

Case 23957DIAMINOCYCLOHEXANE AND DIAMINOCYCLOPENTANE DERIVATIVES

The invention relates to melanin-concentrating hormone receptor antagonists and derivatives thereof. The antagonists and derivatives thereof are useful for the treatment of obesity, hyperphagia, anxiety, depression and related disorders and diseases.

Melanin-concentrating hormone (MCH) is a cyclic peptide that was first isolated
5 from the pituitary of chum salmon (Kawauchi et al. (1983) *Nature* **305**: 321-333). The sequence for MCH has been shown to be identical in all teleost fish where it causes melanin granulation and, hence, regulates color change. Recent reports also suggest MCH plays a role in food intake in teleosts. MCH also inhibits release of ACTH thus acting as an antagonist of α -MSH. MCH was subsequently identified in mammals as a
10 cyclic nonapeptide. The first MCH receptor (later termed MCHR1) is a G-protein coupled receptor (GPCR) and was identified using a "reverse pharmacology" approach. That is, it was demonstrated that the natural ligand of orphan GPCR, SLC-1, was MCH in mammals. Subsequent to this determination, a second MCH receptor (MCHR-2) has been identified. The role of MCH in feeding behavior in mammals has been the subject
15 of investigation for a number of years (Qu, et al. (1996) *Nature*, **380**: 243-247; Rossi et al. (1997) *Endocrinology* **138**: 351-355; Shimada et al. (1998) *Nature* **396**: 670-674). MCH is predominantly expressed in the lateral hypothalamus and the *zona incerta* of the central nervous system (CNS). Central administration of MCH is known to stimulate food intake and regulate energy balance. MCH is upregulated in the lateral hypothalamus
20 during fasting (Rossi et al. (1997) *Endocrinology* **138**: 351-355). Knockout experiments have shown that mice lacking the MCH peptide are lean, hypophagic and maintained elevated metabolic rates. MCH mRNA levels are increased in both normal and obese mice. Transgenic mice that over-express MCH are obese and insulin resistant. Genetically altered animals that lack the gene encoding the MCH receptor are moderately
25 hyperphagic but show resistance to becoming obese and have an increased metabolic rate (Shimada et al. (1998) *Nature* **396**: 670-674). MCH is thought to exert its effects on feeding behavior by binding to an MCH receptor (MCHR1 or MCHR2) resulting in mobilization of intracellular calcium and a concomitant reduction in cyclic AMP levels. The consistency in these findings suggests that MCH antagonism could safely lead to
30 weight loss in humans. In further support of this, a number of studies describe statistically significant reduction of food intake in rodents following acute administration of MCH receptor antagonists and/or statistically significant reduction of body weight

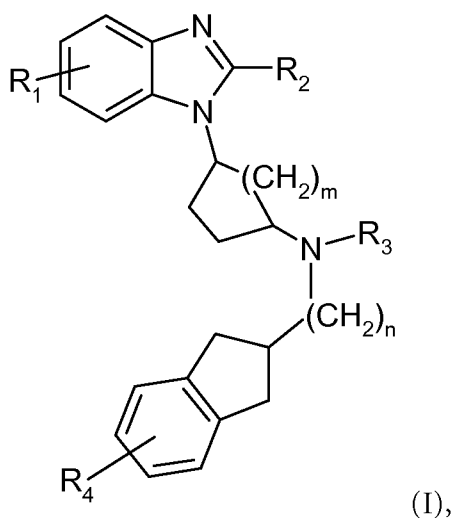
after chronic administration of small molecule MCH receptor antagonists (Borowsky et al. (2002) *Nature Medicine* 8(8):825-830; Souers et al. (2005) *Bioorg. Med. Chem. Lett.* 15: 2752-2757; Vasudevan et al. (2005) *Bioorg. Med. Chem. Lett.* 15: 4174-4179; Kym et al. (2005) *J. Med. Chem.* 5888-91; McBriar et al. (2005) *J. Med. Chem.* 48: 2274; Takekawa et al. (2002) *Eur. J. Pharmacol.* 438(3): 129-135; Kowalski et al. *Eur. J. Pharmacol.* (2004) 497: 41-47). The precise role of MCH in attenuating food intake is not clear from these studies because the small-molecule MCH receptor antagonists described are either 1) unselective for the MCH receptor or 2) no selectivity data is disclosed.

MCHR1 antagonism with a small molecule is now recognized as a promising strategy for the treatment of obesity. The following relate to small-molecule MCH receptor antagonists: Kato et al. WO2001/21577; Chen et al. WO2002/089729; Collins et al. WO2003/105850; Souers et al. US2005/0137243; Hulme et al. WO2005/019167; Tempest et al. WO2005/019240; Barvian et al. WO2004092181; Barvian et al. WO2005/042541; McKittrick et al. WO2002/051809; Sasikumar et al. WO2005/034947; Devita et al. WO2003/045313; Gillig et al. WO2005/040257; and Schwink et al. WO2004/072025.

MCH has been shown to modulate behaviors and disease states other than hyperphagia and obesity. MCHR1 antagonists have been shown to inhibit behavior in rodents that models depression and anxiety in humans (Hervieu (2003) *Expert Opinion on Therapeutic Targets* 7(4), 495-511 and references therein; Georgescu et al. (2005) *Journal of Neuroscience* 25(11), 2933-2940; Chaki et al. (2005) *Journal of Pharm. and Exptl. Therapeutics* 313, 831-839). These rodent models include forced swim test, vocalization and various models of social interaction. Recent studies also support a role of MCHR1 in cognition (Adamantidis et al. (2005) *European Journal of Neuroscience* 21, 2837-2844).

There is still a need for selective MCH receptor antagonists in order to address the role of the MCH receptor in food intake and regulation of body weight. Unlike a number of existing medications for weight loss, it is believed that a selective MCH receptor antagonist would provide a means of safely reducing food intake and body weight in humans. Such selective MCH receptor antagonists would be useful for the treatment of, for example, obesity, hyperphagia, anxiety, depression and related disorders.

In one embodiment of the present invention, provided is a compound of the general formula



wherein

- 5 R_1 is selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, halo and cyano;
- R_2 is selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, alkoxy and hydroxyalkyl;
- R_3 is selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, lower
10 alkylcarbonyl, aryl and heteroaryl;
- R_4 is selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, halo, lower haloalkyl and cyano;
- m is 1 or 2; and
- n is 0 or 1,
- 15 and pharmaceutically acceptable salts thereof.

In another embodiment, the present invention provides a compound of formula (I), wherein

- R_1 is selected from the group consisting of hydrogen, lower alkyl, halo and cyano;
- R_2 is selected from the group consisting of hydrogen, lower alkyl, alkoxy and
20 hydroxyalkyl;

R₃ is selected from the group consisting of hydrogen, lower alkyl, lower alkylcarbonyl and aryl;

R₄ is selected from the group consisting of hydrogen, lower alkyl, halo, lower haloalkyl and cyano;

5 m is 1 or 2; and

n is 0 or 1,

and pharmaceutically acceptable salts thereof.

In a further embodiment, a compound of formula (I) according to the invention is provided, wherein

10 R₁ is lower alkyl, halo or cyano; and

R₃ is hydrogen or lower alkyl.

Furthermore, a compound of formula (I) according to the invention is provided, wherein

R₂ is lower alkyl, alkoxy or hydroxyalkyl; and

15 R₄ is halo or cyano.

In a preferred embodiment, a compound of formula (I) according to the present invention is provided, wherein R₁ is lower alkyl, halo or cyano. More preferably, R₁ is halo or cyano. Most preferred is a compound of formula (I), wherein R₁ is methyl or chloro.

20 In another preferred embodiment, a compound of formula (I) is provided, wherein R₂ is lower alkyl, alkoxy or hydroxyalkyl. More preferably, R₂ is lower alkyl or hydroxyalkyl, with a compound being most preferred, wherein R₂ is methyl or 2-hydroxypropyl.

In a further embodiment, a compound of formula (I) according to the invention is
25 provided, wherein R₃ is hydrogen or acetyl. More preferably, R₃ is hydrogen.

In another preferred embodiment, a compound of formula (I) is provided, wherein R₄ is hydrogen, halo, lower haloalkyl or cyano. More preferably, a compound of formula

(I) is provided, wherein R₄ is hydrogen, bromo, chloro, fluoro, trifluoromethyl or cyano. Also preferred is a compound of formula (I) according to the invention, wherein R₄ is bromo, chloro, fluoro, trifluoromethyl or cyano.

In a further preferred embodiment, a compound of formula (I) is provided,
 5 wherein m is 2, meaning a compound of formula (I) comprising a 1,4-diaminocyclohexyl moiety.

A compound of formula (I), wherein m is 1 is also preferred.

In another preferred embodiment, a compound of formula (I) according to the present invention is preferred, wherein n is 1.

10 Examples of preferred compounds of formula (I) of the present invention are the following:
 cis-4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexyl]-indan-2-yl-amine,
 trans-(S)-(5-bromo-indan-2-ylmethyl)-[3-(2,5-dimethyl-benzoimidazol-1-yl)-
 cyclopentyl]-amine,
 15 trans-(5-chloro-indan-2-ylmethyl)-[3-(2,5-dimethyl-benzoimidazol-1-yl)-cyclopentyl]-
 amine,
 cis-(S)-(5-bromo-indan-2-ylmethyl)-[4-(2,5-dimethyl-benzoimidazole-1-yl)-
 cyclohexyl]-amine hydrochloride,
 cis-(S)-(5-bromo-indan-2-ylmethyl)-[3-(2,5-dimethyl-benzoimidazol-1-yl)-
 20 cyclopentyl]-amine,
 cis-(5-chloro-indan-2-yl)-[4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexyl]-amine;
 hydrochloride,
 cis-(S)-2-(1-{4-[(5-bromo-indan-2-ylmethyl)-amino]-cyclohexyl}-5-chloro-1H-
 benzoimidazol-2-yl)-propan-2-ol,
 25 cis-2-(5-chloro-1-{4-[(5-trifluoromethyl-indan-2-ylmethyl)-amino]-cyclohexyl}-1H-
 benzoimidazol-2-yl)-propan-2-ol,
 cis-2-(5-chloro-1-{4-[(indan-2-ylmethyl)-amino]-cyclohexyl}-1H-benzoimidazol-2-yl)-
 propan-2-ol,
 cis-2-(5-chloro-1-{4-[(5-chloro-indan-2-ylmethyl)-amino]-cyclohexyl}-1H-
 30 benzoimidazol-2-yl)-propan-2-ol,
 cis-(5-chloro-indan-2-ylmethyl)-[4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexyl]-
 amine,
 cis-[4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexyl]-(5-trifluoromethyl-indan-2-
 ylmethyl)-amine,
 35 cis-[4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexyl]-indan-2-ylmethyl-amine,

- cis-(S)-2-({4-[5-chloro-2-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1-yl]-cyclohexylamino}-methyl)-indan-5-carbonitrile,
 cis-(S)-2-{{4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexylamino}-methyl}-indan-5-carbonitrile,
 5 cis-(S)-2-({4-[2-(1-hydroxy-1-methyl-ethyl)-5-methyl-benzoimidazol-1-yl]-cyclohexylamino}-methyl)-indan-5-carbonitrile,
 trans-(S)-2-({4-[2-(1-hydroxy-1-methyl-ethyl)-5-methyl-benzoimidazol-1-yl]-cyclohexylamino}-methyl)-indan-5-carbonitrile,
 cis-2-(1-{4-[(5-fluoro-indan-2-ylmethyl)-amino]-cyclohexyl}-5-methyl-1H-benzoimidazol-2-yl)-propan-2-ol,
 10 trans-2-(1-{4-[(5-fluoro-indan-2-ylmethyl)-amino]-cyclohexyl}-5-methyl-1H-benzoimidazol-2-yl)-propan-2-ol,
 cis-2-(1-{4-[(5-chloro-indan-2-ylmethyl)-amino]-cyclohexyl}-5-methyl-1H-benzoimidazol-2-yl)-propan-2-ol,
 15 trans-2-(1-{4-[(5-chloro-indan-2-ylmethyl)-amino]-cyclohexyl}-5-methyl-1H-benzoimidazol-2-yl)-propan-2-ol,
 cis-(R)-2-({4-[5-chloro-2-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1H-yl]-cyclohexylamino}-methyl)-indan-5-carbonitrile,
 cis-(S)-N-{4-[5-chloro-2-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1-yl]-cyclohexyl}-N-(5-cyano-indan-2-ylmethyl)-acetamide,
 20 cis-(R)-2-(1-{4-[(5-bromo-indan-2-ylmethyl)-amino]-cyclohexyl}-5-chloro-1H-benzoimidazol-2-yl)-propan-2-ol,
 cis-1-{4-[(5-chloro-indan-2-ylmethyl)-amino]-cyclohexyl}-2-methyl-1H-benzoimidazole-5-carbonitrile,
 25 cis-(S)-2-{{4-(5-fluoro-2-methyl-benzoimidazol-1-yl)-cyclohexylamino}-methyl}-indan-5-carbonitrile,
 and pharmaceutically acceptable salts thereof.

