

ALKYL SULFONAMIDE DERIVATIVES

Field of the Invention

- 5 The present invention relates to compounds that are ligands at the neuropeptide Y Y5 receptor, and as such are useful to treat disorders such as depression, anxiety and obesity.

Background of the Invention

- 10 Throughout this application, various publications are referenced to in full citations. The disclosures of these publications are hereby incorporated by reference into this application to describe more fully the state of the art to which this invention pertains.

Neuropeptide Y (NPY) is a 36 amino acid neuropeptide expressed in the peripheral
15 and central nervous system. This peptide is a member of the pancreatic polypeptide family, which also includes pancreatic polypeptide (PP) and peptide YY (PYY). Moreover, the biological effects of NPY are mediated through its interaction with receptors that belong in the superfamily of G protein-coupled receptors.

- 20 Presently, five NPY receptor subtypes have been cloned: Y1 (D. Larhammar, et al., J. Biol. Chem., 1992, 267, 10935-10938); Y2 (C. Gerald, et al., J. Biol. Chem., 1995, 270, 26758-26761); Y4 (J. Bard, et al., J. Biol. Chem., 1995, 270, 26762-26765); Y5 (C. Gerald, et al., J. Biol. Chem., 1995, 270, 26758-26761); and y6 (P. Gregor, et al., J. Biol. Chem., 1996, 271, 27776-27781). All these receptor subtypes are expressed
25 in several species except for the y6 subtype, which has been shown to be expressed in mouse and rabbit but not in rat and primate. A Y3 subtype has been proposed based on pharmacological data. However, the Y3 subtype has yet to be cloned and its existence remains to be fully established.

- 30 NPY exerts numerous physiological effects. On the basis of animal studies, it is evident that a contributory relationship exists between NPY and its receptors with disorders such as depression, anxiety and obesity. For instance, NPY expression is shown to be sensitive to energy status while NPY administration reduces energy expenditure, and another significant ability of NPY is to acutely stimulate feeding (S.
35 Kalra, et al., Endocr. Rev., 1999, 20, 68-100). The NPY Y5 receptor has also been

shown to be a receptor subtype responsible for NPY-induced food intake (C. Gerald, et al., *Nature*, 1996, 382, 168-171).

Additionally, the link between NPY and mood disorders such as depression and anxiety is established in the literature. For example, rats subjected to chronic mild stress exhibit anhedonia, a feature of clinical depression (P. Willner, et al., *Eur. J. Pharmacol.*, 1997, 340, 121-132); they also contain elevated levels of NPY mRNA in hypothalamus accompanied by a reduction in hippocampus (V. Sergeyev, et al., *Psychopharmacology*, 2005, 178, 115-124). The behavioral changes associated with chronic mild stress are reversed by a variety of antidepressants (P. Willner, et al., *Eur. J. Pharmacol.*, 1997, 340, 121-132). In one study of antidepressant therapies, rats treated with citalopram displayed an increased level of hippocampal NPY receptor binding with no change in NPY-like immunoreactivity (H. Husum, et al., *Neuropsychopharmacology*, 2001, 2, 183-191); conversely, electroconvulsive shock produced an increased level of hippocampal NPY-like immunoreactivity with no change in NPY receptor binding. These findings suggest that abnormal levels of NPY play a role in depressive illness, and that agents capable of regulating NPY and/or NPY receptor function particularly in limbic regions are useful for treating depression. Y5 is a NPY receptor expressed in limbic regions (M. Wolak, et al., *J. Comp. Neurol.*, 2003, 22, 285-311; and K. Nichol, et al., *J. Neurosci.*, 1999, 19, 10295-10304). Accordingly, agents capable of regulating Y5 receptor function are therefore predicted to be useful for treating depression.

Animal models of anxiety also reveal abnormal levels of NPY. In one example, maternally separated rats display an anxious and depressive phenotype throughout adulthood (R. Huot, *Psychopharmacology*, 2001, 158, 366-73); they also contain elevated levels of NPY-like immunoreactivity in hypothalamus accompanied by a reduction in hippocampus and cortex (P. Jimenez-Vasquez, *Brain Res. Dev.*, 2001, 26, 149-152; H. Husum and A. Mathe, *Neuropsychopharmacology*, 2002 27:756-64; and H. Husum et al., *Neurosci Lett.*, 2002, 333, 127-130). In a second example, rats subjected to fear conditioning display increased anxiety-like behavior; they also contain elevated levels of NPY in hypothalamus, amygdala and nucleus accumbens accompanied by a reduction in frontal cortex. The behavioral changes produced by fear conditioning can be reversed by treatment with anxiolytic drugs. In one study of fear conditioning, both the anxiety-like behavior and altered expression of NPY were

reversed by treatment with diazepam (R. Krysiak, et al., *Neuropeptides*, 2000, 34, 148-57). These findings further suggest that NPY plays a role in anxiety, and that agents capable of regulating NPY and/or receptor function particularly in limbic regions are useful for treating anxiety. Y5 is a NPY receptor expressed in limbic regions (M. Wolak, et al., *J. Comp. Neurol.*, 2003, 22, 285-311; and K. Nichol, et al., *J. Neurosci.*, 1999, 19, 10295-10304). Accordingly, agents capable of regulating Y5 receptor function are therefore predicted to be useful for treating anxiety.

In our laboratories, compounds of the invention have been evaluated in animal models predictive for antidepressant activity. It has been discovered that these compounds produce effects similar to that observed by known antidepressants.

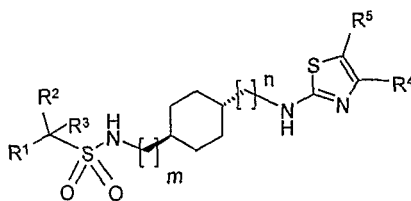
Numerous groups have postulated various selective NPY Y5 small molecule ligands for the treatment of these disorders. In addition to possessing the appropriate pharmacological elements to move forward in the clinic, a compound should have favorable ADME properties such as metabolic stability. Issues relating to drug-drug interactions and toxicity should also be addressed. Metabolic stability of a drug may be predicted by its clearance rate in liver microsomes. Additionally, the cytochrome P450s (CYPs) play a role in metabolism, and CYP inhibition may be used to predict the potential risks of drug-drug interactions and/or toxicity.

Moreover, current treatments for depression, anxiety and obesity are on the market. However, numerous patients do not respond to current treatments. Hence, there remains the need for alternative methods of treatment.

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Summary of the Invention

The objective of the present invention is to provide compounds that are ligands at the NPY Y5 receptor. The present invention relates to compounds of Formula I.



Formula I

wherein R^1 is H or C_1 - C_6 straight chained or branched alkyl;

wherein R^2 is C_1 - C_6 straight chained or branched alkyl;

or wherein R^1 , R^2 and the carbon to which they are attached may form C_3 - C_6 cycloalkyl;

wherein R^3 is H or methyl;

wherein R^4 is 2-pyridyl, 3-pyridyl or pyrazinyl, wherein the 2-pyridyl, 3-pyridyl or pyrazinyl may be substituted with methyl;

wherein R^5 is H or methyl;

wherein m is an integer from 0 to 2 inclusive; and

wherein n is an integer from 0 to 2 inclusive;

or a pharmaceutically acceptable salt thereof.

In separate embodiments of the invention, the compound is selected from one of the specific compounds disclosed in the Experimental Section.

Furthermore, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable carrier. The present invention also provides a process for making a pharmaceutical composition comprising admixing a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable carrier.

Moreover, the present invention provides a method of treating a subject suffering from depression comprising administering to the subject a therapeutically effective amount of a compound of Formula I. The present invention further provides a method of treating a subject suffering from anxiety comprising administering to the subject a therapeutically effective amount of a compound of Formula I. The present invention further provides a method of treating a subject suffering from obesity comprising administering to the subject a therapeutically effective amount of a compound of Formula I.

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Detailed Description of the Invention

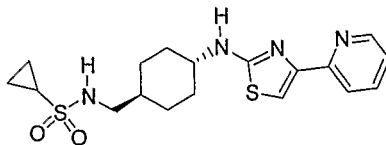
Definitions

In the present invention, the term "straight chained or branched C₁-C₆ alkyl" refers to a saturated hydrocarbon having from one to six carbon atoms inclusive. Examples of such substituents include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2-methyl-1-propyl, n-pentyl and n-hexyl. Similarly, the term "straight chained or branched C₁-C₄ alkyl" refers to a saturated hydrocarbon having from one to four carbon atoms inclusive. Examples of such substituents include, but are not limited to, methyl, ethyl and 1-propyl.

Furthermore, the term "C₃-C₆ cycloalkyl" refers to a saturated cyclohydrocarbon ring having from three to six carbon atoms inclusive. Included within this term are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The specific compounds disclosed in the present invention are identified by their IUPAC names and their respective chemical structure. The names of the compounds were generated using the program Chemistry 4-D Draw Nomenclator™ Database (Version 7.01c, ChemInnovation Software, Inc.). According to ChemInnovation Software Inc., Nomenclator™ automatically assigns systematic names to organic structures according to IUPAC nomenclature rules. Moreover, as described in Formula I, the stereochemistry of the 1,4-cyclohexyl ring is trans and this designation has been added. Accordingly, this application discloses the alkyl sulfonamide derivatives encompassed by Formula I in accordance with IUPAC nomenclature rules.

For illustrative purposes, and without limiting the invention, the compound of example 2b has the following structure:



This compound is constructed from Formula I wherein R¹, R² and the carbon to which they are attached form cyclopropyl; R³ is H; m is 1; n is 0; R⁴ is 2-pyridyl; and R⁵ is H.

Additionally, the invention further provides for certain embodiments of the present invention that are described below.

In a further embodiment, R⁵ is H.

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In another embodiment, R⁵ is methyl.

In one embodiment, R³ is H; R⁴ is 2-pyridyl or pyrazinyl, wherein the 2-pyridyl or pyrazinyl may be substituted with methyl; m is 0 or 1; and n is 0 or 1.

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In one embodiment, R¹ is H or C₁-C₄ straight chained or branched alkyl; and R² is C₁-C₄ straight chained or branched alkyl.

In one embodiment, R¹ is H, methyl or ethyl; R² is methyl or ethyl; and R⁴ is 2-pyridyl, wherein the 2-pyridyl may be substituted with methyl.

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In one embodiment, R¹ is methyl and R² is methyl.

In a further embodiment, n is 1.

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In one embodiment, R¹, R² and the carbon to which they are attached form C₃-C₆ cycloalkyl.

In one embodiment, R⁴ is 2-pyridyl.

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In another embodiment, R¹ is H or C₁-C₄ straight chained or branched alkyl; R² is C₁-C₄ straight chained or branched alkyl; R³ is H; R⁴ is 3-pyridyl or pyrazinyl, wherein the 3-pyridyl or pyrazinyl is substituted with methyl; m is 0 or 1; and n is 0 or 1.

In one embodiment, R¹ is H or C₁-C₄ straight chained or branched alkyl; R² is C₁-C₄ straight chained or branched alkyl; R³ is H; R⁴ is 2-pyridyl, wherein the 2-pyridyl may be substituted with methyl; m is 0 or 1; and n is 0 or 1.

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In one embodiment, R¹ is methyl; R² is methyl; and n is 0.

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In one embodiment, R¹ is methyl; R² is methyl; and m is 0.

In one embodiment, R⁴ is 3-pyridyl, wherein the 3-pyridyl is substituted with methyl.

In one embodiment, R³ is H; m is 0 or 1; and n is 0 or 1; and R⁴ is 2-pyridyl or pyrazinyl, wherein the 2-pyridyl or pyrazinyl may be substituted with methyl.

In another embodiment, R¹ is H or C₁-C₄ straight chained or branched alkyl.

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In one embodiment, R² is C₁-C₄ straight chained or branched alkyl.

In yet another embodiment, R¹ is H, methyl or ethyl; R² is methyl or ethyl; and R⁴ is 2-pyridyl.

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In a further embodiment, m is 1.

In one embodiment, R¹, R² and the carbon to which they are attached form cyclopropyl or cyclobutyl; and n is 0.

