

Compounds that are agonists of muscarinic receptors and that may be effective in treating pain, Alzheimer's disease and/or Schizophrenia.

This application claims priority under 35 U.S.C. § 119(e) to Application No. 60/746,187, filed on May 2, 2006, which is hereby incorporated by reference in its
5 entirety.

BACKGROUND OF THE INVENTION

1. Field of the invention

The present invention relates to agonists of muscarinic receptors. The
10 present invention also provides compositions comprising such agonists, and methods therewith for treating muscarinic receptor mediated diseases. Particularly, the present invention is related to compounds that may be effective in treating pain, Alzheimer's disease, and/or schizophrenia.

2. Discussion of Relevant Technology

The neurotransmitter acetylcholine binds to two types of cholinergic receptors: the ionotropic family of nicotinic receptors and the metabotropic family of muscarinic receptors. Muscarinic receptors belong to the large superfamily of plasma membrane-bound G protein coupled receptors (GPCRs). and show a remarkably
20 high degree of homology across species and receptor subtype. These M1-M5 muscarinic receptors are predominantly expressed within the parasympathetic nervous system which exerts excitatory and inhibitory control over the central and peripheral tissues and participate in a number of physiologic functions, including heart rate, arousal, cognition, sensory processing, and motor control.

25 Muscarinic agonists such as muscarine and pilocarpine, and antagonists, such as atropine have been known for over a century, but little progress has been made in the discovery of receptor subtype-selective compounds, thereby making it difficult to assign specific functions to the individual receptors. See, e.g., DeLapp, N. et al., "Therapeutic Opportunities for Muscarinic Receptors in the Central Nervous
30 System," J. Med. Chem., 43(23), pp. 4333-4353 (2000); Hulme, E. C. et al., "Muscarinic Receptor Subtypes," Ann. Rev. Pharmacol. Toxicol., 30, pp. 633-673 (1990); Caulfield, M. P. et al., "Muscarinic Receptors-Characterization, Coupling, and Function," Pharmacol. Ther., 58, pp. 319-379 (1993); Caulfield, M. P. et al., International Union of Pharmacology. XVII. Classification of Muscarinic Acetylcholine
35 Receptors," Pharmacol. Rev., 50, pp. 279-290 (1998).

The Muscarinic family of receptors is the target of a large number of

pharmacological agents used for various diseases, including leading drugs for COPD, asthma, urinary incontinence, glaucoma, schizophrenia, Alzheimer's (AChE inhibitors), and Pain.

For example, direct acting muscarinic receptor agonists have been shown to
5 be antinociceptive in a variety of animal models of acute pain (Bartolini A., Ghelardini C., Fantetti L., Malcangio M., Malmberg-Aiello P., Giotti A. Role of muscarinic receptor subtypes in central antinociception. *Br. J. Pharmacol.* 105:77-82, 1992.; Capone F., Aloisi A. M., Carli G., Sacerdote P., Pavone F. Oxotremorine-induced modifications of the behavioral and neuroendocrine responses to formalin pain in
10 male rats. *Brain Res.* 830:292-300, 1999.).

A few studies have examined the role of muscarinic receptor activation in chronic or neuropathic pain states. In these studies, the direct and indirect elevation of cholinergic tone was shown to ameliorate tactile allodynia after intrathecal administration in a spinal ligation model of neuropathic pain in rats and these effects
15 again were reversed by muscarinic antagonists (Hwang J.-H., Hwang K.-S., Leem J.-K., Park P.-H., Han S.-M., Lee D.-M. The antiallodynic effects of intrathecal cholinesterase inhibitors in a rat model of neuropathic pain. *Anesthesiology* 90:492-494, 1999; Lee E. J., Sim J. Y., Park J. Y., Hwang J. H., Park P. H., Han S. M. Intrathecal carbachol and clonidine produce a synergistic antiallodynic effect in rats
20 with a nerve ligation injury. *Can J Anaesth* 49:178-84, 2002.). Thus, direct or indirect activation of muscarinic receptors has been shown to elicit both acute analgesic activity and to ameliorate neuropathic pain. Muscarinic agonists and ACHE-Is are not widely used clinically owing to their propensity to induced a plethora of adverse events when administered to humans. The undesirable side-effects include
25 excessive salivation and sweating, enhanced gastrointestinal motility, and bradycardia among other adverse events. These side-effects are associated with the ubiquitous expression of the muscarinic family of receptors throughout the body.

30 **DESCRIPTION OF THE EMBODIMENTS**

To date, five subtypes of muscarinic receptors (M1-M5) have been cloned and sequenced from a variety of species, with differential distributions in the body.

Therefore, it was desirable to provide molecules would permit selective modulation, for example, of muscarinic receptors controlling central nervous function
35 without also activating muscarinic receptors controlling cardiac, gastrointestinal or glandular functions.

There is also a need for methods for treating muscarinic receptor-mediated diseases.

There is also a need for modulators of muscarinic receptors that are selective as to subtypes M1-M5.

5 The term " C_{m-n} " or " C_{m-n} group" refers to any group having m to n carbon atoms.

 The term "alkyl" refers to a saturated monovalent straight or branched chain hydrocarbon radical comprising 1 to about 12 carbon atoms. Illustrative examples of alkyls include, but are not limited to, C_{1-6} alkyl groups, such as methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, and hexyl, and longer alkyl groups, such as heptyl, and octyl. An alkyl
10 can be unsubstituted or substituted with one or two suitable substituents.
15

 The term "alkenyl" refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 2 up to about 12 carbon atoms. The double bond of an alkenyl can be unconjugated or conjugated to another unsaturated group. Suitable alkenyl groups
20 include, but are not limited to C_{2-6} alkenyl groups, such as vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl. An alkenyl can be unsubstituted or substituted with one or two suitable substituents.

 The term "cycloalkyl" refers to a saturated monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms. Examples of cycloalkyls include, but are not limited to, C_{3-7} cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl can be unsubstituted or substituted by one or two suitable substituents. Preferably, the cycloalkyl is a monocyclic ring or bicyclic ring.
25

30 The term "cycloalkenyl" refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 3 up to about 12 carbon atoms.

 The term "aryl" refers to a monovalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (e.g., $4n + 2$
35 delocalized electrons) and comprising 5 up to about 14 carbon atoms.

The term "heterocycle" refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

The term "heteroaromatic" refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-containing structure or molecule has an aromatic character (e.g., $4n + 2$ delocalized electrons).

The term "heterocyclic group," "heterocyclic moiety," "heterocyclic," or "heterocyclo" refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

The term "heterocyclyl" refers a monovalent radical derived from a heterocycle by removing one hydrogen therefrom.

The term "heterocyclylene" refers to a divalent radical derived from a heterocycle by removing two hydrogens therefrom, which serves to links two structures together.

The term "heteroaryl" refers to a heterocyclyl having aromatic character.

The term "heterocycloalkyl" refers to a monocyclic or polycyclic ring comprising carbon and hydrogen atoms and at least one heteroatom, preferably, 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and having no unsaturation. Examples of heterocycloalkyl groups include pyrrolidinyl, pyrrolidino, piperidinyl, piperidino, piperaziny, piperazino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, and pyranyl. A heterocycloalkyl group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the heterocycloalkyl group is a monocyclic or bicyclic ring, more preferably, a monocyclic ring, wherein the ring comprises from 3 to 6 carbon atoms and from 1 to 3 heteroatoms, referred to herein as C_{3-6} heterocycloalkyl.

The term "heteroarylene" refers to a heterocyclylene having aromatic character.

The term "heterocycloalkylene" refers to a heterocyclylene that does not have aromatic character.

The term "six-membered" refers to a group having a ring that contains six ring atoms.

The term "five-membered" refers to a group having a ring that contains five ring atoms.

5 A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl,
10 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4- oxadiazolyl.

A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

15 Heterocycle includes, for example, monocyclic heterocycles such as: aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane 2,3-dihydrofuran, 2,5-dihydrofuran tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran,
20 tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane, homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

In addition, heterocycle includes aromatic heterocycles, for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole,
25 thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4- oxadiazole.

