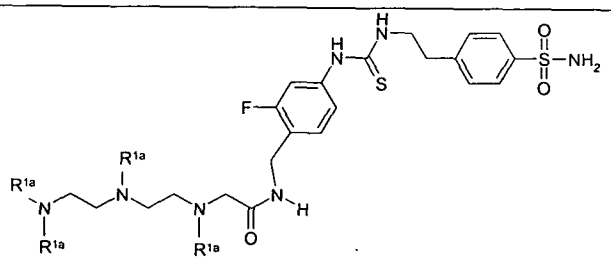
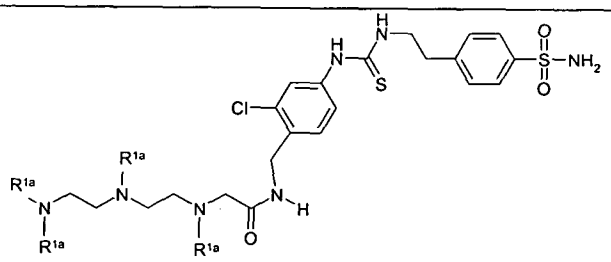
#	Ligand*	IC_{50} (nM)
1	 Aminoethylbenzylsulfonamide	4300

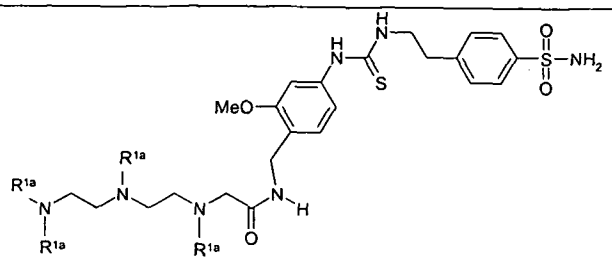
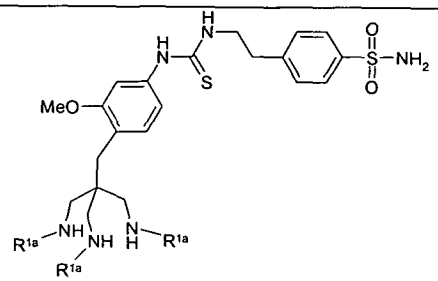
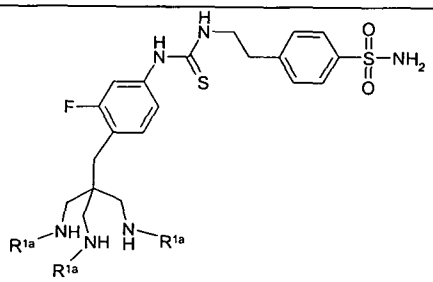
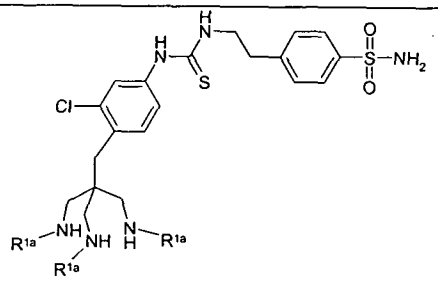
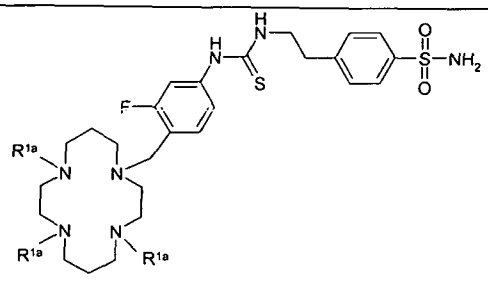
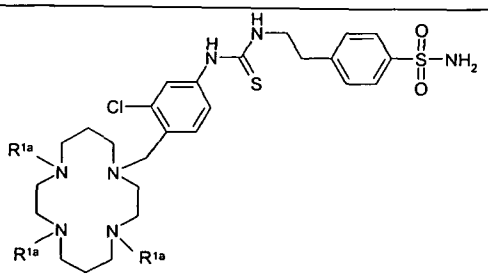
#	Ligand*	IC_{50} (nM)
2	 C14	21.3
3	 C15	13.8
4	 C16	252
5	 C17	16000
6	 C18B	68

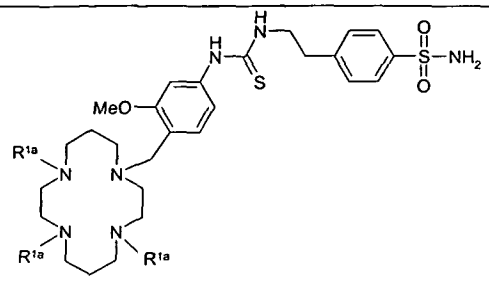
*$R^{1a} = CH_2COOH$

[00357] **Table 2: Additional Representative Compounds of the Invention**

#	Ligand*
7	
8	
9	
10	
11	

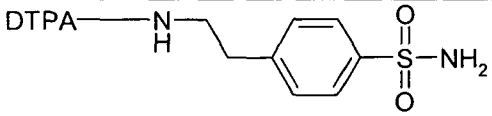
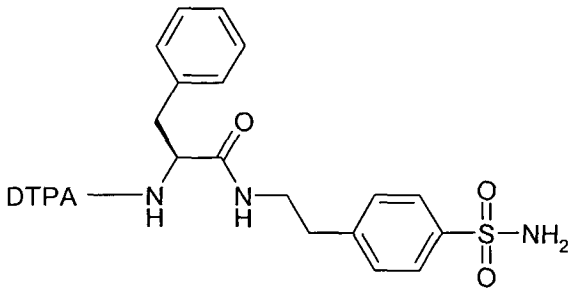
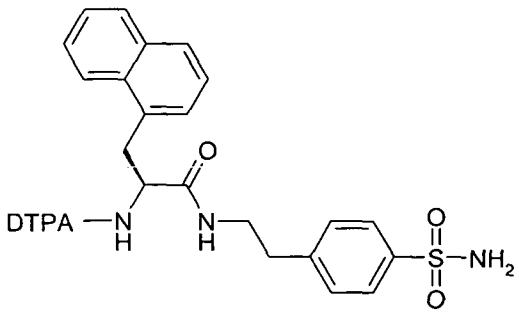
#	Ligand*
12	
13	
14	
15	
16	

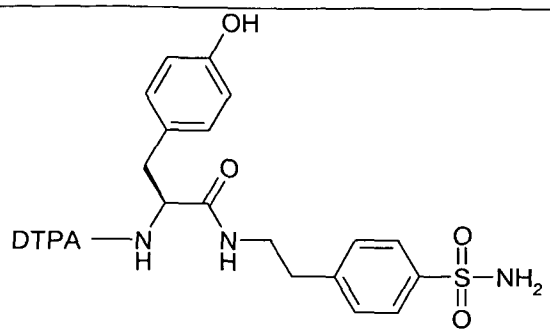
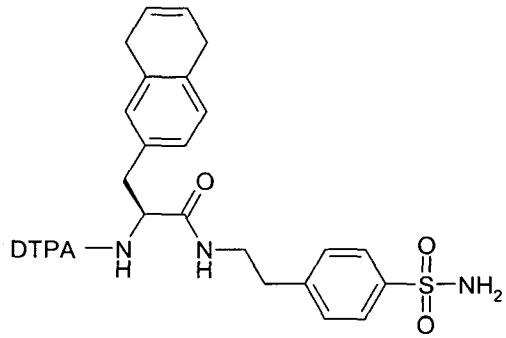
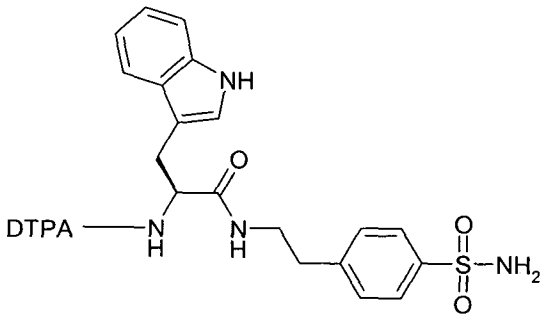
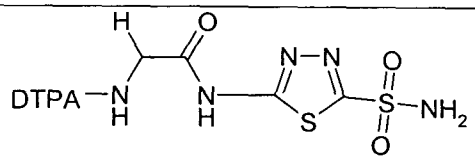
#	Ligand*
17	
18	
19	
20	
21	
22	

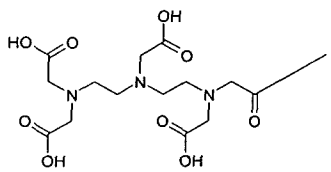
#	Ligand*
23	

*$R^{1a} = CH_2COOH$

[00358] **Table 3: IC_{50} values for the displacement of ^{111}In-C15 binding to SKRC38 cells**

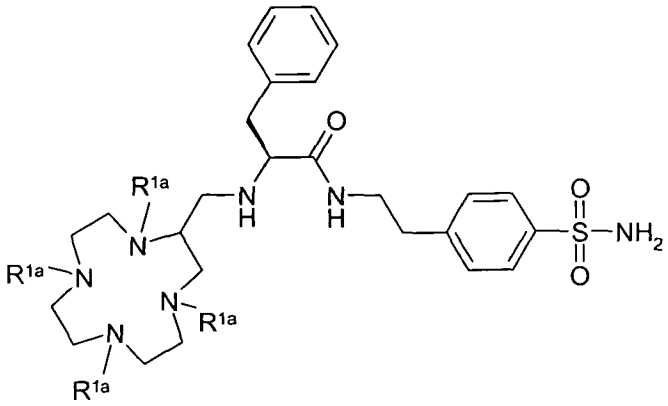
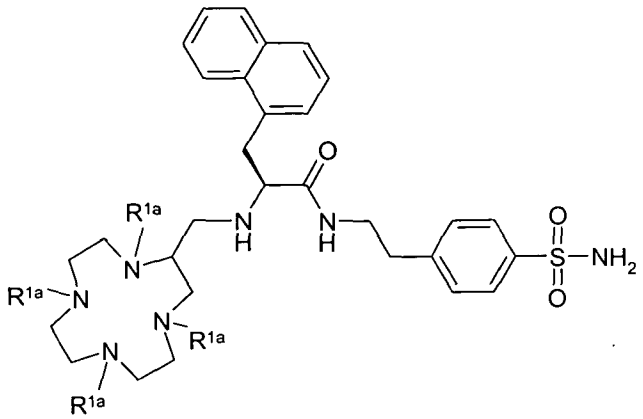
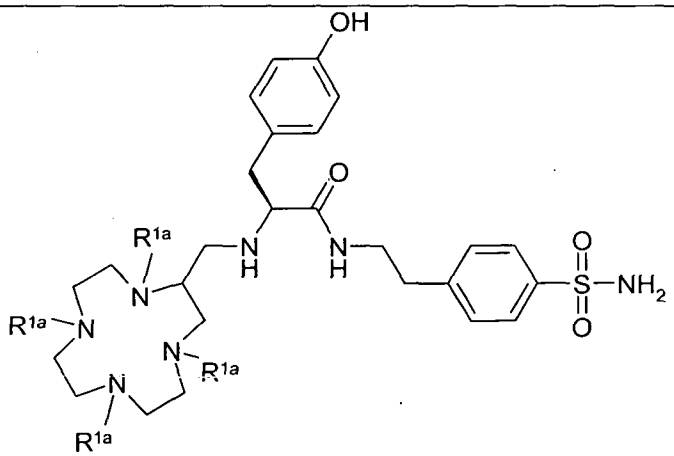
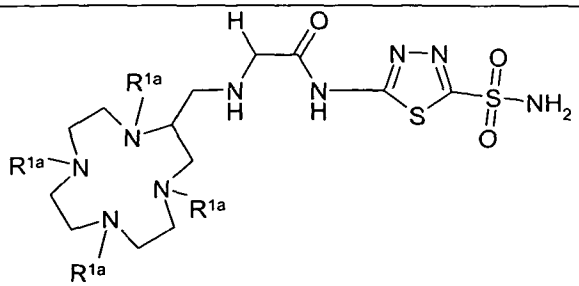
#	Ligand*	MW (Calcd)	MS (Obs)	IC_{50} (nM)
1'		575.59	576.7 $[M+H]^+$	2100
2'		722.78	723.8 $[M+H]^+$	25
3'		772.84	773.8 $[M+H]^+$	18