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Pharmaceutically Acceptable Salts

The present invention also comprises salts of the present compounds, typically, pharmaceutically acceptable salts. Such salts include pharmaceutically acceptable acid addition salts. Acid addition salts include salts of inorganic acids as well as organic acids.

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Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, sulfamic, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, itaconic, lactic, methanesulfonic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methane sulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, *p*-aminobenzoic, glutamic, benzenesulfonic, *p*-toluenesulfonic acids, theophylline acetic acids, as well as the 8-halotheophyllines (for example, 8-bromotheophylline and the like). Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in S. M. Berge, et al., J. Pharm. Sci. 1977, 66, 2, the contents of which are hereby incorporated by reference.

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Furthermore, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol

and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Racemic forms may be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Separation of such diastereomeric salts can be achieved, e.g. by fractional crystallization. The optically active acids suitable for this purpose may include, but are not limited to *d*- or *l*- tartaric, malic or camphorsulfonic acids. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. The compounds of the present invention may also be resolved by the formation and chromatographic separation of diastereomeric derivatives from chiral derivatizing reagents, such as, chiral alkylating or acylating reagents, followed by cleavage of the chiral auxiliary. Any of the above methods may be applied either to resolve the optical antipodes of the compounds of the invention per se or to resolve the optical antipodes of synthetic intermediates, which can then be converted by methods described herein into the optically resolved final products which are the compounds of the invention.

Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in *Enantiomers, Racemates, and Resolutions*, John Wiley and Sons, New York 1981. Optically active compounds were also prepared from optically active starting materials.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming pharmacologically active substances. In general, such prodrugs will be functional derivatives of the compounds of Formula I which are readily convertible *in vivo* into the required compound of Formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

Pharmaceutical compositions

The present invention further provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically

acceptable carrier. The present invention also provides a pharmaceutical composition comprising a therapeutically effective amount of one of the specific compounds disclosed in the Experimental Section and a pharmaceutically acceptable carrier.

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The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known
10 adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

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The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) routes. It will be appreciated that the route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the
20 active ingredient.

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Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, the compositions may be prepared with coatings such as enteric coatings or they may be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art. Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

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Pharmaceutical compositions for parenteral administration include sterile aqueous and nonaqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use.

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Other suitable administration forms include, but are not limited to, suppositories, sprays, ointments, creams, gels, inhalants, dermal patches and implants.

Typical oral dosages range from about 0.001 to about 100 mg/kg body weight per day. Typical oral dosages also range from about 0.01 to about 50 mg/kg body weight per day. Typical oral dosages further range from about 0.05 to about 10 mg/kg body weight per day. Oral dosages are usually administered in one or more dosages, typically, one to three dosages per day. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may also be presented in a unit dosage form by methods known to those skilled in the art. For illustrative purposes, a typical unit dosage form for oral administration may contain from about 0.01 to about 1000 mg, from about 0.05 to about 500 mg, or from about 0.5 to about 200 mg.

For parenteral routes such as intravenous, intrathecal, intramuscular and similar administration, typical doses are in the order of half the dose employed for oral administration.

The present invention also provides a process for making a pharmaceutical composition comprising admixing a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable carrier. In an embodiment of the present invention the compound utilized in the aforementioned process is one of the specific compounds disclosed in the Experimental Section.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound of Formula I contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of Formula I with a molar equivalent of a pharmaceutically acceptable acid. Representative examples of suitable organic and inorganic acids are described above.

For parenteral administration, solutions of the compounds of Formula I in sterile aqueous solution, aqueous propylene glycol, aqueous vitamin E or sesame or

peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The compounds of
5 Formula I may be readily incorporated into known sterile aqueous media using standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. Examples of solid carriers include lactose,
10 terra alba, sucrose, cyclodextrin, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and lower alkyl ethers of cellulose. Examples of liquid carriers include, but are not limited to, syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene and water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl
15 monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the compounds of Formula I and a pharmaceutically acceptable carrier are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of
20 pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and optionally a suitable excipient.
25 Furthermore, the orally available formulations may be in the form of a powder or granules, a solution or suspension in an aqueous or non-aqueous liquid, or an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tableted,
30 placed in a hard gelatin capsule in powder or pellet form or it may be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will range from about 25 mg to about 1 g per dosage unit.

If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion,
35 soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

Treatment of Disorders

As mentioned above, the compounds of Formula I are ligands at the NPY Y5 receptor. The present invention provides a method of treating a subject suffering from depression which comprises administering to the subject a therapeutically effective amount of a compound of this invention. The present invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject a therapeutically effective amount of a compound of this invention. This invention further provides a method of treating a subject suffering from obesity which comprises administering to the subject a therapeutically effective amount of a compound of this invention. In an embodiment of this invention, the subject is a human being.

Additionally, the present invention is directed to use of a compound of Formula I for the preparation of a pharmaceutical composition for treating a subject suffering from depression. This invention further provides for use of a compound of Formula I for the preparation of a pharmaceutical composition for treating a subject suffering from anxiety. This invention also provides for use a compound of Formula I for the preparation of a pharmaceutical composition for treating a subject suffering from depression.

The invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed therein are merely illustrative of the invention as described more fully in the claims which follow thereafter. Furthermore, the variables depicted in Schemes 1-7 are consistent with the variables recited in the Summary of the Invention.

In the Experimental Section, standard acronyms are used. Examples of such acronyms include DMF (N,N-Dimethylformamide); TEA (Triethylamine); DPPA (Diphenylphosphoryl azide); BzNCS (Benzoylisothiocyanate); Et₂O (Diethyl Ether); MTBE (Methyl t-butyl ether); EtOAc (Ethyl Acetate); THF (Tetrahydrofuran); rt (room temperature); h (hour); and min (minutes). Furthermore, in certain instances, the methods of preparing the compounds of the invention are described generally by referring to representative reagents such as bases or solvents. The particular reagent identified is representative but is not inclusive and does not limit the

invention in any way. For example, representative bases include but are not limited to K_2CO_3 , TEA or DIEA (Diisopropylethylamine).

Moreover, the term " α -haloketone of Formula XXII" refers to a ketone with the halogen being chloro, bromo or iodo. α -Haloketones are commercially available. For instance, 2-bromo-1-(2-pyridyl)ethan-1-one and 2-bromo-1-(3-pyridyl)ethan-1-one are sold by Aldrich.

Alternatively, one skilled in the art would be able to synthesize the α -haloketones referred to in this invention via several routes. For example, ketones may be halogenated in the α position with bromine, chlorine, or iodine to afford α -haloketones (V. De Kimpe, The Chemistry of α -Haloketones, α -Haloaldehydes, and α -Haloimines; Wiley: New York, 1988). Additionally, α -haloketones may be synthesized from carboxylic acids by treatment of the acid with TMS-diazomethane followed by Cl_2 or Br_2 treatment.

The term 'PG' as defined in Scheme 5 is used to designate a 'protecting group'. One skilled in the art would be able to select the appropriate protecting group for a particular reaction. Moreover, it may be necessary to incorporate protection and deprotection strategies for substituents such as amino, amido, carboxylic acid and hydroxyl groups in the synthetic methods described below to synthesize the compounds of Formula I. Methods for protection and deprotection of such groups are well known in the art, and may be found in T. Green, et al., Protection Groups in Organic Synthesis, 1991, 2nd Edition, John Wiley & Sons, New York.

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Experimental Section

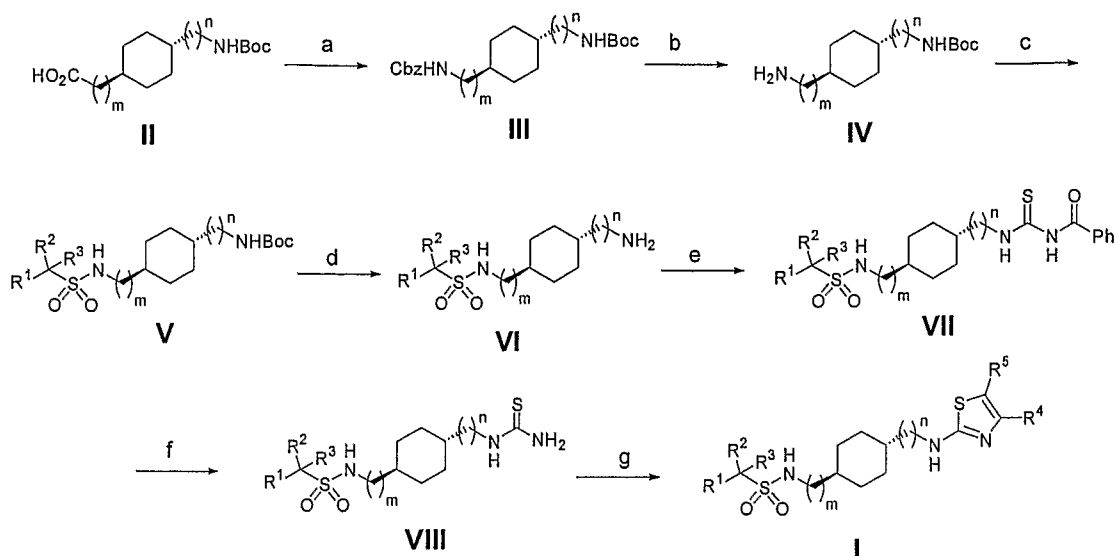
General Methods: Anhydrous solvents were purchased from the Aldrich Chemical Company and used as received. The NMR spectra were measured on a Bruker Avance 400 spectrometer or 300 MHz (Varian) with CDCl_3 , DMSO-d_6 or CD_3OD as the solvent with tetramethylsilane as the internal standard unless otherwise noted. Chemical shifts (δ) are expressed in ppm, coupling constants (J) are expressed in Hz, and splitting patterns are described as follows: s=singlet; d=doublet; t=triplet; q=quartet; br=broad; m=multiplet; dd=doublet of doublets; dt=doublet of triplets; td=triplet of doublets; dq=doublet of quartet. Unless otherwise noted, mass spectra were obtained using electrospray ionization (ESMS, Micromass Platform II or Quattro Micro). For LC-MS spectra, the following methods were used: Method-A: Luna C18 Column, 5% to 95% Acetonitrile/ H_2O with 0.05% formic acid; Method-B: Luna C18 Column, 15% to 85% Acetonitrile/ H_2O with 0.05% formic acid; Method-C: Luna C8 Column, 15% to 85% Methanol in water with 0.05% ammonium formate; Method-D: C18 column, Neutral pH, 20 % to 90 % Acetonitrile/ H_2O with 0.2 % Ammonium formate; or Method-E: C18 Column, Acidic pH, 20 % to 90 % Acetonitrile/ H_2O with 0.2 % AcOH. Thin-layer chromatography (TLC) was carried out on glass plates pre-coated with silica gel 60 F_{254} (0.25 mm, EM Separations Tech.). Preparative TLC was carried out on glass sheets pre-coated with silica gel GF (2 mm, Analtech). Silica gel column chromatography was performed on Merck silica gel 60 (230–400 mesh).

List and source of chemicals

Cyclohexyl sulfonyl chloride, cyclopentyl sulfonyl chloride and isopentyl sulfonyl chloride were obtained from Array Biopharma. 2-Bromo-1-pyrazin-2-yl-ethanone was obtained from Beta pharma Inc. sec-Butyl sulfonyl chloride and 2-pentyl sulfonyl chloride were obtained from Oakwood Products Inc. 2-acetyl–3-methyl pyrazine was obtained from Aldrich.