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline,
30 tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-
35 benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole,

benztriazole, thioxanthine, carbazole, carboline, acridine, pyrrolizidine, and quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

Heterocyclyl includes, for example, monocyclic heterocyclyls, such as: aziridinyl, oxiranyl, thiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-1*H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-1,3-dioxepinyl, and hexamethylene oxidyl.

In addition, heterocyclyl includes aromatic heterocyclyls or heteroaryl, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, furazanyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4 oxadiazolyl.

Additionally, heterocyclyl encompasses polycyclic heterocyclyls (including both aromatic or non-aromatic), for example, indolyl, indolinyl, isoindolinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarinyl, dihydrocoumarinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, isobenzofuranyl, chromenyl, chromanyl, isochromanyl, xanthenyl, phenoxathiinyl, thianthrenyl, indolizinyl, isoindolyl, indazolyl, purinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, phenanthridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, 1,2-benzisoxazolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrrolizidinyl, and quinolizidinyl.

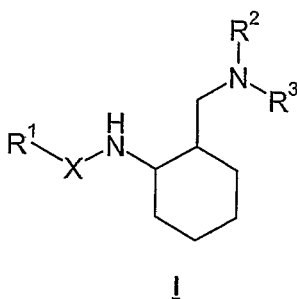
In addition to the polycyclic heterocyclyls described above, heterocyclyl includes polycyclic heterocyclyls wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidinyl, diazabicyclo[2.2.1]heptyl; and 7-oxabicyclo[2.2.1]heptyl.

The term "alkoxy" refers to radicals of the general formula $-O-R$, wherein R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

5 Halogen includes fluorine, chlorine, bromine and iodine.

"RT" or "rt" means room temperature.

In one aspect, an embodiment of the invention provides a compound of Formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



wherein

R^1 is selected from C_{6-10} aryl, C_{2-9} heteroaryl, C_{3-5} heterocycloalkyl, C_{6-10} aryl- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, C_{3-6} cycloalkyl, C_3 -
 15 6cycloalkyl- C_{1-3} alkyl, and C_{1-6} alkyl, wherein said C_{6-10} aryl, C_{2-9} heteroaryl, C_{6-10} aryl- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, C_{3-6} cycloalkyl, C_3 -6cycloalkyl- C_{1-3} alkyl, and C_{1-6} alkyl are optionally substituted with one or more group selected from C_{6-10} aryl, C_{1-9} heteroaryl, C_{3-5} heterocycloalkyl, C_{6-10} aryl- C_{1-3} alkyl, C_{6-10} aryl- O - C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, $-CN$, $-SR$, $-OR$, $-O(CH_2)_m-OR$,
 20 R , $-C(=O)-R$, $-CO_2R$, $-SO_2R$, $-SO_2NR_2$, halogen, $-NO_2$, $-NR_2$, $-(CH_2)_mNR_2$, $-(CH_2)_mNHC(=O)-NR_2$, $-(CH_2)_mNHC(=O)-R$, $-(CH_2)_mN[C(=O)-R]_2$, $-NHC(=O)-R$, $-N[C(=O)R]_2$, $-(CH_2)_mNHS(=O)_2-R$, and $-C(=O)-NR_2$;

R^2 and R^3 are independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and C_{1-6} alkoxy wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{1-6} alkoxy are optionally substituted
 25 by one or more groups selected from amino, halogen, C_{1-6} alkoxy and $-CN$; or R^2 and R^3 together with the nitrogen connected thereto form a heterocycloalkyl, wherein said heterocycloalkyl is optionally substituted with one or more group selected from C_{6-10} aryl, C_{2-9} heteroaryl, C_{3-6} cycloalkyl, C_{3-5} heterocycloalkyl, C_{6-10} aryl- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, $-CN$, $-SR$, $-OR$, $-(CH_2)_mOR$, R , $-CO_2R$, $-SO_2R$, $-SO_2NR_2$, halogen, $-NO_2$, $-NR_2$, $-(CH_2)_mNR_2$, and $-C(=O)-NR_2$;

each R is independently hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl or halogenated C₁₋₆alkyl; and

X is selected from -C(=O)-, -C(=O)-NH-, -C(=O)-O- and -S(=O)₂-, with a proviso that

- 5 when X is -C(=O)- and R² and R³ together with the nitrogen connected thereto form said piperdiny; R¹ is not 4-amino-5-chloro-2-alkoxyphenyl, 4-amino-5-chloro-2-cycloalkoxyphenyl, 4-amino-5-chloro-2-cycloalkyl-alkoxy-phenyl, 4-butoxyphenyl, 3-butoxyphenyl, 4-pentyloxyphenyl, 4-isobutoxyphenyl, 4-benzyloxyphenyl and 7-(2,3-dihydro)benzofuranyl.

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In a particular particular embodiment, the R² and R³ of formula I together with the nitrogen connected thereto form a heterocycloalkyl, wherein said heterocycloalkyl is optionally substituted with one or more group selected from C₆₋₁₀aryl, C₂₋₉heteroaryl, C₃₋₆cycloalkyl, C₃₋₅heterocycloalkyl, C₆₋₁₀aryl-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₅heterocycloalkyl-C₁₋₃alkyl, -CN, -SR, -OR, -(CH₂)_mOR, R, -CO₂R; -SO₂R; -SO₂NR₂, halogen, -NO₂, -NR₂, -(CH₂)_mNR₂, and -C(=O)-NR₂.

In another embodiment, R² and R³ of formula I together with the nitrogen connected thereto form a group selected from piperdiny, 1,4-dioxo-8-azaspiro[4,5]dec-8-yl, piperazinyl, methyl(2-phenylethyl)amino, methyl(pyridin-3-ylmethyl)amino, (4-ethylbenzyl)(methyl)amino, methyl(1-methylpyrrolidin-3-yl)amino, methyl(3-methylbutyl)amino, methyl(propyl)amino, methyl(butyl)amino, butyl(ethyl)amino, diethylamino, benzyl(methyl)amino, morpholin-4-yl, pyrrolidin-1-yl, and azepan-1-yl, wherein said piperdiny, 1,4-dioxo-8-azaspiro[4,5]dec-8-yl, piperazinyl, methyl(2-phenylethyl)amino, methyl(pyridin-3-ylmethyl)amino, (4-ethylbenzyl)(methyl)amino, methyl(1-methylpyrrolidin-3-yl)amino, methyl(3-methylbutyl)amino, methyl(propyl)amino, methyl(butyl)amino, butyl(ethyl)amino, diethylamino, benzyl(methyl)amino, morpholin-4-yl, pyrrolidin-1-yl, and azepan-1-yl are optionally substituted with one or more group selected from C₆₋₁₀aryl, C₂₋₉heteroaryl, C₃₋₆cycloalkyl, C₃₋₅heterocycloalkyl, C₆₋₁₀aryl-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₅heterocycloalkyl-C₁₋₃alkyl, -CN, -SR, -OR, -(CH₂)_mOR, R, -CO₂R; -SO₂R; -SO₂NR₂, halogen, -NO₂, -NR₂, -(CH₂)_mNR₂, and -C(=O)-NR₂.

