Abstract: Provided are certain heteroaryl benzamides, compositions, and methods of their manufacture and use.
HETEROARYL BENZAMIDES, COMPOSITIONS AND METHODS OF USE

[001] This invention was made in part with U.S. Government support under Contract number CA-082566, awarded by the National Cancer Institute. The government may have certain rights in the invention.


[003] Provided herein are certain heteroaryl benzamides, compositions, and methods of their manufacture and use.

[004] Tumor hypoxia has a well defined role in driving tumor progression and metastasis, as well as resistance to therapy. A key mediator of hypoxic stress is HIF-α. HIF is a bHLH heterodimeric transcription factor, made up of an oxygen-labile subunit (HIF-α) and a constitutive subunit (HIF-β).

[005] In the presence of oxygen, hydroxylation on proline residues 564 and 402 by prolyl hydroxylases (PHDs) marks HIF-α for recognition and binding with Von Hippel-Lindau protein (pVHL), leading to degradation of HIF-α. Under hypoxic conditions, activity of the PHDs decrease, which prevents the recognition of HIF-α by pVHL. In cells that lack VHL, stabilized HIF-α binds HIF-β to activate the transcription of genes involved in several processes. HIF transcribes genes that mediate glycolysis, angiogenesis, tissue remodelling, epithelial permeability and vascular tone. These genes, and processes driven by these genes, act to promote tumor growth and survival in hypoxic conditions.

[006] Functional studies indicate that pVHL, the protein product of VHL, is an E3 ubiquitin ligase that targets the α-subunit of the hypoxia-inducible factor (HIF) for proteasomal degradation under normoxia. In addition to its role in HIF regulation, pVHL has been implicated in a variety of processes including extracellular matrix assembly, regulation of microtubule stability, polyubiquitination of atypical PKC family members, regulation of fibronectin, and RNA polymerase II subunits.

[007] There is considerable interest in the identification of HIF inhibitors and a variety of pharmacological HIF inhibitors have been identified, although the interaction of these agents is not directly with HIF, but via modulation of cellular processes in which HIF is integral.
An extension of this therapy would be in the treatment of cells defective in the von Hippel-Lindau gene and diseases associated with such defects.

While many solid tumors respond to different combinations of cytotoxic chemotherapies, kidney cancer is a particularly intractable disease. Renal cell carcinoma (RCC), the most common type of kidney cancer, has proven to be particularly challenging, resistant to both radiation therapy and standard systemic chemotherapies. To date, immunotherapy using interferon or interleukin-2 has had mild success with responses in less than 10% of patients with metastatic RCC. The recent development of anti-angiogenic therapies sunitinib (Sutent) and sorafenib (Nexavar) is encouraging although few patients have durable responses and exhibit increased survival. The targeting of receptor tyrosine kinases, which is not specific to the development of RCC, has become the standard of care for advanced RCC.

One key distinguishing feature in RCC is the loss of function of the VHL tumor suppressor gene, an essential and frequent mutation. In order to specifically target RCC cells without toxicity to normal cells, a synthetic lethal approach, seeking to identify compounds that exhibit selective cytotoxicity to cells that have lost functional VHL, can be used. The concept of synthetic lethality, or conditional genetics, describes the genetic interaction of two genes, both involved in an essential process. When either gene is mutated alone, the cell remains viable. However, the combination of mutations in these two genes results in cell death. In the case of chemical synthetic lethality, the first mutation is essential to the development of cancer, while a second gene is inhibited by a small molecule, resulting in cytotoxic cell death. This approach is particularly attractive because it should not affect normal, non-cancerous tissue.

Compounds that function in a synthetic lethal manner to the loss of VHL and/or selectively target RCC are described herein. Provided is at least one compound of Formula I:

![Formula I](image)

or a pharmaceutically acceptable salt thereof,
wherein:

A is a nitrogen-containing heteroaryl ring chosen from pyridinyl, pyrimidinyl, pyrazinyl, quinolinyl, pyrazolyl, imidazolyl, and thiazolyl, each of which is optionally substituted;

\[ \text{A} \]

is attached to the phenyl ring at either the 3 or 4 position;

R₁, R₂, and R₃ are each independently chosen from hydrogen, optionally substituted alkyl, and optionally substituted alkenyl;

R₄ is chosen from hydrogen, hydroxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, halo, carboxy, nitro, sulfonyl, sulfanyl, and optionally substituted amino;

W is chosen from -NRSO₂⁻, -SO₂NR⁻, and -NRCO⁻, wherein each R is independently chosen from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, each of which, except for hydrogen, is optionally substituted; and

B is an optionally substituted aryl ring,

provided that if A is 3-pyridinyl, R₁, R₂, R₃, and R₄ are each hydrogen, and W is -NHSO₂⁻, then B is not 3-methoxyphenyl, 3,4-dimethylphenyl, 2,3,4-trifluorophenyl, 2,3,5,6-tetramethylphenyl, 2,5-dimethylphenyl, 3-chlorophenyl, 3-trifluoromethylphenyl, 4-methoxyphenyl, 4-tertbutylphenyl, 4-fluorophenyl, or 4-acetylphenyl.

[012] Provided is at least one compound of Formula IA:

\[ \text{A} \]

or a pharmaceutically acceptable salt thereof,

wherein:

A is a nitrogen-containing heteroaryl ring chosen from pyridinyl, pyrimidinyl, pyrazinyl, quinolinyl, pyrazolyl, imidazolyl, and thiazolyl, each of which is optionally substituted;
is attached to the phenyl ring at either the 3 or 4 position;

Ri, R₂, and R₃ are each independently chosen from hydrogen, optionally substituted alkyl, and optionally substituted alkenyl;

R₄ is chosen from hydrogen, hydroxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, halo, carboxy, nitro, sulfonyl, sulfinyl, and optionally substituted amino;

W is chosen from \(-\text{NRSO}_2\), \(-\text{SO}_2\text{NR}\), and \(-\text{NRCO}\), wherein each R is independently chosen from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, each of which, except for hydrogen, is optionally substituted; and

B is an optionally substituted aryl ring.

[013] Also provided is a pharmaceutical composition, comprising at least one compound of Formula I or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

[014] Also provided are methods for treating diseases mediated by HIF-1α and/or HIF-2α.

[015] Also provided are methods of targeting cells which express HIF-1α and/or HIF-2α.

[016] Also provided are methods for treating diseases mediated by defective pVHL protein.

[017] Also provided are methods of targeting cells which have defective pVHL protein.

**Brief Description of the Figures**

[018] **Fig. 1.** (A) Compound 47 inhibits glycolysis in VHL-deficient cells. Lactate (µM/cell), which is converted from pyruvate, the end product of glycolysis, was measured in RCC4 and RCC4/VHL cells treated with either vehicle or compound 47 (5 µM). (B) Relative glucose uptake is inhibited by compound 47 in VHL-deficient cells. Following treatment with compound 47, cells were starved of glucose for 1 hour and then pulsed for 1 hour with \(^{3}\text{H}-2\)-deoxyglucose. (C) Inhibition of glucose in cells that have lost VHL is dependent on compound 47 concentration. Cells were
treated with the indicated concentration and glucose uptake was measured. (D) Relative hexokinase activity is impaired by compound 47 specifically in cells without VHL. Whole cell lysates were examined for hexokinase activity following compound 47 treatment. (E) Glucose uptake and hexokinase activity were measured for active and inactive compound 47 analogs. Only active analogs affected both glucose uptake and hexokinase activity in VHL-defective cells. (F) Relative ATP levels are decreased in response to compound 47 in cells that have lost VHL. (G) Decrease in ATP levels in VHL-deficient cells is dependent on compound 47 concentration. (H) Oxygen consumption (nmol/min/10^6 cells) does not change in response to compound 47.

[019] Figure 2A-G Chemical synthetic lethal screen identifies compounds that specifically target loss of VHL in renal carcinoma. (A) XTT validation of 4-phenylsulfonamido-N-(pyridin-3-yl)benzamides (PPBs): Compound 27 and compound 47 were identified from chemical synthetic lethal screen of renal carcinoma cells that have lost VHL. (B) Clonogenic survival of RCC4 with and without VHL in response to compound 47 (p<0.00005). (C) Representative plates of clonogenic survival in RCC4 and RCC4/VHL cells. Three hundred cells were treated with 5 µM of compound 47 for 10 days. (D) Compound 47-induced cell death is irreversible after three days. Cells were treated with compound 47 (5 µM). The media was replaced after the indicated time and cells were allowed to grow for a total of 10 days (p<0.0005). (E) Clonogenic survival of ACHN with and without shRNA to VHL in response to compound 47 (p<0.0001). (F) Compound 47 induces a necrotic cell death. RCC4 and RCC4/VHL cells were treated for 3 days with 5 µM of compound 47 and amount of cell death was examined by trypan blue staining (p<0.01). (G) Compound 47 toxicity is mediated through HIF. RCC4, RCC4/VHL or RCC4/VHL cell clones overexpressing HIF-2α were treated with compound 47 (p<0.005). All error bars represent the standard error of the mean.

[020] Figure 3A-K Compound 47 inhibits glucose metabolism in W-/-/–-deficient cells. (A) Compound 47 inhibits glucose uptake and glycolysis in W-/-/–-deficient cells. Lactate (mM/cell), which is converted from pyruvate, the end product of glycolysis, was measured in RCC4 and RCC4/VHL cells treated with either vehicle or compound 47 (5 µM)(p<0.01). (B) Relative glucose uptake is inhibited by compound 47 in W-/-/–-deficient cells. Following treatment with compound 47 (5 µM),
cells were starved of glucose for 1 hour and then pulsed for 1 hour with $^3$H-2-deoxyglucose. Counts are normalized to cell number. (C) Inhibition of glucose uptake in cells that have lost VHL is dependent on compound 47 concentration. Cells were treated with the indicated concentration and glucose uptake was measured ("p<0.00005). (D) Relative hexokinase activity is impaired by compound 47 specifically in cells without VHL. Whole cell lysates were examined for hexokinase activity following compound 47 treatment (5 μM). (E) Compound 47 inhibition of glucose uptake is dependent on HIF. RCC4 cells were transfected with siRNA to HIF-1 β, treated with compound 47 (5 μM), and glucose uptake was measured ("p<0.05). (F) Oxygen consumption (nmol/min/1 0$^6$ cells) does not change in response to compound 47 (5 μM). (G) Relative ATP levels are decreased in response to compound 47 (5 μM) in cells that have lost VHL ("p<0.005). (H) Decrease in ATP levels in W-/L-deficient cells is dependent on compound 47 concentration ("p<0.01). (I) Relative mRNA expression of Glut1 in RCC4 and RCC4/VHL as determined by quantitative real-time PCR and normalized to TBP. (J) Relative mRNA expression of GLUT1 in RCC4 and RCC4/VHL as determined by quantitative real-time PCR and normalized to TBP. All error bars represent the standard error of the mean. (K) Compound 47 analog, Compound 116, binds to GLUT1. 4-{2-[1-(6-Aminohexyl]-1 H-1 ,2,3-triazol-4-yl]-4-pyridinyl}-N-(3-methylphenyl)-1 ,3-thiazol-2-amine does not bind to GLUT1. Cell lysates of RCC4 and RCC4/VHL were incubated with Affi-gel immobilized compound 116 or 4-{2-[1-(6-aminoheoxyl]-1 H-1 ,2,3-thiazol-4-yl]-4-pyridinyl]-N-(3-methylphenyl)-1 ,3-thiazol-2-amine and eluted with increasing salt concentration. Elutions were probed for GLUT1.

[021] Figure 4 Glucose uptake and hexokinase activity were measured for active and inactive compound 47 analogs. Only active analogs affected both glucose uptake and hexokinase activity in VHL-defective cells. All error bars represent the standard error of the mean.

[022] Figure 5A-E In vivo monitoring and efficacy of compound 47. (A) FDG-PET imaging demonstrates an in vivo decrease in glucose uptake in a renal clear cell carcinoma xenograft in response to compound 85, a more soluble, active analog of compound 47. 786-O, a renal clear cell carcinoma with a naturally occurring VHL mutation, were implanted subcutaneously into the flanks of CD-1 nude mice.
Representative axial cross section of a mouse prior to treatment (left) and following three daily i.p. injections with compound 85 (1.6 mg/kg)(right), overlaid over CT scan. (B) Quantitatively, compound 85 inhibits FDG-PET in mouse xenografts. Quantification of FDG-PET inhibition by compound 85 as determined by the 90th percentile ROI for percent injected dose per gram (%ID/g) (’p<0.01). (C) Compound 85 is not toxic to normal tissues. (a, b) Kidney of vehicle- and compound 85-treated animals. (c, d) Spleen of vehicle- and compound 85-treated animals. (e, f) Liver of vehicle- and compound 85-treated animals. (g, h) Heart of vehicle-and compound 85-treated animals. (i, j) Salivary gland of vehicle- and compound 85-treated animals. Scale bar represents 100 microns. (D) Compound 85 delays tumor growth. 786-0 tumor-bearing mice were treated daily with vehicle or compound 85 (1.6 mg/kg for the first 3 days, followed by 7.8 mg/kg for the next week)(’p<0.005). (E) Compound 85 delays tumor growth in cells that have lost VHL. ACHN cells expressing a short hairpin RNA to VHL were implanted subcutaneously into the flanks of immunocompromised mice. Once tumors reached an average of >20 mm³, mice were treated daily with compound 85 or vehicle (’p<0.05). All error bars represent the standard error of the mean.

[023] Figure 6 Model of compound 47 mechanism of synthetic lethality.

[024] Figure 7A-E Compound 47 does not induce autophagy, apoptosis, or DNA damage. (A) Clonogenic survival of RCC4 and RCC4/VHL treated with compound 27 (5 µM) (’p<0.05). All error bars represent the standard error of the mean. (B) Compound 47 does not induce autophagy. RCC4 and RCC4/VHL cells were treated with increasing concentrations of compound 47 (1.25, 2.5 and 5 µM), a negative control (DMSO) and a positive control (4-(pyridin-4-yl)-N-(m-tolyl)thiazol-2-amine). Cells were lysed and probed for LC3, a marker of autophagy, or α-tubulin (loading control). (C) Compound 47 does not induce apoptosis. RCC4 and RCC4/VHL cells were treated with vehicle, increasing concentrations of compound 47, and camptothecin. Cells were stained with DAPI and nuclear condensation was examined by fluorescence microscopy. (D) RCC4 cells were treated with compound 47 (5 µM) for the indicated time and stained with Annexin V and propidium iodide and subjected to FACS analysis. (E) Compound 47 does not induce DNA damage. RCC4 and RCC4/VHL cells were subjected to increasing concentrations of
compound 47 (1.25, 2.5, and 5 µM), a negative control (DMSO), and a positive control (doxorubicin). Cells were lysed and subjected to Western blot with the indicated antibodies.

[025] Figure 8A-E  W-/- deficient renal carcinomas are more sensitive to glucose deprivation compared to RCCs with wild-type VHL. (A) Relative mRNA expression levels for different genes involved in glucose metabolism in RCC4 cells relative to RCC4/VHL cells. (B) Glucose uptake is impaired by compound 47 (5 µM) in 786-O cells, which are deficient in VHL, but not 786/VHL, which have wild-type VHL restored. (C) VHL mutant RCC4 cells are more sensitive to glucose deprivation than RCC4/VHL. Cells were grown in media lacking glucose and/or pyruvate for 6 days (’p<0.005). (D) VHL mutant 786-O cells are more sensitive to glucose deprivation than 786/VHL cells (’p<0.05). (E) ACHN tumors with wild-type VHL are insensitive to compound 47 treatment (5 µM). ACHN cells were implanted subcutaneously into the flanks of immunocompromised mice. Once tumors reached an average of >20 mm³, mice were treated daily with compound 85 or vehicle. All error bars represent the standard error of the mean.

[026] Figure 9  Sensitivity of cancer cell lines to GIUT1 inhibition.

[027] As used in the present specification, the following words, phrases, and symbols are generally intended to have the meanings set forth below, except to the extent that the context in which they are used indicated otherwise. The following abbreviations and terms have the indicated meanings throughout:

[028] "Subject" refers to an animal, such as a mammal, that has been or will be the object of treatment, observation, or experiment. The compounds and methods described herein may be useful for both human therapy and veterinary applications. In some embodiments, the subject is a human.

[029] As used herein, "treatment" or "treating" refers to an amelioration of a disease or disorder, or at least one discernible symptom thereof. In another embodiment, "treatment" or "treating" refers to an amelioration of at least one measurable physical parameter, not necessarily discernible by the patient. In yet another embodiment, "treatment" or "treating" refers to reducing the progression of a disease or disorder, either physically, e.g., stabilization of a discernible symptom, physiologically, e.g., stabilization of a physical parameter, or both. In yet another embodiment, "treatment" or "treating" refers to delaying the onset of a disease or disorder.
As used herein, "prevention" or "preventing" refers to a reduction of the risk of acquiring a given disease or disorder.

As used herein, "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "parenteral administration" and "administered parenterally" refer to modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, and intratracheal injection and infusion.

A dash ("-"), that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -CONH₂ is attached through the carbon atom.

The term "alkyl" refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-20, 1-8, or 1-6 carbon atoms, referred to herein as C₂⁻₈ alkyl, C₈ alkyl, and C₆ alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, and the like.

The term "alkenyl" refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond, such as a straight or branched group of 2-20, 2-8, or 2-6 carbon atoms, referred to herein as (C₂⁻C₂₀) alkenyl, (C₂⁻C₈) alkenyl, and (C₂⁻C₆) alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentaeny, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, and 4-(2-methyl-3-butene)-pentenyl.

The term "alkynyl" refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond, such as a straight or branched group of 2-20, 2-8, or 2-6 carbon atoms, referred to herein as C₂⁻C₂₀ alkynyl, C₂⁻C₈ alkynyl,
and C₂-C₆ alkynyl, respectively. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentylnyl, hexynyl, methylpropynyl, 4-methyl-1-butynyl, 4-propyl-2-pentynyl, and 4-butyl-2-hexynyl.

"Cycloalkyl" refers to a saturated hydrocarbon ring group, having the specified number of carbon atoms, such as, for example from 3 to 7 ring carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl as well as bridged and caged saturated ring groups such as, for example, adamantane.

"Alkoxy" groups also include an alkenyl group attached to an oxygen (−O−alkyl). "Alkoxy" groups also include an alkenyl group attached to an oxygen ("alkenyl oxy") or an alkynyl group attached to an oxygen ("alkynyl oxy") groups. Exemplary alkoxy groups include, but are not limited to, groups with an alkyl, alkenyl or alkynyl group of 1-20, 1-8, or 1-6 carbon atoms, referred to herein as (d-C₂₋) alkoxy, (CrC₁₋) alkoxy, and (CrC₂₋) alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyloxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, 3-methylpentoxy, and the like.

"Acyl" refers to the groups (alkyl)-C(O)−, (cycloalkyl)-C(O)−, (aryl)-C(O)−, (heteroaryl)-C(O)−, and (heterocycloalkyl)-C(O)−, wherein the group is attached to the parent structure through the carbonyl functionality and wherein alkyl, cycloalkyl, aryl, heteroaryl, and heterocycloalkyl are as described herein. Acyl groups have the indicated number of carbon atoms, with the carbon of the keto group being included in the numbered carbon atoms. For example a C₂ acyl group is an acetyl group having the formula CH₃(C=O)−.

"Alkoxy carbonyl" refers to an ester group of the formula (alkoxy)(C=O)− attached through the carbonyl carbon wherein the alkoxy group has the indicated number of carbon atoms. Thus, a Cᵣ C₆ alkoxy carbonyl group is an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker.

By "amino" is meant the group −NH₂.

"Aryl" encompasses: 5- and 6-membered carbocyclic aromatic rings, for example, benzene; bicyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, naphthalene, indane, and tetralin; and tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene. For example, aryl includes 5- and 6-membered carbocyclic aromatic rings fused to a
5- to 7-membered heterocycloalkyl ring containing 1 or more heteroatoms chosen from N, O, and S. For such fused, bicyclic ring systems wherein only one of the rings is a carbocyclic aromatic ring, the point of attachment may be at the carbocyclic aromatic ring or the heterocycloalkyl ring. Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene. Aryl, however, does not encompass or overlap in any way with heteroaryl, separately defined below. Hence, if one or more carbocyclic aromatic rings is fused with a heterocycloalkyl aromatic ring, the resulting ring system is heteroaryl, not aryl, as defined herein.

[043] The term "aryloxy" refers to the group -O-aryl.

[044] The term "halo" includes fluoro, chloro, bromo, and iodo, and the term "halogen" includes fluorine, chlorine, bromine, and iodine.

[045] "Heteroaryl" encompasses: 5- to 7-membered aromatic, monocyclic rings containing one or more, for example, from 1 to 4, or in some embodiments, from 1 to 3, heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon; and bicyclic heterocycloalkyl rings containing one or more, for example, from 1 to 4, or in some embodiments, from 1 to 3, heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon and wherein at least one heteroatom is present in an aromatic ring. For example, heteroaryl includes a 5- to 7-membered heterocycloalkyl, aromatic ring fused to a 5- to 7-membered cycloalkyl ring. For such fused, bicyclic heteroaryl ring systems wherein only one of the rings contains one or more heteroatoms, the point of attachment may be at the heteroaromatic ring or the cycloalkyl ring. When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In some embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In some embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include, but are not limited to, (as numbered from the linkage position assigned priority 1), 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyrimidinyl, 3-pyrazolynyl, 2-thiazolyl, imidazolynyl, isoxazolynyl, oxazolynyl, thiazolynyl, thiadiazolynyl, tetrazolyl, thienyl, benzothiophenyl,
furanyl, benzofuranyl, benzoimidazolinyl, indolinyl, pyridizinyl, triazolyl, quinolinyl, and pyrazolyl. Bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a pyridyl group with two points of attachment is a pyridyldiene. Heteroaryl does not encompass or overlap with aryl as defined herein. Substituted heteroaryl also includes ring systems substituted with one or more oxygen (-0 ) substituents, such as pyridinyl N-oxides.

[046] "Heterocycloalkyl" refers to a single aliphatic ring, containing at least 2 carbon atoms in addition to 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen, as well as combinations comprising at least one of the foregoing heteroatoms. Suitable heterocycloalkyl groups include, for example (as numbered from the linkage position assigned priority 1), 2-pyrolinyl, 2,4-imidazolidinyl, 2,3-pyrazolidinyl, 2-piperidyl, 3-piperidyl, 4-piperdyl, and 2,5-piperazinyl. Morpholinyl groups are also contemplated, including 2-morpholinyl and 3-morpholinyl (numbered wherein the oxygen is assigned priority 1). Substituted heterocycloalkyl also includes ring systems substituted with one or more oxo moieties, such as piperidinyl N-oxide, morpholinyl-N-oxide, 1-oxo-1-thiomorpholinyl and 1,1-dioxo-1-thiomorpholinyl.

[047] The term "cyano" as used herein refers to -CN.

[048] The term "carboxy" as used herein refers to -COOH or its corresponding carboxylate salts (e.g., -COONa). The term carboxy also includes "carboxycarbonyl," for example, a carboxy group attached to a carbonyl group, for example, -C(O)-COOH or salts, such as -C(O)-COONa.

[049] The term "nitro" refers to -NO2.

[050] The term "hydroxy" and "hydroxyl" refer to -OH.

[051] The term "sulfiny1" includes the groups: -S(O)-H, -S(O)-(optionally substituted (CrC∞alkyl), -S(O)-optionally substituted ary1), -S(O)-optionally substituted heteroaryl), -S(O)-(optionally substituted heterocycloalkyl); and -S(O)-(optionally substituted amino).

[052] The term "sulfonyl" includes the groups: -S(O2)-H, -S(O2)-(optionally substituted (CrC∞alkyl), -S(O2)-optionally substituted ary1), -S(O2)-optionally substituted heteroaryl), -S(O2)-(optionally substituted heterocycloalkyl), -S(O2)-(optionally substituted alkoxy), -S(O2)-optionally substituted aryloxy),
-S(O<sub>2</sub>)-optionally substituted heteroaryloxy), -S(O<sub>2</sub>)-(optionally substituted heterocyclyloxy); and -S(O<sub>2</sub>)-(optionally substituted amino).

[053] By "optional" or "optionally" is meant that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" encompasses both "alkyl" and "substituted alkyl" as defined below. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible and/or inherently unstable.

[054] The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When a substituent is oxo (i.e., =0) then 2 hydrogens on the atom are replaced. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture, and subsequent formulation as an agent having at least practical utility. Unless otherwise specified, substituents are named into the core structure. For example, it is to be understood that when (cycloalkyl)alkyl is listed as a possible substituent, the point of attachment of this substituent to the core structure is in the alkyl portion.

[055] The terms "substituted" alkyl, alkenyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl (including "substituted" pyridinyl, pyrimidinyl, pyrazinyl, quinolinyl, pyrazolyl, and thiazolyl"), unless otherwise expressly defined, refer respectively to alkyl, alkenyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl wherein one or more (such as up to 5, for example, up to 3) hydrogen atoms are replaced by a substituent independently chosen from:

- R<sup>a</sup>, -OR<sup>b</sup>, -O(CrC<sub>2</sub> alkyl)O- (e.g., methylenedioxy-), -SR<sup>b</sup>, guanidine, guanidine wherein one or more of the guanidine hydrogens are replaced with a lower-alkyl group, -NR<sup>b</sup>R<sup>f</sup>, halo, cyano, oxo (as a substituent for heterocycloalkyl), nitro, -COR<sup>b</sup>, -CO<sub>2</sub>R<sup>b</sup>, -CONR<sup>b</sup>R<sup>f</sup>, -OCOR<sup>b</sup>, -OCO<sub>2</sub>R<sup>a</sup>, -OCON R<sup>b</sup>R<sup>f</sup>, -NR<sup>c</sup>COR<sup>b</sup>, -NR<sup>c</sup>CO<sub>2</sub>R<sup>a</sup>, -NR<sup>c</sup>CONR<sup>b</sup>R<sup>f</sup>, -SOR<sup>a</sup>, -SO<sub>2</sub>R<sup>a</sup>, -SO<sub>2</sub>NR<sup>b</sup>R<sup>f</sup>, and -NR<sup>c</sup>SO<sub>2</sub>R<sup>a</sup>,
where $R^a$ is chosen from optionally substituted CrC$_6$ alkyl, optionally substituted C$_2$-C$_6$ alkenyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, and optionally substituted heteroaryl;

$R^b$ is chosen from hydrogen, optionally substituted CrC$_6$ alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, and optionally substituted heteroaryl; and

$R^c$ is chosen from hydrogen and optionally substituted C$_1$-C$_4$ alkyl; or

$R^b$ and $R^c$, and the nitrogen to which they are attached, form an optionally substituted heterocycloalkyl group; and

where each optionally substituted group is unsubstituted or independently substituted with one or more, such as one, two, or three, substituents independently selected from CrC$_4$ alkyl, aryl, heteroaryl, aryl-C$_r$, C$_r$ alkyl-, heteroaryl-C$_r$, C$_r$ alkyl-, CrC$_4$ haloalkyl-, -Od-C$_4$ alkyl, -Od-C$_4$ alkylphenyl, -Ci-C$_4$ alkyl-OH, -Od-C$_4$ haloalkyl, halo, -OH, -NH$_2$, -d-C$_4$ alkyl-NH$_2$, -N(CrC$_4$ alkyl)(C$_r$, C$_4$ alkyl), -NH(CrC$_4$ alkyl), -N(CrC$_4$ alkyl)(C$_r$, C$_4$ alkylphenyl), -NH(CrC$_4$ alkylphenyl), cyano, nitro, oxo (as a substituent for heteroaryl), -CO$_2$H, -C(O)Od-C$_4$ alkyl, -CON(CrC$_4$ alkyl)(Ci-C$_4$ alkyl), -CONH(CrC$_4$ alkyl), -CONH$_2$, -NHC(O)(CrC$_4$ alkyl), -NHC(O)(phenyl), -N(CrC$_4$ alkyl)C(O)(C$_r$, C$_4$ alkyl), -N(CrC$_4$ alkyl)C(O)(phenyl), -(O(O)CrC$_4$ alkyl, -SO$_2$(CrC$_4$ alkyl), -SO$_2$(phenyl), -SO$_2$(CrC$_4$ haloalkyl), -SO$_2$NH$_2$, -SO$_2$NH(CrC$_4$ alkyl), -SO$_2$NH(phenyl), -NHSO$_2$(CrC$_4$ alkyl), -NHSO$_2$(phenyl), and -NHSO$_2$(CrC$_4$ haloalkyl).

[056] In some embodiments, the terms "substituted" alkyl, alkenyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl (including "substituted" pyridinyl, pyrimidinyl, pyrazinyl, quinolinyl, pyrazolyl, and thiazolyl), unless otherwise expressly defined, refer respectively to alkyl, alkenyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl wherein one or more (such as up to 5, for example, up to 3) hydrogen atoms are replaced by a substituent independently chosen from: -R$_a$, -OR$_b$, -COR$_b$, -CO$_2$R$_b$, NO$_2$-NR$_b$R$_c$, -NR$_c$COR$_b$, -NR$_c$CO$_2$R$_a$, -NR$_c$CONR$_b$R$_c$, -NR$_c$SO$_2$R$_a$ and CN, where $R_a$, $R_b$, and $R_c$ are as described herein.

[057] The term "substituted acyl" refers to the groups (substituted alkyl)-C(O)-, (substituted cycloalkyl)-C(O)-, (substituted aryl)-C(O)-, (substituted heteroaryl)-C(O)-, and (substituted heterocycloalkyl)-C(O)-, wherein substituted alkyl, substituted cycloalkyl, substituted aryl, substituted heteroaryl, and substituted heterocycloalkyl
are as described herein. In some embodiments, the term "substituted acyl" refers to the groups (substituted alkyl)-C(O)-, (substituted aryl)-C(O)-, and (substituted heteroaryl)-C(O)-, wherein substituted alkyl, substituted aryl, and substituted heteroaryl are as described herein.

[058] The term "substituted alkoxy carbonyl" refers to the group (substituted alkyl)-0-C(O)- wherein the group is attached to the parent structure through the carbonyl functionality and wherein "substituted alkyl" is as described herein.

[059] The term "substituted cycloalkoxy" refers to cycloalkyloxy wherein the cycloalkyl constituent is substituted (i.e., -O-(substituted cycloalkyl)) wherein "substituted cycloalkyl" is as described herein.

[060] The term "substituted amino" refers to the group -NR\(^b\)R\(^e\), -NR\(^c\)COR\(^b\), -NR\(^c\)CO\(_2\)R\(^a\), -NR\(^c\)CONR\(^b\)R\(^e\), and -NR\(^c\)SO\(_2\)R\(^a\), wherein R\(^b\) and R\(^e\) are as described herein. The term "substituted amino" also refers to N-oxides of the groups -NH R\(^d\), and NR\(^d\)R\(^d\) each as described herein. N-oxides can be prepared by treatment of the corresponding amino group with, for example, hydrogen peroxide or m-chloroperbenzoic acid. The person skilled in the art is familiar with reaction conditions for carrying out the N-oxidation.

[061] The term "substituted aryl oxy" refers to arloxy wherein the aryl constituent is substituted (i.e., -O-(substituted aryl)) wherein "substituted aryl" is as described herein.

[062] Compounds described herein include, but are not limited to, any stereoisomer, tautomer, rotomer, deuterated analogues, and/or pharmaceutically acceptable salt as defined herein.

[063] The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated.

[064] Compounds that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. The processes described herein can be stereoselective such that any given reaction starting with one or more chiral reagents enriched in one stereoisomer forms a product that is also enriched in one stereoisomer. The reaction can be conducted such that the product of the reaction substantially retains one or more chiral centers present in the
starting materials. The reaction can also be conducted such that the product of the reaction contains a chiral center that is substantially inverted relative to a corresponding chiral center present in the starting materials.

[065] Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional crystallization using a "chiral resolving acid" which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyletartraric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β-camphorsulfonic acid. Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (e.g., dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

[066] Compounds as described herein can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

[067] The compounds disclosed herein can be used in different enriched isotopic forms, e.g., enriched in the content of $^2$H, $^3$H, $^{11}$C, $^{13}$C, $^{14}$C, and or $^{16}$F. In one particular embodiment, the compounds are deuterated. Such deuterated forms can be made by the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997. As described in U.S. Patent Nos. 5,846,514 and 6,334,997, deuteration can improve the efficacy and increase the duration of action of drugs.


[069] Compounds as described herein can also include tautomeric forms, such as keto-enol tautomers. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.
Compounds as described herein also include crystalline and amorphous forms of those compounds, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof. "Crystalline form," "polymorph," and "novel form" may be used interchangeably herein, and are meant to include all crystalline and amorphous forms of the compound, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to. Compounds as described herein also include pharmaceutically acceptable forms of the recited compounds, including chelates, non-covalent complexes, pharmaceutically acceptable prodrugs, and mixtures thereof.

A "solvate" is formed by the interaction of a solvent and a compound. The term "compound" is intended to include solvates of compounds. Similarly, "salts" includes solvates of salts. Similarly, "salts" includes solvates of salts. Suitable solvates are pharmaceutically acceptable solvates, such as hydrates, including monohydrates and hemi-hydrates.

A "chelate" is formed by the coordination of a compound to a metal ion at two (or more) points. The term "compound" is intended to include chelates of compounds. Similarly, "salts" includes chelates of salts.

A "non-covalent complex" is formed by the interaction of a compound and another molecule wherein a covalent bond is not formed between the compound and the molecule. For example, complexation can occur through van der Waals interactions, hydrogen bonding, and electrostatic interactions (also called ionic bonding). Such non-covalent complexes are included in the term "compound".

Compound 47 refers to 4-((4-terf-butylphenylsulfonamido)methyl)- N-(pyridin-3-yl)benzamide, a preparation of which is shown in Example 38. Compound 85 refers to 4-((4-(methylpiperazin-1 -y1)phenylsulfonamido)methyl)- N-(pyridin-3-yl)benzamide, a preparation of which is shown in Example 76. Compound 116 refers to 4-[[[(4-(21-amino-4,7,1 0,1 3,1 6,1 9-hexaoxahenicos-1 -yn-1 -y1)phenyl)sulfonyl]amino)methyl]- N-(3-pyridinyl)benzamide, a preparation of which is shown in Example 100.

Provided is at least one compound of Formula I:
or a pharmaceutically acceptable salt thereof,
wherein:
A is a nitrogen-containing heteroaryl ring chosen from pyridinyl, pyrimidinyl, pyrazinyl, quinolinyl, pyrazolyl, imidazolyl, and thiazolyl, each of which is optionally substituted;

\[
\begin{array}{c}
A \\
\text{is attached to the phenyl ring at either the 3 or 4 position;} \\
R_1, R_2, \text{ and } R_3 \text{ are each independently chosen from hydrogen, optionally substituted alkyl, and optionally substituted alkenyl;}
\end{array}
\]

\[
R_4 \text{ is chosen from hydrogen, hydroxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, halo, carboxy, nitro, sulfonyl, sulfinyl, and optionally substituted amino;}
\]

W is chosen from \(-\text{NRSO}_2\), \(-\text{SO}_2\text{NR}\), and \(-\text{NRCO}\), wherein each R is independently chosen from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, each of which, except for hydrogen, is optionally substituted; and

B is an optionally substituted aryl ring,

provided that if A is 3-pyridinyl, \(R_1\), \(R_2\), and \(R_3\) are each hydrogen, and W is \(-\text{NHSO}_2\), then B is not 3-methoxyphenyl, 3,4-dimethylphenyl, 2,3,4-trifluorophenyl, 2,3,5,6-tetramethylphenyl, 2,5-dimethylphenyl, 3-chlorophenyl, 3-trifluoromethylphenyl, 4-methoxyphenyl, 4-tertbutylphenyl, 4-fluorophenyl, or 4-acetyphenyl.

[076] In some embodiments, A is chosen from 2-thiazolyl, 3-pyrazolyl, 3-quinolinyl, 5-quinolinyl, 2-pyrazinyl, 2-pyrimidinyl, 2-pyridinyl, 3-pyridinyl, and 4-pyridinyl, each of which is optionally substituted. In some embodiments, A is chosen from 2-thiazolyl, 3-pyrazolyl, 3-quinolinyl, 5-quinolinyl, 2-pyrazinyl, 2-pyrimidinyl, 2-pyridinyl, 3-pyridinyl, and 4-pyridinyl,
3-pyridinyl, and 4-pyridinyl. In some embodiments, A is chosen from 2-pyridinyl, 3-pyridinyl, and 4-pyridinyl. In some embodiments, A is 3-pyridinyl.

[077] In some embodiments, A is \((R_5)_n\)

wherein

n is 0, 1 or 2;

for each occurrence, \(R_5\) is independently chosen from alkyl optionally substituted with one or more halo, alkoxy, halo, nitro, heterocycloalkyl, and amino optionally substituted with C(O)R, wherein \(R_6\) is chosen from alkyl and optionally substituted alkoxy; and

\(X_1\) and \(X_2\) are each independently chosen from \(N\), \(NO\), and \(CH\), provided that at least one of \(X_1\) and \(X_2\) is not \(CH\).

[078] In some embodiments, \(X_1\) is \(N\) and \(X_2\) is \(CH\).

[079] In some embodiments, for each occurrence, \(R_5\) is independently chosen from methyl, methoxy, halo, nitro, morpholino, trifluoromethyl, and NHC(O)Me.

[080] In some embodiments, n is 0.

[081] In some embodiments, \(R_1\) is chosen from hydrogen and optionally substituted alkyl. In some embodiments, \(R_1\) is chosen from hydrogen and lower alkyl. In some embodiments, \(R_1\) is hydrogen or methyl. In some embodiments, \(R_1\) is hydrogen.

[082] In some embodiments, \(R_2\) and \(R_3\) are each independently chosen from hydrogen and optionally substituted alkyl. In some embodiments, \(R_2\) is hydrogen.

[083] In some embodiments, \(R_3\) is chosen from hydrogen and lower alkyl. In some embodiments, \(R_3\) is hydrogen.

[084] In some embodiments, \(R_4\) is chosen from hydrogen, hydroxy, lower alkyl, lower alkoxy, halo, carboxy, and nitro. In some embodiments, \(R_4\) is chosen from hydrogen, methyl, halo, and nitro. In some embodiments, \(R_4\) is chosen from hydrogen and lower alkyl. In some embodiments, \(R_4\) is hydrogen.

[085] In some embodiments, W is -NRSO₂. In some embodiments, W is -NRCO-. In some embodiments, W is SO₂NR-.

[086] In some embodiments, R is chosen from hydrogen and lower alkyl. In some embodiments, R is hydrogen.
In some embodiments, B is an optionally substituted phenyl ring.

In some embodiments, B is phenyl optionally substituted with one or more groups chosen from halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, hydroxyl, alkoxy, carboxy, alkoxy carbonyl, NO₂, optionally substituted amino, and CN, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, alkoxy, and aryloxy groups may be optionally independently substituted with one or more groups chosen from halo, alkyl, hydroxyl, alkoxy, carboxy, alkoxy carbonyl, heterocycloalkyl, and optionally substituted amino.

In some embodiments, B is phenyl optionally substituted with one or more groups chosen from optionally substituted amino, halo, and lower alkyl optionally substituted with optionally substituted amino, heterocycloalkyl, alkoxy, or hydroxyl.

In some embodiments, B is phenyl optionally substituted with one or more groups chosen from halo, optionally substituted amino and lower alkyl optionally substituted with optionally substituted amino or heterocycloalkyl.

In some embodiments, B is chosen from phenyl, 2-methylphenyl, 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 2-methoxycarbonylphenyl, 2 trifluoromethylphenyl, 2-cyanophenyl, 3-aminophenyl, 3-methoxyphenyl, 3-methylphenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-trifluoromethylphenyl, t-butylphenyl, 4-ethynylphenyl, 3-cyanophenyl, 3-nitrophenyl, 3-phenylphenyl, 3-(2-pyrimidinyl)phenyl, 3-(1-methyl-1H-pyrazol-3-yl)phenyl, 3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl, 3-(2-methyl-1,3-thiazol-4-yl)phenyl, 3-aminophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-iodophenyl, 4-trifluoromethoxyphenyl, 4-methoxycarboxyphenyl, 4-acetylphenyl, 4-methoxyphenyl, 4-tert-butylphenyl, 4-(3-chloro-1-adamantyl)phenyl, 4-(3-chloro-1-adamantyl)phenyl, 4-tert-butylphenyl, 4-acetoxyphenyl, 4-methoxyphenyl, 4-propylphenyl, 4-tert-butylphenyl, 4-(1-adamantyl)phenyl, 4-(3-chloro-1-adamantyl)phenyl, 4-methoxyphenyl, 4-acetamidophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-iodophenyl, 4-trifluoromethoxyphenyl, 4-methoxycarboxyphenyl, 4-acetylphenyl, 4-trifluoromethylphenyl, 4-cyanophenyl, 4-nitrophenyl, 4'-methoxy[1',1'-biphenyl]-4-yl, 4'-methyl[1',1'-biphenyl]-4-yl, 4'-fluoro[1',1'-biphenyl]-4-yl, 4'-chloro[1',1'-biphenyl]-4-yl, 4-(2-pyrimidinyl)phenyl, 4-(2-methyl-1,3-thiazol-4-yl)phenyl, 4-(1,3-oxazol-5-yl)phenyl, 3,4-dimethoxyphenyl, 3-tert-butyl-4-methoxyphenyl, 2,3,4,5,6-pentamethylphenyl, 2,4-dimethylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 3-fluoro-4-methylphenyl, 3-chloro-2-methylphenyl, 3,4-dichlorophenyl, 3-cyano-4-fluorophenyl,
2-naphthalenyl, 5-(dimethylamino)-2-naphthalenyl, 2,3-dihydro-5-indeneyl, 2-
(dimethylamino)-2,3-dihydro-5-indeneyl, 4-(4-methylpiperazin-1-yl)phenyl, A-
(dimethylamino)methylphenyl, 4-(diethylamino)methylphenyl, A-
(dipropylamino)methylphenyl, 4-(1-pyrrolidinylmethyl)phenyl, 4-(1-
piperidinylmethyl)phenyl, 4-(1-azepanyl)methylphenyl, 4-(4-methylpiperazin-1-
yl)phenyl, 4-(4-methoxy-1-piperazinyl)methylphenyl, 4-(1-piperidinyl)phenyl, 4-
(1-piperidinylmethyl)phenyl, 4-(1-piperidinyl)methylphenyl, 4-(1-piperidinyl)-
methylphenyl, 4-(1-piperidinyl)methylphenyl, 4-(1-piperidinyl)methylphenyl, 4-
(4-morpholinyl)methylphenyl, 4-(4-methoxy-1-piperazinyl)methylphenyl, (21-
amino-4,7,10.1 3.1 6.19-hexaoxahenicos-1-yl)phenyl, ([3-(4-
morpholinyl)propyl]amino)phenyl, 3-(4-methyl-1-piperazinyl)phenyl, 4-[(2-
(dimethylamino)ethyl]amino)phenyl, 3'-(trifluoromethyl)[1,1'-biphenyl], A-
benzylphenyl, 4-[3-(4-morpholinyl)-1-propynyl]phenyl, 4-[3-(4-morpholinyl)-
propynyl]phenyl, 4-[3-(4-morpholinyl)propyl]phenyl, 3-(4-methyl-1-piperazinyl)
phenyl, 3-(propionylamino)phenyl, and 3-(acryloyl)aminophenyl.

[092] In some embodiments, B is chosen from phenyl, 2-methylphenyl, 2-
fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 2-methoxycarbonylphenyl, 2-
trifluoromethylphenyl, 2-cyanophenyl, 3-aminophenyl, 3-methoxyphenyl, 3-
methoxyphenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-
trifluoromethylphenyl, 3-(2-pyrimidinyl)phenyl, 3-(pyridinyl)phenyl, 3-(1-
methyl-1H-pyrazol-3-yl)phenyl, 3-(pyridinyl)phenyl, 3-(4-oxadiazol-2-yl)phenyl, 3-
(2-pyrimidinyl)phenyl, 3-(4-oxadiazol-2-yl)phenyl, 3-(2-pyrimidinyl)phenyl, 4-
aminophenyl, 4-methoxyphenyl, 4-butoxyphenyl, 4-phenoxyphenyl, 4-methylphenyl, 4-propylphenyl, 4-tert-butylphenyl, 4-(1-adamantyl)phenyl, 4-(3-chloro-1-
adamantyl)phenyl, A-
methoxycarbonylethylphenyl, 4-acetamidophenyl, 4-fluorophenyl, 4-chlorophenyl, A-
bromophenyl, 4-iodophenyl, 4-trifluoromethoxyphenyl, 4-methoxycarbonylphenyl, A-
acetylphenyl, 4-trifluoromethylphenyl, 4-cyanophenyl, 4-nitrophenyl, 4'-methoxy[1,1-
biphenyl]-4-yl, 4'-methyl[1,1'-biphenyl]-4-yl, 4-phenylphenyl, 4'-fluoro[1,1-
biphenyl]-4-yl, 4'-chloro[1,1'-biphenyl]-4-yl, 4-(2-pyrimidinyl)phenyl, 4-(1-
/1'-pyrazol-1-yl)phenyl, A-
(2-methyl-1,3-thiazol-4-yl)phenyl, 4-(1,3-oxazol-5-yl)phenyl, 3,4-dimethoxyphenyl, 3-
tert-butyl-4-methoxyphenyl, 2,3,4,5,6-pentamethylphenyl, 2,4-dimethylphenyl, 3,4-
dimethylphenyl, 3,5-dimethylphenyl, 3-fluoro-4-methylphenyl, 3-chloro-2-
methylphenyl, 3-chloro-4-methylphenyl, 3,4-dichlorophenyl, 3-cyano-4-fluorophenyl,
2-naphthalenyl, 5-(dimethylamino)-2-naphthalenyl, 2,3-dihydro-5-indeneyl, 2-(dimethylamino)-2,3-dihydro-5-indeneyl, 4-(4-methylpiperazin-1-yl)phenyl, A-(dimethylamino)methylphenyl, 4-(diethylamino)methylphenyl, A-(dipropylamino)methylphenyl, 4-(1-pyrrolidinylmethyl)phenyl, 4-(1-piperidinylmethyl)phenyl, 4-(1-azepanyl)methylphenyl, 4-(4-morpholinylmethyl)phenyl, 4-(4-methoxy-1-piperidinyl)methylphenyl, and 4-(4-methyl-1-piperazinyl)methylphenyl.

[093] In some embodiments, B is chosen from 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-(2-pyrimidinyl)phenyl, 3-(1-methyl-1/-/-pyrazol-3-yl)phenyl, 3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl, 3-(5-methyl-1,2,4-oxadiazol-2-yl)phenyl, A-butoxyphenyl, 4-tert-butylphenyl, 4-(2-pyrimidinyl)phenyl, 3,4-dimethoxyphenyl, 3-tert-butyl-4-methoxyphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 3-fluoro-4-methylphenyl, 3-chloro-4-methylphenyl, 2-(dimethylamino)-2,3-dihydro-5-indeneyl, A-(4-methylpiperazin-1-yl)phenyl, 4-(dimethylamino)methylphenyl, A-(diethylamino)methylphenyl, 4-(dipropylamino)methylphenyl, 4-(1-pyrrolidinylmethyl)phenyl, 4-(1-piperidinylmethyl)phenyl, 4-(1-azepanyl)methylphenyl, 4-(4-morpholinylmethyl)phenyl, 4-(4-methoxy-1-piperidinyl)methylphenyl, 4-(4-methyl-1-piperazinyl)methylphenyl, and 4-(3-hydroxypropyl)phenyl.

[094] In some embodiments, the radical is attached to the phenyl ring at the 3 position. In some embodiments, the radical is attached to the phenyl ring at the 4 position.

[095] Also provided is at least one compound of Formula II

or a pharmaceutically acceptable salt thereof, wherein $X_1, X_2, W, R_1, R_2, R_3, R_4, R_5, n$, and B are as described herein.
[096] Also provided is at least one compound chosen from:
4-(Phenylsulfonamidomethyl)- \(\text{N-}(\text{pyridin-2-yl})\text{benzamide;}
4-(Phenylsulfonamidomethyl)- \(\text{N-}(\text{pyridin-3-yl})\text{benzamide;}
4-(Phenylsulfonamidomethyl)- \(\text{N-}(\text{pyridin-4-yl})\text{benzamide;}
4-(Phenylsulfonamidomethyl)- \(\text{N-}(\text{thiazol-2-yl})\text{benzamide;}
4-(Phenylsulfonamidomethyl)- \(\text{N-}(\text{7/-/-pyrazol-3-yl})\text{benzamide;}
4-(Phenylsulfonamidomethyl)- \(\text{N-}(\text{quinolin-3-yl})\text{benzamide;}
4-(Phenylsulfonamidomethyl)- \(\text{N-}(\text{quinolin-5-yl})\text{benzamide;}
4-(Phenylsulfonamidomethyl)- \(\text{N-}(\text{pyrazin-2-yl})\text{benzamide;}
4-(Phenylsulfonamidomethyl)- \(\text{N-}(\text{pyrimidin-2-yl})\text{benzamide;}
4-((2-Methylphenylsulfonamido)methyl)- \(\text{N-}(\text{pyridin-3-yl})\text{benzamide;}
4-((2-Fluorophenylsulfonamido)methyl)- \(\text{N-}(\text{pyridin-3-yl})\text{benzamide;}
4-((2-Chlorophenylsulfonamido)methyl)- \(\text{N-}(\text{pyridin-3-yl})\text{benzamide;}
4-((2-Bromophenylsulfonamido)methyl)- \(\text{N-}(\text{pyridin-3-yl})\text{benzamide;}
Methyl 2-((\text{N-}(4-(\text{Pyridin-3-ylcarbamoyl})\text{benzyl})\text{sulfamoyl})\text{benzoate;}
\(\text{N-}(\text{Pyridin-3-yl})\text{-4-}((\text{trifluoromethyl})\text{phenylsulfonamido})\text{methyl})\text{benzamide;}
4-((2-Cyanophenylsulfonamido)methyl)- \(\text{N-}(\text{pyridin-3-yl})\text{benzamide;}
4-((3-Aminophenylsulfonamido)methyl)- \(\text{N-}(\text{pyridin-3-yl})\text{benzamide;}
4-((3-Methylphenylsulfonamido)methyl)- \(\text{N-}(\text{pyridin-3-yl})\text{benzamide;}
4-((3-Chlorophenylsulfonamido)methyl)- \(\text{N-}(\text{pyridin-3-yl})\text{benzamide;}
4-((3-Fluorophenylsulfonamido)methyl)- \(\text{N-}(\text{pyridin-3-yl})\text{benzamide;}
4-((3-Bromophenylsulfonamido)methyl)- \(\text{N-}(\text{pyridin-3-yl})\text{benzamide;}
4-((3-Cyanophenylsulfonamido)methyl)- \(\text{N-}(\text{pyridin-3-yl})\text{benzamide;}
4-((3-Nitrophenylsulfonamido)methyl)- \(\text{N-}(\text{pyridin-3-yl})\text{benzamide;}
4-[[1.1'-Biphenyl]-3-ylsulfonyl]amino)methyl]- \(\text{N-}(\text{3-pyridinyl})\text{benzamide;}
4-[[3-(2-Pyridinyl)phenyl]sulfonyl][amino)methyl]- \(\text{N-}(\text{3-pyridinyl})\text{benzamide;}
4-[[3-(1-Methyl-1/-/-pyrazol-3-yl)phenyl]sulfonyl][amino)methyl]- \(\text{N-}(\text{3-pyridinyl})\text{benzamide;}
4-[[3-(5-Methyl-1 ,3,4-oxadiazol-2-yl)phenyl]sulfonyl][amino)methyl]- \(\text{N-}(\text{3-pyridinyl})\text{benzamide;}
4-[[3-(5-Methyl-1 ,2,4-oxadiazol-3-yl)phenyl]sulfonyl][amino)methyl]- \(\text{N-}(\text{3-pyridinyl})\text{benzamide;}
4-[[3-(2-Methyl-1 ,3-thiazol-4-yl)phenyl]sulfonyl][amino)methyl]- \(\text{N-}(\text{3-pyridinyl})\text{benzamide;}
4-((4-Aminophenylsulfonamido)methyl)- \(\text{N-}(\text{pyridin-3-yl})\text{benzamide;}
4-((4-Butoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Phenoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Methylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Propylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-[(4-(1-Adamantyl)phenyl)sulfonyl]amino)methyl]-N-(3-pyridinyl)benzamide;
4-[(4-(3-Chloro-1-adamantyl)phenyl)sulfonyl]amino)methyl]-N-(3-pyridinyl)benzamide;
Methyl 3-[(4-[(3-Pyridinylamino)carbonyl]benzyl]amino)sulfonyl]phenyl]propanoate;
4-((4-Acetamidophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Chlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Bromophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
N-(Pyridin-3-yl)-4-((4-(trifluoromethoxy)phenylsulfonamido)methyl)b θ nzamid θ;
Methyl 4-((N-(4-(Pyridin-3-ylcarbamoyl)benzyl]amino)sulfonyl]phenyl]propanoate;
4-((4-(Pyridin-3-yl)-4-((4-(trifluoromethyl)phenylsulfonamido)methyl)b θ nzamid θ;
4-((4-Nitrophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((Biphenyl-4-ylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4'-Methoxy[1',1'-biphenyl]-4-yl)sulfonyl]amino)methyl]-N-(3-pyridinyl)benzamide;
4-((4'-Methyl[1',1'-biphenyl]-4-yl)sulfonyl]amino)methyl]-N-(3-pyridinyl)benzamide;
4-((4'-Fluoro[1',1'-biphenyl]-4-yl)sulfonyl]amino)methyl]-N-(3-pyridinyl)benzamide;
4-((4'-Chloro[1',1'-biphenyl]-4-yl)sulfonyl]amino)methyl]-N-(3-pyridinyl)benzamide;
Methyl 4-((3,4-Dimethoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3,4-Dimethoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3,4-Dimethoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3,4-Dimethoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3,4-Dimethoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3,4-Dimethoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3,4-Dimethoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3-Chloro-2-methylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3-Chloro-4-methylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3,4-Dichlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3-Cyano-4-fluorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((Naphthalene-2-sulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((5-(Dimethylamino)naphthalene-1-sulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((2,3-Dihydro-1H-indene-5-sulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
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4-tetra-Butyl-N-(pyridin-3-ylcarbamoyl)benzamide;
4-(4-(4-tert-Butylphenylsulfonamido)methyl)-N-methyl-N-(pyridin-3-yl)benzamide;
N-Methyl-4-(phenylsulfonamidomethyl)-N-(pyridin-3-yl)benzamide;
3-(4-(4-tert-Butylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
3-(Phenylsulfonamidomethyl)-N-(pyridin-3-yl)benzamide;
3-(4-(Phenylsulfonamidomethyl)benzamido)pyridine 1-oxide;
4-((4-Iodophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Bromophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Fluorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
3,5-Dimethyl-\&-(4-(pyridin-3-ylcarbamoyl)benzyl)benzamide;
3,4-Dimethoxy-\&-(4-(pyridin-3-ylcarbamoyl)benzyl)benzamide;
4-[[4-[3-(Methoxy)-1-propynyl]phenyl)sulfonyl]amino]methyl-\&-(3-pyridinyl)benzamide;
4-[[4-(21-Amino-4,7,1 0,1 3,1 6,1 9-hexaoxahenicos-1-yn-1-yl)phenyl)sulfonyl]amino]methyl-\&-(3-pyridinyl)benzamide;
4-[[4-(3-Methoxypropyl)phenyl)sulfonyl]amino]methyl-\&-(3-pyridinyl)benzamide;
4-[[4-(3-Hydroxy-1-propynyl)phenyl)sulfonyl]amino]methyl-\&-(3-pyridinyl)benzamide;
4-[[4-(3-Hydroxypropyl)phenyl)sulfonyl]amino]methyl-\&-(3-pyridinyl)benzamide;
4-[[4-(1-benzyl-1H,2,3-triazol-4-yl)phenyl)sulfonyl]amino]methyl-\&-(3-pyridinyl)benzamide;
4-[[4-(1-benzyl-1H,2,3-triazol-4-yl)phenyl)sulfonyl]amino]methyl-\&-(3-pyridinyl)benzamide;
4-[[4-(1-benzyl-1H,2,3-triazol-4-yl)phenyl)sulfonyl]amino]methyl-\&-(3-pyridinyl)benzamide;
4-[[4-(1-benzyl-1H,2,3-triazol-4-yl)phenyl)sulfonyl]amino]methyl-\&-(3-pyridinyl)benzamide;
4-[[4-(1-benzyl-1H,2,3-triazol-4-yl)phenyl)sulfonyl]amino]methyl-\&-(3-pyridinyl)benzamide;
4-[[4-(1-benzyl-1H,2,3-triazol-4-yl)phenyl)sulfonyl]amino]methyl-\&-(3-pyridinyl)benzamide;
4-[[4-(1-benzyl-1H,2,3-triazol-4-yl)phenyl)sulfonyl]amino]methyl-\&-(3-pyridinyl)benzamide;
4-[[4-(1-benzyl-1H,2,3-triazol-4-yl)phenyl)sulfonyl]amino]methyl-\&-(3-pyridinyl)benzamide;
4-[[4-(1-benzyl-1H,2,3-triazol-4-yl)phenyl)sulfonyl]amino]methyl-\&-(3-pyridinyl)benzamide;
4-(((4-tor-Butylphenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(6-fluoro-3-pyridinyl)benzamide;
4-(((4-tor-Butylphenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(5-fluoro-3-pyridinyl)benzamide;
4-(((4-tor-Butylphenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(4-(trifluoromethyl)-3-pyridinyl)benzamide;
4-(((4-tor-Butylphenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(2-fluoro-3-pyridinyl)benzamide;
4-(((4-tor-Butylphenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(4-methoxy-3-pyridinyl)benzamide;
\(\text{N}^\prime\)-(6-Bromo-3-pyridinyl)-4-(((4-fer-Butylphenyl)sulfonyl]amino)methyl)benzamide;
4-(((3-(4-Morpholinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(4-Morpholinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(1-Piperidinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(1-Piperidinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(21-Amino-4,7,1,0,1,3,1,6,1,9-hexaoxahenicos-1-yl]phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(3-Morpholinyl)propyl]phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(4-Methyl-1-piperazinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(2-(Dimethylamino)ethyl]phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(3-(4-Morpholinyl)propyl]phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(3-(Dimethylamino)propyl]phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((3-(Propionylamino)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(3-(4-Morpholinyl)-1-propynyl]phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(3-(Dimethylamino)-1-propynyl]phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(4-(1-Piperidinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(4-(1-Piperidinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(4-(1-Piperidinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(4-(1-Piperidinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(4-(1-Piperidinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(4-(1-Piperidinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(4-(1-Piperidinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(4-(1-Piperidinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(4-(1-Piperidinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(4-(1-Piperidinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(4-(1-Piperidinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(4-(1-Piperidinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-(((4-(4-(1-Piperidinyl)phenyl)sulfonyl]amino)methyl)-\(\text{N}^\prime\)-(3-pyridinyl)benzamide;
4-[[[3-(Acryloylamino)phenyl]sulfonyl]amino)methyl]-N-(3-pyridinyl)benzamid;  
4-[[[4-(t-Butylphenyl)sulfonyl]amino)methyl]-2-methyl-N-(3-pyridinyl)benzamid;  
4-[[[4-torf-Butylphenyl)sulfonyl]amino)methyl]-2-fluoro-N-(3-pyridinyl)benzamid;  
4-[[[4-torf-Butylphenyl)sulfonyl]amino)methyl]-3-methyl-N-(3-pyridinyl)benzamid;  
4-[[[4-torf-Butylphenyl)sulfonyl]amino)methyl]-3-fluoro-N-(3-pyridinyl)benzamid;  
4-(1-[[[4-torf-Butylphenyl)sulfonyl]amino)thyl]-N-(3-pyridinyl)benzamid;  
4-[[anilinosulfonyl)methyl]-N-(3-pyridinyl)benzamid;  
4-[[4-(4-tert-butylanilino)sulfonyl]methyl]-N-(3-pyridinyl)benzamid;  
4-[[4-(4-fluoroanilino)sulfonyl]methyl]-N-(3-pyridinyl)benzamid;  
4-[[4-(4-methyl-1-piperazinyl)anilino)sulfonyl]methyl]-N-(3-pyridinyl)benzamid;  
4-(1-(4-(t-Butyl)phenylsulfonamido)thyl)-N-(3-pyridinyl)benzamide;  
4-(4-fluoroanilin)sulfonyl][methyl]-N-(3-pyridinyl)benzamide;  
4-[[4-(4-fluorophenyl)sulfamoyl)methyl]-N-(3-pyridinyl)benzamide;  
4-[[4-(4-tert-butylphenyl)sulfamoyl)methyl]-N-(3-pyridinyl)benzamide;  
4-[[4-(4-(4-methylpiperazin-1-yl)phenyl)sulfamoyl)methyl]-N-(3-pyridinyl)benzamide;  
or a pharmaceutically acceptable salt thereof.