Methods of Preparing the Compounds of Formula I

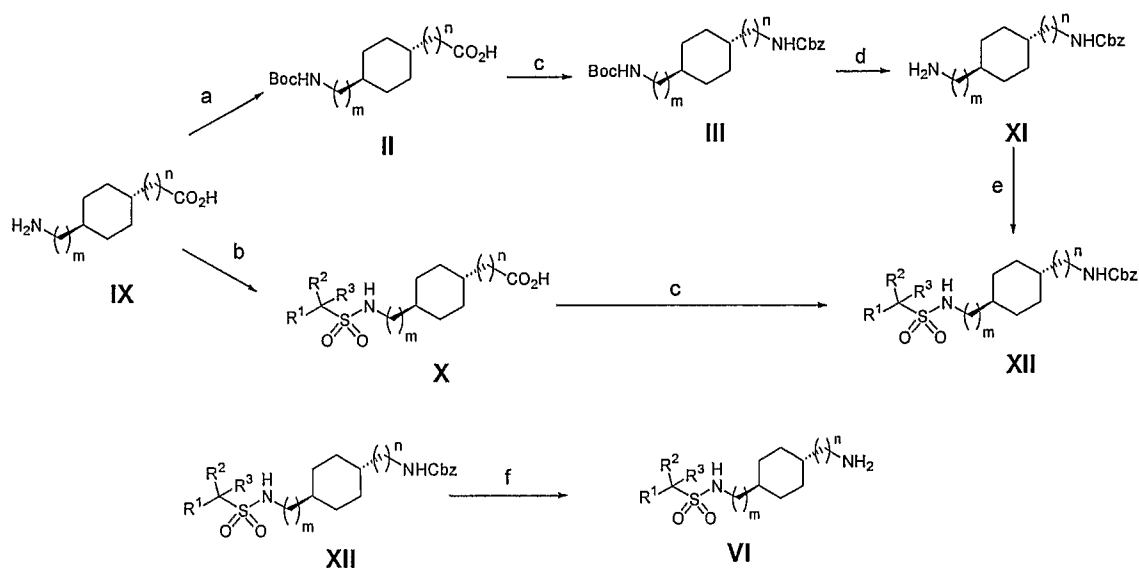
Scheme 1



- 5 (a) DPPA, TEA, Toluene, BnOH, reflux. (b) 10 % Pd-C, H₂, MeOH/ EtOAc. (c) 1M NaOH, Et₂O, (R¹)(R²)(R³)CSO₂Cl. (d) 10 % TFA in CH₂Cl₂. (e) BzNCS, THF, rt. (f) K₂CO₃, MeOH/ H₂O, reflux. (g) α-haloketone of Formula XXII, DIEA, EtOH, reflux.

The compounds of Formula I may be synthesized according to the procedures described in Scheme 1. The compounds of Formula II are commercially available or may be synthesized by one skilled in the art. In summary, the carboxylic acids of Formula II are converted to their Cbz-protected amines to afford the compounds of Formula III. The Cbz protecting group is selectively removed to afford the compounds of Formula IV. The resultant amines are coupled with (R¹)(R²)(R³)CSO₂Cl to afford the intermediates of Formula V. The Boc group is removed and the resultant amines of Formula VI are treated with benzoylisothiocyanate to afford the compounds of Formula VII. The compounds of Formula VII are subjected to basic solvolysis to afford the thiourea intermediates of Formula VIII. These intermediates are coupled with the appropriate α-haloketone of Formula XXII to afford the compounds of the invention.

Scheme 2

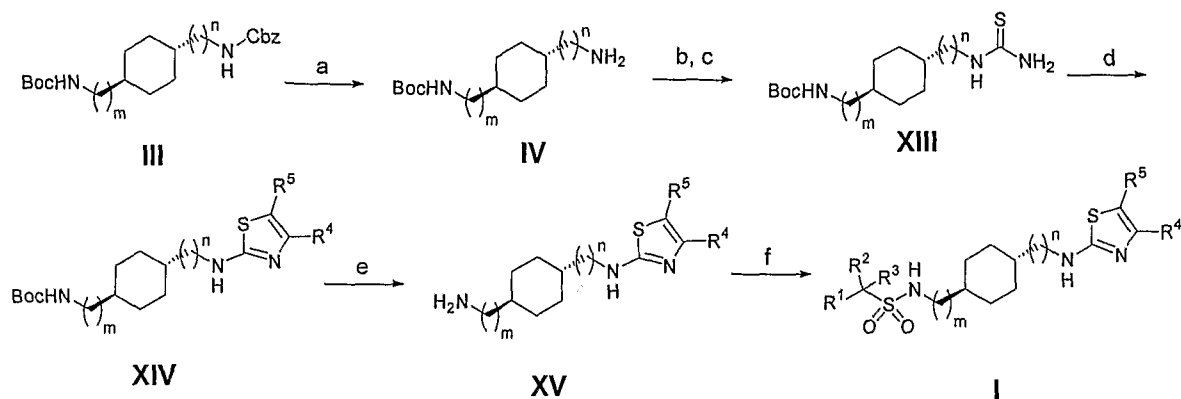


- (a) 1M NaOH, Et₂O, BOC₂O. (b) 1M NaOH, Et₂O, (R¹)(R²)(R³)CSO₂Cl. (c) DPPA, TEA, Toluene, BnOH, reflux. (d) 10 % TFA in CH₂Cl₂. (e) 1M NaOH, Et₂O, (R¹)(R²)(R³)CSO₂Cl. (f) 10 % Pd-C, H₂, EtOH, heat or HBr/ AcOH.

Alternatively, the intermediates of Formula VI may be synthesized according to the procedures outlined in Scheme 2. The starting materials of Formula IX are commercially available or may be synthesized by one skilled in the art. The amino acids of Formula IX may be coupled with (R¹)(R²)(R³)CSO₂Cl to afford the intermediates of Formula X which are further converted to the Cbz-protected amines of Formula XII. Separately, the amino acids of Formula IX may be converted into the mono-Cbz protected intermediates of Formula XI. The amines of Formula XI are coupled with (R¹)(R²)(R³)CSO₂Cl to afford the compounds of Formula XII. The Cbz group of Formula XII is removed to afford the intermediates of Formula VI. Finally, the intermediates of Formula VI may be converted to the compounds of the invention by using the procedures described in Scheme 1.

Additionally, the intermediates of Formula X can be converted to the compounds of Formula V, which are described in Scheme 1, if t-butanol is substituted for benzyl alcohol.

Scheme 3

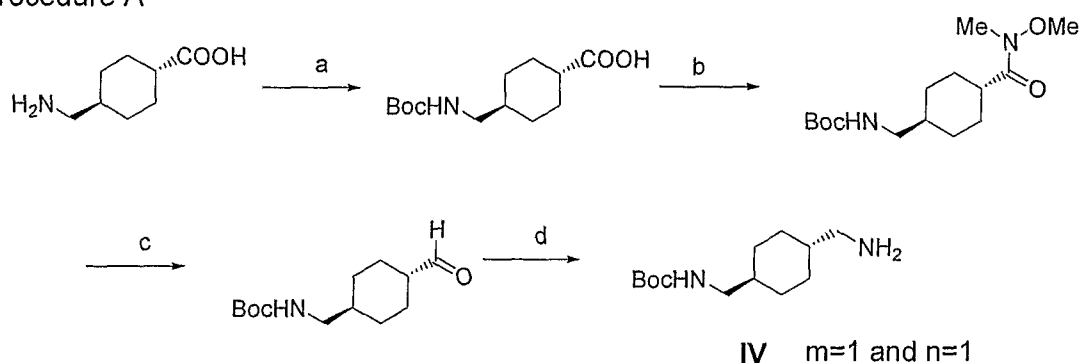


(a) 10 % Pd-C, H₂, EtOAc/ MeOH, rt. (b) BzNCS, THF, rt. (c) K₂CO₃, MeOH/ H₂O, reflux. (d) α -haloketone of Formula XXII, DIEA, EtOH, reflux. (e) 10 % TFA in CH₂Cl₂. (f) (R¹)(R²)(R³)CSO₂Cl, DIEA, CH₂Cl₂, rt.

Additionally, the compounds of Formula I may be synthesized according to the procedures outlined in Scheme 3. In summary, the Cbz group of Formula III is removed to afford the intermediates of Formula IV. These intermediates are converted to the thioureas of Formula XIII. The thiazole ring is formed to afford the compounds of Formula XIV. The BOC group is removed to afford the amines of Formula XV. The compounds of the invention are synthesized by coupling of the amines with (R¹)(R²)(R³)CSO₂Cl.

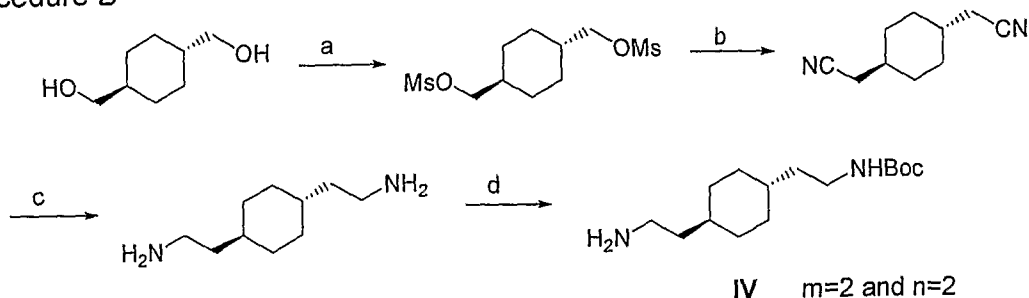
Scheme 4

Procedure A



(a) 1M NaOH/ Et₂O, BOC₂O. (b) CH₂Cl₂, 1-Methylmorpholine, Isobutyl chloroformate, -20 °C, NH(OMe)Me.HCl. (c) LAH, Et₂O, -45 °C. (d) NaCNBH₃, MeOH, NH₄OAc, rt.

Procedure B



(a) CH_2Cl_2 , MsCl , TEA , $0\text{ }^\circ\text{C}$. (b) NaCN , DMF , $80\text{ }^\circ\text{C}$ or Et_4NCN , Toluene , $80\text{ }^\circ\text{C}$. (c) LAH , THF . (d) $0.2\text{ eq. (BOC)}_2\text{O}$, Dioxane , rt .

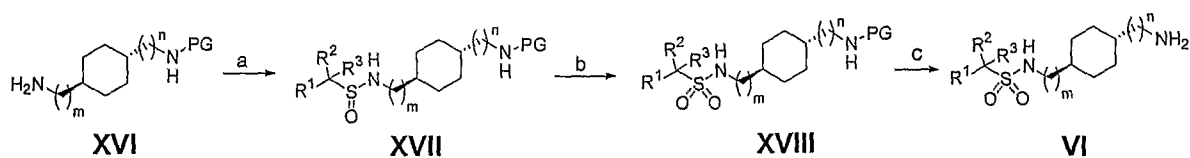
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The compounds of Formula **IV** are used as intermediates in Schemes 1, 2 and 3. These intermediates, wherein $n=1$ and $m=1$ (procedure A) or wherein $n=2$ and $m=2$, (procedure B) are synthesized according to the procedures described in Scheme 4.

- 10 For representative reaction conditions in connection with the synthesis of the diamine in Procedure B see P. Garcia, et al., *J. Org. Chem.*, 1961, 26, 4167-4168. For representative reaction conditions in connection with the synthesis of the mono-protected Boc diamine in Procedure B see J. Hansen, et al., *Synthesis*, 1982, 5, 404-405 and C. Dardonville, et al., *Bioorg. Med. Chem. Lett.*, 2004, 14, 491-493.