In another particular embodiment, R¹ of formula I is selected from 2-cyclopentylethyl, cyclopropylmethyl, methyl, cyclohexyl, cyclopentylmethyl, chromanyl, ethyl, pentyl, 2-phenylethyl, phenyl, benzyl, pyridinyl, pyridinylethyl, 1-benzofuranyl, benzothienyl, furyl, imidazolyl, pyrazolo[1,5-a]pyrimidinyl, pyrazinyl, 1,3-benzothiazolyl, indolyl, indazolyl, thienyl, 1,3-benzodioxinyl, tetrahydro-2H-pyran-

4-ylmethyl, 1-H-1,2,3,-benzotriazol-1-yl, 2-(thien-2-yl)ethyl, (1-benzofuran-4-yl)methyl, 1,3-oxazolyl, 1H-pyrazol-1-yl, 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 2-oxo-2,3-dihydro-2H-benzimidazolyl, isoxazolyl, imidazo[1,2,a]pyridinyl, 2-3-dioxo-2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-2H-1,4-benzoxazinyl; pyrazolyl, 1H-tetrazol-1-yl-methyl, and 3,4-dihydro-2H-1,5-benzodioxepinyl, optionally substituted by 1H-pyrazol-1-yl, fluoro, chloro, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, t-butyl, cyano, bromo, 1,3-oxazol-5-yl, 1H-imidazol-1-yl, (4-oxopiperidin-1-yl)carbonyl, pyridin-3-ylmethyl, [(butylamino)carbonyl]amino, 1,1-dioxidothiomorpholin-4-yl, aminosulfonyl, morpholin-4-yl, diethylaminomethyl, acetyl, (3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)methyl, 1-oxo-indan-4-yl, dimethylaminomethyl, methyl, pyrrolidin-1-yl, ethylthio, acetylamino, dimethylamino, 1H-pyrrol-1-yl, ethyl, ethoxy, fluorophenoxy, propyl, phenyl, methoxycarbonyl, diacetylamino, (methylsulfonylamino)methyl, (cyclopropylsulfonylamino)methyl, 1H-tetrazol-1-yl, pyrazolyl, methylaminocarbonylamino, dimethylaminocarbonylamino, and (methylthio)pyrimidin-4-yl.

In another particular embodiment, R^2 and R^3 formula I together with the nitrogen connected thereto form a group selected from piperdinyl, 1,4-dioxo-8-azaspiro[4,5]dec-8-yl, piperazinyl, methyl(2-phenylethyl)amino, methyl(pyridin-3-ylmethyl)amino, (4-ethylbenzyl)(methyl)amino, methyl(1-methylpyrrolidin-3-yl)amino, methyl(3-methylbutyl)amino, methyl(propyl)amino, methyl(butyl)amino, butyl(ethyl)amino, diethylamino, benzyl(methyl)amino, morpholin-4-yl, pyrrolidin-1-yl, and azepan-1-yl, wherein said piperdinyl, 1,4-dioxo-8-azaspiro[4,5]dec-8-yl, piperazinyl, methyl(2-phenylethyl)amino, methyl(pyridin-3-ylmethyl)amino, (4-ethylbenzyl)(methyl)amino, methyl(1-methylpyrrolidin-3-yl)amino, methyl(3-methylbutyl)amino, methyl(propyl)amino, methyl(butyl)amino, butyl(ethyl)amino, diethylamino, benzyl(methyl)amino, morpholin-4-yl, pyrrolidin-1-yl, and azepan-1-yl are optionally substituted with one or more group selected from phenyl, benzyl, methyl, fluoro, trifluoromethyl, methoxy, allyloxy, (2E)-but-2-en-1-yloxy, (allyloxy)methyl, methoxymethyl, ethoxymethyl, propyl, butyl, pentyl, hexyl, cyclopentyl, pyridin-4-ylmethyl, ethoxy, butoxy, 2-methoxyethoxy, cyclohexyl, and thienylmethyl.

In another particular embodiment, R^2 and R^3 of formula I together with the nitrogen connected thereto form a group selected from piperdinyl, wherein said

piperidinyl is optionally substituted with one or more group selected from phenyl, benzyl, methyl, fluoro, trifluoromethyl, methoxy, allyloxy, (2E)-but-2-en-1-yloxy, (allyloxy)methyl, methoxymethyl, ethoxymethyl, propyl, butyl, pentyl, hexyl, cyclopentyl, pyridin-4-ylmethyl, ethoxy, butoxy, 2-methoxyethoxy, cyclohexyl, and
 5 thienylmethyl.

In a further particular embodiment, the compounds are selected from
trans-(+/-)-4-fluoro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
 10 *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-6-(trifluoromethyl)nicotinamide;
trans-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide;
trans-(+/-)-5-chloro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1-benzofuran-2-carboxamide;
trans-(+/-)-2-(4-methoxyphenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide;
 15 *trans*-(+/-)-4-(difluoromethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-4-(2-methoxyethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+)-4-(2-methoxyethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-4-(2-methoxyethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-3-cyclopentyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide;
 20 *trans*-(+/-)-3-(4-chlorophenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide;
trans-(+/-)-3-(2-methoxyphenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide;
trans-(+/-)-4-*tert*-butyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-4-methoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
 25 *trans*-(+/-)-4-cyano-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-4-bromo-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-4-chloro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-6-(1*H*-imidazol-1-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]nicotinamide;
trans-(+/-)-4-(1,3-oxazol-5-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
 30 *trans*-(+/-)-6-methoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]nicotinamide;
trans-(+/-)-4-(1*H*-imidazol-1-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-4-[(4-oxopiperidin-1-yl)carbonyl]-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-2-pyridin-3-ylacetamide;
 35 *trans*-(+/-)-2-[(butylamino)carbonyl]amino-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;

- trans*-(+/-)-4-(1,1-dioxidothiomorpholin-4-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-4-(aminosulfonyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-2-morpholin-4-yl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]isonicotinamide;
- 5 *trans*-(+/-)-4-[(diethylamino)methyl]-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1-benzothiophene-3-carboxamide;
- trans*-(+/-)-4-acetyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- 10 *trans*-(+/-)-4-[(3-oxo-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)methyl]-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-1-oxo-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]indane-4-carboxamide;
- trans*-(+/-)-5-[(dimethylamino)methyl]-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-2-furamide;
- 15 *trans*-(+/-)-1-methyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1*H*-imidazole-4-carboxamide;
- trans*-(+/-)-2-(4-chlorophenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-6-pyrrolidin-1-ylnicotinamide;
- trans*-(+/-)-5-methyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-7-
- 20 (trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]pyrazine-2-carboxamide;
- trans*-(+/-)-4-(ethylthio)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1,3-benzothiazole-6-carboxamide;
- 25 *trans*-(+/-)-4-(acetylamino)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-5-methoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1*H*-indole-2-carboxamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]thiophene-3-carboxamide;
- trans*-(+/-)-2-phenyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide;
- 30 *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-4-(trifluoromethoxy)benzamide;
- trans*-(+/-)-3-(2-chlorophenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidine-3-carboxamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-4-cyano benzamide;
- 35 *trans*-(+/-)-3-(3-chlorophenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide;

- trans*-(+/-)-6-fluoro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-4*H*-1,3-benzodioxine-8-carboxamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-2-(tetrahydro-2*H*-pyran-4-yl)acetamide;
- 5 *trans*-(+/-)-4-chloro-2,5-difluoro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1*H*-indole-6-carboxamide;
- trans*-(+/-)-3-(1*H*-1,2,3-benzotriazol-1-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-3-(2-thienyl)propanamide;
- 10 *trans*-(+/-)-2-(1-benzofuran-4-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide;
- trans*-(+/-)-4-(dimethylamino)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-3-pyridin-3-ylpropanamide;
- trans*-(+/-)-4,6-dimethyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]nicotinamide;
- trans*-(+/-)-3-(5-methyl-2-furyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1*H*-pyrazole-
- 15 5-carboxamide;
- trans*-(+/-)-2-cyclopropyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide;
- trans*-(+/-)-5-methoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1-benzofuran-2-carboxamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1*H*-indazole-3-carboxamide;
- 20 *trans*-(+/-)-6-(ethylthio)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]nicotinamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrrol-1-yl)benzamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1*H*-indole-4-carboxamide;
- trans*-(+/-)-2-chloro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-3-cyano-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- 25 *trans*-(+/-)-2-methyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-5-(trifluoromethyl)-1,3-oxazole-4-carboxamide;
- trans*-(+/-)-3-chloro-4-methyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]thiophene-2-carboxamide;
- trans*-(+/-)-3-(5-methyl-1*H*-pyrazol-1-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide;
- 30 *trans*-(+/-)-3-methoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-2-(2,3-dihydro-1-benzofuran-5-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1,3-benzodioxole-5-
- 35 carboxamide;