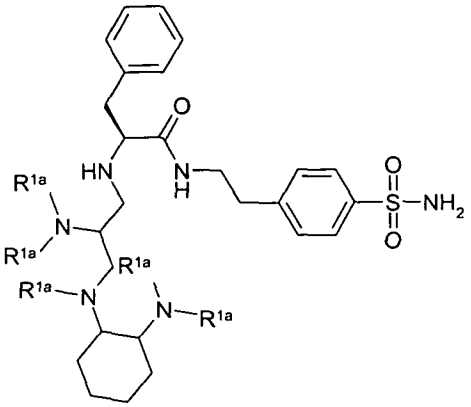
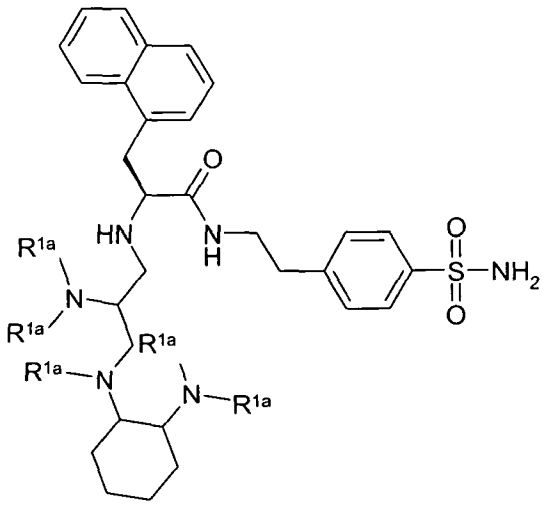
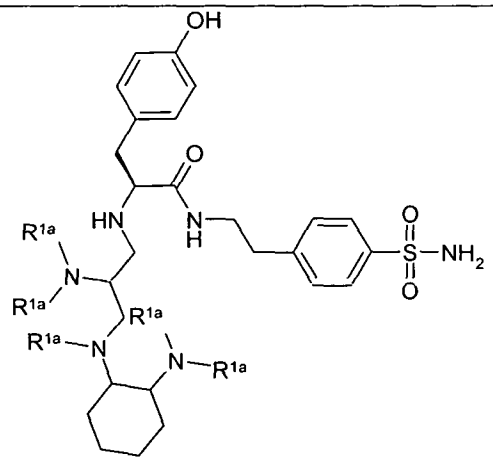
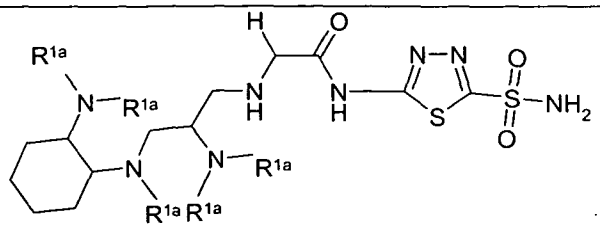
#	Ligand*	MW (Calcd)	MS (Obs)	IC_{50} (nM)
4'		738.78	739.5 $[M+H]^+$	21
5'		774.85	773.7 $[M+H]^+$	96
6'		761.81	762.7 $[M+H]^+$	130
7'		569.7	570.7 $[M+H]^+$	44

*DTPA:  ; R^{1a}: CH_2COOH

[00359] **Table 4: Additional Representative Compounds of the Invention**

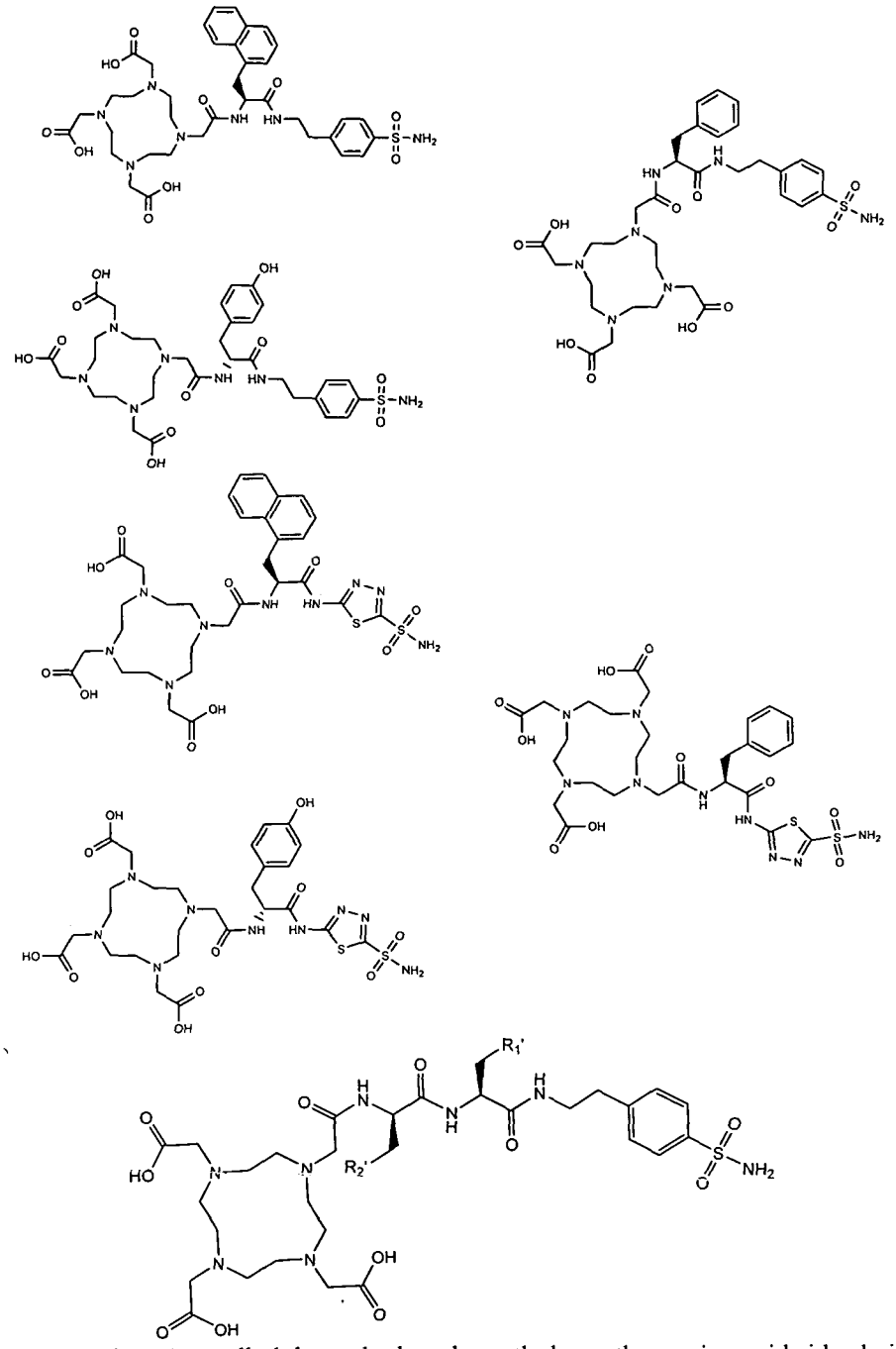
#	Ligand*

#	Ligand*
8'	
9'	
10'	
11'	

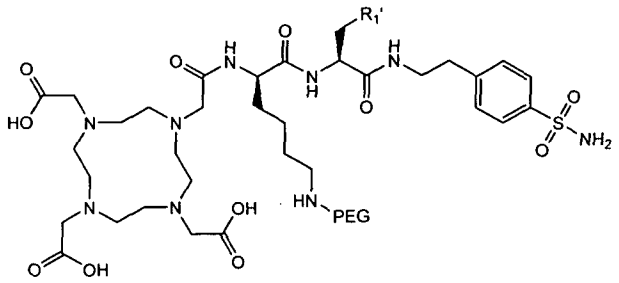
#	Ligand*
12'	
13'	
14'	
15'	

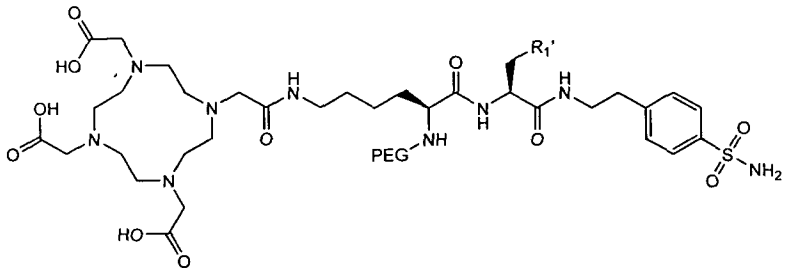
R^{1a}: CH_2COOH

[00360] In addition to the examples listed above, the following compounds of invention can be prepared using the procedures described herein:



R_1' = alkyl, aminoalkyl, hydroxyalkyl, benzyl, phenyl, napthyl, or other amino acid side chain; R_2' = alkyl, aminoalkyl, hydroxyalkyl, benzyl, phenyl, napthyl, or other amino acid side chain.





R_1' = alkyl, aminoalkyl, hydroxyalkyl, benzyl, phenyl, napthyl, or other amino acid side chain; PEG – polyethyleneglycol.

[00361] From the foregoing description, various modifications and changes in the compositions and methods of this invention will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

[00362] All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

[00363] At least some of the chemical names of compounds of the invention as given and set forth in this application, may have been generated on an automated basis by use of a commercially available chemical naming software program, and have not been independently verified. Representative programs performing this function include the Lexichem naming tool sold by Open Eye Software, Inc. and the Autonom Software tool sold by MDL, Inc. In the instance where the indicated chemical name and the depicted structure differ, the depicted structure will control.