Especially preferred is a compound of formula (I) selected from the group consisting of:

- 30 cis-(S)-2-(1-{4-[(5-bromo-indan-2-ylmethyl)-amino]-cyclohexyl}-5-chloro-1H-benzoimidazol-2-yl)-propan-2-ol,
 cis-2-(5-chloro-1-{4-[(indan-2-ylmethyl)-amino]-cyclohexyl}-1H-benzoimidazol-2-yl)-propan-2-ol,
 cis-(5-chloro-indan-2-ylmethyl)-[4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexyl]-
 35 amine,
 cis-(S)-2-({4-[5-chloro-2-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1-yl]-cyclohexylamino}-methyl)-indan-5-carbonitrile,
 cis-(S)-2-{{4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexylamino}-methyl}-indan-5-

- carbonitrile,
cis-(S)-2-({4-[2-(1-hydroxy-1-methyl-ethyl)-5-methyl-benzoimidazol-1-yl]-
cyclohexylamino}-methyl)-indan-5-carbonitrile,
cis-2-(1-{4-[(5-chloro-indan-2-ylmethyl)-amino]-cyclohexyl}-5-methyl-1*H*-
5 benzoimidazol-2-yl)-propan-2-ol,
cis-(S)-*N*-{4-[5-chloro-2-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1-yl]-cyclohexyl}-
N-(5-cyano-indan-2-ylmethyl)-acetamide,
cis-(R)-2-({4-[5-chloro-2-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1*H*-yl]-
cyclohexylamino}-methyl)-indan-5-carbonitrile,
10 *cis*-(S)-2-{{4-(5-fluoro-2-methyl-benzoimidazol-1-yl)-cyclohexylamino}-methyl}-indan-
5-carbonitrile,
and pharmaceutically acceptable salts thereof.

- In another embodiment of the present invention, provided is a pharmaceutical
composition comprising a therapeutically effective amount of a compound according to
15 formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically
acceptable carrier.

- In a further embodiment of the present invention, provided is method for treating
obesity in a patient in need of such treatment, comprising administering a therapeutically
effective amount of a compound according to formula (I) or a pharmaceutically
20 acceptable salt thereof to a patient in need thereof.

- It is to be understood that the terminology employed herein is for the purpose of
describing particular embodiments, and is not intended to be limiting. Further, although
any methods, devices and materials similar or equivalent to those described herein can be
used in the practice or testing of the invention, the preferred methods, devices and
25 materials are now described.

- As used herein, the term "alkyl" means, for example, a branched or unbranched,
saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl group which may be
substituted or unsubstituted. The alkyl group is preferably C₁ to C₁₀-alkyl, more
preferably C₁ to C₆, more preferably methyl, ethyl, propyl (n-propyl or isopropyl), butyl
30 (n-butyl, isobutyl or tertiary-butyl) or pentyl (including n-pentyl and isopentyl), more
preferably methyl. It will be appreciated therefore that the term "alkyl" as used herein
includes alkyl (branched or unbranched), substituted alkyl (branched or unbranched),
alkenyl (branched or unbranched), substituted alkenyl (branched or unbranched),
alkynyl (branched or unbranched) and substituted alkynyl (branched or unbranched).

As used herein, the cycloalkyl group is preferably C₃ to C₁₂-cycloalkyl, more preferably C₄ to C₁₀-cycloalkyl, most preferably C₄ to C₇-cycloalkyl. Thus, preferably the cycloalkyl group is C₃, C₄, C₅, C₆ or C₇-cycloalkyl. It will be appreciated that the term “cycloalkyl” includes substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, cycloalkynyl and substituted cycloalkynyl.

As used herein, the term “lower alkyl” means a branched or unbranched, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl group wherein said lower alkyl group is C₁, C₂, C₃, C₄, C₅, or C₆-alkyl, preferably from 1 to 4 carbon atoms. Typical lower alkyl groups include methyl, ethyl, propyl (n-propyl or isopropyl), butyl (n-butyl, isobutyl or tertiary-butyl), pentyl and hexyl. It will be appreciated that the term “lower alkyl” as used herein includes, for example, lower alkyl (branched or unbranched), lower alkenyl (branched or unbranched), or lower alkynyl (branched or unbranched). When attached to another functional group, lower alkyl as used herein may be divalent, e.g., -lower alkyl-COOH.

As used herein, the term “aryl” means, for example, a substituted or unsubstituted carbocyclic aromatic group, such as phenyl or naphthyl.

The term “heteroaryl” means a substituted or unsubstituted heteroaromatic group containing one or more, preferably one, heteroatom, such as pyridyl, pyrrolyl, furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, triazolyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, indolyl, indazolyl, quinolyl, quinazolyl, benzimidazolyl, benzothiazolyl, benzisoxazolyl and benzisothiazolyl.

The alkyl, cycloalkyl, aryl and heteroaryl groups may be substituted or unsubstituted. Where substituted, there will generally be, for example, 1 to 3 substituents present, preferably 1 substituent. Substituents may include, for example: carbon-containing groups such as alkyl, aryl (e.g. substituted and unsubstituted phenyl), arylalkyl (e.g. substituted and unsubstituted benzyl); halogen atoms and halogen-containing groups such as haloalkyl (e.g. trifluoromethyl); oxygen-containing groups such as alcohols (e.g. hydroxy, hydroxyalkyl, aryl(hydroxy)alkyl), ethers (e.g. alkoxy, aryloxy, alkoxyalkyl, aryloxyalkyl), aldehydes (e.g. carboxaldehyde), ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl), acids (e.g. carboxy, carboxyalkyl), acid derivatives such as esters (e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl), amides (e.g. aminocarbonyl, mono- or di-alkylaminocarbonyl, aminocarbonylalkyl, mono- or di-alkylaminocarbonylalkyl, arylaminocarbonyl), carbamates (e.g. alkoxycarbonylamino, aryloxy carbonylamino, aminocarbonyloxy, mono- or di-alkylaminocarbonyloxy, arylaminocarbonyloxy) and ureas (e.g. mono- or di-alkylaminocarbonylamino or

arylamino-carbonylamino); nitrogen-containing groups such as amines (e.g. amino, mono- or di-alkylamino, aminoalkyl, mono- or di-alkylaminoalkyl), azides, nitriles (e.g. cyano, cyanoalkyl), nitro; sulfur-containing groups such as thiols, thioethers, sulfoxides and sulfones (e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, 5 alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl); and heteroaryl or heterocyclyl groups containing one or more, preferably one, heteroatom selected from nitrogen, oxygen or sulfur (e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, aziridinyl, azetidiny, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazoliny, pyrazolidinyl, 10 tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, hexahydroazepinyl, piperazinyl, morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indoliny, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, 15 chromanyl, isochromanyl, phthalazinyl and carbolinyl).

The lower alkyl groups may be substituted or unsubstituted, preferably unsubstituted. Where substituted, there will generally be, for example, 1 to 3 substituents present, preferably 1 substituent.

The term "alkoxy" means -O-alkyl, wherein alkyl is preferably a lower alkyl group 20 as defined above. Preferred "alkoxy" is C₁-C₆-alkoxy.

The term "alkylcarbonyl" means -CO-alkyl. "Lower alkylcarbonyl" means -CO-alkyl wherein alkyl is a lower alkyl group as defined herein before.

As used herein, the term "halo" means a fluorine, chlorine, bromine or iodine atom, preferably a fluorine, chlorine or bromine atom, and more preferably a fluorine or 25 chlorine atom.

The term "lower haloalkyl" or "halo-C₁-C₆-alkyl" refers to lower alkyl groups as defined above wherein at least one of the hydrogen atoms of the lower alkyl group is replaced by a halogen atom, preferably fluoro or chloro, most preferably fluoro. Among the preferred halogenated lower alkyl groups are trifluoromethyl, difluoromethyl, 30 fluoromethyl and chloromethyl, with trifluoromethyl being especially preferred.

"Pharmaceutically acceptable," such as pharmaceutically acceptable carrier, excipient, etc., means pharmacologically acceptable and substantially non-toxic to the subject to whom the particular compound is administered.

“Pharmaceutically acceptable salt” refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Sample acid-addition salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Sample base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. The chemical modification of a pharmaceutical compound (i.e. drug) into a salt is a well known technique which is used in attempting to improve properties involving physical or chemical stability, e.g., hygroscopicity, flowability or solubility of compounds. See, e.g., H. Ansel et. al., *Pharmaceutical Dosage Forms and Drug Delivery Systems* (6th Ed. 1995) at pp. 196 and 1456-1457.

“Pharmaceutically acceptable ester” refers to a conventionally esterified compound of formula I having a carboxyl group, which esters retain the biological effectiveness and properties of the compounds of formula I and are cleaved *in vivo* (in the organism) to the corresponding active carboxylic acid. Examples of ester groups which are cleaved (in this case hydrolyzed) *in vivo* to the corresponding carboxylic acids are those in which the cleaved hydrogen is replaced with -lower alkyl which is optionally substituted, e.g., with heterocycle, cycloalkyl, etc. Examples of substituted lower alkyl esters are those in which -lower alkyl is substituted with pyrrolidine, piperidine, morpholine, N-methylpiperazine, etc. The group which is cleaved *in vivo* may be, for example, ethyl, morpholino ethyl, and diethylamino ethyl. In connection with the present invention, -CONH₂ is also considered an ester, as the -NH₂ is cleaved *in vivo* and replaced with a hydroxy group, to form the corresponding carboxylic acid.

Further information concerning examples of and the use of esters for the delivery of pharmaceutical compounds is available in *Design of Prodrugs*. Bundgaard H. ed. (Elsevier, 1985). See also, H. Ansel et. al., *Pharmaceutical Dosage Forms and Drug Delivery Systems* (6th Ed. 1995) at pp. 108-109; Krosgaard-Larsen, et. al., *Textbook of Drug Design and Development* (2d Ed. 1996) at pp. 152-191.

In the practice of the method of the present invention, an effective amount of any one of the compounds of this invention or a combination of any of the compounds of this invention or a pharmaceutically acceptable salt or ester thereof, is administered via any of the usual and acceptable methods known in the art, either singly or in combination. The compounds or compositions can thus be administered orally (e.g.,

buccal cavity), sublingually, parenterally (e.g., intramuscularly, intravenously, or subcutaneously), rectally (e.g., by suppositories or washings), transdermally (e.g., skin electroporation) or by inhalation (e.g., by aerosol), and in the form of solid, liquid or gaseous dosages, including tablets and suspensions. The administration can be conducted
5 in a single unit dosage form with continuous therapy or in a single dose therapy ad libitum. The therapeutic composition can also be in the form of an oil emulsion or dispersion in conjunction with a lipophilic salt such as pamoic acid, or in the form of a biodegradable sustained-release composition for subcutaneous or intramuscular administration.

10 Useful pharmaceutical carriers for the preparation of the compositions hereof, can be solids, liquids or gases; thus, the compositions can take the form of tablets, pills, capsules, suppositories, powders, enterically coated or other protected formulations (e.g. binding on ion-exchange resins or packaging in lipid-protein vesicles), sustained release formulations, solutions, suspensions, elixirs, aerosols, and the like. The carrier can be
15 selected from the various oils including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water, saline, aqueous dextrose, and glycols are preferred liquid carriers, particularly (when isotonic with the blood) for injectable solutions. For example, formulations for intravenous administration comprise sterile aqueous solutions of the active ingredient(s)
20 which are prepared by dissolving solid active ingredient(s) in water to produce an aqueous solution, and rendering the solution sterile. Suitable pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, talc, gelatin, malt, rice, flour, chalk, silica, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. The compositions may be
25 subjected to conventional pharmaceutical additives such as preservatives, stabilizing agents, wetting or emulsifying agents, salts for adjusting osmotic pressure, buffers and the like. Suitable pharmaceutical carriers and their formulation are described in Remington's Pharmaceutical Sciences by E. W. Martin. Such compositions will, in any event, contain an effective amount of the active compound together with a suitable carrier so as to
30 prepare the proper dosage form for proper administration to the recipient.

The pharmaceutical preparations can also contain preserving agents, solubilizing agents, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain other therapeutically valuable substances, including
35 additional active ingredients other than those of formula I.

The therapeutically effective amount or dosage of a compound according to this invention can vary within wide limits and may be determined in a manner known in the

art. Such dosage will be adjusted to the individual requirements in each particular case including the specific compound(s) being administered, the route of administration, the condition being treated, as well as the patient being treated. The therapeutically effective amount of the compounds of formula I can vary within wide limits depending on the
5 disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. Preferably, the therapeutically effective amount may be from about 0.01 mg/kg to about 50 mg/kg per day, more preferably from about 0.3 mg/kg to about 10 mg/kg per day.

- 10 The daily dosage can be administered as a single dose or in divided doses, or for parenteral administration it may be given as continuous infusion.

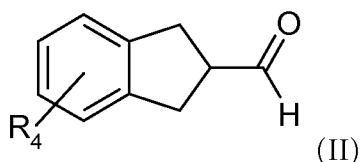
Further, the invention relates to a compound of formula (I) as defined above for use as therapeutic active substance, particularly as therapeutic active substance for the treatment of obesity, hyperphagia, anxiety, depression and related disorders and diseases.

- 15 In another embodiment, the invention relates to the use of a compound of formula (I) as defined above for the treatment of obesity, hyperphagia, anxiety, depression and related disorders and diseases.

- In addition, the invention relates to the use of a compound of formula (I) as defined above for the preparation of medicaments for the treatment of obesity,
20 hyperphagia, anxiety, depression and related disorders and diseases. Preferably, the invention relates to the use of a compound of formula (I) for the preparation of medicaments for the treatment of obesity.