[097] The methods described herein comprise administering to a subject in need thereof, a therapeutically acceptable amount at least one compound or pharmaceutically acceptable salt thereof described above.

[098] In addition to those compounds and pharmaceutically acceptable salts described above, the methods described herein also may comprise the administration of at least one compound chosen from:

4-[(3-Methoxyphenylsulfonamido)methyl]-N-(pyridin-3-yl)benzamide;  
4-[(3,4-dimethylphenylsulfonamido)methyl]-N-(pyridin-3-yl)benzamide;  
3-[((3,4-dimethylphenylsulfonamido)methyl]-N-(pyridin-3-yl)benzamide;  
N-(pyridin-3-yl)-3-((2,3,4-thiophenylsulfonamido)methyl)benzamide;  
N-(pyridin-3-yl)-4-((2,3,4-thiophenylsulfonamido)methyl)benzamide;  
N-(pyridin-3-yl)-3-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;  
N-(pyridin-3-yl)-4-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
3-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide; 4-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide; 4-((3-Chlorophenylsulfonamido)methyl)-N'-(pyridin-3-yl)b θnzamid θ,
4-((4-Methoxyphenylsulfonamido)methyl)-N'-(pyridin-3-yl)b θnzamid θ,
3-((4-tert-Butylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
4-((4-Fluorophenylsulfonamido)methyl)-N'-(pyridin-3-yl)b θnzamid θ, and
4-((4-Acetylphenylsulfonamido)methyl)-N'-(pyridin-3-yl)b θnzamid θ, or a pharmaceutically acceptable salt thereof.

[099] In some embodiments, the subject is a mammal. In some embodiments, the subject is a human.

[0100] The compounds and pharmaceutically acceptable salts described herein can be administered alone, as mixtures, or in combination with other active agents.

[0101] Methods for obtaining the compounds and pharmaceutically acceptable salts described herein will be apparent to those of ordinary skill in the art, suitable procedures being described, for example, in the reaction schemes and examples below, and the references cited herein.

**Reaction Scheme 1**

[0102] Referring to Reaction Scheme 1, Step 1, a compound of Formula 178, is combined with an aqueous solution of base (such as NaOH in water), and treated with a compound of Formula 179, where P is a nitrogen protecting group (such as benzenesulfonyl), and L is a leaving group (such as bromide), to give a compound of Formula 180, which is isolated and optionally purified.

[0103] Referring to Reaction Scheme 1, Step 2, a mixture of a compound of Formula 180 is combined with a halogenating agent (such as oxalyl chloride), an organic base (such as pyridine), in a polar organic solvent (such as DMF and/or THF). A
compound of Formula 181 is then added to give the product, a compound of Formula 182, which is isolated and optionally purified.

[0104] Referring to Reaction Scheme 1, Step 3, a compound of Formula 182 is treated with an acidic mixture (such as hydrobromic acid and acetic acid), to provide a compound of Formula 183, where X is a halogen (such as bromide), where the product, a compound of Formula 184, is isolated and optionally purified.

[0105] Referring to Reaction Scheme 1, Step 4, a mixture of a compound of Formula 183 is combined with a compound of Formula 184, where L is a leaving group (such as chloride) and Q is a substituent group (such as carbonyl or SO₂), and an organic base (such as pyridine) to give the product, a compound of Formula 185, which is isolated and optionally purified.

**Reaction Scheme 2**

[0106] Referring to Reaction Scheme 2, Step 1B, a mixture of a compound of Formula 178 is combined with a compound of Formula 184, where L is a leaving group (such as chloride) and Q is a substituent group (such as carbonyl or SO₂), and an organic base (such as pyridine) to give the product, a compound of Formula 186, which is isolated and optionally purified.

[0107] Referring to Reaction Scheme 1, Step 2B, a mixture of a compound of Formula 186 is combined with a halogenating agent (such as oxalyl chloride), an organic base (such as pyridine), in a polar organic solvent (such as DMF and/or THF). A compound of Formula 181 is then added to give the product, a compound of Formula 185, which is isolated and optionally purified.

[0108] Also provided is a pharmaceutical composition comprising at least one compound and/or pharmaceutically acceptable salt described herein and at least one pharmaceutically acceptable carrier.

[0109] The term "pharmaceutically acceptable carrier" refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and
agents for pharmaceutically active substances is well known in the art, such as, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil or injectable organic esters. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

[0110] A pharmaceutically acceptable carrier may contain physiologically acceptable agents that act, for example, to stabilize or to increase the absorption of a compound or pharmaceutically acceptable salt thereof. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrins, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable carrier, including a physiologically acceptable agent, may depend, for example, on the route of administration of the composition. The pharmaceutical composition also may comprise a liposome or other polymer matrix, which may have incorporated therein, for example, a compound as described herein. Liposomes, for example, which consist of phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

[0111] In some embodiments, a "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent, or encapsulating material, involved in carrying or transporting the subject compounds from one organ, or portion of the body, to another organ, or portion of the body. Each carrier is typically "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials that may serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid;
(16) pyrogen-free water; (17) isotonic saline; (18) Ringer’s solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations. See Remington: The Science and Practice of Pharmacy, 20th ed. (Alfonso R. Gennaro ed.), 2000.

[0112] In some embodiments, a pharmaceutical composition comprising at least one compound and/or salt as described herein may be administered to a subject by any of a number of routes of administration including, for example, orally (for example, drenches as in aqueous or non-aqueous solutions or suspensions, tablets, boluses, powders, granules, pastes for application to the tongue); sublingually; anally, rectally, or vaginally (for example, as a pessary, cream, or foam); parenterally (including intramuscularly, intravenously, subcutaneously, or intrathecal as, for example, a sterile solution or suspension); nasally; intraperitoneal; subcutaneously; transdermal (for example as a patch applied to the skin); or topically (for example, as a cream, ointment or spray applied to the skin). At least one compound and/or salt as described herein may also be formulated for inhalation.

[0113] In some embodiments, at least one compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and compositions suitable for same can be found in, for example, U.S. Patent Nos. 6,1 10,973; 5,763,493; 5,731,000; 5,541,231; 5,427,798; 5,358,970; and 4,1 72,896, as well as in patents cited therein.

[0114] The pharmaceutical compositions described herein may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will vary depending upon the subject being treated and the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound that produces a therapeutic effect.

[0115] In some embodiments, this amount ranges from about 1 percent to about 99 percent of active ingredient.

[0116] In another embodiment, this amount ranges from about 5 percent to about 70 percent, and in a further embodiment from about 10 percent to about 30 percent.
[0117] Methods of preparing these compositions include the step of bringing into association at least one compound and/or pharmaceutically acceptable salt as described herein with at least one carrier and, optionally, one or more accessory ingredients.

[0118] In some embodiments, the pharmaceutical compositions are prepared by uniformly and intimately bringing into association at least one compound and/or pharmaceutically acceptable salt as described herein with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0119] Pharmaceutical compositions suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of at least one compound and/or salt as described herein as an active ingredient. The pharmaceutical compositions described herein may also be administered as a bolus, electuary, or paste.

[0120] In some embodiments, compounds and/or pharmaceutically acceptable salts described herein are mixed with one or more pharmaceutically acceptable excipients, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginites, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using
such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0121] In some embodiments, the tablets, and other solid dosage forms pharmaceutical compositions, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition in that they release the active ingredient(s) only, preferentially, in a certain portion of the gastrointestinal tract, optionally, or in a delayed manner. Examples of embedding compositions that may be used include polymeric substances and waxes. The active ingredient may also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0122] In some embodiments, liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils, cottonseed, groundnut, corn, germ, olive, castor oils, sesame oils, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[0123] In some embodiments, the emulsifiers are chosen from cottonseed, groundnut, corn, germ, olive, castor, and sesame oils.

[0124] Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming, and preservative agents.
Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

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

Alternatively or additionally, pharmaceutical compositions described herein may be formulated for delivery via a catheter, stent, wire, or other intraluminal device. Delivery via such devices may be especially useful for delivery to the bladder, urethra, ureter, rectum, or intestine.

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

Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams, and gels may comprise excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

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

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

[0133] Ophthalmic formulations, eye ointments, powders, solutions, and the like, may also comprise at least one of the compounds or salts as described herein.

[0134] In some embodiments, pharmaceutical compositions as described herein suitable for parenteral administration comprise at least one compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0135] Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0136] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, chelators and the like.

[0137] In some embodiments, isotonic agents, such as sugars, sodium chloride, and the like may be included into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

[0138] In some cases, in order to prolong the effect of a drug, it may be advantageous to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the
drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0139] Injectable depot forms are made by forming microencapsulated matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

[0140] Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested in vivo in recent years for the controlled delivery of drugs. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, may be used to form an implant for the sustained release of a compound at a particular target site.

[0141] As further detailed below, the pharmaceutical compositions described herein may also comprise, or may be used in combination with, one or more known cytotoxic, vascular targeting agents or chemotherapeutic agents including, but not limited to, XelodaTM (capecitabine), PaclitaxelTM, FUDR (fluorouridine) FludaraTM (fludarabine phosphate), GemzarTM (gemcitabine), methotrexate, cisplatin, carboplatin, adriamycin, avastin, tarceva, taxol, tamoxifen, Femora, temezolamide, cyclophosphamide, Erbitux, and Sutent.

[0142] In some embodiments, when pharmaceutically acceptable compositions are for human administration, the aqueous solution is pyrogen free, or substantially pyrogen free. The excipients may be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition may be in dosage unit form such as tablet, capsule, sprinkle capsule, granule, powder, syrup, suppository, injection or the like. The composition may also be present in a transdermal delivery system, e.g., a skin patch.

[0143] The term “pharmaceutically acceptable prodrugs” as used herein represents those prodrugs of a compound of Formula I, IA, or II, or a pharmaceutically
acceptable salt thereof, that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, commensurate with a reasonable benefit / risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds and pharmaceutically acceptable salts described herein.


[0144] The term "pharmaceutically acceptable salt(s)" refers to salts of acidic or basic groups that may be present in compounds used in the present compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmaceutically acceptable anions, including but not limited to hydrochloric, hydrobromic, hydriodic, sulfuric and phosphoric acid, as well as organic acids such as para-toluenesulfonic, methanesulfonic, oxalic, para-bromophenylsulfonic, carbonic, succinic, citric, benzoic and acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phththalate, terephthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycollate, maleate, tartrate, methanesulfonate, propanesulfonates, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, hippurate, gluconate, lactobionate, and the like salts.

[0145] In some embodiments, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as fumaric acid and maleic acid.
Compounds included in the present compositions, that are acidic in nature may react with any number of inorganic and organic bases to form pharmaceutically acceptable base salts. Bases may include, for example, the mineral bases, such as NaOH and KOH, but one of skill in the art would appreciate that other bases may also be used. See Ando et al., Remington: The Science and Practice of Pharmacy, 20th ed. 700-720 (Alfonso R. Gennaro ed.), 2000.

In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare non-toxic pharmaceutically acceptable addition salts.

In some embodiments, the pharmaceutically acceptable addition salts of the compounds described herein may also exist as various solvates, such as, for example, with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates may also be prepared. The source of such solvate may be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

In some embodiments, the compounds and pharmaceutically acceptable salts thereof described herein target cells which express HIF-1 α and/or HIF-2α. In some embodiments, the compounds and pharmaceutically acceptable salts thereof described herein target cells which express HIF-1 α. In some embodiments, the compounds and pharmaceutically acceptable salts thereof described herein target cells which express HIF-2α. In some embodiments, the compounds and pharmaceutically acceptable salts thereof described herein target cells which express HIF-1 α and/or HIF-2α.

In some embodiments, the compounds and pharmaceutically acceptable salts thereof described herein target cells which do not have functional VHL.

In some embodiments, the compounds and pharmaceutically acceptable salts described herein may be used to treat cells, and more particularly, cancerous cells, expressing HIF-1 α and/or HIF-2α. In some embodiments, the compounds and pharmaceutically acceptable salts described herein may be used to treat cells, and
more particularly, cancerous cells, expressing HIF-1α. In some embodiments, the
compounds and pharmaceutically acceptable salts described herein may be used to
treat cells, and more particularly, cancerous cells, expressing HIF-2α. In some
embodiments, the compounds and pharmaceutically acceptable salts described
herein may be used to treat cells, and more particularly, cancerous cells, expressing
HIF-1α and/or HIF-2α.

[0152] In some embodiments, the compounds and pharmaceutically acceptable salts
thereof interfere with glycolysis.

[0153] In certain embodiments, the disease treated or prevented is cancer.

[0154] In some embodiments, the compounds and pharmaceutically acceptable salts
described herein may be used to treat a disease mediated by defective pVHL protein,
such as Von Hippel-Lindau disease (which may also be referred to as
angiomatosis retinae, angiophakomatosis retinae et cerebelli, familial cerebello-
retinal angiomatosis, cerebelloretinal hemangioblastomatosis, Hippel Disease,
Hippel-Lindau syndrome, HLS, VHL, Lindau disease or retinocerebellar
angiomatosis). In some embodiments, the compounds and pharmaceutically
acceptable salts described herein may be used to treat a variety of malignant and/or
benign tumors of the eye, brain, spinal cord, kidney, pancreas, and/or adrenal glands
wherein individuals suffering from VHL may be disposed to such tumors. In some
embodiments, the compounds and pharmaceutically acceptable salts described
herein may be used to treat a disease mediated by defective pVHL protein, such as
ngiomatosis, hemangioblastomas, pheochromocytoma, renal cell carcinoma,
pancreatic cysts and cafe au lait spots.

[0155] Also provided is a method for treating a disease mediated by defective pVHL
protein, comprising administering to a subject at least one compound of Formula I,
IA, or II, or a pharmaceutically acceptable salt thereof, that is specifically cytotoxic to
cells that have elevated HIF levels due to their increased rate and dependence on
glucose uptake and glycolysis. In some embodiments, at least one compound of
Formula I, IA, or II selectively disrupts glucose uptake and utilization in the subject.
In some embodiments, at least one compound of Formula I, IA, or II, or a
pharmaceutically acceptable salt thereof, inhibits HIF-mediated induction of PDK1.

[0156] Also provided is a method of targeting cells which have defective pVHL
protein. In some embodiments, the cells are contacted with at least one compound
of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, that selectively
disrupts glucose uptake and utilization in the cells. In some embodiments, the compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, inhibits HIF-mediated induction of PDK1.

[0157] Also provided is a method for selectively killing cells which have defective pVHL protein. In some embodiments, the cells are contacted with at least one compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, that selectively disrupts glucose uptake and utilization in the cells. In some embodiments, at least one compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, inhibits HIF-mediated induction of PDK1.

[0158] Also provided is a method for treating a disease mediated by HIF-1α and/or HIF-2α comprising administering to a subject at least one compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, that is specifically cytotoxic to cells that have elevated HIF levels due to their increased rate and dependence on glucose uptake and glycolysis. In some embodiments, at least one compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, selectively disrupts glucose uptake and utilization in the subject. In some embodiments, at least one compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, inhibits HIF-mediated induction of PDK1.

[0159] Also provided is a method for treating a disease mediated by cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production, comprising administering to a subject at least one compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, that is specifically cytotoxic to cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production.

[0160] Also provided is a method for selectively killing cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production, comprising administering to the cells at least one compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, that is specifically cytotoxic to cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production. In some embodiments, at least one compound ofFormula I, IA, or II, or a pharmaceutically acceptable salt thereof, selectively disrupts glucose uptake and utilization in cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production.
[0161] Also provided is a method for treating a disease mediated by GLUT1 administering to a subject at least one compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof. Also provided is a method for treating a disease mediated by GLUT1, comprising administering to a subject at least one compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, that is specifically cytotoxic to cells that have elevated GLUT1 levels due to their increased rate and dependence on glucose uptake and glycolysis. In some embodiments, at least one compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, selectively disrupts glucose uptake and utilization in the subject. In some embodiments, at least one compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, inhibits glucose transport by GLUT1.

[0162] Also provided is a method of identifying a compound as a candidate cancer therapy, comprising exposing a first population of cells that have elevated expression of GLUT1 but not GLUT2 to a test compound and assaying cytotoxicity of the test compound, exposing a second population of cells that have elevated expression of GLUT2 but not GLUT1 to the test compound and assaying cytotoxicity of the test compound, and identifying the test compound as a candidate cancer therapy if the test compound induces significantly higher cytotoxicity in the first population of cells than in the second population of cells. Also provided is at least one compound, or a pharmaceutically acceptable salt thereof, identified by such method.

[0163] The subject receiving treatment may be any mammal in need of such treatment. Such mammals include, e.g., humans, ovines, bovines, equines, porcines, canines, felines, non-human primate, mice, and rats. In some embodiments, the subject is a human. In some embodiments, the subject is a non-human mammal.

[0164] "Therapeutically-effective amount" refers to the concentration of a compound that is sufficient to elicit the desired therapeutic effect (e.g., treatment or prevention of a disease). It is generally understood that the effective amount of the compound will vary according to the weight, gender, age, and medical history of the subject. Other factors that influence the effective amount may include, but are not limited to, the severity of the patient's condition, the disorder being treated, the stability of the compound, and, if desired, another type of therapeutic agent being administered with the compounds and pharmaceutically acceptable salts described herein. A larger total dose may be delivered by multiple administrations of the agent. Methods to

[0165] Actual dosage levels of the active ingredients in the pharmaceutical compositions comprising at least one compound or pharmaceutically active salt as described herein may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[0166] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds described herein employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[0167] In general, a suitable daily dose of at least one compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described herein.

[0168] If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six, or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

[0169] In some embodiments, the active compound may be administered two or three times daily. In another embodiment, the active compound is administered once daily.

[0170] The optimal frequency of administration and effective dosage will vary from one individual to another and will depend upon the particular disease being treated and may be determined by one skilled in the art.

[0171] In some embodiments, effective dosages of at least one compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, may range from as low as about 1 mg per day to as high as about 1000 mg per day, including all intermediate dosages there between.

[0172] In another embodiment, effective dosages may range from about 10 mg per day to about 100 mg per day, including all intermediate dosages there between. The
compositions may be administered in a single dosage, or in multiple, divided dosages.

[0173] As described herein, at least one compound of Formula I, IA, or II may be used for treating or preventing cancer. In some embodiments, such methods may, further comprise administration of a chemotherapeutic agent.

[0174] Chemotherapeutic agents that may be coadministered with compounds and pharmaceutical compositions of Formula I, IA, or II may include: alemtuzumab, aminogluthethimide, amsacrine, anastrozole, asparaginase, Bacillus Calmette-Guerin, bevacizumab, bicalutamide, bleomycin, bortezomib, busulfan, camptothecin, capecitabine, carboplatin, carmustine, CeaVac, cetuximab, chlorambucil, cisplatin, cladribine, cladronate, colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, daclizumab, dactinomycin, daunorubicin, dienestrol, diethylstilbestrol, docetaxel, doxorubicin, edrecolomab, erlotinib, estradiol, estramustine, etoposide, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, fludarabine, fluorouracil, gemcitabine, gemtuzumab, gemcitabine, genistein, goserelin, huJ591, hydroxyurea, ibritumomab, idarubicin, ifosfamide, IGN-1 01, imatinib, interferon, interleukin-2, irinotecan, irinotecan, letermore, leucovorin, leuprolide, levamisole, lintuzumab, lomustine, MDX-210, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, mitomomab, nilutamide, nocodazole, octreotide, oxaliplatin, paclitaxel, pamidronate, pentostatin, pertuzumab, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, sorafinib, streptozocin, sunitinib, suramin, tamoxifen, temozolomide, temsirolimus, teniposide, testosterone, thalidomide, thioguanine, thiotepa, titanocene dichloride, topotecan, tositumomab, trastuzumab, trastuzumab, tretinoin, vatalanib, vincristine, vindesine, and vinorelbine.

[0175] Other useful chemotherapeutic agents for combination with the compounds as described herein include MDX-010; MAAb, AME; ABX-EGF; EMD 72 000; apolizumab; labetuzumab; ior-t1; MDX-220; MRA; H-1 1 scFv; Oregovomab; huJ591 MAAb, BZL; visilizumab; TriGem; ThAb; R3; MT-201; G-250, unconjugated; ACA-1 25; Onyvax-1 05; CDP-860; BrevaRex MAAb; AR54; IMC-1 C11; GNoMAb-H; ING-1; Anti-LCG MAbs; MT-103; KSB-303; Therex; KW-2871; Anti-HMI.24; Anti-PTHrP; 2C4 antibody; SGN-30; TRAIL-RI MAAb, CAT; Prostate cancer antibody; H22xKi-4; ABX-MA1; Imuteran; and Monopharm-C.
These chemotherapeutic agents may be categorized by their mechanism of action into, for example, the following groups: anti-metabolites/anti-cancer agents, such as pyrimidine analogs (e.g., 5-fluorouracil, floxuridine, capecitabine, gemcitabine and cytarabine) and purine analogs, folate antagonists and related inhibitors (e.g., mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine (cladribine)); antiproliferative/antimitotic agents including natural products such as vinca alkaloids (e.g., vinblastine, vincristine, and vinorelbine), microtubule disruptors such as taxane (paclitaxel, docetaxel), vincristin, vinblastin, nodocazole, epothilones and navelbine, epidipodophyllotoxins (teniposide), DNA damaging agents (e.g., actinomycin, amsacrine, anthracyclines, bleomycin, busulfan, camptothecin, carboplatin, chlorambucil, cisplatin, cyclophosphamide, Cytoxan, dactinomycin, daunorubicin, docetaxel, doxorubicin, epirubicin, hexamethylmelamine, oxaliplatin, iprophosphamide, melphalan, merchlorethamine, mitomycin, mitoxantrone, nitrosourea, paclitaxel, plicamycin, procarbazine, teniposide, triethylenethiophosphoramide and etoposide (VP16)); antibiotics such as actinomycin (actinomycin D), daunorubicin, doxorubicin (adriamycin), idarubicin, anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin; enzymes (e.g., L-asparaginase, which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine); antiplatelet agents; antiproliferative/antimitotic alkylating agents such as nitrogen mustards (e.g., mechlorethamine, cyclophosphamide and analogs, melphalan, chlorambucil), ethylenimines and methylmelamines (e.g., hexamethylmelamine and thiopeta), alkyl sulfonates-busulfan, nitrosoureas (e.g., carmustine (BCNU) and analogs, streptozocin), trazenes - dacarbazine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (e.g., methotrexate); platinum coordination complexes (e.g., cisplatin, carboplatin), procarbazine, hydroxyurea, mitotane, aminogluthethimide; hormones, hormone analogs (e.g., estrogen, tamoxifen, goserelin, bicalutamide, nilutamide) and aromatase inhibitors (e.g., letrozole, anastrozole); anticoagulants (e.g., heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase and urokinase), aspirin, COX-2 inhibitors, dipyridamole, ticlopidine, clopidogrel, abciximab; antimigratory agents; antisecretory agents (e.g., breveldin); immunosuppressives (e.g., cyclosporine, tacrolimus (FK-506), sirolimus (rapamycin), azathioprine,
mycophenolate mofetil); anti-angiogenic compounds (e.g., TNP-470, genistein) and growth factor inhibitors (e.g., vascular endothelial growth factor (VEGF) inhibitors, fibroblast growth factor (FGF) inhibitors, epidermal growth factor (EGF) inhibitors); angiotensin receptor blocker; nitric oxide donors; anti-sense oligonucleotides; antibodies (e.g., trastuzumab and others listed above); cell cycle inhibitors and differentiation inducers (e.g., tretinoin); mTOR inhibitors, topoisomerase inhibitors (e.g., doxorubicin (adriamycin), amsacrine, camptothecin, daunorubicin, dactinomycin, eniposide, epirubicin, etoposide, idarubicin, irinotecan (CPT-11) and mitoxantrone, topotecan, irinotecan), corticosteroids (e.g., cortisol, dexamethasone, hydrocortisone, methylprednisolone, prednisone, and prenisolone); growth factor signal transduction kinase inhibitors; mitochondrial dysfunction inducers and caspase activators; chromatin disruptors.

[0177] In some embodiments, pharmaceutical compositions comprising at least one compound of Formula I, IA, or II may be coadministered with chemotherapeutic agents either singly or in combination.

[0178] Combination therapies comprising at least one compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof, and a conventional chemotherapeutic agent may be advantageous over combination therapies known in the art because the combination allows the conventional chemotherapeutic agent to exert greater effect at lower dosage. In some embodiments, the effective dose (ED_{50}) for a chemotherapeutic agent, or combination of conventional chemotherapeutic agents, when used in combination with a compound of Formula I, IA, or II, or a pharmaceutically acceptable salt thereof as described herein is at least 2 fold less than the ED_{50} for the chemotherapeutic agent alone. In another embodiment, the ED_{50} is about 5-fold less, about 10-fold less, and further about 25-fold less. Conversely, the therapeutic index (TI) for such chemotherapeutic agent or combination of such chemotherapeutic agent when used in combination with a compound or pharmaceutically acceptable salt described herein may be at least 2-fold greater than the TI for conventional chemotherapeutic regimen alone. In another embodiment, the TI is about 5-fold greater, about 10-fold greater, and further about 25-fold greater.

[0179] In some embodiments, the compounds and pharmaceutically acceptable salts thereof described herein may be administered in combination with radiation therapy.
The invention is further illustrated by the following non-limiting examples. If an abbreviation is not defined, it has generally accepted meaning.

Analyses were carried out in the Campbell Microanalytical Laboratory, University of Otago, Dunedin, NZ. Melting points were determined on an Electrotherm 2300 Melting Point Apparatus. NMR spectra were obtained on a Bruker Avance 400 spectrometer at 400 MHz for $^1$H and 100 MHz for $^{13}$C spectra. Spectra were obtained in [(CD$_3$)$_2$SO] unless otherwise specified, and were referenced to Me$_4$Si. Chemical shifts and coupling constants were recorded in units of ppm and Hz, respectively. Assignments were determined using COSY, HSQC, and HMBC two-dimensional experiments. Low resolution mass spectra were gathered by direct injection of methanolic solutions into a Surveyor MSQ mass spectrometer using an atmospheric pressure chemical ionization (APCI) mode with a corona voltage of 50 V and a source temperature of 400 °C. Solutions in organic solvents were dried with anhydrous MgSO$_4$. Solvents were evaporated under reduced pressure on a rotary evaporator. Thin-layer chromatography was carried out on aluminium-backed silica gel plates (Merck 60 F$_2$S$_6$) with visualization of components by UV light (254 nm) or exposure to I$_2$. Column chromatography was carried out on silica gel (Merck 230-400 mesh). DCM refers to dichloromethane; DME refers to dimethoxyethane, DMF refers to dry N,N-dimethylformamide; ether refers to diethyl ether; EtOAc refers to ethyl acetate; EtOH refers to ethanol; MeOH refers to methanol; pet. ether refers to petroleum ether, boiling range 40-60 °C; THF refers to tetrahydrofuran dried over sodium benzophenone ketyl.

[0182] General Method A. Oxalyl chloride (13 mmol) was added dropwise to a solution of acid (9 mmol) and DMF (4 drops) in dry THF (40 mL), and the mixture stirred at 50 °C for 3 h. The solvent was evaporated and the residue dissolved in pyridine (25 mL). Aminopyridine (9.6 mmol) was added and the solution stirred at 20 °C for 16 h. Water (150 mL) was added, the mixture stirred for another 2 h, the precipitate filtered off, washed with water and dried to give the amide.
[0183] **General Method B.** A suspension of benzylcarbamate (7 mmol) in HBr/AcOH (30%, 30 ml) was stirred at 20 °C for 5 h. Et₂O (150 ml) was added, the mixture was stirred for another 30 min, the precipitate filtered off, washed with Et₂O and dried to give the amine dihydrobromide.

[0184] **General Method C.** A mixture of amine dihydrobromide (0.9 mmol) and benzenesulfonyl chloride (1.0 mmol) in dry pyridine (10 ml) was stirred at 20 °C for 16 h. The solvent was evaporated and the residue stirred in water (20 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, to give the sulfonamide.

**Example 1**

**Preparation of 4-(Phenylsulfonamidomethyl)-V-(pyridin-2-yl)benzamide (9).**

![Chemical Structure](image)

[0185] **4-(Benzyloxy carbonylamino) methylbenzoic acid (2).** Benzyl chloroformate (10.3 ml, 72.7 mmol) and 2 M NaOH solution (33 ml, 66 mmol) were simultaneously added dropwise to a stirred solution of 4-aminomethylbenzoic acid (1) (10.0 g, 66.2 mmol) in 2 M NaOH solution (33 ml) and THF (30 ml) at 0 °C. The mixture was stirred at 20 °C for 16 h, then the organic solvent was evaporated and the residue acidified with 2 M HCl until the pH of the mixture was 2-3. The precipitate was filtered, washed with water (250 ml), washed with EtOH (50 ml), and finally washed with Et₂O (100 ml). The solid was dried under vacuum to give acid 2 (16.43 g, 87%) as a white powder: mp 190-1 92 °C [lit. (Loge et. al., J. Enzyme Inhib. Med. Chem. 2002, 17, 381-390) mp (toluene) 194-1 95 °C; 1H NMR δ 7.85 (br d, 2 H, H-2, H-6), 7.82 (br t, J = 6.1 Hz, 1 H, NHCO₂), 7.30-7.40 (m, 5 H, H-2', H-3', H-4', H-5', H-6'), 7.27 (br d, J = 8.2 Hz, 2 H, H-3, H-5), 5.05 (s, 2 H, OCH₂), 4.24 (d, J = 6.1 Hz, 2 H, CH₂N).

[0186] **Benzyl 4-(pyridine-2-ylcarbamoyl)benzylcarbamate (3).** Method A. Reaction of benzoic acid 2 (2.5 g, 8.8 mmol) and oxalyl chloride (1.15 ml, 13.1 mmol), with subsequent reaction with 2-aminopyridine (0.91 g, 9.6 mmol), gave carbamate 3 (2.43 g, 77%) as a pale pink solid: mp (EtOAc) 127-1 29 °C; 1H NMR δ 10.69 (s, 1 H, NHCO), 8.37-8.39 (m, 1 H, H-3'), 8.19 (d, J = 8.4 Hz, 1 H, H-6'), 7.99 (d, J = 8.3 Hz, 2 H, H-2, H-6), 7.84 (br t, J = 6.0 Hz, 1 H, NHCO₂), 7.80-7.85 (m, 1 H, H-5'), 7.29-7.39 (m, 7 H, H-3, H-5, phenyl), 7.14-7.1 8 (m, 1 H, H-4'), 5.07 (s, 2 H,
OCH₂), 4.09 (d, J = 6.2 Hz, 2 H, CH₂N); ¹³C NMR δ 165.6, 156.3, 152.1, 147.8, 143.8, 137.9, 137.0, 132.5, 128.2 (2), 127.9 (2), 127.7, 127.6 (2), 126.6 (2), 119.6, 114.5, 65.3, 43.5. Anal. Calcd for C₂H₅N₃O₅: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.54; H, 5.46; N, 11.40%.

[0187] 4-(Aminomethyl)-N-(2-pyridinyl)benzamide dihydrobromide (4). Method B. Reaction of benzylcarbamate 3 (2.4 g, 6.6 mmol) gave benzamide 4 (1.65 g, 64%) as a pale pink solid: mp (EtOAc) 281-284 °C; ¹H NMR 5 10.61 (s, 1 H, NHCO), 8.49 (dd, J = 5.4, 1.0 Hz, 1 H, H-3′), 8.38 (br s, 3 H, NH₂-HBr), 8.22 (dd, J = 7.9, 1.6 Hz, 1 H, H-5′), 8.09-8.14 (m, 3 H, H-2, H-6, H-6′), 7.68 (d, J = 8.3 Hz, 2 H, H-3, H-5), 7.46 (t, J = 6.2 Hz, 1 H, H-4′), 4.16 (q, J = 5.8 Hz, 2 H, CH₂N), 7.06 (br s, 1 H, pyrN-HBr); ¹³C NMR δ 165.6, 147.8, 141.7, 138.6, 132.6, 128.8 (2), 128.4 (2), 120.4, 116.1, 41.7. Anal. Calcd for C₉H₅Br₂N₂O: C, 40.13; H, 3.89; N, 10.80. Found: C, 40.26; H, 4.07; N, 10.53%.

[0188] 4-(Phenylsulfonamidomethyl)-N-(pyridin-2-yl)benzamide (9). Method C. Reaction of amine salt 4 (357 mg, 0.9 mmol) and benzenesulfonyl chloride (0.13 ml, 1.0 mmol), followed by column chromatography, eluting with EtOAc, gave benzamide 9 (272 mg, 80%) as a white powder: mp (EtOAc) 169-170 °C; ¹H NMR δ 10.68 (br s, 1 H, NHCO), 8.38 (dd, J = 4.9, 1.8, 0.8 Hz, 1 H, H-6′), 8.24 (br s, 1 H, NHSO₂), 8.18 (br d, J = 8.4 Hz, 1 H, H-3′), 7.97 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.80-7.86 (m, 3 H, H-4′, H-2″, H-6″), 7.62-7.67 (m, 1 H, H-4″), 7.56-7.61 (m, 2 H, H-3″, H-5″), 7.37 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 7.16 (dd, J = 7.3, 4.9, 0.9 Hz, 1 H, H-5′), 4.08 (s, 2 H, CH₂N); ¹³C NMR δ 165.5, 152.0, 147.8, 141.8, 140.6, 137.9, 132.7, 132.3, 129.1 (2), 127.8 (2), 127.2 (2), 126.3 (2), 119.6, 114.6, 45.6; MS m/z 368.4 (MH⁺, 100%). Anal. Calcd for C₉H₇N₃O₃S: C, 62.11; H, 4.66; N, 11.44. Found: C, 62.17; H, 4.86; N, 11.44%.

Example 2
Preparation of 4-(Phenylsulfonamidomethyl)-V-(pyridin-3-yl)benzamide (10).

[0189] Benzyl 4-(pyridine-3-ylcarbamoyl)benzylcarbamate (5). Method A. Reaction of benzoic acid 2 (10.0 g, 35.0 mmol) and oxalyl chloride (4.58 ml, 52.5 mmol), with subsequent reaction with 3-aminopyridine (3.62 g, 38.5 mmol) gave
carbamate 5 (7.82 g, 62%) as a white solid: mp (EtOH) 207-210 °C; 1H NMR δ 10.37 (s, 1 H, NHCO), 8.92 (d, J = 2.3 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.93 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.89 (br t, J = 6.0 Hz, 1 H, NHCO2), 7.41 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 7.31-7.39 (m, 6 H, H-5', H-2", H-3", H-4", H-5", H-6"), 5.06 (s, 2 H, CH2O), 4.30 (d, J = 6.2 Hz, 2 H, CH2N). Anal. Calcd for C21H18N3O5: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.60; H, 5.40; N, 11.63%.

[0190]4-(Aminomethyl)-N-(3-pyridinyl)benzamide dihydrobromide (6). Method B. Reaction of carbamate 5 (2.2 g, 6.1 mmol) gave benzamide 6 (2.35 g, 99%) as a white solid: mp (EtOAc) 292-296 °C; 1H NMR δ 1 LOe (s, 1 H, NHCO), 9.35 (d, J = 2.2 Hz, 1 H, H-2'), 8.70 (ddd, J = 8.5, 2.2, 1.1 Hz, 1 H, H-4'), 8.64 (br d, J = 5.4 Hz, 1 H, H-6'), 8.31 (br s, 3 H, NH2-HBr), 8.09 (br d, J = 8.2 Hz, 2 H, H-2, H-6), 7.96 (dd, J = 8.6, 5.4 Hz, 1 H, H-5'), 7.67 (d, J = 8.4 Hz, 2 H, H-3, H-5), 5.95 (br s, 1 H, pyrN-HBr). 4.16 (q, J = 5.8 Hz, 2 H, CH2N); Anal. Calcd for C13H13BrN3O: C, 40.13; H, 3.89; N, 10.80. Found: C, 39.99; H, 3.94; N, 10.36%

[0191]4-(Phenylsulfonamidomethyl)-N-(pyridin-3-yl)benzamide (10). Method C. Reaction of amine salt 6 (411 mg, 1.1 mmol) and benzenesulfonyl chloride (0.15 ml, 1.2 mmol), followed by column chromatography eluting with EtOAc, gave benzamide 10 (237 mg, 61%) as a white powder: mp (EtOAc) 168-170 °C; 1H NMR δ 10.37 (s, 1 H, NHCO), 8.93 (d, J = 2.3 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.25 (br s, 1 H, NHSO2), 8.18 (ddd, J = 8.4, 2.5, 1.5 Hz, 1 H, H-4'), 7.90 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.83 (br d, J = 8.0 Hz, 2 H, H-2", H-6"), 7.57-7.69 (m, 3 H, H-3", H-4", H-5"), 7.37-7.42 (m, 3 H, H-3, H-5, H-5'), 4.09 (s, 2 H, CH2N); 13C NMR δ 165.4, 144.4, 141.9, 141.7, 140.5, 135.7, 132.9, 129.1 (2), 127.6 (2), 127.3 (2), 127.2, 126.3 (2), 123.3, 45.6; MS m/z 368.4 (MH+, 100%). Anal. Calcd for C13H17N3O3S: C, 62.11; H, 4.66; N, 11.44. Found: C, 62.37; H, 4.82; N, 11.39%

Example 3
Preparation of 4-(Phenylsulfonamidomethyl)-N-(pyridin-4-yl)benzamide (11).

[0192] Benzyl 4-(pyridine-4-ylcarbamoyl)benzylcarbamate (7). Method A. Reaction of benzoic acid 2 (5.8 g, 20.3 mmol) with oxalyl chloride (2.65 ml, 30.4 mmol), with subsequent reaction with 4-aminopyridine (2.10 g, 22.3 mmol) gave
carbamate 7 (2.30 g, 31%) as a pale pink solid: mp (EtOAc) 146-149 °C; 1H NMR δ 10.51 (s, 1 H, NHCO), 8.47 (dd, J = 4.7, 1.6 Hz, 2 H, H-2', H-6'), 7.87-7.93 (m, 3 H, H-2, H-6, NHCO₂), 7.76 (dd, J = 4.7, 1.6 Hz, 2 H, H-3', H-5'), 7.42 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 7.27-7.38 (m, 5 H, H-2", H-3", H-4", H-5", H-6") 5.06 (s, 2 H, CH₂O), 4.29 (d, J = 6.0 Hz, 2 H, CH₂N). Anal. Calcd for C₂₁H₁₉N₃O₃: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.92; H, 5.39; N, 11.71%.

[0193]4-(Aminomethyl)benzamide dihydrobromide (8). Method B. Reaction of carbamate 7 (2.24 g, 6.6 mmol) gave benzamide 8 (1.98 g, 82%) as a white solid: mp (Et₂O) 280-282 °C; 1H NMR δ 14.60 (br s, 1 H, pyrN-HBr), 11.56 (s, 1 H, NHCO), 8.80 (br d, J = 7.3 Hz, 2 H, H-2, H-6), 8.30-8.40 (m, 5 H, H-3', H-5', NH₂-HBr), 8.10 (br d, J = 8.4 Hz, 2 H, H-2, H-6), 7.69 (d, J = 8.4 Hz, 2 H, H-3, H-5), 4.18 (q, J = 5.6 Hz, 2 H, CH₂N). Anal. Calcd for C₁₃H₁₅Br₂N₃O₂V₂H₂O: C, 39.22; H, 4.05; N, 10.55. Found: C, 39.40; H, 4.06; N, 10.48%.

[0194]4-(Phenylsulphonamidomethyl)benzamide (11). Method C. Reaction of amine salt 8 (394 mg, 1.0 mmol) and benzenesulfonyl chloride (0.14 ml, 1.1 mmol), followed by column chromatography eluting with a gradient (0-5%) of MeOH/EtOAc, gave benzamide 11 (232 mg, 63%) as a white powder: mp (MeOH/EtOAc) 231-234 °C; 1H NMR δ 10.51 (s, 1 H, NHCO), 8.47 (dd, J = 4.9, 1.5 Hz, 2 H, H-4', H-6'), 8.26 (br s, 1 H, NHSO₂), 7.89 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.83 (br d, J = 8.1 Hz, 2 H, H-2", H-6"), 7.78 (dd, J = 4.8, 1.6 Hz, 2 H, H-3', H-5'), 7.64-7.68 (m, 1 H, H-4"), 7.57-7.61 (m, 2 H, H-3", H-5"), 7.41 (br d, J = 8.4 Hz, 2 H, H-3, H-5), 4.10 (s, 2 H, CH₂N); 13C NMR δ 165.9, 150.2 (2), 145.8, 142.0, 140.5, 132.8, 132.3, 129.1 (2), 127.7 (2), 126.3 (2), 113.9 (2), 45.6; MS m/z 368.3 (MH⁺, 100%). Anal. Calcd for C₁₉H₁₅N₃O₂S: C, 62.1; H, 4.66; N, 11.44. Found: C, 62.36; H, 4.84; N, 11.47%.

Example 4
Preparation of 4-(Phenylsulphonamidomethyl)-V-(thiazol-2-yl)benzamide (13).

[0195] 4-(Phenylsulphonamidomethyl)benzoic Acid (12). Benzenesulfonyl chloride (1.27 ml, 10.0 mmol) was added dropwise to a stirred solution of 4-aminomethylbenzoic acid (1) (1.51 g, 10 mmol) in 2 M NaOH (10 ml) at 20 °C. The mixture was stirred at 20 °C for 3 h. The pH of the mixture was adjusted to 2-3 with 6
M HCl and the precipitate filtered. The precipitate was washed with water (2 x 20 ml), ether (20 ml) and pet. ether (2 x 20 ml) and air-dried. The residue was purified by chromatography, eluting with 5% MeOH/EtOAc, to give benzoic acid 12 (2.33 g, 80%) as a white powder: mp 223-227 °C; 1H NMR δ 12.20 (br s, 1 H, CO₂H), 8.23 (br s, 1 H, NHSO₂), 7.84 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.78-7.82 (m, 2 H, H-2', H-6'), 7.60-7.64 (m, 1 H, H-4'), 7.55-7.59 (m, 2 H, H-3', H-5'), 7.34 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 4.05 (br d, J = 5.8 Hz, 2 H, CH₂N). Anal. Calcd for C₁₄H₁₃NO₄S: C, 57.72; H, 4.50; N, 4.81. Found: C, 57.46; H, 4.52; N, 4.73%.

[0196] Method A. Reaction of benzoic acid 12 (485 mg, 1.7 mmol) and oxalyl chloride (0.22 ml, 2.5 mmol) and subsequent reaction with 2-aminothiazole (185 mg, 1.8 mmol), followed by column chromatography eluting with a gradient (50-70%) of EtOAc/pet. ether, gave benzamide 13 (221 mg, 36%) as a white powder: mp (EtOAc/pet. ether) 189-191 °C; 1H NMR δ 12.56 (s, 1 H, NHCO), 8.25 (br s, 1 H, NHSO₂), 8.01 (br d, J = 8.4 Hz, 2 H, H-2, H-6), 7.82 (ddd, J = 8.0, 2.1, 1.6 Hz, 2 H, H-2', H-6'), 7.62-7.66 (m, 1 H, H-4'), 7.56-7.61 (m, 2 H, H-3', H-5'), 7.55 (d, J = 3.6 Hz, 1 H, H-4'), 7.39 (br d, J = 8.4 Hz, 2 H, H-3, H-5), 7.27 (t, J = 3.6 Hz, 1 H, H-5'), 4.09 (s, 2 H, CH₂N); 13C NMR δ 164.6, 158.6, 142.4, 140.6, 137.4, 132.3, 130.8, 129.1 (2), 128.0 (2), 127.4 (2), 126.3 (2), 113.7, 45.6; MS m/z 374.3 (MH⁺, 100%).

Anal. Calcd for C₁₇H₁₅N₃O₃S₂: C, 54.67; H, 4.05; N, 11.25. Found: C, 54.94; H, 4.09; N, 11.30%.

Example 5
Preparation of 4-(Phenylsulfonamidomethyl)-N-(7H-pyrazol-3-yl)benzamide (14).

[0197] Method A. Reaction of benzoic acid 12 (402 mg, 1.38 mmol) and oxalyl chloride (0.18 ml, 2.1 mmol) with subsequent reaction with 7/-/-pyrazol-3-amine hydrochloride (126 mg, 1.5 mmol), followed by column chromatography eluting with EtOAc, gave benzamide 14 (396 mg, 80%) as a white powder: mp (EtOAc/pet. ether) 180-182 °C; 1H NMR δ 12.40 (br s, 1 H, NH), 10.71 (s, 1 H, NHCO), 8.22 (br s, 1 H, NHSO₂), 7.91 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.82 (ddd, J = 8.0, 2.1, 1.5 Hz, 2 H, H-2', H-6'), 7.61-7.66 (m, 2 H, H-5', H-4'), 7.55-7.60 (m, 2 H, H-3', H-5'), 7.34...
(br d, J = 8.3 Hz, 2 H, H-3, H-5), 6.62 (br s, 1 H, H-4'), 4.07(s, 2 H, CH\textsubscript{2}N); \textsuperscript{13}C NMR δ 164.0, 147.2, 141.2, 140.6, 132.9, 132.3, 129.1 (2), 128.4, 127.5 (2), 127.1 (2), 126.3 (2), 96.9, 45.6; MS m/z 357.3 (MH\textsuperscript{+}, 100%). Anal. Calcld for Cl\textsubscript{2}H\textsubscript{6}N\textsubscript{4}O\textsubscript{3}S: C, 57.29; H, 4.52; N, 15.72. Found: C, 57.53; H, 4.60; N, 15.73%.

Example 6

Preparation of 4-(Phenylsulfonamidomethyl)-N-(quinolin-3-yl)benzamide (15).

![Chemical structure](image)

[0198] Method A. Reaction of benzoic acid 12 (424 mg, 1.46 mmol) and oxalyl chloride (0.19 ml, 2.2 mmol) with subsequent reaction with 3-aminoquinoline (232 mg, 1.6 mmol), followed by column chromatography eluting with EtOAc, gave benzamide 15 (528 mg, 87%) as a white powder: mp (EtOAc) 186-188 °C; \textsuperscript{1}H NMR δ 10.63 (br s, 1 H, NHCO), 9.15 (d, J = 2.5 Hz, 1 H, H-2'), 8.83 (d, J = 2.5 Hz, 1 H, H-4'), 8.27 (br s, 1 H, NHSO\textsubscript{2}I), 7.95-8.00 (m, 3 H, H-2, H-6, H-8'), 7.84 (ddd, J = 8.0, 2.1, 1.6 Hz, 2 H, H-2", H-6"), 7.63-7.70 (m, 2 H, H-5', H-4"), 7.56-7.62 (m, 4 H, H-6', H-7', H-3", H-5"), 7.44 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 4.11 (s, 2 H, CH\textsubscript{2}N); \textsuperscript{13}C NMR δ 165.6, 145.4, 144.3, 141.8, 140.6, 132.9, 132.7, 132.3 (2), 129.1 (2), 128.4, 127.9, 127.6 (2), 127.3 (3), 126.9, 126.3 (2), 123.3, 45.6; MS m/z + 18.5 (MH\textsuperscript{+}, 100%). Anal. Calcld for C\textsubscript{23}H\textsubscript{13}N\textsubscript{3}O\textsubscript{3}S: C, 66.17; H, 4.59; N, 10.07. Found: C, 66.40; H, 4.58; N, 10.27%.

Example 7

Preparation of 4-(Phenylsulfonamidomethyl)-N-(quinolin-5-yl)benzamide (16).

![Chemical structure](image)

[0199] Method A. Reaction of benzoic acid 12 (440 mg, 1.5 mmol) and oxalyl chloride (0.20 ml, 2.3 mmol) with subsequent reaction with 5-aminoquinoline (240 mg, 1.7 mmol), followed by column chromatography eluting with EtOAc, gave benzamide 16 (426 mg, 68%) as a white powder: mp (EtOAc/pet. ether) 198-201 °C; \textsuperscript{1}H NMR δ 10.48 (br s, 1 H, NHCO), 8.92 (dd, J = 4.2, 1.6 Hz, 1 H, H-2'), 8.32 (br d, J = 8.6 Hz, 1 H, H-4'), 8.27 (br s, 1 H, NHSO\textsubscript{2}I), 8.01 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.97 (d, J = 8.3 Hz, 1 H, H-6'), 7.85 (ddd, J = 8.0, 2.1, 1.6 Hz, 2 H, H-2", H-6"), 7.80 (dd, J = 8.4, 7.5 Hz, 1 H, H-7'), 7.70 (dd, J = 7.4, 5.0 Hz, 1 H, H-8'), 6.99-7.18 (m, 1
H, H-4”), 7.58-7.63 (m, 2 H, H-3”, H-5”), 7.56 (dd, J = 8.6, 4.2 Hz, 1 H, H-3’), 7.44 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 4.1 2 (s, 2 H, CH₂N); ¹³C NMR δ 165.9, 150.4, 148.1 , 141 .6, 140.6, 134.0, 132.9, 132.3, 132.0, 129.1 (2), 128.8, 127.7 (2), 127.3 (2), 127.0, 126.3 (2), 124.1 , 123.6, 120.9, 45.6; MS m/z 418.5 (MH⁺, 100%). Anal. Calcd for C₂₃H₁₉N₃O₃S: C, 66.1 7; H, 4.59; N, 10.07. Found: C, 66.40; H, 4.62; N, 10.29%.

Example 8
Preparation of 4-(Phenylsulfonamidomethyl)-N-(pyrazin-2-yl)benzamide (17).

[0200] Method A. Reaction of benzoic acid 12 (41.3 mg, 1.4 mmol) and oxalyl chloride (0.19 ml, 2.1 mmol) with subsequent reaction with 2-aminopyrazine (149 mg, 1.6 mmol), followed by column chromatography eluting with EtOAc, gave benzamide 24 (398 mg, 76%) as a white powder: mp (EtOAc/pet. ether) 200-202 °C; ¹H NMR δ 11.00 (br s, 1 H, NHCO), 9.41 (d, J = 1.5 Hz, 1 H, H-2’), 8.47 (dd, J = 2.5, 1.5 Hz, 1 H, H-6’), 8.41 (d, J = 2.3 Hz, 1 H, H-5’), 8.20 (br s, 1 H, NHSO₂), 7.98 (br d, J = 8.4 Hz, 2 H, H-2, H-6), 7.84 (ddd, J = 7.0, 2.1 , 1.6 Hz, 2 H, H-2”, H-6”), 7.62-7.67 (m, 1 H, H-4”), 7.56-7.61 (m, 2 H, H-3”, H-5”), 7.39 (br d, J = 8.4 Hz, 2 H, H-3, H-5), 4.09 (s, 2 H, CH₂N); ¹³C NMR δ 165.6, 148.9, 142.4, 142.4, 140.6, 139.8, 137.4, 132.3, 132.0, 129.1 (2), 128.1 (2), 126.3 (2), 45.6; MS m/z 369.2 (MH⁺, 100%). Anal. Calcd for C₁₈H₁₆N₄O₃S: C, 58.68; H, 4.38; N, 15.21 . Found: C, 58.91 ; H, 4.45; N, 15.26%.

Example 9
Preparation of 4-(Phenylsulfonamidomethyl)-N-(pyrimidin-2-yl)benzamide (18).

[0201] Method A. Reaction of benzoic acid 12 (509 mg, 1.8 mmol) and oxalyl chloride (0.23 ml, 2.6 mmol) with subsequent reaction with pyrimidin-2-amine (183 mg, 1.9 mmol), followed by column chromatography eluting with a gradient (0-5%) of MeOH/EtOAc, gave benzamide 18 (262 mg, 41%) as a white powder: mp (MeOH/EtOAc) 180-1 82 °C; ¹H NMR δ 10.91 (s, 1 H, NHCO), 8.72 (d, J = 4.8 Hz, 2 H, H-4’, H-6’), 8.24 (br s, 1 H, NHSO₂), 7.89 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.82 (dd, J = 8.0, 2.1 , 1.5 Hz, 2 H, H-2”, H-6”), 7.62-7.67 (m, 1 H, H-4”), 7.56-7.61 (m, 2
H, H-3", H-5"), 7.37 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 7.26 (t, J = 4.8 Hz, 1 H, H-5"), 4.08 (S, 2 H, CH₂N); 13C NMR 5 165.0, 158.2 (2), 158.1 , 141.9, 140.6, 132.9, 132.3, 129.1 (2), 128.1 (2), 127.2 (2), 126.3 (2), 117.2, 45.6; MS m/z 369.3 (MH⁺, 100%).
Anal. Calcd for C₁₈H₁₆N₄O₃S: C, 58.68; H, 4.38; N, 15.21. Found: C, 58.70; H, 4.48; N, 14.91%.

Example 10
Preparation of 4-((2-Methylphenylsulfonamido)methyl)- N-(pyridin-3-yl)benzamide (19).

[0202] Method C. Reaction of amine salt 6 (400 mg, 1.0 mmol) and 2-toluenesulfonyl chloride (21.6 mg, 1.1 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 19 (264 mg, 67%) as a white powder: mp (EtOAc) 159-161 ºC; 1H NMR 5 10.36 (s, 1 H, NHCO), 8.93 (d, J = 2.3 Hz, 1 H, H-2'), 8.30-8.32 (br s, 1 H, NHSO₂), 8.31 (dd, J = 4.6, 1.5 Hz, 1 H, H-6'), 8.19 (d, J = 8.3 Hz, 1 H, H-4'), 7.89 (d, J = 6.7 Hz, 2 H, H-2, H-6), 7.83 (dd, J = 7.7, 1.1 Hz, 1 H, H-6"), 7.50 (dt, J = 7.5, 1.3 Hz, 1 H, H-5"), 7.34-7.41 (m, 5 H, H-3, H-5, H-5', H-3", H-4"), 4.12 (s, 2 H, CH₂N), 2.59 (s, 3 H, CH₃); 13C NMR 5 165.4, 144.4, 142.0, 141.9, 138.7, 136.3, 135.7, 132.9, 132.4, 132.3, 128.2, 127.5 (2), 127.2 (2), 127.2, 126.1 , 123.3, 45.3, 19.7. Anal. Calcd for C₂₀H₁₉N₃O₃S: C, 62.97; H, 5.02; N, 11.02. Found: C, 63.28; H, 5.06; N, 11.13%.

Example 11
Preparation of 4-((2-Fluoroophenylsulfonamido)methyl)- N-(pyridin-3-yl)benzamide (20).

[0203] Method C. Reaction of amine salt 6 (442 mg, 1.1 mmol) and 2-fluorobenzenesulfonyl chloride (0.17 ml, 1.3 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 20 (21.9 mg, 50%) as a white powder: mp (EtOAc) 189-191 ºC; 1H NMR 5 10.35 (s, 1 H, NHCO), 8.92 (d, J = 2.2 Hz, 1 H, H-2'), 8.58 (br s, 1 H, NHSO₂), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.88 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.79 (dt, J
= 7.6, 1.7 Hz, 1 H, H-6\textsuperscript{\text{a}}), 7.65-7.71 (m, 1 H, H-4\textsuperscript{\text{a}}) 7.36-7.42, (m, 4 H, H-3, H-5, H-5', H-3\textsuperscript{\text{a}}), 7.34 (dd, J = 7.6, 1.0 Hz, 1 H, H-5\textsuperscript{\text{a}}), 4.22 (s, 2 H, CH\textsubscript{2}N); \textsuperscript{13}C NMR δ 165.4, 158.0 (d, J = 253 Hz), 144.4, 141.9, 141.7, 135.7, 135.0 (d, J = 9 Hz), 132.9, 129.4, 128.6 (d, J = 14 Hz), 127.5 (2), 127.2 (3), 124.6 (d, J = 4 Hz), 123.4, 117.0 (d, J = 21 Hz), 45.4; MS m/z 386.4 (MH\textsuperscript{+}, 100%). Anal. Calcd for C\textsubscript{19}H\textsubscript{16}FN\textsubscript{3}O\textsubscript{3}S: C, 59.21 ; H, 4.18; N, 10.90. Found: C, 59.38; H, 4.29; N, 10.85%.