- trans*-(+/-)-5-methyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]thiophene-2-carboxamide;
- trans*-(+/-)-1-ethyl-5-methyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide;
- 5 *trans*-(+/-)-5-ethoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-2-furamide;
- trans*-(+/-)-3-(4-fluorophenoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide;
- trans*-(+/-)-3-fluoro-4-methoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-4-propylbenzamide;
- 10 *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]hexanamide;
- trans*-(+/-)-4-butoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-4-chloro-2-fluoro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-2-oxo-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-2,3-dihydro-1*H*-benzimidazole-5-carboxamide;
- 15 *trans*-(+/-)-2-(4-ethoxyphenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide;
- trans*-(+/-)-3-phenyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]isoxazole-5-carboxamide;
- trans*-(+/-)-2-methoxy-5-methyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-4-methoxy-*N*-{2-[(4-phenylpiperidin-1-yl)methyl]cyclohexyl}benzamide;
- 20 *trans*-(+/-)-*N*-[2-(1,4-dioxo-8-azaspiro[4.5]dec-8-ylmethyl)cyclohexyl]-4-methoxybenzamide;
- trans*-(+/-)-*N*-{2-[(3,5-dimethylpiperidin-1-yl)methyl]cyclohexyl}-4-methoxybenzamide;
- trans*-(+/-)-*N*-{2-[(4-fluoropiperidin-1-yl)methyl]cyclohexyl}-4-methoxybenzamide;
- 25 *trans*-(+/-)-4-methoxy-*N*-(2-{[4-(trifluoromethyl)piperidin-1-yl]methyl}cyclohexyl)benzamide;
- trans*-(+/-)-4-methoxy-*N*-(2-{[4-methoxypiperidin-1-yl]methyl}cyclohexyl)benzamide;
- trans*-(+/-)-4-methoxy-*N*-(2-{[3-(trifluoromethyl)piperidin-1-yl]methyl}cyclohexyl)benzamide;
- 30 *trans*-(+/-)-4-methoxy-*N*-(2-{[3-phenylpiperidin-1-yl]methyl}cyclohexyl)benzamide;
- trans*-(+/-)-*N*-[2-({3-[(allyloxy)methyl]piperidin-1-yl)methyl}cyclohexyl]-4-methoxybenzamide;
- 35 *trans*-(+/-)-*N*-[2-({3-[(allyloxy)methyl]piperidin-1-yl)methyl}cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;

- trans*-(+/-)- *N*-(2-[[3-(methoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)- *N*-(2-[[3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 5 *trans*-(+/-)- *N*-(2-[[3-pentylpiperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)- *N*-(2-[[3-pentylpiperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrazol-1-yl)benzamide;
- trans*-(+/-)- 6-(1*H*-imidazol-1-yl)-*N*-(2-[[3-pentylpiperidin-1-yl]methyl]cyclohexyl)nicotinamide;
- 10 *trans*-(+/-)- *N*-(2-[[3-pentylpiperidin-1-yl]methyl]cyclohexyl)-6-pyrrolidin-1-yl)nicotinamide;
- trans* (±) 6-(1*H*-imidazol-1-yl)-*N*-(2-[[3*R*]-3-pentylpiperidin-1-yl]methyl]cyclohexyl)nicotinamide;
- 15 *trans* (±) 6-(1*H*-imidazol-1-yl)-*N*-(2-[[3*S*]-3-pentylpiperidin-1-yl]methyl]cyclohexyl)nicotinamide;
- trans*-(+/-)- *N*-(2-[[3-hexylpiperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)- *N*-(2-[[3-hexylpiperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-imidazol-1-yl)nicotinamide;
- 20 *trans*-(+/-)- *N*-(2-[[3-hexylpiperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrazol-1-yl)benzamide;
- trans*-(+/-)- *N*-(2-[[3-hexylpiperidin-1-yl]methyl]cyclohexyl)-4-pyrrolidin-1-ylbenzamide;
- 25 *trans*-(+/-)- *N*-(2-[[3-butylpiperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)- *N*-(2-[[3-butylpiperidin-1-yl]methyl]cyclohexyl)-4-pyrrolidin-1-ylbenzamide;
- trans*-(+/-)- *N*-(2-[[3-butylpiperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-imidazol-1-yl)nicotinamide;
- 30 *trans*-(+/-)- *N*-(2-[[3-butylpiperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrazol-1-yl)benzamide;
- cis*-(+/-)- *N*-(2-[[3-butylpiperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-imidazol-1-yl)nicotinamide;
- 35 *trans*-(+/-)-*N*-(2-[[4-(Allyloxy)piperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;

- trans*-(+/-)-*N*-[2-({4-[(2*E*)-But-2-en-1-yloxy]piperidin-1-yl}methyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-6-pyrrolidin-1-yl nicotinamide;
- 5 *trans*-(+/-)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide;
- trans*-(+/-)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-6-(1*H*-imidazol-1-yl)nicotinamide;
- trans*-(±)-*N*-2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-4-
- 10 bromobenzamide;
- Trans*-(±)-(N-2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl)-3-(4-chlorophenyl)propanamide
- Trans*-(±)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-3-(2-methoxyphenyl)propanamide
- 15 *Trans*-(±)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-4-cyanobenzamide
- Trans*-(±)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-4-fluorobenzamide
- Trans*-(±)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-4-
- 20 chlorobenzamide
- Trans*-(±)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-4-[(diethylamino)methyl]benzamide
- Trans*-(±)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-4-[(4-methylpiperazin-1-yl)methyl]benzamide;
- 25 *Trans* (±)-[2-({(3*R*)-3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-6-(1*H*-imidazol-1-yl)nicotinamide;
- Trans*-(±)-[2-({(3*S*)-3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-6-(1*H*-imidazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-[2-[(4-benzylpiperidin-1-yl)methyl]cyclohexyl]-6-(1*H*-pyrazol-1-
- 30 yl)nicotinamide;
- trans*-(+/-)-*N*-[2-[(4-cyclopentylpiperazin-1-yl)methyl]cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-(2-[[methyl(2-phenylethyl)amino]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 35 *trans*-(+/-)-6-(1*H*-pyrazol-1-yl)-*N*-(2-[[4-(pyridin-4-yl)methyl]piperazin-1-yl]methyl)cyclohexyl)nicotinamide;

- trans*-(+/-)-*N*-(2-[[methyl(pyridin-3-ylmethyl)amino]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-(2-[[4-ethylbenzyl(methyl)amino]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 5 *trans*-(+/-)-*N*-(2-[[methyl(1-methylpyrrolidin-3-yl)amino]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-(2-[[methyl(3-methylbutyl)amino]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-(2-[[methyl(propyl)amino]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 10 *trans*-(+/-)-*N*-(2-[[benzyl(methyl)amino]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-(2-[[4-propylpiperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 15 *trans*-(+/-)-*N*-(2-[[2-(methoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-(2-[[butyl(methyl)amino]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-(2-[[butyl(ethyl)amino]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 20 *trans*-(+/-)-6-(1*H*-pyrazol-1-yl)-*N*-(2-[[2-(3-thienylmethyl)piperidin-1-yl]methyl]cyclohexyl)nicotinamide;
- trans*-(+/-)-*N*-(2-[[4,4-difluoropiperidin-1-yl]methyl]cyclohexyl)-4-methoxybenzamide;
- 25 *trans*-(+/-)-4-methoxy-*N*-(2-[[4-methylpiperidin-1-yl]methyl]cyclohexyl)benzamide;
- trans*-(+/-)-4-(2-methoxyethoxy)-*N*-(2-[[4-methylpiperidin-1-yl]methyl]cyclohexyl)benzamide;
- trans*-(+/-)-4-methoxy-*N*-(2-(morpholin-4-ylmethyl)cyclohexyl)benzamide;
- cis*-(+/-)-4-(2-ethoxyethoxy)-*N*-(2-(piperidin-1-ylmethyl)cyclohexyl)benzamide;
- 30 *cis*-(+/-)-4-(2-ethoxyethoxy)-*N*-(2-(pyrrolidin-1-ylmethyl)cyclohexyl)benzamide;
- cis*-(+/-)-*N*-(2-[[diethylamino]methyl]cyclohexyl)-4-(2-ethoxyethoxy)benzamide;
- trans*-(+/-)-4-(2-ethoxyethoxy)-*N*-(2-(piperidin-1-ylmethyl)cyclohexyl)benzamide;
- trans*-(+/-)-*N*-(2-(azepan-1-ylmethyl)cyclohexyl)-4-(2-ethoxyethoxy)benzamide;
- trans*-(+/-)-*N*-(2-[[diethylamino]methyl]cyclohexyl)-4-(2-ethoxyethoxy)benzamide;
- 35 *trans*-(+/-)-*N*-(4-chlorophenyl)-*N'*-(2-(piperidin-1-ylmethyl)cyclohexyl)urea;
- trans*-(+/-)-*N*-(4-cyanophenyl)-*N'*-(2-(piperidin-1-ylmethyl)cyclohexyl)urea;