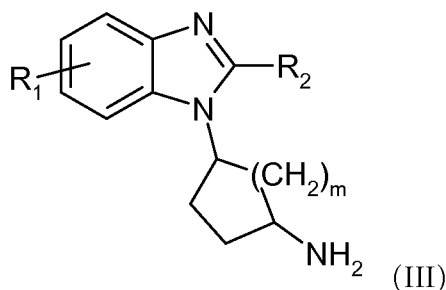
The present invention also relates to processes for the manufacture of a compound of formula (I) as defined above, which processes comprise

- 25 a) reductive amination of a compound of formula (II)



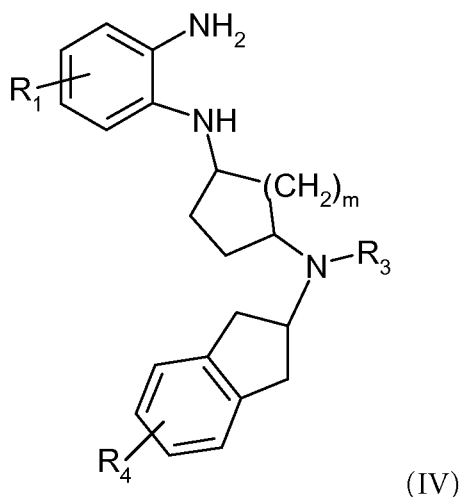
wherein R₄ is as defined herein before, with an amine of the formula (III)

- 13 -



wherein R_1 , R_2 and m are as defined herein before, by using NaCNBH_3 or $\text{NaBH}(\text{OAc})_3$ to obtain a compound of formula (I), wherein n is 1, and, if desired, converting the resulting compound of formula (I) into a pharmaceutically acceptable salt thereof, or

b) ring cyclization of a compound of formula (IV)



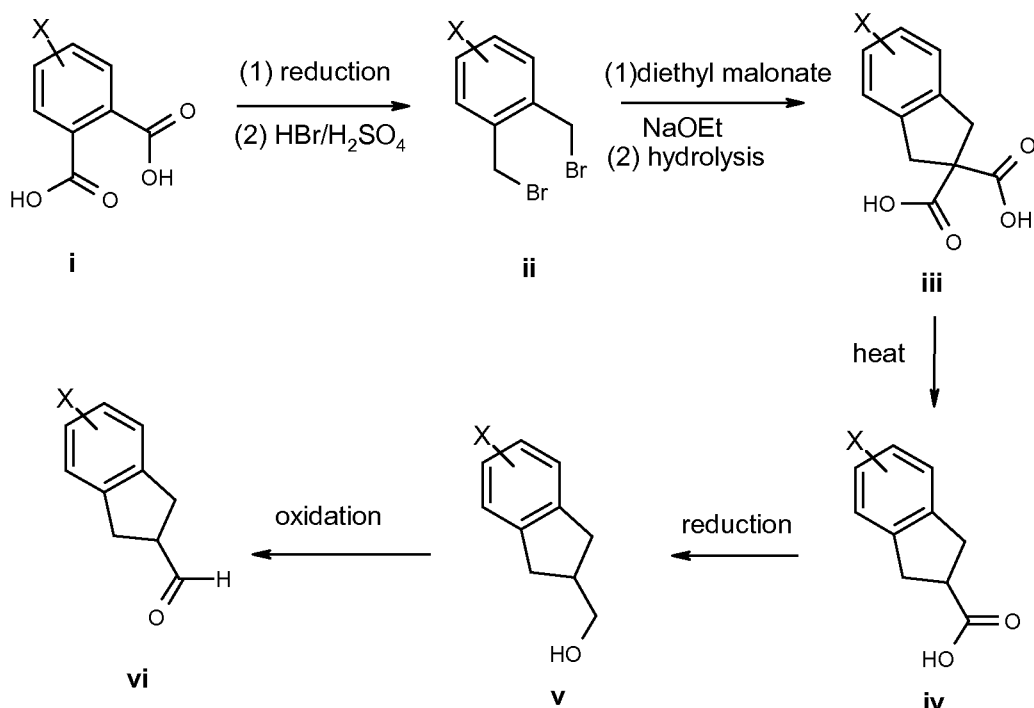
wherein R_1 , R_3 , R_4 , m and n are as defined herein before, with a carboxylic acid of the formula (V)



wherein R_2 is as defined herein before, to obtain a compound of formula (I) wherein n is 0, and, if desired, converting the resulting compound of formula (I) into a pharmaceutically acceptable salt thereof.

15 In more detail, compounds of the present invention can be prepared beginning with commercially available starting materials and utilizing general synthetic techniques and procedures known to those skilled in the art. Outlined below are preferred reaction schemes suitable for preparing such compounds. Further exemplification is found in the specific Examples detailed below.

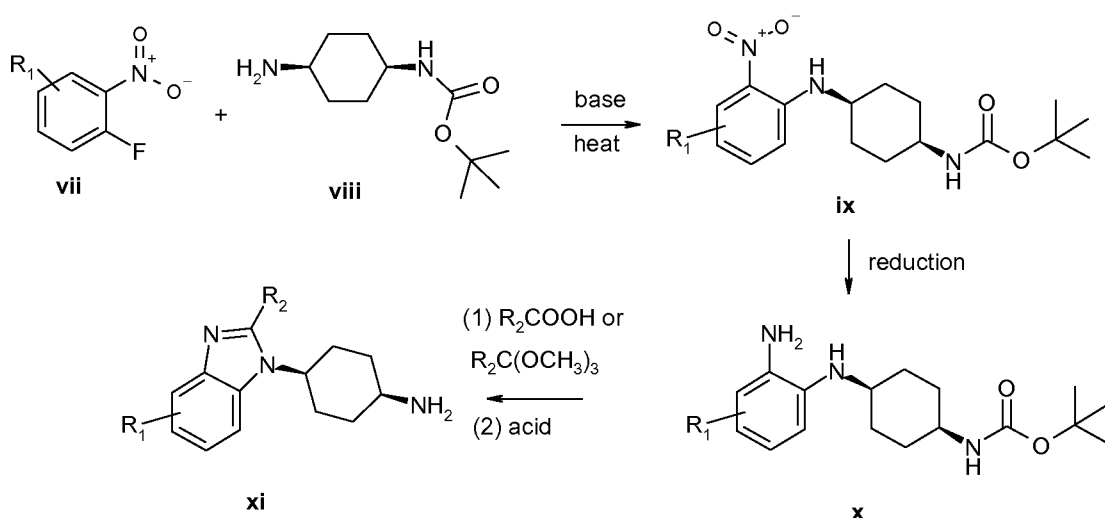
Scheme 1: General method of preparing substituted indan-2-carbaldehyde



The substituted indan-2-carbaldehyde can be prepared from the corresponding carboxylic acid through reduction and oxidation reactions. The indan-2-carboxylic acid
 5 can be prepared with a similar method to literature example (*J. Med. Chem.* **1989**, 38, 1988-1996). The substituted benzene dicarboxylic acid i (X=H, F, Br, Cl, CF₃) can be reduced to a diol which can be converted to dibromide ii. Alkylation of diethyl malonate with the dibromide ii followed by saponification can provide indan-2,2-dicarboxylic acid iii, which can be decarboxylated to produce substituted indan-2-carboxylic acids iv. The
 10 indan-2-carboxylic acid iv can be reduced to a corresponding alcohol v, which can be oxidized to generate the desired substituted indan-2-carbaldehyde vi.

The chiral 5-bromo-indan-2-carboxylic acid (iv where X = 5-Br) can be prepared from the corresponding indene through an asymmetric catalytic hydrogenation with a similar method to literature example (US 5936000) to generate both (R) and (S)-
 15 enantiomers. Conversion of bromide (v where X = 5-Br) to cyanide (v where X = 5-CN) can be accomplished through palladium catalyzed ligand exchange reactions by using zinc cyanide and Pd(PPh₃)₄.

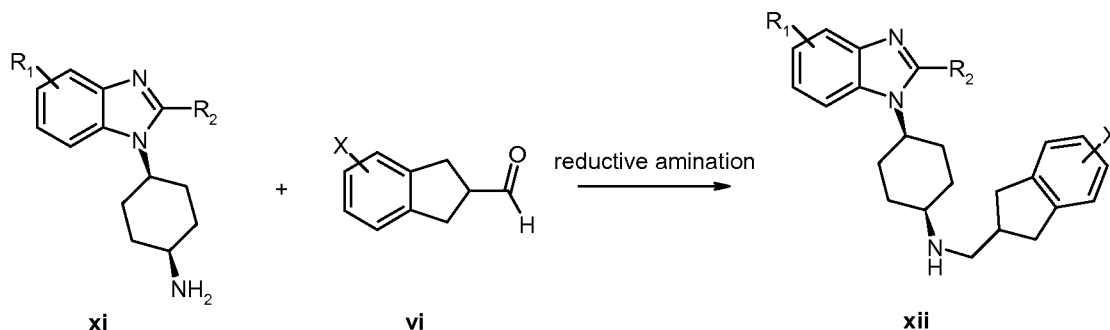
Scheme 2: Method of preparing 4-benzoimidazol-1-yl-cyclohexylamine



The 4-benzoimidazol-1-yl-cyclohexylamine can be prepared by reacting N-Boc-1,4-cyclohexyldiamine viii with substituted fluoro-nitrobenzene vii (R_1 can be H, CH_3 , F, Cl, CN, etc) to provide the N-aryl compound ix. The nitro group in compound ix can be reduced to the corresponding phenylenediamine x. The reaction of phenylenediamine x with carboxylic acid under acidic condition will form the desired benzoimidazole xi. Alternatively, the ring cyclization can be performed by reacting compound x with trimethyl orthoformate to generate the desired benzoimidazole which can be deprotected under acidic condition to provide compound xi.

The same method described in Scheme 2 can be applied to larger or smaller ring systems other than the cyclohexane, and the nitrogen linkage to cycloalkane can be *cis*- or *trans*-configuration.

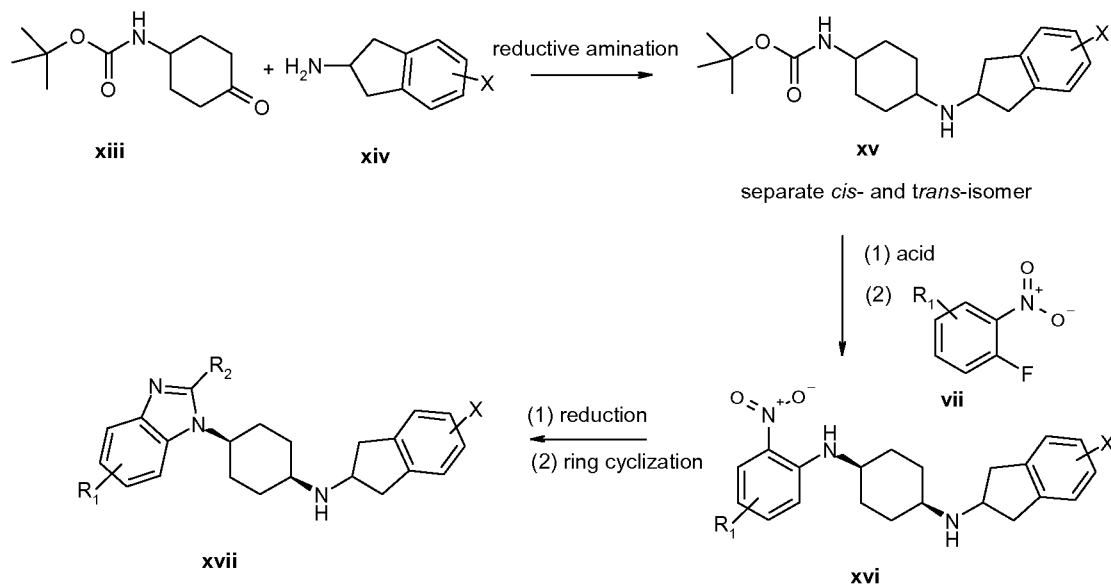
Scheme 3: Coupling of cyclohexylamine with indan-2-carbaldehyde



The coupling of 4-benzoimidazol-1-yl-cyclohexylamine xi with the indan-2-carbaldehyde vi can be accomplished through a reductive amination reaction by using $NaCNBH_3$ or $NaBH(OAc)_3$ to generate the indane derived amine xii. The

diaminocycloalkane can be *cis*- or *trans*-configuration. The same method can be applied to other ring systems.

Scheme 4: Alternative method of coupling indane with benzoimidazole

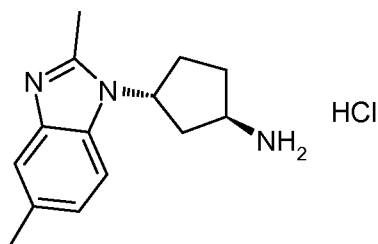


- 5 Alternatively, the aminoindane **xiv** (prepared from indan-2-carboxylic acid **iv** through Curtius rearrangement) can be coupled to N-Boc-4-aminocyclohexanone **xiii** through reductive amination to generate *cis*- and *trans*-isomers **xv** which can be separated. Following the removal of the N-Boc group and nucleophilic aromatic substitution with fluoro-nitrobenzene **vii**, the indane-derived benzoimidazole **xvii** can be
- 10 prepared through reduction and ring cyclization reactions using the same method described in Scheme 2.

EXAMPLES

PART I: PREPARATION OF PREFERRED INTERMEDIATES

trans-3-(2,5-Dimethyl-benzoimidazol-1-yl)-cyclopentylamine; hydrochloride



To a stirred solution of 1,3-cyclopropanediol (5 g, 49 mmol) and imidazole (5 g, 73.4 mmol) in DMF (20 mL) was added *t*-butyldimethylsilyl chloride (5.2 g, 34.5 mmol) and the mixture was stirred for 90 minutes at room temperature. The mixture was diluted with brine (200 mL) and extracted with ether three times (1x100 mL and 2x50 mL). Each extract was washed with a portion of brine. The organic phases were combined, dried over sodium sulfate and evaporated to dryness. The mixture of *cis/trans* isomers was purified by column chromatography using ether and hexanes to give the predominant *trans*-3-(*tert*-butyl-dimethyl-silanyloxy)-cyclopentanol as a colorless liquid (4.1g).