**Example 12**
Preparation of 4-((2-Chlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (21).

[0204] Method C. Reaction of amine salt 6 (424 mg, 1.1 mmol) and 2-chlorobenzenesulfonyl chloride (0.16 ml, 1.2 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 21 (165 mg, 38%) as a white powder: mp (EtOAc) 190-192 °C; \textsuperscript{1}H NMR δ 10.35 (s, 1 H, NHCO), 8.92 (d, J = 2.2 Hz, 1 H, H-2\textsuperscript{\text{b}}), 8.54 (br s, 1 H, NHSO\textsubscript{2}), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6\textsuperscript{\text{b}}), 8.18 (ddd, J = 8.4, 2.5, 1.5 Hz, 1 H, H-4\textsuperscript{\text{b}}), 7.95 (dd, J = 7.4, 1.2 Hz, 1 H, H-6\textsuperscript{\text{b}}), 7.87 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.57-7.64 (m, 2 H, H-3\textsuperscript{\text{b}}, H-5\textsuperscript{\text{b}}), 7.47-7.52 (m, 1 H, H-4\textsuperscript{\text{b}}), 7.36-7.42 (m, 3 H, H-3, H-5, H-5\textsuperscript{\text{b}}), 4.21 (s, 2 H, CH\textsubscript{2}N); \textsuperscript{13}C NMR δ 165.3, 144.4, 141.9, 141.7, 138.1, 135.7, 133.8, 132.9, 131.6, 130.5, 130.2, 127.5 (2), 127.4, 127.2 (2), 127.1, 123.4, 45.5; MS m/z 402.4 (MH\textsuperscript{+}, 100%). Anal. Calcd for C\textsubscript{19}H\textsubscript{18}ClN\textsubscript{3}O\textsubscript{3}S: C, 56.79; H, 4.01; N, 10.46. Found: C, 56.90; H, 4.07; N, 10.57%.

**Example 13**
Preparation of 4-((2-Bromophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (22).

[0205] Method C. Reaction of amine salt 6 (400 mg, 1.0 mmol) and 2-bromobenzenesulfonyl chloride (289 mg, 1.1 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 22 (219 mg, 48%) as a cream coloured powder: mp (EtOAc) 200-202 °C; \textsuperscript{1}H NMR δ 10.35 (s, 1 H, NHCO), 8.93 (d, J = 2.3 Hz, 1 H, H-2\textsuperscript{\text{b}}), 8.51 (br s, 1 H, NHSO\textsubscript{2}), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6\textsuperscript{\text{b}}),
8.1 8 (d, J = 8.3 Hz, 1 H, H-4'), 7.98 (dd, J = 7.6, 1.9 Hz, 1 H, H-5”), 7.88 (d, J = 8.3 Hz, 2 H, H-2, H-6), 7.81 (dd, J = 7.6, 1.4 Hz, 1 H, H-2”), 7.49-7.54 (m, 2 H, H-3”, H-4”), 7.37-7.41 (m, 3 H, H-3, H-5, H-5”), 4.22 (s, 2 H, CH₃N); ¹³C NMR δ 165.4, 144.4, 141.9, 141.7, 139.8, 135.7, 135.1, 133.7, 132.9, 130.4, 128.0, 127.5 (2), 127.2 (2), 127.2, 123.4, 119.1, 45.6. Anal. Calcd for C₂₉H₂₈BrN₃O₅S: C, 51.13; H, 3.61; N, 9.41. Found: C, 51.69; H, 3.78; N, 9.52%.

**Example 14**

**Preparation of Methyl 2-((N-(4-(Pyridin-3-yl)carbamoyl)benzyl)sulfamoyl)benzoate (23)**

![Diagram of Methyl 2-((N-(4-(Pyridin-3-yl)carbamoyl)benzyl)sulfamoyl)benzoate (23)]

[0206] **Method C.** Reaction of amine salt 6 (400 mg, 1.0 mmol) and methyl 2-(chlorosulfonyl)benzoate (365 mg, 1.6 mmol) followed by column chromatography, eluting with EtOAc, gave the benzoate 23 (225 mg, 49%) as a white powder: mp (EtOAc) 155-157 °C; ¹H NMR δ 10.36 (s, 1 H, NHCO), 8.92 (d, J = 2.2 Hz, 1 H, H-2”), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6”), 8.18 (d, J = 8.4 Hz, 1 H, H-4”), 8.11 (br s, 1 H, NHSO₂), 7.90-7.87 (m, 3 H, H-6, H-2”, H-6”), 7.65-7.71 (m, 3 H, H-3, H-4, H-5), 7.67-7.42 (m, 3 H, H-3”, H-5”, H-5”), 4.20 (s, 2 H, CH₃N), 3.86 (s, 3 H, OCH₃); ¹³C NMR δ 167.7, 165.4, 144.4, 141.9, 141.8, 138.1, 135.7, 132.9, 132.4, 131.7, 130.9, 128.6, 128.1, 127.5 (2), 127.2 (2), 127.2, 123.4, 52.8, 45.5. Anal. Calcd for C₂₉H₂₈BrN₃O₅S: C, 59.28; H, 4.50; N, 9.88. Found: C, 59.36; H, 4.46; N, 9.77%.

**Example 15**

**Preparation of N-(pyridin-3-yl)-4-((2-(trifluoromethyl)phenylsulfonamido)methyl)benzamide (24).**

![Diagram of N-(pyridin-3-yl)-4-((2-(trifluoromethyl)phenylsulfonamido)methyl)benzamide (24)]

[0207] **Method C.** Reaction of amine salt 6 (398 mg, 1.0 mmol) and 2-trifluoromethylbenzenesulfonyl chloride (0.17 mL, 1.1 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 24 (149 mg, 34%) as a white powder: mp (EtOAc) 234-237 °C; ¹H NMR δ 10.36 (s, 1 H, NHCO), 8.92 (d, J = 2.2 Hz, 1 H, H-2”), 8.61 (br s, 1 H, NHSO₂), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6”), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4”), 8.10 (br d, J = 8.7 Hz, 1 H, H-6”)’, 7.97 (br dd, J
= 7.2, 1.9 Hz, 1 H, H-3") \*, 7.91 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.80-7.88 (m, 2 H, H-4", H-5"), 7.43 (br d, 2 H, H-3, H-5), 7.39 (ddd, J = 8.3, 4.7, 0.5 Hz, 1 H, H-5"), 4.25 (s, 2 H, CH₂N); \^{13}C \text{ NMR } \delta 165.4, 144.4, 141.9, 141.7, 139.6, 135.6, 133.1, 133.0, 132.7, 129.9, 128.2 (q, J = 6 Hz), 127.6 (2), 127.3 (2), 127.1, 125.9 (q, J = 33 Hz), 123.3, 122.8 (q, J = 274 Hz), 45.7; MS m/z 436.5 (MH\(^+\), 100%). Anal. Calcd for C\(_{26}\)H\(_6\)F\(_3\)N\(_2\)O\(_3\): C, 55.1; H, 3.70; N, 9.65. Found: C, 55.40; H, 3.87; N, 9.66%.

*Assignments interchangeable

**Example 16**

**Preparation of 4-((2-Cyanophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (25).**

![Chemical structure](image)

**[0208]** Method C. Reaction of amine salt 6 (414 mg, 1.1 mmol) and 2-cyanobenzenesulfonyl chloride (240 mg, 1.2 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 25 (140 mg, 34%) as a white powder: mp (EtOAc) 217-220 °C; \(^1\text{H} \text{NMR} \delta 10.36 (s, 1 H, NHCO), 8.92 (d, J = 2.2 Hz, 1 H, H-2"), 8.58 (br s, 1 H, NHSO\(_2\)) \), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6"), 8.15-8.19 (m, 2 H, H-4", H-6"), 8.05 (ddd, J = 8.6, 7.6, 1.2 Hz, 1 H, H-5"), 7.91-7.96 (m, 1 H, H-3"), 7.83-7.88 (m, 3 H, H-2, H-6, H-4"), 7.35-7.42, (m, 3 H, H-3, H-5, H-5"), 4.28 (s, 2 H, CH₂N); MS m/z 393.3 (MH\(^+\), 100%). Anal. Calcd for C\(_{26}\)H\(_6\)N\(_4\)O\(_3\): C, 61.21; H, 4.11; N, 14.28. Found: C, 61.28; H, 4.08; N, 14.19%.

**Example 17**

**Preparation of 4-((3-Aminophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (26).**

![Chemical structure](image)

**[0209]** A mixture of nitrophenylbenzamide 34 (252 mg, 0.6 mmol) and Pd/C (50 mg, catalytic) in EtOH/EtOAc (1:1, 80 ml) was stirred under H\(_2\) (50 psi) at 20 °C for 2 h. The mixture was filtered through Celite, the Celite was washed with EtOH (20 ml), and the solvent was evaporated. The residue was purified by column chromatography, eluting with a gradient (0-5%) of MeOH/EtOAc, to give benzamide 26 (166 mg, 71%) as a white powder: mp (EtOH/EtOAc) 211-213 °C; \(^1\text{H} \text{NMR} \delta...
Example 18
Preparation of 4-((3-Methoxyphenylsulfonamido)methyl)-\(\text{\textit{N}}\)-(pyridin-3-yl)benzamide (27).

[0210] Method C. Reaction of amine salt 6 (477 mg, 1.2 mmol) and 3-methoxybenzenesulfonyl chloride (0.19 mL, 1.4 mmol) followed by column chromatography, eluting with a gradient (50-1 00%) of EtOAc/pet. ether, gave benzamide 27 (247 mg, 51%) as a white powder: mp (MeOH/EtOAc) 148-1 51 °C; \(^1\text{H NMR} \delta 10.39 (s, 1 H, NHCO), 8.93 (d, J = 2.3 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.19 (dd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 8.03 (br s, 1 H, NHSO\(_2\)), 7.92 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.44 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 7.39 (dd, J = 8.3, 4.7 Hz, 1 H, H-5), 7.20 (br t, J = 7.9 Hz, 1 H, H-5"), 7.04 (br t, J = 2.0 Hz, 1 H, H-2"), 6.93 (br ddd, J = 7.6, 1.6, 0.8 Hz, 1 H, H-6"), 6.77 br ddd, J = 8.0, 2.2, 0.8 Hz, 1 H, H-4"), 5.56 (s, 2 H, NH\(_2\)), 4.06 (s, 2 H, CH\(_2\)N); \(^{13}\text{C NMR} \delta 165.5, 149.3, 144.4, 142.0, 141.9, 140.9, 135.7, 132.9, 129.4, 127.6 (2), 127.3 (2), 127.2, 123.4, 117.1, 113.0, 111.0, 45.7; MS m/z 383.4 (MH\(^+\), 100%). Anal. Calcd for C\(_{19}\)H\(_{19}\)N\(_2\)O\(_4\)S: C, 59.67; H, 4.74; N, 14.65. Found: C, 59.48; H, 4.92; N, 14.45%.

Example 19
Preparation of 4-((3-Methylphenylsulfonamido)methyl)-\(\text{\textit{N}}\)-(pyridin-3-yl)benzamide (28)
[021 1] Method C. Reaction of amine salt 6 (400 mg, 1.0 mmol) and 3-toluenesulfonyl chloride (216 mg, 1.1 mmol) followed by column chromatography, eluting with EtOAc, to give benzamide 28 (250 mg, 64%) as a white powder, mp (EtOAc) 180-182 °C; 1H NMR δ 10.37 (s, 1 H, NHCO), 8.93 (d, J = 2.3 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.17-8.20 (m, 2 H, NHSO₂, H-4'), 7.91 (d, J = 8.3 Hz, 2 H, H-2, H-6), 7.60-7.64 (m, 2 H, H-2", H-6"), 7.37-7.48 (m, 5 H, H-3, H-5, H-5', H-4", H-5"), 4.09 (d, J = 6.3 Hz, 2 H, CH₂N), 2.38 (s, 3 H, CH₃); 13C NMR δ 165.4, 144.4, 141.9, 141.8, 140.5, 138.7, 135.7, 132.9, 128.6, 128.9, 127.5 (2), 127.3 (2), 127.2, 126.6, 123.5, 123.4, 45.6, 20.7. Anal. Calcd for C₁₆H₁₁N₂O₃S: C, 62.97; H, 5.02; N, 11.02%. Found: C, 63.19; H, 5.05; N, 11.05%.

Example 20
Preparation of 4-((3-Chlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (29).

![Chemical structure](image)

[021 2] Method C. Reaction of amine salt 6 (400 mg, 1.0 mmol) and 3-fluorobenzenesulfonyl chloride (220 mg, 1.1 mmol) followed by column chromatography, eluting with EtOAc gave benzamide 29 (230 mg, 58%) as a white powder: mp (EtOAc) 181-183 °C; 1H NMR δ 10.37 (s, 1 H, NHCO), 8.93 (d, J = 2.3 Hz, 1 H, H-2'), 8.40 (br s, 1 H, NHSO₂), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (d, J = 8.3 Hz, 1 H, H-4'), 7.91 (d, J = 8.3 Hz, 2 H, H-2, H-6), 7.51-7.67 (m, 4 H, H-2", H-4", H-5", H-6"), 7.37-7.42 (m, 3 H, H-3, H-5, H-5), 4.14 (s, 2 H, CH₂N); 13C NMR δ 165.4, 161.6 (d, J = 248 Hz), 144.4, 142.7 (d, J = 7 Hz), 141.9, 141.5, 135.7, 133.0, 131.5 (d, J = 8 Hz), 127.6 (2), 127.3 (2), 127.2, 123.4, 122.6 (d, J = 3 Hz), 119.4 (d, J = 21 Hz), 113.4 (d, J = 24 Hz), 45.6. Anal. Calcd for C₁₃H₁₁FN₃O₃S: C, 59.21; H, 4.18; N, 10.90. Found: C, 59.24; H, 4.14; N, 10.73%.

Example 21
Preparation of 4-((3-Chlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (30).
[021 3] Method C. Reaction of amine salt 6 (798 mg, 2.1 mmol) and 3-chlorobenzenesulfonyl chloride (0.32 ml, 2.3 mmol) followed by column chromatography, eluting with a gradient (50-100%) of EtOAc/pet. ether, gave benzamide 30 (455 mg, 55%) as a white powder: mp (EtOAc) 181-183 °C; 1H NMR δ 10.36 (s, 1 H, NHCO), 8.92 (d, J = 2.5 Hz, 1 H, H-2'), 8.42 (br s, 1 H, NHSO₂), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.91 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.76-7.79 (m, 2 H, H-2", H-4") 7.71 (dt, J = 8.2, 1.6 Hz, 1 H, H-6"), 7.62 (br t, J = 8.2 Hz, 1 H, H-5"), 7.36-7.43 (m, 3 H, H-3, H-5, H-5'), 4.14 (s, 2 H, CH₂N); 13C NMR δ 165.34, 144.4, 142.5, 141.9, 141.4, 135.7, 133.6, 133.0, 132.2, 131.0, 127.6 (2), 127.4 (2), 127.2, 126.0, 125.0, 123.4, 45.6; MS m/z 402.3 (MH⁺, 100%). Anal. Calcd for C₂₉H₁₆Cl₄N₃O₅S: C, 56.79; H, 4.01; N, 10.46. Found: C, 56.74; H, 4.18; N, 10.51%.

Example 22
Preparation of 4-((3-Bromophenylsulfonamido)methyl)/V-(pyridin-3-yl)benzamide (31).

[021 4] Method C. Reaction of amine salt 6 (392 mg, 1.0 mmol) and 3-bromobenzenesulfonyl chloride (0.16 ml, 1.1 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 31 (271 mg, 60%) as a white powder: mp (MeOH/EtOAc) 181-184 °C; 1H NMR δ 10.36 (s, 1 H, NHCO), 8.92 (d, J = 2.4 Hz, 1 H, H-2'), 8.41 (br s, 1 H, NHSO₂), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.4, 1.5 Hz, 1 H, H-4'), 7.89-7.93 (m, 3 H, H-2, H-6, H-2''), 7.78-7.85 (m, 2 H, H-4", H-6''), 7.55 (t, J = 7.9 Hz, 1 H, H-5''), 7.36-7.43 (m, 3 H, H-3, H-5, H-5'), 4.14 (s, 2 H, CH₂N); 13C NMR δ 165.3, 144.4, 142.6, 141.9, 141.4, 135.7, 135.1, 133.0, 131.3, 128.8, 127.6 (2), 127.4 (2), 127.2, 125.4, 123.4, 122.0, 45.6; MS m/z 446.1, 446.2 (MH⁺, 100%). Anal. Calcd for C₉H₆BrN₃O₅S: C, 51.13; H, 3.61; N, 9.41. Found: C, 51.40; H, 3.75; N, 9.48%.

Example 23
Preparation of 4-((3-(Pyridin-3-yl)-4-((3-(trifluoromethyl)phenylsulfonamido)methyl)benzamide (32).
[0215] Method C. Reaction of amine salt 6 (588 mg, 1.5 mmol) and 3-
trifluoromethylbenzenesulfonyl chloride (0.27 mL, 1.7 mmol) followed by column
c chromatography, eluting with a gradient (50-1 00%) of EtOAc/pet. ether, gave
benzamide 32 (280 mg, 43%) as a white powder: mp (MeOH/EtOAc) 200-201 °C;
1H NMR 5 10.34 (s, 1 H, NHCO), 8.92 (d, J = 2.4 Hz, 1 H, H-2'), 8.52 (br s, 1 H,
NHSO2), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.4, 2.5, 1.5 Hz, 1 H, H-
4'), 8.10 (br d, J = 7.9 Hz, 1 H, H-4*), 7.98-8.03 (m, 2 H, H-2*, H-6*), 7.88 (br d, J =
8.3 Hz, 2 H, H-2, H-6), 7.83 (br t, J = 7.8 Hz, 1 H, H-5*), 7.39 (dd, J = 8.3, 0.6 Hz, 1
H, H-5'), 7.38 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 4.17 (s, 2 H, CH2N); 13C NMR δ
165.2, 144.2, 141.9, 141.8, 141.2, 135.6, 132.9, 130.7, 130.4, 129.7 (q, J = 33 Hz),
128.9 (q, J = 3 Hz), 127.6 (2), 127.4 (2), 127.2, 123.3, 123.2 (q, J = 273 Hz), 122.28
(q, J = 4 Hz), 45.6; MS m/z 436.5 (MH+, 100%). Anal. Calcd for C20H16F3N3O3S: C, 55.1 7;
H, 3.70; N, 9.65. Found: C, 55.40; H, 3.78; N, 9.69%.

Example 24
Preparation of 4-((3-Cyanophenylsulfonamido)methyl)-N-(pyridin-3-
yl)benzamide (33).

[0216] Method C. Reaction of amine salt 6 (41.9 mg, 1.1 mmol) and 3-
cyanobenzenesulfonyl chloride (239 mg, 1.2 mmol) followed by column
chromatography, eluting with EtOAc, gave benzamide 33 (266 mg, 63%) as a white
powder: mp (MeOH/EtOAc) 214-217 7° C; 1H NMR δ 10.36 (s, 1 H, NHCO), 8.92 (d, J =
2.2 Hz, 1 H, H-2'), 8.49 (br s, 1 H, NHSO2), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'),
8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4*), 8.15 (t, J = 1.5 Hz, 1 H, H-2*), 8.07-8.12
(m, 2 H, H-4*, H-6*), 7.90 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.79 (dd, J = 8.0, 7.9 Hz,
1 H, H-5*), 7.36-7.41 (m, 3 H, H-3, H-5, H-5'), 4.17 (s, 2 H, CH2N); 13C NMR δ 165.3,
144.4, 141.9 (2), 141.3, 135.8, 135.6, 133.0, 130.8, 130.6, 129.9, 127.6 (2), 127.4
(2), 127.2, 123.4, 117.4, 112.3, 45.6; MS m/z 393.4 (MH+, 100%). Anal. Calcd for
C20H16N4O3S: C, 61.21%; H, 4.11%; N, 14.28. Found: C, 61.04; H, 4.19; N, 14.00%.

Example 25
Preparation of 4-((3-Nitrophenylsulfonamido)methyl)\(\Lambda^\prime\)-(pyridin-3-yl)benzamide (34).

\[\text{Method C. Reaction of amine salt 6 (940 mg, 2.4 mmol) and 3-nitrobenzenesulfonyl chloride (589 mg, 2.7 mmol) followed by column chromatography, eluting with a gradient (0-5\%) of MeOH/EtOAc, gave benzamide 34 (588 mg, 59\%) as a white powder: mp (MeOH/EtOAc) 228-230 °C; } \text{\(^1\)H NMR } \delta 10.33 (s, 1 H, NHCO), 8.92 (d, J = 2.1 Hz, 1 H, H-2'), 8.63 (br s, 1 H, NHSO\(_2\)), 8.41-8.48 (m, 2 H, H-2'', H-4''), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.15-8.21 (m, 2 H, H-4', H-6''), 7.83-7.90 (m, 3 H, H-2, H-6, H-5'), 7.36-7.41 (m, 3 H, H-3, H-5, H-3'), 4.18 (s, 2 H, CH\(_2\)N); \text{\(^{13}\)C NMR 5} 165.2, 147.7, 144.4, 142.3, 141.9, 141.0, 135.6, 133.0, 132.4, 131.1, 127.6 (2), 127.5 (2), 127.2, 126.8, 123.3, 121.6, 45.7; MS m/z 241 3.5 (MH\(^+\), 100\%). Anal. Calcd for C\(_9\)H\(_6\)N\(_4\)O\(_5\)S: C, 55.33; H, 3.91; N, 13.58. Found: C, 55.57; H, 4.07; N, 13.54%.

Example 26
Preparation of 4-[[[1,1'-Biphenyl]-3-ylsulfonyl]amino]methyl-\(\Lambda^\prime\)-(3-pyridinyl)benzamide (35).

\[\text{Method C. Reaction of amine salt 6 (150 mg, 0.39 mmol) and 3-phenylenesulfonyl chloride (107 mg, 0.42 mmol) followed by column chromatography, eluting with a gradient (0-5\%) of MeOH/DCM, gave benzamide 35 (88 mg, 52\%) as a white powder: mp 180-1 82 °C; } \text{\(^1\)H NMR } \delta 10.33 (s, 1 H, NHCO), 8.91 (d, J = 2.1 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 2 H, H-6', NHSO\(_2\)), 8.17 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4''), 8.02 (t, J = 1.7 Hz, 1 H, H-2''), 7.92 (ddd, J = 7.8, 1.7, 1.1 Hz, 1 H, H-4''), 7.89 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.81 (ddd, J = 7.8, 1.7, 1.1 Hz, 1 H, H-6''), 7.66-7.70 (m, 3 H, H-5'', H-2''', H-6'''), 7.51 (t, J = 7.5 Hz, 2 H, H-3'', H-5'''), 7.37-7.45 (m, 4 H, H-3, H-5, H-5'', H-4'''), 4.15 (s, 2 H, CH\(_2\)N); \text{\(^{13}\)C NMR } \delta 165.3, 144.4, 141.9, 141.7, 141.3, 141.0, 138.5, 135.6, 132.9, 130.5, 129.8, 129.0 (2), 128.1, 127.5 (2), 127.3 (2), 127.2, 126.8 (2), 125.2, 124.3, 123.3, 45.7; MS m/z

**Example 27**


[0219] **Method C.** Reaction of amine salt 6 (175 mg, 0.45 mmol) and 3-pyrimidine-2-ylbenzenesulfonyl chloride (150 mg, 0.59 mmol) gave benzamide 36 (136 mg, 68%) as a dark yellow powder: mp 203-206 °C; ¹H NMR δ 10.31 (s, 1 H, NHCO), 8.96 (d, J = 4.9 Hz, 2 H, H-4″, H-6″), 8.91 (d, J = 2.3 Hz, 1 H, H-2″), 8.82 (t, J = 1.7 Hz, 1 H, H-2″), 8.62 (dt, J = 8.0, 1.3 Hz, 1 H, H-6″ or H-4″), 8.41 (t, J = 6.2 Hz, 1 H, NHSO₂), 8.31 (ddd, J = 4.7, 1.4 Hz, 1 H, H-6″), 8.17 (ddd, J = 8.4, 2.5, 1.5 Hz, 1 H, H-4″), 7.97 (ddd, J = 7.8, 1.8, 1.1 Hz, 1 H, H-4″ or H-6″), 7.87 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.75 (t, J = 7.8 Hz, 1 H, H-5″), 7.52 (t, J = 4.9 Hz, 1 H, H-5″’), 7.37-7.42 (m, 3 H, H-3, H-5, H-5″), 4.14 (s, 2 H, CH₂N); ¹³C NMR δ 165.3, 161.8, 157.8 (2), 144.4, 141.9, 141.5, 141.3, 138.0, 135.6, 132.9, 131.0, 129.7, 128.5, 127.6 (2), 127.3 (2), 127.2, 125.5, 123.3, 120.5, 45.7; MS m/z 446.9 (MH⁺, 100%); HRMS (FAB⁺) calcd for C₂₃H₂₀N₂O₃S (MH⁺) m/z 446.1287, found 446.1286. Anal. calcd for C₂₃H₁₉N₂O₃S₄ (80%): C, 58.4; H, 4.5; N, 10.0. Found: C, 58.4; H, 4.5; N, 10.0.

**Example 28**


[0220] **Method C.** Reaction of amine salt 6 (160 mg, 0.41 mmol) and 3-(1-methyl-1-H-pyrazol-3-yl)benzenesulfonyl chloride (137 mg, 0.54 mmol) followed by column chromatography, eluting with a gradient (0-5%) of MeOH/DCM, gave benzamide 44.
(141 mg, 77%) as a white powder: mp 188-1 91 °C; \(^1\)H NMR 5 10.34 (s, 1 H, NHCO), 8.92 (br s, 1 H, H-2'), 8.28-8.31 (m, 2 H, H-6', NHSO\(_2\)), 8.23 (t, J = 1.6 Hz, 1 H, H-2''), 8.18 (ddd, J = 8.4, 2.4, 1.5 Hz, 1 H, H-4'), 8.01 (dt, J = 8.0, 1.3 Hz, 1 H, H-4'' or H-6''), 7.90 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.78 (d, J = 2.3 Hz, 1 H, H-5''), 7.72 (ddd, J = 7.8, 1.8, 1.1 Hz, 1 H, H-6'' or H-4''), 7.61 (t, J = 7.8 Hz, 1 H, H-5''), 7.37-7.43 (m, 3 H, H-3, H-5, H-5'), 6.77 (d, J = 2.3 Hz, 1 H, H-4''), 4.12 (s, 2 H, CH\(_2\)N), 3.91 (s, 3 H, CH\(_3\)); \(^{13}\)C NMR 5 165.4, 148.4, 144.3, 141.8, 141.7, 141.0, 135.7, 134.3, 132.9, 132.6, 129.5, 128.6, 127.6 (2), 127.3 (2), 127.2, 125.0, 123.4, 122.4, 102.9, 45.6, 38.6; MS m/z 449.0 (MH\(^+\), 100%); HRMS (FAB\(^+\)) calcd for C\(_{23}\)H\(_{22}\)N\(_5\)O\(_3\)S (MH\(^+\)) m/z 448.1443, found 448.1442. Anal. calcd for C\(_{23}\)H\(_{21}\)N\(_5\)O\(_3\)S-V\(_2\)CH\(_3\)OH: C, 60.89; H, 5.00; N, 15.1 1. Found: C, 60.93; H, 4.70; N 15.49 %.

Example 29

Preparation of 4-[[3-(5-Methyl-1,3,4-oxadiazol-2-yl)phenyl[sulfonyl]amino)methyl]-N-(3-pyridinyl)benzamide (38).

[0221] Method C. Reaction of amine salt 6 (150 mg, 0.39 mmol) and 3-(5-methyl-1,3,4-oxadiazol-2-yl)benzenesulfonyl chloride (150 mg, 0.58 mmol) followed by column chromatography, eluting with a gradient (0-1 0%) of MeOH/DCM, gave benzamide 38 (45 mg, 26%) as a white powder: mp (MeOH/DCM) 227-230 °C; \(^1\)H NMR 5 10.30 (s, 1 H, NHCO), 8.91 (d, J = 2.0 Hz, 1 H, H-2'), 8.50 (t, J = 6.3 Hz, 1 H, NHSO\(_2\)), 8.31 (d, J = 3.8 Hz, 1 H, H-6'), 8.24 (t, J = 1.6 Hz, 1 H, H-2''), 8.15-8.1 9 (m, 2 H, H-4', H-4'' or H-6''), 7.99-8.02 (m, 1 H, H-6'' or H-4''), 7.86 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.79 (t, J = 7.9 Hz, 1 H, H-5''), 7.37-7.43 (m, 3 H, H-3, H-5, H-5'), 4.16 (d, J = 6.3 Hz, 2 H, CH\(_2\)N), 2.59 (s, 3 H, CH\(_3\)); \(^{13}\)C NMR 5 165.2, 164.3, 144.3, 141.9, 141.8, 141.2, 132.8, 130.5, 129.7, 129.2, 127.5 (2), 127.4 (2), 127.3, 127.0, 124.3, 124.0, 123.4, 45.7, 10.5, one C not observed; MS m/z 450.9 (MH\(^+\), 100%); HRMS (FAB\(^+\)) calcd for C\(_{22}\)H\(_{20}\)N\(_5\)O\(_4\)S (MH\(^+\)) m/z 450.1 236, found 450.1 238. Anal. calcd for C\(_{22}\)H\(_{19}\)N\(_5\)O\(_4\)S-V\(_2\)CH\(_3\)OH: C, 58.06; H, 4.55; N, 15.04. Found: C, 58.1 3; H, 4.30; N 15.01%.

Example 30
Preparation of 4-[[[3-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl)sulfonyl]amino]methyl]-N-(3-pyridinyl)benzamide (39).

[0222] Method C. Reaction of amine salt 6 (163 mg, 0.42 mmol) and 3-(5-methyl-1,2,4-oxadiazol-3-yl)benzenesulfonyl chloride (130 mg, 0.50 mmol) followed by column chromatography, eluting with a gradient (0-6%) of MeOH/DCM, gave benzamide 39 (115 mg, 61%) as a cream powder: mp 182-1 85 °C; 1H NMR δ 10.30 (s, 1 H, NHCO), 8.91 (d, J = 2.1 Hz, 1 H, H-2'), 8.47 (br s, 1 H, NHSO₂), 8.30-8.33 (m, 2 H, H-6', H-2''), 8.21 (m, 1 H, H-4' or H-6''), 8.17 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4''), 7.99 (dd, J = 7.9, 1.8, 1.2 Hz, 1 H, H-6'' or H-4''), 7.86 (br d, J = 8.3 Hz, 2 H, H-2', H-6'), 7.77 (t, J = 7.8 Hz, 1 H, H-5''), 7.37-7.41 (m, 3 H, H-3, H-5, H-5''), 4.15 (s, 2 H, CH₂N), 2.67 (s, 3 H, CH₃); 13C NMR δ 177.8, 166.5, 165.2, 144.4, 141.9, 141.7, 141.3, 135.6, 132.8, 130.3, 130.2, 129.1, 127.5 (2), 127.4 (2), 127.4, 124.7, 123.3, 45.7, 11.9: MS m/z 450.9 (MH⁺, 100%). Anal. calcd for C₂₂H₁₉N₅O₄S: C, 58.79; H, 4.26; N, 15.58. Found: C, 58.90; H, 4.54; N, 15.36%.

Example 31
Preparation of 4-[[[3-(2-Methyl-1,3-thiazol-4-yl)phenyl)sulfonyl]amino]methyl]-N-(3-pyridinyl)benzamide (40).

[0223] Method C. Reaction of amine salt 6 (165 mg, 0.42 mmol) and 3-(2-methyl-1,3-thiazol-4-yl)benzenesulfonyl chloride (150 mg, 0.55 mmol) followed by column chromatography, eluting with a gradient (0-10%) of MeOH/DCM, gave benzamide 40 (112 mg, 57%) as a white powder: mp 200-202 °C; 1H NMR δ 10.33 (s, 1 H, NHCO), 8.92 (d, J = 2.4 Hz, 1 H, H-2'), 8.36 (t, J = 1.6 Hz, 1 H, H-2''), 8.30-8.32 (m, 2 H, H-6', NHSO₂), 8.16-8.19 (m, 2 H, H-4', H-4'' or H-6''), 8.08 (s, 1 H, H-5''), 7.89 (br d, J = 8.3 Hz, 2 H, H-2', H-6'), 7.77 (m, 1 H, H-6'' or H-4''), 7.64 (t, J = 7.8 Hz, 1 H, H-5''), 7.37-7.42 (m, 3 H, H-3, H-5, H-5''), 4.13 (s, 2 H, CH₂N), 2.73 (s, 3 H, CH₃); 13C NMR δ 166.0, 165.3, 152.0, 144.4, 141.9, 141.6, 141.1, 135.7, 134.9, 132.9, 129.6
Example 32
Preparation of 4-((4-Aminophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (41).

[0224] A mixture of nitrophenylbenzamide 60 (296 mg, 0.72 mmol) and Pd/C (50 mg, catalytic) in EtOH/EtOAc (1:1, 80 ml) was stirred under H₂ (50 psi) at 20 °C for 2 h. The mixture was filtered through Celite, the Celite was washed with EtOH (20 ml), and the solvent was evaporated. The residue was purified by column chromatography, eluting with a gradient (0-5%) of MeOH/EtOAc, to give benzamide 41 (21 0 mg, 76%) as a white powder: mp (EtOH/EtOAc) 219-221 °C; ¹H NMR δ 10.37 (s, 1 H, NHCO), 8.93 (d, J = 2.2 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.92 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.72 (br t, J = 6.4 Hz, 1 H, NHSO₂), 7.47 (ddd, J = 8.7, 2.6, 1.8 Hz, 2 H, H-2", H-6"), 7.42 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 7.38 (dd, J = 8.3, 4.7 Hz, 1 H, H-5'), 6.62 (ddd, J = 8.7, 2.6, 1.8 Hz, 2 H, H-3", H-5"), 5.92 (br s, 2 H, NH₂), 3.98 (d, J = 6.4 Hz, 2 H, CH₂N); ¹³C NMR δ 165.5, 152.4, 144.4, 142.4, 141.9, 135.7, 132.8, 128.4 (2), 127.5 (2), 127.3 (2), 127.2, 125.4, 123.3, 112.6 (2), 45.6; MS m/z 383.4 (MH⁺, 100%). Anal. Calcd for C₁₉H₁₈N₄O₃S-I½H₂O: C, 55.75; H, 5.17; N, 13.68. Found: C, 55.79; H, 4.71; N, 13.46%.

Example 33
Preparation of 4-((4-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (42).

[0225] Method C. Reaction of amine salt 6 (400 mg, 1.0 mmol) and 4-methoxybenzenesulfonyl chloride (234 mg, 1.1 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 42 (31 1 mg, 76%) as a white powder: mp (EtOAc) 208-210 °C; ¹H NMR δ 10.37 (s, 1 H, NHCO), 8.93 (d, J = 2.2 Hz,
Hz, 1 H, H-2'), 8.31 (dd, J = 4.6, 1.5 Hz, 1 H, H-6'), 8.18 (d, J = 8.3 Hz, 1 H, H-4'), 8.08 (br s, 1 H, NHSO$_2$), 7.90 (d, J = 8.4 Hz, 2 H, H-2, H-6), 7.75 (dd, J = 8.9, 3.0 Hz, 2 H, H-2', H-6'), 7.37-7.42 (m, 3 H, H-3, H-5, H-5'), 7.10 (dd, J = 8.9, 3.0 Hz, 2 H, H-3', H-5'), 4.05 (br s, 2 H, CH$_2$N), 3.83 (s, 3 H, OCH$_3$); $^{13}$C NMR δ 165.4, 162.0, 144.4, 141.9, 141.8, 135.7, 132.9, 132.2, 128.5 (2), 127.6 (2), 127.3 (2), 127.2, 123.4, 114.2 (2), 55.5, 45.6. Anal. Calcd for C$_{27}$H$_9$N$_3$O$_4$S: C, 60.44; H, 4.82; N, 10.57. Found: C, 60.73; H, 4.91; N, 10.65%.

**Example 34**

**Preparation of 4-((4-Butoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (43).**

![4-(4-Butoxyphenylsulfonamido)methyl]-N-(pyridin-3-yl)benzamide](image)

**[0226] Method C.** Reaction of amine salt 6 (395 mg, 1.0 mmol) and A-butoxybenzenesulfonyl chloride (277 mg, 1.1 mmol) followed by column chromatography, eluting with a gradient (50-100%) of EtOAc/pet. ether, gave benzamide 43 (31.9 mg, 71%) as a white powder: mp (EtOAc/pet. ether) 189-191 °C; $^1$H NMR 5.10.36 (s, 1 H, NHCO), 8.92 (d, J = 2.0 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.19 (dd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 8.07 (br s, 1 H, NHSO$_2$), 7.89 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.71 (dd, J = 8.9, 3.0, 2.0 Hz, 2 H, H-2', H-6'), 7.35-7.41 (m, 3 H, H-3, H-5, H-5'), 7.07 (dd, J = 8.9, 3.0, 2.0 Hz, 2 H, H-3', H-5'), 4.00-4.06 (m, 4 H, CH$_2$O, CH$_2$N), 1.65-1.73 (m, 2 H, CH$_2$), 1.37-1.47 (m, 2 H, CH$_2$), 0.91 (t, J = 7.4 Hz, 3 H, CH$_3$); $^{13}$C NMR δ 165.4, 161.5, 144.4, 141.9, 140.7, 135.7, 132.9, 132.0, 128.5 (2), 127.5 (2), 127.3 (2), 127.1, 123.3, 114.6 (2), 67.6, 45.6, 30.4, 18.5, 13.5; MS m/z 440.6 (MH$^+$, 100%). Anal. Calcd for C$_{25}$H$_{25}$N$_3$O$_4$S: C, 62.85; H, 5.73; N, 9.56. Found: C, 63.07; H, 5.84; N, 9.52%.

**Example 35**

**Preparation of 4-((4-Phenoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (44).**

![4-(4-Phenoxyphenylsulfonamido)methyl]-N-(pyridin-3-yl)benzamide](image)

**[0227] Method C.** Reaction of amine salt 6 (31.8 mg, 0.82 mmol) and A-phenoxyphenylsulfonyl chloride (241 mg, 0.90 mmol) followed by column
chromatography, eluting with EtOAc, gave benzamide 44 (184 mg, 49%) as a white powder: mp (MeOH/EtOAc) 200-202 °C; 1H NMR δ 10.37 (s, 1 H, NHCO), 8.93 (d, J = 2.3 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.22 (m, 1 H, NHSO₂), 8.19 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.90 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.76 (ddd, J = 8.9, 2.1, 2.0 Hz, 2 H, H-2", H-6") 7.37-7.45 (m, 5 H, H-3, H-5, H-5', H-3", H-5"), 7.23 (dt, J = 7.4, 1.0 Hz, 1 H, H-4''), 7.11 (dt, J = 7.6, 1.0 Hz, 2 H, H-2", H-6''), 7.07 (ddd, J = 8.9, 2.9, 2.0 Hz, 2 H, H-2", H-6''), 4.11 (s, 2 H, CH₂N); 13C NMR δ 165.4, 160.2, 154.8, 144.4, 141.9, 141.6, 135.7, 134.7, 132.8, 130.2 (2), 129.9 (2), 127.5 (2), 127.4 (2), 127.2, 124.7, 123.4, 119.8 (2), 117.5 (2), 45.6; MS m/z 460.6 (MH⁺, 100%). Anal. Calcd for C₂₅H₂₁N₃O₄S: C, 65.34; H, 4.61; N, 9.14. Found: C, 65.41; H, 4.55; N, 9.22%.

Example 36
Preparation of 4-((4-Methylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (45).

[0228] Method C. Reaction of amine salt 6 (530 mg, 1.4 mmol) and 4-toluenesulfonyl chloride (286 mg, 1.5 mmol) followed by column chromatography, eluting with a gradient (0-10%) of MeOH/EtOAc, gave benzamide 45 (218 mg, 42%) as a white powder: mp (EtOAc) 194-197 °C; 1H NMR δ 10.37 (s, 1 H, NHCO), 8.92 (d, J = 2.2 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.19 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 8.16 (br s, 1 H, NHSO₂), 7.90 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.70 (br d, J = 8.3 Hz, 2 H, H-2", H-6''), 7.36-7.44 (m, 5 H, H-3, H-5, H-5', H-3", H-5"), 4.06 (s, 2 H, CH₂N), 2.39 (s, 3 H, CH₃); 13C NMR δ 165.4, 144.4, 142.5, 141.9 (2), 141.8, 137.6, 132.9, 129.5 (2), 127.5 (2), 127.3 (2), 127.2, 126.4 (2), 123.4, 45.6, 20.9; MS m/z 382.5 (MH⁺, 100%). Anal. Calcd for C₂₀H₁₉N₃O₃S: C, 62.97; H, 5.02; N, 11.02. Found: C, 62.23; H, 5.11; N, 11.16%.

Example 37
Preparation of 4-((4-Propylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (46).
[0229] Method C. Reaction of amine salt 6 (400 mg, 1.0 mmol) and 4-propylbenzenesulfonyl chloride (247 mg, 1.1 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 46 (300 mg, 71%) as a white powder: mp (EtOAc) 190-191 °C; ¹H NMR δ 10.35 (s, 1 H, NHCO), 8.92 (d, J = 2.3 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.15-8.20 (m, 2 H, H-4', NHSO₂), 7.88 (d, J = 8.3 Hz, 2 H, H-2, H-6), 7.70 (d, J = 8.3 Hz, 2 H, H-2'', H-6''), 7.36-7.40 (m, 5 H, H-3, H-5, H-5', H-3'', H-5''), 4.09 (d, J = 6.4 Hz, 2 H, CH₂N), 2.62 (t, J = 7.6 Hz, 2 H, CH₂), 1.59 (s, J = 7.4 Hz, 2 H, CH₂), 0.87 (t, J = 7.3 Hz, 3 H, CH₃); ¹³C NMR 5 165.4, 146.9, 144.4, 141.9, 141.7, 138.0, 135.7, 132.8, 128.9 (2), 127.5 (2), 127.3 (2), 127.2 (2), 126.4, 123.3, 45.6, 36.8, 23.6, 13.4. Anal. Calcd for C₂₂H₂₃N₃O₃S: C, 64.53; H, 5.66; N, 10.26. Found: C, 64.46; H, 5.73; N, 10.16%.

Example 38
Preparation of 4-[[4-(4-ferf-Butylphenyl)sulfonylamido)methyl]-/Λ-(3-pyridin-3-yl)benzamide (47).

[0230] Method C. Reaction of amine salt 6 (740 mg, 1.9 mmol) and 4-tert-butylbenzenesulfonyl chloride (490 mg, 2.1 mmol) followed by column chromatography, eluting with a gradient (50-100%) of EtOAc/pet. ether, gave benzamide 47 (560 mg, 70%) as a white powder: mp (EtOAc) 210-212 2 °C; ¹H NMR δ 10.35 (s, 1 H, NHCO), 8.90 (d, J = 2.3 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.13-8.20 (m, 2 H, NHSO₂, H-4'), 7.86 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.68 (br d, J = 8.6 Hz, 2 H, H-2'', H-6''), 7.54 (br d, J = 8.6 Hz, 2 H, H-3'', H-5''), 7.35-7.40 (m, 3 H, H-3, H-5, H-5'), 4.09 (s, 2 H, CH₂N), 1.29 [s, 9 H, C(CH₃)₃]; ¹³C NMR δ 165.4, 155.2, 144.4, 141.9, 141.7, 137.7, 135.7, 132.8, 127.5 (2), 127.3 (2), 127.2, 126.2 (2), 125.8 (2), 123.4, 45.7, 34.6, 30.6 (3); MS m/z 424.5 (MH⁺, 100%). Anal. Calcd for C₂₅H₃₅N₃O₃S: C, 65.22; H, 5.95; N, 9.92. Found: C, 65.19; H, 6.10; N, 9.84%.

Example 39
[0231] **Method C.** Reaction of amine salt 6 (200 mg, 0.51 mmol) and 4-adamantan-1-ylbenzenesulfonyl chloride (208 mg, 0.67 mmol) followed by column chromatography, eluting with a gradient (50-75%) of EtOAc/pet. ether gave benzamide 48 (73 mg, 28%) as a white powder: mp (H_2O) 220-222 °C; 1H NMR δ 10.32 (s, 1 H, NHCO), 8.93 (d, J = 2.3 Hz, 1 H, H-2'), 8.30 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.1 6-8.20 (m, 2 H, NHSO_2, H-4'), 7.83 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.66 (br d, J = 8.6 Hz, 2 H, H-2", H-6"), 7.47 (br d, J = 8.6 Hz, 2 H, H-3", H-5"), 7.39 (dd, J = 8.4, 4.7, 1 H, H-5'), 7.35 (br d, J = 8.6 Hz, 2 H, H-3, H-5), 4.1 0 (d, J = 6.3 Hz, 2 H, CH_2N), 1.98-2.03 (m, 3 H, 3 x CH), 1.83 (br s, 6 H, 3 x CH_2), 1.75-1.84 (m, 6 H, 3 x CH_2); 13C NMR 5 165.3, 155.1, 144.4, 141.8, 141.5, 137.8, 135.7, 132.7, 127.4 (2), 127.3 (2), 127.1, 126.2 (2), 125.3 (2), 123.3, 45.7, 42.0 (3), 36.0, 35.8 (3), 28.0 (3); MS m/z 503.2 (MH+, 100%). Anal. calcd for C_{29}H_{31}N_{3}O_{3}S: C, 69.43; H, 6.23; N, 8.38. Found: C, 69.25; H, 6.30; N, 8.50%.

**Example 40**

**Preparation of 4-[[[(4-(3-chloro-1-adamantyl)phenyl)sulfonyl]amino)methyl]-V-(3-pyridinyl)benzamide (49).**

[0232] **Method C.** Also isolated from the above reaction was the chloride 49 (23 mg, 8%) as a white powder: mp (H_2O) 229-232 °C; 1H NMR δ 10.32 (s, 1 H, NHCO), 8.93 (d, J = 2.3 Hz, 1 H, H-2'), 8.30 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.1 7-8.23 (m, 2 H, NHSO_2, H-4'), 7.83 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.67 (br d, J = 8.6 Hz, 2 H, H-2", H-6"), 7.50 (br d, J = 8.6 Hz, 2 H, H-3", H-5"), 7.38 (dd, J = 8.3, 4.7, 1 H, H-5'), 7.34 (br d, J = 8.6 Hz, 2 H, H-3, H-5), 4.1 1 (d, J = 6.3 Hz, 2 H, CH_2N), 2.22 (br s, 4 H, 2 x CH_2), 2.1 0 (br d, J = 2.5 Hz, 4 H, 2 x CH_2), 1.75-1.84 (m, 4 H, 2 x CH_2), 1.57-1.65 (m, 2 H, CH_2); 13C NMR δ 165.3, 152.9, 144.4, 141.8, 141.4, 138.3, 135.7, 132.7, 127.4 (2), 127.3 (2), 127.1, 127.0, 126.3 (2), 125.4 (2), 123.3, 69.5, 51.5 (2), 46.0 (2), 40.4, 40.0 (2), 33.6, 31.2 (2); MS m/z 533.3 (MH+, 100%). Anal. calcd for C_{29}H_{30}ClN_{3}O_{3}S: C, 64.97; H, 5.64; N, 7.84. Found: C, 64.97; H, 5.94; N, 7.65%.

**Example 41**
Preparation of Methyl 3-{4-[(4-[(3-pyridinylamino)carbonyl]benzyl)amino]sulfonyl}phenyl]propanoate (50).

[0233] Method C. Reaction of amine salt 6 (500 mg, 1.29 mmol) and 3-(4-chlorosulfonyl)phenylpropionate (407 mg, 1.55 mmol) followed by column chromatography, eluting with a gradient (0-10%) of MeOH/DCM, gave benzamide 50 (427 mg, 73%) as a white powder: mp 181-1 82 °C; 1H NMR δ 10.35 (s, 1 H, NHCO), 8.92 (d, J = 2.0 Hz, 1 H, H-2"), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6"), 8.1 8 (dd, J = 8.3, 2.5, 1.5 Hz, 2 H, H-4", NHSO₂), 7.89 (br d, J = 8.3 Hz, 2 H, H-3", H-5"), 7.71 (br d, J = 8.4 Hz, 2 H, H-3", H-5"), 7.37-7.43 (m, 5 H, H-2', H-6', H-2", H-6", H-5"), 4.08 (s, 2 H, CH₂N), 3.57 (s, 3 H, CH₃), 2.93 (t, J = 7.6 Hz, 2 H, H-3), 2.67 (t, J = 7.6 Hz, 2 H, H-2); 13C NMR δ 172.3, 165.4, 145.3, 144.4, 141.9, 141.7, 138.4, 135.7, 132.9, 128.9 (2), 127.5 (2), 127.2, 126.4 (2), 123.3, 51.2, 45.6, 34.1, 29.8; MS m/z 455.0 (MH⁺, 100%); Anal. Calcd for C₂₃H₂₃N₃O₅S: C, 60.91; H, 5.1 1; N, 9.27. Found: C, 60.97; H, 5.02; N, 9.25%.

Example 42
Preparation of 4-[(4-Acetamidophenyl)sulfonamido)methyl]-V-(pyridin-3-yl)benzamide (51).

[0234] Acetic anhydride (0.1 0 ml, 1.1 mmol) was added dropwise to a stirred solution of 4-aminophenylsulfonamide 48 (210 mg, 0.55 mmol) in pyridine (10 ml) and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in water (20 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with a gradient (0-10%) of MeOH/EtOAc, to give benzamide 51 (150 mg, 64%) as a white powder: mp (MeOH/EtOAc) 229-231 °C; 1H NMR δ 10.36 (br s, 1 H, NHCO), 10.32 (br s, 1 H, NHCO), 8.93 (d, J = 2.2 Hz, 1 H, H-2"), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6"), 8.1 8 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4"), 8.1 0 (br s, 1 H, NHSO₂), 7.91 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.75 (br s, 4 H, H-
3", H-5", H-2", H-6"), 7.37-7.43 (m, 3 H, H-3, H-5, H-5), 4.06 (s, 2 H, CH₂N), 2.08 (s, 3 H, COCH₃); ¹³C NMR δ 168.8, 165.4, 144.4, 142.7, 141.9, 141.8, 135.7, 134.1, 132.9, 127.6 (2), 127.5 (2), 127.3 (2), 127.1, 123.3, 118.5 (2), 45.6, 24.0; MS m/z 425.4 (MH⁺, 100%). Anal. Calcd for C₆H₁₂N₄O₄S: C, 59.42; H, 4.75; N, 13.20. Found: C, 59.63; H, 4.97; N, 12.89%.

**Example 43**

Preparation of 4-((4-Fluorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (52).

![Chemical Structure](image)

[0235] **Method C.** Reaction of amine salt 6 (453 mg, 1.2 mmol) and A-fluorobenzenesulfonyl chloride (249 mg, 1.3 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 52 (288 mg, 64%) as a white powder: mp (EtOAc/pet. ether) 189.1-191°C; ¹H NMR δ 10.37 (s, 1 H, NHCO), 8.93 (d, J = 2.3 Hz, 1 H, H-2"'), 8.27-8.31 (m, 2 H, NHSO₂, H-6"'), 8.19 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4"'), 7.91 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.85-7.89 (m, 2 H, H-2", H-6"), 7.36-7.45 (m, 5 H, H-3, H-5, H-5", H-3", H-5"), 4.10 (s, 2 H, CH₂N); ¹³C NMR δ 165.4, 164.0 (d, J = 251 Hz), 144.4, 141.9, 141.6, 137.0 (d, J = 3 Hz), 135.7, 133.0, 129.4 (2, q, J = 10 Hz), 127.6 (2), 127.3 (2), 127.2, 123.4, 116.2 (2, q, J = 23 Hz), 45.6; MS m/z 436.5 (MH⁺, 100%). Anal. Calcd for C₁₅H₁₄F₃N₃O₃S·V₈: C, 59.88; H, 4.51; N, 10.65. Found: C, 59.79; H, 4.29; N, 10.86%.

**Example 44**

Preparation of 4-((4-Chlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (53).

![Chemical Structure](image)

[0236] **Method C.** Reaction of amine salt 6 (400 mg, 1.0 mmol) and A-chlorobenzenesulfonyl chloride (239 mg, 1.1 mmol) followed by column chromatography, eluting with a gradient (0-5%) of MeOH/EtOAc, gave the benzamide 53 (150 mg, 36%) as a cream coloured powder: mp (EtOAc) 229-231°C; ¹H NMR δ 10.36 (s, 1 H, NHCO), 8.92 (d, J = 2.2 Hz, 1 H, H-2"'), 8.36 (br t, J = 6.3 Hz, 1 H, NHSO₂), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6"'), 8.15-8.19 (m, 1 H, H-4"),
7.90 (d, J = 8.4 Hz, 2 H, H-2, H-6), 7.81 (d, J = 8.8 Hz, 2 H, H-2", H-6"), 7.66 (d, J = 8.8 Hz, 2 H, H-3", H-5"), 7.37-7.41 (m, 3 H, H-3, H-5, H-5"), 4.1 1 (d, J = 6.2 Hz, 2 H, CH₂N); ¹³C NMR δ 165.4, 144.4, 141.9, 141.5, 139.4, 137.1, 135.7, 133.0, 129.2 (2), 128.3 (2), 127.6 (2), 127.4 (2), 127.2, 123.4, 45.6. Anal. Calcd for C₁₅H₁₄Cl₃N₃O₆S: C, 56.79; H, 4.01; N, 10.46. Found: C, 56.80; H, 3.93; N, 10.47%.

Example 45
Preparation of 4-((4-Bromophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (54).

[0237] Method C. Reaction of amine salt 6 (353 mg, 0.91 mmol) and A-bromobenzenesulfonyl chloride (278 mg, 1.1 mmol) followed by column chromatography, eluting with a gradient (0-1 0%) of MeOH/EtOAc, gave benzamide 54 (326 mg, 80%) as a white powder: mp (MeOH/EtOAc) 244-247 °C; ¹H NMR δ 10.37 (s, 1 H, NHCO), 8.92 (d, J = 2.3 Hz, 1 H, H-2'), 8.36 (br s, 1 H, NHSO₂). 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.1 8 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.91 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.80 (ddd, J = 8.7, 2.2, 2.0 Hz, 2 H, H-2", H-6"), 7.73 (ddd, J = 8.7, 2.2, 2.0 Hz, 2 H, H-3", H-5"), 7.36-7.42 (m, 3 H, H-3, H-5, H-5"), 4.1 1 (S, 2 H, CH₂N); ¹³C NMR δ 165.4, 144.4, 141.9, 141.5, 139.8, 135.7, 133.0, 132.1 (2), 128.4 (2), 127.6 (2), 127.4 (2), 127.2, 126.1, 123.4, 45.6. MS m/z 446.4, 448.5 (MH⁺, 100%). Anal. Calcd for C₁₅H₁₄BrN₃O₆S: C, 51.13; H, 3.61; N, 9.41. Found: C, 50.90; H, 3.41; N, 9.20%.

Example 46
Preparation of N-(Pyridin-3-yl)-4-((4-(trifluoromethoxy)phenylsulfonamido)methyl)benzamide (55).

[0238] Method C. Reaction of amine salt 6 (400 mg, 1.0 mmol) and A-trifluoromethoxybenzenesulfonyl chloride (0.19 mL, 1.1 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 55 (276 mg, 59%) as a white powder: mp (EtOAc/pet. ether) 221-223 °C; ¹H NMR δ 10.35 (s, 1 H, NHCO), 8.91 (d, J = 2.0 Hz, 1 H, H-2'), 8.42 (br s, 1 H, NHSO₂), 8.30 (dd, J = 4.7, 1.5 Hz, 1 H, H-
6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.92 (ddd, J = 8.9, 3.0, 2.0 Hz, 2 H, H-2', H-6'), 7.88 (br d, J = 8.4 Hz, 2 H, H-2, H-6), 7.55 (br d, J = 8.9 Hz, 2 H, H-3', H-5'), 7.39 (m, 3 H, H-3, H-5, H-5'), 4.14 (s, 2 H, CH₂N); ¹³C NMR δ 165.3, 150.6 (q, J = 3 Hz), 144.4, 141.9, 141.4, 139.6, 135.7, 133.0, 128.9 (2), 127.6 (2), 127.4 (2), 127.2, 123.4, 121.3 (2), 119.7 (q, J = 258 Hz), 45.6; MS m/z 452.5 (MH⁺, 100%). Anal. Calcd for C₂₀H₁₆F₃N₅O₄S: C, 53.21; H, 3.57; N, 9.31. Found: C, 53.32; H, 3.74; N, 9.36%.

Example 47
Preparation of Methyl 4-((4-(Pyridin-3-ylcarbamoyl)benzyl)sulfamoyl)benzoate (56).

[0239] Method C. Reaction of amine salt 6 (1.69 g, 4.3 mmol) and methyl 4-(chlorosulfonyl)benzoate (1.02 g, 4.3 mmol) followed by column chromatography, eluting with a gradient (0-20%) of MeOH/EtOAc, gave benzoate 56 (553 mg, 30%) as a white powder: mp (MeOH/EtOAc) 212-215 °C; ¹H NMR δ 10.34 (s, 1 H, NHCO), 8.92 (d, J = 2.4 Hz, 1 H, H-2'), 8.47 (br s, 1 H, NHSO₂), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 8.12 (ddd, J = 8.6, 1.9, 1.7 Hz, 2 H, H-3, H-5), 7.93 (ddd, J = 8.6, 1.9, 1.7 Hz, 2 H, H-2, H-6), 7.88 (br d, J = 8.3 Hz, 2 H, H-2', H-6'), 7.36-7.42 (m, 3 H, H-3', H-5', H-5'), 4.14 (s, 2 H, CH₂N), 3.88 (s, 3 H, CO₂CH₃). Anal. Calcd for C₂₁H₁₇F₃N₅O₅S₂·CH₃OH: C, 58.49; H, 4.80; N, 9.52. Found: C, 58.55; H, 4.51; N, 9.35%.

Example 48
Preparation of 4-((4-Acetylphenylsulfonyl)methyl)-N-(pyridin-3-yl)benzamide (57).

[0240] Method C. Reaction of amine salt 6 (400 mg, 1.0 mmol) and 4-acetylbenzenesulfonyl chloride (247 mg, 1.1 mmol) followed by column chromatography, eluting with a gradient (0-10%) of MeOH/EtOAc, gave benzamide 57 (229 mg, 54%) as a white powder: mp (MeOH/EtOAc) 229-231 °C; ¹H NMR δ 10.35 (s, 1 H, NHCO), 8.92 (d, J = 2.2 Hz, 1 H, H-2'), 8.45 (br s, 1 H, NHSO₂), 8.30
(dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 8.11 (ddd, J = 8.5, 1.9, 1.8 Hz, 2 H, H-3", H-5"), 7.92 (ddd, J = 8.5, 1.9, 1.8 Hz, 2 H, H-2", H-6")
7.88 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.36-7.42 (m, 3 H, H-3, H-5, H-5'), 4.13 (s, 2 H, CH₂N), 2.62 (s, 3 H, COCH₃); ν<sup>13</sup>C NMR δ 197.2, 165.4, 144.4, 144.3, 141.9, 141.4, 139.3, 135.6, 128.8 (2), 127.6 (2), 127.4 (2), 127.2, 126.7 (2), 123.4, 45.6, 26.8; MS m/z 410.5 (MH⁺, 100%). Anal. Calcd for C₂₇H₂₇N₃O₄S: C, 61.60; H, 4.68; N, 10.26. Found: C, 61.63; H, 4.84; N, 10.31%.

Example 49
Preparation of N-(Pyridin-3-yl)-4-((4-
(trifluoromethyl)phenylsulfamido)methyl)benzamide (58).