[00364] Chemical structures shown herein were prepared using ISIS® /DRAW. Any open valency appearing on a carbon, oxygen or nitrogen atom in the structures herein indicates the presence of a hydrogen atom. Where a chiral center exists in a structure but no specific stereochemistry is shown for the chiral center, both enantiomers associated with the chiral structure are encompassed by the structure.

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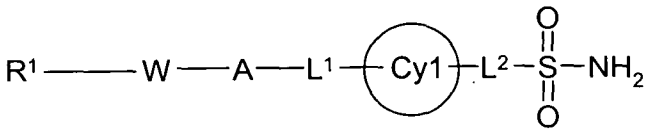
WHAT IS CLAIMED IS:

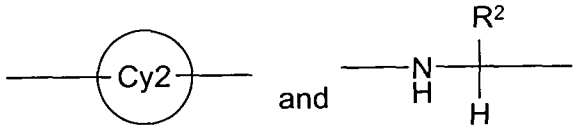
1. A compound having a formula I':



I'

wherein

W is a group selected from:



;

each Cy1 and Cy2 are independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

A is selectected from $-(CH_2)_n$-NH-C(=O)-, $-(CH_2)_n$-C(=O)NH-, $-(CH_2)_n$-NHC(=O)-NH-, and $-(CH_2)_n$-NH-C(=S)-NH-; n is 0, 1, or 2;

L^1 is a single bond, substituted or unsubstituted C_1-C_4 alkylene; or $-(CH_2)_m$-NH-C(=O)-; m is 2 or 3;

L^2 is a single bond, or substituted or unsubstituted C_1-C_4 alkylene;

R^1 is a metal chelator group or a fluorescent ligand; provided the metal chelator group or the fluorescent ligand contains at least 2 or more N; and each N atom is substituted with at least one CH_2COOH group; and

R^2 is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted CH_2-cycloalkyl, substituted or unsubstituted CH_2-heterocycloalkyl, substituted or unsubstituted CH_2-aryl, substituted or unsubstituted CH_2-heteroaryl, substituted or unsubstituted CH_2-SH;

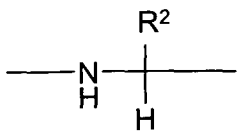
or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof;

provided that the compound is other than

14-[4-(aminosulfonyl)phenyl]-3,6,9-tris(carboxymethyl)-11-oxo-3,6,9,12-tetraazatetradecanoic acid.

2. A compound according to claim 1, wherein W is Cy2; and Cy2 is as in claim 1.

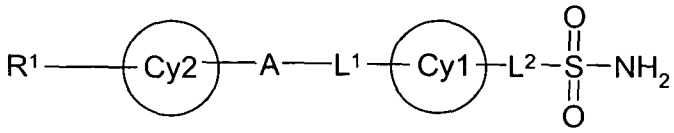
3. A compound according to claim 1, wherein W is



;

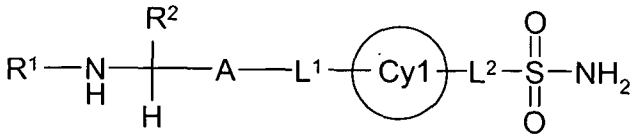
and R^2 is as in claim 1.

4. A compound according to claim 1, wherein the compound is according to formula Ia or Ib;



Ia

or



Ib

and wherein A, Cy1, Cy2, L^1, L^2, R^1, and R^2 are as in claim 1;

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof;

provided that the compound is other than

14-[4-(aminosulfonyl)phenyl]-3,6,9-tris(carboxymethyl)-11-oxo-3,6,9,12-tetraazatetradecanoic acid.

5. A compound according to any one of claims 1-4, wherein n is 1 or 2.

6. A compound according to any one of claims 1-4, wherein n is 0.

7. A compound according to any one of claims 1-4, wherein A is $-(CH_2)_n$-NH-C(=O)-; and n is 0.

8. A compound according to any one of claims 1-4, wherein A is$-(CH_2)_n$-C(=O)NH-; and n is 0.

9. A compound according to any one of claims 1-4, wherein A is $-(CH_2)_n$-NHC(=O)-NH-; and n is 0.

10. A compound according to any one of claims 1-4, wherein A is $-(CH_2)_n$–NH-C(=S)-NH-; and n is 0.

11. A compound according to any one of claims 1-4, wherein A is $-(CH_2)_n$-NH-C(=O)-; and n is 1.

12. A compound according to any one of claims 1-4, wherein A is$-(CH_2)_n$-C(=O)NH-; and n is 1.

13. A compound according to any one of claims 1-4, wherein A is $-(CH_2)_n$-NHC(=O)-NH-; and n is 1.

14. A compound according to any one of claims 1-4, wherein A is $-(CH_2)_n$–NH-C(=S)-NH-; and n is 1.

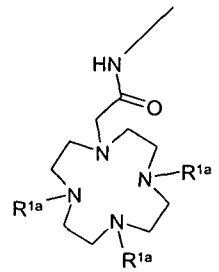
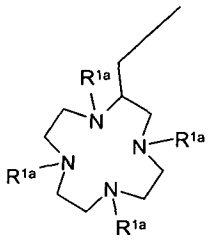
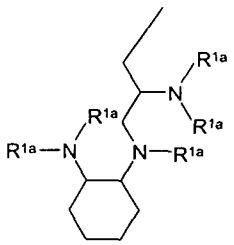
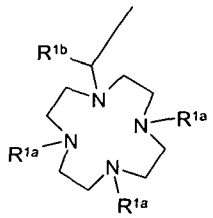
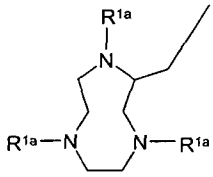
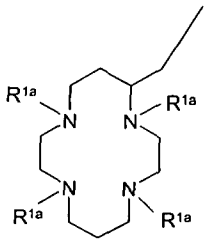
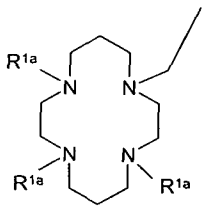
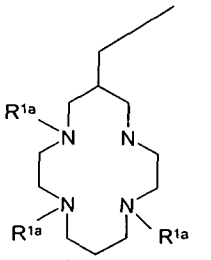
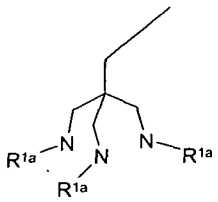
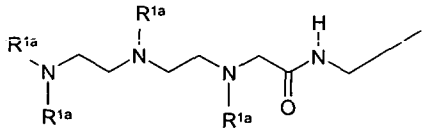
15. A compound according to any one of claims 1-14, wherein R^1 is a metal chelator group containing at least 2 or more N; and each N atom is substituted with at least one CH_2COOH group.

16. A compound according to any one of claims 1-14, wherein R^1 is a heterocycloalkylmethyl group; and the heterocycle contains 2 or more N atoms.

17. A compound according to any one of claims 1-14, wherein R^1 is a heterocycloalkylmethyl group; the heterocycle contains 2 or more N atoms; and each N atom is substituted with a CH_2COOH group.

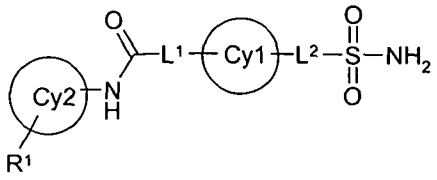
18. A compound according any one of claims 1-14, wherein R^1 is triazacyclononanemethyl, tetrazacyclododecanemethyl, or tetraazacyclotetradecanemethyl; and each N atom is substituted with CH_2COOH.

19. A compound according to any one of claims 1-14, wherein R^1 is

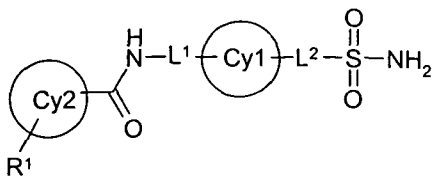











each R^{1a} is CH_2CO_2H; and R^{1b} is CO_2H.

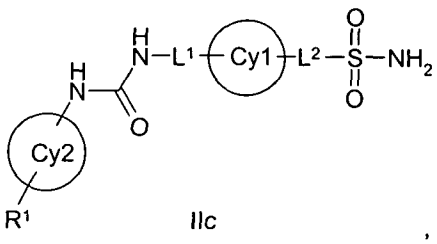
20. A compound according to claim 1, wherein the compound is according to formula IIa, IIb, IIc, IId, IIe, IIf, IIg, or IIh:



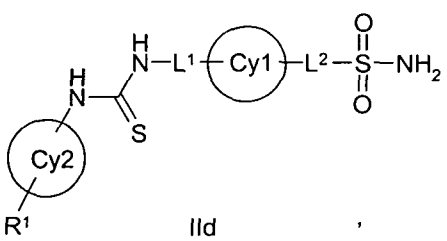
IIa



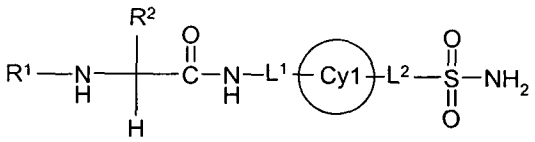
IIb



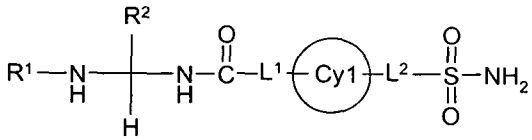
IIc



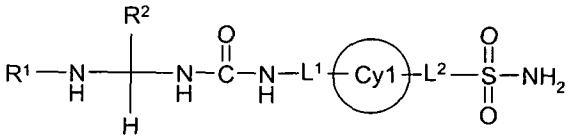
IId



IIe

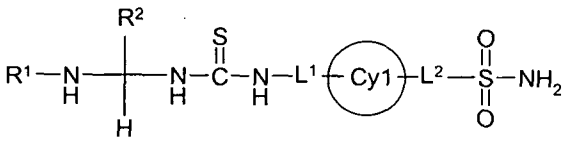


IIf



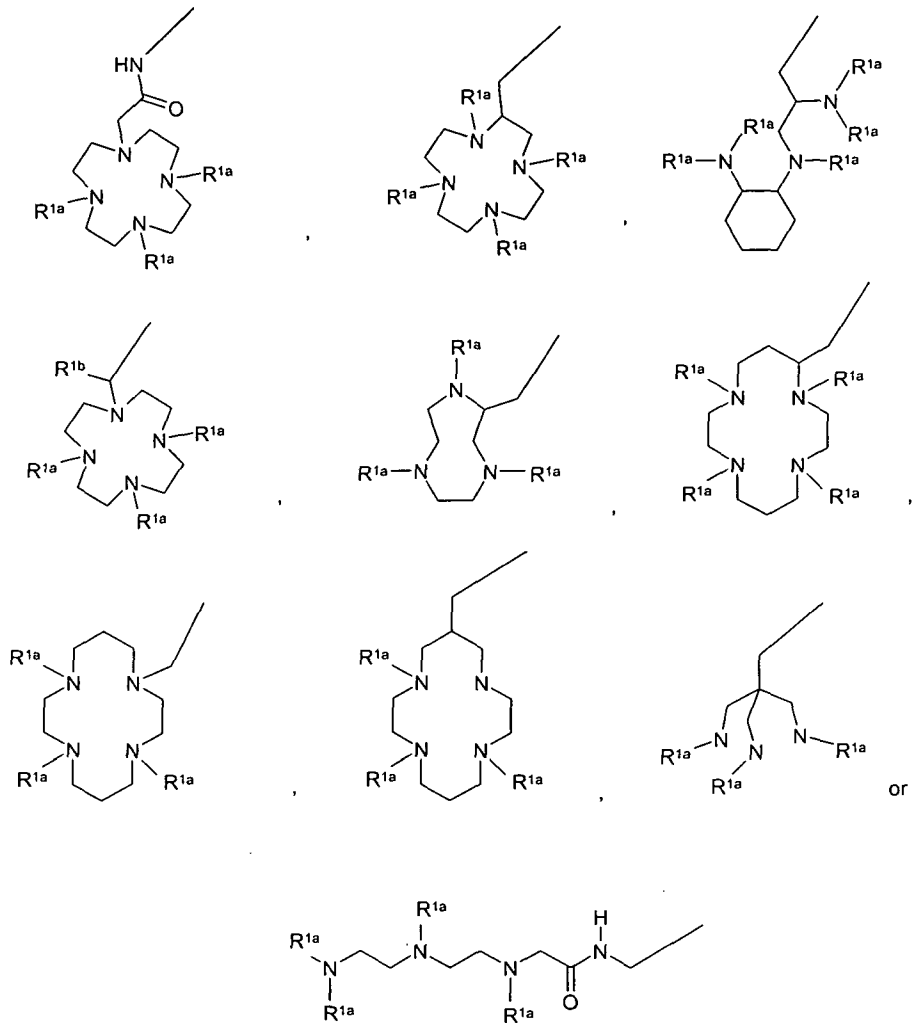
IIg

or



IIh

wherein Cy1, Cy2, L^1, L^2 and R^2 are as in claim 1; and R^1 is selected from substituted or unsubstituted

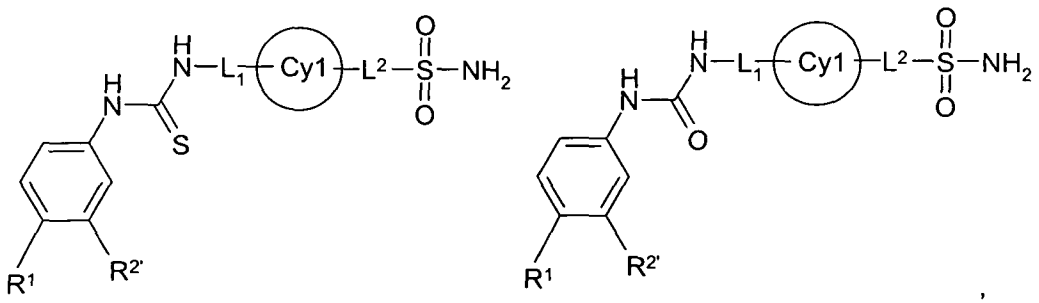


each R^{1a} is CH_2CO_2H; and R^{1b} is CO_2H.

21. A compound according to any one of claims 1-20, wherein Cy2 is substituted or unsubstituted phenyl.

22. A compound according to any one of claims 1-20, wherein Cy2 is phenyl, unsubstituted or substituted with one or more groups selected from halo, alkyl, alkoxy, and trihaloalkyl.

23. A compound according to claim 1, wherein the compound is according to formula IIIa or IIIb:



IIIa or IIIb

and wherein Cy1 is independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; each L^1 and L^2 is a single bond or substituted or unsubstituted C_1-C_4 alkylene; R^1 is as in claim 1; and $R^{2'}$ is H, alkyl, halo, haloalkyl, or alkoxy.

24. A compound according to any one of claims 1-23, wherein L^1 is a single bond.

25. A compound according to any one of claims 1-23, wherein L^1 is $-CH_2-$, $-CH_2-CH_2-$, or $-CH_2CH_2CH_2-$.

26. A compound according to any one of claims 1-23, wherein L^1 is $-CH_2-CH_2-$; or $-CH_2-CH_2-NH-C(=O)-$;

27. A compound according to any one of claims 1-26, wherein L^2 is $-CH_2-$.

28. A compound according to any one of claims 1-26, wherein L^2 is a single bond.

29. A compound according to any one of claims 1-28, wherein Cy1 is substituted or unsubstituted phenyl.

30. A compound according to any one of claims 1-28, wherein Cy1 is phenyl, unsubstituted or substituted with one or more groups selected from halo, alkyl, alkoxy, sulfonamido, and trihaloalkyl.

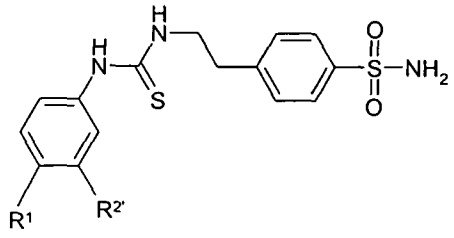
31. A compound according to any one of claims 1-28, wherein Cy1 is phenyl, unsubstituted or substituted with one or more groups selected from Cl, F, Br, I, CF_3, SO_2NH_2, and Me.

32. A compound according to any one of claims 1-28, wherein Cy1 is substituted or unsubstituted thiadiazolyl.

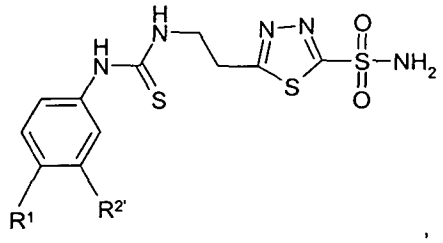
33. A compound according to any one of claims 1-28, wherein Cy1 is substituted or unsubstituted pyrimidinyl.

34. A compound according to any one of claims 1-28, wherein Cy1 is substituted or unsubstituted benzothiazolyl.

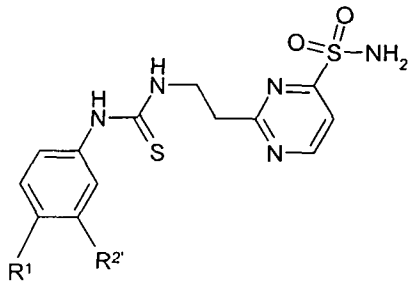
35. A compound according to claim 1, wherein the compound is according to formula IVa, IVb, IVc IVd, IVe, IVf, IVg or IVh:



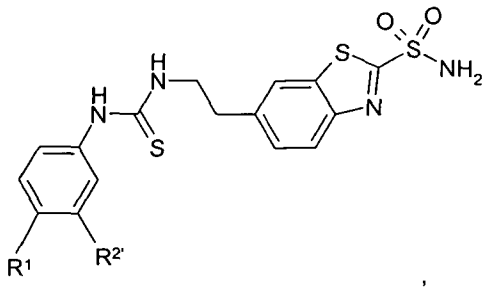
IVa



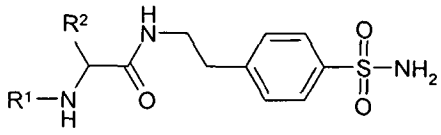
IVb



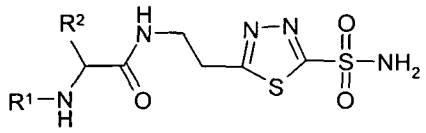
IVc



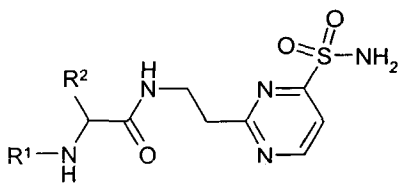
IVd



IVe

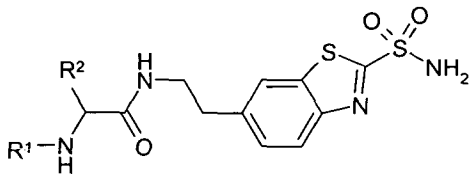


IVf



IVg

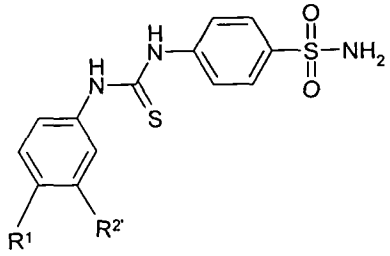
or



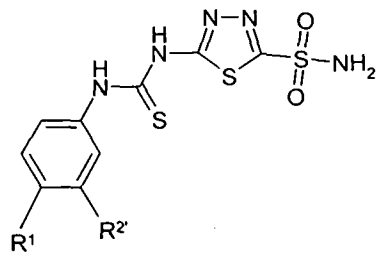
IVh

and wherein R^1 and R^2 are as in claim 1; and $R^{2'}$ is H, alkyl, halo, haloalkyl, or alkoxy.

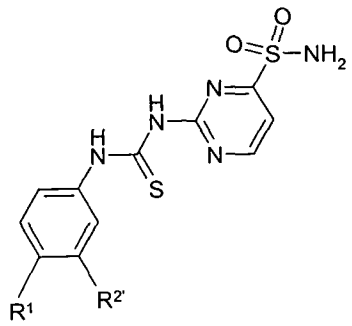
36. A compound according to claim 1, wherein the compound is according to formula Va, Vb, Vc, Vd, Ve, Vf, Vg or Vh:



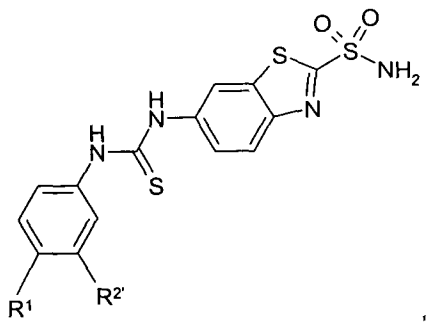
Va



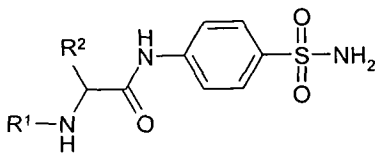
Vb



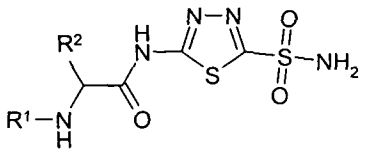
Vc



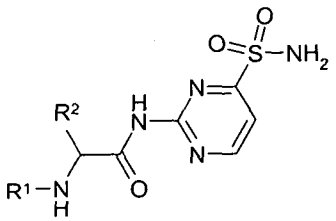
Vd



Ve

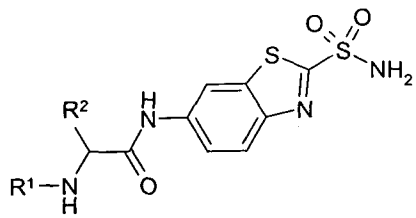


Vf



Vg

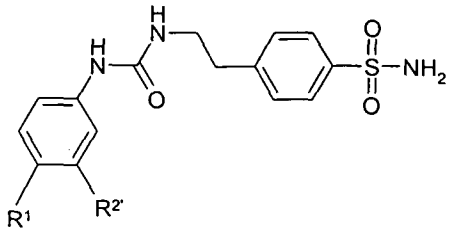
or



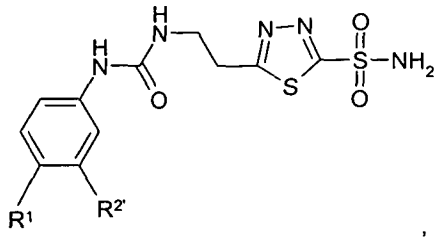
Vh

and wherein R^1 and R^2 are as in claim 1; and $R^{2'}$ is H, alkyl, halo, haloalkyl, or alkoxy .