- trans*-(+/-)-*N*-(4-methoxyphenyl)-*N'*-[2-(piperidin-1-ylmethyl)cyclohexyl]urea;
trans-(+/-)-2-methoxy-4-methyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzenesulfonamide;
trans-(+/-)-methyl 3-([2-(piperidin-1-ylmethyl)cyclohexyl]amino)sulfonylthiophene-2-carboxylate;
5 *trans*-(+/-)-5-[2-(methylthio)pyrimidin-4-yl]-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]thiophene-2-sulfonamide;
trans-(+/-)-1-(4-chlorophenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]methanesulfonamide;
10 *trans*-(+/-)-*N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-4-(1,3-oxazol-5-yl)benzamide;
trans-(+/-)-*N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-6-(trifluoromethyl)nicotinamide;
trans-(+/-)-*N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-4-(2-methoxyethoxy)benzamide;
15 *trans*-(+/-)-*N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-3-(4-chlorophenyl)propanamide;
trans-(+/-)-*N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-4-(1*H*-imidazol-1-yl)benzamide;
20 *trans*-(+/-)-*N*-{2-[(3-(ethoxymethyl)piperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-imidazol-1-yl)nicotinamide;
trans-(+/-)-*N*-{2-[(3-(ethoxymethyl)piperidin-1-yl)methyl]cyclohexyl}-4-(1,3-oxazol-5-yl)benzamide;
trans-(+/-)-*N*-{2-[(3-(ethoxymethyl)piperidin-1-yl)methyl]cyclohexyl}-4-(1*H*-imidazol-1-yl)benzamide;
25 *trans*-(+/-)-*N*-2-[[3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-[[[methylsulfonyl]amino]methyl]benzamide;
trans-(+/-)-*N*-{2-[(3-propylpiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-imidazol-1-yl)nicotinamide;
30 *trans*-(+/-)-4-(1*H*-imidazol-1-yl)-*N*-{2-[(3-propylpiperidin-1-yl)methyl]cyclohexyl}benzamide;
trans-(+/-)-*N*-{2-[(3-isobutylpiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-imidazol-1-yl)nicotinamide;
trans-(+/-)-4-(1*H*-imidazol-1-yl)-*N*-{2-[(3-isobutylpiperidin-1-yl)methyl]cyclohexyl}benzamide;
35 *trans*-(+/-)-4-Bromo-*N*-{2-[(3-propylpiperidin-1-yl)methyl]cyclohexyl}benzamide;

- trans*-(+/-)-3-(4-Chlorophenyl)-*N*-{2-[(3-propylpiperidin-1-yl)methyl]cyclohexyl}propanamide;
- trans*-(+/-)-4-Bromo-*N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}benzamide;
- trans*-(+/-)-*N*-{2-[(3-Butylpiperidin-1-yl)methyl]cyclohexyl}-4-
 5 [(diethylamino)methyl]benzamide;
- trans*-(+/-)-3-(4-Chlorophenyl)-*N*-(2-{[3-(ethoxymethyl)piperidin-1-yl]methyl}cyclohexyl)propanamide;
- N*-[(1*S*,2*R*)-2-{[4-[(2*E*)-But-2-en-1-yloxy]piperidin-1-yl]methyl}cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 10 *N*-[(1*S*,2*R*)-2-{[4-Butoxypiperidin-1-yl]methyl}cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
- N*-(1*S*,2*R*)-2-{[(3*R*)-3-(2-Methoxyethoxy)piperidin-1-yl]methyl}cyclohexyl)-4-(1*H*-pyrazol-1-yl)benzamide;
- N*-(1*R*,2*S*)-2-{[(3*R*)-3-(2-Methoxyethoxy)piperidin-1-yl]methyl}cyclohexyl)-4-(1*H*-
 15 pyrazol-1-yl)benzamide;
- N*-[(1*S*,2*R*)-2-{[(3*R*)-3-[(Allyloxy)methyl]piperidin-1-yl]methyl}cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
- N*-[(1*R*,2*S*)-2-{[(3*R*)-3-[(Allyloxy)methyl]piperidin-1-yl]methyl}cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 20 *N*-[(1*R*,2*S*)-2-{[(3*R*)-3-[(Allyloxy)methyl]piperidin-1-yl]methyl}cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide
- N*-[(1*S*,2*R*)-2-{[(3*R*)-3-[(Allyloxy)methyl]piperidin-1-yl]methyl}cyclohexyl]-6-(1*H*-imidazol-1-yl)nicotinamide;
- (*N*-[(1*S*,2*R*)-2-{[(3*R*)-3-ethoxypiperidin-1-yl]methyl}cyclohexyl)pyrazine-2-
 25 carboxamide;
- N*-[(1*S*,2*R*)-2-{[(3*R*)-3-ethoxypiperidin-1-yl]methyl}cyclohexyl]-6-(ethylthio)nicotinamide;
- N*-[(1*S*,2*R*)-2-{[(3*R*)-3-ethoxypiperidin-1-yl]methyl}cyclohexyl]-6-pyrrolidin-1-yl)nicotinamide;
- 30 *N*-[(1*S*,2*R*)-2-(azepan-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide;
- N*-[(1*S*,2*R*)-2-(azepan-1-ylmethyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
- N*-[(1*S*,2*R*)-2-{[(3*R*)-3-(allyloxy)piperidin-1-yl]methyl}cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide;
- N*-[(1*R*,2*S*)-2-{[(3*R*)-3-(ethoxymethyl)piperidin-1-yl]methyl}cyclohexyl)-4-(1*H*-
 35 pyrrol-1-yl)benzamide;

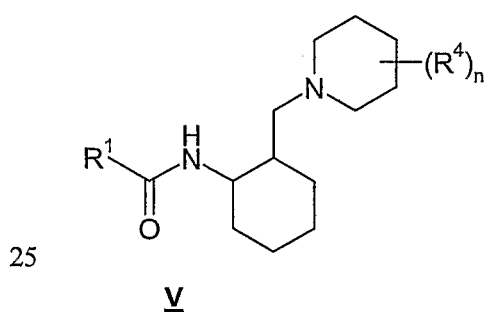
- N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-(1*H*-pyrrol-1-yl)benzamide;
- N*-((1*R*,2*S*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-6-pyrrolidin-1-ynicotinamide;
- 5 *N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-6-pyrrolidin-1-ynicotinamide;
- N*-[(1*S*,2*R*)-2-(piperidin-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide;
- N*-[(1*S*,2*R*)-2-(piperidin-1-ylmethyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
- N*-((1*S*,2*R*)-2-(((3*R*)-3-(allyloxy)piperidin-1-yl)methyl)cyclohexyl)-4-(1*H*-pyrrol-1-yl)benzamide;
- 10 *N*-((1*S*,2*R*)-2-(((3*R*)-3-(allyloxy)piperidin-1-yl)methyl)cyclohexyl)-3-cyclopentylpropanamide;
- N*-((1*S*,2*R*)-2-(((3*R*)-3-(allyloxy)piperidin-1-yl)methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 15 *N*-((1*S*,2*R*)-2-(((3*S*)-3-(allyloxy)piperidin-1-yl)methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- N*-((1*S*,2*R*)-2-(((3*S*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-(2-methoxyethoxy)benzamide;
- 3-(4-chlorophenyl)-*N*-((1*S*,2*R*)-2-(((3*S*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)propanamide;
- 20 *N*-((1*S*,2*R*)-2-(((3*S*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-(((methylsulfonyl)amino)methyl)benzamide;
- 4-[(diethylamino)methyl]-*N*-((1*S*,2*R*)-2-(((3*S*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide;
- 25 *N*-[(1*S*,2*R*)-2-(((3*R*)-3-(allyloxy)methyl)piperidin-1-yl)methyl)cyclohexyl]-6-(1*H*-imidazol-1-yl)nicotinamide;
- 4-chloro-*N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide;
- N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide;
- 30 *N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)cyclohexanecarboxamide;
- N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-2-phenylacetamide;
- N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-3-phenylpropanamide;
- 35