[0241] Method C. Reaction of amine salt 6 (397 mg, 1.0 mmol) and A-
trifluoromethylbenzenesulfonyl chloride (275 mg, 1.1 mmol) followed by column
chromatography, eluting with EtOAc, gave benzamide 58 (272 mg, 61%) as a white
powder: mp (EtOAc) 243-246 °C; ¹H NMR δ 10.35 (s, 1 H, NHCO), 8.92 (d, J = 2.5
Hz, 1 H, H-2'), 8.54 (br s, 1 H, NHSO₂), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18
(ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.99 (br d, J = 8.3 Hz, 2 H, H-3", H-5"), 7.94 (br
d, J = 8.3 Hz, 2 H, H-2", H-6"), 7.88 (br d, J = 8.4 Hz, 2 H, H-2, H-6), 7.37-7.41 (m, 3
H, H-3, H-5, H-5'), 4.16 (s, 2 H, CH₂N); ν<sup>13</sup>C NMR δ 165.3, 144.5, 144.4, 141.9, 141.3,
135.7, 133.0, 132.0 (q, J = 32 Hz), 127.6 (2), 127.4 (2), 127.3 (2), 127.2, 126.2 (2, q,
J = 4 Hz), 123.4 (q, J = 272 Hz), 123.3, 45.6; MS m/z 436.5 (MH⁺, 100%). Anal.
Calcd for C₂₀H₁₆F₃N₃O₃S: C, 55.17; H, 3.70; N, 9.65. Found: C, 55.39; H, 3.80; N,
9.58%.

Example 50
Preparation of 4-((4-Cyanophenylsulfamido)methyl)-N-(pyridin-3-
yl)benzamide (59).

[0242] Method C. Reaction of amine salt 6 (424 mg, 1.1 mmol) and A-
cyanobenzenesulfonyl chloride (242 mg, 1.2 mmol) followed by column
chromatography, eluting with a gradient (0-5%) of MeOH/EtOAc, gave benzamide
59 (201 mg, 47%) as a white powder: \( \text{mp (MeOH/EtOAc)}^2 \) 249-251 °C; \(^1\text{H NMR} \) \( \delta \) 10.36 (s, 1 H, NHCO), 8.93 (d, \( J = 2.2 \) Hz, 1 H, H-2'), 8.56 (br s, 1 H, NHSO\(_2\)), 8.31 (dd, \( J = 4.7 \), 1.5 Hz, 1 H, H-6'), 8.18 (dd, \( J = 8.3 \), 2.3, 1.5 Hz, 2 H, H-3", H-5"), 7.95 (dd, \( J = 8.3 \), 1.9 Hz, 2 H, H-2", H-6"), 7.89 (br d, \( J = 8.3 \) Hz, 2 H, H-2, H-6'), 7.37-7.42 (m, 3 H, H-3, H-5, H-5'), 4.15 (s, 2 H, CH\(_2\)N); \(^{13}\text{C NMR} \) 5 165.3, 144.7, 144.3, 141.9, 141.2, 135.6, 133.2 (2), 133.0, 127.6 (2), 127.4 (2), 127.2, 127.1 (2), 123.4, 117.6, 114.7, 45.6; MS m/z 393.4 (MH\(^+\), 100%). Anal. Calcd for C\(_{20}\)H\(_6\)N\(_4\)O\(_3\)S: C, 61.21; H, 4.11; N, 14.28. Found: C, 61.16; H, 4.09; N, 14.17%.

Example 51

Preparation of 4-(((4'-Nitrophenylsulfonamido)methyl)-\( \Lambda \)-(pyridin-3-yl)benzamide (60).

![Structural formula](image)

[0243] Method C. Reaction of amine salt 6 (984 mg, 2.5 mmol) and 4-nitrobenzenesulfonyl chloride (620 mg, 2.8 mmol) followed by column chromatography, eluting with a gradient (0-1 0%) of MeOH/EtOAc, gave benzamide 60 (687 mg, 66%) as a white powder: \( \text{mp (MeOH/EtOAc)}^2 \) 241-243 °C; \(^1\text{H NMR} \) \( \delta \) 10.34 (s, 1 H, NHCO), 8.90 (d, \( J = 2.5 \) Hz, 1 H, H-2'), 8.64 (br s, 1 H, NHSO\(_2\)), 8.37 (dd, \( J = 8.5 \), 1.9, 1.8 Hz, 2 H, H-3", H-5"), 8.31 (dd, \( J = 4.7 \), 1.5 Hz, 1 H, H-6"), 8.17 (dd, \( J = 8.3 \), 2.5, 1.5 Hz, 1 H, H-4'), 8.10 (ddd, \( J = 8.5 \), 1.9, 1.8 Hz, 2 H, H-2", H-6"), 7.88 (br d, \( J = 8.3 \) Hz, 2 H, H-2, H-6), 7.35-7.41 (m, 3 H, H-3, H-5, H-5'), 4.13 (s, 2 H, CH\(_2\)N); \(^{13}\text{C NMR} \) \( \delta \) 165.3, 149.4, 146.2, 144.4, 141.9, 141.1, 135.6, 133.0, 127.9 (2), 127.6 (2), 127.4 (2), 127.2, 124.4 (2), 123.3, 45.6; MS m/z 413.5 (MH\(^+\), 100%). Anal. Calcd for Cl\(_3\)H\(_6\)N\(_4\)O\(_3\)S: C, 55.33; H, 3.91; N, 13.58. Found: C, 55.58; H, 3.99; N, 13.57%.

Example 52

Preparation of 4-(((4'-Methoxy[1,1'-biphenyl]-4-yl)sulfonyl]amino)methyl)-\( \Lambda \)-(3-pyridinyl)benzamide (61).

![Structural formula](image)
[0244] **Method C.** Reaction of amine salt 6 (200 mg, 0.51 mmol) and 4'-methoxy-(1,1'-biphenyl)-4-sulfonyl chloride (189 mg, 0.67 mmol) gave benzamide 61 (157 mg, 65%) as a cream powder: mp 244-247 °C; \(^1\)H NMR \(\delta 10.34\) (s, 1 H, NHCO), 8.91 (d, \(J = 2.2\) Hz, 1 H, H-2'), 8.31 (dd, \(J = 4.7\), 1.5 Hz, 1 H, H-6'), 8.26 (br s, 1 H, NHSO\_2), 8.17 (ddd, \(J = 8.4\), 2.5, 1.5 Hz, 1 H, H-4'), 7.89 (br d, \(J = 8.3\) Hz, 2 H, H-2, H-6), 7.78-7.84 (m, 4 H, H-2", H-3", H-5", H-6"), 7.68 (br d, \(J = 8.9\) Hz, 2 H, H-2", H-6"), 7.37-7.43 (m, 3 H, H-3, H-5, H-5'), 7.03 (br d, \(J = 8.8\) Hz, 2 H, H-3", H-5''), 4.12 (br s, 2 H, CH\_2N), 3.80 (s, 3 H, OCH\_3); \(^{13}\)C NMR \(\delta 165.4, 159.5, 144.4, 143.4, 141.9, 141.7, 138.5, 135.6, 132.9, 130.7, 128.1 (2), 127.5 (2), 127.4 (2), 127.2, 127.0 (2), 126.5 (2), 123.3, 114.4 (2), 55.1, 45.7; MS \(m/z\) 475.0 (MH\(^+\), 100%). Anal. calcd for C\(_{26}\)H\(_{23}\)N\(_3\)O\(_4\)S: C, 65.94; H, 4.90; N, 8.87. Found: C, 65.63; H, 5.04; N, 8.79%.

**Example 53**

Preparation of 4-(((4'-Methyl[1,1'-biphenyl]-4-sulfonylamino)methyl)-\(\mathrm{N}\)-(3-pyridinyl)benzamide (62).

[\(\begin{array}{c}
\text{N} \\
\text{O} \\
\text{S} \\
\text{Me}
\end{array}\)]

[0245] **Method C.** Reaction of amine salt 6 (200 mg, 0.51 mmol) and 4'-methyl(1,1'-biphenyl)-4-sulfonyl chloride (178 mg, 0.67 mmol) gave benzamide 62 (231 mg, 98%) as a yellow powder: mp 263-266 °C; \(^1\)H NMR \(\delta 10.33\) (s, 1 H, NHCO), 8.91 (d, \(J = 2.4\) Hz, 1 H, H-2'), 8.31 (dd, \(J = 4.7\), 1.4 Hz, 1 H, H-6'), 8.28 (t, \(J = 6.4\) Hz, 1 H, NHSO\_2), 8.17 (ddd, \(J = 8.4\), 2.4, 1.5 Hz, 1 H, H-4'), 7.89 (br d, \(J = 8.3\) Hz, 2 H, H-2, H-6), 7.81-7.90 (m, 4 H, H-2", H-3", H-5", H-6"), 7.62 (br d, \(J = 8.1\) Hz, 2 H, H-2", H-6"), 7.37-7.43 (m, 3 H, H-3, H-5, H-5'), 7.29 (br d, \(J = 8.0\) Hz, 2 H, H-3", H-5"'), 4.13 (d, \(J = 6.2\) Hz, 2 H, CH\_2N), 2.35 (s, 3 H, CH\_3); \(^{13}\)C NMR \(\delta 165.4, 144.4, 143.7, 141.9, 141.6, 139.0, 137.8, 135.6, 135.5, 132.9, 129.5 (2), 127.5 (2), 127.4 (2), 127.2, 127.0 (2), 126.9 (2), 126.7 (2), 123.3, 45.7, 20.5; MS \(m/z\) 459.0 (MH\(^+\), 100%); HRMS (FAB\(^+\)) calcd for C\(_{26}\)H\(_{24}\)N\(_3\)O\(_4\)S (MH\(^+\)) \(m/z\) 458.1538, found 458.1540. Anal. calcd for C\(_{26}\)H\(_{23}\)N\(_3\)O\(_4\)S\(\_\frac{1}{2}\)H\(_2\)O: C, 66.94; H, 5.19; N, 9.01. Found: C, 67.04; H, 5.29; N, 8.82%.

**Example 54**

Preparation of 4-(((Biphenyl-4-ylsulfonamido)methyl)-\(\mathrm{N}\)-(pyridin-3-yl)benzamide (63).
[0246] Method C. Reaction of amine salt 6 (305 mg, 0.78 mmol) and A-biphenylsulfonyl chloride (238 mg, 0.94 mmol) followed by column chromatography, eluting with a gradient (0-1 0%) of MeOH/ EtOAc, gave benzamide 63 (263 mg, 76%) as a white powder: mp (MeOH/EtOAc) 248-250 °C; 1H NMR δ 10.36 (s, 1 H, NHCO), 8.92 (d, J = 1.7 Hz, 1 H, H-2'), 8.29-8.34 (m, 2 H, NHSO₂, H-6'), 8.17 (ddd, J = 8.3, 2.3, 1.4 Hz, 1 H, H-4'), 7.90 (br d, J = 8.4 Hz, 2 H, H-2', H-6), 7.83-7.87 (m, 4 H, H-2'', H-3'', H-5'', H-6''), 7.71 (br d, J = 8.5 Hz, 2 H, H-2'', H-6''), 7.46-7.51 (m, 2 H, H-3'', H-5''), 7.36-7.44 (m, 4 H, H-3, H-5, H-5', H-4''), 4.13 (d, J = 5.6 Hz, 2 H, CH₂N); 13C NMR δ 165.4, 144.4, 143.8, 141.9, 141.6, 139.3, 138.5, 135.7, 132.9, 128.9 (2), 128.3, 127.6 (2), 127.4 (2), 127.2 (2), 127.1, 127.0 (2), 126.9 (2), 123.3, 45.7; MS m/z 444.6 (MH⁺, 100%). Anal. Calcd for C₂₅H₂₀F₃NS₂·AEtOAc: C, 67.08; H, 4.98; N, 9.03. Found: C, 67.11; H, 4.73; N, 9.32%.

Example 55
Preparation of 4-(((4'-Fluoro[1,1'-biphenyl]-4-yl)sulfonyl)amino)methyl)-N-(3-pyridinyl)benzamide (64).

[0247] Method C. Reaction of amine salt 6 (200 mg, 0.51 mmol) and 4'-fluoro(1,1'-biphenyl)-4-sulfonyl chloride (181 mg, 0.668 mmol) gave benzamide 64 (159 mg, 67%) as a cream powder: mp (MeOH/DCM) 249-250 °C; 1H NMR δ 10.34 (s, 1 H, NHCO), 8.91 (d, J = 2.5 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 2 H, H-6', NHSO₂), 8.17 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.89 (br d, J = 8.3 Hz, 2 H, H-2', H-6), 7.82-7.87 (m, 4 H, H-2'', H-3'', H-5'', H-6''), 7.77 (dd, J = 8.9, 5.4 Hz, 2 H, H-2'', H-6''), 7.37-7.43 (m, 3 H, H-3, H-5, H-5'), 7.31 (t, J = 8.9 Hz, 2 H, H-3'', H-5''), 4.13 (s, 2 H, CH₂N); 13C NMR δ 165.4, 162.3 (d, J = 246 Hz), 144.4, 142.7, 141.9, 141.6, 139.3, 135.6, 134.9 (d, J = 3 Hz), 132.9, 129.0 (2) (d, J = 8 Hz), 127.6 (2), 127.4 (2), 127.2 (2), 127.1, 127.0 (2), 123.3, 115.8 (2) (d, J = 22 Hz), 45.7; MS m/z 463.0 (MH⁺, 100%). Anal. calcd for C₂₅H₂₀F₃N₃O₃S: C, 65.06; H, 4.37; N, 9.10. Found: C, 64.66; H, 4.31; N, 9.01%.

Example 56
Preparation of 4-({[(4'-Chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino}methyl)-N-(3-pyridinyl)benzamide (65).

[0248] Method C. Reaction of amine salt 6 (200 mg, 0.51 mmol) and 4-(4'-chlorophenyl)benzenesulfonyl chloride (177 mg, 0.62 mmol) gave benzamide 65 (208 mg, 85%) as a white powder: mp (H₂O) 276-278 °C; ¹H NMR δ 10.33 (s, 1 H, NHCO), 8.91 (d, J = 2.4 Hz, 1 H, H-2'), 8.30-8.33 (m, 2 H, H-6', NHSO₂), 8.16 (dd, J = 8.4, 2.5, 1.5 Hz, 1 H, H-4'), 7.89 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.84-7.86 (m, 4 H, H-2", H-3", H-5", H-6"), 7.75 (br d, J = 8.6 Hz, 2 H, H-2", H-6"), 7.37-7.42 (m, 3 H, H-3, H-5, H-5'), 4.13 (d, J = 6.2 Hz, 2 H, CH₂N); ¹³C NMR 5 165.4, 144.4, 142.4, 141.9, 141.6, 139.7, 137.2, 135.6, 133.3, 132.9, 128.9 (2), 128.7 (2), 127.6 (2), 127.4 (2), 127.3 (2), 127.2, 127.1 (2), 123.3, 45.7; MS m/z 479.0 (MH⁺, 100%). Anal. calcld for C₂₃H₁₉N₅O₃S: C, 62.82; H, 4.22; N, 8.79. Found: C, 62.61; H, 4.36; N, 8.59%.

Example 57


[0249] Method C. Reaction of amine salt 6 (180 mg, 0.46 mmol) and 4-pyrimidin-2-ylbenzenesulfonyl chloride (130 mg, 0.51 mmol) gave benzamide 66 (152 mg, 74%) as a yellow powder: mp (H₂O) 278-280 °C; ¹H NMR δ 10.33 (s, 1 H, NHCO), 8.96 (d, J = 4.9 Hz, 2 H, H-4", H-6"), 8.90 (d, J = 2.2 Hz, 1 H, H-2'), 8.56 (d, J = 8.6 Hz, 2 H, H-3", H-5"), 8.37 (br s, 1 H, NHSO₂), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6"), 8.16 (dd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4"), 7.97 (d, J = 8.6 Hz, 2 H, H-2", H-6"), 7.90 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 7.38 (dd, J = 8.3, 4.7, 1 H, H-5"), 4.15 (s, 2 H, CH₂N); ¹³C NMR δ 165.3, 161.9, 157.8 (2), 144.4, 142.4, 141.9, 141.6, 140.5, 135.6, 132.9, 128.2 (2), 127.6 (2), 127.3 (2), 127.2, 126.9 (2), 123.3, 120.5, 45.7; MS m/z 446.9 (MH⁺, 100%). Anal. calcld for C₂₉H₂₅N₅O₃S: C, 61.95; H, 4.46; N, 15.5%.
Example 58
Preparation of 4-[[[4-(1 H-Pyrazol-1-yl)phenyl]sulfonyl]amino)methyl]-\(\text{N}\)-(3-pyridinyl)benzamide (67).

\[ \text{N}-(3-\text{pyridinyl})\text{benzamide} \]

[0250] Method C. Reaction of amine salt 6 (170 mg, 0.44 mmol) and 4-(1 H-pyrazol-1-yl)benzenesulfonyl chloride (159 mg, 0.66 mmol) gave benzamide 67 (167 mg, 88%) as a pale yellow powder: mp (H₂O) 243-245 °C; \(^1\)H NMR \(\delta\) 10.34 (s, 1 H, NHCO), 8.91 (d, \(J = 2.0\) Hz, 1 H, H-2'), 8.61 (d, \(J = 2.3\) Hz, 1 H, H-5''), 8.31 (dd, \(J = 4.7, 1.4\) Hz, 1 H, H-6'), 8.28 (br s, 1 H, NHCO₂), 8.17 (dd, \(J = 8.4, 2.5, 1.5\) Hz, 1 H, H-4'), 8.05 (br d, \(J = 8.9\) Hz, 2 H, H-3', H-5''), 7.89-7.93 (m, 4 H, H-2, H-6, H-2', H-6''), 7.82 (d, \(J = 1.7\) Hz, 1 H, H-3''), 7.42 (br d, \(J = 8.4\) Hz, 2 H, H-3, H-5), 7.39 (ddd, \(J = 8.4, 4.7, 0.6\), 1 H, H-5'), 6.60 (dd, \(J = 2.5, 1.8\) Hz, 1 H, H-4''), 4.12 (s, 2 H, CH₂N); \(^{13}\)C NMR \(\delta\) 165.4, 144.4, 142.1, 142.0, 141.9, 141.6, 137.6, 135.6, 133.0, 128.2, 128.1 (2), 127.6 (2), 127.4 (2), 127.2 (2), 123.3, 118.3, 108.6, 45.7; MS m/z 434.9 (MH⁺, 100%). Anal. calcd for C₂₂H₁₉N₅O₃S: C, 60.96; H, 4.42; N, 16.16. Found: C, 60.63; H, 4.57; N 15.84%.

Example 59
Preparation of 4-[[[4-(2-Methyl-1,3-thiazol-4-yl)phenyl]sulfonyl]amino)methyl]-\(\text{N}\)-(3-pyridinyl)benzamide (68).

[0251] Method C. Reaction of amine salt 6 (154 mg, 0.40 mmol) and 4-(2-methyl-1,3-thiazol-4-yl)benzenesulfonyl chloride (130 mg, 0.48 mmol) followed purification by column chromatography, eluting with a gradient (0-1 0%) of MeOH/DCM gave benzamide 68 (14 mg, 62%) as a yellow powder: mp (MeOH/DCM) 221-223 °C; \(^1\)H NMR \(\delta\) 10.34 (s, 1 H, NHCO), 8.91 (d, \(J = 2.2\) Hz, 1 H, H-2'), 8.31 (dd, \(J = 4.7, 1.4\) Hz, 1 H, H-6'), 8.27 (br s, 1 H, NHCO₂), 8.17 (ddd, \(J = 8.4, 2.5, 1.5\) Hz, 1 H, H-4'), 8.09-8.14 (m, 3 H, H-3', H-5', H-5''), 7.90 (d, \(J = 8.3\) Hz, 2 H, H-2, H-6), 7.86 (d, \(J = 8.6\) Hz, 2 H, H-2', H-6''), 7.37-7.43 (m, 3 H, H-3, H-5, H-5'), 4.12 (s, 2 H, CH₂N), 2.72 (s, 3 H, CH₃); \(^{13}\)C NMR \(\delta\) 166.0, 165.3, 152.1, 144.4, 141.9, 141.7, 139.4, 137.5, 135.6, 132.9, 127.6 (2), 127.3 (2), 127.2, 127.0 (2), 126.3 (2), 123.3, 116.4, 45.6,
18.8; MS m/z 465.9 (MH+, 100%). Anal. calcd for C_{23}H_{20}N_{4}O_{3}S_{2}: C, 59.46; H, 4.34; N, 12.06. Found: C, 59.69; H, 4.45; N, 12.03%.

Example 60
Preparation of 4-[[4-(1,3-Oxazol-5-yl)phenyl]sulfonyl]amino)methyl]-\(N\)-(3-pyridinyl)benzamide (69).

![Chemical Structure](image)

[0252] Method C. Reaction of amine salt 6 (160 mg, 0.41 mmol) and 4-(1,3-oxazol-5-yl)benzenesulfonyl chloride (150 mg, 0.62 mmol) gave benzamide 69 (123 mg, 69%) as a dark yellow powder: mp (H_2O) 240-242 °C; \(^1\)H NMR δ 10.33 (s, 1 H, NHCO), 8.91 (br s, 1 H, H-2'), 8.53 (s, 1 H, H-2") 8.31-8.34 (m, 2 H, H-6', NHSO\(_2\)), 8.17 (m, 1 H, H-4'), 7.87-7.94 (m, 7 H, H-2, H-6, H-2", H-3", H-5", H-6", H-4"), 7.37-7.42 (m, 3 H, H-3, H-5, H-5'), 4.12 (d, J = 6.3 Hz, 2 H, CH\(_2\)N): \(^{13}\)C NMR δ 165.4, 152.6, 149.1, 144.3, 141.7, 141.6, 140.0, 135.7, 132.9, 130.7, 127.6 (2), 127.4 (2), 127.3 (2), 124.5 (2), 124.1, 123.4, 45.6, one C not observed; MS m/z 435.9 (MH+, 100%); HRMS (FAB\(^+\)) calcd for C\(_{22}\)H\(_{19}\)N\(_4\)O\(_4\)S (MH\(^+\)) m/z 435.1 127, found 435.1 124. Anal. calcd for C\(_{22}\)H\(_{19}\)N\(_4\)O\(_4\)S-V\(_2\)H\(_2\)O: C, 59.58; H, 4.32; N, 12.63. Found: C, 59.55; H, 4.27; N, 12.45%.

Example 61
Preparation of 4-((3,4-Dimethoxyphenylsulfonylamido)methyl)-\(N\)-(pyridin-3-yl)benzamide (70).

![Chemical Structure](image)

[0253] Method C. Reaction of amine salt 6 (407 mg, 1.1 mmol) and 3,4-dimethoxybenzenesulfonamide (272 mg, 1.2 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 70 (295 mg, 66%) as a white powder: mp (EtOAc) 164-1 66 °C; \(^1\)H NMR δ 10.36 (s, 1 H, NHCO), 8.93 (d, J = 2.2 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 8.06 (br s, 1 H, NHSO\(_2\)), 7.91 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.41 (br d, 2 H, H-3, H-5), 7.35-7.40 (m, 2 H, H-5', H-6"), 7.30 (d, J = 2.1 Hz, 1 H, H-2"), 7.10 (d, J = 8.5 Hz, 1 H, H-5"), 4.04 (s, 2 H, CH\(_2\)N), 3.83 (s, 3 H, OCH\(_3\)), 3.81 (s, 3 H, OCH\(_3\)); \(^{13}\)C NMR 5 165.4, 151.3, 148.6, 144.4, 141.9, 141.8, 135.7, 132.9, 132.0, 127.5 (2),
127.3 (2), 127.2, 123.4, 120.1, 111.1, 109.4, 55.7, 55.6, 45.7; MS m/z 428.5 (MH⁺, 100%). Anal. Calcd for C₂₇H₂₁N₃O₅S: C, 59.00; H, 4.95; N, 9.83. Found: C, 59.27; H, 5.01; N, 9.93%.

Example 62
Preparation of 4-(((3-ferf-Butyl-4-methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (71).

[0254] Method C. Reaction of amine salt 6 (391 mg, 1.0 mmol) and 3-ferf-butyl-4-methoxybenzene sulfonyl chloride (290 mg, 1.1 mmol) followed by column chromatography, eluting with a gradient (70-1 00%) of EtOAc/pet. ether, gave benzamide 71 (221 mg, 49%) as a white powder: mp (EtOAc) 189-192 °C; ¹H NMR δ 10.33 (s, 1 H, NHCO), 8.91 (d, J = 2.3 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.17 (ddd, J = 8.3, 2.4, 1.5 Hz, 1 H, H-6”), 7.64 (dd, J = 8.5, 2.3 Hz, 1 H, H-6”), 7.60 (d, J = 2.3 Hz, 1 H, H-5”), 7.36-7.42 (m, 3 H, H-3, H-5, H-5”), 7.11 (d, J = 8.6 Hz, 1 H, H-5”), 4.07 (br s, 2 H, CH₂N), 3.88 (s, 3 H, OCH₃), 1.33 [s, 9 H, C(CH₃)₃]; ¹³C NMR δ 165.3, 160.9, 144.4, 141.9, 141.8, 137.8, 135.6, 132.7, 131.7, 127.5 (2), 127.3 (2), 127.2, 126.5, 124.6, 123.3, 111.7, 55.5, 45.6, 34.5, 29.0 (3); MS m/z 454.8 (MH⁺, 100%). Anal. Calcd for C₂₇H₂₁N₃O₅S: C, 63.56; H, 6.00; N, 9.26. Found: C, 63.53; H, 5.98; N, 9.34%.

Example 63
Preparation of 4-(((2,3,4,5,6-Pentamethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (72).

[0255] Method C. Reaction of amine salt 6 (329 mg, 0.85 mmol) and 2,3,4,5,6-pentamethylbenzene sulfonyl chloride (230 mg, 0.93 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 72 (191 mg, 51%) as a white powder: mp (EtOAc) 229-231 °C; ¹H NMR δ 10.32 (s, 1 H, NHCO), 8.92 (d, J = 2.3 Hz, 1 H, H-2”), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6”), 8.17 (ddd, J = 8.3, 2.4, 1.5 Hz, 1
H, H-4’), 8.00 (br s, 1 H, NHSO₂), 7.85 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.39 (ddd, J = 8.3, 4.7, 0.3 Hz, 1 H, H-5’), 7.31 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 4.06 (s, 2 H, CH₂N), 2.48 (s, 6 H, 2 x CH₃), 2.20 (s, 3 H, CH₃), 2.15 (s, 6 H, 2 x CH₃); ¹³C NMR δ 165.3, 144.4, 141.9, 141.8, 138.5, 136.9, 135.7, 134.0, 133.2 (2), 132.6, 127.3 (2), 127.2 (2), 127.1 (2), 123.4, 45.6, 18.6 (2), 17.2, 16.5 (2); MS m/z 438.7 (MH⁺, 100%). Anal. Calcd for C₂₄H₂₇N₃O₅S: C, 65.88; H, 6.22; N, 9.60. Found: C, 65.92; H, 6.12; N, 9.70%.

Example 64
Preparation of 4-((2,4-Dimethylphenylsulfonamido)methyl)- N-(pyridin-3-yl)benzamide (73).

[0256] Method C. Reaction of amine salt 6 (333 mg, 0.86 mmol) and 2,4-dimethylbenzene sulfonyl chloride (193 mg, 0.94 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 73 (156 mg, 46%) as a white powder: mp (EtOAc) 180-1 82 °C; ¹H NMR δ 10.35 (s, 1 H, NHCO), 8.92 (d, J = 2.2 Hz, 1 H, H-2’), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6’), 8.16-8.21 (m, 2 H, H-4’, NHSO₂), 7.89 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.70 (d, J = 8.0 Hz, 1 H, H-6”), 7.35-7.41 (m, 3 H, H-3, H-5, H-5”), 7.19 (br s, 1 H, H-3”), 7.15 (br d, J = 8.0 Hz, 1 H, H-5”), 4.07 (s, 2 H, CH₂N), 2.54 (s, 3 H, CH₃), 2.32 (s, 3 H, CH₃); ¹³C NMR δ 165.4, 144.4, 142.4, 142.0, 141.9, 136.2, 135.8, 135.6, 132.9, 132.8, 128.5, 127.5 (2), 127.2 (2), 127.1, 126.4, 123.4, 45.3, 20.5, 19.6; MS m/z 396.5 (MH⁺, 100%). Anal. Calcd for C₂₄H₂₉N₃O₅S: C, 63.78; H, 5.35; N, 10.63. Found: C, 64.07; H, 5.38; N, 10.73%.

Example 65
Preparation of 4-((3,4-Dimethylphenylsulfonamido)methyl)- N-(pyridin-3-yl)benzamide (74).

[0257] Method C. Reaction of amine salt 6 (284 mg, 0.73 mmol) and 3,4-dimethylbenzene sulfonyl chloride (164 mg, 0.83 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 74 (130 mg, 45%) as a white powder: mp (EtOAc) 181-1 83 °C; ¹H NMR δ 10.37 (s, 1 H, NHCO), 8.92 (d, J = 2.2
Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 8.10 (br s, 1 H, NHSO₂), 7.90 (br d, J = 8.4 Hz, 2 H, H-2, H-6), 7.50-7.56 (m, 2 H, H-2', H-6'), 7.37-7.43 (m, 3 H, H-3, H-5, H-5'), 7.34 (d, J = 7.7 Hz, 1 H, H-5'), 4.07 (br d, J = 4.8 Hz, 2 H, CH₂N), 2.29 (s, 3 H, CH₃), 2.28 (s, 3 H, CH₃); ¹³C NMR δ 165.4, 144.4, 141.8, 141.3, 137.8, 137.3, 135.7, 132.9, 129.9, 127.5 (2), 127.3 (2), 127.2, 127.1, 124.0, 123.4, 45.6, 19.3, 19.2; MS m/z 396.6 (MH⁺, 100%). Anal. Calcd for C₂₇H₂₂N₅S: C, 63.78; H, 5.35; N, 10.63. Found: C, 64.01; H, 5.36; N, 10.65%.

Example 66
Preparation of 4-((3,5-Dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (75).

[0258] Method C. Reaction of amine salt 6 (404 mg, 1.0 mmol) and 3,5-dimethylbenzenesulfonyl chloride (234 mg, 1.1 mmol) followed by column chromatography, eluting with EtOAc, to give benzamide 75 (277 mg, 67%) as a white powder: mp (EtOAc/pet. ether) 181-183 °C; ¹H NMR δ 10.37 (s, 1 H, NHCO), 8.93 (d, J = 2.5 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 8.13 (br s, 1 H, NHSO₂), 7.91 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.37-7.43 (m, 5 H, H-3, H-5, H-5', H-2', H-6'), 7.26 (br s, 1 H, H-4'), 4.08 (s, 2 H, CH₂N), 2.34 (s, 6 H, 2 x CH₃); ¹³C NMR δ 165.4, 144.4, 141.9, 141.8, 140.4, 138.5 (2), 135.7, 132.9, 127.5 (2), 127.3 (2), 127.2, 123.8 (2), 123.4, 45.6, 20.6 (2); MS m/z 396.4 (MH⁺, 100%). Anal. Calcd for C₂₇H₂₂N₅S: C, 63.78; H, 5.35; N, 10.63. Found: C, 63.77; H, 5.41; N, 10.77%.

Example 67
Preparation of 4-((3-Fluoro-4-methylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (76).

[0259] Method C. Reaction of amine salt 6 (392 mg, 1.0 mmol) and 3-fluoro-4-methylbenzene sulfonyl chloride (231 mg, 1.1 mmol) followed by column
chromatography, eluting with EtOAc, gave benzamide 76 (192 mg, 48%) as a white powder: mp (EtOAc) 202-204 °C; 1H NMR δ 10.36 (s, 1 H, NHCO), 8.93 (d, J = 2.3 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 8.28 (br s, 1 H, NHSO₂), 7.91 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.48-7.57 (m, 3 H, H-2", H-5", H-6"), 7.36-7.42 (m, 3 H, H-3, H-5, H-5'), 4.11 (s, 2 H, CH₂N), 2.30 (d, J = 1.9 Hz, 3 H, CH₃); 13C NMR 5 165.4, 159 (d, J = 247 Hz), 144.4, 141.9, 141.5, 139.9 (d, J = 7 Hz), 135.6, 132.9, 132.3 (d, J = 5 Hz), 129.4 (d, J = 17 Hz), 127.6 (2), 127.4 (2), 127.2, 123.3, 122.3 (d, J = 3 Hz), 113.0 (d, J = 25 Hz), 45.6, 14.0 (d, J = 4 Hz); MS m/z 400.5 (MH⁺, 100%). Anal. Calcd for C₂₀H₁₈F₂N₃O₃S: C, 60.14; H, 4.54; N, 10.59. Found: C, 60.19; H, 4.53; N, 10.59%.

Example 68
Preparation of 4-((3-Chloro-2-methylphenylsulfonamido)methyl)-N-(pyridin-3-yI)benzamide (77)

[0260] Method C. Reaction of amine salt 6 (400 mg, 1.0 mmol) and 3-chloro-2-methylbenzenesulfonyl chloride (255 mg, 1.1 mmol) followed by column chromatography, eluting with EtOAc, gave the benzamide 77 (274 mg, 64%) as a white powder: mp (EtOAc) 218-221 °C; 1H NMR δ 10.35 (s, 1 H, NHCO), 8.93 (d, J = 2.3 Hz, 1 H, H-2'), 8.55 (br s, 1 H, NHSO₂), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.19 (d, J = 8.3 Hz, 1 H, H-4'), 7.89 (d, J = 8.3 Hz, 2 H, H-2, H-6), 7.84 (dd, J = 7.9, 1.0 Hz, 1 H, H-4''), 7.70 (dd, J = 8.0, 0.8 Hz, 1 H, H-6''), 7.35-7.41 (m, 4 H, H-3, H-5, H-5', H-5''), 4.16 (s, 2 H, CH₂N), 2.61 (s, 3 H, CH₃); 13C NMR δ 165.3, 144.4, 141.9, 141.7, 141.1, 135.7 (2), 133.9, 133.0, 132.9, 127.5 (2), 127.3 (2), 127.3 (2), 127.2, 123.4, 45.4, 16.4. Anal. Calcd for C₂₀H₁₈F₂N₃O₃S: C, 57.76; H, 4.36; N, 10.10. Found: C, 57.79; H, 4.23; N, 10.04%. * assignments interchangeable.

Example 69
Preparation of 4-((3-Chloro-4-methylphenylsulfonamido)methyl)-N-(pyridin-3-yI)benzamide (78).
[0261] **Method C.** Reaction of amine salt 6 (400 mg, 1.0 mmol) and 3-chloro-4-methylbenzenesulfonyl chloride (255 mg, 1.1 mmol) followed by column chromatography, eluting with EtOAc, gave the sulfonamide 78 (267 mg, 63%) as a white powder: mp (EtOAc) 203-205 °C; 1H NMR δ 10.36 (s, 1 H, NHCO), 8.93 (d, J = 2.3 Hz, 1 H, H-2'), 8.30-8.33 (m, 2 H, H-6', NHSO2), 8.18 (d, J = 8.3 Hz, 1 H, H-4'), 7.90 (d, J = 8.3 Hz, 2 H, H-2, H-6), 7.73 (d, J = 1.8 Hz, 1 H, H-2''), 7.66 (dd, J = 8.0, 1.8 Hz, 1 H, H-6''), 7.55 (d, J = 8.0 Hz, 1 H, H-5''), 7.37-7.41 (m, 3 H, H-3, H-5, H-5''), 4.11 (d, J = 4.8 Hz, 2 H, CH2N), 2.39 (s, 3 H, CH3); 13C NMR δ 165.3, 144.4, 141.9, 141.4, 140.4, 139.8, 135.7, 133.7, 132.9, 131.8, 127.6 (2), 127.4 (2), 127.2, 126.5, 125.0, 123.4, 45.7, 19.5. Anal. Calcd for C20H18ClN3O3S: C, 57.76; H, 4.36; N, 10.10. Found: C, 57.97; H, 4.48; N, 10.3%.  

**Example 70**  
Preparation of 4-((3-Cyano-4-fluorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (79).  

![Chemical Structure](image)

[0262] **Method C.** Reaction of amine salt 6 (379 mg, 0.97 mmol) and 3,4-dichlorobenzene sulfonyl chloride (263 mg, 1.1 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 79 (144 mg, 34%) as a white powder: mp (EtOAc) 219-221 °C; 1H NMR δ 10.34 (s, 1 H, NHCO), 8.92 (d, J = 2.4 Hz, 1 H, H-2'), 8.48 (br s, 1 H, NHSO2), 8.30 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (dd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.88-7.93 (m, 3 H, H-2, H-6, H-2''), 7.85 (d, J = 8.4 Hz, 1 H, H-5''), 7.75 (dd, J = 8.4, 2.2 Hz, 1 H, H-6''), 7.37-7.42 (m, 3 H, H-3, H-5, H-5''), 4.16 (s, 2 H, CH2N); 13C NMR δ 165.2, 144.4, 141.9, 141.2, 141.0, 135.6, 135.3, 133.7, 131.9, 131.4, 128.2, 127.6 (2), 127.4 (2), 127.2, 126.5, 123.3, 45.6; MS m/z 436.6 (MH+, 100%), 438.6 (MH+, 70%). Anal. Calcd for C19H16F2N2O3S: C, 52.30; H, 3.47; N, 9.63. Found: C, 52.50; H, 3.46; N, 9.67%.  

**Example 71**  
Preparation of 4-((3-Cyano-4-fluorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (80).  

![Chemical Structure](image)
[Method C. Reaction of amine salt 6 (422 mg, 1.1 mmol) and 3-cyano-4-fluorobenzene sulfonyl chloride (262 mg, 1.2 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 80 (149 mg, 34%) as a white powder: mp (EtOAc) 211-21 3 °C; 1H NMR δ 10.35 (s, 1 H, NHCO), 8.91 (d, J = 2.4 Hz, 1 H, H-2”), 8.49 (br s, 1 H, NHSO₂), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6”), 8.26 (dd, J = 6.0, 2.4 Hz, 1 H, H-2”), 8.18 (ddd, J = 8.3, 2.4, 1.5 Hz, 1 H, H-4”), 8.14 (ddd, J = 8.9, 5.0, 2.4 Hz, 1 H, H-6”), 7.91 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.73 (t, J = 9.0 Hz, 1 H, H-5”), 7.37-7.42 (m, 3 H, H-3, H-5, H-5”), 4.18 (s, 2 H, CH₂N); 13C NMR δ 165.3, 164.0 (d, J = 262 Hz), 144.4, 141.9, 141.1, 138.1 (d, J = 3 Hz), 135.6, 134.2, (d, J = 10 Hz), 133.0, 132.5, 127.6 (2), 127.5 (2), 127.2, 123.3, 117.7 (d, J = 21 Hz), 112.7, 101.2 (d, J = 16 Hz), 45.6; MS m/z 411.6 (MH⁺, 100%). Anal. Calcd for C₂₀H₁₅F₅N₄O₃S: C, 58.53; H, 3.68; N, 13.65. Found: C, 58.59; H, 3.74; N, 13.58%. Example 72
Preparation of 4-((Naphthalene-2-sulfonamido)methyl)-N-(pyridin-3-yl)benzamide (81).

[Method C. Reaction of amine salt 6 (400 mg, 1.0 mmol) and 2-naphthalenesulfonyl chloride (256 mg, 1.1 mmol) followed by column chromatography, eluting with EtOAc gave benzamide 81 (280 mg, 65%) as a white powder: mp (EtOAc) 210-21 3 °C; 1H NMR δ 10.32 (s, 1 H, NHCO), 8.91 (d, J = 2.3 Hz, 1 H, H-2”), 8.45 (d, J = 1.5 Hz, 1 H, H-1”), 8.34 (br t, J = 6.1 Hz, 1 H, NHSO₂), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6”), 8.12-8.1 6 (m, 3 H, H-4”, H-3”, H-4”), 8.04 (d, J = 7.8 Hz, 1 H, H-5”), 7.84-7.89 (m, 3 H, H-2, H-6, H-8”), 7.65-7.70 (m, 2 H, H-6”, H-7), 7.36-7.43 (m, 3 H, H-3, H-5, H-5”), 4.13 (d, J = 6.0 Hz, 2 H, CH₂N); 13C NMR δ 165.3, 144.4, 141.9, 141.7, 137.5, 135.6, 134.0, 132.9, 131.6, 129.3, 129.0, 128.5, 127.7, 127.5 (2), 127.4, 127.3 (2), 127.3, 127.2, 123.3, 122.1, 45.7. Anal. Calcd for C₂₃H₁₃N₃O₃S: C, 66.17; H, 4.59; N, 10.07. Found: C, 66.13; H, 4.77; N, 10.1 0%. * assignment interchangeable

Example 73
Preparation of 4-((5-(Dimethylamino)naphthalene-1-sulfonamido)methyl)-N-(pyridin-3-yl)benzamide (82).
[0265] Method C. Reaction of amine salt 6 (417 mg, 1.1 mmol) and 5-(dimethylamino)naphthalene sulfonyl chloride (318 mg, 1.2 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 82 (20 mg, 4%) as a white powder: mp (EtOAc) 208-21 1 °C; $^1$H NMR $\delta$ 10.28 (s, 1 H, NHCO), 8.90 (d, J = 2.3 Hz, 1 H, H-2'), 8.55 (m, 1 H, NSO$_2$), 8.42 (d, J = 8.5 Hz, 1 H, H-2''), 8.32 (d, J = 9.0 Hz, 1 H, H-8'), 8.30 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.15 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 8.10 (dd, J = 7.3, 1.2 Hz, 1 H, H-4''), 7.77 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.55-7.62 (m, 2 H, H-3', H-7'), 7.38 (ddd, J = 8.3, 4.7, 0.5 Hz, 1 H, H-5'), 7.28 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 7.26 (d, J = 7.3 Hz, 1 H, H-6''), 4.13 (s, 2 H, CH$_2$N), 2.81 [s, 6 H, N(CH$_3$)$_2$]; $^{13}$C NMR $\delta$ 165.3, 151.3, 144.5, 141.9 (2), 141.8, 136.0, 135.6, 132.6, 129.4, 128.9, 128.3, 127.8, 127.3 (3), 127.2 (2), 123.4, 123.3, 119.0, 115.0, 45.5, 44.9 (2); MS m/z 461.8 (MH$^+$, 100%). Anal. Calcd for C$_{28}$H$_{24}$N$_4$O$_3$S: C, 65.20; H, 5.25; N, 12.17. Found: C, 65.08; H, 5.31; N, 11.91%.

Example 74
Preparation of 4-((2,3-Dihydro-1 H-indene-5-sulfonamido)methyl)-N-(pyridin-3-yl)benzamide (83).

[0266] Method C. Reaction of amine salt 6 (438 mg, 1.1 mmol) and 2,3-dihydro-1 H-indene-5-sulfonyl chloride (268 mg, 1.2 mmol) followed by column chromatography, eluting with EtOAc, gave benzamide 83 (229 mg, 50%) as a white powder: mp (EtOAc) 179-1 81 °C; $^1$H NMR $\delta$ 10.35 (s, 1 H, NHCO), 8.92 (d, J = 2.3 Hz, 1 H, H-2'), 8.30 (ddd, J = 8.3, 2.4, 1.5 Hz, 1 H, H-4'), 8.15 (br s, 1 H, NSO$_2$), 7.89 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.57-7.61 (m, 2 H, H-2', H-6'), 7.36-7.42 (m, 4 H, H-3, H-5, H-5', H-7'), 4.07 (s, 2 H, CH$_2$N), 2.88-2.93 (m, 4 H, H-1', H-3''), 2.04 (m, 2 H, H-2''); $^{13}$C NMR $\delta$ 165.4, 148.7, 144.8, 144.4, 141.9, 141.8, 138.5, 135.7, 132.8, 127.5 (2), 127.3 (2), 127.2, 124.6, 124.5, 123.3, 122.2, 45.7, 32.1, 31.9, 30.5; MS m/z 408.6 (MH$^+$, 100%). Anal. Calcd for C$_{22}$H$_{21}$N$_3$O$_3$S: C, 64.85; H, 5.19; N, 10.31. Found: C, 64.78; H, 5.20; N, 10.29%.
Example 75
Preparation of 4-((2-(Dimethylamino)-2,3-dihydro-1H-indene-5-sulfonamido)methyl)-N-(pyridin-3-yl)benzamide (84).

[0267] Method C. Reaction of amine salt 6 (142 mg, 0.36 mmol) and 2-(dimethylamino)-2,3-dihydro-1/-indene-5-sulfonamido chloride (100 mg, 0.38 mmol) followed by column chromatography, eluting with a gradient (0-1%) of MeOH/DCM, gave benzamide 84 (15 mg, 9%) as a white gum: 1H NMR δ 10.36 (s, 1 H, NHCO), 8.94 (d, J = 2.4 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.19 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 8.15 (br t, J = 6.4 Hz, 1 H, NHSO2), 7.89 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.59 (br d, J = 7.9 Hz, 1 H, H-7'), 7.55 (br s, 1 H, H-4'), 7.34-7.42 (m, 4 H, H-3, H-5, H-5', H-6'), 4.07 (d, J = 6.4 Hz, 2 H, CH2N), 3.03-3.12 (m, 2 H, CH2), 2.81-2.89 (m, 2 H, CH2), 2.21-2.32 [m, 7 H, H-2', N(CH3)2]; 13C NMR δ 165.3, 146.2, 144.4, 142.4, 141.9, 141.7, 138.9, 135.7, 132.8, 127.5 (2), 127.5 (2), 127.1, 124.9, 124.7, 123.3, 122.2, 66.8, 45.6, 42.7 (2), 36.1, 35.9.

Example 76
Preparation of 4-((4-(4-Methylpiperazin-1-yl)phenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (85).

[0268] A mixture of fluoride 52 (696 mg, 1.8 mmol) and 4-methylpiperazine (3.0 ml) in DMSO (3 ml) was stirred in a sealed tube at 140 °C for 16 h. The solvent was evaporated and the residue was purified by column chromatography on neutral alumina, eluting with a gradient (0-5%) of MeOH/DCM, to give benzamide 85 (786 mg, 94%) as a white solid: mp (MeOH/DCM) 246-249 °C; 1H NMR δ 10.39 (s, 1 H, NHCO), 8.91 (d, J = 2.4 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.19 (ddd, J = 8.3, 2.4, 1.5 Hz, 1 H, H-4'), 7.95 (t, J = 6.3 Hz, 1 H, NHSO2), 6.90 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.63 (d, J = 8.9 Hz, 2 H, H-2', H-6'), 7.36-7.42 (m, 3 H, H-3, H-5, H-5'), 7.08 (d, J = 8.9 Hz, 2 H, H-3', H-5'), 6.40 (d, J = 6.3 Hz, 2 H, CH2N), 3.47 (br s, 4 H, 2 x CH2N), 2.94 (br s, 4 H, 2 x CH2N), 2.57 (s, 3 H, NCH3); MS m/z 466.8 (MH+, 100%). The compound was recrystallized as the dihydrochloride salt. Anal.
Calcd for C$_{24}$H$_{28}$ClN$_5$O$_3$S: C, 57.42; H, 5.62; N, 13.95. Found: C, 57.14; H, 5.62; N, 13.76%.

Example 77

[0269] Method C. Reaction of amine salt 6 (300 mg, 0.77 mmol) and A-(bromomethyl)benzenesulfonyl chloride (249 mg, 0.93 mmol) gave the intermediate bromide. Dimethylamine (40% solution in H$_2$O, 2.0 ml, 39.5 mmol) was added and the mixture was warmed to 20 °C and stirred for a further 2 h. H$_2$O (50 ml) was added and the solvent evaporated and the residue triturated with H$_2$O (25 ml). The crude solid was purified by column chromatography, eluting with a gradient (0-1 0%) of MeOH/DCM followed by 1% cNH$_2$-10% MeOH/DCM, to give benzamide 86 (138 mg, 42%) as a pale yellow powder: mp 186-188 °C; $^1$H NMR δ 10.36 (s, 1 H, NHCO), 8.93 (br s, 1 H, H-2'), 8.32-8.35 (m, 2 H, H-6', NHSO$_2$), 8.18 (ddd, J = 8.4, 2.3, 1.5 Hz, 1 H, H-4'), 7.88 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.83 (br d, J = 8.1 Hz, 2 H, H-2", H-6"), 7.60 (br d, J = 7.8 Hz, 2 H, H-3", H-5"), 7.38-7.41 (m, 3 H, H-3, H-5, H-5'), 4.13 (d, J = 6.3 Hz, 2 H, CH$_2$N), CH$_2$, N(CH$_3$)$_2$ not observed; $^{13}$C NMR δ 165.3, 144.4, 141.9, 141.6, 139.9, 135.7, 132.8, 129.8 (2), 127.5 (2), 127.3 (2), 127.2, 126.5 (2), 123.4, 61.3, 45.6, 43.9 (2), one C not observed; MS m/z 425.9 (MH$^+$, 100%).

Anal, calcd for C$_{21}$H$_{24}$N$_4$O$_3$S-V$_2$CH$_2$Cl$_2$: C, 57.87; H, 5.40; N, 12.00. Found: C, 57.74; H, 5.61; N, 12.17%.

Example 78

[0270] Method C. Reaction of amine salt 6 (300 mg, 0.77 mmol) and A-(bromomethyl)benzenesulfonyl chloride (249 mg, 0.93 mmol) gave the intermediate
bromide. Diethylamine (0.5 ml, 4.9 mmol) was added and the mixture was warmed to 20 °C and stirred for a further 5 h. The solvent was evaporated, H₂O (10 ml) added to the residue, the resulting precipitate triturated with H₂O (2 x 15 ml) and filtered. The crude solid was purified by column chromatography, eluting with a gradient (0-1 0%) of MeOH/DCM, to give benzamide 87 (66 mg, 19%) as a yellow powder: mp (MeOH/DCM) 159-1 62 °C; ¹H NMR δ 10.35 (s, 1 H, NHCO), 8.92 (d, J = 2.4 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.20 (br s, 1 H, NHSO₂), 8.18 (ddd, J = 8.4, 2.5, 1.5 Hz, 1 H, H-4'), 7.87 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.73 (br s, 2 H, H-2", H-6"), 7.49 (br s, 2 H, H-3", H-5"), 7.37-7.41 (m, 3 H, H-3, H-5, H-5'), 4.11 (d, J = 5.9 Hz, 2 H, CH₂N), 3.58 (s, 2 H, CH₂N), 2.45 (br s, 4 H, 2 x CH₂), 0.96 (br s, 6 H, 2 x CH₃); ¹³C NMR δ 165.4, 144.4, 141.9, 141.7, 135.7, 132.8, 128.8 (2), 127.5 (2), 127.3 (2), 127.1, 126.4 (2), 123.4, 56.2, 55.9 (2), 45.6, 11.3 (2), two C not observed; MS m/z 454.1 (MH⁺, 100%); HRMS (FAB⁺) calcd for C₂₄H₂₉N₄O₃S (MH⁺) m/z 453.1960, found 453.1962. Anal. calcd for C₂₄H₂₉N₄O₃S-2H₂O: C, 59.00; H, 6.60, N, 11.47. Found: C, 58.67; H, 5.83; N, 11.26%.

**Example 79**

**Preparation of 4-[[[4-{[(Dipropylamino)methyl]phenyl}sulfonyl]amino]methyl]-/V-(3-pyridinyl)benzamide (88).**

![Chemical Structure]

[0271] **Method C.** Reaction of amine salt 6 (150 mg, 0.39 mmol) and 4-(bromomethyl)benzenesulfonyl chloride (125 mg, 0.46 mmol) gave the intermediate bromide. Dipropylamine (0.21 ml, 1.5 mmol) was added and the mixture was warmed to 20 °C and stirred for a further 3 h. The solvent was evaporated and the residue was dissolved in DCM (50 ml), washed with H₂O (10 ml) and dried. The crude solid was purified by column chromatography, eluting with a gradient (0-1 0%) of MeOH/DCM and recrystallized from DCM/MeOH/iPr₂O. The solid was then triturated with H₂O (5 ml) and EtOAc (2 ml) to give benzamide 88 (42 mg, 23%) as a pale yellow powder: mp (MeOH/DCM) 184-1 87 0°C; ¹H NMR δ 10.35 (s, 1 H, NHCO), 8.92 (d, J = 2.4 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.17-8.21 (m, 2 H, H-4", NHSO₂), 7.87 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.73 (br d, J = 8.3 Hz, 2 H, H-2", H-6"), 7.48 (br d, J = 8.3 Hz, 2 H, H-3", H-5"), 7.37-7.40 (m, 3 H, H-3, H-5, H-5'), 4.10 (d, J = 6.1 Hz, 2 H, CH₂N), 3.58 (s, 2 H, CH₂N), 2.32 (t, J = 7.4 Hz, 4
H, 2 x CH₂N), 1.41 (sextet, J = 7.3 Hz, 4 H, 2 x CH₂), 0.81 (t, J = 7.4 Hz, 6 H, 2 CH₃); ¹³C NMR δ 165.3, 145.2, 144.4, 141.8, 141.7, 138.8, 135.7, 132.8, 128.7 (2), 127.5 (2), 127.3 (2), 127.1, 126.2 (2), 123.3, 57.4, 55.3 (2), 45.6, 19.6 (2), 11.6 (2); MS m/z 482.1 (MH⁺, 100%); HRMS (FAB⁺) calcd for C₂₆H₃₃N₄O₃S (MH⁺) m/z 481.2273, found 481.2271. Anal. calcd for C₂₆H₃₂N₄O₃S·H₂O·CH₃OH: C, 64.52; H, 6.81; N, 11.47. Found: C, 64.39; H, 6.82; N, 11.55%.

Example 80

[0272] Method C. Reaction of amine salt 6 (300 mg, 0.77 mmol) and 4-(bromomethyl)benzenesulfonyl chloride (249 mg, 0.93 mmol) gave the intermediate bromide. Pyrrolidine (0.4 mL, 4.8 mmol) was added and the mixture was warmed to 20 °C and stirred for a further 5 h. The solvent was removed under reduced pressure, H₂O (10 mL) added to the residue, the resulting precipitate triturated with H₂O (2 x 15 mL) and filtered. The crude solid was purified by column chromatography, eluting with a gradient (0-10%) of MeOH/DCM, to give benzamide 89 (191 mg, 55%) as a yellow powder: mp (MeOH/DCM) 114-118 °C; ¹H NMR δ 10.36 (s, 1 H, NHCO), 8.93 (d, J = 2.3 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 2 H, H-6', NHSO₂), 8.18 (dd, J = 8.4, 2.5, 1.5 Hz, 1 H, H-4'), 7.88 (br d, J = 8.3 Hz, 2 H, H-2', H-6'), 7.79 (br d, J = 7.4 Hz, 2 H, H-2'', H-6''), 7.59 (br s, 2 H, H-3'', H-5''), 7.37-7.41 (m, 3 H, H-3, H-5, H-5'), 4.11 (d, J = 6.2 Hz, 2 H, CH₂N), 3.94 (s, 2 H, CH₂N), 2.73 (br s, 4 H, 2 x NCH₂), 1.80 (br s, 4 H, 2 x CH₂); ¹³C NMR δ 165.4, 144.4, 141.9, 141.6, 140.2, 135.7, 132.8, 129.8 (2), 127.5 (2), 127.3 (2), 127.2, 126.5 (2), 123.3, 57.5, 53.2 (2), 45.6, 22.7 (2), one C not observed; MS m/z 452.0 (MH⁺, 100%); MS m/z 452.0 (MH⁺, 100%); HRMS (FAB⁺) calcd for C₂₄H₂₇N₄O₃S (MH⁺) m/z 451.1804, found 451.1806.

Example 81
[0273] Method C. Reaction of amine salt 6 (150 mg, 0.39 mmol) and A-(bromomethyl)benzenesulfonyl chloride (109 mg, 0.41 mmol) gave the intermediate bromide. Piperidine (0.20 mL, 1.9 mmol) was added and the mixture was warmed to 20 °C and stirred for 3 h. The solvent was evaporated and the residue was dissolved in DCM (50 mL), washed with H₂O (100 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (0-10%) of MeOH/DCM, to give benzamide 91 (77 mg, 42%) as a cream.

Example 82


[0274] Method C. Reaction of amine salt 6 (150 mg, 0.39 mmol) and A-(bromomethyl)benzenesulfonyl chloride (125 mg, 0.46 mmol) gave the intermediate bromide. Hexamethylenamine (0.22 mL, 1.9 mmol) was added and the mixture was warmed to 20 °C and stirred for a further 4 h. The solvent was evaporated and H₂O (20 mL) added to the residue. The resulting solid was filtered and washed with H₂O (50 mL). The crude solid was purified by column chromatography, eluting with a gradient (0-1 0%) of MeOH/DCM, to give benzamide 91 (77 mg, 42%) as a cream.
powder: mp (MeOH/DCM) 170-172 °C; 1H NMR δ 10.35 (s, 1 H, NHCO), 8.92 (d, J = 2.4 Hz, 1 H, H-2), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-5'), 8.22 (br s, 1 H, NHSO₂), 8.18 (ddd, J = 8.4, 2.5, 1.7 Hz, 1 H, H-4'), 7.87 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.74 (br d, J = 7.8 Hz, 2 H, H-2*, H-6*), 7.49 (br d, J = 6.3 Hz, 2 H, H-3', H-5'), 7.37-7.41 (m, 3 H, H-3, H-5, H-5'), 4.12 (d, J = 6.3 Hz, 2 H, CH₂N), 3.66 (s, 2 H, CH₂N), 2.55 (br s, 4 H, 2 x NCH₂), 1.55 (br s, 8 H, 4 x CH₂); 13C NMR δ 165.4, 144.4, 141.9, 141.7, 139.1, 135.7, 132.8, 128.9 (2), 127.5 (2), 127.3 (2), 127.1, 126.3 (2), 123.4, 60.9, 54.8 (2), 45.6, 27.5 (2), 26.3 (2), one C not observed; MS m/z 480.1 (MH⁺, 100%); HRMS (FAB⁺) calcd for C₂₆H₃₃N₄O₄S (MH⁺) m/z 479.21 17, found 479.21 13.

Example 83
Preparation of 4-[[4-(4-Morpholinylmethyl)phenyl]sulfonyl]amino)methyl]-/V-(3-pyridinyl)benzamide (92).