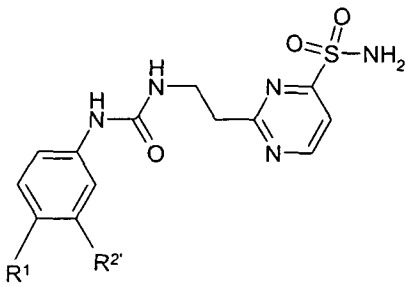
37. A compound according to claim 1, wherein the compound is according to formula VIa, VIb, VIc or VId:



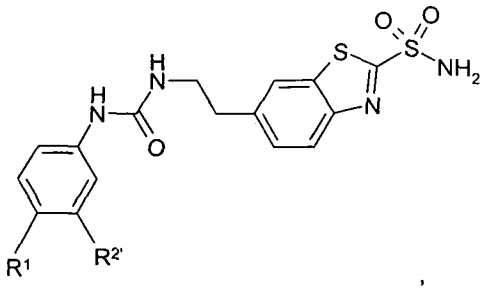
VIa



VIb



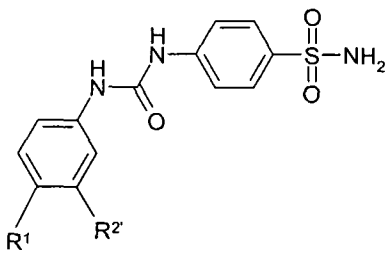
VIc or



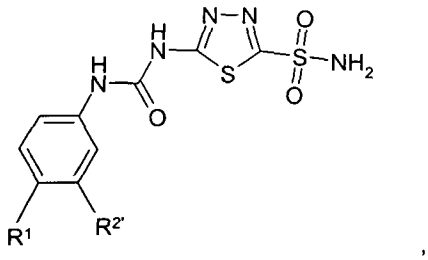
VId

and wherein R^1 is as in claim 1; and $R^{2'}$ is H, alkyl, halo, haloalkyl, or alkoxy.

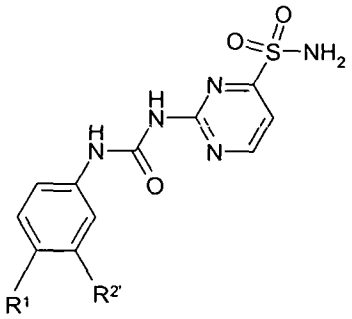
38. A compound according to claim 1, wherein the compound is according to formula VIIa, VIIb, VIIc or VIId:



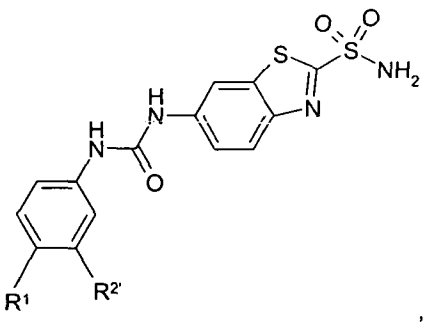
VIIa



VIIb



VIIc or



VIId

and wherein R^1 is as in claim 1; and $R^{2'}$ is H, alkyl, halo, haloalkyl, or alkoxy.

39. A compound according to any one of claims 23-36, wherein $R^{2'}$ is H, Me, CF_3, Cl, F, or OMe.

40. A compound according to any one of claims 35-36, wherein the compound is according to formula IVe, IVf, IVg, IVh, Ve, Vf, Vg, or Vh; and the group –[NH-C(R2)-C(O)-]- represents an amino acid residue.

41. A compound according to any one of claims 35-36, wherein the compound is according to formula IVe, IVf, IVg, IVh, Ve, Vf, Vg, or Vh; wherein the group –[NH-C(R2)-C(O)-]- represents an amino acid residue; and the amino acid residue is selected from –Ala-, -Arg-, -Asn-, -Asp-, -Cis-, -Glu-, -Gln-, -Gly-, -His-, -Ile-, -Leu-, -Lys-, -Met-, -Phe-, -Ser-, -Thr-, -Trp-, -Tyr-, and -Val-.

42. A compound according to any one of claims 35-36, wherein the compound is according to formula IVe, IVf, IVg, IVh, Ve, Vf, Vg, or Vh; wherein the group –[NH-C(R2)-C(O)-]- represents an amino acid residue; and the amino acid residue is selected from –Phe-, -Trp-, and -Tyr-.

43. A compound according to any one of claims 1-42, wherein R^2, when present, is H, CH_2Ph, CH_2-naphthyl, CH_2-dihydronaphthyl, CH_2-indol-3-yl, CH_2-imidazolyl, CH_2-(4-hydroxy)phenyl, CH_2-cyclohexyl, or CH_2-[4-$(CO_2H)_2$-CH-O-]phenyl;

44. A compound according to any one of claims 1-42, wherein R^2, when present, is H.

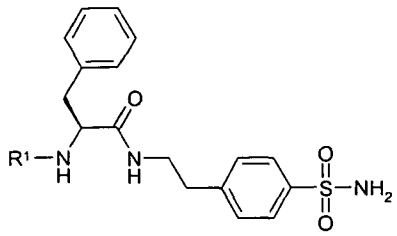
45. A compound according to any one of claims 1-42, wherein R^2, when present, is substituted or unsubstituted alkyl.

46. A compound according to any one of claims 1-42, wherein R^2, when present, is Me, i-Pr, i-Bu, or sec-Bu.

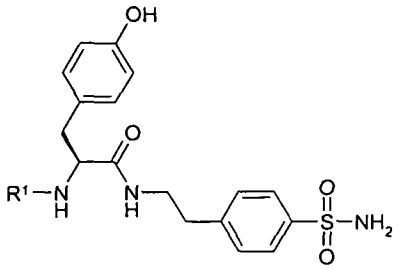
47. A compound according to any one of claims 1-42, wherein R^2, when present, is alkyl substituted with SH, or amino.

48. A compound according to any one of claims 1-42, wherein R^2, when present, is CH_2Ph, CH_2-naphthyl, CH_2-indol-3-yl, or CH_2-(4-hydroxy)phenyl.

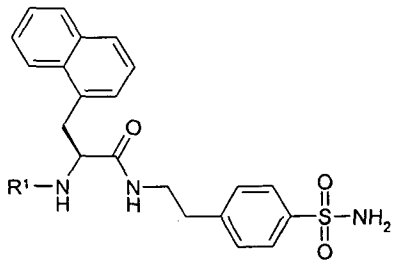
49. A compound according to claim 1, wherein the compound is according to formula VIIIa, VIIIb, VIIIc, VIIId or VIIIe:



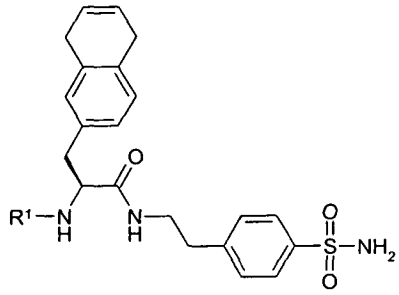
VIIIa



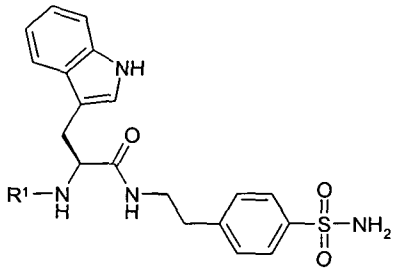
VIIIb



VIIIc



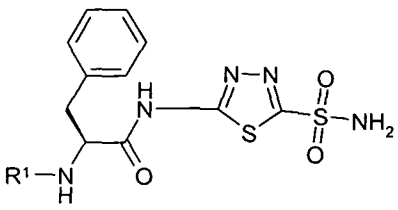
VIIId



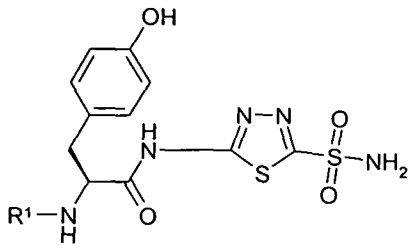
VIIIe

and wherein R^1 is as in claim 1.

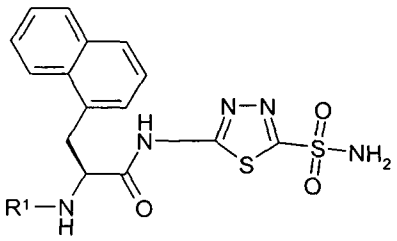
50. A compound according to claim 1, wherein the compound is according to formula IXa, IXb, IXc, IXd, or IXe:



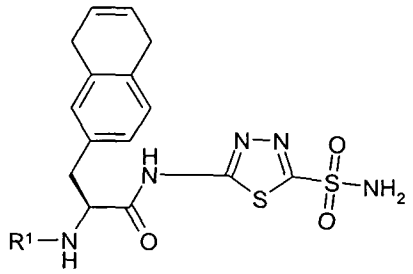
IXa



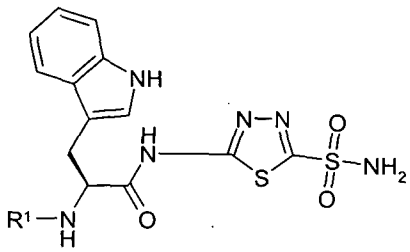
IXb



IXc

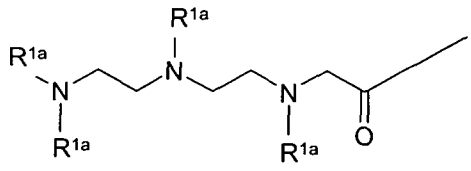


IXd



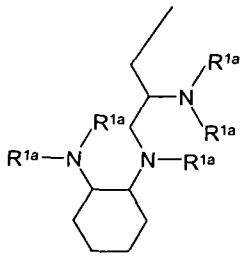
IXe

51. A compound according to any one of claims 1-50, wherein R^1 is



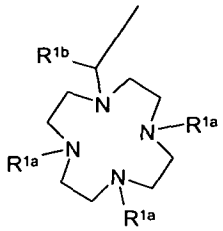
and wherein R^{1a} is as in claim 19.