The *trans*-3-(*tert*-butyl-dimethyl-silanyloxy)-cyclopentanol (1.08 g, 5 mmol) was combined with triphenylphosphine (1.44 g, 5.49 mmol) in dry THF (25 mL) and the stirring solution was chilled to 0°C. Diethyl azodicarboxylate (DEAD, 960 mg, 5.51 mmol) was added over 5 minutes. The mixture was stirred for 5 minutes and diphenylphosphoryl azide (DPPA, 1.185 mL, 5.49 mmol) was added over 5 minutes. The resulting mixture was stirred for 17 hours at room temperature. The reaction mixture was evaporated to a small volume and partitioned with ether (100 mL) and water (50 mL). The organic layer was dried over sodium sulfate, filtered and evaporated. The residue was purified by flash column chromatography eluting with ether and hexane mixtures to produce *cis*-3-(azido-cyclopentyloxy)-*tert*-butyl-dimethyl-silane as pale yellow oil (930 mg).

The *cis*-3-(azido-cyclopentyloxy)-*tert*-butyl-dimethyl-silane (930 mg, 3.85 mmol) was dissolved in ethanol (10 mL) and treated with platinum(IV) oxide monohydrate (100 mg). The mixture was stirred at room temperature under 1 atmosphere of hydrogen for 90 minutes and then filtered through Celite. Solvent was evaporated to give *cis*-3-(*tert*-butyl-dimethyl-silanyloxy)-cyclopentylamine as a colorless oil (500 mg). LRMS: calcd for C₁₁H₂₅NOSi (m/e) 215.1705, obsd 216.1 (M+H).

The *cis*-3-(*tert*-butyl-dimethyl-silanyloxy)-cyclopentylamine (500 mg, 2.32 mmol) was dissolved in THF (10 mL) and di-*tert*-butyl dicarbonate (610 mg, 2.79 mmol) was added. The mixture was stirred for 4 hours and solvents were evaporated. The residue was purified by chromatography on silica gel eluting with mixtures of ethyl ether and hexanes to afford *cis*-3-(*tert*-butyl-dimethyl-silanyloxy)-cyclopentyl]-carbamic acid *tert*-butyl ester as an oil (520 mg).

The above *cis*-3-(*tert*-butyl-dimethyl-silanyloxy)-cyclopentyl]-carbamic acid *tert*-butyl ester (1.43 g, 4.5 mmol) was dissolved in acetonitrile (35 mL). To this solution was added 5% aqueous hydrogen fluoride (2.0 mL) and the mixture was stirred for 19 hours at room temperature in a Nalgene bottle. The mixture was treated carefully with a

suspension of sodium bicarbonate (1 g) in water (2 mL). Volatiles were removed under reduced pressure at 30 °C. The remainder was partitioned between brine (50 mL) and ethyl ether (50 mL). The aqueous phase was further extracted with ethyl ether (2 x 50 mL). Each extract was washed with a portion of brine. The extracts were combined, dried
5 over sodium sulfate, filtered and the filtrate was evaporated to provide *cis*-(3-hydroxy-cyclopentyl)-carbamic acid *tert*-butyl ester as colorless oil (850 mg).

To a stirring solution of *cis*-(3-hydroxy-cyclopentyl)-carbamic acid *tert*-butyl ester (850 mg, 4.22 mmol) and triphenylphosphine (1.53 g, 5.83 mmol) in THF (25 mL) cooled to 2 °C was added DEAD reagent (0.92 mL, 5.84 mmol) over 5 minutes. The mixture
10 was stirred for 5 minutes and DPPA (1.26 mL, 5.84 mmol) was added over 5 minutes. Stirring was continued for 17 hours at room temperature. The mixture was evaporated to dryness. The residue was stirred in ethyl ether briefly and the white solid triphenylphosphine oxide was removed by filtration (1 g). The filtrate was again reduced in volume and purified by silica gel chromatography eluting with ethyl acetate and
15 hexanes to afford *trans*-(3-azido-cyclopentyl)-carbamic acid *tert*-butyl ester (950 mg).

The carbamic acid *tert*-butyl ester (500 mg, 2.2 mmol) prepared above was dissolved in 20 mL of ethyl alcohol and THF (1:1). The solution was stirred at room temperature under one atmospheric of hydrogen in the presence of PtO₂ (50 mg) for 90 minutes. The mixture was filtered and the filtrate was evaporated to provide *trans*-(3-
20 amino-cyclopentyl)-carbamic acid *tert*-butyl ester as a white solid (440 mg).

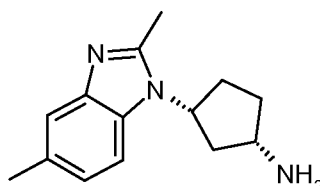
The *trans*-(3-amino-cyclopentyl)-carbamic acid *tert*-butyl ester (420 mg, 2.09 mmol) was mixed with 4-fluoro-3-nitrotoluene (342 mg, 2.2 mmol) and potassium carbonate (915 mg, 6.6 mmol) in DMF (20 mL). The stirring mixture was heated at 85 °C for 16.5 hours. The reaction mixture was evaporated under reduced pressure. The residue
25 was partitioned with 50 mL of dichloromethane and 50 mL of brine. The aqueous phase was extracted again with 50 mL of dichloromethane and each organic extract was washed with a portion of brine. After drying, filtering and evaporation of solvents, the crude mixture was purified on silica gel eluting with ethyl acetate and hexanes to give *trans*-[3-(4-methyl-2-nitro-phenylamino)-cyclopentyl]-carbamic acid *tert*-butyl ester as a orange
30 oil (305 mg). ¹H-NMR is consistent with the assigned structure. LC-MS showed a single peak, C₁₇H₂₅N₃O₄ (m/e) calcd 335.1845, obsd 336.2 (M+1).

The *trans*-[3-(4-methyl-2-nitro-phenylamino)-cyclopentyl]-carbamic acid *tert*-butyl ester (320 mg, 0.95 mmol) and palladium on charcoal (10% Pd on carbon, 35 mg) in methanol (15 mL) were shaken at 52 psi of hydrogen pressure for 2.5 hours. The
35 mixture was filtered through Celite®. Solvents were evaporated to yield *trans*-[3-(2-amino-4-methyl-phenylamino)-cyclopentyl]-carbamic acid *tert*-butyl ester as a pale

brown oil (290 mg). This material (290 mg, 0.95 mmol) was dissolved in a solution (5 mL) of acetic acid and trimethyl orthoacetate (4:1 v/v). The mixture was stirred at 70°C for 60 minutes and solvents were evaporated. The residue was extracted with ethyl acetate (25 mL) and saturated aqueous sodium bicarbonate (20 mL). The aqueous phase was
5 again extracted with a portion of ethyl acetate and each organic phase was washed with brine. The extracts were combined, dried over sodium sulfate, filtered and evaporated to give *trans*-[3-(2,5-dimethyl-benzoimidazol-1-yl)-cyclopentyl]-carbamic acid *tert*-butyl ester as a light brown foam (320 mg). ¹H-NMR is consistent with the assigned structure. LC-MS showed a single peak, C₁₉H₂₇N₃O₂ (m/e) calcd 329.2103, obsd 330.2 (M+H).

10 The *trans*-[3-(2,5-dimethyl-benzoimidazol-1-yl)-cyclopentyl]-carbamic acid *tert*-butyl ester prepared above (320 mg, 0.95 mmol) was dissolved in HCl (4M) in dioxane (5.0 mL) and the solution was stirred for 15 minutes. Solids came out of solution and 1 mL of methanol was added to dissolve the precipitate. Stirring was continued for 60 minutes and the reaction mixture was evaporated to a sticky solid which was stirred with
15 ethyl ether. The resulting solid was filtered to provide *trans*-3-(2,5-dimethyl-benzoimidazol-1-yl)-cyclopentylamine hydrochloride salt as an off white powder (250 mg). LR-MS calcd for C₁₄H₁₉N₃ (m/e) 229.1579, obsd 230.2 (M+H).

cis-3-(2,5-Dimethyl-benzoimidazol-1-yl)-cyclopentylamine



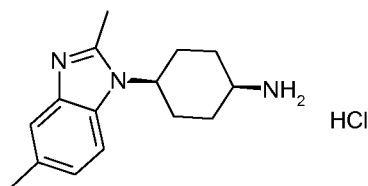
20 To a solution of *cis*-(3-hydroxy-cyclopentyl)-carbamic acid *tert*-butyl ester (750 mg, 3.72 mmol, prepared in previous intermediate) in THF (20 mL) at 2°C was added triphenylphosphine (1.1 g, 4.19 mmol) and diethyl azodicarboxylate (0.7 mL, 4.4 mmol). The solution was stirred for 10 minutes. Acetic acid (0.6 mL, 10.48 mmol) in THF (5 mL) was added over 2 minutes and the mixture was first stirred at 2°C for 20 minutes and
25 then at room temperature for 3 hours. The mixture was evaporated to dryness and the residue was stirred with ethyl ether (20 mL). The resulting solid was removed by filtration. The filtrate was evaporated and the residue was purified by flash column chromatography eluting with ethyl ether and hexane to produce acetic acid *trans*-3-*tert*-butoxycarbonylamino-cyclopentyl esters a white solid (453 mg).

30 The ester prepared above (430 mg, 1.76 mmol) was dissolved in THF (1 mL) and methanol (1 mL). To this solution was added 4N aqueous sodium hydroxide solution (1 mL) and the solution was stirred for 60 minutes at room temperature. Solvents were

evaporated and the residue was partitioned with dichloromethane (25 mL) and brine (25 mL). The aqueous phase was further extracted with dichloromethane (25 mL). The organic extract was washed with brine and dried over sodium sulfate. Solvents were evaporated to give *trans*-(3-hydroxy-cyclopentyl)-carbamic acid *tert*-butyl ester as a
5 white solid (350 mg).

The *trans*-(3-hydroxy-cyclopentyl)-carbamic acid *tert*-butyl ester was converted to *cis*-(3-amino-cyclopentyl)-carbamic acid *tert*-butyl ester using the same method described previously. The resulting compound was further converted to *cis*-[3-(2,5-dimethyl-benzoimidazol-1-yl)-cyclopentyl]-carbamic acid *tert*-butyl ester using the same
10 method described in the preparation of the hydrochloride salt of *trans*-3-(2,5-dimethyl-benzoimidazol-1-yl)-cyclopentylamine. After the acid cleavage of the carbamic acid *tert*-butyl ester and base extraction, *cis*-3-(2,5-dimethyl-benzoimidazol-1-yl)-cyclopentylamine was obtained as pale brown oil. LR-MS calcd for C₁₄H₁₉N₃ (m/e) 229.1579, obsd 230.2 (M+H).

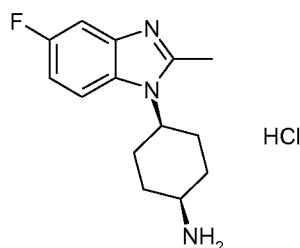
15 *cis*-4-(2,5-Dimethyl-benzoimidazol-1-yl)-cyclohexylamine; hydrochloride



To a mixture of *tert*-butyl *cis*-4-aminocyclohexanecarbamate (1.27 g, 5.93 mmol) and 4-fluoro-3-nitrotoluene (0.92 g, 5.93 mmol) in DMF (20 mL) was added potassium carbonate (1.64 g, 11.88 mmol). The mixture was heated at 85°C and stirred overnight.
20 The mixture was cooled to room temperature and the solid was filtered. The filtrate was evaporated to dryness. The residue was extracted with ethyl acetate and brine. The organic layer was dried over sodium sulfate and solvents were evaporated. The resulting material was purified through flash column chromatography using hexanes and ethyl acetate (4:1) to give an orange colored solid as *cis*-[4-(4-methyl-2-nitro-phenylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester (1.88 g). This material (1.80 g, 5.17 mmol) was
25 suspended in a mixture of methanol (50 mL) and water (25 mL). To this suspension was added ammonium chloride (4.15 g, 77.6 mmol) and zinc dust (3.36 g, 51.6 mmol). The mixture was stirred at room temperature for 20 minutes and THF (20 mL) was added. The mixture was stirred an additional 1 hr during which the orange color disappeared.
30 The mixture was filtered and rinsed with THF and ethyl acetate. The filtrate was extracted with brine and ethyl acetate. Solvents were evaporated to give *cis*-[4-(2-amino-4-methyl-phenylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester (1.65 g). LC-MS showed a single peak, C₁₈H₂₉N₃O₂ (m/e) calcd 319.2260, obsd 320.3 (M+H).

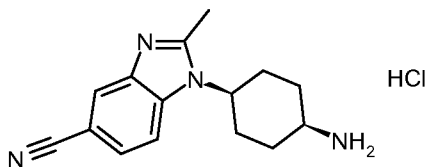
The above compound (850 mg, 2.65 mmol) was mixed with acetic acid (8 mL) and trimethyl orthoacetate (2 mL). The mixture was heated at 65°C for 2 hrs. Solvents were evaporated and the residue was extracted with ethyl acetate and sodium bicarbonate solution. The organic layer was dried over sodium sulfate and solvents were evaporated to give a pale brown solid as *cis*-[4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexyl]-carbamic acid *tert*-butyl ester. This solid was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (3 mL) was added. The mixture was stirred at room temperature for 2 hrs. Solvents were evaporated and the residue was dissolved in methylene chloride (4 mL). To this solution was added gaseous hydrogen chloride in dioxane (4M, 4 mL). Solvents were evaporated and the residue was triturated with ether. Solids were filtered and washed with ether to give a hydrochloride salt of *cis*-4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexylamine (630 mg). LC-MS showed a single peak, C₁₅H₂₁N₃ (m/e) calcd 243.1735, obsd 244.2 (M+H).

cis-4-(5-Fluoro-2-methyl-benzoimidazol-1-yl)-cyclohexylamine; hydrochloride



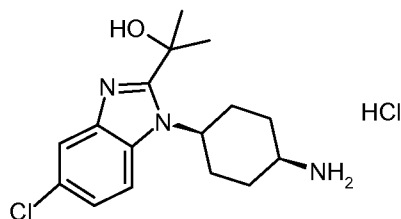
This compound was prepared with the same method as the preparation of *cis*-4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexylamine described previously. ¹H-NMR (DMSO-d₆) δ 8.75 (dd, 1H), 8.56 (br s, 3H), 7.66 (dd, 1H), 7.38 (dt, 1H), 4.57 (t, 1H), 3.47 (br s, 1H), 2.89 (s, 3H), 2.38 (m, 2H), 1.88-2.09 (m, 6H).

cis-1-(4-Amino-cyclohexyl)-2-methyl-1H-benzoimidazole-5-carbonitrile; hydrochloride



This compound was prepared with the same method as the preparation of *cis*-4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexylamine described previously. ¹H-NMR (DMSO-d₆) δ 8.63 (d, 1H), 8.42 (br s, 3H), 8.24 (s, 1H), 7.77 (d, 1H), 4.47 (t, 1H), 3.48 (br s, 1H), 2.80 (s, 3H), 2.38 (m, 2H), 2.00 (m, 4H), 1.84 (br d, 2H).