[0275] Method C. Reaction of amine salt 6 (150 mg, 0.39 mmol) and 4-(bromomethyl)benzenesulfonyl chloride (125 mg, 0.46 mmol) gave the intermediate bromide. Morpholine (0.20 ml, 2.3 mmol) was added and the mixture was warmed to 20 °C and stirred for a further 5 h. The solvent was evaporated and the residue dissolved in CH₂Cl₂ (60 ml), washed with H₂O (80 ml). The solvent was evaporated and the crude solid purified by column chromatography, eluting with a gradient (0-10%) of MeOH/DCM, to give benzamide 92 (122 mg, 68%) as a yellow powder: mp (MeOH/DCM) 158-160 °C; 1H NMR δ 10.34 (s, 1 H, NHCO), 8.92 (d, J = 2.3 Hz, 1 H, H-2), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-5'), 8.23 (br s, 1 H, NHSO₂), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.87 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.75 (br d, J = 8.3 Hz, 2 H, H-2*, H-6*), 7.48 (br d, J = 8.4 Hz, 2 H, H-3', H-5'), 7.36-7.41 (m, 3 H, H-3, H-5, H-5'), 4.11 (s, 2 H, CH₂NH), 3.57 (t, J = 4.6 Hz, 4 H, 2 x OCH₂), 3.52 (s, 2 H, CH₂N), 2.34 (t, J = 4.6 Hz, 4 H, 2 x NCH₂); 13C NMR δ 165.4, 144.4, 142.7, 141.8, 141.7, 139.3, 135.7, 132.8, 129.2 (2), 127.5 (2), 127.3 (2), 127.1, 126.3 (2), 123.4, 66.0 (2), 61.5, 53.0 (2), 45.6; MS m/z 468.0 (MH⁺, 100%). Anal. calcd for C₂₆H₂₆N₄O₄S: C, 61.78; H, 5.62; N, 12.01. Found: C, 62.01; H, 5.74; N, 12.13%.

Example 84

[0276] Method C. Reaction of amine salt 6 (340 mg, 0.87 mmol) and 4-(bromomethyl)benzenesulfonyl chloride (283 mg, 1.1 mmol) gave the intermediate bromide. 4-Methoxypiperidine hydrochloride (266 mg, 1.8 mmol) was added and the mixture was warmed to 20 °C and stirred for a further 150 mins. The solvent was evaporated, H₂O (30 ml) added to the residue and the resulting precipitate filtered. The aqueous layer was extracted with DCM (2 x 20 ml) and combined with the crude solid. The solvent was evaporated and the crude solid purified by column chromatography, eluting with a gradient (0-10%) of MeOH/DCM, to give benzamide 93 (67 mg, 16%) as a pale yellow powder: mp (MeOH/DCM) 182-184 °C; ′H NMR δ 10.34 (s, 1 H, NHCO), 8.92 (d, J = 2.2 Hz, 1 H, H-2'), 8.30 (dd, J = 4.6, 1.2 Hz, 1 H, H-6'), 8.22 (t, J = 6.3 Hz, 1 H, NHSO₂), 8.18 (ddd, J = 8.4, 2.4, 1.5 Hz, 1 H, H-4'), 7.86 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.73 (br d, J = 8.2 Hz, 2 H, H-2', H-6'), 7.46 (br d, J = 8.0 Hz, 2 H, H-3'', H-5''), 7.36-7.40 (m, 3 H, H-3, H-5, H-5''), 4.11 (d, J = 6.3 Hz, 2 H, CH₂N), 3.50 (s, 2 H, CH₂N), 3.17 (s, 3 H, CH₃), 3.13 (m, 1 H, CH), 2.59 (m, 2 H, 2 x CH), 2.07 (m, 2 H, 2 x CH), 1.80 (m, 2 H, 2 x CH), 1.41 (m, 2 H, 2 x CH); ¹³C NMR δ 165.3, 144.4, 143.4, 141.8, 139.2, 135.7, 132.8, 129.0 (2), 127.5 (2), 127.3 (2), 127.1 (2), 123.3, 75.3, 61.1, 54.6, 50.3 (2), 45.6, 30.4 (2); MS m/z 496.1 (MH⁺, 100%); HRMS (FAB⁺) calcd for C₂₆H₃₀N₄O₄S (MH⁺) m/z 495.2066, found 495.2073. Anal, calcd for C₂₆H₃₀N₄O₄S·V₂CH₃OH: C, 62.33; H, 6.32; N, 10.97. Found: C, 62.28; H, 6.02; N 11.26%.

Example 85
[0277] Method C. Reaction of amine salt 6 (250 mg, 0.64 mmol) and 4-(bromomethyl)benzenesulfonyl chloride (208 mg, 0.77 mmol) gave the intermediate bromide. 1-Methylpiperazine (0.36 mL, 3.3 mmol) was added and the mixture was warmed to 20 °C and stirred for 4 h. The solvent was evaporated, H₂O (25 mL) was added to the residue and the resulting precipitate filtered. The crude solid was purified by column chromatography, eluting with a gradient (0-1 0%) of MeOH/DCM, to give benzamide 94 (115 mg, 37%) as a pale tan powder: mp (MeOH/DCM) 158-162 °C; ¹H NMR δ 10.36 (s, 1 H, NHCO), 8.93 (d, J = 2.4 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.25 (t, J = 6.4 Hz, 1 H, NHSO₂), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.87 (br d, J = 8.3 Hz, 2 H, H-2', H-6), 7.75 (br d, J = 8.3 Hz, 2 H, H-2", H-6"), 7.48 (br d, J = 8.2 Hz, 2 H, H-3", H-5"), 7.36-7.41 (m, 3 H, H-3, H-5, H-5'), 4.11 (d, J = 6.3 Hz, 2 H, CH₂N), 3.58 (s, 2 H, CH₂N), 2.80 (br s, 4 H, 2 x NCH₂), CH₃, 2 x NCH₂ not observed; ¹³C NMR δ 165.4, 144.4, 142.4, 141.9, 141.7, 139.4, 135.7, 132.8, 129.2 (2), 127.5 (2), 127.3 (2), 127.2, 126.4 (2), 123.3, 60.4, 53.3 (2), 50.3 (2), 45.6, 43.4; MS m/z 481.1 (MH⁺, 100%). Anal. calcd for C₂₅H₂₉N₅O₃S-CH₂Cl₂: C, 55.32; H, 5.53; N, 12.41. Found: C, 54.97; H, 5.91; N, 12.69%.

Example 86
Preparation of 4-tert-Butyl-/V-(4-(pyridin-3-ylcarbamoyl)benzyl)benzamide (95).

[0278] Method A. Reaction of 4-tert-butylbenzoic acid (207 mg, 1.2 mmol) and oxalyl chloride (0.15 mL, 1.7 mmol) with subsequent reaction with amine salt 6 (542 mg, 1.4 mmol), followed by column chromatography eluting with a gradient (0-1 0%) of MeOH/EtOAc, gave benzamide 95 (246 mg, 55%) as a white powder: mp (EtOAc) 182-184 °C; ¹H NMR δ 10.37 (s, 1 H, NHCO), 9.03 (t, J = 6.0 Hz, 1 H, NHCO), 8.92 (d, J = 2.2 Hz, 1 H, H-2'), 8.30 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.95 (br d, J = 8.3 Hz, 2 H, H-2', H-6), 7.86 (ddd, J = 8.5, 2.0, 1.8 Hz, 2 H, H-2", H-6"), 7.50 (ddd, J = 8.5, 2.0, 1.8 Hz, 2 H, H-3", H-5"), 7.47 (d, J = 8.3 Hz, 2 H, H-3', H-5'), 7.42 (t, J = 7.7 Hz, 2 H, CH₂N), 2.87 (s, 2 H, CH₂N), 2.69 (br s, 4 H, 2 x NCH₂), CH₃, 2 x NCH₂ not observed; ¹³C NMR δ 165.4, 144.4, 142.4, 141.9, 141.7, 139.4, 135.7, 132.8, 129.2 (2), 127.5 (2), 127.3 (2), 127.2, 126.4 (2), 123.3, 60.4, 53.3 (2), 50.3 (2), 45.6, 43.4; MS m/z 481.1 (MH⁺, 100%). Anal. calcd for C₂₅H₂₉N₅O₃S-CH₂Cl₂: C, 55.32; H, 5.53; N, 12.41. Found: C, 54.97; H, 5.91; N, 12.69%.
Hz, 2 H, H-3, H-5), 7.38 (ddd, J = 8.3, 2.0, 0.5 Hz, 1 H, H-5'), 4.56 (d, J = 6.0 Hz, 2 H, CH₃N), 1.31 [S, 9 H, (CH₃)₂]; ¹³C NMR δ 166.1, 165.6, 154.0, 144.4, 143.8, 141.9, 135.7, 132.6, 131.4, 127.6 (2), 127.1, 127.0 (2), 126.9 (2), 125.0 (2), 123.3, 42.2, 34.5, 30.8 (3); MS m/z 388.6 (MH⁺, 100%). Anal. Calcd for C₂₄H₂₅N₃O₂·C, 74.39; H, 6.50; N, 10.84. Found: C, 74.33; H, 6.52; N, 10.81%.

Example 87
Preparation of 3,5-Dimethyl- N-(4-(pyridin-3-ylcarbamoyl)benzyl)benzamide (96).

[0279] Method A. Reaction of 3,5-dimethylbenzoic acid (333 mg, 2.2 mmol) and oxalyl chloride (0.29 ml, 3.3 mmol) with subsequent reaction with amine salt 6 (1.04 g, 2.7 mmol), followed by column chromatography eluting with a gradient (0-10%) of MeOH/EtOAc, gave benzamide 96 (184 mg, 23%) as a white powder: mp (EtOAc) 241-243 °C; ¹H NMR δ 10.37 (s, 1 H, NHCO), 9.00 (t, J = 6.0 Hz, 1 H, NHCO), 8.94 (d, J = 2.3 Hz, 1 H, H-2'), 8.30 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.94 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.52 (br s, 2 H, H-2", H-6"), 7.47 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 7.38 (ddd, J = 8.3, 4.7, 0.5 Hz, 1 H, H-5'), 7.17 (s, 1 H, H-4"), 4.54 (d, J = 6.0 Hz, 2 H, CH₃N), 2.32 [s, 6 H, 2 x CH₃]; ¹³C NMR δ 166.4, 165.6, 144.4, 143.8, 141.9, 137.3 (2), 135.7, 134.2, 132.7, 132.4, 127.7 (2), 127.1, 127.0 (2), 124.9 (2), 123.3, 42.3, 20.7 (2); MS m/z 360.5 (MH⁺, 100%). Anal. Calcd for C₂₂H₂₀N₃O₂·C, 73.52; H, 5.89; N, 11.69. Found: C, 73.22; H, 6.00; N, 11.59%.

Example 88
Preparation of 3,4-Dimethoxy- N-(4-(pyridin-3-ylcarbamoyl)benzyl)benzamide (97).

[0280] Method A. Reaction of 3,4-dimethoxybenzoic acid (247 mg, 1.4 mmol) and oxalyl chloride (0.18 ml, 2.0 mmol) with subsequent reaction with amine salt 6 (580 mg, 1.5 mmol), followed by column chromatography eluting with a gradient (0-10%)
of MeOH/EtOAc, gave benzamide 97 (41.1 mg, 70%) as a white powder: mp (EtOAc) 219-220 °C; $^1$H NMR δ 10.37 (s, 1 H, NHCO), 8.97 (t, J = 6.0 Hz, 1 H, NHCO), 8.92 (d, J = 2.3 Hz, 1 H, H-2), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4), 7.96 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.55 (dd, J = 8.4, 2.0 Hz, 1 H, H-6), 7.51 (d, J = 2.0 Hz, 1 H, H-2), 7.48 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 7.38 (dd, J = 8.3, 4.7 Hz, 1 H, H-5), 7.03 (d, J = 8.4 Hz, 1 H, H-5), 6.14 (br d, J = 6.0 Hz, 2 H, CH$_2$N), 3.82 (s, 3 H, OCH$_3$), 3.81 (s, 3 H, OCH$_3$); $^{13}$C NMR δ 165.7, 165.6, 151.3, 148.2, 144.4, 143.9, 141.9, 135.6, 132.7, 127.7 (2), 127.1, 127.0 (2), 126.4, 123.3, 120.4, 110.9, 110.6, 55.5, 55.4, 42.3; MS m/z 392.6 (MH$^+$, 100%). Anal. Calcd for C$_{32}$H$_{21}$N$_3$O$_4$: C, 67.51; H, 5.41; N, 10.74. Found: C, 67.24; H, 5.36; N, 10.75%

Example 89

Preparation of 4-[(4-tert-Butylphenylsulfonamido)methyl]-(N-methyl-N-(3-pyridinyl))benzamide (99).

[0281]4-(4-tert-Butylphenylsulfonamidomethyl)benzoic Acid (98). 4-tert-Butylbenzenesulfonyl chloride (4.85 g, 20.8 mmol) was added dropwise to a stirred solution of 4-aminomethylbenzoic acid (3.0 g, 19.9 mmol) in 2 M NaOH (20 mL) at 20 °C. The mixture was stirred at 20 °C for 3 h. The pH of the mixture was adjusted to 2-3 with 6 M HCl and the precipitate filtered. The precipitate was washed with water (2 x 20 mL), ether (20 mL) and pet. ether (2 x 20 mL) and air-dried. The crude solid was purified by column chromatography, eluting with a gradient (5-20%) of MeOH/EtOAc, to give benzoic acid 98 (4.88 g, 71%) as a white powder: mp 290-291 °C; $^1$H NMR δ 12.84 (br s, 1 H, CO$_2$H), 8.16 (br t, J = 6.1 Hz, 1 H, NH$_2$SO$_2$), 7.78 (br d, J = 8.2 Hz, 2 H, H-2, H-6), 7.68 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-2', H-6'), 7.53 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-3', H-5'), 7.27 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 4.05 (br d, J = 6.1 Hz, 2 H, CH$_2$N), 1.29 [s, 9 H, C(CH$_3$)$_3$]. Anal. calcd for C$_{38}$H$_{29}$N$_3$O$_4$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.32; H, 6.14; N, 4.06%.

[0282]4-[(4-tert-Butylphenylsulfonamido)methyl]-(N-methyl-N-(3-pyridinyl))benzamide (99). Method A. Reaction of benzoic acid 98 (404 mg, 1.2 mmol) and oxalyl chloride (0.15 mL, 1.7 mmol) and subsequent reaction with 3-aminomethylpyridine (138 mg, 1.3 mmol), followed by column chromatography, eluting with EtOAc, gave benzamide 99 (137 mg, 27%) as a white powder: mp
(EtOAc) 141-143 °C; ¹H NMR δ 8.34 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.31 (d, J = 2.3 Hz, 1 H, H-2'), 8.05 (br t, J = 6.4 Hz, 1 H, NHSO₂), 7.66-7.71 (m, 3 H, H-4', H-2'', H-6''), 7.57 (ddd, J = 8.7, 2.2, 1.8 Hz, 2 H, H-3'', H-5''), 7.33 (ddd, J = 8.1 , 4.7, 0.6 Hz, 1 H, H-5'), 7.19 (d, J = 8.3 Hz, 2 H, H-2, H-6), 7.11 (d, J = 8.3 Hz, 2 H, H-3, H-5), 3.93 (br d, J = 6.4 Hz, 2 H, CH₂N), 3.37 (s, 3 H, NCH₃), 1.30 [s, 9 H, C(CH)₃]; ¹³C NMR δ 169.3, 155.3, 148.1, 147.0, 141.0, 139.5, 137.9, 134.5, 134.1, 128.4 (2), 126.9 (2), 126.3 (2), 125.9 (2), 123.8, 45.5, 37.8, 34.8, 30.8 (3); MS m/z 438.6 (MH⁺, 100%). Anal. calcd for C₂₄H₂₇N₃O₅S-V₂EtOAc: C, 64.84; H, 6.49; N, 8.73. Found: C, 64.74; H, 6.36; N, 8.85%.

Example 90
Preparation of N-Methyl-4-(((phenylsulfonyl)amino)methyl)-N-(3-pyridinyl)benzamide (100).

[0283] Method A. Reaction of benzoic acid 12 (406 mg, 1.4 mmol) and oxalyl chloride (0.18 ml, 2.1 mmol) and subsequent reaction with 3-aminomethylpyridine (165 mg, 1.5 mmol), followed by column chromatography, eluting with EtOAc, gave benzamide 100 (85 mg, 16%) as a white powder: mp (EtOAc) 170-172 °C; ¹H NMR δ 8.34 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.32 (d, J = 2.3 Hz, 1 H, H-2'), 8.12 (br t, J = 6.3 Hz, 1 H, NHSO₂), 7.77 (ddd, J = 7.0, 2.1, 1.5 Hz, 2 H, H-2'', H-6''), 7.69 (ddd, J = 8.2, 2.6, 1.5 Hz, 1 H, H-4'), 7.59-7.63 (m, 1 H, H-4''), 7.53-7.58 (m, 2 H, H-3'', H-5''), 7.34 (ddd, J = 8.2, 4.7, 0.6 Hz, 1 H, H-5'), 7.19 (d, J = 8.3 Hz, 2 H, H-2, H-6), 7.11 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 3.94 (d, J = 6.3 Hz, 2 H, CH₂N), 3.38 (s, 3 H, NCH₃); ¹³C NMR δ 169.3, 148.1, 147.1, 140.7, 139.4, 134.5, 134.1, 132.3, 129.1 (2), 128.3 (2), 126.9 (2), 126.4 (2), 123.4, 45.6, 37.8; MS m/z 381.6 (MH⁺, 100%). Anal. calcd for C₂₀H₁₉N₃O₅S-VEtOAc: C, 62.52; H, 5.25; N, 10.41. Found: C, 62.36; H, 5.23; N, 10.57%.

Example 91
Preparation of 3-[[4-ferf-Butylphenylsulfonamido)methyl]-V-(3-pyridinyl)benzamide (102).
3-(4-tert-Butylphenylsulfonamidomethyl)benzoic Acid (101). 4-tert-Butylbenzenesulfonyl chloride (1.36 g, 5.9 mmol) was added in small portions to a stirred solution of 3-aminomethylbenzoic acid (1.0 g, 5.3 mmol) in 1 M NaOH (10 ml) at 20 °C. The mixture was stirred at 20 °C for 16 h. The pH of the mixture was adjusted to 2-3 with 6 M HCl and the precipitate filtered. The precipitate was washed with water (2 x 20 ml), ether (20 ml) and pet. ether (2 x 20 ml) and air-dried. The crude solid was purified by column chromatography, eluting with a gradient (0-5%) of MeOH/ EtOAc, to give benzoic acid 101 (1.25 g, 65%) as a white powder: mp (MeOH/ EtOAc) 191-1 93 0°C; 1H NMR δ 12.87 (br s, 1 H, CO2H), 8-1 S-I S (l, J = 6.4 Hz, 1 H, NHSO2), 7.82 (br s, 1 H, H-2), 7.77 (br t, J = 7.7, 1.3 Hz, 1 H, H-6), 7.68 (dd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-2’, H-6’), 7.54 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-3’, H-5’), 7.44 (br d, J = 7.9 Hz, 1 H, H-4), 7.37 (br t, J = 7.6 Hz, 1 H, H-5), 4.05 (br d, J = 6.1 Hz, 2 H, CH2N), 1.29 [s, 9 H, C(CH3)3]; MS m/z 380.5 (MH+, 100%). Anal. calcd for C18H21NO4S: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.44; H, 6.23; N, 4.03%.

3-[(Phenylsulfonamido)methyl]-N-(3-pyridinyl)benzamide (102). Method A. Reaction of benzoic acid 101 (0.35 g, 1.0 mmol) and oxaly chloride (0.13 ml, 1.5 mmol) and subsequent reaction with 3-aminopyridine (105 mg, 1.1 mmol), followed by column chromatography, eluting with EtOAc, gave benzamide 102 (285 mg, 67%) as a white powder: mp (EtOAc) 183-1 86 °C; 1H NMR δ 10.37 (s, 1 H, CONH), 8.92 (d, J = 2.2 Hz, 1 H, H-2), 8.31 (dd, J = 4.6, 1.5 Hz, 1 H, H-6’), 8.1 3-8.20 (m, 2 H, H-5, H-4’), 7.83-7.86 (m, 2 H, H-2, NHSO2), 7.73 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-2”, H-6”), 7.57 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-3”, H-5”), 7.44-7.49 (m, 2 H, H-4, H-6), 7.39 (br d, J = 8.7, 4.4 Hz, 1 H, H-5’), 4.09 (br d, J = 6.2 Hz, 2 H, CH2N), 1.29 [s, 9 H, C(CH3)3]; 13C NMR δ 165.6, 155.3, 144.6, 142.0, 138.2, 137.8, 135.8, 134.2, 131.0, 128.3, 127.3, 127.1, 126.4 (2), 125.9 (2), 123.5, 45.9, 34.8, 30.8 (3), 1 C not observed; MS m/z 424.6 (MH+, 100%). Anal. calcd for C23H25N3O3S-ACH3OH: C, 64.71; H, 6.07; N, 9.73. Found: C, 64.76; H, 6.15; N, 9.71%.

Example 92
Preparation of 3-[(Phenylsulfonamido)methyl]-N-(3-pyridinyl)benzamide (104).
[0286] 3-(Phenylsulfonamidomethyl)benzoic Acid (103). Benzenesulfonyl chloride (0.80 mL, 6.2 mmol) was added dropwise to a stirred solution of 3-aminomethylbenzoic acid (1.06 g, 5.7 mmol) in 1 M NaOH (12 mL) at 20 °C. The mixture was stirred at 20 °C for 16 h. The pH of the mixture was adjusted to 2-3 with 6 M HCl and the precipitate filtered. The precipitate was washed with water (2 x 20 mL), ether (20 mL) and pet. ether (2 x 20 mL) and air-dried. The crude solid was purified by column chromatography, eluting with a gradient (0-5%) of MeOH/EtOAc, to give benzoic acid 103 (0.96 g, 56%) as a white powder: mp (MeOH/EtOAc) 171-173 °C; 1H NMR δ 12.91 (br s, 1 H, CO₂H), 8.23 (t, J = 6.3 Hz, 1 H, NHSO₂), 7.85 (br s, 1 H, H-2), 7.77-7.81 (m, 3 H, H-6, H-2', H-6'), 7.53-7.58 (m, 2 H, H-3', H-5'), 7.46 (br d, J = 7.8 Hz, 1 H, H-4), 7.39 (br t, J = 7.6 Hz, 1 H, H-5), 4.06 (d, J = 6.3 Hz, 2 H, CH₂N); MS m/z 292.5 (MH⁺, 100%). Anal. calcd for C₈H₉NO₄S: C, 57.72; H, 4.50; N, 4.81. Found: C, 57.77; H, 4.47; N, 4.78%.

[0287] 3-[(Phenylsulfonamido)methyl]/-[(3-pyridinyl)benzamide (104). Method A. Reaction of benzoic acid 103 (0.56 g, 1.9 mmol) and oxalyl chloride (0.25 mL, 2.9 mmol) and subsequent reaction with 3-aminopyridine (200 mg, 2.1 mmol), followed by column chromatography, eluting with EtOAc, gave benzamide 104 (535 mg, 76%) as a white powder: mp (EtOAc) 74-78 °C; 1H NMR δ 10.40 (s, 1 H, CONH), 8.93 (d, J = 2.3 Hz, 1 H, H-2'), 8.32 (dd, J = 4.6, 1.5 Hz, 1 H, H-6'), 8.23 (br t, J = 6.2 Hz, 1 H, NHSO₂), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.81-7.87 (m, 4 H, H-2, H-6, H-2', H-6''), 7.55-7.65 (m, 3 H, H-3, H-4, H-5'), 7.45-7.50 (m, 2 H, H-4, H-5), 7.39 (br dd, J = 8.3, 4.6 Hz, 1 H, H-5'), 4.09 (br d, J = 6.2 Hz, 2 H, CH₂N); 13C NMR δ 165.7, 144.6, 142.0, 140.6, 138.1, 135.7, 134.3, 132.4, 131.0, 129.2 (2), 128.3, 127.4, 127.1, 126.5 (2), 126.4, 123.5, 45.9; MS m/z 368.8 (MH⁺, 100%). Anal. calcd for C₈H₉N₂O₃S·2EtOAc: C, 61.68; H, 4.92; N, 10.79. Found: C, 61.74; H, 4.90; N, 10.72%.

Example 93
Preparation of N-(1-Oxido-3-pyridinyl)-4-((phenylsulfonamido)methyl)benzamide (105).
A mixture of MCPBA (223 mg, 0.65 mmol) and benzamide 10 (0.16 ml, 0.4 mol) in DCM (15 ml) was stirred at 20 °C for 16 h. The mixture was diluted with DCM (20 ml), washed with saturated aqueous KHCO₃ (2 x 5 ml), water (5 ml), brine (5 ml) and dried. The solvent was evaporated and the residue purified by column chromatography, eluting with a gradient (0-5%) of MeOH/DCM, to give N-oxide 105 (106 mg, 64%) as a white powder: mp (MeOH/ EtOAc) 230-231 °C; ¹H NMR δ 10.52 br s, 1 H, NHCO), 8.92 (t, J = 1.7 Hz, 1 H, H-2"), 8.32 (br s, 1 H, NHSO₂), 8.00 (ddd, J = 6.4, 1.7, 0.8 Hz, 1 H, H-6"), 7.88 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.82 (ddd, J = 6.9, 2.0, 1.4 Hz, 2 H, H-2", H-6"), 7.68 (ddd, J = 8.5, 1.7, 1.4 Hz, 1 H, H-4"), 7.57-7.66 (m, 3 H, H-3, H-4", H-5"), 7.37-7.43 (m, 3 H, H-3, H-5, H-5"), 4.08 (s, 2 H, CH₂N); ¹³C NMR δ 165.7, 142.2, 140.5, 138.4, 133.9, 132.5, 132.4, 130.8, 129.2 (2), 127.8 (2), 127.4 (2), 126.4 (2), 126.1, 116.7, 45.7; MS m/z 384.5 (MH⁺, 100%). Anal. calcd for Cl₃H₁₇N₃O₄S: C, 59.52; H, 4.47; N, 10.96. Found: C, 59.47; H, 4.36; N, 10.99%.

Example 94
Preparation of 4-((4-iodophenylsulfonamido)methyl)- N-(pyridin-3-yl)benzamide (106).

A mixture of 4-(aminomethyl)- N-(3-pyridyl)benzamide 6 (727 mg, 3.2 mmol) and 4-iodobenzenesulfonyl chloride (970 mg, 3.2 mmol) in dry pyridine (10 ml) was stirred at 20 °C for 16 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with a gradient (0-20%) of MeOH/EtOAc, to give benzamide 106 (1.47 g, 93%) as a cream powder: mp (MeOH/ EtOAc) 249-251 °C; ¹H NMR δ 10.36 (s, 1 H, NHCO), 8.93 (d, J = 2.3 Hz, 1 H, H-2"), 8.34 (br s, 1 H, NHSO₂), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6"), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4"), 7.97 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-2", H-6"), 7.90 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.56 (dd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-3", H-5"), 7.37-7.42 (m, 3 H, H-3, H-5, H-5"), 4.09 (s, 2 H, CH₂N); ¹³C NMR δ 165.5, 144.5, 142.0, 141.6, 140.3, 138.1 (2), 135.8, 133.1, 128.2 (2), 127.7 (2), 127.5 (2), 127.3, 123.5, 100.3, 45.7; MS m/z 494.6 (MH⁺, 100%).
Example 95
Preparation of 4-((4-Ethynylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide (107).

[0290] PdCl₂(PPh₃)₂ (47 mg, 66 μmol) was added to a stirred, degassed solution of iodide 106 (327 mg, 0.66 mmol), TMS-acetylene (0.93 ml, 6.6 mmol) and Cul (13 mg, 66 μmol) in Et₃N (3 ml) and DMF (3 ml), and the mixture was stirred in a sealed pressure vessel at 20 °C for 2 h. The mixture was cooled to 20 °C, diluted with EtOAc (150 ml) and washed with water (3 x 50 ml), washed with brine (50 ml) and dried. The solvent was evaporated and the residue suspended in MeOH (20 ml) and K₂CO₃ (110 mg, 0.72 mmol) was added. The mixture was stirred at 20 °C for 1 h. The solvent was evaporated and the residue purified by column chromatography, eluting with a gradient (0-5%) of MeOH/DCM, to give benzamide 107 (200 mg, 77%) as a tan powder: mp (EtOAc) 182-185 °C; ¹H NMR δ 10.36 (s, 1 H, NHCO), 8.92 (d, J = 2.2 Hz, 1 H, H-2'), 8.35 (br t, J = 4.0 Hz, 1 H, NHSO₂), 8.31 (br dd, J = 4.6, 1.2 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.4, 1.5 Hz, 1 H, H-4'), 7.90 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.81 (ddd, J = 8.6, 1.9, 1.6 Hz, 2 H, H-2", H-6"), 7.68 (ddd, J = 8.6, 1.9, 1.6 Hz, 2 H, H-3", H-5"), 7.37-7.42 (m, 3 H, H-3, H-5, H-5'), 4.45 (s, 1 H, CH), 4.11 (br d, J = 4.0 Hz, 2 H, CH₂N); ¹³C NMR δ 165.5, 144.4, 142.0, 141.7, 140.7, 135.7, 133.1, 132.4 (2), 127.7 (2), 127.4 (2), 127.3 (2), 126.8, 125.7, 123.5, 83.8, 82.1, 47.7; MS m/z 392.5 (MH⁺, 100%). Anal. calcd for C₂₂H₁₇N₇O₃S: C, 64.43; H, 4.38; N, 10.73. Found: C, 64.26; H, 4.38; N, 10.43%.

Example 96
Preparation of 4-[(4-Bromophenylsulfonamido)methyl]-N-(4-pyridinyl)benzamide (109).

[0291] 4-((4-Bromophenylsulfonamido)methyl)benzoic Acid (108). A-

Bromobenzenesulfonyl chloride (2.36 g, 10.14 mmol) was added to a stirred solution of 4-aminomethylbenzoic acid (1.73 g, 9.22 mmol) in 1 M NaOH (19 ml) at 20 °C. The mixture was stirred at 20 °C for 3 h. The pH of the mixture was adjusted to 2-3
with 6 M HCl and the precipitate filtered. The precipitate was washed with water (2 x 20 ml_), ether (20 ml_) and pet. ether (2 x 20 ml_) and air-dried. The residue was purified by chromatography, eluting with a gradient (0-20%) of MeOH/EtOAc, to give benzoic acid 108 (2.44 g, 71%) as a white powder: mp 268-271 °C; 1H NMR δ 12.82 (br s, 1 H, CO₂H), 8.34 (br t, J = 6.1 Hz, 1 H, NHSO₂), 7.85 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.78 (ddd, J = 8.7, 2.2, 2.0 Hz, 2 H, H-2', H-6'), 7.70 (ddd, J = 8.7, 2.2, 2.0 Hz, 2 H, H-3', H-5'), 7.34 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 4.10 (br d, J = 6.0 Hz, 2 H, CH₂N). Anal. calcd for C₁₄H₁₂BrNSO₂·ACH₃OH: C, 45.23; H, 3.46; N, 3.70. Found: C, 44.95; H, 3.24; N, 3.68%.

[0292] 4-[(4-Bromophenylsulfonamido)methyl]-N-(4-pyridinyl)benzamide (109).

**Method A.** Reaction of benzoic acid 108 (920 mg, 2.5 mmol) and oxalyl chloride (0.33 ml_, 3.7 mmol) and subsequent reaction with 4-aminopyridine (260 mg, 2.7 mmol), followed by column chromatography, eluting with EtOAc, gave benzamide 109 (146 mg, 13%) as a white powder: mp (EtOAc) 219-222 °C; 1H NMR δ 10.52 (s, 1 H, NHCO), 8.48 (dd, J = 4.9, 1.5 Hz, 2 H, H-2', H-6'), 8.05 (br t, J = 6.3 Hz, 1 H, NHSO₂), 7.89 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.77-7.81 (m, 4 H, H-3', H-5', H-2'', H-6''), 7.78 (br dddd, J = 8.7, 2.0, 1.0 Hz, 2 H, H-3, H-5), 7.40 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 4.10 (d, J = 6.3 Hz, 2 H, CH₂N); 13C NMR δ 166.0, 150.1 (2), 146.0, 141.9, 139.9, 132.9, 132.3 (2), 128.5 (2), 127.9 (2), 127.5 (2), 126.2, 114.0 (2), 45.7; MS m/z 368.4/370.4 (MH⁺, 100%). Anal. calcd for C₁₈H₁₆BrN₃O₃S·½H₂O: C, 50.1 2; H, 3.76; N, 9.23. Found: C, 50.1 2; H, 3.45; N, 8.33%.

**Example 97**

Preparation of 4-[(4-Fluorobenzenesulfonyl)methyl]-N-(4-pyridinyl)benzamide (111).

![Chemical structure](image)

[0293] 4-(4-Fluorobenzenesulfonylamidomethyl)benzoic Acid (110). 4-

Fluorobenzenesulfonyl chloride (1.85 g, 9.49 mmol) was added to a stirred solution of 4-aminomethylbenzoic acid (1.62 g, 8.63 mmol) in 1 M NaOH (17 ml_) at 20 °C. The mixture was stirred at 20 °C for 16 h. The pH of the mixture was adjusted to 2-3 with 6 M HCl and the precipitate filtered. The precipitate was washed with water (2 x 20 ml_), ether (20 ml_) and pet. ether (2 x 20 ml_) and air-dried. The residue was
purified by chromatography, eluting with a gradient (0-20\%) of MeOH/EtOAc, to give benzoic acid 110 (2.23 g, 84\%) as a white powder: mp 231-234 °C; \(^1\)H NMR 5 8.28 (t, \(J = 6.3\) Hz, 1 H, NHSO\(_2\)), 7.80-7.85 (m, 4 H, H-2, H-6, H-2', H-6'), 7.31-7.40 (m, 4 H, H-3, H-5, H-3', H-5'), 4.07 (d, \(J = 6.3\) Hz, 2 H, CH\(_2\)N), CO\(_2\)H not observed. Anal. calcd for C\(_4\)H\(_{12}\)FNO\(_4\)S: C, 54.36; H, 3.91; N, 4.53. Found: C, 54.51; H, 3.81; N, 4.57%.

[0294] 4-[(4-Fluorophenylsulfonamido)methyl]-\(\text{N}^\text{a}\)-(4-pyridinyl)benzamide (111).

Method A. Reaction of benzoic acid 110 (840 mg, 2.7 mmol) and oxalyl chloride (0.36 ml, 4.1 mmol) and subsequent reaction with 4-aminopyridine (282 mg, 3.0 mmol), followed by column chromatography, eluting with EtOAc, gave benzamide 111 (406 mg, 39\%) as a white powder: mp (EtOAc) 231-233 °C; \(^1\)H NMR \(\delta\) 10.50 (s, 1 H, NHCO), 8.47 (dd, \(J = 4.8\), 1.5 Hz, 2 H, H-2', H-6'), 8.30 (t, \(J = 5.9\) Hz, 1 H, NHSO\(_2\)), 7.85-7.91 (m, 4 H, H-2, H-6, H-2', H-6'), 7.78 (br ddd, \(J = 4.8\), 1.5 Hz, 2 H, H-3', H-5'), 7.39-7.45 (m, 4 H, H-3, H-5, H-3', H-5'), 4.1 0 (d, \(J = 5.9\) Hz, 2 H, CH\(_2\)N); \(^13\)C NMR \(\delta\) 166.0, 164.1 (d, \(J = 250\) Hz), 150.3 (2), 145.9, 142.0, 137.8 (d, \(J = 3\) Hz), 133.0, 129.5 (2, d, \(J = 9\) Hz), 127.8 (2), 127.5 (2), 116.3 (2, d, \(J = 22\) Hz), 114.0 (2), 45.7; MS m/z 386.5 (MH\(^+\), 100\%). Anal. calcd for C\(_9\)H\(_9\)F\(_2\)N\(_2\)O\(_4\)S: C, 59.21; H, 4.18; N, 10.90. Found: C, 59.34; H, 4.12; N, 10.78%.

Example 98

Preparation of 4-[[4-[3-(Methyloxy)-1-propynyl]phenyl)sulfonylamino]methyl]-\(\text{N}^\text{a}\)-(3-pyridinyl)benzamide (112).

[0295] \text{PdCl}_2(\text{PPh}_3)_2 (29 mg, 42 \mu\text{mol}) was added to a stirred, degassed solution of iodide 106 (208 mg, 0.42 mmol), 3-methoxypropyne \((53 \mu\text{mol}, 0.63\) mmol) and CuI (8 mg, 42 \mu\text{mol}) in Et\(_3\)N \((2 \text{ml})\) and DMF \((2 \text{ml})\), and the mixture was stirred in a sealed pressure vessel at 50 °C for 4 h. The mixture was cooled to 20 °C, diluted with EtOAc \((150 \text{ml})\) and washed with water \((3 \times 50 \text{ml})\), washed with brine \((50 \text{ml})\) and dried. The solvent was evaporated and the residue purified by column chromatography, eluting with a gradient \((0-5\%)\) of MeOH/EtOAc, to give benzamide 112 (157 mg, 86\%) as a cream powder: mp (MeOH/EtOAc) 200-201 °C; \(^1\)H NMR \(\delta\) 10.37 (s, 1 H, NHCO), 9.1 0 (br s, 1 H, H-2'), 8.50 (br s, 1 H, H-6'), 8.35 (br s, 1 H, NHSO\(_2\)), 8.20 (br d, \(J = 8.3\) Hz, 1 H, H-4'), 7.59 (d, \(J = 8.3\) Hz, 2 H, H-2, H-6), 7.60
(dd, J = 8.5, 1.8 Hz, 2 H, H-2", H-6"), 7.65 (dd, J = 8.5, 1.8 Hz, 2 H, H-3", H-5"), 7.50 (br s, 1 H, H-5'), 7.40 (d, J = 8.3 Hz, 2 H, H-3), 4.35 (s, 2 H, CH₂O), 4.11 (br s, 2 H, CH₂Ni), 3.29 (s, 3 H, OCH₃): ¹³C NMR δ 165.5, 146.7, 144.4, 142.1, 141.6, 140.5, 135.8, 133.1, 132.1, 127.7, 127.5, 127.1, 126.8, 125.9, 89.0, 84.5, 59.4, 57.0, 45.7; MS m/z 436.8 (MH⁺, 100%). Anal. calcd for C₃₃H₂₁N₃O₄S: C, 63.43; H, 4.86; N, 9.54.

Example 99
Preparation of 4-[4-iodophenylsulfonamido)methyl]-N-methyl-N-(4-pyridinyl)benzamide (116).

[0296] A mixture of 4-(aminomethyl)-N-(4-pyridinyl)benzamide 8 (520 mg, 2.3 mmol) and 4-iodobenzenesulfonyl chloride (690 mg, 2.3 mmol) in dry pyridine (20 mL) was stirred at 20 °C for 16 h. The solvent was evaporated and the residue stirred in water (20 mL) for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (0-30%) of MeOH/EtOAc, to give benzamide 113 (906 mg, 80%) as a cream powder: mp (EtOAc) 270-273 °C; ¹H NMR δ 10.50 (s, 1 H, NHCO), 8.48 (br d, J = 4.8 Hz, 2 H, H-2", H-6"), 8.34 (br t, J = 6.2 Hz, 1 H, NHSO₂), 7.96 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-2", H-6"), 7.89 (br d, J = 8.4 Hz, 2 H, H-2, H-6), 7.78 (br dd, J = 6.3, 1.4 Hz, 2 H, H-3", H-5"), 7.56 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-3", H-5"), 7.40 (br d, J = 8.4 Hz, 2 H, H-3, H-5), 4.10 (d, J = 6.2 Hz, 2 H, CH₂Ni): ¹³C NMR δ 166.0, 150.3 (2), 145.9, 141.9, 140.2, 138.1, 136.4, 133.0, 128.2 (2), 127.8 (2), 127.5 (2), 114.0, 100.3, 45.7; MS m/z 494.6 (MH⁺, 100%). Anal. calcd for C₁₉H₁₆N₂O₅Si: C, 46.26; H, 3.27; N, 8.52. Found: C, 46.49; H, 3.24; N, 8.46.

Example 100
[0297] tert-Butyl 3,6,9,1 2,15,18-Hexaoxahenicos-20-yn-1 -ylcarbamate (114).

Mesyl chloride (1.78 ml, 23.0 mmol) was added dropwise to a stirred suspension of hexaethylene glycol (5.42 g, 19.2 mmol) and Ag₂O (4.67 g, 20.2 mmol) in dry DCM (50 ml) at 20 °C and the mixture was stirred at 20 °C for 3 days. The mixture was filtered through Celite® and the solvent evaporated. The residue was purified by column chromatography, eluting with a gradient (0-10%) of MeOH/EtOAc, to give 17-hydroxy-3,6,9,1 2,15-pentaoxaheptadec-1 -yl methanesulfonate (3.52 g, 51%) as a colourless oil: ¹H NMR (CDCl₃) δ 4.36-4.40 (m, 2 H, CH₂OSO₂), 3.76-3.78 (m, 2 H, CH₂O), 3.70-3.74 (m, 2 H, CH₂O), 3.64-3.67 (m, 16 H, 8 x CH₂O), 3.59-3.62 (m, 2 H, CH₂O), 3.09 (s, 3 H, SO₂CH₃), 2.80 (br s, 1 H, OH); MS m/z 361.6 (MH⁺, 100%).

A mixture of the mesylate (3.52 g, 9.8 mmol) and NaN₃ (1.27 g, 19.5 mmol) in dry DMF (20 ml) was stirred at 110 °C for 2 h. The mixture was cooled to 20 °C and the solvent evaporated. The residue was purified by column chromatography, eluting with 10% MeOH/EtOAc, to give 17-azido-3,6,9,1 2,15-pentaoxaheptadecan-1 -ol (2.98 g, 99%) as a colourless oil: ¹H NMR (CDCl₃) δ 3.71-3.74 (m, 2 H, CH₂O), 3.65-3.69 (m, 18 H, 9 x CH₂O), 3.39 (br t, J = 5.2 Hz, 2 H, CH₃N₃), 2.82 (br s, 1 H, OH); MS m/z 308.5 (MH⁺, 100%).

A mixture of azide (2.98 g, 9.7 mmol) and Pd/C (100 mg) in EtOH (50 ml) was stirred under H₂ (60 psi) for 1 h. The mixture was filtered through Celite® and washed with EtOH (3 x 20 ml) and the solvent was evaporated. The crude residue was dissolved in DCM (50 ml) and difurfyl dicarbonate (2.56 g, 11.7 mmol) in DCM (20 ml) was added dropwise and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and residue was purified by column chromatography, eluting with 10% MeOH/EtOAc, to give tert-butyl 17-hydroxy-3,6,9,1 2,15-pentaoxaheptadec-1 -ylcarbamate (2.97 g, 80%) as a colourless oil: ¹H NMR (CDCl₃) δ 5.17 (br s, 1 H, NHCO₂), 3.70-3.74 (m, 2 H, CH₂O), 3.60-3.68 (m, 18 H, 9 x CH₂O), 3.54 (br t, J = 5.1 Hz, 2 H, CH₂O), 3.31 (br q, J = 5.1 Hz, 2 H, CH₃N₃), 2.81 (br s, 1 H, OH), 1.44 [s, 9 H, C(CH₃)₃]; MS m/z 382.5 (MH⁺, 100%).

NaH (343 mg, 8.56 mmol) was added in small portions to a stirred solution of alcohol (2.97 g, 7.8 mmol) in THF (50 ml) at 0 °C and the resulting mixture stirred at 0 °C for 30 min. Propargyl bromide (0.87 ml, 7.8 mmol) was added followed by tetrabutylammonium iodide (29 mg, 78 µmol) and the mixture was stirred at 20 °C for 16 h. The reaction was quenched with sat. aq. NH₄Cl and extracted with EtOAc (4 x 50 ml). The combined organic fraction was washed with brine (50 ml), dried and the
solvent evaporated. The residue was purified by column chromatography, eluting with 80% EtOAc/pet. ether, to give the acetylene 114 (2.56 g, 79%) as a colourless oil: $^1$H NMR (CDCl$_3$) $\delta$ 5.05 (br s, 1 H, NHCO$_2$), 4.20 (d, $J = 2.4$ Hz, 2 H, CH$_2$C=C), 3.68-3.71 (m, 4 H, 2 x CH$_2$O), 3.64-3.67 (m, 12 H, 6 x CH$_2$O), 3.60-3.63 (m, 4 H, 2 x CH$_2$O), 3.54 (br t, $J = 5.2$ Hz, 2 H, CH$_2$O), 3.31 (br q, $J = 5.2$ Hz, 2 H, CH$_2$N), 2.42 (t, $J = 2.4$ Hz, 1 H, CH), 1.44 [s, 9 H, C(CH$_3$)$_3$]; MS m/z 420.7 (MH$^+$, 100%); HRMS calcd for C$_{20}$H$_{38}$N$_4$O$_8$S (MH$^+$) m/z 420.2592, found 420.2590 (0.4 ppm).

[0298] tert-Butyl 21-{4-[[4-[(3-hexaaxahenicos-20-yn-1-ylcarbamate 115). PdCl$_2$(PPh$_3$)$_2$ (36 mg, 51 $\mu$mol) was added to a stirred, degassed solution of iodide 106 (250 mg, 510 $\mu$mol), acetylene 114 (320 mg, 770 $\mu$mol) and Cul (10 mg, 51 $\mu$mol) in Et$_3$N (3 ml) and DMF (3 ml), and the mixture was stirred in a sealed pressure vessel at 50 °C for 3 h. The mixture was cooled to 20 °C, diluted with EtOAc (150 ml) and washed with water (3 x 50 ml), washed with brine (50 ml) and dried. The solvent was evaporated and the residue purified by column chromatography, eluting with a gradient (0-5%) of MeOH/EtOAc, to give carbamate 115 (367 mg, 92%) as a tan oil: $^1$H NMR (CDCl$_3$) $\delta$ 8.61 (br s, 1 H, H-2'), 8.41 (br s, 1 H, NHSO$_2$), 8.31 (d, $J = 4.6$ Hz, 1 H, H-6'), 8.25 (ddd, $J = 8.3$, 2.4, 1.4 Hz, 1 H, H-4'), 7.79-7.84 (m, 4 H, H-2, H-6, H-2", H-6"), 7.55 (dd, $J = 8.6$, 1.8 Hz, 2 H, H-3", H-5"), 7.28-7.34 (m, 3 H, H-3, H-5, H-5'), 5.78 (br s, 1 H, NHCO), 5.07 (br s, 1 H, NHCO$_2$), 4.42 (s, 2 H, CH$_2$O), 4.22 (br d, $J = 6.0$ Hz, 2 H, CH$_2$N), 3.74-3.77 (m, 2 H CH$_2$O), 3.68-3.71 (m, 2 H CH$_2$O), 3.55-3.66 (m, 18 H, 9 x CH$_2$O), 3.25 (br dd, $J = 5.4$, 5.2 Hz, 2 H, CH$_2$N), 1.43 [s, 9 H, C(CH$_3$)$_3$]; MS m/z 786.0 (MH$^+$, 100%); HRMS calcd for C$_{95}H$_{54}N$_4$O$_{16}$S (MH$^+$) m/z 785.3426, found 785.3410 (2.5 ppm).

[0299]4-[[[[4-(21-Amino-4,7,10,13,16,19-hexaaxahenicos-1-yn-1-yl)phenyl]sulfonyl]amino)methyl]-V-(3-pyridinyl)benzamide 116. A solution of carbamate 115 (360 mg, 0.46 mmol) in HCl saturated MeOH (10 ml) was stood at 20 °C for 16 h. The solvent was evaporated and the crude oil purified by preparative HPLC [gradient elution 5-55% of (90%MeCN/H$_2$O)/(0.02% v/v aqueous CF$_3$CO$_2$H)] to give the amine as the trifluoracetate salt (270 mg, 73%) as a brown gum: $^1$H NMR $\delta$ 11.34 (s, 1 H, NHCO), 9.42 (d, $J = 2.2$ Hz, 1 H, H-2'), 8.88 (d, $J = 8.8$ Hz, 1 H, H-4'), 8.64 (d, $J = 4.9$ Hz, 1 H, H-4'), 8.47 (br s, 1 H, NHSO$_2$), 8.04 (br d, $J = 8.3$ Hz, 2
H, H-2, H-6), 7.96 (m, 4 H, NH₂-CF₃CO₂H, H-5'), 7.82 (dd, J = 8.5, 1.8 Hz, 2 H, H-2", H-6"), 7.65 (dd, J = 8.5, 1.8 Hz, 2 H, H-3", H-5"), 7.44 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 4.43 (s, 2 H, CH₂O), 4.12 (br d, J = 6.2 Hz, 2 H, CH₂N), 3.51-3.65 (m, 22 H, 11 x CH₂O), 2.95 (br q, J = 5.5 Hz, 2 H, CH₂N); ¹³C NMR 5 165.9, 142.5, 140.5, 138.6, 137.0, 134.7, 133.5, 132.0 (2), 131.9, 129.1, 128.1 (2), 127.7 (2), 127.5 (2), 127.1, 126.8 (2), 125.8, 89.2, 84.3, 69.7 (3), 69.6 (2), 69.5, 68.8, 66.6, 58.0, 48.5, 45.7, 38.8; HRMS calcd for C₃₄H₄₅N₄O₅S (MH⁺) m/z 685.2902, found 685.2898 (1.2 ppm).

Example 101

[0300] A mixture of acetylene 98 (103 mg, 0.24 mmol) and Pd/C (30 mg) in EtOH (50 ml) was stirred under H₂ (60 psi) for 1 h. The mixture was filtered through Celite, washed with EtOH. The solvent was evaporated and the crude solid was crystallized to give methyl ether 117 (62 mg, 59%) as a cream powder: mp (MeOH/EtOAc) 172-174 °C; ¹H NMR δ 10.36 (s, 1 H, NHCO), 8.92 (d, J = 2.2 Hz, 1 H, H-2'), 8.31 (br dd, J = 4.5, 1.5 Hz, 1 H, H-6'), 8.15-8.21 (m, 2 H, H-4', NHSO₂), 7.89 (br d, J = 8.2 Hz, 2 H, H-2, H-6), 7.71 (br d, J = 8.2 Hz, 2 H, H-2", H-6"), 7.35-7.42 (m, 5 H, H-3, H-5, H-5', H-3", H-5"), 4.09 (s, 2 H, CH₂N), 3.31 (t, J = 6.3 Hz, 2 H, CH₂O), 3.22 (s, 3 H, OCH₃), 2.65-2.70 (m, 2 H, CH₂), 1.76-1.83 (m, 2 H, CH₂); ¹³C NMR δ 165.5, 146.7, 144.5, 142.0, 141.8, 138.2, 135.8, 133.0, 129.0 (2), 127.6 (2), 127.4 (2), 127.3, 126.6 (2), 123.4, 70.9, 57.8, 45.7, 31.5, 30.4; MS m/z 440.7 (MH⁺, 100%). Anal. calcd for C₂₃H₂₅N₃O₄S·H₂O: C, 60.38; H, 5.95; N, 9.18. Found: C, 60.1 3; H, 5.60; N, 9.16%.

Example 102
Preparation of 4-[[[4-(1-benzyl-1 H-1,2,3-triazol-4-yl)phenyl)sulfonyl]amino)methyl]-N-(3-pyridinyl)benzamide (118).

[0301] TBTA (28 mg, 53 µmol) was added to a suspension of CuSO₄·H₂O (13 mg, 53 µmol), sodium ascorbate (21 mg, 106 µmol), acetylene 107 (208 mg, 0.53 mmol) and benzyl azide (0.14 ml, 1.06 mmol) in water (1 ml) and DMSO (1 ml). The
mixture was stirred at 20 °C for 24 h. The mixture was diluted with water (50 ml) and stirred at 20 °C for 30 min. The mixture was filtered, washed with water (3 x 5 ml) and dried. The precipitate was suspended in MeOH/EtOAc (1:1, 10 ml), filtered and washed with EtOAc to give benzamide 118 (240 mg, 86%) as a grey powder: mp (MeOH/EtOAc) 256-260 °C; ¹H NMR δ 10.37 (s, 1 H, NHCO), 8.79 (s, 1 H, H-2′), 8.25-8.30 (m, 2 H, H-6′, NHSO₂), 8.20 (br d, J = 8.2 Hz, 1 H, H-4′), 8.06 (d, J = 8.4 Hz, 2 H, H-3″, H-5″), 7.85-7.94 (m, 4 H, H-2, H-6, H-2″, H-6″), 7.57 (br s, 1 H, H-5″′), 7.33-7.46 (m, 8 H, H-3, H-5, H-5′, H-2″′, H-3″′, H-4″′, H-5″′, H-6″′), 5.67 (s, 2 H, CH₂N), 4.11 (br d, J = 6.1 Hz, 2 H, CH₂N); ¹³C NMR δ 165.5, 144.5, 142.0, 141.7, 140.2, 135.8, 133.1, 131.9 (2), 127.7 (2), 127.4 (2), 127.3 (2), 126.9, 125.6 (2), 122.8, 53.1, 47.7 (1 C not observed); MS m/z 525.6 (MH⁺, 100%). Anal. calcd for C₂₈H₂₄N₆O₃S·H₂O: C, 61.98; H, 4.83; N, 15.48. Found: C, 61.60; H, 4.33; N, 15.41%.

Example 103

Preparation of 4-[((4-(3-Hydroxy-1-propynyl)phenyl)sulfonyl)amino)methyl]-V-(3-pyridinyl)benzamide (119).

[0302] PdCl₂(PPh₃)₂ (105 mg, 149 μmol) was added to a stirred, degassed solution of iodide 106 (734 mg, 1.49 mmol), propargyl alcohol (132 μl, 2.23 mmol) and Cul (28 mg, 149 μmol) in Et₃N (3 ml) and DMF (3 ml), and the mixture was stirred in a sealed pressure vessel at 50 °C for 4 h. The mixture was cooled to 20 °C, diluted with EtOAc (150 ml) and washed with water (3 x 50 ml), washed with brine (50 ml) and dried. The solvent was evaporated and the residue purified by column chromatography, eluting with a gradient (0-5%) of MeOH/EtOAc, to give benzamide 119 (460 mg, 73%) as a cream powder: mp (MeOH/EtOAc) 207-210 °C; ¹H NMR δ 10.36 (s, 1 H, NHCO), 8.92 (d, J = 2.4 Hz, 1 H, H-2′), 8.34 (br s, 1 H, NHSO₂), 8.31 (dd, J = 4.6, 1.5 Hz, 1 H, H-6″), 8.18 (ddd, J = 8.4, 2.5, 1.5 Hz, 1 H, H-4″), 7.91 (d, J = 8.3 Hz, 2 H, H-2, H-6), 7.80 (dd, J = 8.5, 1.9 Hz, 2 H, H-2″, H-6″), 7.62 (dd, J = 8.5, 1.9 Hz, 2 H, H-3″, H-5″), 7.36-7.42 (m, 3 H, H-3, H-5, H-5″), 5.38 (br t, J = 5.9 Hz, 1 H, OH), 4.35 (br d, J = 5.8 Hz, 2 H, CH₂O), 4.11 (br s, 2 H, CH₂N); ¹³C NMR δ 165.5, 144.5, 142.0, 141.7, 140.2, 135.8, 133.1, 131.9 (2), 127.7 (2), 127.4 (2), 111
127.3, 126.8 (2), 126.4, 123.1, 93.0, 82.4, 49.4, 45.7; MS m/z 422.5 (MH+, 100%).
Anal. calcd for C_{22}H_{19}N_{3}O_{4}S: C, 62.69; H, 4.54; N, 9.97. Found: C, 62.99; H, 4.38; N, 10.07%.

Example 104

[0303] A mixture of acetylene 119 (405 mg, 0.96 mmol) and Pd/C (60 mg) in EtOH (150 ml) was stirred under H₂ (60 psi) for 1 h. The mixture was filtered through Celite, washed with EtOH. The solvent was evaporated and the crude solid was crystallized to give methyl ether 120 (295 mg, 72%) as a cream powder: mp (MeOH/EtOAc) 177-1 79 °C; 1H NMR δ 10.36 (s, 1 H, NHCO), 8.92 (d, J = 2.2 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 8.14 (br s, 1 H, NHSO₂), 7.90 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.72 (br d, J = 8.3 Hz, 2 H, H-2', H-6''), 7.37-7.42 (m, 5 H, H-3, H-5, H-5', H-3'', H-5''), 4.48 (br s, 1 H, OH), 4.08 (s, 2 H, CH₂N), 3.38-3.41 (m, 2 H, CH₂O), 2.69 (dd, J = 7.9, 7.6 Hz, 2 H, CH₂), 1.68-1.77 (m, 2 H, CH₂); 13C NMR δ 165.5, 147.2, 144.5, 142.0, 141.9, 138.0, 135.8, 133.0, 129.0 (2), 127.6 (2), 127.4 (2), 127.3, 126.5 (2), 123.5, 59.9, 45.7, 33.8, 31.4; MS m/z 426.6 (MH+, 100%). Anal. calcd for C_{22}H_{23}N_{3}O_{4}S: C, 62.10; H, 5.45; N, 9.88. Found: C, 62.27; H, 5.41; N, 9.94%.

Example 105
Preparation of 4-[[4-(21-Amino-4,7,1 0,1 3,1 6,1 9-hexaoxahenicos-1 -yn-1-yl)phenyl]sulfonyl]amino)methyl]-N-(4-pyridinyl)benzamide (122).

[0304] tert-Butyl 21-4-[[4-[4-[(4-Pyridinylamino)carbonyl]benzyl]amino)sulfonyl]phenyl]-3,6,9,1 2,5,18-hexaoxahenicos-20-yn-1-ylcarbamate (121). PdCl₂(PPh₃)₂ (40 mg, 57 µmol) was added to a stirred, degassed solution of iodide 113 (284 mg, 570 µmol), acetylene 114 (362 mg, 863 µmol) and Cul (11 mg, 57 µmol) in Et₃N (3 ml) and DMF (3 ml), and the mixture was stirred in a sealed pressure vessel at 50 °C for 3 h. The mixture
was cooled to 20 °C, diluted with EtOAc (150 mL) and washed with water (3 x 50 mL), washed with brine (50 mL) and dried. The solvent was evaporated and the residue purified by column chromatography, eluting with a gradient (0-10%) of MeOH/EtOAc, to give carbamate 121 (427 mg, 95%) as a tan oil: 1H NMR (CDCl₃) δ 8.52 (dd, J = 6.3, 1.5 Hz, 2 H, H-2', H-6'); 8.42 (br s, 1 H, NHSO₂), 7.78-7.84 (m, 4 H, H-2, H-6, H-2", H-6") 7.64 (dd, J = 6.3, 1.5 Hz, 2 H, H-3', H-5'), 7.54 (ddd, J = 8.6, 1.9, 1.6 Hz, 2 H, H-3", H-5"), 7.33 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 5.45 (br s, 1 H, NHCO), 5.06 (br s, 1 H, NHCO₂), 4.42 (s, 2 H, CH₂O), 4.23 (d, J = 6.2 Hz, 2 H, CH₂N), 3.74-3.77 (m, 2 H CH₂O), 3.68-3.71 (m, 2 H CH₂O), 3.55-3.65 (m, 18 H, 9 x CH₂O), 3.24 (br d, J = 5.3 Hz, 2 H, CH₂N), 1.43 [s, 9 H, C(CHg)₃]; MS m/z 786.0 (MH⁺, 100%); HRMS calcd for C₃₉H₅₃N₄O₉S (MH⁺) m/z 785.3426, found 785.3436 (1.0 ppm).