15

Scheme 5



(a) TEA , CH_2Cl_2 , $(\text{R}^1)(\text{R}^2)(\text{R}^3)\text{CS}(\text{O})\text{Cl}$. (b) NaIO_4 , RuCl_3 (cat) or mCPBA . (c) deprotection

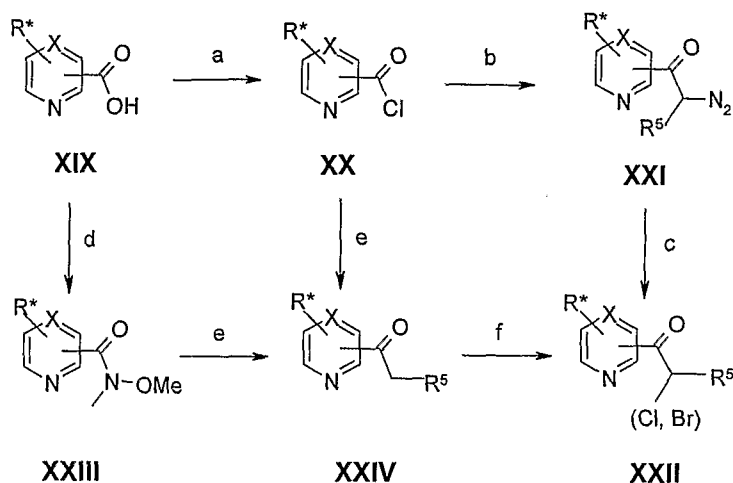
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The sulfonamides of Formula **VI** may also be synthesized according to the procedures outlined in Scheme 5. In summary, the compounds of Formula **XVI** are reacted with $(\text{R}^1)(\text{R}^2)(\text{R}^3)\text{CS}(\text{O})\text{Cl}$ to afford the sulfinamides of Formula **XVII**. These compounds are oxidized to the intermediates of Formula **XVIII**. The protecting group is removed to form the intermediates of Formula **VI**. Finally, the intermediates of Formula **VI** may be converted to the compounds of the invention by using the procedures described in Scheme 1.

25

For representative reaction conditions, see S. Weinreb, J. Org. Chem., 1997, 62, 8604-8608; J. Ellman, Tetrahedron Lett., 2001, 42, 1433-1436; B. Sharpless, Org. Lett., 1999, 1, 783-786; and WO 01/37826.

5 Scheme 6



(a) $(\text{COCl})_2$, cat. DMF, CH_2Cl_2 , rt. (b) 2M TMSCH_2N_2 in Et_2O , Dioxane, rt. (c) 4M HCl in dioxane, rt. or HBr in AcOH, rt. (d) $\text{HNMe}(\text{OMe})\cdot\text{HCl}$, EDC, HOBT, CH_2Cl_2 , rt. (e) EtMgBr , THF, -78°C , (f) Br_2 , 33% or 48% HBr in AcOH, rt.

10

The α -haloketones of Formula XXII may be synthesized according to the procedures described in Scheme 6. The acids of Formula XIX are commercially available or may be synthesized by one skilled in the art. The acids of Formula XIX may be converted to the corresponding acid chlorides of Formula XX. The acid chlorides may be treated with trimethylsilyldiazomethane or ethylmagnesiumbromide to afford the intermediates of Formulas XXI (wherein R^5 is H) or XXIV (wherein R^5 is methyl), respectively. These intermediates may be converted to the α -haloketones of Formula XXII, wherein R^5 is H or methyl, respectively. Alternatively, the acids of Formula XIX may be converted to the corresponding Weinreb amides of Formula XXIII which are further converted to the α -haloketones of Formula XXII using ethylmagnesium bromide (wherein R^5 is methyl). Similarly, if methylmagnesium bromide is substituted for ethylmagnesium bromide, R^5 is H.

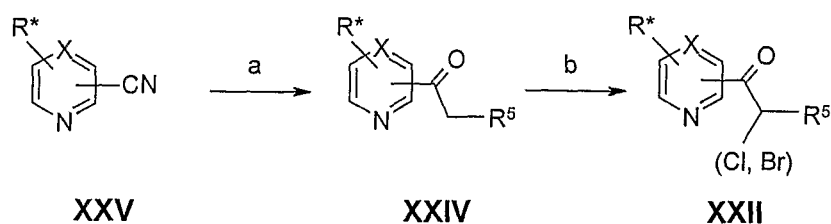
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For clarity purposes, the moiety R^* is used to denote that the 2-pyridyl, 3-pyridyl or pyrazinyl group is optionally substituted with methyl. The variable X is used to denote CH or N.

For representative reaction conditions in connection with the conversion of the carboxylic acids to bromoketones using trimethylsilyldiazomethane, see A. Gangjee, et al., *Bioorg. Med. Chem.*, 2003, 11, 5155–5170. For representative reaction conditions in connection with the conversion of the α -haloketones from ketones using Br_2/AcOH or sulurylchloride and MeOH, see N. Ikemoto, et al., *Tetrahedron*, 2003, 59, 1317-1325; or using Pyridine- Br_3 , HBr/ AcOH, see W.C. Patt and M.A. Massa, *Tetrahedron Lett.*, 1997, 38, 1297-1300.

Scheme 7



Alternatively, the α -haloketones of Formula **XXII** may be synthesized according to the procedures described in Scheme 7 from the starting materials of Formula **XXV**.

The cyano compounds are treated with ethylmagnesium bromide to afford the intermediates of Formula **XXIV**, wherein R^5 is methyl. Similarly, if methylmagnesium bromide is substituted for ethylmagnesium bromide, R^5 is H. The intermediates of Formula **XXIV** are further converted to the α -haloketones of Formula **XXII**.

For clarity purposes, the moiety R^* is used to denote that the 2-pyridyl, 3-pyridyl or pyrazinyl group is optionally substituted with methyl. The variable X is used to denote CH or N.

For representative reaction conditions in connection with the transformation of the cyano group, see N.B. Mehta, *J. Clin. Psychiatry*, 1983, 44, 56; and S. W. Baldwin and J. E. and Fredericks, *Tetrahedron Lett.*, 1982, 23, 1235-1238.

Preparation of intermediates

Representative compounds of Formulas II-VIII were synthesized as follows:

5 Intermediate of Formula II

trans-4-[[*(tert*-butoxy)carbonylamino]methyl]cyclohexanecarboxylic acid: Boc₂O (41.7 g, 190 mmol) was added to a stirred biphasic solution containing *trans*-4-(aminomethyl)cyclohexanecarboxylic acid (25.0 g, 159 mmol), NaHCO₃ (20 g, 238 mmol), water (300 mL) and Et₂O (200 mL) at rt. The pH of the solution was adjusted to pH ~ 9.0 by adding additional quantities of saturated aqueous NaHCO₃. After stirring for 24 h at rt, the layers were separated and the aqueous layer was acidified to pH 4.0 with 1M aqueous HCl. The aqueous layer was extracted with EtOAc. The organic layer was isolated and washed successively with water and brine. The organic layer was concentrated *in vacuo* and dried under high vacuum to yield the desired product as a colorless solid (23.3 g, 57 %). ¹H NMR (CDCl₃) δ 4.60 (br s, 1H), 2.99 (t, 2H, J=6.4 Hz), 2.29–2.23 (m, 3H), 2.05 (dd, 2H, J=13.6 and 3.2 Hz), 1.84 (dd, 2H, J=13.2 and 2.8 Hz), 1.44 (s, 9H), 1.42 (br m, 1H), 0.97 (dq, 2H, J=25.6, 12.4 and 3.2 Hz).

20 Intermediate of Formula III

(*tert*-butoxy)-N-({*trans*-4-[(phenylmethoxy)carbonylamino]cyclohexyl}methyl)carboxamide:

trans-4-[[*(tert*-butoxy)carbonylamino]methyl]cyclohexanecarboxylic acid (20.3 g, 0.073 mol) was suspended in toluene (420 mL) and chilled to –10 °C in a dry ice bath. DPPA (15.8 mL, 0.073 mol) was added and chilling was continued. TEA (15.3 mL, 0.11 mol) was added drop wise over 10 min. The solution color turned from milky white to clear. The mixture was removed from the ice bath, warmed to 10 °C and then slowly heated to 70 °C. After 15 h, nitrogen evolution was observed to be finished and the solution color turned to yellow. The mixture was cooled to 47 °C and benzyl alcohol (22.8 mL, 0.220 mol) was added. The mixture was heated to 110 °C and stirred overnight. The mixture was cooled to 50 °C and concentrated *in vacuo* to obtain amber solids. The solids were treated with deionized water (400 mL) and EtOAc (150 mL). The mixture was shaken for 10 min and the layers were isolated. The aqueous layer was extracted several times with EtOAc. The organic layers were combined, dried and concentrated *in vacuo*. The resultant solid was

trituated in MTBE to afford a white solid (17.8 g, 67 %) as the desired product. ¹H NMR (CDCl₃) δ 7.34–7.286 (m, 3H), 7.13 (d, 2H, J=8.0 Hz), 6.78 (t, 1H, J=6.0 Hz), 4.97 (s, 2H), 3.3–3.14 (br, m, 1H), 2.73 (t, 1H, J=6.3 Hz), 1.78 (d, 2H, J=10.6 Hz), 1.64 (d, 2H, J=11.8 Hz), 1.35 (s, 6H), 1.35–1.00 (m, 3H), 0.87 (q, 2H, J=12.5 and 2.8 Hz).

Intermediate of Formula IV

N-[(*trans*-4-aminocyclohexyl)methyl](*tert*-butoxy)carboxamide: 10 % Pd-C (0.20 g) was added to a stirred solution of (*tert*-butoxy)-N-[(*trans*-4-[(phenylmethoxy)carbonylamino]cyclohexyl)methyl]carboxamide (2.0 g, 5.5 mmol) in EtOAc/ MeOH (1 : 1, 50 mL) at rt. The mixture was degassed and purged with H₂ twice, and further stirred at rt under a static atmosphere of H₂ for 2 h. The mixture was filtered through celite and the filter cake was washed with EtOAc. The filtrate was concentrated *in vacuo* to afford the desired compound as a colorless solid (1.3 g, 91 %). ¹H NMR (CDCl₃) δ 4.59 (br, s, 1H), 2.97 (t, 2H, J=6.4 Hz), 2.63–2.58 (m, 1H), 1.87 (d, 2H, J=12.4 Hz), 1.75 (d, 2H, J=12.4 Hz), 1.44 (s, 9H), 1.37 (m, 1H), 1.12–0.96 (m, 4H). ESMS *m/e*: 173 ((M+H)-55)⁺.

Intermediate of Formula V

(*tert*-butoxy)-N-[(*trans*-4-[(methylethyl)sulfonyl]amino)cyclohexyl)methyl]carboxamide: Isopropyl sulfonyl chloride (6.2 mL, 7.9 g, 56 mmol) was added drop wise at rt to a stirred biphasic solution containing N-[(*trans*-4-aminocyclohexyl)methyl](*tert*-butoxy)carboxamide (10 g, 44 mmol), 1M aqueous NaOH (100 mL) and Et₂O (100 mL). After stirring for 2 h, a white precipitate appeared. The precipitate was collected by filtration, washed with Et₂O and dried *in vacuo* to obtain the desired product as a colorless solid (9.5 g, 65 %). ¹H NMR (CDCl₃) δ 4.58 (br s, 1H), 3.89 (d, 1H, J=8.0 Hz), 3.23 (septet, 1H, J=4.4 Hz), 2.96 (t, 2H, J=6.4 Hz), 2.61 (m, 1H), 2.09 (d, 2H, J=11.6 Hz), 1.89–1.74 (m, 3H), 1.44 (s, 9H), 1.37 (d, 6H, J=6.8 Hz), 1.22 (dq, 1H, J=13.2 and 3.6 Hz), 1.09–1.00 (br m, 3H). ESMS *m/e*: 279 ((M+H)-55)⁺.

Intermediate of Formula VI

[*trans*-4-(aminomethyl)cyclohexyl][(methylethyl)sulfonyl]amine: TFA (5 mL) was added at rt to a stirred solution containing (*tert*-butoxy)-N-[(*trans*-4-[(methylethyl)sulfonyl]amino)cyclohexyl)methyl]carboxamide (1.3 g, 3.9 mmol) and CH₂Cl₂ (45

mL). After 4 h, the solution was concentrated *in vacuo* and the residue was re-dissolved in CHCl_3 . The CHCl_3 solution was washed successively with 1M aqueous NaOH and brine, dried over Na_2SO_4 and then concentrated *in vacuo* to provide the free base as a colorless solid (0.88 g, 97 %). ^1H NMR (CDCl_3) δ 3.19–3.09 (m, 2H), 2.82 (dd, 2H, $J=13.6$ and 7.2 Hz), 2.07 (d, 2H, $J=13.6$ Hz), 1.88 (d, 2H, $J=6.0$ Hz), 1.64–1.60 (br m, 2H), 1.51–1.30 (m, 2H), 1.34 (d, 6H, $J=6.8$ Hz), 1.23–1.08 (m, 3H). ESMS m/e : 235 ($\text{M}+\text{H}$)⁺.