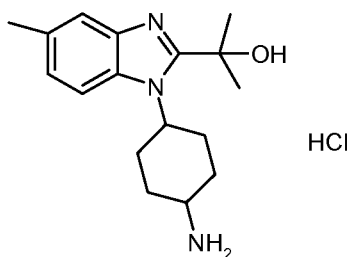
cis-2-[1-(4-Amino-cyclohexyl)-5-chloro-1*H*-benzoimidazol-2-yl]-propan-2-ol;
hydrochloride



To a mixture of *cis*-[4-(2-amino-4-chloro-phenylamino)-cyclohexyl]-carbamic
5 acid *tert*-butyl ester (1.25 g, 3.67 mmol, prepared from 1-chloro-4-fluoro-3-nitrobenzene
and *tert*-butyl *cis*-4-aminocyclohexanecarbamate) and 2-hydroxyisobutyric acid (2.7 g,
25.9 mmol) in water (5 mL) was added concentrated hydrochloric acid (3.25 mL, 40
mmol). The mixture was stirred and heated at 110°C for 2 days. The dark colored
solution was treated with ammonium hydroxide (15 mL, 225 mmol) and extracted with
10 methylene chloride. The organic layer was washed with brine and dried over sodium
sulfate. After the evaporation of solvents, a red colored solid was obtained (1.1 g). This
material was dissolved in THF (20 mL) and treated with di-*tert*-butyl-dicarbonate (950
mg, 4.3 mmol). The mixture was stirred at room temperature overnight. Solvents were
evaporated and the residue was purified through flash column chromatography using
15 ethyl acetate and hexanes (1:4) to give [4-(5-chloro-2-(1-hydroxy-1-methyl-ethyl)-
benzoimidazol-1-yl)-cyclohexyl]-carbamic acid *tert*-butyl ester (600 mg). This
compound was dissolved in methylene chloride (4 mL) and trifluoroacetic acid (1 mL)
was added. The solution was stirred at room temperature for 1 hr. Solvents were
evaporated and the residue was extracted with methylene chloride and sodium hydroxide
20 solution (1N). The organic layer was dried over sodium sulfate and solvents were
evaporated. The residue was dissolved in methylene chloride and treated with hydrogen
chloride in dioxane (4M). Solvents were evaporated and the residue was triturated with
ether. The purple solid was filtered to give a hydrochloride salt of *cis*-2-[1-(4-amino-
cyclohexyl)-5-chloro-1*H*-benzoimidazol-2-yl]-propan-2-ol. ¹H-NMR (CD₃OD) δ 7.96
25 (d, 1H), 7.57 (s, 1H), 7.21 (d, 1H), 5.34 (m, 1H), 2.61 (m, 2H), 1.72-1.89 (m, 13H).

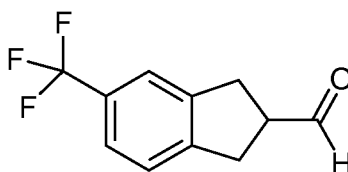
A minor product of *trans*-isomer was also isolated from the condensation of the *cis*-
[4-(2-amino-4-chloro-phenylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester with 2-
hydroxyisobutyric acid. Using the same method, the *trans*-isomer was converted to *trans*-
2-[1-(4-amino-cyclohexyl)-5-chloro-1*H*-benzoimidazol-2-yl]-propan-2-ol.

cis/trans-2-[1-(4-Amino-cyclohexyl)-5-methyl-1*H*-benzoimidazol-2-yl]-propan-2-ol;
hydrochloride



This compound was prepared with the same method as the preparation of 2-[1-(4-amino-cyclohexyl)-5-chloro-1*H*-benzoimidazol-2-yl]-propan-2-ol described previously.
¹H-NMR indicated a mixture of *cis/trans*-isomer. LC-MS calcd for C₁₇H₂₅N₃O (m/e) 287.1998, obsd 288.2 (M+H).

5-Trifluoromethyl-indan-2-carbaldehyde



To a solution of 4-trifluoromethylbenzene-1,2-dicarboxylic acid (5.85 g, 25 mmol) in THF (50 mL) at -78°C was added borane in THF (1.0 M, 75 mL) and the mixture was stirred for 10 minutes. The mixture was then allowed to warm to room temperature and stirred overnight. Methanol (30 mL) was added and solvents were evaporated. The mixture was partitioned between ether and aqueous hydrochloric acid (1N). The organic layer was washed with brine and concentrated sodium bicarbonate solution. After the evaporation of solvents, colorless oil was obtained as (2-hydroxymethyl-4-trifluoromethyl-phenyl)-methanol (5.15 g). ¹H-NMR (CDCl₃) δ 7.58 (m, 2H), 7.51 (s 1H), 4.79 (s, 4H), 2.88 (m, 2H).

The above diol (5.15 g, 25 mmol) was suspended in aqueous hydrobromic acid (48%, 100 mL) containing concentrated sulfuric acid (1 mL). The mixture was refluxed for 15 hrs. The solution was extracted with petroleum ether (150 mL) and ether (75 mL). The organic layer was washed with water and brine and dried over sodium sulfate. Solvents were evaporated to give a brown oil as 1,2-*bis*-bromomethyl-4-trifluoromethylbenzene (7.72 g). ¹H-NMR (CDCl₃) δ 7.62 (s, 1H), 7.58 (d, 1H), 7.54 (d, 1H), 4.66 (s, 4H).

Sodium (1.12 g, 48.6 mmol) was added to ethanol (16 mL). The solution was heated to reflux until all sodium was dissolved. To this solution was added diethyl

malonate (3.71 g, 23.19 mmol) in ether (45 mL) and the above 1,2-bis-bromomethyl-4-trifluoromethylbenzene (7.7 g, 23.19 mmol) in ether (45 mL). The mixture was refluxed for 16 hrs and the precipitate was filtered out. The filtrate was evaporated and the residue was treated with water (35 mL) and potassium hydroxide (5.30 g). The mixture was
5 stirred and refluxed for 5 hrs and treated with water (20 mL). The resulting mixture was extracted with ether (50 mL). The aqueous phase was acidified with concentrated hydrochloric acid and cooled in an ice bath. Solids were filtered and washed with water. After air drying, 5-trifluoromethyl-indan-2,2-dicarboxylic acid was obtained (3.08 g). LC-MS showed a single peak, $C_{12}H_{19}F_3O_4$ (m/e) calcd 274.0453, obsd 273.0 (M-H).

10 The above dicarboxylic acid (3.07 g, 11.2 mmol) was heated to 200 °C until evolution of gas ceased. The oily material was heated at 200 °C for 15 more minutes and cooled down to room temperature. This material was refluxed in hexanes (100 mL) and insoluble material removed by filtration. The filtrate was evaporated to give a solid as 5-trifluoromethyl-indan-2-carboxylic acid (2.49 g). LC-MS showed a single peak,
15 $C_{11}H_9F_3O_2$ (m/e) calcd 230.0555, obsd 229.0 (M-H). 1H -NMR ($CDCl_3$) δ 7.47 (s, 1H), 7.44 (d, 1H), 7.31 (d, 1H), 3.44 (m, 1H), 3.33 (m, 4H).

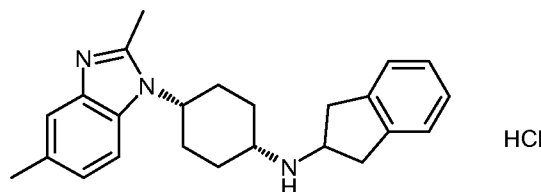
The above 5-trifluoromethyl-indan-2-carboxylic acid (1.03 g, 4.47 mmol) was dissolved in THF (25 mL) and cooled to 0°C. To this solution was added a solution of borane in THF (1M, 6.5 mL). The mixture was warmed to room temperature and stirred
20 for 1 hr. The mixture was treated with water (5 mL) and solvents were evaporated. The residue was extracted with ether and hydrochloric acid (1M). The organic phase was washed with brine and sodium bicarbonate solution. The ether solution was dried and solvents were evaporated to give oily material as 5-trifluoromethyl-indan-2-yl-methanol (0.98 g).

25 The above 5-trifluoromethyl-indan-2-yl-methanol (216 mg, 1 mmol) was dissolved in methylene chloride (15 mL) and the solution was cooled in an ice bath. To this solution was added Dess-Martin reagent (450 mg, 1.06 mmol) in four portions. The mixture was warmed to room temperature and stirred for 1 hr. The mixture was evaporated to dryness and the residue was triturated with petroleum ether (14 mL) and
30 ether (7 mL). The precipitate was filtered out and the filtrate was extracted with ether and sodium bicarbonate solution. The organic layer was dried over sodium sulfate and solvents were evaporated to give 5-trifluoromethyl-indan-2-carbaldehyde (210 mg) as pale green oil. 1H -NMR ($CDCl_3$) δ 9.78 (s, 1H), 7.48 (s, 1H), 7.43 (d, 1H), 7.32 (d, 1H), 3.33-3.38 (m, 3H), 3.15-3.27 (m, 2H).

PART II: PREPARATION OF PREFERRED COMPOUNDS

Example 1

cis-4-(2,5-Dimethyl-benzoimidazol-1-yl)-cyclohexyl]-indan-2-yl-amine; hydrochloride



5 Sodium cyanoborohydride (590 mg, 9.39 mmol) was added to a solution of Boc-4-aminocyclohexanone (1.00 g, 4.69 mmol) and 2-aminoindane hydrochloride (955 mg, 5.63 mmol) in ethanol (25 mL). After stirring for 16 h, the reaction mixture was poured into aqueous 1.0M sodium hydroxide solution (75 mL) and extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. Filtration followed by removal of volatiles under reduced pressure
10 afforded a gummy solid. Flash chromatography (0-5% methanol in ethyl acetate) provided (in order of elution): *cis*-[4-(indan-2-ylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester (700 mg; 45%) and *trans*-[4-(indan-2-ylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester (300 mg; 19%) as gummy solids.

15 *cis*-[4-(Indan-2-ylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester (315 mg; 0.95 mmol) was added to 2M hydrogen chloride in dioxane and methanol (1:1, 6 mL) and the solution was stirred for 1 hr at room temperature. All volatiles were removed under reduced pressure and the resulting foamy solid was partitioned between chloroform and 1M potassium carbonate solution. The aqueous phase was extracted three times with
20 chloroform and the combined organic layers were dried over sodium sulfate. Filtration followed by removal of volatiles under reduced pressure afforded *N*-indan-2-yl-cyclohexane-1,4-*cis*-diamine (220 mg).

A mixture of *N*-indan-2-yl-cyclohexane-1,4-*cis*-diamine (220 mg, 0.96 mmol), 3-nitro-4-fluorotoluene (225 mg, 1.45 mmol) and potassium carbonate (305 mg, 2.87
25 mmol) in *n*-butanol (5 mL) was heated to reflux for 17 h. The reaction mixture was then filtered and all volatiles were removed under reduced pressure. The crude product was purified by flash chromatography (0-10% methanol in chloroform) to yield *N*-(2-nitro-4-methyl-phenyl)-*N'*-indan-2-yl-cyclohexane-*cis*-1,4-diamine as an orange waxy solid (305 mg, 87%).

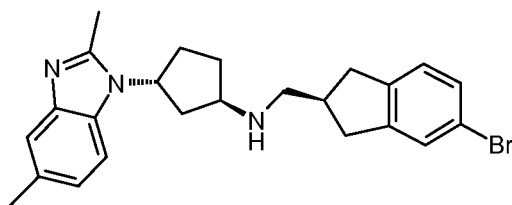
30 A mixture of *N*-(2-nitro-4-methyl-phenyl)-*N'*-indan-2-yl-cyclohexane-*cis*-1,4-diamine (300 mg, 0.82 mmol) and 10% Pd on carbon (50 mg) in ethanol (15 mL) were

shaken under hydrogen pressure (40 psi) for 90 min. The catalyst was then removed by filtration through Celite® and all volatiles were removed under reduced pressure to yield the product phenylenediamine as a light brown waxy solid (260 mg) which was used without further purification.

- 5 The aforementioned phenylenediamine (100 mg, 0.299 mmol) was dissolved in acetic acid (2.8 mL) and trimethyl orthoacetate (0.7 mL) and the solution was heated to 70°C for 1 h. The reaction mixture was cooled to room temperature and all volatiles were removed under reduced pressure. The residue was suspended in 1.0 M aqueous potassium carbonate and extracted three times with ethyl acetate. The combined organic
10 layers were washed with brine and dried over sodium sulfate. Filtration followed by removal of volatiles under reduced pressure gave brown oil. Purification by flash chromatography (2.5-5% methanol in methylene chloride) gave [*cis*-4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexyl]-indan-2-yl-amine as a foamy solid (85 mg) which was converted to a hydrochloride salt. ¹H-NMR is consistent with the assigned structure.
15 LRMS calcd for C₂₄H₂₉N₃ (m/e) 359.2361, obsd 360.2 (M+H).