Example 106
Preparation of 4-((4-ferf-Butylphenylsulfonamido)methyl)/V-(pyridin-4-yl)benzamide (122). A solution of carbamate 121 (41.0 mg, 0.52 mmol) in HCl saturated MeOH (10 mL) was stood at 20 °C for 16 h. The solvent was evaporated and the crude oil was purified by preparative HPLC [gradient elution 5-55% of (90%MeCN/H₂O)/(0.02% v/v aqueous CF₃CO₂H)] to give the amine 122 as the trifluoracetate salt (21.7 mg, 52%) as a tan gum: 1H NMR δ 11.42 (s, 1 H, NHCO), 8.76 (d, J = 7.1 Hz, 2 H, H-2', H-6'), 8.41 (br t, J = 6.3 Hz, 1 H, NHSO₂), 8.28 (d, J = 7.1 Hz, 2 H, H-3', H-5'), 7.97 (d, J = 8.4 Hz, 2 H, H-2, H-6), 7.81 (dd, J = 8.5, 1.8 Hz, 2 H, H-2", H-6"), 7.77 (br s, 3 H, NH₃ “CF₃CO₂⁻”), 7.65 (dd, J = 8.5, 1.8 Hz, 2 H, H-3”, H-5"), 7.46 (d, J = 8.4 Hz, 2 H, H-3, H-5), 4.43 (s, 2 H, CH₂O), 4.13 (d, J = 6.3 Hz, 2 H, CH₂N), 3.63-3.66 (m, 2 H CH₂O), 3.51-3.61 (m, 20 H, 10 x CH₂O), 2.95-3.02 (m, 2 H, CH₂N); 13C NMR δ 166.8, 158.3, 152.8, 143.1, 153.0 (2), 140.4, 132.1 (2), 131.9, 128.3 (2), 127.6 (2), 126.8 (2), 125.9, 115.1 (2), 89.2, 84.3, 69.7 (br, 8), 69.6 (2), 69.5, 68.8, 66.6, 58.0, 45.6; MS m/z 685.2 (MH⁺, 100%); HRMS calcd for C₃₉H₄₅N₄O₉S (MH⁺) m/z 685.2902, found 685.2893 (1.9 ppm).

Example 106
Preparation of 4-((4-ferf-Butylphenylsulfonamido)methyl)/V-(pyridin-4-yl)benzamide (123).
A mixture of 4-(aminomethyl)-Λ-(4-pyridinyl)benzamide dihydrobromide 8 (399 mg, 1.03 mmol) and 4-tert-butylbenzenesulfonyl chloride (263 mg, 1.13 mmol) in dry pyridine (10 ml) was stirred at 20 °C for 16 h. The solvent was evaporated and the residue stirred in water (20 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with a gradient (0-1 0%) of MeOH/EtOAc, to give benzamide 123 (189 mg, 43%) as a white powder: mp (MeOH/EtOAc) 261-263 °C; ¹H NMR 5 10.48 (s, 1 H, NHCO), 8.47 (dd, J = 4.8, 1.5 Hz, 2 H, H-2', H-6'), 8.19 (br t, J = 6.3 Hz, 1 H, NHSO₂), 7.66 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.77 (dd, J = 4.8, 1.5 Hz, 2 H, H-3', H-5'), 7.70 (ddd, J = 8.6, 2.2, 2.0 Hz, 2 H, H-2'', H-6''), 7.54 (ddd, J = 8.6, 2.2, 2.0 Hz, 2 H, H-3'', H-5''), 7.38 (d, J = 8.3 Hz, 2 H, H-3, H-5), 4.09 (br d, J = 6.3 Hz, 2 H, CH₂N), 1.28 [s, 9 H, C(CH₃)₃]; ¹³C NMR δ 165.9, 155.2, 150.1 (2), 145.8, 142.0, 137.8, 132.7, 127.6 (2), 127.4 (2), 126.2 (2), 125.8 (2), 113.9 (2), 45.6, 34.6, 30.6 (3); MS m/z 424.5 (MH⁺, 100%). Anal, calcld for C₂₃H₂₅N₃O₃S: C, 65.23; H, 5.95; N, 9.92. Found: C, 65.29; H, 6.05; N, 9.88%.

Example 107
Preparation of 4-[[[4-(tert-Butylphenyl)sulfonyl]amino]methyl]-V-(5-methyl-3-pyridinyl)benzamide (125).

4-(terM3utylphenyl)sulfonyl chloride 4.85 g, 20.84 mmol) was added in small portions to a stirred solution of 4-aminomethylbenzoic acid (3.0 g, 19.85 mmol) in 2 M NaOH solution (20 ml) and the mixture was stirred at 20 °C for 16 h. The pH was adjusted to 2 with 6 M HCl and the resulting precipitate was filtered, washed with water (2 x 10 ml), dried, washed with pet. ether (2 x 10 ml) and the material dried to give acid 124 (4.88 g, 71%) as a white powder: mp (MeOH) 290-291 °C; ¹H NMR δ 12.84 (br s, 1 H, CO₂H), 8.19 (t, J = 6.4 Hz, 1 H, NHSO₂), 7.79 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.66 (ddd, J = 8.8, 2.2, 1.9 Hz, 2 H, H-2', H-6'), 7.52 (ddd, J = 8.8, 2.2, 1.9 Hz, 2 H, H-3', H-5'), 7.31 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 4.07 (d, J = 6.4 Hz, 2 H, CH₂N). Anal, calcld for C₈H₆(NO₃)₅S: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.32; H, 6.14; N, 4.06%.  

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4-({[(4-tert-Butylphenyl)sulfonyl]amino}methyl)-N-(5-methyl-3-pyridinyl)benzamide (125). Oxalyl chloride (94 µL, 1.1 mmol) was added dropwise to a stirred suspension of benzoic acid 124 (250 mg, 0.7 mmol) and DMF (1 drop) in dry THF (20 mL) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 mL). 2-Methyl-3-pyridinylamine (86 mg, 0.8 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 mL) for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzamide 125 (156 mg, 50%) as a white powder: mp (EtOAc) 189-1 91 °C; 1H NMR δ 10.27 (s, 1 H, CONH), 8.71 (d, J = 2.3 Hz, 1 H, H-2'), 8.18 (br s, 1 H, NHSO2), 8.16 (d, J = 1.2 Hz, 1 H, H-6'), 8.00-8.04 (m, 1 H, H-4'), 7.86 (br d, J = 8.4 Hz, 2 H, H-2, H-6), 7.70-7.74 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-2", H-6"), 7.55 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-3", H-5"), 7.37 (br d, J = 8.4 Hz, 2 H, H-3, H-5), 4.09 (br s, 2 H, CH2N), 2.31 (s, 3 H, CH3), 1.29 [s, 9 H, C(CH3)3]; 13C NMR δ 165.4, 155.3, 144.9, 141.7, 139.3, 137.9, 135.4, 133.0, 132.7, 127.7, 127.6 (2), 127.4 (2), 126.3 (2), 125.9 (2), 45.8, 34.8, 30.7 (3), 17.9; MS m/z 438.6 (MH+, 100%). Anal. calcd for C24H27N3O3S: C, 65.88; H, 6.22; N, 9.60. Found: C, 65.72; H, 6.37; N, 9.58%.

Example 108

Preparation of 4-({[(4-tert-Butylphenyl)sulfonyl]amino}methyl)-N-(2-methyl-3-pyridinyl)benzamide (126).

Oxalyl chloride (132 µL, 1.5 mmol) was added dropwise to a stirred suspension of benzoic acid 124 (350 mg, 1.0 mmol) and DMF (1 drop) in dry THF (20 mL) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 mL). 2-Methyl-3-pyridinylamine was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 mL) for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography,
eluting with EtOAc, to give benzamide 126 (266 mg, 60%) as a white powder: mp (EtOAc) 188-190 °C; 1H NMR δ 9.95 (s, 1 H, CONH), 8.34 (dd, J = 4.8, 1.6 Hz, 1 H, H-2'), 8.19 (br t, J = 6.4 Hz, 1 H, NHSO₂), 7.87 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.68-7.74 (m, 3 H, H-4'; H-2', H-6'), 7.56 (ddd, J = 8.6, 2.2, 2.0 Hz, 2 H, H-3", H-5"), 7.36 (br d, J = 8.4 Hz, 2 H, H-3, H-5), 7.27 (dd, J = 8.0, 4.8 Hz, 1 H, H-5'), 4.09 (d, J = 6.4 Hz, 2 H, CH₂N), 2.43 (s, 3 H, CH₃), 1.30 [s, 9 H, C(CH₃)₂]; 13C NMR δ 165.1, 155.3, 153.9, 146.1, 141.7, 137.9, 133.8, 132.7, 132.4, 127.5 (2), 127.4 (2), 126.3 (2), 125.9 (2), 121.4, 45.8, 34.8, 30.8 (3), 21.0; MS m/z 438.6 (MH⁺, 100%). Anal. calcd for C₂₄H₂₇N₃O₃S: C, 65.88; H, 6.22; N, 9.60. Found: C, 66.13; H, 6.40; N, 9.41%.

Example 109
Preparation of 4-(((4-tert-Butylphenyl)sulfonyl)amino)methyl)-N-(6-methyl-3-pyridinyl)benzamide (127).

[0310]Oxalyl chloride (132 µl, 1.5 mmol) was added dropwise to a stirred suspension of benzoic acid 124 (348 mg, 1.0 mmol) and DMF (1 drop) in dry THF (20 ml) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 ml). 6-Methyl-3-pyridinylamine (120 mg, 1.1 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzamide 127 (322 mg, 74%) as a white powder: mp (EtOAc) 235-237 °C; 1H NMR δ 10.25 (s, 1 H, CONH), 8.77 (d, J = 2.5 Hz, 1 H, H-2'), 8.19 (br t, J = 6.3 Hz, 1 H, NHSO₂), 8.04 (dd, J = 8.4, 2.5 Hz, 1 H, H-4'), 7.85 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.70 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-2", H-6"), 7.55 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-3", H-5"), 7.37 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 7.23 (d, J = 8.4 Hz, 1 H, H-5'), 4.09 (s, 2 H, CH₂N), 2.44 (s, 3 H, CH₃), 1.28 [s, 9 H, C(CH₃)₂]; 13C NMR δ 165.2, 155.2, 152.7, 141.6, 141.3, 137.8, 133.2, 133.0, 127.9, 127.5 (2), 127.4 (2), 126.3 (2), 125.8 (2), 122.5, 45.7, 34.7, 30.7 (3),...
23.3; MS m/z 438.6 (MH+, 100%). Anal, calcd for C_{24}H_{27}N_{3}O_{3}S: C, 65.88; H, 6.22; N, 9.60. Found: C, 65.72; H, 6.23; N, 9.62%.

**Example 110**

**Preparation of 4-([(4-ferf-Butylphenyl)sulfonyl]amino)methyl)/-V-(6-methoxy-3-pyridinyl)benzamide (128).**

[0312]TNethylamine (0.4 ml, 3 mmol) was added dropwise to a stirred solution of benzoic acid 124 (250 mg, 0.72 mmol), EDCI (154 mg, 0.8 mmol), HOBt (108 mg, 0.8 mmol) and 6-methoxypyrindin-3-amine (134 mg, 1.1 mmol) in anhydrous DCM (10 ml), and the reaction mixture was stirred at 20 °C for 4 d. The solution was diluted with DCM (100 ml), washed with H_{2}O (2 x 50 ml), and washed with brine (50 ml). The combined organic phase was dried, filtered and the solvent evaporated. The residue was purified by column chromatography, eluting with 4% MeOH/DCM, to give benzamide 128 (71 mg, 22%) as a pink powder: mp (MeOH/DCM) 238-240 °C; \(^1\)H NMR δ 10.1 8 (s, 1 H, CONH), 8.49 (d, J = 2.5 Hz, 1 H, H-2'), 8.1 8 (t, J = 6.3 Hz, 1 H, NHSO\(_2\)), 8.02 (dd, J = 8.9, 2.7 Hz, 1 H, H-4'), 7.84 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.69 (br d, J = 8.6 Hz, 2 H, H-2', H-6'), 7.55 (br d, J = 8.6 Hz, 2 H, H-3', H-5'), 7.36 (br d, J = 8.3 H, 2 H, H-3, H-5), 6.84 (d, J = 8.9 Hz, 1 H, H-5'), 4.08 (d, J = 6.3 Hz, 2 H, CH\(_2\)NH\(_2\)), 3.84 (s, 3 H, OCH\(_3\)), 1.29 [s, 9 H, C(CH\(_3\))\(_3\)]; \(^{13}\)C NMR δ 165.0, 159.9, 155.3, 141.5, 138.9, 137.9, 133.0, 132.6, 129.9, 127.5 (2), 127.4 (2), 126.3 (2), 125.9 (2), 109.9, 53.1, 45.8, 34.7, 30.8 (3); MS m/z 455.3 (MH+, 100%). Anal, calcd for C_{24}H_{27}N_{3}O_{4}S: C, 63.56; H, 6.00; N, 9.26. Found: C, 63.29; H, 6.00; N, 9.13%.

**Example 111**

**Preparation of 4-([(4-tert-Butylphenyl)sulfonyl]amino)methyl)/-V-(6-chloro-3-pyridinyl)benzamide (129).**

[0312]Oxalyl chloride (0.1 3 ml, 1.44 mmol) was added to a stirred solution of carboxylic acid 124 (250 mg, 0.72 mmol) and a catalytic amount of DMF (2 drops) in anhydrous THF (20 ml), and the solution was heated at reflux temperature for 2 h.
The solvent was evaporated and the residue was dried under high vacuum. The residue was dissolved in anhydrous pyridine (10 ml), 6-chloropyridin-3-amine (102 mg, 0.8 mmol) was added, and the reaction mixture was stirred at 20 °C for 16 h then at 60 °C for 3 h. The solvent was evaporated and the residue was suspended in cold water (50 ml) and stirred at 0 °C for 1 h. The solid was filtered, washed with water (20 ml) and dried. The residue was purified by column chromatography, eluting with 50% EtOAc/pet. ether to give benzamide 129 (60 mg, 19%) as a white solid: mp (EtOAc/pet. ether) 251-253 °C; 1H NMR δ 10.48 (s, 1 H, CONH), 8.78 (d, J = 2.5 Hz, 1 H, H-2'), 8.24 (dd, J = 3.8, 2.8 Hz, 1 H, H-4'), 8.19 (br t, J = 6.3 Hz, 1 H, NHSO2), 7.86 (br d, J = 8.6 Hz, 2 H, H-6), 7.69 (dt, J = 8.6, 2.0 Hz, 2 H, H-2", H-6"), 7.55 (dt, J = 8.6, 2.0 Hz, 2 H, H-3", H-5"), 7.52 (d, J = 8.8 Hz, 1 H, H-5'), 7.38 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 4.09 (d, J = 6.1 Hz, 2 H, CH2NHSO2), 1.28 [s, 9 H, C(CH3)3]; 13C NMR δ 165.5, 155.3, 144.0, 142.0, 141.5, 137.9, 135.4, 132.6, 130.9, 127.6 (2), 127.5 (2), 126.3 (2), 125.9 (2), 124.0, 45.8, 34.8, 30.8 (3); MS m/z 459.2 (MH+, 100%). Anal. calcd for C23H24ClNiO1S: C, 60.32; H, 5.28; N, 9.18. Found: C, 60.27; H, 5.28; N, 9.10%.

Example 112

Preparation of 4-((4-tert-Butylphenyl)sulfonyl)aminomethyl)-5/(4-chloro-3-pyridinyl)benzamide (130).

[0313]Oxalyl chloride (0.13 ml, 1.44 mmol) was added to a stirred solution of carboxylic acid 124 (250 mg, 0.72 mmol) and a catalytic amount of DMF (2 drops) in anhydrous THF (20 ml) and the solution was heated at reflux temperature for 2 h. The solvent was evaporated and the residue was dried under high vacuum. The residue was dissolved in anhydrous pyridine (10 ml), 4-chloropyridin-3-amine (102 mg, 0.8 mmol) was added, and the reaction mixture was stirred at 60 °C for 3 h. The solvent was evaporated and the residue was suspended in cold H2O (50 ml) and stirred at 0 °C for 1 h. The solid was filtered, washed with H2O (50 ml) and dried. The residue was purified by column chromatography, eluting with 4% MeOH/DCM, to give benzamide 130 (112 mg, 34%) as a white solid: mp (MeOH/DCM) 125-128 °C; 1H NMR δ 10.22 (s, 1 H, CONH), 8.67 (s, 1 H, H-2'), 8.44 (d, J = 5.2 Hz, 2 H, H-6'), 8.19 (t, J = 6.4 Hz, 1 H, NHSO2), 7.88 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.70 (br
\[ d, J = 8.6 \text{ Hz}, 2 \text{ H}, -2", -6") \], 7.67 \( d, J = 5.3 \text{ Hz}, 1 \text{ H}, -5") \], 7.55 \( \text{br d}, J = 8.6 \text{ Hz}, 2 \text{ H}, -3", -5") \], 7.38 \( \text{br d}, J = 8.3 \text{ Hz}, 2 \text{ H}, -3, -5\) \], 4.10 \( \text{d}, J = 6.3 \text{ Hz}, 2 \text{ H} \), 

CH\(_2\)NHSO\(_2\)_2], 1.30 \{s, 9 \text{ H}, C(CHs)_3\}; \( ^{13}\text{C} \) NMR (DMSO-C\(_2\)N\(_2\)) 5 165.3, 155.3, 149.3, 147.9, 142.0, 139.4, 137.9, 132.2, 132.0, 127.7 (2), 127.5 (2), 126.3 (2), 125.9 (2), 124.6, 45.7, 34.8, 30.8 (3); MS m/z 459.2 (MH\(^+\), 100%). Anal. calcd for C\(_{23}\)H\(_{24}\)ClN\(_3\)O\(_3\)S: C, 60.32; H, 5.28; N, 9.18. Found: C, 60.46; H, 5.36; N, 8.95%.

**Example 113**

Preparation of 4-[[((4-ferf-Butylphenyl)sulfonyl]amino)methyl]-\(\text{V}-(2\text{-chloro-3-pyridinyl})\)benzamide (131).

[0314]Oxalyl chloride (0.13 ml, 1.44 mmol) was added to a stirred solution of carboxylic acid 124 (250 mg, 0.72 mmol) and a catalytic amount of DMF (2 drops) in anhydrous THF (15 ml) and the solution was heated at reflux temperature for 2 h. The solvent was evaporated and the residue was dried under high vacuum. The residue was dissolved in anhydrous pyridine (10 ml), 2-chloropyridin-3-amine (102 mg, 0.8 mmol) was added, and the reaction mixture was stirred at 20 °C for 16 h. The pyridine was evaporated and the residue was suspended in cold water (50 ml) and stirred at 0 °C for 1 h. The solid was filtered, washed with water (10 ml) and dried. The residue was purified by column chromatography eluting with 40% EtOAc/pet.ether followed by 2% MeOH/DCM, to give benzamide 131 (13.1 mg, 40%) as a white solid: mp (MeOH/DCM) 161-1 62 °C; \( ^{1}\)H NMR \( \delta \) 10.10 (s, 1 H, CONH), 8.31 (dd, J = 4.6, 1.8 Hz, 1 H, H-6’), 8.19 (t, J = 6.4 Hz, 1 H, NHSO\(_2\)\(_2\)), 8.05 (dd, J = 7.9, 1.8 Hz, 1 H, H-4’), 7.88 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.70 (dt, J = 8.6, 2.0 Hz, 2 H, H-2”, H-6”), 7.56 (dt, J = 8.7, 2.0 Hz, 2 H, H-3”, H-5”), 7.50 (dd, J = 7.9, 4.7 Hz, 1 H, H-5’), 7.38 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 4.10 (d, J = 6.3 Hz, 2 H, CH\(_2\)NHSO\(_2\)_2]; 1.29 \{s, 9 \text{ H}, C(CH\(_3\)_3\}; \( ^{13}\text{C} \) NMR \( \delta \) 165.2, 155.3, 146.6, 146.2, 142.1, 137.9, 136.7, 132.2, 132.1, 127.6 (2), 127.5 (2), 126.3 (2), 125.9 (2), 123.4, 45.7, 34.8, 30.8 (3); MS m/z 459.2 (MH\(^+\), 100%). Anal. calcd for C\(_{23}\)H\(_{24}\)ClN\(_3\)O\(_3\)S: C, 60.32; H, 5.28; N, 9.18. Found: C, 60.46; H, 5.36; N, 8.95%.
Example 114
Preparation of 4-(((4-ferf-Butylphenyl)sulfonyl)amino)methyl)-V-(4-methyl-3-pyridinyl)benzamide (132).

[0315]Oxalyl chloride (132 µL, 1.5 mmol) was added dropwise to a stirred suspension of benzoic acid 124 (350 mg, 1.0 mmol) and DMF (1 drop) in dry THF (20 mL) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 mL). 5-Methyl-3-pyridylamine (prepared by reduction of 5-methyl-3-nitropyridine (152 mg, 1.1 mmol) in EtOH (50 mL) under H₂ (60 psi) for 2 h, filtering through Celite and evaporation of the solvent) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 mL) for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50-1 00%) of EtOAc/pet. ether, to give benzamide 132 (154 mg, 35%) as a white powder: mp (EtOAc) 183-185 °C; ¹H NMR δ 10.00 (s, 1 H, CONH), 8.45 (s, 1 H, H-2), 8.31 (d, J = 4.8 Hz, 1 H, H-6), 8.19 (br t, J = 6.3 Hz, 1 H, NHSO₂), 7.87 (d, J = 8.3 Hz, 2 H, H-2, H-6), 7.70 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-2", H-6"), 7.55 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-3", H-5"), 7.37 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 7.32 (d, J = 4.8 Hz, 1 H, H-5), 4.10 (d, J = 6.3 Hz, 2 H, CH₂N), 2.39 (s, 3 H, CH₃), 1.29 (s, 9 H, C(CH₃)₃); ¹³C NMR δ 165.3, 155.3, 147.4, 146.7, 142.9, 141.1, 137.9, 133.5, 132.6, 127.6 (2), 127.4 (2), 126.3 (2), 125.9 (2), 125.3, 45.8, 34.8, 30.8 (3), 17.3; MS m/z 438.7 (MH⁺, 100%). Anal. calcd for C₂₄H₂₇N₃O₃S: C, 65.88; H, 6.22; N, 9.60. Found: C, 65.69; H, 6.35; N, 9.44%.

Example 115
Preparation of 4-(((4-ferf-Butylphenyl)sulfonyl)amino)methyl)-V-(5-chloro-3-pyridinyl)benzamide (133).

[0316]Oxalyl chloride (132 µL, 1.5 mmol) was added dropwise to a stirred suspension of benzoic acid 124 (350 mg, 1.0 mmol) and DMF (1 drop) in dry THF
(20 ml_) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 ml). 5-Chloro-3-pyridinylamine (143 mg, 1.1 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with a gradient (30-50%) of EtOAc/pet. ether, to give benzamide 133 (243 mg, 53%) as a white powder: mp (EtOAc) 217-219 9 °C; 1H NMR δ 10.98 (s, 1 H, CONH), 8.38 (d, J = 5.4 Hz, 1 H, H-6'), 8.29 (d, J = 2.0 Hz, 1 H, H-2'), 8.17 (br s, 1 H, NHSO₂), 7.92 (d, J = 8.4 Hz, 2 H, H-2, H-6), 7.70 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-2', H-6'), 7.56 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-3', H-5'), 7.35 (br d, J = 8.4 Hz, 2 H, H-3, H-5), 7.30 (dd, J = 5.4, 2.0 Hz, 1 H, H-4'), 4.08 (br s, 2 H, CH₂N), 1.29 [s, 9 H, C(CH₃)₃]; 13C NMR δ 166.0, 155.3, 153.4, 149.3, 143.9, 142.2, 137.9, 132.3, 128.0 (2), 127.3 (2), 126.3 (2), 125.9 (2), 119.7, 114.0, 45.7, 34.8, 30.8 (3); MS m/z 458.8 (MH⁺, 100%). Anal. calcd for C₂₃H₂₄ClN₃O₃S: C, 60.32; H, 5.28; N, 9.18. Found: C, 60.07; H, 5.28; N, 8.81%.

Example 116
Preparation of 4-(([(4-tert-Butylphenyl)sulfonyl]amino)methyl)quinoline-2-(2-nitro-3-pyridinyl)benzamide (134).

[0317]Oxalyl chloride (132 µL, 1.5 mmol) was added dropwise to a stirred suspension of benzoic acid 124 (355 mg, 1.0 mmol) and DMF (1 drop) in dry THF (20 ml) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 ml). 2-Nitro-3-pyridinylamine (156 mg, 1.1 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50-1 00%) of EtOAc/pet. ether, to give benzamide 134 (64 mg, 13%) as a cream powder: mp (EtOAc) 191-1 93 °C; 1H NMR δ 10.78 (s, 1 H, CONH), 8.42 (dd, J = 4.5, 1.5 Hz, 1 H, H-6'), 8.28 (dd, J = 8.2, 1.5
Hz, 1 H, H-4'), 8.20 (br t, J = 6.4 Hz, 1 H, NHSO₂), 7.88 (dd, J = 8.2, 4.5 Hz, 1 H, H-5'), 7.85 (d, J = 8.4 Hz, 2 H, H-2, H-6), 7.71 (dd, J = 8.6, 1.8 Hz, 2 H, H-2"", H-6"), 7.56 (dd, J = 8.6, 1.8 Hz, 2 H, H-3", H-5"), 7.40 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 4.10 (d, J = 6.3 Hz, 2 H, CH₃N), 1.29 [s, 9 H, C(CH₃)₃]; ¹³C NMR δ 165.1, 155.4, 150.9, 144.1, 142.6, 137.8, 136.1, 131.6, 129.2, 127.7 (2), 127.6 (2), 127.3, 126.4 (2), 125.9 (2), 45.7, 34.8, 30.8 (3); MS m/z 469.8 (MH⁺, 100%). Anal. calcd for C₂₇H₃₂N₄O₄S: C, 63.76; H, 6.34; N, 11.02. Found: C, 63.77; H, 6.51; N, 10.81%.

Example 117

[0318]Oxalyl chloride (132 µL, 1.5 mmol) was added dropwise to a stirred suspension of benzoic acid 124 (350 mg, 1.0 mmol) and DMF (1 drop) in dry THF (20 mL) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 mL). 6-(4-morpholinyl)-3-pyridinylamine (200 mg, 1.1 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 mL) for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50-100%) of EtOAc/pet. ether, to give benzamide 135 (262 mg, 51%) as a white powder; mp (EtOAc) 264-266 °C; ¹H NMR 5 10.05 (s, 1 H, CONH), 8.45 (d, J = 2.6 Hz, 1 H, H-2'), 8.17 (br t, J = 6.0 Hz, 1 H, NHO₂), 7.91 (dd, J = 9.1, 2.6 Hz, 1 H, H-4'), 7.84 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.69 (ddd, J = 8.6, 2.1, 1.8 Hz, 2 H, H-2", H-6"), 7.54 (ddd, J = 8.6, 2.1, 1.8 Hz, 2 H, H-3", H-5"), 7.34 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 6.86 (d, J = 9.1 Hz, 1 H, H-5'), 4.08 (br d, J = 6.0 Hz, 2 H, CH₂N), 3.71 (br t, J = 4.8 Hz, 4 H, 2 x CH₂O), 3.40 (br t, J = 4.8 Hz, 4 H, 2 x CH₂N), 1.29 [s, 9 H, C(CH₃)₃]; ¹³C NMR 5 164.8, 156.1, 155.3, 141.3, 140.3, 137.9, 133.2, 131.1, 127.4 (2), 127.3 (2), 127.0, 126.3 (2), 125.9 (2), 106.6, 65.9 (2), 45.8, 45.6 (2), 37.8, 30.8 (3); MS m/z 509.8 (MH⁺, 100%). Anal. calcd for C₂₇H₃₂N₄O₄S: C, 63.76; H, 6.34; N, 11.02. Found: C, 63.77; H, 6.51; N, 10.81%.
Example 118


[0319]Oxalyl chloride (132 µL, 1.5 mmol) was added dropwise to a stirred suspension of benzoic acid 124 (350 mg, 1.0 mmol) and DMF (1 drop) in dry THF (20 mL) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 mL). 6-Trifluoromethyl-3-pyridinylamine (180 mg, 1.1 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 mL) for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50-1 00%) of EtOAc/pet. ether, to give benzamide 136 (268 mg, 54%) as a white powder: mp (EtOAc) 249-252 °C; 1H NMR δ 10.69 (s, 1 H, CONH), 9.09 (d, J = 2.4 Hz, 1 H, H-2'), 8.48 (dd, J = 8.6, 2.2 Hz, 1 H, H-4'), 8.23 (br s, 1 H, NHSO₂), 7.86-7.93 (m, 3 H, H-2, H-6, H-5'), 7.70 (ddd, J = 8.6, 2.2, 2.0 Hz, 2 H, H-2", H-6"), 7.55 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-3", H-5"), 7.40 (d, J = 8.4 Hz, 2 H, H-3, H-5), 4.11 (br s, 2 H, CH₂N), 1.28 [s, 9 H, C(CH₃)₃]; 13C NMR δ 165.9, 155.3, 142.2, 141.7, 140.7 (q, J = 34.1 Hz), 138.8, 137.9, 132.4, 127.8 (2), 127.6, 127.5 (2), 126.3 (2), 125.9 (2), 121.8 (q, J = 273.0 Hz), 121.1 (q, J = 2.8 Hz), 45.7, 34.7, 30.7 (3); MS m/z 493.0 (MH⁺, 100%). Anal. calcd for C₂₄H₂₄F₃N₃O₃S: C, 58.65; H, 4.92; N, 8.55. Found: C, 58.82; H, 4.94; N, 8.41%.

Example 119

Preparation of N-[6-(Acetylamino)-3-pyridinyl]-4-(((4-ferf-butylphenyl)sulfonyl)amino)methyl)benzamide (137).

[0320]Oxalyl chloride (132 µL, 1.5 mmol) was added dropwise to a stirred suspension of benzoic acid 124 (350 mg, 1.0 mmol) and DMF (1 drop) in dry THF (20 mL) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The
solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 ml). 6-Acetyl-3-pyridinylamine (168 mg, 1.1 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with a gradient (60-1 00%) of EtOAc/pet. ether, to give benzamide 137 (290 mg, 60%) as a white powder: mp (EtOAc) 240-243 °C; 1H NMR δ 10.42 (s, 1 H, CONH), 10.27 (s, 1 H, CONH), 8.69 (t, J = 1.7 Hz, 1 H, H-2”), 8.18 (br s, 1 H, NHSO₂), 8.03-8.09 (m, 2 H, H-4”, H-5”), 7.85 (br d, J = 8.4 Hz, 2 H, H-2, H-6), 7.70 (ddd, J = 8.6, 2.2, 2.0 Hz, 2 H, H-2’, H-6’), 7.55 (ddd, J = 8.6, 2.2, 2.0 Hz, 2 H, H-3’, H-5’), 7.37 (br d, J = 8.4 Hz, 2 H, H-3, H-5), 4.09 (br s, 2 H, CH₂N), 2.09 (s, 3 H, CH₃), 1.29 [S, 9 H, C(CH₃)₃]; ¹³C NMR 5 168.8, 165.1, 155.3, 147.9, 141.6, 140.0, 137.9, 133.0, 131.6, 130.0, 127.5 (2), 127.4 (2), 126.3 (2), 125.9 (2), 113.0, 45.8, 34.8, 30.6 (3), 23.8; MS m/z 481.8 (MH⁺, 100%). Anal. calcd for C₆₂H₅₈N₄O₄S: C, 62.48; H, 5.87; N, 11.66. Found: C, 62.51; H, 5.91; N, 11.88%.

Example 120


[0321]Oxalyl chloride (132 µL, 1.5 mmol) was added dropwise to a stirred suspension of benzoic acid 124 (350 mg, 1.0 mmol) and DMF (1 drop) in dry THF (20 ml) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 ml). 6-Fluoro-3-pyridinylamine (124 mg, 1.1 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50-1 00%) of EtOAc/pet. ether, to give benzamide 138 (253 mg, 57%) as a white powder: mp (EtOAc) 254-257 °C; 1H NMR δ 10.43 (s, 1 H, CONH), 8.57 (dd, J = 2.7, 1.3 Hz, 1 H, H-2’), 8.31 (ddd, J = 8.9, 7.4, 2.8 Hz, 1 H, H-4’), 8.19 (br s, 1 H, NHSO₂), 7.86 (dd, J = 8.4, 1.7 Hz, 2 H, H-2, H-6), 7.70 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-2”, H-6”), 7.55 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H,
H-3", H-5"), 7.38 (br d, J = 8.4 Hz, 2 H, H-3, H-5), 7.20 (dd, J = 8.9, 3.2 Hz, 1 H, H-5'), 4.09 (br s, 2 H, CH₂), 3.58 (t, J = 8.6 Hz, 2 H, CH₂), 3.24 (t, J = 8.2 Hz, 2 H, CH₂), 2.65 (br s, 2 H, CH₂), 2.20 (br s, 2 H, CH₂), 1.97 (br s, 2 H, CH₂), 1.12 (d, J = 6.8 Hz, 6 H, CH₃), 1.00 (d, J = 6.8 Hz, 3 H, CH₃), 0.89 (d, J = 6.8 Hz, 3 H, CH₃).

**Example 121**

**Preparation of 4-(((4-tert-Butylphenyl)sulfonyl)amino)methyl)-V-[4-(5-fluoro-3-pyridinyl)benzamide (139).**

![Chemical structure of compound 139](image)

[0322]Oxalyl chloride (132 μL, 1.5 mmol) was added dropwise to a stirred suspension of benzoic acid 124 (350 mg, 1.0 mmol) and DMF (1 drop) in dry THF (20 mL) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 mL). 5-Fluoro-3-pyridinylamine (124 mg, 1.1 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 mL) for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50-70%) of EtOAc/pet. ether, to give benzamide 139 (186 mg, 42%) as a white powder: mp (EtOAc) 214-217 °C; ¹H NMR δ 10.58 (s, 1 H, CONH), 8.78 (t, J = 1.6 Hz, 1 H, H-2'), 8.32 (d, J = 2.6 Hz, 1 H, H-6'), 8.16-8.21 (m, 2 H, NHSO₂, H-4'), 7.87 (br d, J = 8.4 Hz, 2 H, H-2, H-6), 7.70 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-2", H-6"), 7.55 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-3", H-5"), 7.40 (br d, J = 8.4 Hz, 2 H, H-3, H-5), 4.10 (br s, 2 H, CH₂N), 1.28 [s, 9 H, C(CH₃)₃]; ¹³C NMR δ 165.8, 158.6 (d, J = 253.0 Hz), 155.3, 142.1, 137.9 (d, J = 4.0 Hz), 137.0 (d, J = 6.2 Hz), 132.6, 132.0 (d, J = 22.6 Hz), 127.7 (2), 127.5 (2), 126.3 (2), 125.9 (2), 113.9 (d, J = 22.5 Hz), 45.7, 34.8, 30.7 (3); MS m/z 442.7 (MH⁺, 100%). Anal. calcd for C₂₃H₂₄FN₃O₅S: C, 62.57; H, 5.48; N, 9.52. Found: C, 62.48; H, 5.58; N, 9.52%.

**Example 122**

**Preparation of 4-(((4-ferf-Butylphenyl)sulfonyl)amino)methyl)-V-[4-(trifluoromethyl)-3-pyridinyl]benzamide (140).**

125
[0323]Oxalyl chloride (132 µL, 1.5 mmol) was added dropwise to a stirred suspension of benzoic acid 124 (350 mg, 1.0 mmol) and DMF (1 drop) in dry THF (20 mL) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 mL). 4-Trifluoromethyl-3-pyridinylamine (180 mg, 1.1 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 mL) for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzamide 140 (265 mg, 53%) as a white powder: mp (EtOAc) 121-1 23 °C; 1H NMR δ 10.29 (s, 1 H, CONH), 8.78 (dd, J = 5.1 , 1.6 Hz, 1 H, H-6'), 8.76 (s, 1 H, H-2'), 8.19 (t, J = 6.2 Hz, 1 H, NHSO₂), 7.86 (br d, J = 8.4 Hz, 2 H, H-2, H-6), 7.84 (d, J = 5.1 Hz, 1 H, H-5'), 7.71 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-2", H-6"), 7.56 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-3", H-5"), 7.38 (br d, J = 8.4 Hz, 2 H, H-3, H-5), 4.10 (br s, 2 H, CH₂N), 1.30 [s, 9 H, C(CH₃)₃]; 13C NMR 5 166.3, 155.3, 152.0, 148.9, 142.1, 137.9, 133.7 (q, J = 31.2 Hz), 131.9, 130.9, 127.6 (2), 127.5 (2), 126.4 (2), 125.9 (2), 122.4 (d, J = 274.6 Hz), 120.2 (q, J = 4.4 Hz), 45.7, 34.8, 30.8 (3); MS m/z 492.8 (MH⁺, 100%). Anal. calcd for C₂₄H₂₄F₃N₃O₃S·H₂O: C, 56.57; H, 5.14; N, 8.24. Found: C, 56.76; H, 5.28; N, 8.30%.

Example 123
Preparation of 4-(((4-tert-Butylphenyl)sulfonyl)amino)methyl)/V-(2-fluoro-3-pyridinyl)benzamide (141).

[0324]Oxalyl chloride (132 µL, 1.5 mmol) was added dropwise to a stirred suspension of benzoic acid 124 (350 mg, 1.0 mmol) and DMF (1 drop) in dry THF (20 mL) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 mL). 2-Fluoro-3-pyridinylamine (124 mg, 1.1 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the
residue suspended in ice/water (50 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with a gradient (0-20%) of MeOH/EtOAc, to give benzamide 141 (276 mg, 62%) as a white powder: mp (EtOAc) 198-200 °C; 1H NMR δ 10.1 8 (s, 1 H, CONH), 8.21 (t, J = 6.2 Hz, 1 H, NHSO₂), 8.1 6 (ddd, J = 9.6, 7.8, 1.2 Hz, 1 H, H-4'), 8.07 (dt, J = 4.8, 1.5 Hz, 1 H, H-6'), 7.86 (br d, J = 8.4 Hz, 2 H, H-2, H-6), 7.69 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-2", H-6"), 7.54 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-3", H-5"), 7.40 (ddd, J = 7.8, 4.8, 1.2 Hz, 1 H, H-5), 7.37 (br d, J = 8.4 Hz, 2 H, H-3, H-5), 4.1 0 (br s, 2 H, CH₂N), 1.29 [s, 9 H, C(CH₃)₃]; ¹³C NMR δ 165.3, 156.3 (d, J = 237.5 Hz), 155.3, 143.2 (d, J=14.3 Hz), 142.0, 137.9, 136.6 (d, J = 3.4 Hz), 132.1, 127.7 (2), 127.5 (2), 126.3 (2), 125.9 (2), 122.1 (d, J = 4.0 Hz), 121.2 (d, J = 27.6 Hz), 45.8, 34.7, 30.8 (3); MS m/z 442.6 (MH⁺, 100%). Anal. calcd for C₂₃H₂₅FN₃O₃S: C, 62.57; H, 5.48; N, 9.52. Found: C, 62.46; H, 5.27; N, 9.46%.

Example 124
Preparation of 4-(((4-ferf-Butylphenyl)sulfonyl]amino)methyl)-V-(4-methoxy-3-pyridinyl)benzamide (142).

[0325]Oxalyl chloride (132 µL, 1.5 mmol) was added dropwise to a stirred suspension of benzoic acid 124 (350 mg, 1.0 mmol) and DMF (1 drop) in dry THF (20 ml) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 ml). 4-Methoxy-3-pyridinylamine [prepared by stirring 4-methoxy-3-nitropyridine (202 mg, 1.32 mmol) with Pd/C (50 mg) in EtOH under H₂ (60 psi) for 1 h, filtered through Celite and the solvent was evaporated] was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with a gradient (0-20%) of MeOH/EtOAc, to give benzamide 142 (165 mg, 36%) as a white powder: mp (EtOAc) 231-233 °C; 1H NMR δ 9.28 (s, 1 H, CONH), 8.76 (d, J = 2.2 Hz, 1 H, H-2'), 8.20 (t, J = 6.2 Hz, 1 H, NHSO₂), 7.77 (d, J = 8.2 Hz, 2 H, H-2, H-6), 7.67-7.73 (m, 3 H, H-6', H-2", H-6"), 7.54 (d, J = 8.6 Hz, 2 H, H-3", H-5"), 7.38 (d, J = 8.3 Hz, 2 H, H-3, H-5), 7.30 (d, J =
7.3 Hz, 1 H, H-5'), 4.08 (d, J = 6.2 Hz, 2 H, CH₂N), 3.77 (s, 3 H, OCH₃), 1.28 [s, 9 H, C(CH₃)₃]; ¹³C NMR δ 168.8, 163.9, 155.3, 142.0, 139.9, 137.9, 132.3, 128.6, 128.5, 126.9 (2), 126.9 (2), 126.3 (2), 125.9 (2), 112.5, 45.7, 43.9, 34.7, 30.7 (3); MS m/z 454.8 (MH⁺, 100%). Anal. calcd for C₂₄H₂₇N₃O₄S⁻H₂CH₃OH: C, 62.67; H, 6.23; N, 8.95. Found: C, 62.65; H, 6.11; N, 9.17%.

Example 125
Preparation of ¹⁻(6-Bromo-3-pyridinyl)-4-(((4-tert-butylyphenyl)sulfonylamino)methyl)benzamide (143).

[0326]Oxalyl chloride (132 μL, 1.5 mmol) was added dropwise to a stirred suspension of benzoic acid 124 (350 mg, 1.0 mmol) and DMF (1 drop) in dry THF (20 mL) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 mL). 6-Bromo-3-pyridinylamine (210 mg, 1.2 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 mL) for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (0-20%) of MeOH/EtOAc, to give benzamide 143 (351 mg, 69%) as a white powder: mp (EtOAc) 242-244 °C; ¹H NMR δ 10.48 (s, 1 H, CONH), 8.78 (d, J = 2.8 Hz, 1 H, H-2'), 8.20 (br t, J = 6.0 Hz, 1 H, NHSO₂), 8.17 (dd, J = 8.7, 2.8 Hz, 1 H, H-4'), 7.86 (dd, J = 8.3, 1.6 Hz, 2 H, H-2, H-6), 7.69 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-2', H-6'), 7.63 (d, J = 8.7 Hz, 1 H, H-5'), 7.54 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-3', H-5'), 7.38 (d, J = 8.3 Hz, 2 H, H-3, H-5), 4.09 (d, J = 6.0 Hz, 2 H, CH₂N), 1.28 [s, 9 H, C(CH₃)₃]; ¹³C NMR δ 156.5, 155.3, 142.1, 142.0, 137.9, 135.8, 134.4, 132.6, 130.7, 127.8, 126.7 (2), 127.5 (2), 126.3 (2), 125.9 (2), 45.8, 34.8, 30.8 (3); MS m/z 502.5/504.5 (MH⁺, 100%). Anal. calcd for C₂₃H₂₄BrN₃O₃S: C, 54.98; H, 4.81; N, 8.36. Found: C, 55.05; H, 5.01; N, 8.28%.

Example 126
Preparation of 4-(((3-(4-Morpholinyl)phenyl)sulfonylamino)methyl)-¹⁻(3-pyridinyl)benzamide (144).
[0327] A mixture of fluoride 29 (110 mg, 0.29 mmol) and morpholine (2 ml) in DMSO (1 ml) was stirred in a sealed tube at 130 °C for 72 h. The solvent was evaporated and the residue was suspended in ice/water (50 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with a gradient (0-10%) of MeOH/EtOAc, to give benzamide 144 (113 mg, 86%) as a white powder: mp (EtOAc) 160-162 °C; ¹H NMR δ 10.36 (s, 1 H, CONH), 8.93 (d, J = 2.2 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 1.5 Hz, 1 H, H-4'), 8.14 (t, J = 6.0 Hz, 1 H, NHSO₂), 7.91 (br d, J = 8.3 Hz, 2 H, H-2', H-6), 7.37-7.45 (m, 4 H, H-3', H-5', H-3'', H-5''), 7.13-7.26 (m, 3 H, H-5', H-2'', H-4''), 4.08 (d, J = 6.0 Hz, 2 H, CH₂N), 3.75 (br dd, J = 4.9, 4.7 Hz, 4 H, 2 x CH₂O), 3.15 (br dd, J = 4.9, 4.7 Hz, 4 H, 2 x CH₂N); ¹³C NMR δ 165.5, 151.2, 144.5, 142.0, 141.9, 141.4, 135.8, 133.0, 129.7, 127.7 (2), 127.4 (2), 127.3, 123.5, 118.5, 116.5, 111.9, 65.9 (2), 47.8 (2), 45.8; MS m/z 453.6 (MH⁺, 100%). Anal. calcd for C₂₃H₂₄N₄O₄S: C, 61.05; H, 5.35; N, 12.38. Found: C, 61.12; H, 5.49; N, 12.21%.

Example 127

[0328] A mixture of fluoride 52 (108 mg, 0.28 mmol) and morpholine (2 ml) in DMSO (1 ml) was stirred in a sealed tube at 130 °C for 16 h. The solvent was evaporated and the residue was suspended in ice/water (50 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with a gradient (0-10%) of MeOH/EtOAc, to give benzamide 145 (110 mg, 87%) as a white powder: mp (EtOAc) 206-208 °C; ¹H NMR δ 10.36 (s, 1 H, CONH), 8.93 (d, J = 2.1 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.19 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.94 (t, J = 6.0 Hz, 1 H, NHSO₂), 7.90 (br d, J = 8.3 Hz, 2 H, H-2', H-6), 7.61 (ddd, J = 9.0, 2.8, 1.9 Hz, 2 H, H-2'', H-
6"), 7.36-7.42 (m, 3 H, H-3, H-5, H-5' ), 7.02 (ddd, J = 9.0, 2.8, 1.9 Hz, 2 H, H-3", H-5"), 4.02 (d, J = 6.0 Hz, 2 H, CH₂N), 3.72 (br dd, J = 5.0, 4.8 Hz, 4 H, 2 x CH₂O), 3.25 (br dd, J = 5.0, 4.8 Hz, 4 H, 2 x CH₂N); ¹³C NMR 5 165.4, 153.2, 144.4, 141.9, 141.8, 135.7, 132.8, 128.8, 128.0 (2), 127.5 (2), 127.3 (2), 127.2, 123.3, 113.4 (2), 65.7 (2), 49.6 (2), 45.6; MS m/z 453.6 (MH⁺, 100%). Anal, calcd for C₂₃H₂₄N₄O₄S: C, 61.05; H, 5.35; N, 12.38. Found: C, 61.11; H, 5.57; N, 12.49%.

Example 128

[0329] A mixture of fluoride 52 (107 mg, 0.28 mmol) and piperidine (2 ml) in DMSO (1 ml) was stirred in a sealed tube at 130 °C for 16 h. The solvent was evaporated and the residue was suspended in ice/water (50 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with a gradient (0-10%) of MeOH/EtOAc, to give benzamide 146 (97 mg, 77%) as a white powder: mp (EtOAc) 220-223 °C; ¹H NMR δ 10.35 (s, 1 H, CONH), 8.93 (d, J = 2.2 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.19 (dd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.86-7.91 (m, 3 H, H-2, H-6, NHSO₂), 7.55 (br d, J = 9.0 Hz, 2 H, H-2", H-6"), 7.36-7.41 (m, 3 H, H-3, H-5, H-5'), 6.96 (br d, J = 9.0 Hz, 2 H, H-3", H-5"), 4.02 (d, J = 5.6 Hz, 2 H, CH₂N), 3.28-3.32 (m, 4 H, 2 x CH₂N), 1.56 (br s, 6 H, 3 x CH₂); ¹³C NMR 5 165.4, 153.0, 144.4, 142.0, 141.8, 135.7, 132.7, 128.0, 127.5 (3), 127.3 (2), 127.2 (2), 127.1, 113.4 (2), 47.8 (2), 45.6, 24.6 (2), 23.7; MS m/z 451.7 (MH⁺, 100%). Anal, calcd for C₂₄H₂₆N₄O₃S: C, 63.98; H, 5.82; N, 12.44. Found: C, 63.76; H, 5.77; N, 12.62%.

Example 129

[0330] A mixture of fluoride 52 (119 mg, 0.31 mmol) and 4-methoxypiperidine (0.75 g) in DMSO (2 ml) was stirred in a sealed tube at 130 °C for 16 h. The mixture
suspended in ice/water (50 ml ) for 1 h. The precipitate was filtered, washed with water (5 ml ) and dried. The crude solid was purified by column chromatography, eluting with a gradient (0-10%) of MeOH/EtOAc, to give benzamide 147 (124 mg, 83%) as a white powder: mp (EtOAc) 197-198 °C; 1H NMR δ 10.35 (s, 1 H, CONH), 8.93 (d, J = 2.2 Hz, 1 H, H-2°), 8.30 (dd, J = 4.7, 1.5 Hz, 1 H, H-6°), 8.19 (ddd, J = 8.3, 2.4, 1.5 Hz, 1 H, H-4°), 7.89 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.91 (br s, 1 H, NHSO₂), 7.56 (br d, J = 9.0 Hz, 2 H, H-2°, H-6°), 7.35-7.42 (m, 3 H, H-3, H-5, H-5°), 7.00 (br d, J = 9.0 Hz, 2 H, H-3°, H-5°), 4.02 (br s, 2 H, CH₂N), 3.58-3.66 (m, 2 H, 2 x CHN), 3.34-3.40 (m, 1 H, OCH), 3.24 (s, 3 H OCH₃), 3.03-3.11 (m, 2 H, 2 CH), 1.84-1.92 (m, 2 H, 2 CH), 1.42-1.52 (m, 2 H, 2 CH); 13C NMR δ 165.5, 152.7, 144.5, 142.1, 142.0, 135.8, 132.9, 128.2 (2), 127.7, 127.6 (2), 127.4 (2), 127.2, 123.5, 113.7 (2), 75.0, 54.9, 45.8, 44.6 (2), 29.7 (2); MS m/z 481.6 (MH⁺, 100%).

Anal. calcd for C₂₅H₂₈N₄O₄S: C, 62.48; H, 5.87; N, 11.66. Found: C, 62.18; H, 5.91; N, 11.61%.

Example 130


[0331] tert-Butyl 21-4-[[4-(3-Pyridinylamino)carbonyl]benzyl]amino)sulfonyl]phenyl) -3,6,9,12,15,18-hexaoxahenicos-1-ylcarbamate (148). A mixture of alkyne 115 (743 mg, 0.95 mmol) and 10% Pd/C (250 mg, 0.1 mmol) in absolute EtOH (30 mL) was stirred at 20 °C under of H₂ (60 psi) for 16 h. The mixture was filtered through Celite, washed with EtOH (100 mL), and the solvent was evaporated. The residue was purified by column chromatography, eluting with a gradient (3-5%) of MeOH/DCM, to give the carbamate 148 (650 mg, 87%) as a pale yellow oil: 1H NMR δ 10.35 (s, 1 H, CONH), 8.92 (d, J = 2.4 Hz, 1 H, H-2°), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6°), 8.17-8.20 (m, 2 H, NHSO₂, H-4°), 7.88 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.88 (br d, J = 8.3 Hz, 2 H, H-2°, H-6°), 7.37-7.40 (m, 5 H, H-5°, H-3, H-5, H-3°, H-5°), 6.69 (br s, 1 H, NHCO₂), 4.08 (d, J = 5.0 Hz, 2 H, CH₂N), 3.45-3.52 (m, 20 H, CH₂O), 3.37 (t, J = 6.2 Hz, 4 H,
H-3′″, H-20″). 3.05 (q, J = 6.0 Hz, 2 H, H-21″). 2.69 (t, J = 7.7 Hz, 2 H, H-1″). 1.77-1.84 (m, 2 H, H-21″), 1-37 [s, 9 H, C(CH₃)₃]: HRMS calcd for C₃₉H₆₆N₄O₇S (M⁺) m/z 789.3739; found 789.3723 (1.6 ppm).


Trifluoroacetic acid (0.74 mL, 10 mmol) was added to a solution of carbamate 148 (313 mg, 0.4 mmol) in anhydrous DCM (5 mL) and the reaction mixture was stirred at 20 °C for 2 h. The solvent was evaporated and the residue was purified by column chromatography, eluting with 8% MeOH/DCM containing 1% aqueous NH₃, to give the amine 149 (195 mg, 71%) as a colourless oil: ¹H NMR δ 10.35 (br s, 1 H, CONH), 8.92 (d, J = 2.2 Hz, 1 H, H-2″), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6″), 8.18 (d, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4″), 7.88 (br, d, J = 8.3 Hz, 2 H, H-2, H-6), 7.70 (br, d, J = 8.3 Hz, 2 H, H-2″), 7.37-7.40 (m, 5 H, H-5′, H-3, H-5, H-3′, H-5″), 4.08 (s, 2 H, CH₂NSO₂), 3.45-3.52 (m, 20 H, CH₂O), 3.37 (t, J = 6.3 Hz, 2 H, H-3″), 3.34 (t, J = 5.8 Hz, 2 H, H-20″), 2.70 (t, J = 7.9 Hz, 2 H, H-1″), 2.63 (t, J = 5.7 Hz, 2 H, H-21″), 1.80 (t, J = 6.4, 7.9 Hz, 2 H, H-2″), NH.SO₂ and NH₂ not observed; ¹³C NMR 5165.4, 146.6, 144.4, 141.9, 141.7, 138.0, 135.7, 132.8, 128.9 (2), 127.5 (2), 127.3 (2), 127.2, 126.4 (2), 123.3, 72.2, 69.69 (2), 69.66 (4), 69.62 (2), 69.4, 69.3, 69.1, 45.6, 40.9, 31.3, 30.4; HRMS calcd for C₃₄H₄₈N₄O₇S (M⁺) m/z 689.3215; found 389.3224 (-1.0 ppm).

Example 131

[0333] A mixture of fluoride 52 (113 mg, 0.29 mmol) and 3-(4-morpholinyl)propylamine (2.0 ml) in DMSO (1 ml) was stirred in a sealed tube at 130 °C for 16 h. The mixture suspended in ice/water (50 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with a gradient (5-10%) of MeOH/DCM followed by 1% aqueous NH₃/10% MeOH/DCM, to give benzamide 150 (135 mg, 91%) as a white powder: mp (EtOAc) 181-183 °C; ¹H NMR δ 10.36 (s, 1 H, CONH), 8.93 (d, J
= 2.3 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.19 (ddd, J = 8.3, 2.4, 1.5 Hz, 1 H, H-4'), 7.90 (br d, J = 8.3 Hz, 2 H, H-2', H-6''), 7.36-7.43 (m, 3 H, H-3', H-5', H-5''), 6.62 (br d, J = 8.8 Hz, 2 H, H-3'', H-6''), 6.48 (br t, J = 5.4 Hz, 1 H, NH), 3.98 (br d, J = 6.4 Hz, 2 H, CH₂N), 3.58 (br t, J = 4.6 Hz, 4 H, 2 x CH₂N), 3.10 (dt, J = 6.5, 5.4 Hz, 2 H, CH₂N), 2.30-2.38 (m, 6 H, CH₂H, 2 x CH₂O), 1.68 (p, J = 6.9 Hz, 2 H, 2 x CH₂); ¹³C NMR δ 165.5, 152.0, 144.5, 142.3, 142.0, 135.8, 132.9, 128.4 (2), 127.6 (2), 127.4 (2), 127.2, 125.2, 123.4 (2), 110.8, 66.2 (2), 55.9, 53.4 (2), 45.7, 40.5, 25.3; MS m/z 510.8 (MH⁺, 100%). The compound was formulated as the HCl salt. Anal. calcd for C₆₅H₅₂N₂O₄S·HCl: C, 61.28; H, 6.13; N, 13.74. Found: C, 61.27; H, 6.15; N, 13.84%.

Example 132

Preparation of 4-[[3-(4-Methyl-1-piperazinyl)phenylsulfonyl]amino)methyl]N-(3-pyridinyl)benzamide (151).

[0334] A mixture of fluoride 29 (110 mg, 0.29 mmol) and 4-methylpiperazine (2 ml_) in DMSO (1 ml_) was stirred in a sealed tube at 130 °C for 72 h. The solvent was evaporated and the residue was suspended in ice/water (50 ml_) for 1 h. The precipitate was filtered, washed with water (5 ml_) and dried. The crude solid was purified by column chromatography, eluting with a gradient (5-1 0%) of MeOH/DCM followed by 1% aqueous NH₄Cl·10% MeOH/DCM, to give starting material 29 (67 mg, 60%) and benzamide 151 (45 mg, 33%) as a white powder. ¹H NMR δ 10.36 (s, 1 H, CONH), 8.93 (d, J = 2.4 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3 Hz, 2 H, H-2', H-6'), 7.37-7.43 (m, 4 H, H-3, H-5, H-5', H-5''), 7.25 (br d, J = 1.9 Hz, 1 H, H-2''), 7.16-7.21 (m, 2 H, H-4'', H-6''), 4.07 (d, J = 6.3 Hz, 2 H, CH₂N), 3.15-3.320 (m, 6 H, 3 x CH₂N), 2.48-2.52 (m, 2 H, CH₂N), 2.20 (s, 3 H, NCH₃); ¹³C NMR δ 165.5, 151.0, 144.5, 142.0, 141.9, 141.4, 135.8, 133.0, 129.7, 127.7 (2), 127.4 (2), 127.3, 123.5, 118.7, 116.1, 112.1, 54.2 (2), 43.7 (2), 45.8, 45.4; MS m/z 466.7 (MH⁺, 100%).
Example 133
Preparation of 4-{[(4-{[2- (Dimethylamino)ethyl]amino}phenyl)sulfonyl]amino}methyl)- Λ-(3-pyridinyl)benzamide (152).

[0335] A mixture of fluoride 52 (170 mg, 0.44 mmol) and N,N-dimethylethylenediamine (2.0 ml) in DMSO (1 ml) was stirred in a sealed tube at 130 °C for 40 h. The mixture suspended in ice/water (50 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with a gradient (5-10%) of MeOH/DCM followed by 1% aqueous NH₃ to give benzamide 152 (171 mg, 86%) as a white powder: mp (EtOAc) 166-168 °C; ¹H NMR δ 10.36 (s, 1 H, CONH), 8.93 (d, J = 2.2 Hz, 1 H, H-2), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.90 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.76 (t, J = 6.4 Hz, 1 H, NHSO₂), 7.50 (d, J = 8.9 Hz, 2 H, H-2", H-6"), 7.35-7.43 (m, 3 H, H-3, H-5, H-5'), 6.66 (d, J = 8.9 Hz, 2 H, H-3", H-5"), 6.28 (br t, J = 5.3 Hz, 1 H, NH), 3.99 (d, J = 6.4 Hz, 2 H, CH₂N), 3.14 (dt, J = 6.5, 5.3 Hz, 2 H, CH₂N), 2.43 (t, J = 6.5 Hz, 2 H, CH₂N), 2.18 [s, 6 H, N(CH₃)₂]; ¹³C NMR δ 165.4, 151.7, 144.5, 142.1, 141.9, 135.8, 132.8, 128.3 (2), 127.5 (2), 127.3 (2), 127.1, 125.3, 123.3 (2), 110.8, 57.4, 45.6, 45.1 (2), 40.3; MS m/z 454.7 (MH⁺, 100%). Anal. calcd for C₉₃H₇₇N₅O₃S: C, 60.91; H, 6.00; N, 15.44.