52. A compound according to any one of claims 1-50, wherein R^1 is



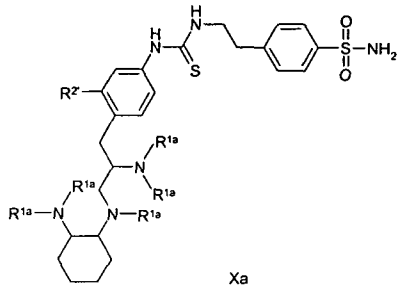
and wherein R^{1a} is as in claim 19.

53. A compound according to any one of claims 1-50, wherein R^1 is

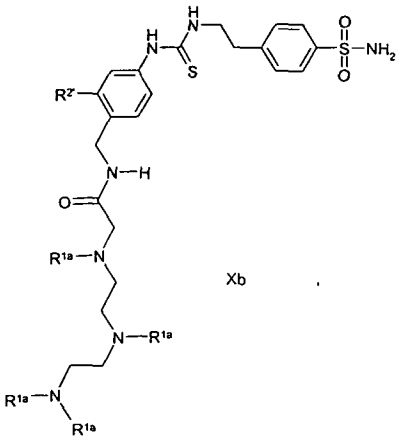


and wherein R^{1a} and R^{1b} are as in claim 19.

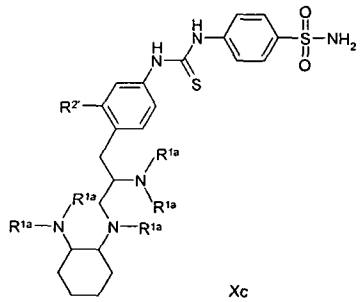
54. A compound according to claim 1, wherein the compound is according to formula Xa, Xb, Xc or Xd:



Xa

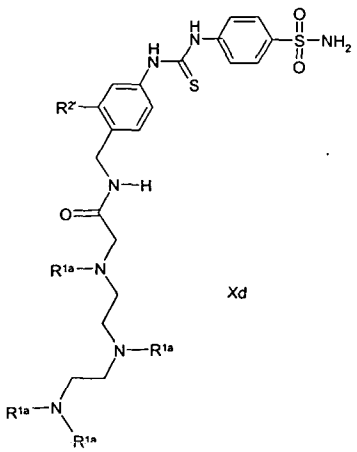


Xb



Xc

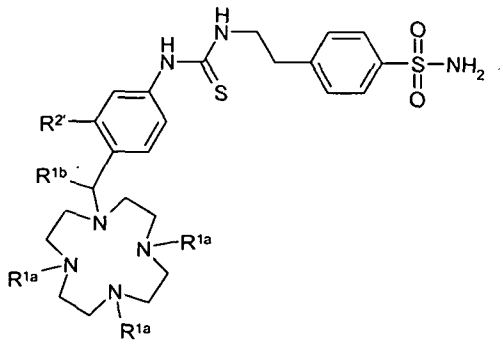
or



Xd

and wherein R^{1a} is as in claim 19; and $R^{2'}$ is H or alkoxy.

55. A compound according to claim 1, wherein the compound is according to formula XI:



XI

and wherein R^{1a} and R^{1b} are as in claim 1; and $R^{2'}$ is H or alkoxy.

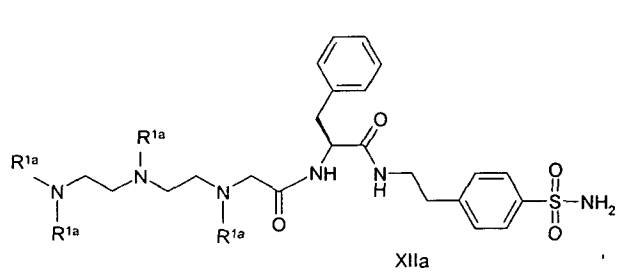
56. A compound according to any one of claims 23-55, wherein $R^{2'}$ is H.

57. A compound according to any one of claims 23-55, wherein $R^{2'}$ is methoxy.

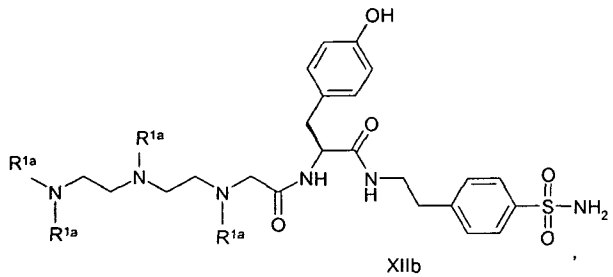
58. A compound according to any one of claims 1-57, wherein R^{1a} is CH_2COOH.

59. A compound according to any one of claims 1-57, wherein R^{1b} is COOH.

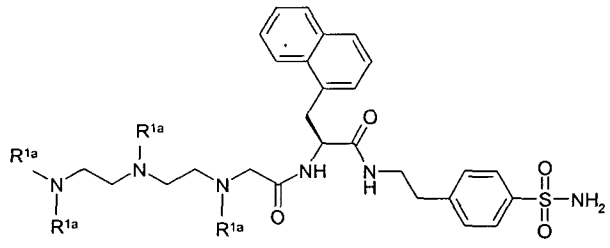
60. A compound according to claim 1, wherein the compound is according to formula XIIa, XIIb, XIIc, XIId or XIIe:



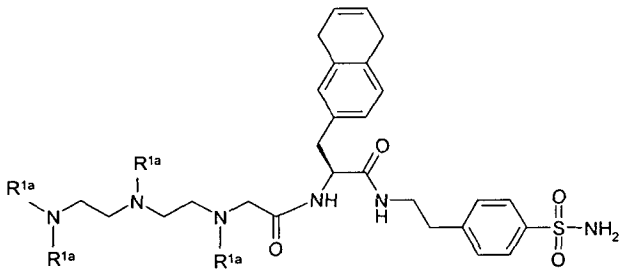
XIIa



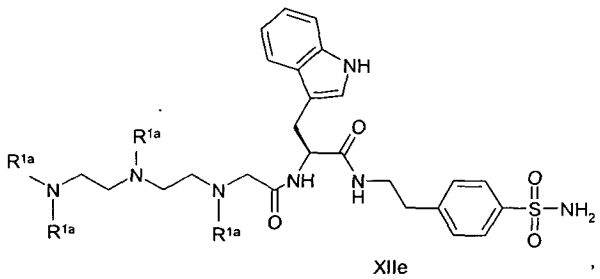
XIIb



XIIc



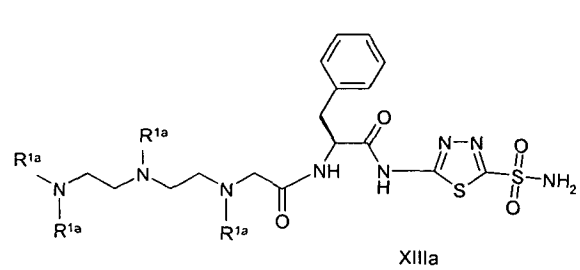
XIId



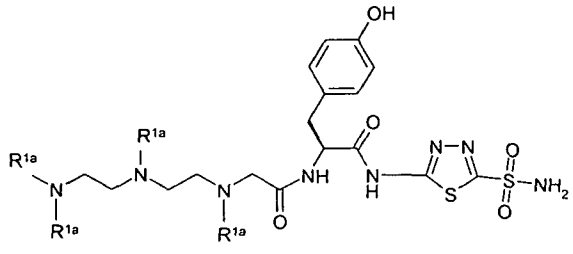
XIIe

each R^{1a} is CH_2CO_2H.

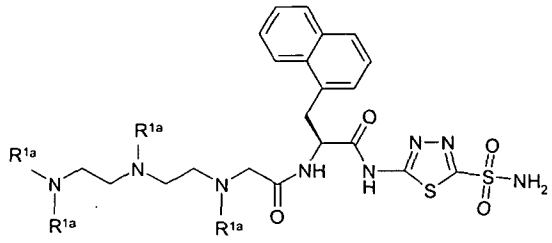
61. A compound according to claim 1, wherein the compound is according to formula XIIIa, XIIIb, XIIIc, XIIId or XIIIe:



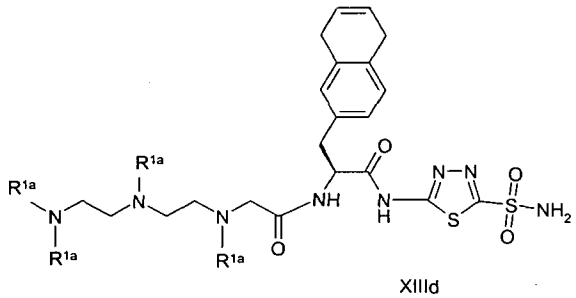
XIIIa



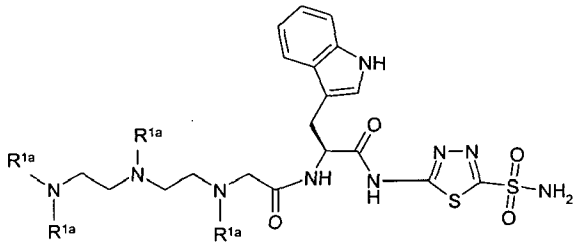
XIIIb



XIIIc



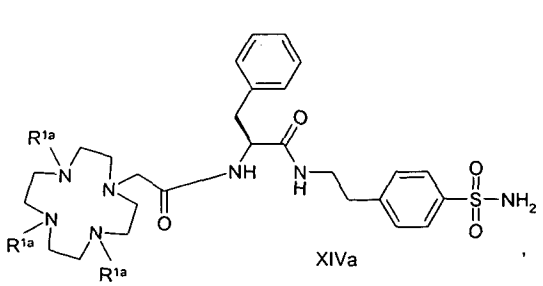
XIIId



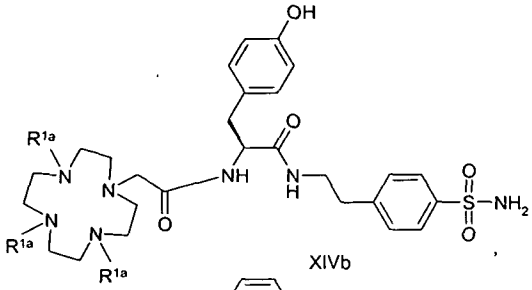
XIIIe

each R^{1a} is CH_2CO_2H.