Example 2

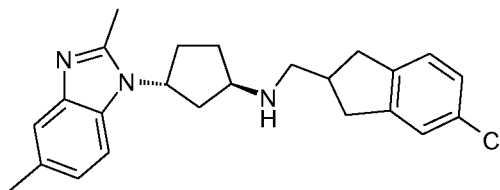
trans-(S)-(5-Bromo-indan-2-ylmethyl)-[3-(2,5-dimethyl-benzoimidazol-1-yl)-cyclopentyl]-amine



- 20 To a solution of *trans*-3-(2,5-dimethyl-benzoimidazol-1-yl)-cyclopentyl amine hydrochloride (250 mg, 0.47 mmol) and (S)-5-bromo-indan-2-carbaldehyde (113 mg, 0.5 mmol) in methanol (5 mL) containing 5% acetic acid was added a solution of sodium cyanoborohydride (32 mg, 0.509 mmol) in THF (0.5 mL). After stirring for 1 hour, the mixture was evaporated to dryness under reduced pressure and the residue was
25 partitioned with saturated aqueous sodium bicarbonate solution (50 mL) and dichloromethane (3x 25 mL). Each extract was washed with brine. Following the drying of the extracts from sodium sulfate, filtration and evaporation, the residue was purified by flash chromatography eluting with ethyl acetate and hexanes in the presence of 4% methanol to afford *trans*-(S)-(5-bromo-indan-2-ylmethyl)-[3-(2,5-dimethyl-
30 benzoimidazol-1-yl)-cyclopentyl]-amine as an off-white foam (102 mg). ¹H-NMR is consistent with the assigned structure. LC-MS showed a single peak, C₂₄H₂₈BrN₃ (m/e) calcd 437.1467, obsd 438.1 (M+H).

Example 3

trans-(5-Chloro-indan-2-ylmethyl)-[3-(2,5-dimethyl-benzoimidazol-1-yl)-cyclopentyl]-amine

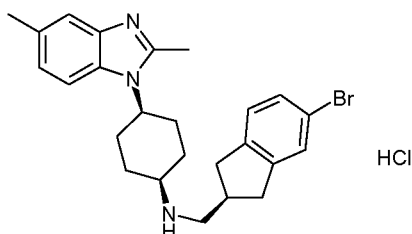


5 This compound was prepared from *trans*-3-(2,5-dimethyl-benzoimidazol-1-yl)-cyclopentylamine hydrochloride and 5-chloro-indan-2-carbaldehyde using the same reductive amination method described in previous example. ¹H-NMR is consistent with the assigned structure. LC-MS showed a single peak, C₂₄H₂₈ClN₃ (m/e) calcd 393.1972, obsd 394.2 (M+H).

10

Example 4

cis-(S)-(5-Bromo-indan-2-ylmethyl)-[4-(2,5-dimethyl-benzoimidazole-1-yl)-cyclohexyl]-amine hydrochloride

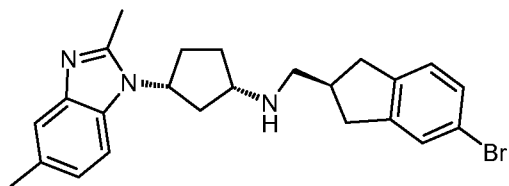


The hydrochloride salt of *cis*-4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexylamine (104.5 mg, 0.33 mmol) was mixed with (S)-5-bromo-indan-2-carbaldehyde (75 mg, 0.33 mmol) in 5 mL of methanol containing 5% acetic acid. The mixture was stirred at room temperature for 10 minutes and sodium cyanoborohydride (20.5 mg, 0.33 mmol) in 0.2 mL of THF was added. The mixture was stirred at room temperature for 3 hours. The mixture was evaporated and the residue was extracted with methylene chloride and concentrated sodium bicarbonate solution. The organic layer was washed with brine and solvents were evaporated. The residue was purified through flash column chromatography using 5% of methanol in methylene chloride. The pure fraction was concentrated and then dissolved in methylene chloride (2 mL). A solution of hydrogen chloride in ether (1 mL, 1N) was added. Solvents were evaporated and the residue was triturated with ether and petroleum ether. The solid material was filtered to give the desired compound as hydrochloride salt (41 mg). LC-MS showed a single peak, C₂₅H₃₀BrN₃ (m/e) calculated 451.1623, observed 452.0 (M+H). ¹H-NMR (CD₃OD) δ

8.31 (d, 1H), 7.53 (s, 1H), 7.44 (d, 1H), 7.40 (s, 1H), 7.30 (d, 1H), 7.15 (d, 1H), 4.68 (m, 1H), 3.62 (br s, 1H), 3.19-3.35 (m, 4H), 3.08 (m, 1H), 2.94 (s, 3H), 2.85 (m, 2H), 2.58 (m, 2H), 2.52 (s, 3H), 2.42 (br d, 2H), 2.07-2.24 (m, 4H).

Example 5

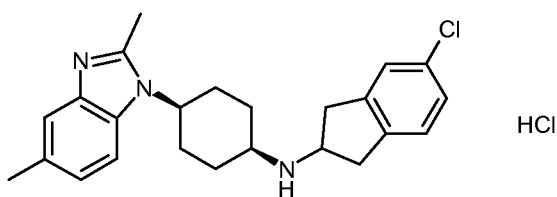
5 *cis*-(S)-(5-Bromo-indan-2-ylmethyl)-[3-(2,5-dimethyl-benzoimidazol-1-yl)-cyclopentyl]-amine



This compound was prepared from *cis*-3-(2,5-dimethyl-benzoimidazol-1-yl)-cyclopentylamine hydrochloride and (S)-5-bromo-indan-2-carbaldehyde using the same
10 reductive amination method described in previous example. ¹H-NMR is consistent with the assigned structure. LC-MS showed a single peak, C₂₄H₂₈BrN₃ (m/e) calcd 437.1467, obsd 438.1 (M+H).

Example 6

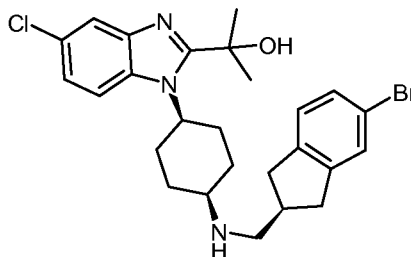
15 *cis*-(5-Chloro-indan-2-yl)-[4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexyl]-amine; hydrochloride



This compound was prepared with the same method as the preparation of *cis*-4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexyl-indan-2-yl-amine described in previous
20 example. ¹H-NMR is consistent with the assigned structure, LRMS for C₂₄H₂₈ClN₃ (m/e) calcd 393.1972, obsd 394.3 (M+H)

Example 7

cis-(S)-2-(1-{4-[(5-Bromo-indan-2-ylmethyl)-amino]-cyclohexyl}-5-chloro-1*H*-benzoimidazol-2-yl)-propan-2-ol

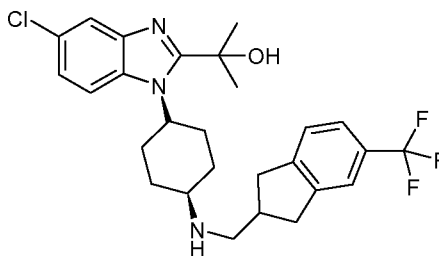


5 This compound was prepared from the hydrochloride salt of *cis*-2-[1-(4-amino-cyclohexyl)-5-chloro-1*H*-benzoimidazol-2-yl]-propan-2-ol and (S)-5-bromo-indan-2-carbaldehyde. LC-MS showed a single peak, C₂₆H₃₁BrClN₃O (m/e) calcd 515.1339, obsd 516.1 (M+H). ¹H-NMR (CD₃OD) δ 7.96 (d, 1H), 7.59 (s, 1H), 7.36 (s, 1H), 7.26 (d, 1H), 7.18 (d, 1H), 7.12 (d, 1H), 5.38 (m, 1H), 3.16 (m, 2H), 3.03 (br s, 1H), 2.67-2.83 (m, 7H), 2.07 (m, 2H), 1.72 (br s, 10H).

10

Example 8

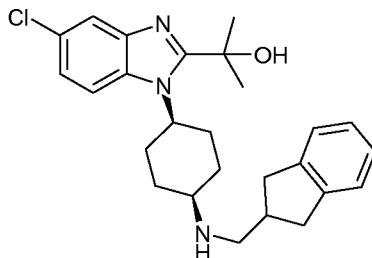
cis-2-(5-Chloro-1-{4-[(5-trifluoromethyl-indan-2-ylmethyl)-amino]-cyclohexyl}-1*H*-benzoimidazol-2-yl)-propan-2-ol



15 This compound was prepared from the hydrochloride salt of *cis*-2-[1-(4-amino-cyclohexyl)-5-chloro-1*H*-benzoimidazol-2-yl]-propan-2-ol and 5-trifluoromethyl-indan-2-carbaldehyde. ¹H-NMR is consistent with the assigned structure, LC-MS showed a single peak, C₂₇H₃₁ClF₃N₃O (m/e) calcd 505.2108, obsd 506.1 (M+H).

Example 9

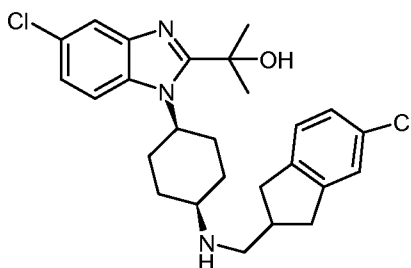
cis-2-(5-Chloro-1-{4-[(indan-2-ylmethyl)-amino]-cyclohexyl}-1*H*-benzoimidazol-2-yl)-propan-2-ol



- 5 This compound was prepared from the hydrochloride salt of *cis*-2-[1-(4-amino-cyclohexyl)-5-chloro-1*H*-benzoimidazol-2-yl]-propan-2-ol and indan-2-carbaldehyde. ¹H-NMR is consistent with the assigned structure, LC-MS showed a single peak, C₂₆H₃₂ClN₃O (m/e) calcd 437.2234, obsd 438.2 (M+H).

Example 10

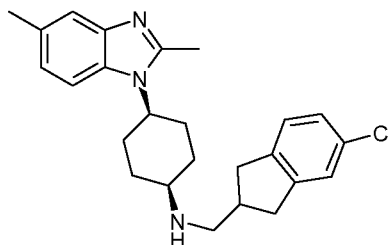
- 10 *cis*-2-(5-Chloro-1-{4-[(5-chloro-indan-2-ylmethyl)-amino]-cyclohexyl}-1*H*-benzoimidazol-2-yl)-propan-2-ol



- 15 This compound was prepared from the hydrochloride salt of *cis*-2-[1-(4-amino-cyclohexyl)-5-chloro-1*H*-benzoimidazol-2-yl]-propan-2-ol and 5-chloro-indan-2-carbaldehyde. ¹H-NMR is consistent with the assigned structure, LC-MS showed a single peak, C₂₆H₃₁Cl₂N₃O (m/e) calcd 471.1844, obsd 472.1 (M+H).

Example 11

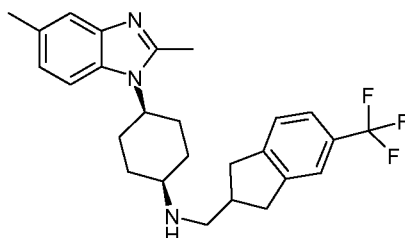
cis-(5-Chloro-indan-2-ylmethyl)-[4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexyl]-amine



- 5 This compound was prepared from the hydrochloride salt of *cis*-4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexylamine and 5-chloro-indan-2-carbaldehyde. ¹H-NMR is consistent with the assigned structure, LC-MS showed a single peak, C₂₅H₃₀ClN₃ (m/e) calcd 407.2128, obsd 408.2 (M+H).

Example 12

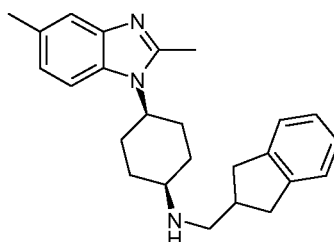
- 10 *cis*-[4-(2,5-Dimethyl-benzoimidazol-1-yl)-cyclohexyl]-(5-trifluoromethyl-indan-2-ylmethyl)-amine



- This compound was prepared from the hydrochloride salt of *cis*-4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexylamine and 5-trifluoromethyl-indan-2-carbaldehyde. ¹H-NMR is consistent with the assigned structure, LC-MS showed a single peak, C₂₆H₃₀F₃N₃ (m/e) calcd 441.2392, obsd 442.2 (M+H).
- 15

Example 13

cis-[4-(2,5-Dimethyl-benzoimidazol-1-yl)-cyclohexyl]-indan-2-ylmethyl-amine

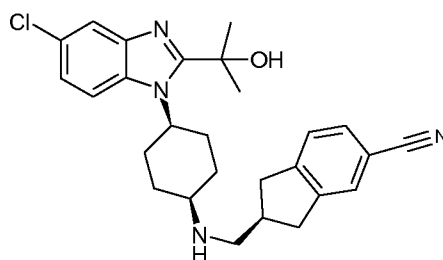


This compound was prepared from the hydrochloride salt of *cis*-4-(2,5-dimethylbenzoimidazol-1-yl)-cyclohexylamine and indan-2-carbaldehyde. ¹H-NMR is consistent with the assigned structure, LC-MS showed a single peak, C₂₅H₃₁N₃ (m/e) calcd 373.2518, obsd 374.2 (M+H).