- N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-2,3-dihydro-1-benzofuran-5-carboxamide;
- 2-cyclopentyl-N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)acetamide;
- 5 2-chloro-N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-3-fluoroisonicotinamide hydrochloride salt;
- (2S)-N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)chromane-2-carboxamide hydrochloride salt;
- (2R)-N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)chromane-2-carboxamide hydrochloride salt;
- 10 N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4,6-dimethylnicotinamide hydrochloride salt;
- N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-2,7-dimethylimidazo[1,2-a]pyridine-3-carboxamide hydrochloride salt;
- 15 N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-2-(3-methoxyphenyl)acetamide hydrochloride salt;
- 2-(2,3-dioxo-2,3-dihydro-1H-indol-1-yl)-N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)acetamide hydrochloride salt;
- N2-acetyl-N1-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)glycinamide hydrochloride salt;
- 20 N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-2-(1H-tetrazol-1-yl)acetamide hydrochloride salt;
- N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-5,7-dimethylpyrazolo[1,5-a]pyrimidine-2-carboxamide hydrochloride salt;
- 25 N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-3,4-dihydro-2H-1,5-benzodioxepine-6-carboxamide hydrochloride salt;
- N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-methyl-3,4-dihydro-2H-1,4-benzoxazine-7-carboxamide hydrochloride salt;
- N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-5-phenyl-1H-pyrazole-4-carboxamide hydrochloride salt;
- 30 N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-(1H-tetrazol-1-yl)benzamide hydrochloride salt;
- 4-[(diethylamino)methyl]-N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide;
- 35 N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-(2-methoxyethoxy)benzamide;

- $N-((1S,2R)-2-[[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl]-4-[[[(methylsulfonyl)amino]methyl]benzamide;$
 $4-[(acetylamino)methyl]-N-((1S,2R)-2-[[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide;$
 5 $4-[(diacetylamino)methyl]-N-((1S,2R)-2-[[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide;$
 $N-((1S,2R)-2-[[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-[[[(ethylsulfonyl)amino]methyl]benzamide;$
 $4-[[[(cyclopropylsulfonyl)amino]methyl]-N-((1S,2R)-2-[[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide;$
 10 $N-((1S,2R)-2-[[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-[[[(methylamino)carbonyl]amino]methyl]benzamide;$
 $4-[[[(dimethylamino)carbonyl]amino]methyl]-N-((1S,2R)-2-[[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide;$
 15 $N-((1S,2R)-2-[[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-[[[(isobutyrylamino)methyl]benzamide;$
 $N-((1S,2R)-2-[[[3-cyclohexyl]piperidin-1-yl]methyl]cyclohexyl)-6-(1H-pyrazol-1-yl)nicotinamide;$
 $N-((1S,2R)-2-[[[3-phenyl]piperidin-1-yl]methyl]cyclohexyl)-6-(1H-pyrazol-1-yl)nicotinamide;$
 20

and pharmaceutically acceptable salts thereof.

In another embodiment, the invention provides a compound of formula V, a pharmaceutically acceptable salt thereof, diastereomer, enantiomer, or mixture thereof:



wherein

- R^1 is selected from C_{6-10} aryl, C_{2-9} heteroaryl, C_{3-5} heterocycloalkyl, C_{6-10} aryl- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-3} alkyl, and C_{1-6} alkyl, wherein said C_{6-10} aryl, C_{2-9} heteroaryl, C_{6-10} aryl- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-3} alkyl,
 30

- alkyl, and C₁₋₆alkyl are optionally substituted with one or more group selected from C₆₋₁₀aryl, C₁₋₉heteroaryl, C₃₋₅heterocycloalkyl, C₆₋₁₀aryl-C₁₋₃alkyl, C₆₋₁₀aryl-O-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₅heterocycloalkyl-C₁₋₃alkyl, -CN, -SR, -OR, -O(CH₂)_m-OR, R, -C(=O)-R, -CO₂R, -SO₂R, -SO₂NR₂, halogen, -NO₂, -NR₂, -(CH₂)_mNR₂, -
- 5 (CH₂)_mNHC(=O)-NR₂, -NHC(=O)-R, -N[C(=O)R]₂, -(CH₂)_mNHC(=O)-R, - (CH₂)_mN[C(=O)-R]₂, -(CH₂)_mNHS(=O)₂-R, and -C(=O)-NR₂; and
- R⁴ is selected from C₆₋₁₀aryl, C₂₋₉heteroaryl, C₃₋₆cycloalkyl, C₃₋₅heterocycloalkyl, C₆₋₁₀aryl-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₅heterocycloalkyl-C₁₋₃alkyl, -CN, -SR, -OR, -(CH₂)_mOR, -O(CH₂)_mOR, -O(CH₂)_mNR₂, -(CH₂)_mO(CH₂)_nOR, -
- 10 (CH₂)_mO(CH₂)_nNR₂, R, -CO₂R; -SO₂R; -SO₂NR₂, halogen, -NO₂, -NR₂, -(CH₂)_mNR₂, and -C(=O)-NR₂;
- each R is independently hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl or halogenated C₁₋₆alkyl;
- with a proviso that
- 15 R¹ is not 4-amino-5-chloro-2-alkoxyphenyl, 4-amino-5-chloro-2-cycloalkoxyphenyl, 4-amino-5-chloro-2-cycloalkyl-alkoxy-phenyl, 4-butoxyphenyl, 3-butoxyphenyl, 4-pentyloxyphenyl, 4-isobutoxyphenyl, 4-benzoyloxyphenyl and 7-(2,3-dihydro)benzofuranyl.
- In a particular embodiment, R¹ of formula V is selected from C₆₋₁₀aryl, C₂₋₉heteroaryl, C₃₋₅heterocycloalkyl, C₆₋₁₀aryl-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₅heterocycloalkyl-C₁₋₃alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₃alkyl, and C₃₋₆alkyl, wherein said C₆₋₁₀aryl, C₂₋₉heteroaryl, C₆₋₁₀aryl-C₁₋₃alkyl, C₆₋₁₀aryl-O-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₃alkyl, and C₃₋₆alkyl are optionally substituted by one or more groups selected from 1H-pyrazol-1-yl, fluoro,
- 25 chloro, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, t-butyl, cyano, bromo, 1,3-oxazol-5-yl, 1H-imidazol-1-yl, (4-oxopiperidin-1-yl)carbonyl, pyridin-3-ylmethyl, [(butylamino)carbonyl]amino, 1,1,-dioxidothiomorpholin-4-yl, aminosulfonyl, morpholin-4-yl, diethylaminomethyl, acetyl, (3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)methyl, 1-oxo-indan-4-yl,
- 30 dimethylaminomethyl, methyl, pyrrolidin-1-yl, ethylthio, acetylamino, dimethylamino, 1H-pyrrol-1-yl, ethyl, ethoxy, fluorophenoxy, propyl, phenyl, methoxycarbonyl, diacetylamino, (methylsulfonylamino)methyl, (cyclopropylsulfonylamino)methyl, 1H-tetrazol-1-yl, pyrazolyl, methylaminocarbonylamino, dimethylaminocarbonylamino, and (methylthio)pyrimidin-4-yl.
- 35 In another particular embodiment, R¹ of formula V is selected from 2-cyclopentylethyl, cyclopropylmethyl, ethyl, methyl, cyclohexyl, cyclopentylmethyl,