Intermediate of Formula VII

N-([[(*trans*-4-[(methylethyl)sulfonyl]amino)cyclohexyl)methyl]amino]thioxomethyl)benzamide: Benzoylisoithiocyanate (1.6 g, 10 mmol) was added to a solution of [*trans*-4-(aminomethyl)cyclohexyl][(methylethyl)sulfonyl]amine (2.3 g, 10 mmol) in THF (100 mL) under an argon atmosphere and then stirred at rt overnight. The reaction mixture was concentrated *in vacuo* and the resultant gum-like material was triturated with hexanes to obtain the product as a pale yellow solid. (3.8 g, 96 %). ^1H NMR (CDCl_3) δ 10.86 (s, 1H), 9.08 (s, 1H), 7.86 (d, 1H, $J=4.0$ Hz), 7.64 (dt, 1H, $J=5.6$ and 1.2 Hz), 7.54–7.49 (m, 3H), 4.18 (d, 1H, $J=8.4$ Hz), 3.59 (t, 2H, $J=6.0$ Hz), 3.25 (septet, 1H, $J=4.0$ Hz), 2.14 (dd, 2H, $J=7.2$ and 2.4 Hz), 1.91 (d, 2H, $J=6.4$ Hz), 1.74 (m, 1H), 1.29 (d, 6H, $J=12.8$ Hz), 1.25–1.12 (m, 2H). ESMS m/e : 398 ($\text{M}+\text{H}$)⁺.

Intermediate of Formula VIII

(*trans*-4-[(aminothioxomethyl)amino]methyl)cyclohexyl[(methylethyl)sulfonyl]amine: K_2CO_3 (2.00 g, 14.5 mmol) was added to a solution containing N-([[(*trans*-4-[(methylethyl)sulfonyl]amino)cyclohexyl)methyl]amino]thioxomethyl)benzamide (3.80 g, 9.57 mmol), MeOH (75 mL) and H_2O (25 mL). The resulting turbid mixture was refluxed for 16 h. Note that upon refluxing the mixture turned into a clear homogenous solution. The solution was allowed to cool and concentrated *in vacuo* to yield a solid. This solid was dissolved in acetone and filtered through a pad of celite, followed by additional washings of the celite with acetone. The filtrate was concentrated *in vacuo* to afford the desired product as a pale yellow solid (2.20 g, 79 %). ^1H NMR (CDCl_3) δ 6.98 (br s, 1H), 6.39–6.32 (br s, 2H), 3.50 (br s, 1H), 3.32 (m, 1H), 3.14 (m, 2H), 2.16–2.13 (br m, 1H), 1.94–1.92 (m, 2H), 1.82–1.79 (m, 2H), 1.52–1.36 (m, 2H), 1.38 (d, 6H, $J=6.8$ Hz), 1.26–1.10 (m, 2H). ESMS m/e : 294 ($\text{M}+\text{H}$)⁺.

Representative compounds of Formulas X through XIII and VI were synthesized as follows:

Intermediate of Formula X

5 *trans*-4-(((methylethyl)sulfonyl)amino)methyl)cyclohexanecarboxylic acid: Isopropyl sulfonyl chloride (10.9 g, 77.0 mmol) was added drop wise to a solution of *trans*-4-(aminomethyl)cyclohexanecarboxylic acid (10.0 g, 63.7 mmol) in 1M aqueous NaOH (150 mL, 150 mmol), cooled in an ice bath. The solution was stirred for 24 h and then acidified to pH ~ 4 with 2 M aqueous HCl. The solids were collected by filtration
10 and dried in a vacuum oven at rt to afford the desired product as a white solid (5.0 g, 33 %). ¹H NMR (CDCl₃) δ 4.91 (br s, 1H), 3.20 (septet, 1H, J=6.8 Hz), 2.92 (d, 2H, J=6.8 Hz), 2.24 (tt, 1H, J=12.4 and 3.6 Hz), 2.03 (dd, 2H, J=10.4 and 3.2 Hz), 1.92 (dd, 2H, J=10.8 and 3.2 Hz), 1.48–1.41 (m, 3H), 1.34 (d, 6H, J=6.8 Hz), 1.01 (dq, 2H, J=25.2, 13.2 and 3.6 Hz). ESMS *m/e*: 264 (M+H)⁺.

15

Intermediate of Formula XI

N-[*trans*-4-(aminomethyl)cyclohexyl](phenylmethoxy)carboxamide: (tert-butoxy)-N-([*trans*-4-[(phenylmethoxy)carbonylamino]cyclohexyl]methyl)carboxamide (4 g, 11 mmol) was treated with 25 % TFA in CH₂Cl₂ (50 mL). After stirring 5 h at 40 °C, the
20 crude product was washed with aqueous NaHCO₃ and then brine. The solution was dried over Na₂SO₄ and dried under vacuum to afford the desired product as an oil (quantitative yield). ¹H NMR (DMSO-d) δ 7.18-7.03 (m, 5H), 4.78 (s, 2H), 3.06-2.96 (m, 1H), 2.35 (d, 2H, J = 6.8 Hz), 1.62-1.48 (m, 4H), 1.20-1.11 (m, 1H), 0.97-0.69 (m, 4H). ESMS *m/e*: 263 (M+H)⁺.

25

Intermediate of Formula XII

N-[*trans*-4-(((methylethyl)sulfonyl)amino)methyl)cyclohexyl](phenylmethoxy)carboxamide: Isopropyl sulfonyl chloride (6.6 g, 46 mmol) was added drop wise to a solution containing N-[*trans*-4-(aminomethyl)cyclohexyl](phenylmethoxy)
30 carboxamide (11 g, 42 mmol), TEA (7.0 g, 70 mmol) in anhydrous CH₂Cl₂ (150 mL) at 0 °C. The reaction was allowed to warm to rt and stirred overnight. The solution was washed with saturated aqueous NaHCO₃, dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography using an increasing gradient of EtOAc in Hexanes. The fractions containing the product
35 were combined and concentrated *in vacuo*. Recrystallization from EtOH gave the

desired product (5.0 g, 32 %). ^1H NMR (CDCl_3) 7.38-7.31 (m, 5H), 5.08 (s, 2H), 4.66-4.57 (br m, 1H), 4.13-4.06 (br m, 1H), 3.49-3.4 (br m, 1H), 3.19-3.11 (m, 1H), 2.97 (t, 2H, $J=6.7$ Hz), 2.08-2.05 (br m, 2H), 1.86-1.83 (br m, 2H), 1.50-1.40 (m, 1H), 1.36 (d, 6H, $J=0.9$ Hz), 1.18-0.99 (m, 4H). ESMS m/e : 369 ($\text{M}+\text{H}$) $^+$.

5

Intermediate of Formula XII to Intermediate of Formula VI

[(*trans*-4-aminocyclohexyl)methyl][(methylethyl)sulfonyl]amine: N-[*trans*-4-

{[(methylethyl)sulfonyl]amino}methyl)cyclohexyl](phenylmethoxy)carboxamide (62 g,

0.168 mole) and 10% Pd-C (12 g) in anhydrous EtOH (600 mL) was shaken at 55

10 psi at 60 °C under H_2 atmosphere. The solution was shaken for 6 h. The white

solids dissolved within 2 h. The catalyst was filtered off and the solids were

washed with EtOH (3 x 150 mL). The combined EtOH filtrate was concentrated in

vacuo. Toluene (200 mL) was added and evaporated to obtain the desired product

as a white solid (quantitative yield). ^1H NMR (CDCl_3) δ 3.60 (br s, 2H), 3.06 (quintet,

15 1H), 2.69 (d, 2H, $J=11.2$ Hz), 2.58 (m, 1H), 1.79 (d, 2H, $J=11.2$ Hz), 1.68 (d, 2H,

$J=11.2$ Hz), 1.24 (br m, 1H), 1.14 (d, 6H, $J=11.2$ Hz), 1.09 (2H, q, $J=22.5$ and 9.0 Hz)

and 0.86 (2H, q, $J=22.5$ and 9.0 Hz).

Intermediate of Formula XIII

20 N-({*trans*-4-[(aminothioxomethyl)amino]cyclohexyl)methyl}(tert-butoxy)carboxamide:

Benzoylisothiocyanate (0.755 g, 4.63 mmol) was added to a stirred solution of (tert-

butoxy)carboxamidemethylcyclohexyl-*trans*-4-amine (1.2 g, 4.6 mmol) in THF (50

mL) at rt under argon atmosphere. After stirring for 24 h, the solution was

concentrated *in vacuo* to afford a viscous material. Trituration of the viscous material

25 with Hexanes afforded N-({*trans*-4-[(aminothioxomethyl)amino]cyclohexyl}

methyl}(tert-butoxy)carboxamidebenzamide as a pale yellow color solid (1.71 g, 90

% yield). ^1H NMR (CDCl_3) δ 10.61 (d, 1H, $J=7.2$ Hz), 8.89 (s, 1H), 7.82 (d, 1H, $J=7.6$

Hz), 7.63 (t, 1H, $J=7.2$ Hz), 7.54-7.49 (m, 3H), 4.61 (br s, 1H), 4.24-4.19 (m, 1H),

3.02 (t, 2H, $J=6.0$ Hz), 2.27 (dd, 2H, $J=7.6$ and 2.0 Hz), 1.86 (d, 2H, $J=11.6$ Hz), 1.45

30 (s, 10H), 1.32 (dq, 2H, $J=24.8$, 12.4 and 3.2 Hz), 1.28 (dq, 2H, $J=25.6$, 13.2 and 2.4

Hz). ESMS m/e : 336 (($\text{M}+\text{H}$) - 55) $^+$. N-({*trans*-4-[(aminothioxomethyl)amino]

cyclohexyl)methyl}(tert-butoxy)carboxamide benzamide (1.65 g, 4.0 mmol) was

dissolved in MeOH (25 mL). Water (5 mL) was added followed by the addition of

K_2CO_3 (1.66 g, 12.0 mmol). The resultant mixture was allowed to reflux overnight.

35 After refluxing for 16 h, the solvents were removed *in vacuo* and the resultant solid

was dried under high vacuum. The solid was re-dissolved in acetone and filtered through a pad of celite. Concentration of the filtrate *in vacuo* afforded the desired product as a pale yellow color solid (1.1 g). ¹H NMR (CDCl₃) δ 6.17 (br s, 1H), 4.85 (br s, 1H), 2.99 (t, 2H, J=7.2 Hz), 2.09 (d, 2H, J=12.0 Hz), 1.83 (d, 2H, J=12.0 Hz), 1.44 (s, 10H), 1.29–0.78 (m, 4H). ESMS *m/e*: 288 (M+H)⁺.

Intermediates of Formula XIV

(tert-butoxy)-N-({4-[(*trans*-4-(2-pyridyl)(1,3-thiazol-2-yl))amino]cyclohexyl)methyl)

carboxamide: DIEA (0.63 mL, 3.6 mmol) was added to a solution of 2-bromo-1-(2-pyridyl)ethan-1-one (500 mg, 1.8 mmol) in anhydrous EtOH (10 mL) under an argon atmosphere. After stirring for 5 min at rt, N-({*trans*-4-[(aminothioxomethyl)amino]cyclohexyl)methyl}(tert-butoxy)carboxamide (520 mg, 1.8 mmol) was added and the reaction was refluxed overnight. EtOH was removed *in vacuo* and the residue was re-dissolved in CH₂Cl₂. The organic layer was washed with water, brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography, eluting with 2.5 % methanolic ammonia in EtOAc to yield the desired product (651 mg, 93 %). ¹H NMR (CD₃OD) δ 8.40 (d, 1H, J=6Hz), 7.86 (d, 1H, J=10 Hz), 7.74 (t, 1H, J=9.8 Hz), 7.19 (t, 1H, J=8Hz), 7.11 (s, 1H), 6.56 (br s, 1H), 3.45 (t, 1H J=9.5 Hz), 2.84 (t, 2H, J=7.7 Hz), 2.11 (d, 2H, J=15 Hz), 1.75 (d, 2H, J=15.5 Hz), 1.35 (s, 9H), 1.20-1.13 (m, 2H), 1.08-0.96 (m, 2H). ESMS *m/e*: 389 (M+H)⁺.