Found: C, 60.93; H, 6.00; N, 15.54%.

Example 134
Preparation of Λ-(3-Pyridinyl)-4-[[3'-{(trifluoromethyl)[1,1'-biphenyl]-4-yl}sulfonyl]amino)methyl]benzamide (153).

[0336] PdCl₂(dppe) (25 mg, 0.03 mmol) was added to a degassed solution of iodide 106 (150 mg, 0.3 mmol), 3-trifluoromethylboronic acid (75 mg, 0.39 mmol) and K₂CO₃ (41.5 mg, 0.3 mmol) in a mixture of toluene/ethanol/H₂O/DMF (5:3:2:2, 12 ml) and the mixture was heated at 90 °C for 16 h. The mixture was cooled to 20 °C, partitioned between EtOAc (200 ml) and H₂O (50 ml), and washed with brine (50
ml_/). The organic phase was dried, filtered and the solvent was evaporated. The
residue was purified by column chromatography, eluting with a gradient (3-5%) of
MeOH/DCM, to give benzamide 153 (147 mg, 96%) as a white powder: mp
(MeOH/DCM) 227-229 °C; 1H NMR δ 10.33 (s, 1 H, CONH), 8.90 (d, J = 2.4 Hz, 1
H, H-2"), 8.35 (t, J = 6.4 Hz, 1 H, NHSO₂), 8.31 (dd, J = 1.4, 4.6 Hz, 1 H, H-6"), 8.16
(ddd, J = 1.6, 2.4, 8.3 Hz, 1 H, H-4"), 8.05-8.03 (m, 2 H, H-2", H-4"), 7.95 (br d, J =
8.5 Hz, 2 H, H-2', H-6), 7.89 (br. d, J = 8.7 Hz, 4 H, H-2, H-6, H-3', H-5'), 7.79 (br. d,
J = 7.8 Hz, 1 H, H-6"), 7.72 (br. t, J = 8.0, 1 H, H-5"), 7.42 (br. d, J = 8.3 Hz, 2 H, H-
3', H-5), 7.38 (dd, J = 4.7, 8.4 Hz, 1 H, H-5"), 4.14 (d, J = 6.3 Hz, 2 H, CH₂NH); 13C
NMR 5 165.4, 144.4, 142.1, 141.8, 141.5, 140.1, 139.5, 135.6, 132.9, 131.1, 130.0,
129.8 (q, J = 31.8 Hz), 127.7 (2), 127.6 (2), 127.4 (2), 127.1 (2), 124.9 (q, J = 3.7
Hz), 124.0 (q, J = 272.5 Hz), 123.4, (q, J = 3.9 Hz), 123.3, 45.7, 1 resonance not
observed; MS m/z 513.4 (MH+, 100%). Anal. calcd for C₂₈H₂₀F₃N₅O₃S: C, 61.05; H,
3.94; N, 8.21. Found: C, 61.13; H, 3.84; N, 8.22%.

Example 135
Preparation of 4-{[(4-Benzylphenyl)sulfonyl]amino)methyl}-N-(3-
pyridinyl)benzamide (154).

[0337] PdCl₂(dpff) (25 mg, 0.03 mmol) was added to a degassed solution of iodide
106 (150 mg, 0.3 mmol), 2-benzyl-4,4,5,5-tetramethyl-1 ,3,2-dioxaborolane (87 mg,
0.39 mmol) and K₂CO₃ (41.5 mg, 3 mmol) in a mixture of toluene/ethanol/H₂O/DMF
(5:3:2:2, 12 ml_) and the mixture was heated at 90 °C for 16 h. The mixture was
cooled to 20 °C, partitioned between EtOAc (200 ml_) and H₂O (50 ml_), and washed
with brine (50 ml_). The organic phase was dried, filtered and the solvent evaporated.
The residue was purified by column chromatography, eluting with 30% EtOAc/pet.
ether, to give benzamide 154 (40 mg, 29%) as a white powder: mp (EtOAc/pet.
ether) 198-200 °C; 1H NMR δ 10.36 (s, 1 H, CONH), 8.93 (d, J = 2.3 Hz, 1 H, H-2"),
8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.17-8.20 (m, 2 H, NHSO₂, H-4'), 7.88 (br d, J =
8.3 Hz, 2 H, H-2, H-6), 7.73 (br d, J = 8.3 Hz, 2 H, H-2", H-6"), 7.37-7.43 (m, 5 H, H-
3, H-5, H-5', H-3", H-5"), 7.28-7.32 (m, 2 H, H-3", H-5"), 7.23-7.25 (m, 2 H, H-2",
6"), 7.17-7.21 (m, 1 H, H-4"), 4.07 (s, 2 H, CH₂NH), 4.03 (s, 2 H, CH₂Ph); 13C NMR
Example 136


[0338] MsCl (22 µL, 0.29 mmol) was added to a solution of alcohol 119 (100 mg, 0.24 mmol) and NEt₃ (67 µL, 0.48 mmol) in anhydrous THF (10 mL) at -20 °C and the reaction mixture was stirred at -20 °C for 1 h. The mixture was diluted with EtOAc (100 mL), washed with H₂O (30 mL) and then washed with brine (30 mL). The organic phase was dried, filtered and the solvent was evaporated. Morpholine (0.44 mL, 5.0 mmol) was added to a solution of crude mesylate in anhydrous THF (20 mL) and the solution was stirred at 50 °C for 2 h. The solution was cooled to 20 °C, partitioned between EtOAc (200 mL) and saturated aqueous NaHCO₃ solution (50 mL), and the organic fraction was washed with NaHCO₃ (50 mL). The organic phase was dried, filtered and the solvent was evaporated. The residue was purified by column chromatography, eluting with 5% MeOH/DCM containing 0.5% aqueous NH₃, to give benzamide 155 (56 mg, 47%) as a white powder: mp (MeOH/DCM) 209-211 °C; ¹H NMR 5:10.36 (s, 1 H, CONH), 8.92 (d, J = 2.3 Hz, 1 H, H-2'), 8.34 (d, J = 6.3 Hz, 1 H, NHSO₂), 8.31 (dd, J = 1.3, 4.7 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.4, 1.5 Hz, 1 H, H-4'), 7.90 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.78 (br d, J = 8.5 Hz, 2 H, H-2", H-6"), 7.62 (br d, J = 8.5 Hz, 2 H, H-3", H-5"), 7.37-7.41 (m, 3 H, H-3, H-5, H-5'), 4.10 (d, J = 6.3 Hz, 2 H, CH₂NH), 3.61 (t, J = 4.5 Hz, 4 H, 2 x CH₂O), 3.54 (s, 2 H, CH₂C=O), 2.51 (m, 4 H, 2 x CH₂N); ¹³C NMR 5:165.4, 144.4, 141.9, 141.9, 140.0, 135.7, 133.0, 131.9 (2), 127.6 (2), 127.3 (2), 127.2, 126.7 (2), 126.2, 123.3, 88.4, 83.7, 65.9 (2), 5.16 (2), 46.8, 45.6; MS m/z 492.4 (MH⁺, 100%); Anal. calcd for C₂₆H₂₆N₄O₄S: C, 63.66; H, 5.34; N, 11.42; Found: C, 63.65; H, 5.33; N, 11.37%.
Example 137

[0339] MsCl (41 µL, 0.53 mmol) was added to a solution of alcohol 119 (185 mg, 0.44 mmol) and Et₃N (0.13 mL, 0.88 mmol) in anhydrous THF (10 mL) at -20 °C and the reaction mixture was stirred at -20 °C for 1 h. The solution was then diluted with EtOAc (100 mL), washed with H₂O (30 mL) then brine (30 mL). The organic phase was dried, filtered and the solvent was evaporated. A 2 M solution of dimethylamine in THF (2.2 mL, 4.4 mmol) was added to a solution of crude mesylate in anhydrous DMF (10 mL) and the reaction mixture was stirred at 50 °C for 2 h. The solution was cooled to 20 °C, then partitioned between EtOAc (200 mL) and saturated aqueous NaHCO₃ solution (50 mL), and washed with NaHCO₃ (50 mL). The organic phase was dried, filtered and the solvent was evaporated. The residue was purified by column chromatography, eluting with 5% MeOH/DCM containing 0.5% aqueous NH₃, to give benzamide 156 (93 mg, 47%) as a pale yellow solid: mp (MeOH/DCM) 200-202 °C; ¹H NMR δ 10.35 (s, 1 H, CONH), 8.93 (d, J = 2.3 Hz, 1 H, H-2'), 8.30-8.35 (m, 2 H, NSO₂, H-6'), 8.18 (ddd, J = 8.3, 2.4, 1.5 Hz, 1 H, H-4'), 7.90 (br. d, J = 8.3 Hz, 2 H, H-2, H-6), 7.78 (br. d, J = 8.5 Hz, 2 H, H-2", H-6"), 7.62 (br d, J = 8.5 Hz, 2 H, H-3", H-5"), 7.36-7.41 (m, 3 H, H-5', H-3, H-5), 4.10 (d, J = 6.2 Hz, 2 H, CH₂NH), 3.48 (s, 2 H, CH₂N(CH₃)₂), 2.23 [s, 6 H, N(CH₃)₂]; ¹³C NMR δ 165.4, 144.4, 141.9, 141.5, 139.9, 135.7, 133.0, 131.9 (2), 127.6 (2), 127.3 (2), 127.1, 126.7 (2), 126.4, 123.3, 88.6, 83.6, 47.5, 45.6, 43.6 (2); MS m/z 450.2 (MH⁺, 100%). Anal. calcd for C₂₄H₂₄N₄O₃S: C, 64.27%; H, 5.39%; N, 12.49%; Found: C, 64.41%; H, 5.38%; N, 12.42%.

Example 138
Preparation of 4-[[4-[(tert-Butylphenyl)sulfonyl](methyl)amino]methyl]-Ν-(3-pyridinyl) benzamide (157).
[0340] Mel (8 µl, 0.12 mmol) was added to a stirred suspension of benzamide 47 (50 mg, 0.12 mmol) and Cs₂CO₃ (80 mg, 0.24 mmol) in anhydrous DMF (2 mL), and the reaction mixture was stirred at 20 °C for 16 h. The mixture was partitioned between EtOAc (100 mL) and H₂O (30 mL), and the organic fraction was washed with brine (30 mL). The organic phase was dried, filtered and the solvent was evaporated. The residue was purified by column chromatography, eluting with 5% MeOH/DCM, to give benzamide 157 (30 mg, 57%) as a white powder. mp (MeOH/DCM) = 215-218 °C; ¹H NMR δ 10.41 (s, 1 H, CONH), 8.92 (d, J = 2.3, 1 H, H-2''), 8.31 (dd, J = 4.6, 1.4 Hz, 1 H, H-6''), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4''), 7.97 (d, J = 8.3 Hz, 2 H, H-2, H-6), 7.79 (dt, J = 8.6, 1.7 Hz, 2 H, H-2'', H-6''), 7.68 (dt, J = 8.6, 1.8 Hz, 2 H, H-3'', H-5''), 7.48 (d, J = 8.3 Hz, 2 H, H-3, H-5), 7.39 (ddd, J = 8.3, 4.6, 0.4 Hz, 1 H, H-5''), 4.25 (s, 2 H, CH₂N), 2.60 (s, 3 H, NCH₃), 1.34 [s, 9 H, C(CH₃)₃]; 1³C NMR δ 165.6, 156.1, 144.2, 141.6, 140.3, 135.9, 134.2, 133.6, 128.1 (2), 128.0 (2), 127.6, 127.1 (2), 126.3 (2), 123.6, 52.9, 34.9, 34.7, 30.8 (3); MS m/z 439.2 (MH⁺, 100%); Anal. calcd for C₂₄H₂₇N₂O₃S: C, 65.88; H, 6.22; N, 9.60; Found: C, 65.78; H, 6.31; N, 9.69%.

Example 139
Preparation of 4-[[4-(tert-Butylphenyl)sulfonyl][(ethyl)amino]methyl]-N-(3-pyridinyl)benzamide (158).

[0341] Ethyl iodide (38 µl, 0.47 mmol) was added to a stirred suspension of benzamide 47 (200 mg, 0.47 mmol) and Cs₂CO₃ (308 mg, 0.94 mmol) in anhydrous DMF (5 mL), and the reaction mixture was stirred at 20 °C for 24 h. The mixture was partitioned between EtOAc (150 mL) and H₂O (50 mL), and the organic fraction was washed with brine (50 mL). The organic phase was dried, filtered and the solvent was evaporated. The residue was purified by column chromatography, eluting with 30% EtOAc/pet. ether to give benzamide 158 (63 mg, 30%) as a white solid; mp (EtOAc/pet. ether) 163-1 65 °C; ¹H NMR δ 10.41 (s, 1 H, CONH), 8.93 (d, J = 2.4 Hz, 1 H, H-2''), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6''), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4''), 7.95 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.80 (dt, J = 8.6, 2.0 Hz, 2 H, H-2'', H-6''), 7.65 (dt, J = 8.6, 1.9 Hz, 2 H, H-3'', H-5''), 7.49 (br d, J = 8.3 Hz, 2 H, H-3, H-5),...
7.39 (dd, J = 8.8, 4.7 Hz, 1 H, H-5'), 4.41 (s, 2 H, CH₂NEtSO₂), 3.16 (q, J = 7.2 Hz, 2 H, CH₂CH₃), 1.33 [s, 9 H, C(CH₃)₂], 0.88 (t, J = 7.1 Hz, 3 H, CH₂C₂); ¹³C NMR δ 165.5, 155.7, 144.4, 141.9, 141.5, 136.2, 135.7, 133.3, 127.7 (2), 127.7 (2), 127.2, 126.7 (2), 126.1 (2), 123.3, 50.4, 43.0, 34.7, 30.7 (3), 13.6; MS m/z 453.3 (MH⁺, 100%). Anal. calcd for C₂₅H₂₉N₃O₃S: C, 66.49; H, 6.47; N, 9.31. Found: C, 66.66; H, 6.67; N, 9.25%.

Example 140
Preparation of 4-[[4-tert-Butylphenyl)sulfonyl](propyl)amino)methyl]-V-(3-pyridinyl)benzamide (159).

[0342] Propyl iodide (46 µl, 0.47 mmol) was added to a stirred suspension of benzamide 47 (200 mg, 0.47 mmol) and Cs₂CO₃ (308 mg, 0.94 mmol) in anhydrous DMF (5 ml.), and the reaction mixture was stirred at 20 °C for 24 h. The mixture was partitioned between EtOAc (150 ml.) and H₂O (50 ml.), and the organic fraction was washed with brine (50 ml.). The organic phase was dried, filtered and the solvent was evaporated. The residue was purified by column chromatography, eluting with 40% EtOAc/pet. ether to give benzamide 159 (132 mg, 60%) as a white solid; mp (EtOAc/pet. ether) 177-1 79 °C; ¹H NMR δ 10.41 (s, 1 H, CONH), 8.92 (d, J = 2.3 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.94 (br. d., J = 8.3 Hz, 2 H, H-2, H-6), 7.79 (dt, J = 8.6, 1.9 Hz, 2 H, H-2", H-6"), 7.64 (dt, J = 8.6, 1.9 Hz, 2 H, H-3", H-5"), 7.48 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 7.39 (dd, J = 8.3, 4.7, 0.4 Hz, 1 H, H-5'), 4.39 (s, 2 H, CH₂NPrSO₂), 3.06 (br t, J = 7.5 Hz, 2 H, NCH₂CH₂CH₃), 1.33 [s, 9 H, C(CH₃)₂], 1.33-1.27 (m, 2 H, NCH₂CH₂CH₃), 0.67 (t, J = 7.4 Hz, 3 H, NCH₂CH₂CH₃); ¹³C NMR δ 165.5, 155.7, 144.4, 141.9, 141.5, 136.2, 135.7, 133.3, 127.7 (2), 127.7 (2), 127.2, 126.7 (2), 126.1 (2), 123.4, 51.3, 50.5, 34.8, 30.7 (3), 21.3, 10.8; MS m/z 467.3 (MH⁺, 100%). Anal. calcd for C₂₅H₃₁N₃O₃S: C, 67.07; H, 6.71; N, 9.02. Found: C, 66.78; H, 6.78; N, 8.93%.

Example 141
Preparation of 4-[[4-3-(4-Morpholinyl)propyl]phenyl)sulfonyl]amino)methyl]-V-(3-pyridinyl)benzamide (160).
A mixture of alkyne 155 (190 mg, 0.39 mmol) and 10% Pd/C (70 mg, 0.06 mmol) in MeOH (20 ml) was stirred at 20 °C under of H₂ (60 psi) for 4 h. The mixture was filtered through Celite, the pad was washed with MeOH (100 ml), and the solvent was evaporated. The residue was purified by column chromatography, eluting with 6% MeOH/DCM containing 0.5% aqueous NH₃, to give the benzamide 160 (50 mg, 26%) as a white powder: mp (MeOH/DCM) 170-171 °C; ¹H NMR δ 10.35 (s, 1 H, CONH), 8.92 (d, J = 2.3 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.20-8.1 6 (m, 2 H, NHSO₂, H-4'), 7.88 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.69 (br d, J = 8.3 Hz, 2 H, H-2, H-6', 7.40-7.37 (m, 5 H, H-3, H-5, H-5', H-3'', H-5''), 4.08 (d, J = 6.3 Hz, 2 H, CH₂NHSO₂), 3.54 (t, J = 4.6 Hz, 4 H, H-2'', H-6''), 2.66 (t, J = 7.4 Hz, 2 H, H-1''), 2.31 (t, J = 4.3 Hz, 4 H, H-3'', H-5''), 2.25 (t, J = 7.2 Hz, 2 H, H-3''), 1.73 (q, J = 7.4 Hz, 2 H, H-2''); ¹³C NMR δ 165.5, 147.1, 144.5, 142.0, 141.8, 138.1, 135.8, 133.0, 129.0 (2), 127.6 (2), 127.4 (2), 127.2, 126.5 (2), 126.5, 66.2 (2), 57.4, 53.2 (2), 45.8, 32.6, 27.4; MS m/z 496.4 (MH⁺, 100%). Anal. calcd for C₂₆H₃₀N₄O₄S: C, 63.14; H, 6.11; N, 11.33. Found: C, 63.10; H, 6.19; N, 11.36%.

Example 142

A mixture of alkyne 156 (250 mg, 0.56 mmol) and 10% Pd/C (80 mg, 0.07 mmol) in MeOH (20 ml) was stirred at 20 °C under of H₂ (60 psi) for 4 h. The mixture was filtered through Celite, the pad was washed with MeOH (100 ml), and the solvent was evaporated. The residue was purified by column chromatography, eluting with 6% MeOH/DCM containing 0.5% aqueous NH₃, to give benzamide 161 (100 mg, 40%) as a white powder: mp (MeOH/DCM) 169-170 °C; ¹H NMR δ 10.35 (s, 1 H, CONH), 8.92 (d, J = 2.2 Hz, 1 H, H-2'), 8.31 (dd, J = 1.5 Hz, 1 H, H-6'), 8.1 6-8.20 (m, 2 H, NHSO₂, H-4'), 7.88 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.70 (br d, J
= 8.3 Hz, 2 H, H-2", H-6")], 7.38-7.40 (m, 5 H, H-3, H-5, H-5', H-3", H-5")], 4.08 (d, J = 6.1 Hz, 2 H, CH₂NSO₂), 2.65 (t, J = 7.4 Hz, 2 H, H-1")]. 2.18 (t, J = 7.2 Hz, 2 H, H-3"). 2.11 [s, 6 H, N(CH₃)₂]. 1.69 (br q, J = 7.3 Hz, 2 H, H-2")]; ¹³C NMR δ 165.5, 147.1, 144.5, 142.0, 141.8, 138.1, 135.8, 133.0, 129.0 (2), 127.6 (2), 127.4 (2), 127.3, 126.5 (2), 123.4, 58.3, 45.7, 45.1 (2), 32.6, 28.5; MS m/z 454.3 (MH⁺, 100%).
Anal. calcd for C₂₄H₂₈N₄O₃S·H₂O: C, 61.26; H, 6.43; N, 11.91. Found: C, 61.61; H, 6.17; N, 11.90%.

Example 143

[0345] Propionyl chloride (25 µL, 0.29 mmol) was added dropwise to a stirred solution of aniline 26 (106 mg, 0.28 mmol) and 2Pr₂NEt₂ (54 µL, 0.31 mmol) in dry THF (10 mL) and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue was suspended in ice/water (30 mL) for 1 h. The precipitate was filtered, washed with water (10 mL) and dried. The residue was purified by column chromatography, eluting with a gradient (0-1 0%) of MeOH/CH₂Cl₂, to give benzamide 162 (78 mg, 64%) as a white powder: mp (EtOH/CH₂Cl₂) 215-218 °C; ¹H NMR δ 10.38 (s, 1 H, CONH), 10.17 (s, 1 H, CONH), 8.93 (d, J = 2.2 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.28 (t, J = 6.3 Hz, 1 H, NSO₂), 8.16-8.21 (m, 2 H, H-4', H-2''), 7.91 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.77 (dt, J = 8.0, 1.7 Hz, 1 H, H-6''), 7.51 (t, J = 7.8 Hz, 1 H, H-5''), 7.47 (dt, J = 7.8, 1.6 Hz, 1 H, H-4''), 7.37-7.44 (m, 3 H, H-3, H-5, H-5'), 4.08 (s, 2 H, CH₂N), 2.35 (q, J = 7.5 Hz, 2 H, CH₂CO), 1.09 (t, J = 7.5 Hz, 3 H, CH₃); ¹³C NMR δ 172.4, 165.5, 144.5, 142.0, 141.9, 141.0, 139.9, 135.8, 133.0, 129.7, 127.7 (2), 127.4 (2), 127.3 123.5, 122.3, 120.6, 116.7, 45.7, 29.5, 9.5; MS m/z 439.5 (MH⁺, 100%). Anal. calcd for C₂₀H₂₂N₄O₄S·C₆H₅: C, 60.26; H, 5.06; N, 12.78. Found: C, 59.97; H, 5.18; N, 12.39%.

Example 144
Acryloyl chloride (50 µl, 0.62 mmol) was added dropwise to a stirred solution of aniline 26 (225 mg, 0.59 mmol) and JPr₂NEt₂ (113 µl, 0.65 mmol) in dry THF (10 ml) and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue was suspended in ice/water (30 ml) for 1 h. The precipitate was filtered, washed with water (10 ml) and dried. The residue was purified by column chromatography, eluting with a gradient (0-100%) of MeOH/EtOAc, to give benzamide 163 (76 mg, 30%) as a white powder: mp (EtOH/EtOAc) 178-180 °C; ¹H NMR δ 10.44 (s, 1 H, CONH), 10.36 (s, 1 H, CONH), 8.92 (d, J = 2.3 Hz, 1 H, H-2'), 8.25-8.33 (m, 3 H, NHSO₂, H-6', H-2''), 8.18 (ddd, J = 8.4, 2.3, 1.6 Hz, 1 H, H-4'), 7.91 (br d, J = 8.2 Hz, 2 H, H-2, H-6), 7.87 (dt, J = 7.5, 1.7 Hz, 1 H, H-6''), 7.50-7.58 (m, 2 H, H-4'', H-5''), 7.36-7.45 (m, 3 H, H-3, H-5, H-5''), 6.44 (dd, J = 17.0, 10.0 Hz, 1 H, =CH₂), 6.30 (dd, J = 17.0, 2.0 Hz, 1 H, =CH₂), 5.80 (dd, J = 10.0, 2.0 Hz, 1 H, =CH), 4.08 (d, J = 6.2 Hz, 2 H, CH₂N); ¹³C NMR δ 165.5, 163.5, 144.5, 142.0, 141.8, 141.1, 139.6, 135.8, 133.0, 131.5, 129.8, 127.6 (2), 127.5, 127.4 (2), 127.3, 123.5, 122.7, 121.2, 117.1, 45.8; MS m/z 437.6 (MH⁺, 100%). Anal. calcd for C₃₂H₂₀N₄O₄S: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.27; H, 4.67; N, 12.70%.

Example 145
Preparation of 4-(((4-tert-Butylphenyl)sulfonyl)amino)methyl)-2-methyl-Ν-(3-pyridinyl)benzamide (167).

[0347] 4-Cyano-2-methyl benzoic acid (164). A solution of nBuLi in THF (2.5 M, 2.24 ml, 5.6 mmol) was added dropwise to a stirred solution of 4-bromo-3-methylbenzonitrile (1.0 g, 5.1 mmol) in dry THF (50 ml) at -78 °C and the solution stirred at -78 °C for 1 h. A stream of dry CO₂ was bubbled through the solution for 10 min and the mixture warmed to 20 °C. The mixture was diluted with water (100 ml) and washed with Et₂O (3 x 20 ml). The aqueous phase was acidified to pH 2 with cHCl and extracted with CHCl₃ (3 x 50 ml) and the organic fraction was dried and the solvent evaporated to give crude acid 164 (0.67 g, 82%) as a tan powder: mp
(CHCl₃) 193-1 95 °C; ¹H NMR δ 3.43 (br s, 1 H, CO₂H), 7.90 (d, J = 8.0 Hz, 1 H, H-6), 7.82 (br s, 1 H, H-3), 7.77 (dd, J = 8.0, 1.0 Hz, 1 H, H-5), 2.53 (s, 3 H, CH₃).

[0348]4-Cyano-2-methyl-W-(3-pyrdinyl)benzamide (165). Oxalyl chloride (720 μL, 8.32 mmol) was added dropwise to a stirred suspension of benzoic acid 164 (670 mg, 4.16 mmol) and DMF (1 drop) in dry THF (25 mL) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 mL). 3-Pyridinylamine (430 mg, 4.60 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 mL) for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzamide 165 (608 mg, 62%) as a white powder: mp (EtOAc) 193-1 95 °C; ¹H NMR δ 10.70 (s, 1 H, CONH), 8.86 (d, J = 2.3 Hz, 1 H, H-2'), 8.33 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.16 (ddd, J = 8.3, 2.4, 1.5 Hz, 1 H, H-4), 7.85 (br s, 1 H, H-3), 7.81 (br dd, J = 7.9, 1.0 Hz, 1 H, H-5), 7.69 (d, J = 7.9 Hz, 1 H, H-6), 7.41 (dd, J = 8.3, 4.7 Hz, 1 H, H-5'), 2.42 (s, 3 H, CH₃); MS m/z 238.4 (MH⁺, 100%). Anal. calcd for Cl₄H₄N₃O: C, 70.87; H, 4.67; N, 11.71. Found: C, 70.68; H, 4.75; N, 17.52%.

[0349]4-(Aminomethyl)-2-methyl-/V-(3-pyridinyl)benzamide (166). A mixture of benzamide 165 (410 mg, 1.72 mmol) and 10% Pd/C (50 mg) and CHCl₃ (0.43 mL, 5.2 mmol) in EtOH (100 mL) was stirred under H₂ (60 psi) at 20 °C for 16 h. The mixture was filtered through Celite, the Celite was washed with EtOH (20 mL), and the solvent was evaporated. The residue was partitioned between dilute aqueous NH₃ solution (30 mL) and CHCl₃ (3 x 30 mL) and the organic fraction dried and the solvent evaporated to give crude amine 166 (338 mg, 81%) as a gum: ¹H NMR δ 10.43 (s, 1 H, CONH), 8.87 (d, J = 2.2 Hz, 1 H, H-2'), 8.29 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.37 (br d, J = 8.3 Hz, 1 H, H-4'), 7.45 (br d, J = 7.7 Hz, 1 H, H-6), 7.37 (ddd, J = 8.3, 4.7, 0.5 Hz, 1 H, H-5'), 7.24-7.28 (m, 2 H, H-3, H-5), 3.73 (s, 2 H, CH₂N), 2.38 (s, 3 H, CH₃), 2.05 (s, 2 H, NH₂); MS m/z 242.4 (MH⁺, 100%).

[0350]4-(((4-ferf-Butylphenyl)sulfonyl)amino)methyl)-2-methyl-/V-(3-pyridinyl)benzamide (167). A mixture of benzamide 166 (334 mg, 1.38 mmol) and 4-tert-butylbenzenesulfonyl chloride (354 mg, 1.52 mmol) in dry pyridine (10 mL) was stirred at 20 °C for 16 h. The solvent was evaporated and the residue stirred in water (40 mL) for 1 h. The precipitate was filtered, washed with water (5 mL) and dried.
The crude solid was purified by column chromatography, eluting with EtOAc, to give benzamide 167 (369 mg, 61%) as a white powder: mp (EtOAc) 162-163 °C; \(^1\)H NMR δ 10.43 (s, 1 H, CONH), 8.86 (d, J = 2.2 Hz, 1 H, H-2'), 8.30 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.13-8.18 (m, 2 H, NHSO\(_2\), H-4'), 7.73 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-2", H-6"), 7.60 (br d, J = 8.6, 2.2, 1.9 Hz, 2 H, H-3", H-5"), 7.43 (d, J = 7.8 Hz, 1 H, H-6), 7.37 (dd, J = 8.3, 4.7 Hz, 1 H, H-5'), 7.18 (br d, J = 7.8 Hz, 1 H, H-5), 7.12 (br s, 1 H, H-3), 4.08 (s, 2 H, CH\(_2\)N), 2.32 (s, 3 H, CH\(_3\)), 1.31 [S, 9 H, C(CH\(_3\))\(_3\)], \(^{13}\)C NMR δ 167.9, 155.2, 144.3, 141.2, 149.7, 137.9, 135.8, 135.4, 135.0, 129.6, 127.3, 126.4, 126.3 (2), 125.9 (2), 124.6, 123.5, 45.6, 34.7, 30.7 (3), 19.3; MS m/z 438.6 (MH\(^+\), 100%). Anal. calcd for C\(_{24}\)H\(_{27}\)N\(_3\)O\(_3\)S: C, 65.88; H, 6.22; N, 9.60. Found: C, 65.95; H, 6.40; N, 9.33%.

**Example 146**

**Preparation of 4-(((4-tert-Butylphenyl)sulfonyl)amino)methyl)-2-fluoro-/V-(3-pyridinyl)benzamide (170).**

![Diagram](image)

\[0351\]4-Cyano-2-fluoro-/V-(3-pyridinyl)benzamide (168). Oxalyl chloride (0.79 ml, 9.08 mmol) was added dropwise to a stirred suspension of 4-cyano-2-fluorobenzoic acid (1.00 g, 6.06 mmol) and DMF (1 drop) in dry THF (40 ml_) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 ml_). 3-Pyridinylamine (0.627 g, 6.67 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 ml_) for 1 h. The precipitate was filtered, washed with water (5 ml_) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzamide 168 (1.36 g, 93%) as a white powder: mp (EtOAc) 140-142 °C; \(^1\)H NMR δ 10.86 (s, 1 H, CONH), 8.85 (d, J = 2.2 Hz, 1 H, H-2'), 8.36 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.14 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 8.08 (dd, J= 1.0, 1.1 Hz, 1 H, H-3), 7.85-7.93 (m, 2 H, H-5, H-6), 7.42 (ddd, J = 8.3, 4.7, 0.4 Hz, 1 H, H-5'); MS m/z 242.3 (MH\(^+\), 100%). Anal. calcd for C\(_{13}\)H\(_8\)FN\(_3\)O\(_2\)H\(_2\): C, 62.40; H, 3.63; N, 16.79. Found: C, 62.53; H, 3.50; N, 16.92%.

\[0352\]4-(Aminomethyl)-2-fluoro-/N-(3-pyridinyl)benzamide (169). A mixture of benzamide 168 (163 mg, 0.68 mmol) and 10% Pd/C (30 mg) and cHCl (0.17 ml, 2.0
mmol) in EtOH (50 ml_) was stirred under H₂ (60 psi) at 20 °C for 16 h. The mixture was filtered through Celite, the Celite was washed with EtOH (20 ml_), and the solvent was evaporated. The residue was partitioned between dilute aqueous NH₃ solution (30 ml_) and CHCl₃ (3 x 30 ml_) and the organic fraction dried and the solvent evaporated to give crude amine 169 (127 mg, 54%) as a white powder: mp (CHCl₃) 90-91 °C: ¹H NMR δ 10.51 (s, 1 H, CONH), 8.86 (d, J = 2.3 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.16 (br d, J = 8.3 Hz, 1 H, H-4'), 7.63 (t, J = 7.7 Hz, 1 H, H-6), 7.39 (ddd, J = 8.2, 4.7, 0.6 Hz, 1 H, H-5'), 7.34 (d, J = 11.7 Hz, 1 H, H-3), 7.28 (dt, J = 7.8, 0.7 Hz, 1 H, H-5), 3.78 (s, 2 H, CH₂N), 2.01 (s, 2 H, NH₂); MS m/z 246.4 (MH⁺, 100%). Anal. calcd for C₁₃H₁₂FN₃O: C, 63.66; H, 4.93; N, 17.13. Found: C, 63.54; H, 5.01 ; N, 17.01%.

[0353]4-(((4-tert-Butylphenyl)sulfonyl)amino)methyl)-2-fluoro-1/V-(3-pyridinyl)benzamide (170). A mixture of benzamide 169 (116 mg, 0.34 mmol) and 4-tert-butylbenzenesulfonyl chloride (86 mg, 0.37 mmol) in dry pyridine (10 ml_) was stirred at 20 °C for 16 h. The solvent was evaporated and the residue stirred in water (40 ml_) for 1 h. The precipitate was filtered, washed with water (5 ml_) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzamide 170 (111 mg, 74%) as a white powder: mp (EtOAc) 185-1 87 °C; ¹H NMR δ 10.52 (s, 1 H, CONH), 8.85 (d, J = 2.3 Hz, 1 H, H-2'), 8.32 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.27 (br s, 1 H, NHSO₂), 8.13 (br d, J = 8.8 Hz, 1 H, H-4'), 7.70 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-2", H-6"), 7.55-7.61 (m, 3 H, H-6, H-3", H-5"), 7.39 (ddd, J = 8.3, 4.7, 0.4 Hz, 1 H, H-5'), 7.20 (br dd, J = 8.0, 1.3 Hz, 1 H, H-5), 7.15 (br d, J = 11.4 Hz, 1 H, H-3), 4.10 (s, 2 H, CH₂N), 1.29 (s, 9 H, C(CH₃)₃); ¹³C NMR δ 162.9, 158.8 (d, J = 249.9 Hz), 155.4, 144.8, 143.7 (d, J = 7.7 Hz), 141.4, 137.8, 135.5, 129.8 (d, J = 2.7 Hz), 126.8, 126.3 (2), 126.0 (2), 123.6, 123.4, 122.7 (d, J = 14.5 Hz), 114.9 (d, J = 22.8 Hz), 45.2, 34.8, 30.7 (3); MS m/z 442.6 (MH⁺, 100%). Anal. calcd for C₂₃H₂₄FN₃O₃S: C, 62.57; H, 5.48; N, 9.52. Found: C, 62.56; H, 5.57; N, 9.46%.

Example 147
Preparation of 4-(((4-tert-Butylphenyl)sulfonyl)amino)methyl)-3-methyl-1/V-(3-pyridinyl)benzamide (*).
[0354] 4-Cyano-3-methyl benzoic acid (171). A solution of nBuLi in THF (2.5 M, 4.49 ml, 11.2 mmol) was added dropwise to a stirred solution of 4-bromo-2-methylbenzonitrile (2.0 g, 10.2 mmol) in dry THF (100 ml) at -78 °C and the solution stirred at -78 °C for 1 h. A stream of dry CO2 was bubbled through the solution for 10 min and the mixture warmed to 20 °C. The mixture was diluted with water (100 ml) and washed with Et2O (3 x 20 ml). The aqueous phase was acidified to pH 2 with cHCl and extracted with CHCl3 (3 x 50 ml) and the organic fraction was dried and the solvent evaporated to give crude acid 171 (1.05 g, 64%) as a tan powder: mp (EtOAc) 215-21 7 °C; 1H NMR δ 13.49 (br s, 1 H, CO2H), 7.99 (br s, 1 H, H-2), 7.91 (br d, J = 7.9 Hz, 1 H, H-5), 7.87 (br d, J = 8.0 Hz, 1 H, H-6), 2.55 (s, 3 H, CH3).

[0355] 4-Cyano-3-methyl-W-(3-pyridinyl)benzamide (172). Oxaly chloride (763 µl, 8.75 mmol) was added dropwise to a stirred suspension of benzoic acid 171 (940 mg, 5.83 mmol) and DMF (1 drop) in dry THF (40 ml) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 ml). 3-Pyridinylamine (603 mg, 6.41 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzamide 172 (1.43 g, 99%) as a white powder: mp (EtOAc) 189-190 °C; 1H NMR δ 10.64 (s, 1 H, CONH), 8.92 (d, J = 2.4 Hz, 1 H, H-2), 8.34 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.18 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 8.02 (br s, 1 H, H-2), 7.97 (d, J = 8.1 Hz, 1 H, H-5), 7.91 (dd, J = 8.1, 1.0 Hz, 1 H, H-6), 7.41 (dd, J = 8.3, 4.7 Hz, 1 H, H-5'), 2.59 (s, 3 H, CH3); MS m/z 238.4 (MH+, 100%). Anal. calcd for C14H11N2O: C, 70.87; H, 4.67; N, 17.68. Found: C, 70.95; H, 4.67; N, 17.68.

[0356] 4-(((4-tert-Butylphenyl)sulfonylamino)methyl)-3-methyl-W-(3-pyridinyl)benzamide (173). A mixture of benzamide 172 (240 mg, 1.00 mmol) and 10% Pd/C (50 mg) and cHCl (0.25 ml, 3.0 mmol) in EtOH (50 ml) was stirred under H2 (60 psi) at 20 °C for 16 h. The mixture was filtered through Celite, the Celite was washed with EtOH (20 ml), and the solvent was evaporated. The residue was partitioned between dilute aqueous NH3 solution (30 ml) and CHCl3 (3 x 30 ml) and the organic fraction dried and the solvent evaporated to give crude amine as a gum which was used directly. A mixture of crude amine (288 mg, 1.19 mmol) and 4-tert-
butylbenzenesulfonyl chloride (306 mg, 1.31 mmol) in dry pyridine (10 mL) was stirred at 20 °C for 16 h. The solvent was evaporated and the residue stirred in water (40 mL) for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzamide **173** (44 mg, 10%) as a white powder: mp (EtOAc) 203-205 °C; **1**H NMR δ 10.32 (s, 1 H, CONH), 8.91 (d, J = 2.3 Hz, 1 H, H-2'), 8.30 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.17 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 8.06 (t, J = 6.2 Hz, 1 H, NHSO₂), 7.68-7.75 (m, 4 H, H-2, H-6, H-2", H-6"), 7.57 (ddd, J = 8.6, 2.2, 1.9 Hz, 2 H, H-3", H-5"), 7.33-7.40 (m, 2 H, H-5, H-5'), 4.04 (d, J = 6.2 Hz, 2 H, CH₂N), 2.30 (s, 3 H, CH₃), 1.30 [s, 9 H, C(CH₃)₃]; MS m/z 438.6 (MH⁺, 100%).

**Example 148**

Preparation of 4-(((4-tert-Butylphenyl)sulfonyl]amino)methyl)-3-fluoro-3-(3-pyridinyl)benzamide (175).

![Chemical structure](image)

**[0357]**4-Cyano-3-fluoro-3-(3-pyridinyl)benzamide (174). Oxalyl chloride (0.79 mL, 9.08 mmol) was added dropwise to a stirred suspension of 4-cyano-3-fluorobenzoic acid (1.00 g, 6.06 mmol) and DMF (1 drop) in dry THF (40 mL) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 mL). 3-Pyridinylamine (627 mg, 6.67 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 mL) for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzamide **174** (1.19 g, 81%) as a white powder: mp (EtOAc) 189-191 °C; **1**H NMR δ 10.71 (s, 1 H, CONH), 8.92 (d, J = 2.4 Hz, 1 H, H-2'), 8.36 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.13-8.20 (m, 2 H, H-5, H-4'), 8.06 (dd, J = 10.0, 1.4 Hz, 1 H, H-2), 7.97 (dd, J = 8.0, 1.5 Hz, 2 H, H-6), 7.43 (ddd, J = 8.3, 4.7, 0.7 Hz, 1 H, H-5'); MS m/z 242.3 (MH⁺, 100%). Anal, calcd for C₁₃H₈FN₂O: C, 64.73; H, 3.34; N, 17.42. Found: C, 64.51; H, 3.31; N, 17.05%.

**[0358]**4-(((4-tert-Butylphenyl)sulfonyl]amino)methyl)-3-fluoro-W-(3-pyridinyl)benzamide (175). A mixture of benzamide **174** (330 mg, 1.37 mmol) and 10% Pd/C (30 mg) and CHCl (0.34 mL, 4.1 mmol) in EtOH (30 mL) was stirred under
H₂ (60 psi) at 20 °C for 16 h. The mixture was filtered through Celite, the Celite was washed with EtOH (20 ml), and the solvent was evaporated. The residue was partitioned between dilute aqueous NH₃ solution (30 ml) and CHCl₃ (3 x 30 ml) and the organic fraction dried and the solvent evaporated to give crude amine which was used directly. A mixture of amine (106 mg, 0.43 mmol) and 4-tert-butylenzaldehyde chloride (111 mg, 0.48 mmol) in dry pyridine (10 ml) was stirred at 20 °C for 16 h. The solvent was evaporated and the residue stirred in water (40 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzamide 175 (45 mg, 7%) as a white powder: mp (EtOAc) 198-200 °C; ¹H NMR δ 10.40 (s, 1 H, CONH), 8.90 (d, J = 2.3 Hz, 1 H, H-2'), 8.33 (dd, J = 4.7, 1.2 Hz, 1 H, H-6'), 8.23 (t, J = 5.6 Hz, 1 H, NHSO₂), 8.15 (ddd, J = 8.4, 2.5, 1.5 Hz, 1 H, H-4' ), 7.71 (br d, J = 8.0 Hz, 1 H, H-6), 7.63-7.68 (m, 3 H, H-5, H-2", H-6") 7.52 (br d, J = 8.5 Hz, 2 H, H-3", H-5") 7.46 (br t, J = 7.8 Hz, 1 H, H-2) 7.40 (br dd, J = 8.3, 4.7 Hz, 1 H, H-5") 4.12 (d, J = 5.6 Hz, 2 H, CH₂N), 1.27 [s, 9 H, C(CH₃)₃]; MS m/z 442.6 (MH⁺, 100%).

Example 149

Preparation of 4-(1-[[4-tert-Butylphenyl)sulfonyl]amino]ethyl)-N-(3-pyridinyl)benzamide (177).

[0359]4-Acetyl- N-(3-pyridinyl)benzamide (176). Oxalyl chloride (0.67 ml, 7.68 mmol) was added dropwise to a stirred suspension of 4-acetylbenzoic acid (0.97 g, 5.12 mmol) and DMF (1 drop) in dry THF (40 ml) and the solution was stirred at 20 °C for 2 h, then at 66 °C for 1 h. The solution was cooled to 20 °C, then the solvent was evaporated and the residue dissolved in dry pyridine (10 ml). 3-Pyridinylamine (505 mg, 5.38 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice/water (50 ml) for 1 h. The precipitate was filtered, washed with water (5 ml) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzamide 176 (1.05 g, 85%) as a white powder: mp (EtOAc) 169-171 °C; ¹H NMR δ 10.59 (s, 1 H, CONH), 8.94 (d, J = 2.2 Hz, 1 H, H-2'), 8.34 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.20 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 8.07-8.13 3 (m, 4 H, H-2, H-3, H-5, H-6), 7.42
(ddd, J = 8.3, 4.7, 0.6 Hz, 1 H, H-5'), 2.26 (s, 3 H, COCH₃); MS m/z 241.3 (MH⁺, 100%). Anal. calcd for CᵣH₂₂N₂O₂: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.69; H, 5.05; N, 11.72%.

[0360] 4-((4-(tert-Butylphenyl)sulfonylamino)methyl)-3-nitro-N-(pyridin-3-yl)benzamide (177). NaCNBH₃ (40 mg, 0.63 mmol) was added to a stirred solution of benzamide 176 (21.7 mg, 0.90 mmol) and NH₂OAc (0.70 g, 9.0 mmol) in dry MeOH (10 mL) and the mixture was stirred at 20 °C for 16 h. The solvent was evaporated and the residue was partitioned between dilute aqueous NH₃ solution (30 mL) and CHCl₃ (3 x 30 mL). The combined organic fraction was dried and the solvent evaporated to give crude 4-(1-aminoethyl)-N-(3-pyridinyl)benzamide (21.0 mg; 98%) as a white foam: ¹H NMR δ 10.34 (s, 1 H, CONH), 8.93 (d, J = 2.2 Hz, 1 H, H-2'), 8.30 (dd, J = 4.7, 1.5 Hz, 1 H, H-6'), 8.19 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.92 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.53 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 7.39 (ddd, J = 8.3, 4.7, 0.5 Hz, 1 H, H-5), 4.07 (q, J = 6.6 Hz, 2 H, CH₃N), 1.27 (s, 3 H, CH₃). A mixture of amine (210 mg, 0.87 mmol) and 4-te/?-butylbenzenesulfonfyl chloride (213 mg, 0.91 mmol) in dry pyridine (10 mL) was stirred at 20 °C for 16 h. The solvent was evaporated and the residue stirred in water (40 mL) for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzamide 177 (163 mg; 43%) as a white powder: ¹H NMR δ 10.34 (s, 1 H, CONH), 8.90 (d, J = 2.4 Hz, 1 H, H-2'), 8.31 (dd, J = 4.7, 1.4 Hz, 1 H, H-6'), 8.21 (d, J = 8.4 Hz, 1 H, NHSO₂), 8.15 (ddd, J = 8.3, 2.5, 1.5 Hz, 1 H, H-4'), 7.74 (br d, J = 8.3 Hz, 2 H, H-2, H-6), 7.51 (ddd, J = 8.5, 2.1, 1.8 Hz, 2 H, H-2, H-6'), 7.36-7.41 (m, 3 H, H-5, H-3', H-5'), 7.28 (br d, J = 8.3 Hz, 2 H, H-3, H-5), 4.39-4.49 (m, 2 H, CH₂N), 1.28 (d, J = 7.0 Hz, 3 H, CH₂), 1.27 [s, 9 H, C(CH₃)_3]; ¹³C NMR δ 165.3, 155.8, 146.9, 144.4, 141.9, 138.2, 135.7, 132.4, 127.3 (2), 127.2, 126.1 (2), 125.4 (2), 123.4, 52.6, 34.5, 30.6 (3), 23.4; MS m/z 438.6 (MH⁺, 100%).

Example 150

[0361] Using procedures similar to those described herein, the following compounds may be prepared and tested:

4-((4-(tert-butyl)phenylsulfonamido)methyl)-3-nitro-N-(pyridin-3-yl)benzamide;
(S)-4-(1-(4-(tert-buty1)phenylsulfonamido)ethyl)-N-(pyridin-3-y1)benzamide and (R)-4-
(1-(4-(tert-buty1)phenylsulfonamido)ethyl)-N-(pyridin-3-y1)benzamide and mixtures thereof;
4-(N-phenylsulfamoylmethyl)-N-(pyridin-3-y1)benzamide; 4-((N-(4-fluorophenyl)sulfamoyl)methy1)-N-(pyridin-3-y1)benzamide; 4-((N-(4-tert- buty1phenyl)sulfamoyl)methyl)-N-(pyridin-3-y1)benzamide; 4-((N-(4-(4-methylpiperazin-1y1)phenyl)sulfamoyl)methyl)-N-(pyridin-3-y1)benzamide.)

Example 151

Biological Methods

[0362] Cell culture. RCC4 parental and RCC4 with VHL-reintroduced (RCC4/VHL), SN1 2C and SN1 2C-CSCG-VHL shRNA were maintained in DMEM supplemented with 10% FCS.

[0363] IC_{50} Assays. IC_{50} values for compounds were determined by XTT assay. For 2,3-bis[2-methoxy-4-nitro-5-sulfophenyl]-2H-tetrazolium-5-carboxanilide inner salt (XTT) assays, five thousand cells were plated in 96-well plates. The next day, vehicle or drug was added to each well and incubated for four days. Media was aspirated and phenol red-free medium with 0.3 mg/mL XTT and 2.65 ug/mL N-methyl dibenzopyrazin e methyl sulfate was added. This was incubated at 37 °C for 1-2 hours and absorbance was read at 450 nm. IC_{50} values for each compound were calculated using linear interpolation.

[0364] Clonogenic assay. Three hundred cells were plated into 60-mm tissue culture dishes in DMEM. The next day, cells were treated with vehicle or drug and were further incubated for an additional 10 days. After 10 days, the media was removed and colonies were fixed and stained in 95% ethanol and 0.1% crystal violet for 15 minutes. The stain was removed and plates were washed in deionized water. Colonies were quantified. All conditions were measured in triplicate and all experiments were performed in triplicate.

[0365] Glucose uptake. One hundred thousand cells were plated into 6-well plates. The following day, the cells were treated with vehicle or drug and incubated for the indicated time. Cells were washed twice in phosphate buffered saline and low glucose media was added for 30 minutes. Cells were then incubated with 0.5 microCi of tritiated-2-deoxyglucose and incubated for an hour at 37 °C. Cells were washed twice in PBS and then lysed in 0.2 N NaOH and 0.2% SDS. Lysates were
transferred to scintillation tubes with scintillation fluid and quantified by scintillation counter.

**[0366] In vivo experiments.** Five million cells were injected into the flanks of nu/nu mice (4-6 weeks old males) and allowed to grow to approximately 50 mm$^3$. The mice were injected daily by intra-peritoneal to deliver either vehicle or drug. Tumors were measured every other day and tumor volume was calculated as 0.5 length by width squared.

**[0367] IC50 values and selectivity ratios for certain exemplary compounds are described below.** The designation A reflects an IC50 of < 1 µM; B reflects an IC50 ranging from 1 to 20 µM; and C is an IC50 of > 20 µM. The designation "a" reflects a ratio of RCC4/RCC-VHL+ ranging from 1 to 10; "b" reflects from 10 to 100; "c" reflects a ratio of > 100, and "nd" represents "not determined".

### Table 1

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Example 152 - Synthetic Lethal Targeting of Glucose Metabolism in Renal Carcinoma

Methods

[0368] Cell Culture and Reagents. All cells were grown in DMEM + 10% FCS. ACHN and ACHN shVHL were a kind gift from George V. Thomas (UCLA). HIF overexpressing clones were described previously. Transfection of RNA oligos were performed with DharmaFECT Reagent 1 (Dharmacon), according to manufacturer’s directions. ON-TARGETplus SMART pools against HIF-1 β/ARNT were purchased.
from Dharmacon. Glut1 was detected with anti-GLUT1 antibody from NeoMarkers/LabVision/Fisher. Pyruvate/lactate levels and hexokinase activity were both measured by fluorometric assay (BioVision and Sigma-Aldrich, respectively). ATP levels were measured by bioluminescence assay (ATP Determination Kit from Molecular Probes/Invitrogen). In vitro kinase activities were performed by Millipore KinaseProfiler. Affi-Gel 10 (BioRad) activated affinity media was coupled to analogs to generate immobilized affinity linkers.

Cell Viability Assays. For 2,3-bis[2-methoxy-4-nitro-5-sulfophenyl]-2H-tetrazolium-5-carboxanilide (XTT) assays, five thousand cells were plated in 96-well plates. The next day, vehicle (DMSO) or drug was added by serial dilution. Four days later, media were aspirated, XTT solution (0.3 mg/ml of XTT (Sigma), 2.65 mg/ml N-methyl dibenxopyrazine methyl sulfate (Simga) in phenol red-free media) was added, and the plates were incubated at 37°C for 1-2 hours. Metabolism of XTT was quantified by measuring the absorbance at 450 nm. \( \text{IC}_{50} \) were calculated using linear interpolation. For clonogenic survival assays, three hundred cells were plated per 60 mm tissue culture dish. The cells were allowed to attach overnight and then treated with vehicle or drug for 14 days. Colonies were fixed and stained with crystal violet (0.1% crystal violet in 95% ethanol). All conditions were measured in triplicate and each experiment was done in duplicate or triplicate. To determine necrosis, cells were treated with drug for a given time point. Media and cells were collected, centrifugated, and resuspended in 0.4% trypan blue (Invitrogen). Live and dead cells were counted on a hematocytometer.

Glucose Uptake. One hundred thousand cells were plated per well in a six-well plate. The next day, cells were treated with the indicated concentration of drug and incubated for the indicated time. Cells were then washed twice with phosphate-buffered saline, incubated in low-glucose medium for 30 minutes, and \( ^{3} \text{H}-2\text{-deoxyglucose} \) (0.5 µCi) was added in 1 ml of glucose-free media for an additional hour. Cells were washed twice in PBS and lysed (0.2 N NaOH and 0.2% sodium dodecyl sulfate). Glucose uptake was quantified with a scintillation counter.

Oxygen Consumption. Following treatment with vehicle or drug, cells were trypsinized, suspended at 5 million cells per ml in DMEM + 10% FCS, and oxygen consumption was measured in 0.5 ml volume using an Oxytherm electrode unit (Hansatech).
Quantitative Real-time RT-PCR. Total RNA was extracted from cells (TRIzol, Invitrogen) as per manufacturer's directions. Total RNA (1.5 µg) was reversed transcribed with random hexamers and MMLV-RT. Power SYBR Green PCR reactions were performed in triplicate for each sample and analyzed using the ABI Prism 7900HT sequence detection system. Data were normalized to TBP levels.

In Vivo Studies and Immunohistochemistry. All experiments were approved by Stanford's Administrative Panel on Laboratory Animal Care (APLAC) and in accordance with both institutional and national guidelines. Five million cells were implanted subcutaneously into the flanks of nude mice (4-6 weeks old)(Charles River Laboratories). Tumors were measured with calipers. Volume was calculated by the following formula: width^2 x 0.5 length. Once tumors reached an average size of >20 mm^3, mice were randomized into vehicle (DMSO diluted in 16% cremaphor EL/PBS) or treated groups. Mice were treated with compound 85 (1.6 mg/kg for the first 3 days, followed by 7.8 mg/kg for the 7-9 days). Five-micron sections were cut for immunohistochemistry. Sections were counterstained with hematoxylin and eosin. For 2-[¹⁸F]-fluoro-2-deoxy-glucose-positron emission tomography imaging, mice bearing tumors were fasted overnight. The next day, the mice were anesthetized with 2% isoflurane and injected intraperitoneal^ with 250 µCi of FDG. Mice were imaged for 10 minutes at one hour post-injection, using a Rodent R4 microPET system (Concorde Microsystems). Data were reconstructed into three-dimensional volumes using an ordered subset expectation maximization algorithm and were calibrated into units of percent injected dose per gram.

Statistical Analyses. Student's t test was used to determine significance. All error bars represent the standard error of the mean.

Primers

[0376] Gluti /SLC2A1 :
Forward: 5'-GGCCAAGAGGTGTGCTAAAGAA-S'
Reverse: 5'-ACAGCGTTGATGCCAGACAG-S'

[0379]Glut2/SLC2A2 :
Forward: 5'-GTCACTGGGACCCCTGGTTTC-S'
Reverse: 5'-AGTTGTGATAGGCTTTTCGCA-S'
Results

In order to discover classes of drugs that would selectively target RCC, we screened approximately 64,000 compounds to identify small molecules that function in a synthetic lethal manner to the loss of VHL. We employed multiple RCC cell lines with naturally occurring VHL mutations and, as a negative control, their genetically matched counterparts with reintroduced wild-type VHL. These matched cell lines, engineered to stably express enhanced yellow fluorescent protein, were treated with a small molecule library at a concentration of 10-20 µM for four days. Fluorescence
was measured on day four as a surrogate marker for viability and growth. From this fluorescent-based cell assay, two classes of drugs exhibited toxicity to cells that had lost VHL, but were relatively non-toxic to cells with functional VHL. Here we characterize the selective cytotoxicity of a second class, which includes compound 27 and compound 47 (i.e., 4-((4-(tert-butyl)phenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide), members of a family of 4-(phenylsulfonamido)-N-(pyridin-3-yl)tenzamides (PPBs). Both short-term metabolic assays and long-term survival assays were used to validate the primary screen (Fig. 2A and 2B). Metabolic activity was measured by 2,3-bis[2-methoxy-4-nitro-5-sulfophenyl]-2/-/-tetrazolim-5-carboxanilide (XTT) after four days of treatment with compound 27 and compound 47. We observed a significant decrease in the number of RCC4 cells that had lost VHL compared to their wild-type counterparts (RCC4/VHL) in a concentration-dependent manner (Fig. 2A). Clonogenic survival confirmed that these PPBs were specifically toxic to RCC4 cells while the RCC4/VHL cells were relatively unaffected (Fig. 1B, 1C, and 7A). Approximately 80% of RCC4 cells treated with compound 47 were killed following treatment whereas RCC4 cells treated under the same conditions were largely able to recover (Fig. 2D). To corroborate the VHL-dependence of PPB resistance, we examined a cell line, ACHN, which normally maintains functional VHL. We found that only the ACHN renal carcinoma cells where VHL expression was silenced by shRNA were sensitive to compound 47 (Fig. 2E). Thus, our chemical synthetic screening using a fluorescent, cell-based assay has identified compounds that are specifically cytotoxic to cells that have impaired VHL function.

[0401] Having previously demonstrated a selective sensitivity of W-/-/-deficient cells to autophagic cell death, we next sought to determine whether compound 47 acts by the same mechanism or whether this small molecule targets a different pathway. Treatment with compound 47 did not induce any morphologic or biochemical features of autophagy, such as intracellular accumulation of vacuoles (data not shown) or LC3 processing (Fig. 7B). Incubation of W-/-/-deficient and isogenic matched wild-type VHL RCCs with compound 47 showed no nuclear condensation in either cell line (Fig. 7C), nor an increase in either propidium iodide or annexin V staining (Fig. 7D), suggesting that compound 47 is not killing these cells by apoptosis. Compound 47 did not increase total p53 or phospho-p53 levels, also indicating that compound 47 does not induce a DNA damage response in treated
cells (Fig. 7E). However, RCC cells without VHL undergo a necrotic cell death in response to compound 47 as measured by the ability of the cells to exclude trypan blue, an indicator of cell membrane integrity. Treatment with compound 47 resulted in greater than 80% of RCC4 cells exhibiting necrotic cell death, while RCC4/VHL cells were relatively insensitive (Fig. 2F). Taken together, these results indicate that compound 47 is synthetic lethal to the loss of VHL by causing a necrotic cell death. These results also demonstrate that compound 47 acts in a manner distinct from the autophagic cell death pathway we previously described for 4-(pyridin-4-yl)-N-(m-tolyl)thiazol-2-amine.