- chromanyl, pentyl, 2-phenylethyl, phenyl, benzyl, pyridinyl, pyridinylethyl, 1-benzofuranyl, benzothienyl, furyl, imidazolyl, pyrazolo[1,5-a]pyrimidinyl, pyrazinyl, 1,3-benzothiazolyl, indolyl, indazolyl, thienyl, 1,3-benzodioxinyl, tetrahydro-2H-pyran-4-ylmethyl, 1-H-1,2,3-benzotriazol-1-yl, 2-(thien-2-yl)ethyl, (1-benzofuran-4-yl)methyl, 1,3-oxazolyl, 1H-pyrazol-1-yl, 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 2-oxo-2,3-dihydro-2H-benzimidazolyl, isoxazolyl, imidazo[1,2,a]pyridinyl, 2-3-dioxo-2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-2H-1,4-benzoxazinyl; pyrazolyl, 1H-tetrazol-1-yl-methyl, and 3,4-dihydro-2H-1,5-benzodioxepinyl, which are optionally substituted by one or more groups selected from C₆₋₁₀aryl, C₂₋₉heteroaryl, C₃₋₅heterocycloalkyl, C₆₋₁₀aryl-C₁₋₃alkyl, C₆₋₁₀aryl-O-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₅heterocycloalkyl-C₁₋₃alkyl, -CN, -SR, -OR, -O(CH₂)_m-OR, R, -C(=O)-R, -CO₂R, -SO₂R, -SO₂NR₂, halogen, -NO₂, -NR₂, -(CH₂)_mNR₂, -(CH₂)_mNHC(=O)-NR₂, -NHC(=O)-R, -(CH₂)_mNHC(=O)-R, -(CH₂)_mN[C(=O)-R]₂, -N[C(=O)R]₂, -(CH₂)_mNS(=O)₂-R, and -C(=O)-NR₂.
- 15 In another particular embodiment, R¹ of formula V is selected from 2-cyclopentylethyl, cyclopropylmethyl, ethyl, methyl, cyclohexyl, cyclopentylmethyl, chromanyl, pentyl, 2-phenylethyl, phenyl, benzyl, pyridinyl, pyridinylethyl, 1-benzofuranyl, benzothienyl, furyl, imidazolyl, pyrazolo[1,5-a]pyrimidinyl, pyrazinyl, 1,3-benzothiazolyl, indolyl, indazolyl, thienyl, 1,3-benzodioxinyl, tetrahydro-2H-pyran-4-ylmethyl, 1-H-1,2,3-benzotriazol-1-yl, 2-(thien-2-yl)ethyl, (1-benzofuran-4-yl)methyl, 1,3-oxazolyl, 1H-pyrazol-1-yl, 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 2-oxo-2,3-dihydro-2H-benzimidazolyl, isoxazolyl, imidazo[1,2,a]pyridinyl, 2-3-dioxo-2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-2H-1,4-benzoxazinyl; pyrazolyl, 1H-tetrazol-1-yl-methyl, and 3,4-dihydro-2H-1,5-benzodioxepinyl, which are optionally substituted by one or more groups selected from 1H-pyrazol-1-yl, fluoro, chloro, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, t-butyl, cyano, bromo, 1,3-oxazol-5-yl, 1H-imidazol-1-yl, (4-oxopiperidin-1-yl)carbonyl, pyridin-3-ylmethyl, [(butylamino)carbonyl]amino, 1,1,-dioxidothiomorpholin-4-yl, aminosulfonyl, morpholin-4-yl, diethylaminomethyl, acetyl, (3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)methyl, 1-oxo-indan-4-yl, dimethylaminomethyl, methyl, pyrrolidin-1-yl, ethylthio, acetylamino, dimethylamino, 1H-pyrrol-1-yl, ethyl, ethoxy, fluorophenoxy, propyl, phenyl, methoxycarbonyl, diacetylamino, (methylsulfonylamino)methyl, (cyclopropylsulfonylamino)methyl, 1H-tetrazol-1-yl, pyrazolyl, methylaminocarbonylamino, dimethylaminocarbonylamino, and (methylthio)pyrimidin-4-yl.

In another particular embodiment, R⁴ of formula V is selected from phenyl, benzyl, methyl, fluoro, trifluoromethyl, methoxy, allyloxy, (2E)-but-2-en-1-yloxy, (allyloxy)methyl, methoxymethyl, ethoxymethyl, propyl, butyl, pentyl, hexyl, cyclopentyl, pyridin-4-ylmethyl, ethoxy, butoxy, 2-methoxyethoxy, cyclohexyl, and thienylmethyl.

In a further embodiment, the two substituents on the cyclohexyl ring of formula I or V are in trans positions.

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I or V. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present invention includes any geometrical isomer of a compound of Formula I or V. It will further be understood that the present invention encompasses tautomers of the compounds of the Formula I or V.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the Formula I or V.

Within the scope of the invention are also salts of the compounds of the Formula I or V. Generally, pharmaceutically acceptable salts of compounds of the present invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a

suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

In one embodiment, the compound of Formula I or V above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition
5 salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

We have now found that the compounds of the invention have activity as pharmaceuticals, in particular as agonists of M1 receptors. More particularly, the compounds of the invention exhibit selective activity as agonist of the M1 receptors
10 and are useful in therapy, especially for relief of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive. Additionally, compounds of the present invention are useful in other disease states in which dysfunction of M1 receptors is present or implicated.
15 Furthermore, the compounds of the invention may be used to treat cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, schizophrenia, Alzheimer's disease, anxiety disorders, depression, obesity, gastrointestinal disorders and cardiovascular disorders.

In a particular embodiment, the compounds may be used to treat
20 schizophrenia or Alzheimer's disease.

In another embodiment, the compounds may be used to treat pain.

In another particular embodiment, the compounds may be used to treat neuropathic pain.

Compounds of the invention are useful as immunomodulators, especially for
25 autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of M1 receptors is present or implicated in that paradigm. This may
30 involve the use of isotopically labeled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhea, depression, anxiety and stress-related disorders such as post-traumatic stress
35 disorders, panic disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder, urinary incontinence, premature ejaculation, various mental

illnesses, cough, lung oedema, various gastro-intestinal disorders, e.g. constipation, functional gastrointestinal disorders such as Irritable Bowel Syndrome and Functional Dyspepsia, Parkinson's disease and other motor disorders, traumatic brain injury, stroke, cardioprotection following myocardial infarction, obesity, spinal injury and drug
5 addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain
10 the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

Also within the scope of the invention is the use of any of the compounds according to the Formula I or V above, for the manufacture of a medicament for the
15 treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula I or V above, is administered to a patient in need of such treatment.

20 Thus, the invention provides a compound of Formula I or V or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of Formula I or V or a pharmaceutically acceptable salt or solvate thereof, as
25 hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be construed accordingly. The term "therapy" within the context of the present invention further encompasses to
30 administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for
35 the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain. In a particular

embodiment, the compounds are useful in therapy for neuropathic pain. In an even more particular embodiment, the compounds are useful in therapy for chronic neuropathic pain.

5 In use for therapy in a warm-blooded animal such as a human, the compound of the invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracically, intravenously, epidurally, intrathecally, transdermally, intracerebroventricularly and by injection into the joints.

10 In one embodiment of the invention, the route of administration may be oral, intravenous or intramuscular.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

15 For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid and liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

20 A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in 25 suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized moulds and allowed to cool and solidify.

30 Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the 35 active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds
5 may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents,
10 stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

15 Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

A therapeutically effective amount for the practice of the present invention
20 may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of Formula I or V as defined above for the manufacture of a medicament.

25 Also within the scope of the invention is the use of any compound of Formula I or V for the manufacture of a medicament for the therapy of pain.