(tert-butoxy)-N-[(*trans*-4-{[4-(3-methylpyrazin-2-yl)(1,3-thiazol-2-yl)]amino}

cyclohexyl)methyl]carboxamide: DIEA (2.0 g, 16 mmol) was added to a solution containing 2-bromo-1-(3-methylpyrazin-2-yl)ethan-1-one (3.0 g, 14 mmol), N-({*trans*-4-[(aminothioxomethyl)amino]cyclohexyl)methyl}(tert-butoxy)carboxamide (3 g, 10 mmol) and EtOH (10 mL). The mixture was refluxed for 3 h, cooled to rt and concentrated *in vacuo*. The residue was taken up in CH₂Cl₂, washed with NaHCO₃, brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by silica gel column chromatography with an increasing gradient of EtOAc in Hexanes gave the desired product (3.3 g, 82 %). ¹H NMR (CDCl₃) δ 8.42-8.38 (m, 2H), 7.05 (s, 1H), 5.05 (d, 1H, J=7.5 Hz), 4.65-4.58 (m, 1H), 3.40-3.3 (br, m, 1H), 3.02 (t, 2H, J=6.4 Hz), 2.84 (s, 3H), 2.26 (d, 2H, J=12.7 Hz), 1.86 (d, 2H, J=12.6 Hz), 1.52-1.42 (m, 10H), 1.30-1.05 (m, 4H). ESMS *m/e*: 404 (M+H)⁺.

Intermediates of Formula XV

[*trans*-4-(aminomethyl)cyclohexyl](4-(2-pyridyl)(1,3-thiazol-2-yl))amine: (tert-butoxy)-N-({*trans*-4-[(4-(2-pyridyl)(1,3-thiazol-2-yl))amino]cyclohexyl)methyl)

carboxamide (651 mg, 1.68 mmol) was treated with 4 M HCl in dioxane (8 mL) under argon atmosphere. The reaction mixture was stirred at rt overnight and the product precipitated from the reaction mixture. The resulting precipitate was collected by filtration as the hydrochloride salt (507 mg). ¹H NMR (CDCl₃) δ 8.70 (d, 1H, J=6.5 Hz), 8.49 (t, 1H, J=10 Hz), 8.42 (d, 2H, J=10 Hz), 7.87 (s, 1H), 7.85 (d, 1H, J=8.5 Hz), 3.81 (m, 1H), 2.86 (d, 2H, J=8.5 Hz), 2.25 (d, 2H, J=15.5 Hz), 1.95 (d, 2H, J=15 Hz), 1.72 (m, 1H), 1.40 (q, 2H, J=15 Hz), 1.27 (q, 2H, J=16 Hz). ESMS *m/e*: 289 (M+H)⁺.

[*trans*-4-(aminomethyl)cyclohexyl](4-(3-methylpyrazin-2-yl)(1,3-thiazol-2-yl))amine:

Analogously, N-Boc deprotection was performed as described in the procedure above. ¹H NMR (CD₃OD) δ 8.67-8.61 (m, 2H), 7.53 (s, 1H), 3.68-3.59 (br m, 1H), 2.89-2.84 (m, 5H), 2.27 (d, 2H, J=12.8 Hz), 2.02 (d, 2H, J=12.0 Hz), 1.82-1.72 (m, 2H), 1.63-1.54 (m, 1H), 1.34-1.24 (m, 4H). ESMS *m/e*: 304 (M+H)⁺.

Intermediates of Formula IV (wherein m=n=1)

Representative compounds as described in Scheme 4 were synthesized as follows:

(*trans*-4-[(tert-butoxy)carbonylamino]methyl)cyclohexyl)-N-methoxy-N-methylcarboxamide: 1-Methylmorpholine (5.0 g, 49.6 mmol) was added to a stirred solution of *trans*-4-[(tert-butoxy)carbonylamino]methylcyclohexanecarboxylic acid (8.5 g, 33 mmol) in CH₂Cl₂ (100 mL). The solution was cooled to -20 °C and isobutyl chloroformate (5.9 g, 43.0 mmol) was added drop wise over a period of 10 min. The resulting pale yellow color solution was allowed to warm to rt and then stirred for an additional hour. The solution was cooled to -20 °C and 1-Methylmorpholine (5.0 g, 50 mmol) was added followed by the addition of a solution of N, O-dimethylhydroxylamine (3.9 g, 40 mmol) in CH₂Cl₂. After the addition was complete, the solution was warmed to rt and was stirred overnight. The reaction was quenched with water and washed successively with aqueous citric acid, water, and brine. The CH₂Cl₂ layer was concentrated *in vacuo* and the resulting material was purified by silica gel column chromatography (30 % EtOAc in Hexanes) to afford the desired product as a colorless viscous material (7.8 g, 79 %). ¹H NMR (CDCl₃) δ 4.67 (br s, 1H), 3.69 (s, 3H), 3.18 (s, 3H), 2.99 (t, 2H, J=6.4 Hz), 2.65 (br m, 1H, J=9.6 Hz), 1.83

(d, 2H, J=10.0 Hz), 1.53–1.49 (m, 3H), 1.44 (s, 9H), 1.0–0.91 (m, 4H). ESMS *m/e*: 300 (M+H)⁺.

(tert-butoxy)-N-[(*trans*-4-formylcyclohexyl)methyl]carboxamide: A solution of 1M LAH
5 in THF (24.7 mL, 24.7 mmol) was added over a period of 15 min to a stirred solution
of (*trans*-4-[(*tert*-butoxy)carbonylamino]methyl)cyclohexyl)-N-methoxy-N-
methylcarboxamide (7.4 g, 24.7 mmol) in Et₂O (200 mL) under argon atmosphere at
–78 °C. After the addition was complete, the reaction was stirred for an additional 15
min then allowed to warm to 0 °C for 1 h and then re-cooled to –78 °C. The reaction
10 was quenched with 1N aqueous KHSO₄ and filtered over celite containing Na₂SO₄.
The celite was washed with Et₂O and the filtrate was concentrated *in vacuo* to afford
the desired product as a viscous gum (6.0 g). ¹H NMR (CDCl₃) δ 9.62 (s, 1H), 4.67
(br s, 1H), 3.00 (t, 2H, J=6.0 Hz), 2.19 (t, 1H, J=8.8 Hz), 2.03 (d, 2H, J=13.2 Hz),
1.89 (d, 2H, J=13.2 Hz), 1.44 (s, 9H), 1.27 (dq, 2H, J=25.6, 13.2 and 3.6 Hz), 1.05–
15 0.95 (m, 2H). ESMS *m/e*: 186 ((M+H)-55)⁺.

N-[(*trans*-4-(aminomethyl)cyclohexyl)methyl](*tert*-butoxy)carboxamide: NaCNBH₃
(2.4 g, 38 mmol) was added to stirred a solution containing the (*tert*-butoxy)-N-
[(*trans*-4-formylcyclohexyl)methyl]carboxamide (6.0 g, 25 mmol), ammonium acetate
20 (29 g, 374 mmol) and MeOH (100 mL) under argon atmosphere at rt. The solution
was stirred for 18 h at rt then concentrated *in vacuo*. The crude product was purified
by silica gel column chromatography to yield the desired amine (1.5 g, 26 %). ¹H
NMR (CDCl₃) δ 4.64 (br s, 1H), 2.97 (t, 2H, J=6.4 Hz), 2.53 (d, 1H, J=6.4 Hz), 2.41
(d, 1H, J=6.4 Hz), 1.79 (q, 2H, J=19.6 and 9.2 Hz), 1.44 (s, 9H), 1.50–1.30 (br m,
25 4H), 1.0–0.81 (m, 4H). ESMS *m/e*: 242 (M+H)⁺.

Intermediate of Formula XX

2-Methyl-nicotinoyl chloride: Oxalyl chloride (2.78 g, 21.75 mmol) was added to a
stirred solution of 2-methyl-nicotinic acid (2.0 g, 14.5 mmol) in CH₂Cl₂ (50 mL) at rt
30 under an argon atmosphere. A drop of DMF was added to initiate the reaction. After
stirring for 24 h at rt, the solvents were removed *in vacuo* to afford the acid chloride
as a solid (2.85 g, >99 %). ESMS *m/e*: 155 (M+H)⁺.

Intermediates of Formula XXII

35 2-Chloro-1-(2-methyl-pyridin-3-yl)-ethanone: A 2M ethereal solution of
trimethylsilyldiazomethane (15 mL, 11.60 g, 101.7 mmol) was added drop wise to a

solution of 2-methyl-nicotinoyl chloride (2.85 g, 14.9 mmol) in dioxane (30 mL) at 0 °C. The reaction temperature was raised to rt to afford 2-diazenyl-1-(2-methyl-pyridin-3-yl)-ethanone, which was used without further purification. 4M HCl in dioxane (10 mL) was added to the crude diazenyl derivative at 0 °C and the reaction
5 was stirred for 2 h at rt. The solution was concentrated *in vacuo* to afford the desired compound (2.81 g, 94 %) as a brown colored solid as the HCl salt. ESMS *m/e*: 170 (M+H)⁺.

2-Bromo-1-pyridin-2-yl-propan-1-one: 33 % Hydrogen bromide in acetic acid was
10 added (7.8 mL, 45.1 mmol) to a solution of 1-pyridin-2-yl-propan-1-one (6.0 g, 45.1 mmol) in acetic acid (50 mL) with vigorous stirring. Bromine (2.32 mL, 45.1 mmol) was added to the solution and the reaction was stirred at rt for 2 h. The orange colored solution was concentrated *in vacuo* to give the desired compound (15.7 g, >99) as a semi solid. ESMS *m/e*: 213 (M+H)⁺.

15 The following compounds were prepared analogously:

2-Bromo-1-(3-methyl-pyridin-2-yl)-propan-1-one. ESMS *m/e*: 228 (M+H)⁺.

2-Bromo-1-(4-methyl-pyridin-2-yl)-propan-1-one. ESMS *m/e*: 228 (M+H)⁺.

20 2-Bromo-1-pyrazin-2-yl-ethanone. ESMS *m/e*: 201 (M+H)⁺.

2-Bromo-1-(6-methyl-pyridin-2-yl)-propan-1-one. ESMS *m/e*: 228 (M+H)⁺.

Intermediate of Formula XXIII

6-Methyl-pyridine-2-carboxylic acid N-methoxy-N-methyl-amide: DIEA (1.85 mL,
25 1.37 g, 10.62 mmol) was added to a stirred solution of 6-methyl-pyridine-2-carboxylic acid (0.97 g, 7.01 mmol) in CH₂Cl₂ (30 mL) at rt. The reaction mixture was cooled to 0 °C and isobutyl chloroformate (1.06 g, 1.20 mL, 7.79 mmol) was added. The reaction was stirred for 30 min at 0 °C, then a solution of N,O-dimethyl-hydroxyl-amine hydrochloride (1.03 g, 10.62 mmol) and DIEA (1.85 mL, 1.37 g, 10.62 mmol)
30 in CH₂Cl₂ was added. After stirring for 18 h at rt, the organic layer was diluted with CH₂Cl₂ and carefully washed with saturated aqueous NaHCO₃. The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by silica gel flash chromatography (50 % EtOAc in Hexanes) to furnish the product as an oil (1.16 g, 91 %). ESMS *m/e*: 181 (M+H)⁺.

Intermediate of Formula XXIV

1-Pyridin-2-yl-propan-1-one: 3M Et₂O solution of ethylmagnesium bromide (19.2 mL, 57.6 mmol) was added to a stirred solution of pyridine-2-carbonitrile (5.0 g, 48.0 mmol) in THF (80 mL) at -78 °C. The reaction mixture was allowed to warm to rt.