5

Example 14

cis-(S)-2-({4-[5-Chloro-2-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1-yl]-cyclohexylamino}-methyl)-indan-5-carbonitrile

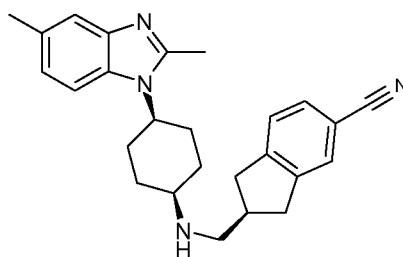


This compound was prepared from the hydrochloride salt of *cis*-2-[1-(4-amino-
10 cyclohexyl)-5-chloro-1*H*-benzoimidazol-2-yl]-propan-2-ol and (S)-5-cyano-indan-2-carbaldehyde. LC-MS showed a single peak, C₂₇H₃₁ClN₄O (m/e) calcd 462.2186, obsd 463.2 (M+H). ¹H-NMR (CD₃OD) δ 7.96 (d, 1H), 7.59 (s, 1H), 7.57 (s, 1H), 7.49 (d, 1H), 7.38 (d, 1H), 7.18 (d, 1H), 5.38 (m, 1H), 3.22 (m, 2H), 2.75-2.97 (m, 8H), 2.01 (m, 2H), 1.72 (s, 6H), 1.68 (m, 4H).

15

Example 15

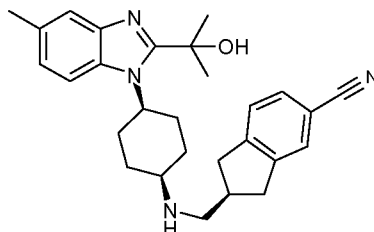
cis-(S)-2-{[4-(2,5-Dimethylbenzoimidazol-1-yl)-cyclohexylamino]-methyl}-indan-5-carbonitrile



This compound was prepared from the hydrochloride salt of *cis*-4-(2,5-dimethylbenzoimidazol-1-yl)-cyclohexylamine and (S)-5-cyano-indan-2-carbaldehyde. ¹H-NMR is
20 consistent with the assigned structure, LC-MS showed a single peak, C₂₆H₃₀N₄ (m/e) calcd 398.2470, obsd 399.3 (M+H).

Example 16

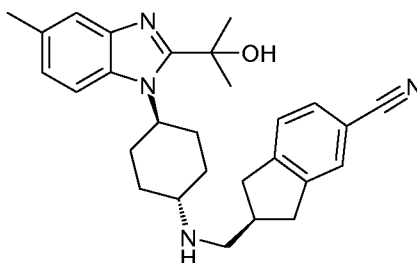
cis-(S)-2-({4-[2-(1-Hydroxy-1-methyl-ethyl)-5-methyl-benzoimidazol-1-yl]-cyclohexylamino}-methyl)-indan-5-carbonitrile



5 This compound was prepared from the hydrochloride salt of 2-[1-(4-amino-cyclohexyl)-5-methyl-1*H*-benzoimidazol-2-yl]-propan-2-ol (prepared as *cis/trans*-isomer mixture) and (S)-2-formyl-indan-5-carbonitrile through the same reductive amination method described previously. The crude mixture was separated through flash column chromatography using methylene chloride and methanol (20:1 to 10:1). The fraction
10 with less retention time (higher R_f) gave *cis*-(S)-2-({4-[2-(1-hydroxy-1-methyl-ethyl)-5-methyl-benzoimidazole-1-yl]-cyclohexylamino}-methyl)-indan-5-carbonitrile. The analysis of the ^1H -NMR confirmed the *cis*-conformation of the cyclohexane. LC-MS showed a single peak, $\text{C}_{28}\text{H}_{34}\text{N}_4\text{O}$ (m/e) calcd 442.2733, obsd 443.3 (M+H). ^1H -NMR (CD $_3$ OD) δ 7.82 (d, 1H), 7.55 (s, 1H), 7.49 (d, 1H), 7.41 (s, 1H), 7.38 (d, 1H), 7.03 (d, 1H), 5.30 (m, 1H), 3.23 (m, 2H), 2.71-2.93 (m, 8H), 2.43 (s, 3H), 1.98 (br d, 2H), 1.72 (s, 6H), 1.64 (m, 4H).
15

Example 17

trans-(S)-2-({4-[2-(1-Hydroxy-1-methyl-ethyl)-5-methyl-benzoimidazol-1-yl]-cyclohexylamino}-methyl)-indan-5-carbonitrile

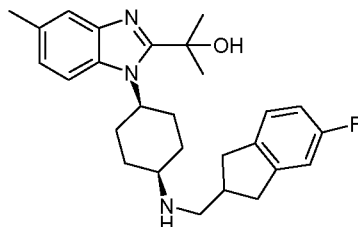


20

This compound was isolated as the second isomer (later fraction) in the preparation of *cis*-(S)-2-({4-[2-(1-hydroxy-1-methyl-ethyl)-5-methyl-benzoimidazole-1-yl]-cyclohexylamino}-methyl)-indan-5-carbonitrile. The analysis of the ^1H -NMR confirmed the *trans*-conformation of the cyclohexane. LC-MS showed a single peak,
25 $\text{C}_{28}\text{H}_{34}\text{N}_4\text{O}$ (m/e) calcd 442.2733, obsd 443.2 (M+H).

Example 18

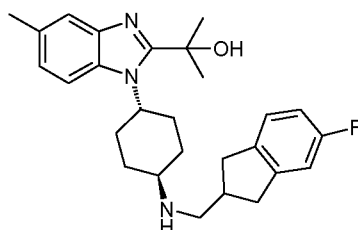
cis-2-(1-{4-[(5-Fluoro-indan-2-ylmethyl)-amino]-cyclohexyl}-5-methyl-1*H*-benzoimidazol-2-yl)-propan-2-ol



5 This compound was prepared from the hydrochloride salt of 2-[1-(4-amino-cyclohexyl)-5-methyl-1*H*-benzoimidazol-2-yl]-propan-2-ol (prepared as *cis/trans*-isomer mixture) and 5-fluoro-indan-2-carbaldehyde. The less polar of the two substances isolated by chromatography gave *cis*-2-(1-{4-[(5-fluoro-indan-2-ylmethyl)-amino]-cyclohexyl}-5-methyl-1*H*-benzoimidazol-2-yl)-propan-2-ol. The analysis of the ¹H-NMR confirmed the *cis*-conformation of the cyclohexane. LC-MS showed a single peak,
10 C₂₇H₃₄FN₃O (m/e) calcd 435.2686, obsd 436.3 (M+H).

Example 19

trans-2-(1-{4-[(5-Fluoro-indan-2-ylmethyl)-amino]-cyclohexyl}-5-methyl-1*H*-benzoimidazol-2-yl)-propan-2-ol

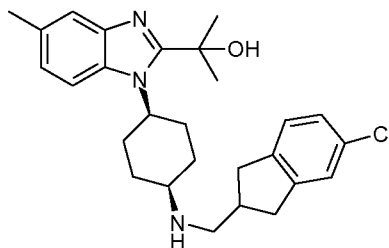


15

This compound was isolated as the second and more polar product in the preparation of *cis*-2-(1-{4-[(5-fluoro-indan-2-ylmethyl)-amino]-cyclohexyl}-5-methyl-1*H*-benzoimidazol-2-yl)-propan-2-ol. The analysis of the ¹H-NMR confirmed the *trans*-conformation of the cyclohexane. LC-MS showed a single peak, C₂₇H₃₄FN₃O (m/e) calcd
20 435.2686, obsd 436.3 (M+H).

Example 20

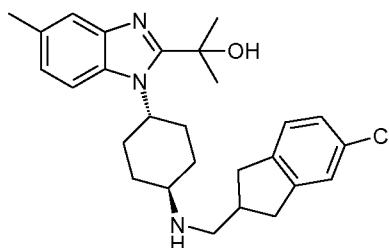
cis-2-(1-{4-[(5-Chloro-indan-2-ylmethyl)-amino]-cyclohexyl}-5-methyl-1H-benzoimidazol-2-yl)-propan-2-ol



5 This compound was prepared from the hydrochloride salt of 2-[1-(4-amino-
cyclohexyl)-5-methyl-1*H*-benzoimidazol-2-yl]-propan-2-ol (prepared as *cis/trans*-isomer
mixture) and 5-chloro-indan-2-carbaldehyde. The less polar of the two substances
isolated by chromatography gave *cis*-2-(1-{4-[(5-chloro-indan-2-yl)methyl]-amino}-
cyclohexyl)-5-methyl-1*H*-benzoimidazol-2-yl)-propan-2-ol. The analysis of the ¹H-NMR
10 confirmed the *cis*-conformation of the cyclohexane. LC-MS showed a single peak,
C₂₇H₃₄ClN₃O (m/e) calcd 451.2390, obsd 452.3 (M+H). ¹H-NMR (CD₃OD) δ 7.83 (d,
1H), 7.40 (s, 1H), 7.20 (s, 1H), 7.17 (d, 1H), 7.10 (d, 1H), 7.03 (d, 1H), 5.32 (m, 1H),
3.16 (m, 2H), 2.96 (br s, 1H), 2.73-2.85 (m, 7H), 2.43 (s, 3H), 2.00 (m, 2H), 1.72 (s, 6H),
1.68 (m, 4H).

Example 21

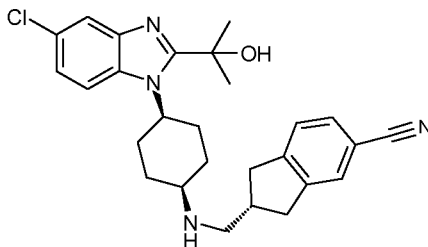
trans-2-(1-{4-[(5-Chloro-indan-2-ylmethyl)-amino]-cyclohexyl}-5-methyl-1H-benzoimidazol-2-yl)-propan-2-ol



This compound was isolated as the second and more polar substance in the preparation of *cis*-2-(1-{4-[(5-chloro-indan-2-ylmethyl)-amino]-cyclohexyl}-5-methyl-1*H*-benzimidazol-2-yl)-propan-2-ol. The analysis of the ¹H-NMR confirmed the *trans*-conformation of the cyclohexane. LC-MS showed a single peak, C₂₇H₃₄ClN₃O (m/e) calcd 451.2390, obsd 452.3 (M+H).

Example 22

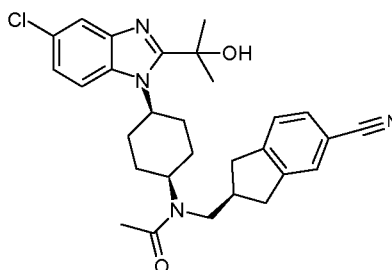
cis-(R)-2-({4-[5-Chloro-2-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1*H*-yl]-cyclohexylamino}-methyl)-indan-5-carbonitrile



- 5 This compound was prepared from the hydrochloride salt of *cis*-2-[1-(4-amino-cyclohexyl)-5-chloro-1*H*-benzoimidazol-2-yl]-propan-2-ol and (R)-5-cyano-indan-2-carbaldehyde. ¹H-NMR is consistent with the assigned structure, LC-MS showed a single peak, C₂₇H₃₁ClN₄O (m/e) calcd 462.2186, obsd 463.2 (M+H).

Example 23

- 10 *cis*-(S)-N-{4-[5-Chloro-2-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1-yl]-cyclohexyl}-N-(5-cyano-indan-2-ylmethyl)-acetamide

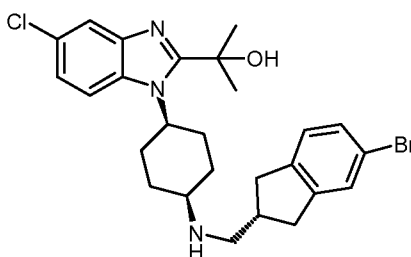


- To a solution of *cis*-(S)-2-({4-[5-chloro-2-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1-yl]-cyclohexylamino}-methyl)-indan-5-carbonitrile (25 mg, 0.054 mmol) in methylene chloride (5 mL) was added triethylamine (11 mg, 0.108 mmol), acetyl chloride (5 mg, 0.063 mmol) and trace amount of 4-dimethylaminopyridine. The mixture was stirred at room temperature for 65 hours. The reaction mixture was diluted with dichloromethane and the solution was washed with saturated aqueous sodium bicarbonate solution followed by brine. The organic extract was dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was subjected to column chromatography, eluting with dichloromethane and ethyl acetate in the presence of 4% methanol to give *cis*-(S)-N-{4-[5-chloro-2-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1-yl]-cyclohexyl}-N-(5-cyano-indan-2-ylmethyl)-acetamide (15 mg). LC-MS showed a single peak, C₂₉H₃₃ClN₄O₂ (m/e) calcd 504.2292, obsd 505.3. ¹H-NMR (CD₃OD) δ 7.67 (br, 1H), 7.59 (s, 2H), 7.50 (d, 1H), 7.40 (d, 1H), 7.23 (d, 1H), 5.57 (m,
- 15
- 20
- 25

1H), 3.48 (br d, 2H), 3.15 (m, 2H), 2.97 (m, 1H), 2.84 (m, 2H), 2.59 (br, 2H), 2.32 (br, 1H), 2.11 (br s, 2H), 1.93 (m, 4H), 1.72 (s, 6H), 1.28 (s, 3H).