As the hypoxia-inducible factor family of transcription factors are the best-characterized VHL targets, we next examined whether toxicity was HIF-dependent. A non-degradable, constitutively active HIF was overexpressed in RCC4/VHL cells. Two individual HIF-overexpressing clones were tested for their sensitivity to compound 47. Ectopic expression of HIF in cells with wild-type VHL sensitized these cells to compound 47 treatment, suggesting that deregulated HIF expression in VHL-deficient cells is responsible for their selective cytotoxicity to compound 47 (Fig. 2G). These data suggest that compound 47 represents a new class of drugs that function in a synthetic lethal manner to VHL mutation, preferentially targeting W-/-_-deficient cells. Furthermore, the sensitivity of RCCs that lack functional VHL to compound 47 is directly linked to the aberrant upregulation of HIF.

As the central mediator of oxygen homeostasis, HIF plays an important role in the cellular adaptation to low oxygen conditions through the regulation of genes involved in metabolism and energy production. Inactivation of VHL results in an increase in the half-life of HIF protein. In turn, HIF directs the transcription of many genes, including those involved in glucose metabolism (Fig. 8A). We hypothesized that compound 47 might have an effect on metabolic pathways, which if inhibited, would lead to necrotic cell death. This possibility, along with the increased expression of glucose transporters in W-/-_-deficient RCCs, directed us to investigate how compound 47 affects glucose metabolism. To examine whether this compound alters the rate of glycolysis in W-/-_-deficient cells, we measured the intracellular production of lactate, which is rapidly converted from pyruvate, the end-product of glycolysis. Treatment with compound 47 significantly inhibited lactate production in W-/L-deficient cells by approximately 60% compared to control-treated cells (Fig. 3A). Baseline levels of lactate production were lower in wild-type VHL cells.
compared to W-/L-deficient cells, likely due to the constitutive expression of HIF and subsequent overexpression of glucose transporters and glycolytic enzymes. However, treatment with compound 47 did not affect glycolysis in cells with wild-type VHL cells.

[0404] We then examined whether this decrease in glycolysis in response to compound 47 was due to a decrease in glucose uptake or whether compound 47 inhibited a particular glycolytic enzyme. To test this, we measured glucose uptake using 2-deoxy-D-[\textsuperscript{3}H] glucose, a non-hydrolyzable, radioactive glucose analog, following two days of treatment with compound 47. Compound 47 impaired glucose uptake in RCC4 and 786-0 cells but not in the matched isogenic cells expressing wild-type VHL (Fig. 3B and 8B). RCC4/VHL cells had lower baseline levels of glucose uptake compared to RCC4 cells and were unaffected by treatment with compound 47. Furthermore, compound 47 inhibited glucose uptake in RCC4 cells in a dose-dependent manner, but glucose levels in RCC4/VHL cells were relatively stable with increasing concentrations of compound 47 (Fig. 3C). Because the phosphorylation of glucose to glucose-6-phosphate is important for preventing glucose efflux from the cell, we asked whether compound 47 might function by inhibiting the phosphorylation of glucose by hexokinase. Hexokinase activity was inhibited by compound 47 only after three days of treatment in VHL-deficient RCC4 cells but hexokinase activity of RCC4/VHL cells with wild-type VHL was unchanged by compound 47 (Fig. 3D). Again, the baseline activity of hexokinase is higher in RCC4 cells, consistent with W-/L-deficient RCCs having higher rates of glycolysis, and that the hexokinase gene is a HIF target (Fig. 3A). The decrease in hexokinase activity occurred subsequent to changes in glucose uptake, indicating that inhibition of hexokinase is not directly responsible for the differential cytotoxicity of compound 47 in cells with and without VHL. Furthermore, inhibitors of hexokinase did not result in selective cytotoxicity to W-/L-deficient cells (data not shown). These data indicate that compound 47 decreases glycolysis by decreasing glucose transport and not by inhibiting a particular glycolytic step or enzyme per se.

[0405] To further investigate the relationship between HIF and compound 47 toxicity, we silenced HIF-1 β in RCC4 cells and assessed its affect on glucose uptake. Transiently inhibiting HIF-1 β, the constitutively expressed binding partner of HIF-1 α and HIF-2α reduces HIF activity in RCC4 cells to the levels found in wild-type VHL.
cells. Glucose uptake was insensitive to treatment with compound 47 when the HIF-1β was silenced in RCC4 cells, further supporting the concept that the HIF-dependent glucose uptake was responsible for the differential toxicity of compound 47 to W-/-/-deficient renal carcinomas (Fig. 3E).

We next investigated how a decrease in glycolysis could lead to selective necrotic cell death. One possibility is that the reduction in glycolysis lowers the availability of pyruvate, the essential precursor for the generation of acetyl-CoA. As previous studies have indicated that RCCs have decreased oxygen consumption because of constitutive HIF expression and the subsequent induction of genes, such as PDK1 and MXH, that inhibit the conversion of pyruvate to acetyl-CoA, we hypothesized that compound 47 may be inhibiting oxidative phosphorylation and the use of pyruvate. We therefore examined oxygen consumption as a marker of oxidative phosphorylation and ATP production in treated and untreated cells. While there was a difference in oxygen consumption between W-/-/-deficient and wild-type VHL cells, there was no difference in oxygen consumption between cells treated with compound 47 and those that were not treated (Fig. 3F). This finding demonstrates that the mitochondria and the oxidative pathway remain unaffected by compound 47. However, the decrease in glucose uptake in response to treatment with compound 47 in W-/-/-deficient cells results in a 75% decrease in ATP levels (Fig. 3G).

Furthermore, inhibition of ATP production in response to compound 47 treatment is dose-dependent (Fig. 3H). Taken together, these data suggest that loss of VHL is associated with reduced oxidative phosphorylation and greater dependence on glycolysis for ATP production. By disrupting glycolysis, compound 47 functions in a synthetic lethal manner to VHL mutation, ultimately killing W-/-/-deficient cells by inhibiting their primary mechanism of energy production.

These data support an emerging model that renal cells with defective VHL, like a range of other cancers, are highly dependent on aerobic glycolysis for energy production. We further examined this conditional genetic interaction of glucose dependency and VHL interaction by depriving the cells of glucose in a growth curve assay. RCC4 cells and 786-O cells lacking functional VHL were sensitive to changes in glucose levels, while the isogenically matched cells with wild-type VHL continued to grow despite the absence of glucose (Fig. 8C and Fig. 8D). Conversely, when cells were deprived of pyruvate, cells with and without VHL were
relatively unaffected. These results suggest that W-/-deficient cells are more sensitive than cells with VHL to changes in glucose. The addition of pyruvate was unable to overcome deprivation of glucose and the inhibition of glycolysis because of the increased expression of PDK and MXH that inhibit the conversion of pyruvate to acetyl-CoA. Together, these data demonstrate that W-/-deficient cells are unable to utilize oxidative phosphorylation to overcome their dependence on glycolysis for energy production.

[0408] We next wanted to investigate the differential glucose uptake between RCCs with and without VHL treated with compound 47 that subsequently lead to the selective death of W-/-deficient cells. We first examined the message levels of the two main glucose transporters, GLUT1 and GLUT2 by quantitative real-time PCR. GLUT1 is an inducible, high-affinity glucose transporter, while GLUT2 is the glucose transporter responsible for basal glucose uptake. Other family members, such as GLUT3 and GLUT4, are not expressed in renal cells. GLUT1 was highly expressed in cells lacking VHL, while cells with VHL had very low levels of GLUT1 (Fig. 3I). In contrast, GLUT2 was highly expressed in cells with wild-type VHL. Cells deficient in VHL had very low levels of GLUT2 that could barely be detected (Fig. 3J). The expression of the two different glucose transporters suggests that compound 47 kills cells with mutant VHL by inhibiting the higher affinity glucose transporter, depriving W-/L-deficient cells of glucose and consequently, energy needed to sustain the cells. In order to more directly test this, we performed binding assays to see whether compound 47 was directly interacting with GLUT1. An analog of compound 47, compound 116 was synthesized and linked to an immobilized linker (Affi-gel 10). Cell lysates from both RCC4 and RCC4/VHL were incubated with the Affi-gel-compound 47. Following washing of the resin-bound compound 47, this affinity column was eluted with several fractions of increasing salt concentration with a final elution of urea. These elution fractions were then subjected to immunoblotting for GLUT1. GLUT1 bound to compound 116, an analog of compound 47, in RCC4 cells but not RCC4/VHL cells (Fig. 3K). Importantly, GLUT1 did not bind a similarly prepared resin linked to 4-[2-[1-(6-aminohexyl)-1 H-1 ,2,3-triazol-4-yl]-4-pyridinyl]-N-(3-methylphenyl)-1 ,3-thiazol-2-amine, the compound implicated in autophagic cell death, in either RCC4 or RCC4/VHL cells, indicating the specificity of the interaction between GLUT1 and compound 47. Thus, binding of compound 47 to the high affinity glucose transporter,
GLUT1, prevents glucose uptake in W-/L-deficient cells leading to an inhibition of glycolysis and ATP production. This impairment of GLUT1 activity results in necrotic cell death in cells that lack VHL. We also investigated whether the small molecule compound 47 functioned as a kinase inhibitor. In vitro testing of a broad range of 50 different kinases demonstrated no significant decrease in any of the kinases examined (Table 2).

**Table 2**

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[0409] To determine a pharmacological structure-activity relationship (SAR), analogs of the selective cytotoxin compound 47 were synthesized and tested in a 4-day viability assay using paired RCC lines with and without VHL (See Table 1). All analogs of compound 47 that selectively killed W-/_/deficient RCCs inhibited glucose uptake, whereas all inactive analogs that did not kill W-/_/deficient cells did not inhibit glucose uptake (Fig. 4). To determine whether this assay reflected a specific inhibition of glucose uptake rather than broad toxicity, we also investigated cytotoxins that are known to act by a different mechanism. The compounds (e.g. 4-(pyridin-4-yl)-N-(m-tolyl)thiazol-2-amine), which induced VHL-dependent, HIF-independent autophagic cell death, did not decrease glucose uptake in this assay, indicating that compound 47 cytotoxicity is dependent on glucose metabolism (Table 1 and Fig. 4). These data suggest that compound 47 is specifically cytotoxic to cells that have elevated HIF levels due to their increased rate and dependence on glucose uptake and glycolysis.

[0410] The high utilization of glucose by cancer cells compared to normal cells is the basis of fluoro-deoxyglucose positron emission tomography (FDG-PET) in the diagnosis of cancer. We hypothesized that if compound 47 was functioning by inhibiting glucose uptake, we could monitor the effects of compound 47 by FDG-PET. Pre-treatment scans of animals inoculated with subcutaneous W-/_/deficient human renal cell carcinomas revealed a high glucose uptake within the tumors (Fig. 5A). Following three daily doses of compound 85, a more soluble analog of compound 47, subsequent scanning revealed a striking decrease in glucose uptake within the tumors (Fig. 5A). Despite a variation in initial tumor FDG uptake, treatment with compound 85 consistently decreased FDG uptake, suggesting that the inhibition of glucose uptake by compound 85 may lead to tumor control (Fig. 5B). Importantly, animals treated with compound 85 exhibited no normal tissue toxicity (Fig. 5C). Control animals that were given either vehicle or 4-(pyridin-4-yl)-N-(m-tolyl)thiazol-2-amine did not have a decrease in glucose uptake (data not shown). Moreover, these results demonstrate that the effectiveness of compound 47 and its analog compound 85 can be directly monitored by clinically by FDG-PET.
We next tested whether the PPBs are effective at treating tumors in a xenograft model of RCC. Daily systemic treatment of mice with W-/-/-deficient xenografts with compound 85 for ten to fourteen days markedly delayed tumor growth in two renal cell carcinoma model systems: 786-0 with a naturally occurring VHL mutation and ACHN expressing short hairpin RNA to VHL (Fig. 5D and 5E). In both of these models, treatment with compound 85 delayed tumor growth compared to tumors treated with vehicle alone. Importantly, ACHN tumors with wild-type VHL grew at similar rates as those treated with compound 85 or treated with vehicle control, indicating that compound 85 is differentially cytotoxic to tumors that have lost VHL function, a common and frequent event in renal cell carcinoma (Fig. 8A). Taken together, we have identified an agent that is selectively toxic to a particular genotype found in the vast majority of kidney cancers. Furthermore, through its mechanism of action of inhibiting glucose metabolism, we are able to follow its effectiveness with FDG-PET, a clinically utilized imaging modality.

Compound 47 represents the second class of small molecules that we have identified that selectively kill RCCs lacking functional VHL. However, compound 47 is distinct from the previous class in its mechanism of killing RCC. Compound 47 and other compounds of Formula I, IA, or II, or pharmaceutically acceptable salts thereof, act by disrupting glucose uptake and utilization. The selective cytotoxicity of this effect provides direct evidence to support an emerging model of dependence on glycolysis in many cancer cell types, including the majority of RCCs. In this model, the disruption of VHL or other regulators of HIF leads to active inhibition of mitochondrial activity through the HIF-mediated induction of PDK1, a kinase that blocks the activity of pyruvate dehydrogenase and the production of acetyl-CoA (Fig. 6). Thus, W-/-/-deficient RCCs are selectively sensitive to compound 47 because aberrant HIF stabilization results in diminished mitochondrial activity, causing these cells to become highly dependent on glucose uptake for glycolysis and ATP production. By inhibiting glucose uptake and retention, compound 47 specifically targets the Achilles’ heel of RCCs. Cells with an intact VHL pathway are not strictly dependent on glycolysis for viability and therefore insensitive to compound 47 toxicity. Our findings indicate that the differential metabolism of cancer cells can be exploited for the preferential targeting of these cells by small molecules.

Our results have a number of implications for the development of new cancer therapeutics. Firstly, our method of screening for compounds that are synthetically
lethal to the loss of VHL should be adaptable to other tumor types with distinct genotypes, such as the loss-of-function of a particular tumor suppressor gene or gain-of-function of a specific oncogene. Secondly, the selective cytotoxicity of compound 47 may not be restricted only to W-/-deficient tumors alone. It is likely that a number of other cancer types possess genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production and therefore sensitive to PPBs. This is currently an active area of research. Similarly, cells with wild-type VHL could be sensitized to compound 47 by inactivating VHL. It should also be noted that targeting GLUT1 in human renal cell cancers is feasible as Glut1 heterozygous knockout mice are viable and recapitulate the human GLUT1 deficiency syndrome, which is effectively treated by a ketogenic diet. It is important to reiterate here that we did not observe any normal tissue toxicity, including brain, in these studies. Finally, our data show that the effectiveness of compound 47 can be monitored by in vivo imaging. This property offers the potential advantages of enabling dosage optimization and more importantly, identification of which kidney cancers will respond best to compound 47 treatment in Phase I clinical trials. Being able to track the response of a particular tumor is both cost-effective and lends itself to personalized medicine, which are two of the primary objectives of future cancer therapy.

[0414] Example 153 - A Broad Range of Cancer Cells Are Sensitive to Glut1 Inhibition

[0415] A broad range of cancer types were tested and shown to be sensitive to GLUT1 inhibition. (Fig. 9.)

[0416] While some embodiments have been shown and described, various modifications and substitutions may be made thereto without departing from the spirit and scope of the invention. For example, for claim construction purposes, it is not intended that the claims set forth herein be construed in any way narrower than the literal language thereof, and it is thus not intended that exemplary embodiments from the specification be read into the claims. Accordingly, it is to be understood that the present invention has been described by way of illustration and not limitations on the scope of the claims.
WHAT IS CLAIMED:

1. A compound of Formula I:

\[
\begin{array}{c}
\text{A} \\
\text{O} \quad \text{N} \\
\text{R}_1 \quad \text{R}_2 \\
\text{3} \quad \text{4} \\
\text{R}_3 \quad \text{R}_4 \\
\text{W} \\
\text{B}
\end{array}
\]

Formula I

or a pharmaceutically acceptable salt thereof,

wherein:

A is a nitrogen-containing heteroaryl ring chosen from pyridinyl, pyrimidinyl, pyrazinyl, quinolinyl, pyrazolyl, imidazolyl, and thiazolyl, each of which is optionally substituted;

is attached to the phenyl ring at either the 3 or 4 position;

R\(_i\), R\(_2\), and R\(_3\) are each independently chosen from hydrogen, optionally substituted alkyl, and optionally substituted alkenyl;

R\(_4\) is chosen from hydrogen, hydroxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, halo, carboxy, nitro, sulfonyle, sulfinyl, and optionally substituted amino;

W is chosen from -NRSO\(_2\)-, -SO\(_2\)NR-, and -NRCO-, wherein each R is independently chosen from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, each of which, except for hydrogen, is optionally substituted; and

B is an optionally substituted aryl ring,

provided that if A is 3-pyridinyl, R\(_i\), R\(_2\), and R\(_3\) are each hydrogen, and W is -NHSO\(_2\)-, then B is not 3-methoxyphenyl, 3,4-dimethylphenyl, 2,3,4-trifluorophenyl, 2,3,5,6-tetramethylphenyl, 2,5-dimethylphenyl, 3-chlorophenyl, 3-trifluoromethylphenyl, 4-methoxyphenyl, 4-tertbutylphenyl, 4-fluorophenyl, or 4-acetylphenyl.
2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein A is chosen from 2-thiazolyl, 3-pyrazolyl, 3-quinolinyl, 5-quinolinyl, 2-pyrazinyl, 2-pyrimidinyl, 2-pyridinyl, 3-pyridinyl, and 4-pyridinyl, each of which is optionally substituted.

3. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein A is chosen from 2-thiazolyl, 3-pyrazolyl, 3-quinolinyl, 5-quinolinyl, 2-pyrazinyl, 2-pyrimidinyl, 2-pyridinyl, 3-pyridinyl, and 4-pyridinyl.

4. The compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein A is chosen from 2-pyridinyl, 3-pyridinyl, and 4-pyridinyl.

5. The compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein A is 3-pyridinyl.

6. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

\[
\begin{align*}
\text{A is } & (R_5)^n \\
\text{wherein} & \\
n & = 0, 1 \text{ or } 2; \\
\text{for each occurrence, } R_5 & \text{ is independently chosen from alkyl optionally substituted with one or more halo, alkoxy, halo, nitro, heterocycloalkyl, and amino optionally substituted with } C(O)R_a, \text{ wherein } R_a \text{ is chosen from alkyl and optionally substituted alkoxy; and} \\
X_1 & \text{ and } X_2 \text{ are each independently chosen from } N, NO, \text{ and } CH, \text{ provided that at least one of } X_1 \text{ and } X_2 \text{ is not } CH.
\end{align*}
\]

7. The compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein \( X_1 \) is \( N \) and \( X_2 \) is \( CH \).
8. The compound according to claim 6 or 7, or a pharmaceutically acceptable salt thereof, wherein for each occurrence, R5 is independently chosen from methyl, methoxy, halo, nitro, morpholino, trifluoromethyl, and NHC(O)Me.

9. The compound according to claim 6 or 7, or a pharmaceutically acceptable salt thereof, wherein n is 0.

10. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R1 is chosen from hydrogen and optionally substituted alkyl.

11. The compound according to claim 10, or a pharmaceutically acceptable salt thereof, wherein R1 is chosen from hydrogen and lower alkyl.

12. The compound according to claim 11, or a pharmaceutically acceptable salt thereof, wherein R1 is hydrogen or methyl.

13. The compound according to claim 12, or a pharmaceutically acceptable salt thereof, wherein R1 is hydrogen.

14. The compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R2 and R3 are each independently chosen from hydrogen and optionally substituted alkyl.

15. The compound according to claim 14, or a pharmaceutically acceptable salt thereof, wherein R2 is hydrogen.

16. The compound according to claim 14 or 15, or a pharmaceutically acceptable salt thereof, wherein R3 is chosen from hydrogen and lower alkyl.

17. The compound according to claim 16, or a pharmaceutically acceptable salt thereof, wherein R3 is hydrogen.
18. The compound according to any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein \( R_4 \) is chosen from hydrogen, methyl, halo, and nitro.

19. The compound according to claim 18, or a pharmaceutically acceptable salt thereof, wherein \( R_4 \) is hydrogen.

20. The compound according to any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein \( W \) is \(-\text{NRSO}_2^-\).

21. The compound according to any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein \( W \) is \(-\text{SO}_2\text{NR}^-\).

22. The compound according to any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein \( W \) is \(-\text{NRCO}^-\).

23. The compound according to any one of claims 20 to 22, or a pharmaceutically acceptable salt thereof, wherein \( R \) is chosen from hydrogen and lower alkyl.

24. The compound according to claim 23, or a pharmaceutically acceptable salt thereof, wherein \( R \) is hydrogen.

25. The compound according to any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein \( B \) is an optionally substituted phenyl ring.

26. The compound according to claim 25, or a pharmaceutically acceptable salt thereof, wherein \( B \) is phenyl optionally substituted with one or more groups chosen from halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, hydroxyl, alkoxy, aryloxy, acyl, carboxy, alkoxy carbonyl, \( \text{NO}_2 \), optionally substituted amino, and CN, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, alkoxy, and aryloxy groups may be optionally independently substituted with one or more groups chosen from halo, alkyl, hydroxyl, alkoxy, carboxy, alkoxy carbonyl, heterocycloalkyl, and optionally substituted amino.
27. The compound according to claim 26, or a pharmaceutically acceptable salt thereof, wherein B is phenyl optionally substituted with one or more groups chosen from optionally substituted amino, halo, and lower alkyl optionally substituted with optionally substituted amino, heterocycloalkyl, alkoxy, or hydroxyl.

28. The compound according to claim 27, or a pharmaceutically acceptable salt thereof, wherein B is phenyl optionally substituted with one or more groups chosen from halo, optionally substituted amino and lower alkyl optionally substituted with optionally substituted amino or heterocycloalkyl.

29. The compound according to claim 25, or a pharmaceutically acceptable salt thereof, wherein B is chosen from phenyl, 2-methylphenyl, 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 2-methoxy carbonylphenyl, 2-trifluoromethylphenyl, 2-cyanophenyl, 3-aminophenyl, 3-methoxyphenyl, 3-methylphenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-trifluoromethylphenyl, 1,1'-butylphenyl, 1-ethynylphenyl, 3-cyanophenyl, 3-nitrophenyl, 3-phenylphenyl, 3-(2-pyrimidinyl)phenyl, 3-(1-methyl-1/-/-pyrazol-3-yl)phenyl, 3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl, 3-(5-methyl-1,2,4-oxadiazol-2-yl)phenyl, 3-(2-methyl-1,3-thiazol-4-yl)phenyl, 4-aminophenyl, 4-methoxyphenyl, 4-butoxyphenyl, 4-phenoxyphenyl, 4-methylphenyl, 4-propylphenyl, 4-tert-butylphenyl, 4-(1-adamantyl)phenyl, 4-(3-chloro-1-adamantyl)phenyl, 4-methoxycarbonylphenyl, 4-acetamidophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-iodophenyl, 4-trifluoromethoxyphenyl, 4-methoxy carbonylphenyl, 4-acetylphenyl, 4-trifluoromethylphenyl, 4-cyanophenyl, 4-nitrophenyl, 4'-methoxy[1,1'-biphenyl]-4-yl, 4'-methyl[1,1'-biphenyl]-4-yl, 4'-fluoro[1,1'-biphenyl]-4-yl, 4'-chloro[1,1'-biphenyl]-4-yl, 4-(2-pyrimidinyl)phenyl, 4-(1/-/-pyrazol-1-yl)phenyl, 4-(2-methyl-1,3-thiazol-4-yl)phenyl, 4-(1,3-oxazol-5-yl)phenyl, 3,4-dimethoxyphenyl, 3-tert-butyl-4-methoxyphenyl, 2,3,4,5,6-pentamethylphenyl, 2,4-dimethylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 3-fluoro-4-methylphenyl, 3-chloro-2-methylphenyl, 3-chloro-4-methylphenyl, 3,4-dichlorophenyl, 3-cyano-4-fluorophenyl, 2-naphthalenyl, 5-(dimethylamino)-2-naphthalenyl, 2,3-dihydro-5-indenyl, 2-(dimethylamino)-2,3-dihydro-5-indenyl, 4-(4-methylpiperazin-1-yl)phenyl, 4-(dimethylamino)methylphenyl, 4-(diethylamino)methylphenyl, 4-(dipropylamino)methylphenyl, 4-(1-pyrrolidinylmethyl)phenyl, 4-(1-
The compound according to claim 29, or a pharmaceutically acceptable salt thereof, wherein B is chosen from 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-(2-pyrimidinyl)phenyl, 3-(1-methyl-1/-/-pyrazol-3-yl)phenyl, 3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl, 3-(5-methyl-1,2,4-oxadiazol-2-yl)phenyl, 4-butoxyphenyl4-tert-butylphenyl, 4-(2-pyrimidinyl)phenyl, 3,4-dimethoxyphenyl, 3-tert-butyl-4-methoxyphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 3-fluoro-4-methylphenyl, 3-chloro-4-methylphenyl, 2-(dimethylamino)-2,3-dihydro-5-indeneyl, A-(A-
morpholinylmethyl)phenyl, 4-(1-azepanylmethyl)phenyl, A-(A-
morpholinylmethyl)phenyl, 4-(4-methoxy-1-piperidinyl)methylphenyl, 4-(4-methyl-1-piperazinyl)methylphenyl, 4-(3-hydroxypropyl)phenyl, 3-morpholinophenyl, A-(A-
morpholinylmethyl)phenyl, 4-(4-methoxy-1-piperidinyl)methylphenyl, 4-(4-methyl-1-
piperazinyl)methylphenyl, 4-(3-hydroxypropyl)phenyl, 3-morpholinophenyl, A-
morpholinophenyl, (i-
piperidinyl)phenyl, (4-methoxy-1-piperidinyl)phenyl, (21-
aminopiperidinyl)propyl]phenyl, 4-(4-methoxy-1-piperidinyl)phenyl, (21-
amino-4,7,1 0,1 3,1 6,1 9-hexaoxahenicos-1-y)phenyl, [3-(4-
morpholinyl)propyl]amino]phenyl, 3-(4-methyl-1-piperazinyl)phenyl, 4-
(3-
hydroxypropyl)phenyl, 3-(4-methyl-1-piperazinyl)phenyl, 4-
(3-
hydroxypropyl)phenyl, 3-(propionylamino)phenyl, and 3-
(acryloylamino)phenyl.

The compound according to claim 1, or a pharmaceutically acceptable salt thereof selected from

4-(Phenylsulfonamidomethyl)-N-(pyridin-2-yl)benzamide;
4-(Phenylsulfonamidomethyl)-N-(pyridin-3-yl)benzamide;
4-(Phenylsulfonamidomethyl)-N-(pyridin-4-yl)benzamide;
4-(Phenylsulfonamidomethyl)-N-(thiazol-2-yl)benzamide;
4-(Phenylsulfonamidomethyl)-N-(7/-/-pyrazol-3-yl)benzamide;
4-(Phenylsulfonamidomethyl)-N-(quinolin-3-yl)benzamide;
4-(Phenylsulfonamidomethyl)-N-(quinolin-5-yl)benzamide;
4-(Phenylsulfonamidomethyl)-N-(pyrazin-2-yl)benzamide;
4-(Phenylsulfonamidomethyl)-N-(pyrimidin-2-yl)benzamide;
4-((2-Methylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((2-Fluorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((2-Chlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((2-Bromophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
Methyl 2-(N-(4-(Pyridin-3-ylcarbamoyl)benzyl)sulfamoyl)benzoate;
N-(Pyridin-3-yl)-4-((2-(trifluoromethyl)phenylsulfonamido)methyl)benzamide;
4-((2-Cyanophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3-Aminophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3-Methylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3-Fluorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3-Bromophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3-Cyanophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3-Nitrophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Aminophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Butoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Phenoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Methylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Aminophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Butoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Phenoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Methylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Propylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-(1-Adamantyl)phenyl)sulfonyl)amino)methyl]-N-(3-pyridinyl)benzamide;
4-((4-(3-Chloro-1-adamantyl)phenyl)sulfonyl)amino)methyl]-N-(3-pyridinyl)benzamide;
Methyl 3-{4-[(3 Pyridinylamino)carbonyl]benzyl}amino)sulfonyl]phenyl}
propanoate;
4-((4-Ac θ tamidophenylsulfonamido)methyl)- Ν′-(pyridin-3-yl)b θ nzamid θ;
4-((4-Chlorophenylsulfonamido)methyl)- Ν′-(pyridin-3-yl)b θ nzamid θ;
4-((4-Bromophenylsulfonamido)methyl)- Ν′-(pyridin-3-yl)b θ nzamid θ;
Λ-(Pyridin-3-yl)-4-((4-(trifluoromethoxy)phenylsulfonamido)methyl)b θ nzamid θ;
Methyl 4-((4-Ac θ θ tamidophenylsulfonamido)methyl)- Ν′-(pyridin-3-yl)b θ nzamid θ;
Λ-(Pyridin-3-yl)-4-((4-(trifluoromethyl)phenylsulfonamido)methyl)b θ nzamid θ;
4-((4-Cyanophenylsulfonamido)methyl)- Ν′-(pyridin-3-yl)b θ nzamid θ;
4-((4-Nitrophenylsulfonamido)methyl)- Ν′-(pyridin-3-yl)b θ nzamid θ;
4-((Biphenyl-4-ylsulfonamido)methyl)- Ν′-(pyridin-3-yl)b θ nzamid θ;
4-((4′-Methoxy[1',1'-biphenyl]-4-yl)sulfonyl]amino)methyl)Λ-(3-pyridinyl)b θ nzamid θ;
4-((4′-Methyl[1',1'-biphenyl]-4-yl)sulfonyl]amino)methyl)- Ν′-(3-pyridinyl)b θ nzamid θ;
4-((4′-Fluoro[1',1'-biphenyl]-4-yl)sulfonyl]amino)methyl)- Ν′-(3-pyridinyl)b θ nzamid θ;
4-((4′-Chloro[1',1'-biphenyl]-4-yl)sulfonyl]amino)methyl)- Ν′-(3-pyridinyl)b θ nzamid θ;
4-[(4′-(2-Pyrimidinyl)phenyl)sulfonyl]amino)methyl]- Ν′-(3-pyridinyl)b θ nzamid θ;
4-((3,4-Dimethoxyphenylsulfonamido)methyl)- Ν′-(3-pyridinyl)b θ nzamid θ;
4-((3,4-Dimethylphenylsulfonamido)methyl)- Ν′-(3-pyridinyl)b θ nzamid θ;
4-((3,5-Dimethylphenylsulfonamido)methyl)- Ν′-(3-pyridinyl)b θ nzamid θ;
4-((3-Fluoro-4-methylphenylsulfonamido)methyl)- Ν′-(3-pyridinyl)b θ nzamid θ;
4-((3-Chloro-2-methylphenylsulfonamido)methyl)- Ν′-(3-pyridinyl)b θ nzamid θ;
4-((3-Chloro-4-methylphenylsulfonamido)methyl)- Ν′-(3-pyridinyl)b θ nzamid θ;
4-((3,4-Dichlorophenylsulfonamido)methyl)- Ν′-(3-pyridinyl)b θ nzamid θ;
4-((3-Cyano-4-fluorophenylsulfonamido)methyl)- Ν′-(3-pyridinyl)b θ nzamid θ;
4-((Naphthal θne-2-sulfonamido)methyl)- Ν′-(3-pyridinyl)b θ nzamid θ;
4-((5-Dimethylamino)naphthal θne-1 -sulfonamido)methyl)- Ν′-(pyridin-3-yl)b θ nzamid θ;
4-((2,3-Dihydro-1 θ ind θne-5-sulfonamido)methyl)- Ν′-(pyridin-3-yl)b θ nzamid θ;
4-((2-(Dimethylamino)-2,3-dihydro-1H-indene-5-sulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-(4-Methylpiperazin-1-yl)phenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-[(4-[(Dimethylamino)methyl]phenyl)sulfonylamino]methyl-N-(3-pyridinyl)benzamide;
4-[(4-[(Diethylamino)methyl]phenyl)sulfonylamino]methyl-N-(3-pyridinyl)benzamide;
4-[(4-[(Dipropylamino)methyl]phenyl)sulfonylamino]methyl-N-(3-pyridinyl)benzamide;
4-[(4-[(1-Pyrrolidinylmethyl)phenyl]sulfonylamino)methyl]-(3-pyridinyl)benzamide;
4-[(4-[(1-Piperidinylmethyl)phenyl]sulfonylamino)methyl]-(3-pyridinyl)benzamide;
4-[(4-[(1-Azepanylmethyl)phenyl]sulfonylamino)methyl]-(3-pyridinyl)benzamide;
4-[(4-[4-(1-Morpholinylmethyl)phenyl]sulfonylamino)methyl]-(3-pyridinyl)benzamide;
4-[(4-[(4-Methoxy-1-piperidinyl)methyl]phenyl)sulfonylamino]methyl]-N-(3-pyridinyl)benzamide;
4-[(4-[(4-Methyl-1-piperazinyl)methyl]phenyl)sulfonylamino]methyl]-N-(3-pyridinyl)benzamide;
4-([4-(4-ferf-Butylphenylsulfonamido)methyl]-N-methyl-N-(pyridin-3-yl)benzamide;
4-((4-ferf-Butylphenylsulfonamido)methyl)-N-methyl- (4-pyridinyl)benzamide;
3,5-Dimethyl-N-(4-(pyridin-3-ylcarbamoyl)benzyl)benzamide;
3,4-Dimethoxy-N-(4-(pyridin-3-ylcarbamoyl)benzyl)benzamide;
4-[(4-[(3-(Methyloxy)-1-propynyl)phenyl]sulfonylamino)methyl]-N-(3-pyridinyl)benzamide;
4-((2-(Dimethylamino)-2,3-dihydro-1H-indene-5-sulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-\(\text{[(4-(21-Amino-4,7,10,13,16,19-hexaoxahenicos-1-yn-1-yl)phenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(3-pyridinyl)b θ nzamid θ;
4-\(\text{[(4-(3-Methoxypropyl)phenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(3-pyridinyl)b θ nzamid θ;
4-\(\text{[(4-(1-benzyl-1H-1,2,3-triazol-4-yl)phenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(3-pyridinyl)benzamide;
4-\(\text{[(4-(3-Hydroxy-1-propynyl)phenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(3-pyridinyl)benzamide;
4-\(\text{[(4-tolf-Butylphenyl)sulfonylamido} \)methyl\( \text{-} \)N-(4-pyridinyl)b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(5-methyl-3-pyridinyl)b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(2-methyl-3-pyridinyl)b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(6-methyl-3-pyridinyl)b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(6-methoxy-3-pyridinyl)b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(6-chloro-3-pyridinyl)b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(4-chloro-3-pyridinyl)b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(2-chloro-3-pyridinyl)b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(4-methyl-3-pyridinyl)b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(5-chloro-3-pyridinyl)b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(2-nitro-3-pyridinyl)b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-[6-(4-morpholinyl)-3-pyridinyl]b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-[6-(thfluoromethyl)-3-pyridinyl]b θ nzamid θ;
\(\text{N-}[6-(Acetylamino)-3-pyridinyl]-4-(\text{[(4-tolf-}
\text{butylphenyl)sulfonyl]amino} \)methyl)b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(6-fluoro-3-pyridinyl)b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(5-fluoro-3-pyridinyl)b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-[4-(thfluoromethyl)-3-pyridinyl]b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(2-fluoro-3-pyridinyl)b θ nzamid θ;
4-\(\text{[(4-tolf-Butylphenyl)sulfonyl]amino} \)methyl\( \text{-} \)N-(4-methoxy-3-pyridinyl)b θ nzamid θ;
\(\text{N-}[6-(Bromo-3-pyridinyl)]-4-(\text{[(4-tolf-}
\text{butylphenyl)sulfonyl]amino} \)methyl)b θ nzamid θ;
4-[[[3-(4-Morpholinyl)phenyl]sulfonyl]amino]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[3-(4-Morpholinyl)phenyl]sulfonyl]amino]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[4-(1-Piperidinyl)phenyl]sulfonyl]amino]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[4-(1-Piperidinyl)phenyl]sulfonyl]amino]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[3-(4-Methyl-1-piperazinyl)phenyl]sulfonyl]amino]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[3'-[trifluoromethyl][1',1'-biphenyl]-4-yl]sulfonyl]amino]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[4-Benzylphenyl]sulfonyl]amino]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[4-tol-Butylphenyl]sulfonyl](methyl)amino]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[4-tol-Butylphenyl]sulfonyl](ethyl)amino]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[4-tol-Butylphenyl]sulfonyl](propyl)amino]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[4-[3-(Acryloylamino)phenyl]sulfonyl]amino]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[4-tol-Butylphenyl]sulfonyl](anilino)sulfonyl]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[3-(4-Morpholinyl)phenyl]sulfonyl]amino]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[3-(4-Morpholinyl)phenyl]sulfonyl]amino]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[4-tol-Butylphenyl]sulfonyl](anilino)sulfonyl]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[3-(Propionylamino)phenyl]sulfonyl]amino]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[3-(Acryloylamino)phenyl]sulfonyl]amino]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[[[4-tol-Butylphenyl]sulfonyl](anilino)sulfonyl]methyl]-2-methyl-\textit{N}-(3-pyridinyl)benzamide;
4-[[[4-tol-Butylphenyl]sulfonyl](anilino)sulfonyl]methyl]-2-fluoro-\textit{N}-(3-pyridinyl)benzamide;
4-[[[4-tol-Butylphenyl]sulfonyl](anilino)sulfonyl]methyl]-3-methyl-\textit{N}-(3-pyridinyl)benzamide;
4-[[[4-tol-Butylphenyl]sulfonyl](anilino)sulfonyl]methyl]-3-fluoro-\textit{N}-(3-pyridinyl)benzamide;
4-(1-[[[4-tol-Butylphenyl]sulfonyl]amino]ethyl)-\textit{N}-(3-pyridinyl)benzamide;
4-[[anilinosulfonyl]methyl]-\textit{N}-(3-pyridinyl)benzamide;
4-[(4-fluoroanilino)sulfonyl]methyl}-N-(3-pyridinyl)benzamide;
4-[(4-fluoroanilino)sulfonyl]methyl}-N-(3-pyridinyl)bNZamidθ;  
4-((4-(1-(4-(1-{((4-tοrt-butyl)phenyl}sulfonamido)methyl)-2-methyl-N-(pyridin-3-yl)bθNZamidθ; 
4-((4-(1-{((4-tοrt-butyl)phenyl}sulfonamido)methyl)-2-fluoro-N-(pyridin-3-yl)bθNZamidθ; 
4-((4-(1-{((4-tοrt-butyl)phenyl}sulfonamido)methyl)-3-fluoro-N-(pyridin-3-yl)bθNZamidθ; 
4-((4-(1-{((4-tοrt-butyl)phenyl}sulfonamido)methyl)-3-nitro-N-(pyridin-3-yl)bθNZamidθ; 
4-1-(4-{((4-tοrt-butyl)phenyl}sulfonamido)θthyl)-N-(pyridin-3-yl)bθNZamidθ; 
4-(N-phenylsulfamoylmethyl)-N-(pyridin-3-yl)benzamide; 
4-((N-(4-fluorophenyl)sulfamoyl)methyl)-N-(pyridin-3-yl)benzamide; 
4-((N-(4-tert-butyl)phenyl)sulfamoyl)methyl)-N-(pyridin-3-yl)benzamide; 
4-((N-(4-methylpiperazin-1-yl)phenyl)sulfamoyl)methyl)-N-(pyridin-3-yl)bθNZamidθ, or a pharmaceutically acceptable salt thereof.

32. A pharmaceutical composition comprising at least one compound of Formula IA:

or a pharmaceutically acceptable salt thereof, wherein:

A is a nitrogen-containing heteroaryl ring chosen from pyridinyl, pyrimidinyl, pyrazinyl, quinolinyl, pyrazolyl, imidazolyl, and thiazolyl, each of which is optionally substituted;

-\[H_{\text{R}_1}\] is attached to the phenyl ring at either the 3 or 4 position;

R\text{i, } R_2, \text{ and } R_3 \text{ are each independently chosen from hydrogen, optionally substituted alkyl, and optionally substituted alkenyl; }

R_4 \text{ is chosen from hydrogen, hydroxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted cycloalkyl, }


substituted heteroaryl, halo, carboxy, nitro, sulfonyl, sulfinyl, and optionally substituted amino;

W is chosen from -NRSO₂⁻, -SO₂NR⁻, and -NRCO⁻, wherein each R is independently chosen from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, each of which, except for hydrogen, is optionally substituted; and

B is an optionally substituted aryl ring,

and at least one pharmaceutically acceptable carrier.

33. A method for treating a disease mediated by HIF-1α and/or HIF-2α, said method comprising administering to a subject at least one compound of any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof or at least one compound chosen from

4-((3-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
4-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
3-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
N-(pyridin-3-yl)-3-((2,3,4-thfluorophenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,3,4-thfluorophenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-3-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-3-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
3-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3-Chlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
N-(Pyridin-3-yl)-4-((3-(trifluoromethyl)phenylsulfonamido)methyl)benzamide,
4-((4-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
3-((4-tert-Butylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
4-((4-Fluorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, and
4-((4-Acetylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, or a pharmaceutically acceptable salt thereof.

34. The method of claim 33, wherein said disease is cancer or Von Hippel Lindau syndrome.
35. A method of targeting cells which express HIF-1α and/or HIF-2α. Said method comprising contacting cells with at least one compound of any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof or at least one compound selected from

4-((3-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
4-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
3-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
N-(pyridin-3-yl)-3-((2,3,4-thfluorophenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,3,4-thfluorophenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-3-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
3-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3-Chlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
N-(Pyridin-3-yl)-4-((3-(trifluoromethyl)phenylsulfonamido)methyl)benzamide,
4-((4-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
3-((2,3,4-thfluorophenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-3-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
3-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Acetylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, or a pharmaceutically acceptable salt thereof.

36. A method for treating a disease mediated by defective pVHL protein, said method comprising administering to a subject at least one compound of any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt thereof or at least one compound selected from

4-((3-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
4-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
3-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
N-(pyridin-3-yl)-3-((2,3,4-thfluorophenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,3,4-thfluorophenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-3-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
3-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3-Chlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, N-(Pyridin-3-yl)-4-((3-(trifluoromethyl)phenylsulfonamido)methyl)b θ nzamid θ,
4-((4-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, 3-((4-tethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, 4-((4-Fluorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, and 4-((4-Acetylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, or a pharmaceutically acceptable salt thereof.

37. A method for treating a disease mediated by defective pVHL protein, comprising administering to a subject at least one compound of any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof or at least one compound selected from 4-((3-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, 4-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide; 3-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide; N-(pyridin-3-yl)-3-((2,3,4-thluorophenylsulfonamido)methyl)benzamide; N-(pyridin-3-yl)-4-((2,3,4-thluorophenylsulfonamido)methyl)benzamide; N-(pyridin-3-yl)-3-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide; N-(pyridin-3-yl)-4-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide; 4-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide; 4-((3-Chlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, N-(Pyridin-3-yl)-4-((3-(trifluoromethyl)phenylsulfonamido)methyl)benzamide, 4-((4-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, 3-((4-tethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, 4-((4-Fluorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, and 4-((4-Acetylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, or a pharmaceutically acceptable salt thereof, wherein said compound or pharmaceutically acceptable salt is specifically cytotoxic to cells that have elevated HIF levels due to their increased rate and dependence on glucose uptake and glycolysis.

38. The method of claim 37, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, selectively disrupts glucose uptake and utilization in the subject.
39. The method of claim 37 or 38, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, inhibits HIF-mediated induction of PDK1.

40. A method of targeting cells which have defective pVHL protein, said method comprising contacting cells with at least one compound of any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof or at least one compound selected from

4-((3-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
4-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
3-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
N-(pyridin-3-yl)-3-((2,3,4-thfluorophenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,3,4-thfluorophenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-3-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
3-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3-Chlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
N-(Pyridin-3-yl)-4-((3-(trifluoromethyl)phenylsulfonamido)methyl)benzamide,
4-((4-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
3-((4-tert-Butylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
4-((4-Fluorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, and
4-((4-Acetylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, or a pharmaceutically acceptable salt thereof.

41. The method of claim 40, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, selectively disrupts glucose uptake and utilization in the cells.

42. The method of claim 40 or 41, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, inhibits HIF-mediated induction of PDK1.

43. A method for selectively killing cells which have defective pVHL protein comprising contacting cells with at least one compound of any one of claims 1 to 31,
or a pharmaceutically acceptable salt thereof or at least one compound selected from
4-((3-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
4-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
3-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
N-(pyridin-3-yl)-3-((2,3,4-thfluorophenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,3,4-thfluorophenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-3-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
3-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3-Chlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
N-(Pyridin-3-yl)-4-((3-(trifluoromethyl)phenylsulfonamido)methyl)benzamide,
4-((4-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
3-((4-tert-Butylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
4-((4-Fluorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
4-((4-Acetylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
or a pharmaceutically acceptable salt thereof,
wherein said at least one compound, or a pharmaceutically acceptable salt thereof,
is capable of targeting cells having defective pVHL protein and killing said selected cells.

44. The method of claim 43, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, selectively disrupts glucose uptake and utilization in the cells.

45. The method of claim 43, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, inhibits HIF-mediated induction of PDK1.

46. A method for treating a disease mediated by HIF-1α and/or HIF-2α comprising administering to a subject at least one compound of any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof or at least one compound selected from
4-((3-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
4-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
3-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
N-(pyridin-3-yl)-3-((2,3,4-trifluorophenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,3,4-trifluorophenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-3-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
3-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3-Chlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
3-((4-tert-Butylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Fluorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((4-Acetylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, or a pharmaceutically acceptable salt thereof,
wherein said at least one compound, or a pharmaceutically acceptable salt thereof is specifically cytotoxic to cells that have elevated HIF levels due to their increased rate and dependence on glucose uptake and glycolysis.

47. The method of claim 46, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, selectively disrupts glucose uptake and utilization in the subject.

48. The method of claim 46, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, inhibits HIF-mediated induction of PDK1.

49. A method for treating a disease mediated by cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production, comprising administering to a subject at least one compound of any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof or at least one compound selected from
4-((3-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
3-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
N-(pyridin-3-yl)-3-((2,3,4-thfluorophenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,3,4-trifluorophenylsulfonamido)methyl)benzamide;  
N-(pyridin-3-yl)-3-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;  
3-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;  
4-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;  
4-((3-Chlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,  
4-((4-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,  
3-((4-t-Butylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,  
4-((4-Fluorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,  
and  
4-((4-Acetylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, or a pharmaceutically acceptable salt thereof,  
wherein said at least one compound, or a pharmaceutically acceptable salt thereof, is specifically cytotoxic to cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production.

50. A method for selectively killing cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production, comprising contacting the cells with at least one compound of any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof or at least one compound selected from  
4-((3-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,  
4-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;  
3-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;  
N-(pyridin-3-yl)-3-((2,3,4-thfluorophenylsulfonamido)methyl)benzamide;  
N-(pyridin-3-yl)-4-((2,3,4-thfluorophenylsulfonamido)methyl)benzamide;  
N-(pyridin-3-yl)-3-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;  
N-(pyridin-3-yl)-4-((2,3,5,6-tetramethylphenylsulfonamido)methyl)benzamide;  
3-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;  
4-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;  
4-((3-Chlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,  
N-(Pyridin-3-yl)-4-((3-(trifluoromethyl)phenylsulfonamido)methyl)benzamide,  
4-((4-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,  
3-((4-t-Butylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,  
4-((4-Acetylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,  
3-((4-t-Butylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
4-((4-Fluorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, and
4-((4-Acetylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, or a pharmaceutically acceptable salt thereof,
wherein said at least one compound, or a pharmaceutically acceptable salt thereof,
is specifically cytotoxic to cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production.

51. The method of claim 50, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, selectively disrupts glucose uptake and utilization in cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production.

52. A method for treating a disease mediated by GLUT1, said method comprising administering to a subject at least one compound of any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof or at least one compound selected from
4-((3-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
4-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
3-((3,4-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
N-(pyridin-3-yl)-3-((2,3,4-thflurophenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,3,4-thfluorophenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-3-((2,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
N-(pyridin-3-yl)-4-((2,5,6-tetramethylphenylsulfonamido)methyl)benzamide;
3-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((2,5-dimethylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide;
4-((3-Chlorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
N-(Pyridin-3-yl)-4-((3-(trifluoromethyl)phenylsulfonamido)methyl)benzamide,
4-((4-Methoxyphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
3-((4-tert-Butylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide,
4-((4-Fluorophenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, and
4-((4-Acetylphenylsulfonamido)methyl)-N-(pyridin-3-yl)benzamide, or a pharmaceutically acceptable salt thereof.
53. The method of claim 52, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, selectively disrupts glucose uptake and utilization in the subject.

54. The method of claim 52 or 53, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, inhibits glucose transport by GLUT1.

55. A method of identifying a compound as a candidate cancer therapy, comprising exposing a first population of cells that have elevated expression of GLUT1 but not GLUT2 to a test compound and assaying cytotoxicity of the test compound, exposing a second population of cells that have elevated expression of GLUT2 but not GLUT1 to the test compound and assaying cytotoxicity of the test compound, and identifying the test compound as a candidate cancer therapy if the test compound induces significantly higher cytotoxicity in the first population of cells than in the second population of cells.

56. A compound identified by the method of claim 55.

57. A method of targeting cells which have defective pVHL protein said method comprising contacting cells with at least one compound, or a pharmaceutically acceptable salt thereof, capable of targeting cells which have defective pVHL protein.

58. The method of claim 57, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, selectively disrupts glucose uptake and utilization in the cells but does not selectively induce autophagy in the cells.

59. The method of claim 57, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, inhibits HIF-mediated induction of PDK1.

60. A method for selectively killing cells which have defective pVHL protein comprising contacting cells with at least one compound, or a pharmaceutically acceptable salt thereof, capable of targeting cells having defective pVHL protein and killing said selected cells.
61. The method of claim 60, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, selectively disrupts glucose uptake and utilization in the cells but does not selectively induce autophagy in the cells.

62. The method of claim 60, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, inhibits HIF-mediated induction of PDK1.

63. A method for treating a disease mediated by HIF-1α and/or HIF-2α comprising administering to a subject at least one compound, or a pharmaceutically acceptable salt thereof, that is specifically cytotoxic to cells that have elevated HIF levels due to their increased rate and dependence on glucose uptake and glycolysis.

64. The method of claim 63, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, selectively disrupts glucose uptake and utilization in the subject but does not selectively induce autophagy in the subject.

65. The method of claim 63, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, inhibits HIF-mediated induction of PDK1.

66. A method for treating a disease mediated by cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production, comprising administering to a subject at least one compound, or a pharmaceutically acceptable salt thereof, that is specifically cytotoxic to cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production.

67. A method for selectively killing cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production, comprising administering to the cells at least one compound, or a pharmaceutically acceptable salt thereof, that is specifically cytotoxic to cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production.
68. The method of claim 67, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, selectively disrupts glucose uptake and utilization in cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production but does not selectively induce autophagy in the cells.

69. A method for treating a disease mediated by GLUT1, comprising administering to a subject at least one compound, or a pharmaceutically acceptable salt thereof, that is specifically cytotoxic to cells that have elevated GLUT1 levels due to their increased rate and dependence on glucose uptake and glycolysis.

70. The method of claim 69, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, selectively disrupts glucose uptake and utilization in the subject but does not selectively induce autophagy in the subject.

71. The method of any one of claims 69, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, inhibits glucose transport by GLUT1.

72. A method for treating a disease mediated by defective pVHL protein, comprising administering to a subject at least one compound or pharmaceutically acceptable salt which is specifically cytotoxic to cells that have elevated HIF levels due to their increased rate and dependence on glucose uptake and glycolysis.

73. The method of claim 72, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, selectively disrupts glucose uptake and utilization in the subject.

74. The method of claim 72 or 73, wherein the at least one compound, or a pharmaceutically acceptable salt thereof, inhibits HIF-mediated induction of PDK1.
Fig. 1D

- RCC4
- RCC4/VHL

Hexokinase Activity

Time (Hours)

Fig. 1E

- Glucose Uptake
- Hexokinase

Control

47

28

70

92

85

Active Analogs

Inactive

Compound A

Compound C
Fig. 5C

Fig. 5D

786-O

Tumor Volume (mm³)

Days of Treatment

Fig. 5E

ACHN + shVHL

Tumor Volume (mm³)

Days of Treatment
VHL

HIF-1α

compounds

HIF-1β

Glucose Transporters
(ie Glut1)

Glucose Retention
(ie Hexokinase)

Oxygen Consumption

Glycolysis

PDK1

Pyruvate

Fig. 6
Fig. 7D

![Flow cytometry plots for Propidium Iodide vs Annexin V showing different days: control, Day 1, Day 2, Day 3.](image)

Fig. 7E

![Western blot for Phospho-p53 and Total p53 in RCC4 and RCC4/VHL.](image)
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/33 (2010.01)
USPC - 514/183

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)
IPC(8)- A61K 31/33 (2010.01)
USPC: 514/183

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8)- A61K 31/33 (2010.01)
USPC- 514,34,403,183,359; 548/100,335 1

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST: PGPB, USPT, EPAB, JPAB; Thomson Innovation; SureChem; GoogleScholar; Dialog
Renal cell carcinoma, Von Hippel Lindau protein (pVHL), Phenylsulfonylamidomethyl pyridin benzamide, arylsulamides, aryl sulfonamides, Von Hippel Lindau protein, (pVHL)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>This document can be viewed by entering the doc number at the following url: <a href="http://ep.espacenet.com/numberSearch?locale=en_EP">http://ep.espacenet.com/numberSearch?locale=en_EP</a></td>
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Further documents are listed in the continuation of Box C.

* Special categories of cited documents
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
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Date of the actual completion of the international search: 30 November 2010 (30.11.2010)
Date of mailing of the international search report: 29. DEC 2010

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PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/2 10 (second sheet) (July 2009)
INTERNATIONAL SEARCH REPORT

Observations where certain claims were found unsearchable

(Continuation of item 2 of first sheet)

<table>
<thead>
<tr>
<th>Box No. II</th>
<th>Observations where certain claims were found unsearchable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Claims Nos because they relate to subject matter not required to be searched by this Authority, namely</td>
</tr>
<tr>
<td>2</td>
<td>Claims Nos because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically</td>
</tr>
<tr>
<td>3</td>
<td>Claims Nos 10-30, 33-54 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)</td>
</tr>
</tbody>
</table>

Observations where unity of invention is lacking

(Continuation of item 3 of first sheet)

<table>
<thead>
<tr>
<th>Box No. III</th>
<th>Observations where unity of invention is lacking</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims</td>
</tr>
<tr>
<td>2</td>
<td>As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees</td>
</tr>
<tr>
<td>3</td>
<td>As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos</td>
</tr>
<tr>
<td>4</td>
<td>No required additional search fees were timely paid by the applicant Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos 1-4 and 31, restricted to the first compound of claim 31</td>
</tr>
</tbody>
</table>

Remark on Protest

<table>
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<tr>
<th>Box No. IV</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee</td>
</tr>
<tr>
<td>2</td>
<td>The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation</td>
</tr>
<tr>
<td>3</td>
<td>No protest accompanied the payment of additional search fees</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2009)
Continued from Box III

Group III, claims 55-56, 69-71, drawn to a method of identifying a compound as a candidate cancer therapy by exposing a first population of cells that have elevated expression of GLUT1 but not GLUT2 to a test compound and assaying cytotoxicity of the test compound, exposing a second population of cells that have elevated expression of GLUT2 but not GLUT1 to the test compound and assaying cytotoxicity of the test compound, and identifying the test compound as a candidate cancer therapy if the test compound induces significantly higher cytotoxicity in the first population of cells than in the second population of cells, and using a compound identified by said method.

Group IV, claims 57-65, 72-74, drawn to a method of targeting cells which have defective pVHL protein by contacting cells with at least one compound, or a pharmaceutically acceptable salt thereof, capable of targeting cells which have defective pVHL protein.

Group V, claims 66-68, drawn to a method for treating a disease mediated by cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production, comprising administering to a subject at least one compound, or a pharmaceutically acceptable salt thereof, that is specifically cytotoxic to cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production.

The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions of Group I-V do not include the inventive concept of a pharmaceutical composition comprising a compound of Formula I, as required by Group II.

The inventions of Groups I-, II, IV-V do not include the inventive concept of a method of identifying a compound as a candidate cancer therapy by exposing a first population of cells that have elevated expression of GLUT1 but not GLUT2 to a test compound and assaying cytotoxicity of the test compound, exposing a second population of cells that have elevated expression of GLUT2 but not GLUT1 to the test compound and assaying cytotoxicity of the test compound, and identifying the test compound as a candidate cancer therapy if the test compound induces significantly higher cytotoxicity in the first population of cells than in the second population of cells, as required by Group III.

The inventions of Groups I-, II, III and V do not include the inventive concept of a method of targeting cells which have defective pVHL protein, said method comprising contacting cells with at least one compound, or a pharmaceutically acceptable salt thereof, capable of targeting cells which have defective pVHL protein, as required by Group IV.

The inventions of Groups I-, IV-V do not include the inventive concept of a method for treating a disease mediated by cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production, comprising administering to a subject at least one compound, or a pharmaceutically acceptable salt thereof, that is specifically cytotoxic to cells comprising genetic or epigenetic alterations that make them highly dependent on aerobic glycolysis for energy production, as required by Group V.

The inventions of Group I-V and II share the technical feature of compound of Formula I. However, this shared technical feature does not represent a contribution over prior art. Specifically, PubChem entry CID 24538156 (2008-02-29) [Retrieved from the Internet 4 October 2010 <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cs=24538156&loc=ec_rsc>] discloses 4-[[4-acetylphenyl)sulfonylamino][3-methyl]-N-pyrindin-2-ylbenzam ide, which is the compound wherein A is pyridine, R1, R2, R3 and R4 are H, W is NH-S(02) and B is C(CH3 substituted ary1) (as defined in the instant Specification in para0055) such that Rb is alkyl). As said compound of Formula I was known at the time of the invention, this cannot be considered a special technical feature that would otherwise unite the groups.

The special technical feature of the inventions listed as Group I-V is the specific compound recited therein. The inventions do not share a special technical feature, because the common structural core shared by the compounds, i.e. Formula I was known in the art at the time of the invention, as evidenced by PubChem entry CID 24538156 that discloses a compound of Formula I 4-[[4-acetylphenyl)sulfonylamino][3-methyl]-N-pyrindin-2-ylbenzam ide, which is the compound wherein A is pyridine, R1, R2, R3 and R4 are H, W is NH-S(02) and B is C(CH3 substituted ary1). Without a shared special technical feature, the inventions lack unity with one another.

The inventions of Group V through V therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.