- 5 The reaction mixture was acidified with aqueous citric acid solution. THF was removed in vacuo and the product was extracted with EtOAc. The organic layers were combined and washed with aqueous NaHCO₃ and brine. Upon concentration in vacuo, the product was obtained as a pale yellow colored liquid. ESMS *m/e*: 271 (2M+H)⁺.

10

The following compounds were prepared analogously:

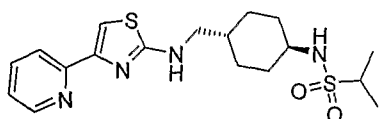
1-(3-Methyl-pyridin-2-yl)-propan-1-one. ESMS *m/e*: 150 (M+H)⁺.

1-(4-Methyl-pyridin-2-yl)-propan-1-one. ESMS *m/e*: 150 (M+H)⁺.

- 15 1-(6-Methyl-pyridin-2-yl)-propan-1-one. ESMS *m/e*: 150 (M+H)⁺.

The following compounds of the invention were prepared from intermediate Formula VI, synthesized according to the procedures described in Schemes 1 and 2:

- 20 **Example 1a** [(methylethyl)sulfonyl]((*trans*-4-[(4-(2-pyridyl)(1,3-thiazol-2-yl))amino]methyl)cyclohexyl)amine:



N-([[(*trans*-4-[(methylethyl)sulfonyl]amino)cyclohexyl)methyl]amino]thioxomethyl)

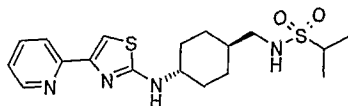
- amide (0.60 g, 2.0 mmol) was added to a stirred solution of 2-bromo-1-(2-pyridyl)ethan-1-one hydrobromide (0.57 g, 2.0 mmol) in EtOH (20 mL) at rt followed by the addition of DIEA (1.05 mL, 6.0 mmol). The reaction mixture was heated at reflux for 4 h, cooled to rt, and concentrated *in vacuo*. The resultant residue was re-dissolved in CHCl₃ and washed successively with aqueous citric acid, water and brine. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (60 % EtOAc in Hexanes) to afford the desired product as a tan colored solid (0.56 g, 69 %). ¹H NMR (CDCl₃) δ 8.58 (d, 1H, J=4.8 Hz), 7.89 (dt, 1H, J=7.6 and 1.2 Hz), 7.71 (td, 1H, J=7.8 and 2.0 Hz), 7.17 (td, 1H, J=4.8 and 1.2Hz), 5.25 (br s, 1H), 3.85 (d, 1H, J=8.4 Hz), 3.25 (br m, 1H), 3.18 (t, 2H, J=6.4 Hz), 2.14 (dt, 2H, J=12.0 and 1.2 Hz), 2.19 (br, d,

2H, J=12.8 Hz), 1.62 (br m, 3H), 1.38 (d, 6H, J=6.8 Hz), 1.25 (dq, 2H, J=12.8 and 1.6 Hz). LC-MS m/e: 395 (M+H)⁺; t_R = 2.14 min (Method-A).

The following compounds were prepared analogously:

5

Example 1b [(methylethyl)sulfonyl]({trans-4-[(4-(2-pyridyl)(1,3-thiazol-2-yl))amino]cyclohexyl)methyl)amine:



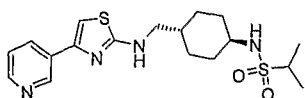
10

Prepared from N-({[(trans-4-[(methylethyl)sulfonyl]methylamino]cyclohexyl)amino]thioxomethyl) amide and 2-bromo-1-(2-pyridyl)ethan-1-one.

Yield: 76 %. LC-MS: m/e 395 (M+H)⁺; t_R = 5.28 min (Method-B).

Example 1c [(methylethyl)sulfonyl](trans-4-[(4-(3-pyridyl)(1,3-thiazol-2-yl))amino]methyl)cyclohexyl)amine:

15

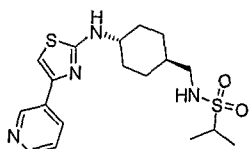


Prepared from N-({[(trans-4-[(methylethyl)sulfonyl]amino]cyclohexyl)methyl]amino}thioxomethyl) amide and 2-bromo-1-(3-pyridyl)ethan-1-one.

Yield: 31 %. LC-MS: m/e 395 (M+H)⁺; t_R = 2.02 min (Method-A).

20

Example 1d [(methylethyl)sulfonyl]({trans-4-[(4-(3-pyridyl)(1,3-thiazol-2-yl))amino]cyclohexyl)methyl)amine:

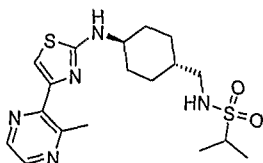


Prepared from N-({[(trans-4-[(methylethyl)sulfonyl]methylamino]cyclohexyl)amino]thioxomethyl) amide and 2-bromo-1-(3-pyridyl)ethan-1-one.

25

Yield: 27 %. LC-MS: m/e 395 (M+H)⁺; t_R = 2.37 min (Method-C).

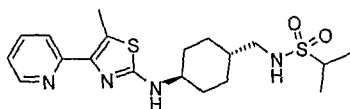
Example 1e [(methylethyl)sulfonyl]({trans-4-[(4-(3-methylpyrazin-2-yl)(1,3-thiazol-2-yl))amino]cyclohexyl)methyl)amine:



Prepared from N-({[(*trans*-4-[(methylethyl)sulfonyl]methylamino)cyclohexyl]amino}thioxomethyl) amide and 2-bromo-1-(3-methylpyrazin-2-yl)ethan-1-one.

Yield: 44 %. LC-MS: m/e 410 ($M+H$)⁺; t_R = 2.05 min (Method-A).

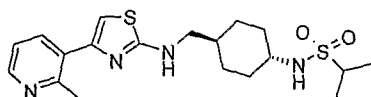
- 5 **Example 1f** [(methylethyl)sulfonyl]({*trans*-4-[(4-(2-pyridyl)(5-methyl-thiazol-2-yl))amino] cyclohexyl}methyl)amine:



Prepared from N-({[(*trans*-4-[(methylethyl)sulfonyl]methylamino)cyclohexyl]amino}thioxomethyl) amide and 2-bromo-1-pyridin-2-yl-propan-1-one.

- 10 Yield: 41 %. LC-MS m/e : 409 ($M+H$)⁺; t_R = 0.70 min (Method-E).

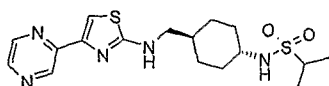
Example 1g [(methylethyl)sulfonyl]({*trans*-4-[(4-(2-methyl-pyridin-3-yl)(1,3-thiazol-2-yl))amino]methyl} cyclohexyl)amine:



- 15 Prepared from N-({[(*trans*-4-[(methylethyl)sulfonyl]amino)cyclohexyl]methyl]amino}thioxomethyl) amide and 2-chloro-1-(2-methyl-pyridin-3-yl)-ethanone.

Yield: 47 %. LC-MS m/e : 409 ($M+H$)⁺; t_R = 0.52 min (Method-E).

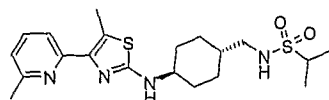
- 20 **Example 1h** [(methylethyl)sulfonyl]({*trans*-4-[(4-(2-pyrazinyl)(1,3-thiazol-2-yl))amino]methyl} cyclohexyl)amine:



Prepared from N-({[(*trans*-4-[(methylethyl)sulfonyl]amino)cyclohexyl]methyl]amino}thioxomethyl) amide and 2-bromo-1-pyrazin-2-yl-ethanone.

Yield: 37 %. LC-MS m/e : 396 ($M+H$)⁺; t_R = 0.95 min (Method-D).

- 25 **Example 1i** [(methylethyl)sulfonyl]({*trans*-4-[(4-(6-methyl-pyridin-2-yl)(5-methyl-thiazol-2-yl))amino] cyclohexyl}methyl)amine:

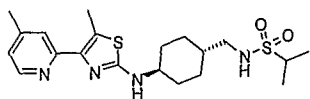


Prepared from N-({[(*trans*-4-[(methylethyl)sulfonyl]methylamino)cyclohexyl]amino}thioxomethyl) amide and bromo-1-(6-methyl-pyridin-2-yl)-propan-1-one.

- 30

Yield: 68 %. LC-MS m/e: 423 (M+H)⁺; t_R = 0.74 min (Method-E).

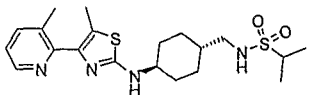
Example 1j [(methylethyl)sulfonyl]({trans-4-[(4-(4-methyl-pyridin-2-yl)(5-methyl-thiazol-2-yl))amino] cyclohexyl)methyl)amine:



Prepared from N-({[(trans-4-[(methylethyl)sulfonyl]methylamino)cyclohexyl]amino}thioxomethyl) amide and 2-bromo-1-(4-methyl-pyridin-2-yl)-propan-1-one.

Yield: 72 %. LC-MS m/e: 423 (M+H)⁺; t_R = 0.67 (Method-E).

Example 1k [(methylethyl)sulfonyl]({trans-4-[(4-(3-methyl-pyridin-2-yl)(5-methyl-thiazol-2-yl))amino]cyclohexyl)methyl)amine:

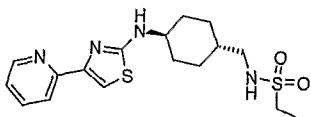


Prepared from N-({[(trans-4-[(methylethyl)sulfonyl]methylamino)cyclohexyl]amino}thioxomethyl) amide and bromo-1-(3-methyl-pyridin-2-yl)-propan-1-one.

Yield: 79 %. LC-MS m/e: 423 (M+H)⁺; t_R = 0.66 min (Method-E).

The following compounds of the invention were synthesized according to the procedures described in Scheme 3.

Example 2a (ethylsulfonyl)({trans-4-[(4-(2-pyridyl)(1,3-thiazol-2-yl))amino] cyclohexyl)methyl)amine:



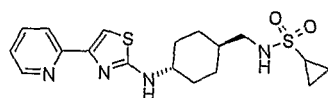
N,N-diisopropyl-N-ethylamine (0.52 ml, 3.0 mmol) was added to a solution of [trans-4-(aminomethyl)cyclohexyl](4-(2-pyridyl)(1,3-thiazol-2-yl))amine (578 mg, 2.00 mmol)

in CH₂Cl₂ at -78 °C. Ethanesulfonyl chloride (0.19 mL, 2.0 mmol) was then added slowly to the solution and stirring was continued for 45 min. The reaction was allowed to warm to rt then stirred for an additional 3 h. Saturated aqueous NaHCO₃ was added to the reaction mixture and stirred for 15 min. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The organic layers were

combined, dried over Na₂SO₄, and concentrated *in vacuo*. Purification by silica gel column chromatography using 8/ 2/ 1/ 1: Hexanes/ EtOAc/ MeOH/ TEA as the eluent afforded the desired product as a beige solid (655 mg, 86 %). Further purification

was achieved by triturating with cold CH_2Cl_2 . ^1H NMR (CDCl_3) δ 8.58 (ddd, 1H, $J=0.8, 1.8$ and 4.8 Hz), 7.90 (d, 1H, $J=6.9$ Hz), 7.71 (dt, 1H, $J=1.9, 7.5$ Hz), 7.28 (s, 1H), 7.19–7.14 (m, 1H), 5.00 (br d, 1H, $J=8.0$ Hz), 4.17 (br s, 1H), 3.35 (m, 1H), 3.05 (q, 2H, $J=14.7$ and 7.2 Hz) 3.04 (t, 2H, $J = 8.3$ Hz), 2.29 (br d, 2H, $J=4.5$ Hz), 1.92 (br d, 2H, $J=6.6$ Hz), 1.36 (m, 1H), 1.38 (t, 3H, $J=7.4$ Hz), 1.17 (m, 4H). LCMS: m/e 381 ($\text{M}+\text{H}$) $^+$.