Example 24

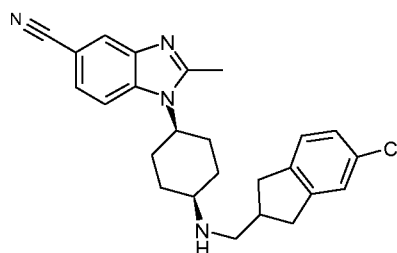
cis-(R)-2-(1-{4-[(5-Bromo-indan-2-ylmethyl)-amino]-cyclohexyl}-5-chloro-1*H*-benzoimidazol-2-yl)-propan-2-ol



This compound was prepared from the hydrochloride salt of *cis*-2-[1-(4-amino-cyclohexyl)-5-chloro-1*H*-benzoimidazol-2-yl]-propan-2-ol and (R)-5-bromo-indan-2-carbaldehyde. ¹H-NMR is consistent with the assigned structure, LC-MS showed a single peak, C₂₆H₃₁BrClN₃O (m/e) calcd 515.1339, obsd 516.2 (M+H).

Example 25

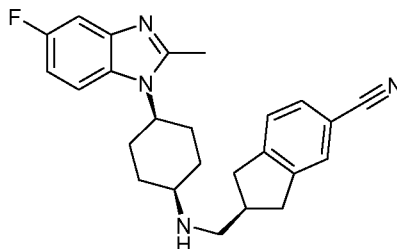
cis-1-{4-[(5-Chloro-indan-2-ylmethyl)-amino]-cyclohexyl}-2-methyl-1*H*-benzoimidazole-5-carbonitrile



This compound was prepared from the hydrochloride salt of *cis*-1-(4-amino-cyclohexyl)-2-methyl-1*H*-benzoimidazole-5-carbonitrile and 5-chloro-indan-2-carbaldehyde. ¹H-NMR is consistent with the assigned structure, LC-MS showed a single peak, C₂₅H₂₇ClN₄ (m/e) calcd 418.1924, obsd 419.2 (M+H).

Example 26

cis-(S)-2-{{4-(5-Fluoro-2-methyl-benzimidazol-1-yl)-cyclohexylamino}-methyl}-indan-5-carbonitrile



5 This compound was prepared from the hydrochloride salt of *cis*-4-(5-fluoro-2-methyl-benzimidazol-1-yl)-cyclohexylamine and (S)-2-formyl-indan-5-carbonitrile through the same reductive amination method described previously. LC-MS showed a single peak, C₂₅H₂₇FN₄ (m/e) calcd 402.2220, obsd 403.2 (M+H). ¹H-NMR (CD₃OD) δ 7.82 (q, 1H), 7.56 (s, 1H), 7.48 (d, 1H), 7.39 (d, 1H), 7.22 (d, 1H), 6.99 (t, 1H), 4.37 (m, 1H), 3.25 (m, 2H), 2.96 (br s, 1H), 2.65-2.90 (m, 7H), 2.61 (s, 3H), 1.99 (br d, 2H), 1.74 (m, 2H), 1.65 (br d, 2H).

Example 27

MCHR Filter Binding Assay

Competition binding assay was conducted in MultiScreen 0.65 μM glass fiber type B filter plates (96-well, Millipore). The MultiScreen plates were pretreated by incubation with 0.5% polyvinylpyrrolidone solution containing 1% BSA and 0.1% tween-20 for 12 hours at 4°C and washed five times with ice-cold 10 mM Tris buffer, pH 7.5, followed by incubation with 200 μL of binding buffer (50 mM HEPES, 2.5 mM CaCl₂, 0.05 mM BSA, 1 mM phenanthroline, 0.03 mM Triton X-100) for 5 min at room temperature and plates were drained before the binding reactions. The binding assay was performed by pre-incubating 2.8 μg of membranes from CHO-K1 cells stably expressing the recombinant human MCHR1 receptors, and various concentrations (final concentration 0.059 nM to 45 μM) of unlabeled MCH or antagonists in binding buffer for 15 min at room temperature. The competition reaction was started by adding final concentration (0.2 nM) [Phe¹³, [¹²⁵I]Tyr¹⁹]-MCH (PerkinElmer). The final volume of the reaction was 90 μL per well. After 60 min incubation time at room temperature the reaction was stopped by rapid filtration over 96-well filter plates. Following termination of the binding reactions, the filters were washed with ice-cold binding buffer (4 × 200 μL), and were air dried for 30 min. Scintillation cocktail (60 μL) was added to each well and radioactivity bound to the plates was determined using a Micro-beta plate reader (Wallace/PerkinElmer). The

inhibition potency of antagonist was expressed as IC_{50} , the concentration of compound at which the binding of radio labeled MCH to MCHR1 was inhibited by 50%. The potency is listed in the following table 1:

Table 1

Example	Activity in MCHR binding assays A= $IC_{50}<0.01\ \mu M$; B= $IC_{50}<0.1\ \mu M$; C= $IC_{50}<1\ \mu M$
1	C
2	C
3	C
4	B
5	C
6	B
7	B
8	C
9	B
10	B
11	B
12	C
13	C
14	A
15	B
16	A
17	C
18	B

Example	Activity in MCHR binding assays A=IC ₅₀ <0.01 μ M; B=IC ₅₀ <0.1 μ M; C=IC ₅₀ <1 μ M
19	C
20	B
21	C
22	A
23	C
24	B
25	B
26	A

The compounds were assayed for their inhibition activity against the binding of MCH to MCHR. The results for five compounds selected from the examples in Part II above are shown in the table 2 below:

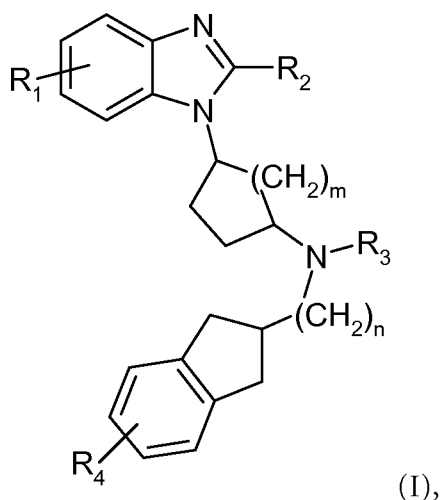
5

Table 2

Example	MCHR IC ₅₀ (nM)	Ki (nM)
7	24	19
14	2.2	1.8
20	26	21
23	193	154
26	3.0	2.0

Claims

1. A compound of the general formula (I):



wherein

- 5 R_1 is selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, halo and cyano;
- R_2 is selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, alkoxy and hydroxyalkyl;
- 10 R_3 is selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, lower alkylcarbonyl, aryl and heteroaryl;
- R_4 is selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, halo, lower haloalkyl and cyano;
- m is 1 or 2; and
- n is 0 or 1,
- 15 and pharmaceutically acceptable salts thereof.

2. The compound of formula (I) according to claim 1, wherein

- R_1 is selected from the group consisting of hydrogen, lower alkyl, halo and cyano;
- R_2 is selected from the group consisting of hydrogen, lower alkyl, alkoxy and hydroxyalkyl;

R₃ is selected from the group consisting of hydrogen, lower alkyl, lower alkylcarbonyl and aryl;

R₄ is selected from the group consisting of hydrogen, lower alkyl, halo, lower haloalkyl and cyano;

5 m is 1 or 2; and

n is 0 or 1,

and pharmaceutically acceptable salts thereof.

3. The compound of formula (I) according to claims 1 or 2, wherein

R₁ is lower alkyl, halo or cyano; and

10 R₃ is hydrogen or lower alkyl.

4. The compound of formula (I) according to claims 1 or 2, wherein

R₂ is lower alkyl, alkoxy or hydroxyalkyl; and

R₄ is halo or cyano.

5. The compound of formula (I) according to any one of claims 1 to 4, wherein R₁

15 is lower alkyl, halo or cyano.

6. The compound of formula (I) according to any one of claims 1 to 5, wherein R₁

is halo or cyano.

7. The compound of formula (I) according to any one of claims 1 to 5, wherein R₁

is methyl or chloro.

8. The compound of formula (I) according to any one of claims 1 to 7, wherein R₂

20 is lower alkyl, alkoxy or hydroxyalkyl.

9. The compound of formula (I) according to any one of claims 1 to 8, wherein R₂

is lower alkyl or hydroxyalkyl.

10. The compound of formula (I) according to any one of claims 1 to 9, wherein R₂ is methyl or 2-hydroxypropyl.

11. The compound of formula (I) according to any one of claims 1, 2 or 4 to 10, wherein R₃ is hydrogen or acetyl.

5 12. The compound of formula (I) according to any one of claims 1 to 11, wherein R₃ is hydrogen.

13. The compound of formula (I) according to any one of claims 1 to 3 or 5 to 12, wherein R₄ is hydrogen, halo, lower haloalkyl or cyano.

10 14. The compound of formula (I) according to any one of claims 1 to 3 or 5 to 13, wherein R₄ is hydrogen, bromo, chloro, fluoro, trifluoromethyl or cyano.

15. The compound of formula (I) according to any one of claims 1 to 3 or 5 to 13, wherein R₄ is bromo, chloro, fluoro, trifluoromethyl or cyano.

16. The compound of formula (I) according to any one of claims 1 to 15, wherein m is 2.

15 17. The compound of formula (I) according to any one of claims 1 to 16, wherein n is 1.

18. The compound of formula (I) according to claim 1, wherein said compound is selected from the group consisting of
cis-(S)-2-(1-{4-[(5-bromo-indan-2-ylmethyl)-amino]-cyclohexyl}-5-chloro-1*H*-
20 benzoimidazol-2-yl)-propan-2-ol,
cis-2-(5-chloro-1-{4-[(indan-2-ylmethyl)-amino]-cyclohexyl}-1*H*-benzoimidazol-2-yl)-
propan-2-ol,
cis-(5-chloro-indan-2-ylmethyl)-[4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexyl]-
amine,
25 *cis*-(S)-2-({4-[5-chloro-2-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1-yl]-
cyclohexylamino}-methyl)-indan-5-carbonitrile,
cis-(S)-2-{{4-(2,5-dimethyl-benzoimidazol-1-yl)-cyclohexylamino}-methyl}-indan-5-
carbonitrile,

- cis*-(S)-2-({4-[2-(1-hydroxy-1-methyl-ethyl)-5-methyl-benzoimidazol-1-yl]-cyclohexylamino}-methyl)-indan-5-carbonitrile,
cis-2-(1-{4-[(5-chloro-indan-2-ylmethyl)-amino]-cyclohexyl}-5-methyl-1*H*-benzoimidazol-2-yl)-propan-2-ol,
5 *cis*-(S)-*N*-{4-[5-chloro-2-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1-yl]-cyclohexyl}-*N*-(5-cyano-indan-2-ylmethyl)-acetamide,
cis-(R)-2-({4-[5-chloro-2-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1*H*-yl]-cyclohexylamino}-methyl)-indan-5-carbonitrile,
cis-(S)-2-{{4-(5-fluoro-2-methyl-benzoimidazol-1-yl)-cyclohexylamino}-methyl}-indan-
10 5-carbonitrile,
and pharmaceutically acceptable salts thereof.

19. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

- 15 20. A method for treating obesity, comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1 to a patient in need thereof

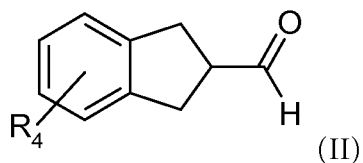
21. A compound of formula (I) according to any one of claims 1 to 18 for use as therapeutically active substance.

- 20 22. The compound of formula (I) according to any one of claims 1 to 18 for use for treating obesity, hyperphagia, anxiety or depression.

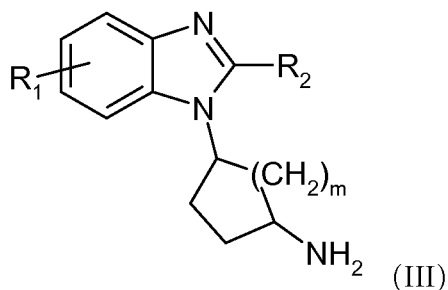
23. Use of a compound of formula (I) according to any one of claims 1 to 18 for the preparation of medicaments for the treatment of obesity, hyperphagia, anxiety or depression.

- 25 24. A process for the manufacture of a compound of formula (I) according to claim 1, which process comprises reductive amination of a compound of formula (II)

- 45 -

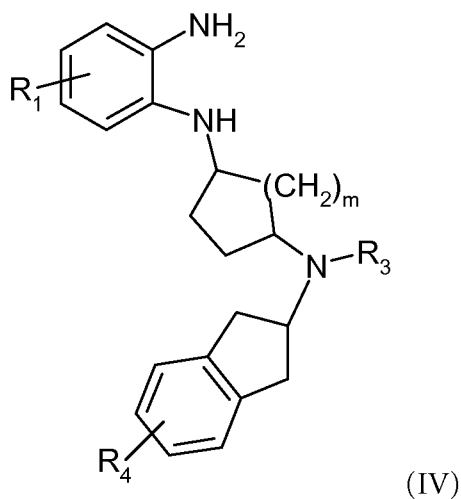


wherein R_4 is as defined in claim 1, with an amine of the formula (III)



- wherein R_1 , R_2 and m are as defined in claim 1, by using NaCNBH_3 or
- 5 $\text{NaBH}(\text{OAc})_3$ to obtain a compound of formula (I), wherein n is 1, and, if desired, converting the resulting compound of formula (I) into a pharmaceutically acceptable salt thereof.

25. A process for the manufacture of a compound of formula (I) according to claim 1, which process comprises ring cyclization of a compound of formula (IV)



wherein R_1 , R_3 , R_4 , m and n are as defined in claim 1, with a carboxylic acid of the formula (V)



wherein R_2 is as defined in claim 1, to obtain a compound of formula (I) wherein n is 0, and, if desired, converting the resulting compound of formula (I) into a pharmaceutically acceptable salt thereof.

26. The novel compounds, processes and methods as well as the use of such
5 compounds substantially as described herein before.