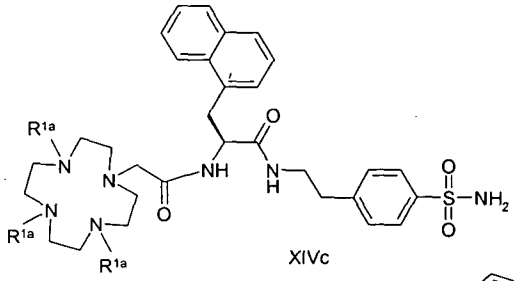
62. A compound according to claim 1, wherein the compound is according to formula XIVa, XIVb, XIVc, XIVd or XIVe:



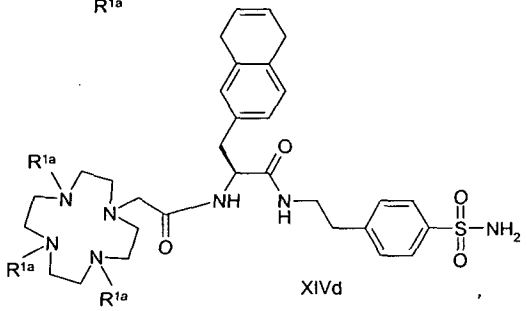
XIVa



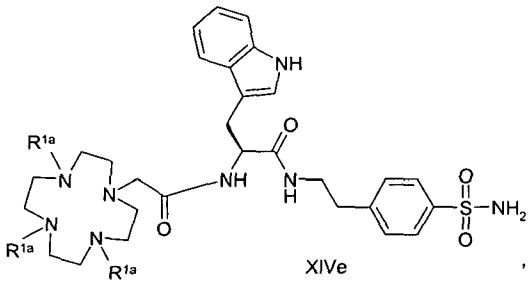
XIVb



XIVc



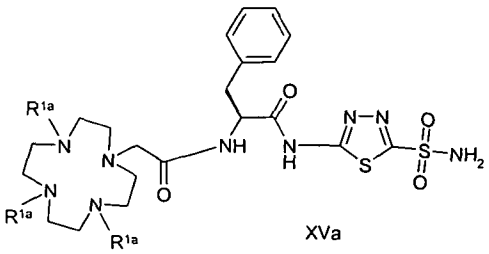
XIVd



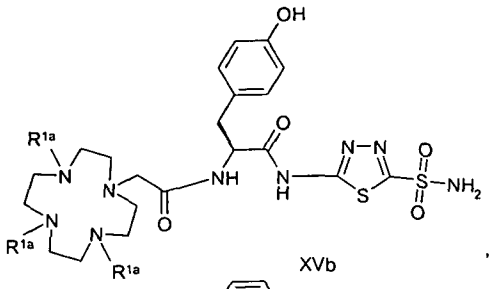
XIVe

each R^{1a} is CH_2CO_2H.

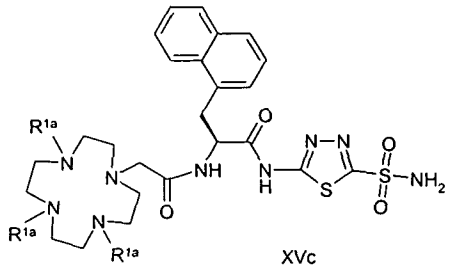
63. A compound according to claim 1, wherein the compound is according to formula XVa, XVb, XVc, XVd or XVe:



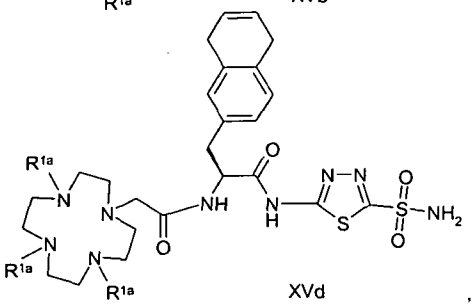
XVa



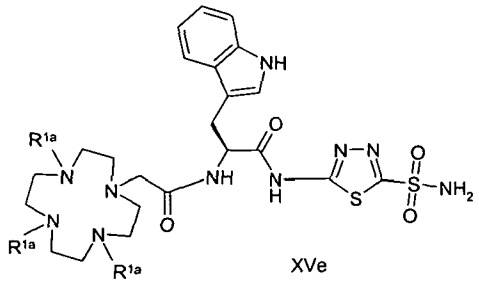
XVb



XVc



XVd



XVe

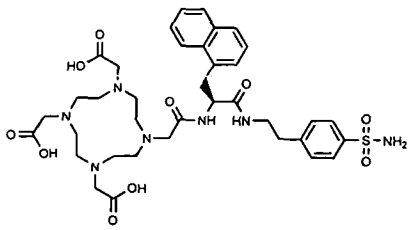
each R^{1a} is CH_2CO_2H.

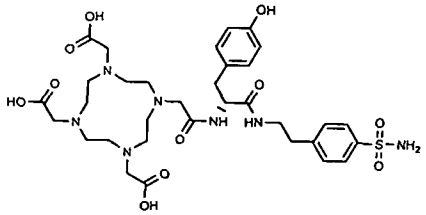
64. A compound according to claim 1 wherein the compound is selected from the compounds exemplified in Table 1, 2, 3 or 4;

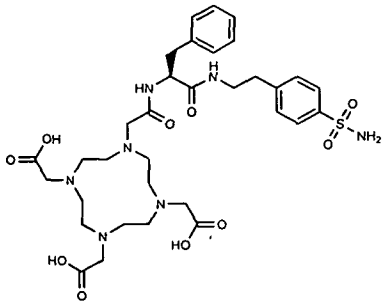
or a pharmaceutically acceptable salt, solvate or prodrug thereof;

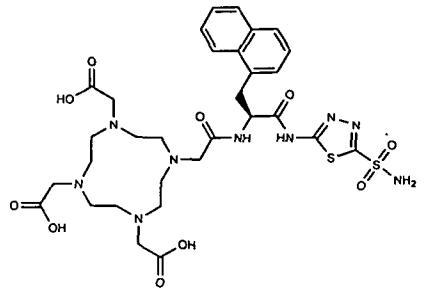
and stereoisomers, isotopic variants and tautomers thereof.

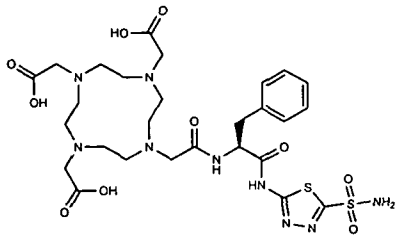
65. A compound according to claim 1 wherein the compound is selected from;

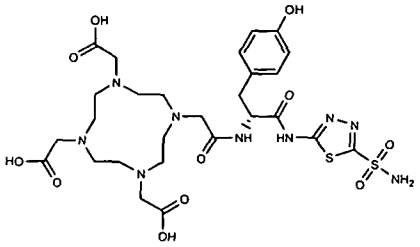


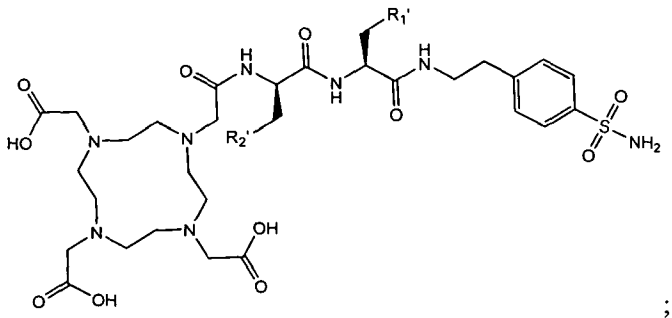


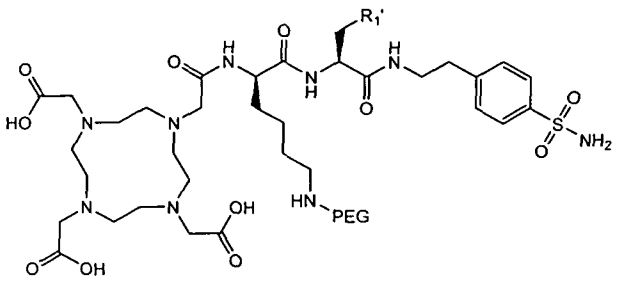


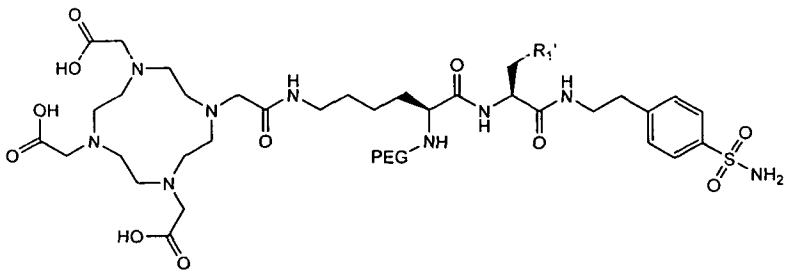












wherein R_1' = alkyl, aminoalkyl, hydroxyalkyl, benzyl, phenyl, napthyl, or an amino acid side chain; PEG – polyethyleneglycol; R_2' = alkyl, aminoalkyl, hydroxyalkyl, benzyl, phenyl, napthyl, or an amino acid side chain;

or a pharmaceutically acceptable salt, solvate or prodrug thereof;

and stereoisomers, isotopic variants and tautomers thereof.

66. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of any of claims 1-65.

67. The pharmaceutical composition of claim 66, wherein the carrier is a parenteral carrier.

68. The pharmaceutical composition of claim 66, wherein the carrier is an oral carrier.

69. The pharmaceutical composition of claim 66, wherein the carrier is a topical carrier.

70. A method for identifying or detecting hypoxic tumors which comprises administering to the mammal an effective amount of a compound according to any of claims 1-65 or a pharmaceutical composition according to any of claims 66-69.

71. A compound according to any one of claims 1-65, or a pharmaceutically acceptable salt or solvate thereof, for use as a probe for the identification of hypoxic tumors.

72. The method or use according to any one of claims 70-72, wherein the hypoxic tumor is Carbonic hydrase IX-positive.

73. The use according to any one of claims 70-72, wherein the identification of tumor is carried out by radiographic imaging with ^{111}In, ^{68}Ga or ^{64}Cu.

74. The use according to any one of claims 70-73, wherein the identification of tumor is carried out by positron-emission tomography (PET).

75. The use according to any one of claims 70-73, wherein the identification of tumor is carried out by single photon emission tomography (SPECT).

76. The use according to any one of claims 70-73, wherein the identification of tumor is carried out by gamma scintigraphy.

77. A method for defining CAIX positive tumors which comprises administering to the mammal an effective amount of a compound according to any of claims 1-65 or a pharmaceutical composition according to any of claims 66-69.

78. A method for defining tumor hypoxia for dose painting in radiation planning which comprises administering to the mammal an effective amount of a compound according to any of claims 1-46 or a pharmaceutical composition according to any of claims 70-73.

79. The method or use according to any one of claims 70-78, wherein the tumor is selected from: head, breast, neck, kidney, giomas, mesothelomas, stomach, colon, pancreatic, biliary, cervix, endometrial, and squamal or basal cell carcinomas.

80. The method of claim 79, wherein the tumor is a head tumor.

81. The method of claim 79, wherein the tumor is a breast tumor.

82. The method of claim 79, wherein the tumor is a colon tumor.

83. The method of claim 79, wherein the tumor is a kidney tumor.

84. A compound according to any one of claims 1-65, or a pharmaceutically acceptable salt or solvate thereof, for use as a pharmaceutical.

85. A compound according to any one of claims 1-65, or a pharmaceutically acceptable salt or solvate thereof, for use as a pharmaceutical or medicament.