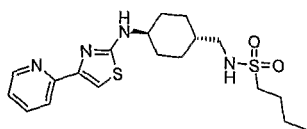
Example 2b (cyclopropylsulfonyl)({*trans*-4-[(4-(2-pyridyl)(1,3-thiazol-2-yl))amino]cyclohexyl)methyl)amine:



Prepared from [*trans*-4-(aminomethyl)cyclohexyl](4-(2-pyridyl)(1,3-thiazol-2-yl))amine and cyclopropanesulfonyl chloride.

Yield: 80 %. LCMS: m/e 393.2 ($\text{M}+\text{H}$) $^+$; $t_R = 5.19$ min (Method-B).

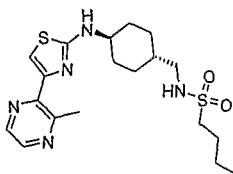
Example 2c (butylsulfonyl)({*trans*-4-[(4-(2-pyridyl)(1,3-thiazol-2-yl))amino]cyclohexyl)methyl)amine:



Prepared from [*trans*-4-(aminomethyl)cyclohexyl](4-(2-pyridyl)(1,3-thiazol-2-yl))amine and butanesulfonyl chloride.

Yield: 98 %. LCMS: m/e 409.2 ($\text{M}+\text{H}$) $^+$; $t_R = 6.20$ min (Method-B).

Example 2d (butylsulfonyl)[({*trans*-4-[4-(3-methylpyrazin-2-yl)(1,3-thiazol-2-yl)]amino}cyclohexyl)methyl]amine:



Prepared from [*trans*-4-(aminomethyl)cyclohexyl](4-(3-methylpyrazin-2-yl)(1,3-thiazol-2-yl))amine and butanesulfonyl chloride.

Yield: 19 %. LCMS: m/e 424 ($\text{M}+\text{H}$) $^+$; $t_R = 2.28$ min (Method-A).

Formulations

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art.

5

For example, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/ or diluents and subsequently compressing the mixture in a conventional tableting machine may prepare tablets. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colorings, flavorings, preservatives etc. may be used provided that they are compatible with the active ingredients.

10

1) Tablets containing 5.0 mg of Compound 2b calculated as the free base:

15	Compound	5.0 mg
	Lactose	60 mg
	Maize starch	30 mg
	Hydroxypropylcellulose	2.4 mg
	Microcrystalline cellulose	19.2 mg
20	Croscarmellose Sodium Type A	2.4 mg
	Magnesium stearate	0.84 mg

2) Tablets containing 0.5 mg of Compound 2b calculated as the free base:

	Compound	0.5 mg
25	Lactose	46.9 mg
	Maize starch	23.5 mg
	Povidone	1.8 mg
	Microcrystalline cellulose	14.4 mg
	Croscarmellose Sodium Type A	1.8 mg
30	Magnesium stearate	0.63 mg

3) Syrup containing 25 mg of Compound 2b per milliliter:

	Compound	25 mg
	Sorbitol	500 mg
35	Hydroxypropylcellulose	15 mg
	Glycerol	50 mg

	Methyl-paraben	1 mg
	Propyl-paraben	0.1 mg
	Ethanol	0.005 mL
	Flavor	0.05 mg
5	Saccharin	0.5 mg
	Water	1 mL

In-Vitro Methods

10 The pharmacological properties of the compounds of the present invention were evaluated at the cloned human NPY Y5 receptor using the protocols disclosed in U.S. Patent No. 6,124,331, the contents of which are hereby incorporated by reference.

15 Using this protocol, the binding by the compound to a radiolabeled ligand (¹²⁵I-labeled PYY or an alternative radioligand such as ¹²⁵I-labeled NPY) to membranes of cloned human NPY Y5 receptors expressed in COS-7 cells was determined *in vitro*.

Radioligand Binding

20 Membrane suspensions were diluted in binding buffer supplemented with 0.1 % bovine serum albumin to yield an optimal membrane protein concentration so that ¹²⁵I-PYY bound by membranes in the assay was less than 10 % of ¹²⁵I-PYY delivered to the sample (100,000 dpm/ sample = 0.08 nM for competition binding assays). ¹²⁵I-PYY and small molecule ligand competitors were also diluted to desired

25 concentrations in supplemented binding buffer. Individual samples were then prepared in 96-well polypropylene microtiter plates by mixing ¹²⁵I-PYY, competing peptides or supplemented binding buffer (25 μ L), and finally, membrane suspensions (200 μ L). Samples were incubated in at 30 °C for 120 min. Incubations were terminated by filtration over Whatman GF/C filters (pre-coated with 1%

30 polyethyleneimine and air-dried before use), followed by washing with 5 mL of ice-cold binding buffer. Filter-trapped membranes were impregnated with MeltiLex solid scintillant (Wallac, Turku, Finland) and counted for ¹²⁵I-PYY in a Wallac Beta-Plate Reader. Alternatively, incubations were carried out in GF/C filter plates (pre-coated with 1 % polyethyleneimine and air-dried before use), followed by vacuum filtration

35 and three washes of 300 μ L of ice-cold binding buffer. 50 μ L of UltimaGold (Packard) scintillant were added and counted for ¹²⁵I-PYY in a Wallac MicroBeta Trilux. Non-

specific binding was defined by 300 nM human PYY. Specific binding in time course and competition studies was typically 80 %; most non-specific binding was associated with the filter. Binding data were analyzed using nonlinear regression and statistical techniques available in the GraphPAD Prism package (San Diego, Calif.).

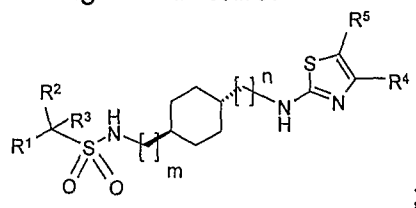
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The binding affinities for the compounds in the present invention, exemplified above, at the NPY Y5 receptor were determined to be 75 nM or less. For the majority of the compounds, the K_i values are 10 nM or less, and for a group of compounds the K_i values are 5 nM or less.

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What is claimed:

Claim 1. A compound having the structure:



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wherein R¹ is H or C₁-C₆ straight chained or branched alkyl;

wherein R² is C₁-C₆ straight chained or branched alkyl;

10 or wherein R¹, R² and the carbon to which they are attached may form C₃-C₆ cycloalkyl;

wherein R³ is H or methyl;

15 wherein R⁴ is 2-pyridyl, 3-pyridyl or pyrazinyl, wherein the 2-pyridyl, 3-pyridyl or pyrazinyl may be substituted with methyl;

wherein R⁵ is H or methyl;

20 wherein m is an integer from 0 to 2 inclusive; and

wherein n is an integer from 0 to 2 inclusive;

or a pharmaceutically acceptable salt thereof.

25

Claim 2. The compound of claim 1, wherein R⁵ is H.

Claim 3. The compound of claim 1, wherein R⁵ is methyl.

30 Claim 4. The compound of claim 2, wherein R³ is H;

wherein R⁴ is 2-pyridyl or pyrazinyl, wherein the 2-pyridyl or pyrazinyl may be substituted with methyl;

35 wherein m is 0 or 1; and

wherein n is 0 or 1.

Claim 5. The compound of claim 4, wherein R¹ is H or C₁-C₄ straight chained or branched alkyl; and wherein R² is C₁-C₄ straight chained or branched alkyl.

5 Claim 6. The compound of claim 5, wherein R¹ is H, methyl or ethyl;

wherein R² is methyl or ethyl; and

wherein R⁴ is 2-pyridyl, wherein the 2-pyridyl may be substituted with methyl.

10

Claim 7. The compound of claim 6, wherein R¹ is methyl and wherein R² is methyl.

Claim 8. The compound of claim 7, wherein n is 1.

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Claim 9. The compound of claim 4, wherein R¹, R² and the carbon to which they are attached form C₃-C₆ cycloalkyl.

Claim 10. The compound of claim 9, wherein R⁴ is 2-pyridyl.

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Claim 11. The compound of claim 3, wherein R¹ is H or C₁-C₄ straight chained or branched alkyl;

wherein R² is C₁-C₄ straight chained or branched alkyl;

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wherein R³ is H;

wherein R⁴ is 3-pyridyl or pyrazinyl, wherein the 3-pyridyl or pyrazinyl is substituted with methyl;

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wherein m is 0 or 1; and

wherein n is 0 or 1.

35 Claim 12. The compound of claim 3, wherein R¹ is H or C₁-C₄ straight chained or branched alkyl;

wherein R² is C₁-C₄ straight chained or branched alkyl;

40 wherein R³ is H;

wherein R⁴ is 2-pyridyl, wherein the 2-pyridyl may be substituted with methyl;

wherein m is 0 or 1; and

5

wherein n is 0 or 1.

Claim 13. The compound of claim 12, wherein R¹ is methyl; wherein R² is methyl; and wherein n is 0.

10

Claim 14. The compound of claim 11, wherein R¹ is methyl; wherein R² is methyl; and wherein m is 0.

Claim 15. The compound of claim 14, wherein R⁴ is 3-pyridyl, wherein the 3-pyridyl is substituted with methyl.

15

Claim 16. The compound of claim 1, wherein the compound is selected from the group consisting of [(methylethyl)sulfonyl](*trans*-4-[(4-(2-pyridyl)(1,3-thiazol-2-yl))amino]methyl)cyclohexyl)amine; [(methylethyl)sulfonyl](*trans*-4-[(4-(2-pyridyl)(1,3-thiazol-2-yl))amino] cyclohexyl)methyl)amine;

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[(methylethyl)sulfonyl](*trans*-4-[(4-(3-pyridyl)(1,3-thiazol-2-yl))amino]methyl)cyclohexyl)amine; [(methylethyl)sulfonyl](*trans*-4-[(4-(3-pyridyl)(1,3-thiazol-2-yl))amino] cyclohexyl)methyl)amine; [(methylethyl)sulfonyl](*trans*-4-[(4-(3-methylpyrazin-2-yl)(1,3-thiazol-2-yl))amino]cyclohexyl)methyl)amine;

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[(methylethyl)sulfonyl](*trans*-4-[(4-(2-pyridyl)(5-methyl-thiazol-2-yl))amino]cyclohexyl)methyl)amine; [(methylethyl)sulfonyl](*trans*-4-[(4-(2-methyl-pyridin-3-yl)(1,3-thiazol-2-yl))amino]methyl) cyclohexyl)amine; [(methylethyl)sulfonyl](*trans*-4-[(4-(2-pyrazinyl)(1,3-thiazol-2-yl))amino]methyl) cyclohexyl)amine;

[(methylethyl)sulfonyl](*trans*-4-[(4-(6-methyl-pyridin-2-yl)(5-methyl-thiazol-2-

30

yl))amino] cyclohexyl)methyl)amine; [(methylethyl)sulfonyl](*trans*-4-[(4-(4-methyl-pyridin-2-yl)(5-methyl-thiazol-2-yl))amino] cyclohexyl)methyl)amine;

[(methylethyl)sulfonyl](*trans*-4-[(4-(3-methyl-pyridin-2-yl)(5-methyl-thiazol-2-

yl))amino]cyclohexyl)methyl)amine; (ethylsulfonyl)(*trans*-4-[(4-(2-pyridyl)(1,3-thiazol-2-yl))amino] cyclohexyl)methyl)amine; (cyclopropylsulfonyl)(*trans*-4-[(4-(2-

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pyridyl)(1,3-thiazol-2-yl))amino] cyclohexyl)methyl)amine; (butylsulfonyl)(*trans*-4-[(4-(2-pyridyl)(1,3-thiazol-2-yl))amino] cyclohexyl)methyl)amine; and

(butylsulfonyl)[({*trans*-4-[4-(3-methylpyrazin-2-yl)(1,3-thiazol-2-yl)]amino}cyclohexyl)methyl]amine.

5 Claim 17. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

Claim 18. Use of a compound as defined in claim 1 for the preparation of a pharmaceutical composition for treating a subject suffering from depression.

10 Claim 19. Use of a compound as defined in claim 1 for the preparation of a pharmaceutical composition for treating a subject suffering from anxiety.

Claim 20. Use of a compound as defined in claim 1 for the preparation of a pharmaceutical composition for treating a subject suffering from obesity.

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