86. A compound according to any one of claims 1-65, or a pharmaceutically acceptable salt or solvate thereof, for use as a diagnostic or prognostic agent.

87. The compound according to claim 86, wherein said compound is administered to a subject under treatment or examination.

88. Use of a compound according to any of claims 1-65, in the manufacture of a medicament for the use in combination therapy.

89. The use according to claim 88 wherein the therapy is antitumor therapy.

FIG. 1

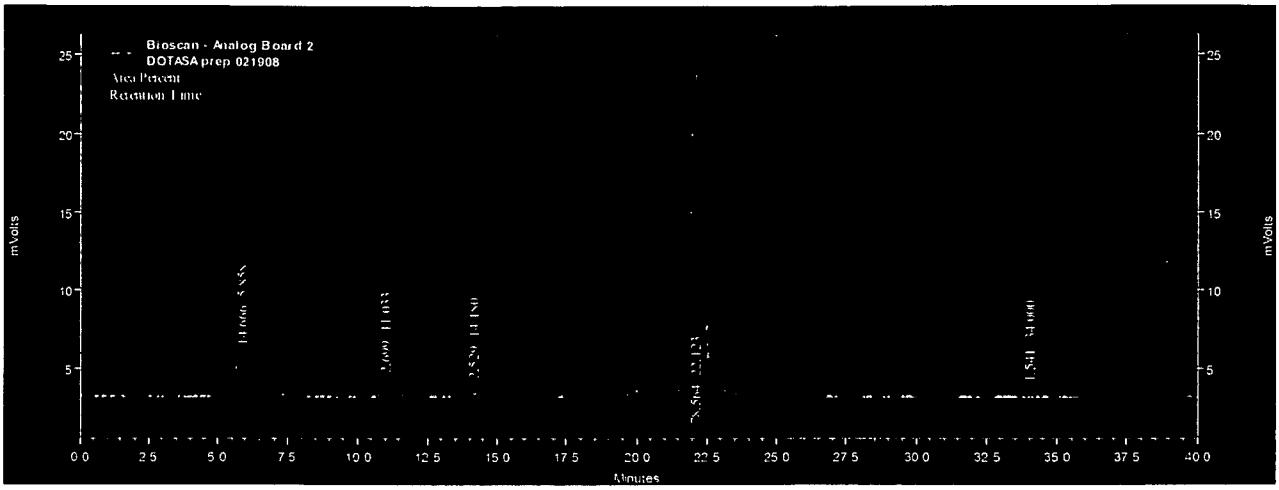

Bioscan - Analog Board 2
DOTASA prep 021908
Area Percent
Retention Time
mVolts
Minutes
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
22.5
25.0
27.5
30.0
32.5
35.0
37.5
40.0
5
10
15
20
25

FIG. 2A

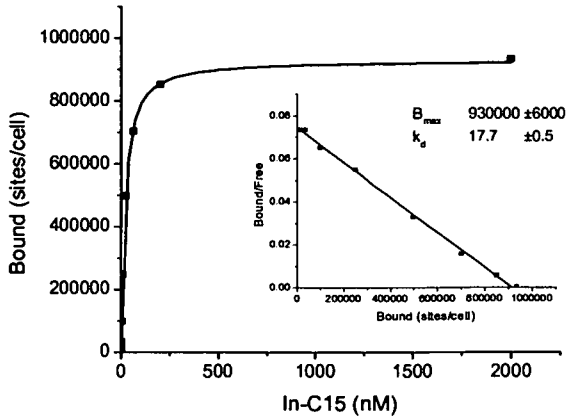

Bound (sites/cell)
In-C15 (nM)
B max 930000 ±6000
k d 17.7 ±0.5
Bound/Free
Bound (sites/cell)

FIG. 2B

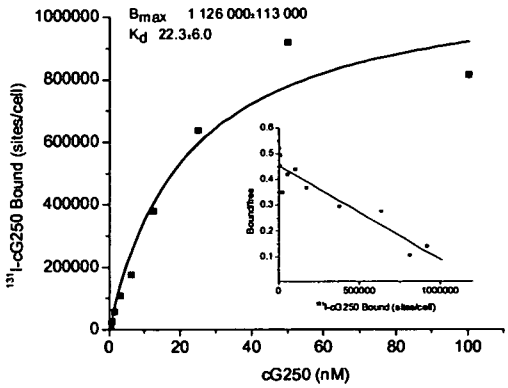

B max 1 126 000±113 000
K d 22.3±6.0
131I-cG250 Bound (sites/cell)
cG250 (nM)
Bound/free

FIG. 3

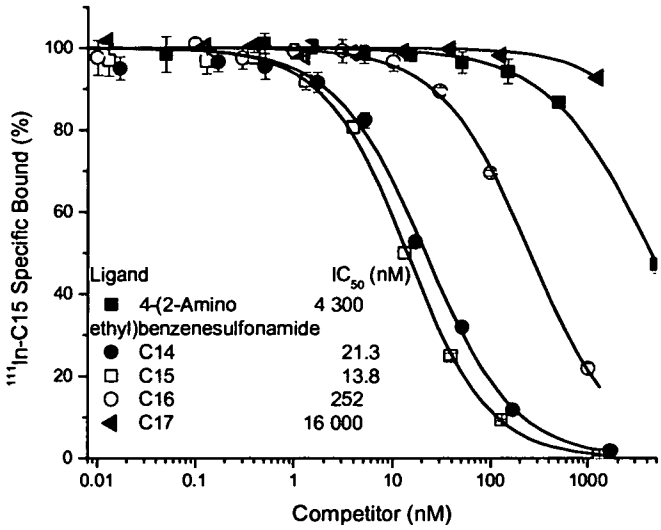

100
80
60
40
20
0
^{111}In-C15 Specific Bound (%)
0.01
0.1
1
10
100
1000
Competitor (nM)
Ligand
IC_{50} (nM)
4-(2-Amino ethyl)benzenesulfonamide 4 300
C14 21.3
C15 13.8
C16 252
C17 16 000

FIG. 4A

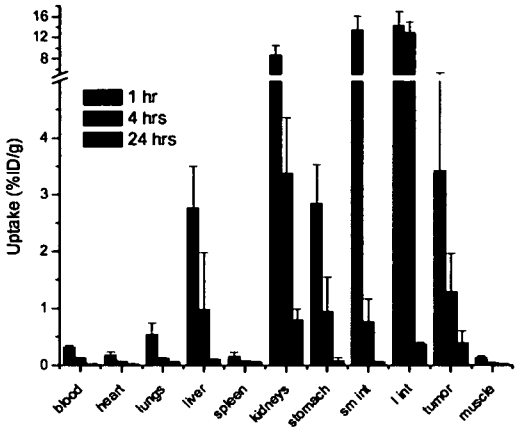
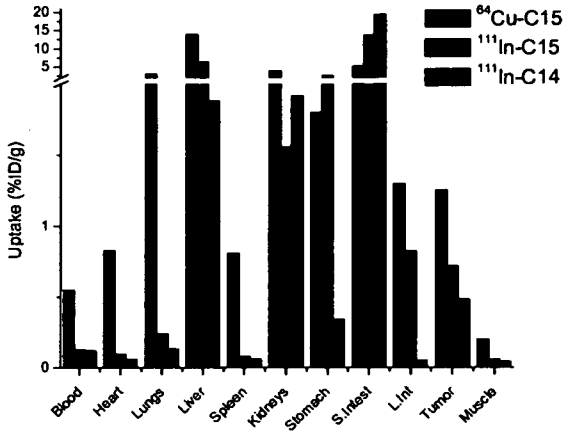

Uptake (%ID/g)
16
12
8
4
3
2
1
0
1 hr
4 hrs
24 hrs
blood
heart
lungs
liver
spleen
kidneys
stomach
sm int
l int
tumor
muscle

FIG. 4B


Uptake (%ID/g)
20
15
10
5
1
0
64Cu-C15
111In-C15
111In-C14
Blood
Heart
Lungs
Liver
Spleen
Kidneys
Stomach
S.Intest
L.Int
Tumor
Muscle

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/001760

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C311/46 C07C335/20 C07D257/02 C07K5/062 A61K31/17
A61K31/18 A61K31/395 A61K38/05 A61P35/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D C07K A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A. SCOZZAFAVA, ET AL.: "Carbonic anhydrase inhibitors. A general approach for the preparation of water-soluble sulfonamides incorporating polyamino-polycarboxylate tails and of their metal complexes possessing long-lasting, topical intraocular pressure-lowering properties" JOURNAL OF MEDICINAL CHEMISTRY, vol. 45, no. 7, 22 February 2002 (2002-02-22), pages 1466-1476, XP002595850 American Chemical Society, Washington, DC, US ISSN: 0022-2623 DOI: 10.1021/jm0108202 table 1; compounds 40, 402, 50, 502, 60, 602, 70	1,3-5, 12,15, 24,28, 32,43, 44,51, 58,66,69

-/--

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

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 August 2010	25/08/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	English, Russell

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/001760

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A. SCOZZAFAVA, ET AL.: "Carbonic anhydrase inhibitors: synthesis of sulfonamides incorporating dtpa tails and of their zinc complexes with powerful topical antiglaucoma properties" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 11, no. 4, 26 February 2001 (2001-02-26), pages 575-582, XP004230063 Elsevier Science Publishers, Oxford, GB ISSN: 0960-894X DOI: 10.1016/S0960-894X(00)00722-8 table 1; compounds dtpa-0, dtpa-02	1,3-5, 12,15, 24,28, 32,43, 44,51, 58,66,69
X	A.L. BANERJEE, ET AL.: "Inhibition of matrix metalloproteinase-9 by 'multi-prong' surface binding groups" CHEMICAL COMMUNICATIONS, no. 20, 7 March 2005 (2005-03-07), pages 2549-2551, XP002596195 Royal Society of Chemistry, Cambridge, GB ISSN: 0022-4936 DOI: 10.1039/b501780g table 1; compound conjugate 4	1,3,4,6, 8,15,24, 27, 29-31,66
A	M. RAMI, ET AL.: "Carbonic anhydrase inhibitors: Copper(II) complexes of polyamino-polycarboxylamido aromatic/heterocyclic sulphonamides are very potent inhibitors of the tumour-associated isoforms IX and XII" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 18, no. 2, 15 January 2008 (2008-01-15), pages 836-841, XP002596378 Elsevier Science Publishers, Oxford, GB ISSN: 0960-894X DOI: 10.1016/j.bmcl.2007.11.025 page 837, right-hand column, lines 21-27; table 1	1-89
A	M. RAMI, ET AL.: "Carbonic anhydrase inhibitors: design of membrane-impermeant copper(II) complexes of DTPA-, DOTA-, and TETA-tailed sulphonamides targeting the tumour-associated transmembrane isoform IX" CHEMMEDCHEM, vol. 3, no. 11, 27 October 2008 (2008-10-27), pages 1780-1788, XP002596371 Wiley-VCH Verlag, Weinheim, DE ISSN: 1860-7179 DOI: 10.1002/cmdc.200800267 page 1785, left-hand column, lines 13-20; table 1	1-89