Additionally provided is the use of any compound according to Formula I or V for the manufacture of a medicament for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain,
30 cancer pain, and visceral pain.

A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula I or V above, is administered to a patient in need of such therapy.

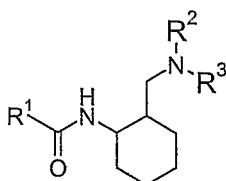
Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I or V or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I or V or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

Further, there is provided a pharmaceutical composition comprising a compound of Formula I or V or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

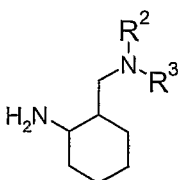
In a further aspect, the present invention provides a method of preparing the compounds of the present invention.

In one embodiment, the invention provides a process for preparing a compound of Formula II, comprising:



II

reacting a compound of Formula III with a compound of $R^1\text{-COCl}$ or $R^1\text{-COOH}$,

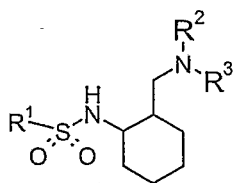


20 III

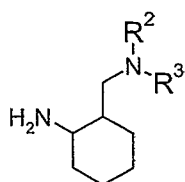
wherein R^1 , R^2 , and R^3 are defined as those of formula I or V.

Optionally, the step of reacting a compound of formula III with a compound of $R^1\text{-COCl}$ or $R^1\text{-COOH}$ is carried out in the presence of a base, such as diisopropylethylamine, or triethylamine, optionally in the presence of catalyst such as HATU.

In another embodiment, the invention provides a process for preparing a compound of Formula IV, comprising:

**IV**

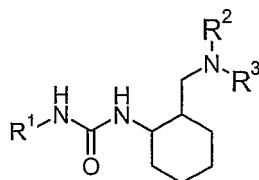
reacting a compound of Formula III with a compound of R^1SO_2Cl ,

5 **III**

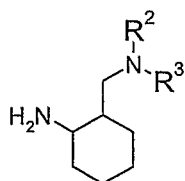
wherein R^1 , R^2 , and R^3 are defined as those of formula I or V.

Optionally, the step of reacting a compound of formula III with a compound of R^1SO_2Cl is carried out in the presence of a base, such as diisopropylethylamine, or triethylamine.

- 10 In another embodiment, the invention provides a process for preparing a compound of Formula VI, comprising

**VI**

reacting a compound of Formula III with R^1NCO ,



15

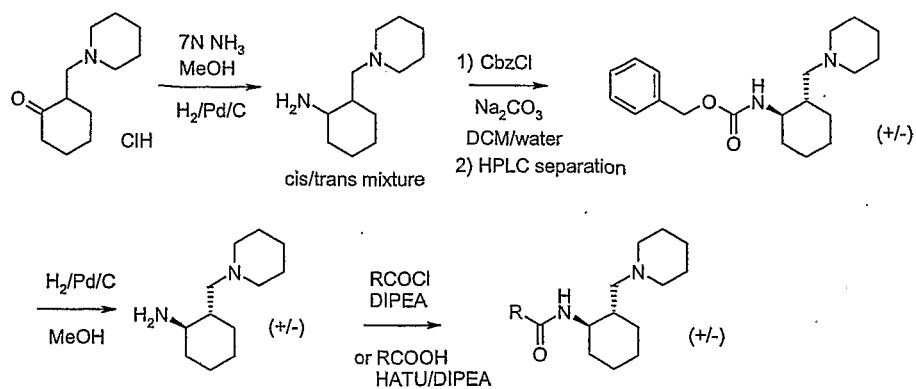
III

wherein R^1 , R^2 , and R^3 are defined as those of formula I or V.

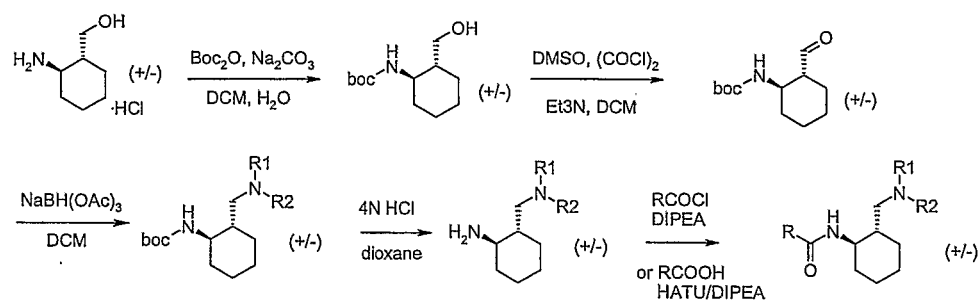
Compounds of the present invention may also be prepared according to the synthetic routes as depicted in Schemes 1-17.

20

Scheme 1. (Examples 1-88)

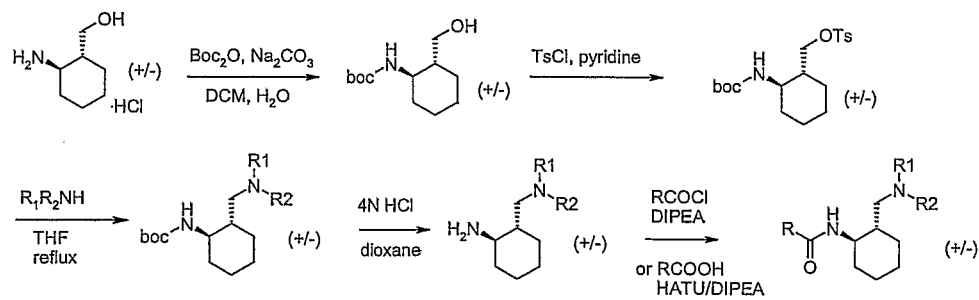


Scheme 2. (Examples 89-96)

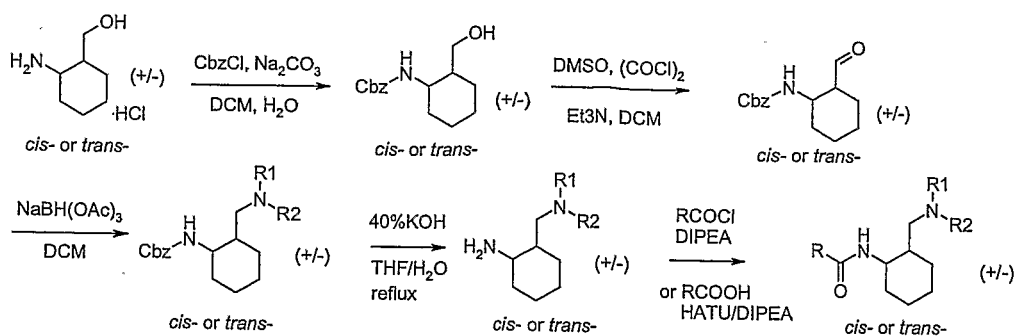


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Scheme 3. Examples 146-149)

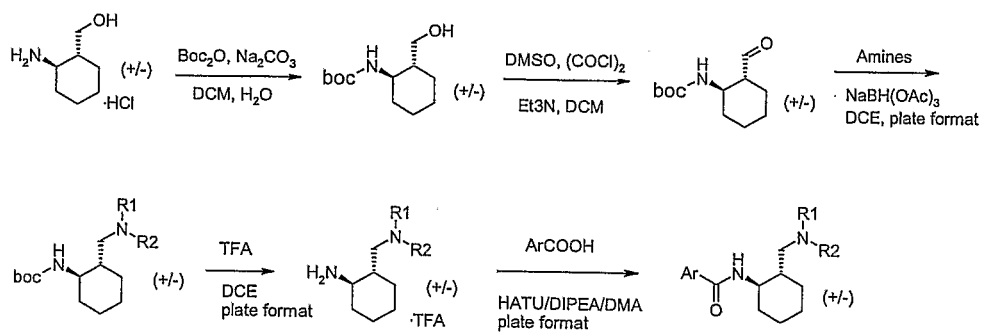


Scheme 4. (Examples 150-155)



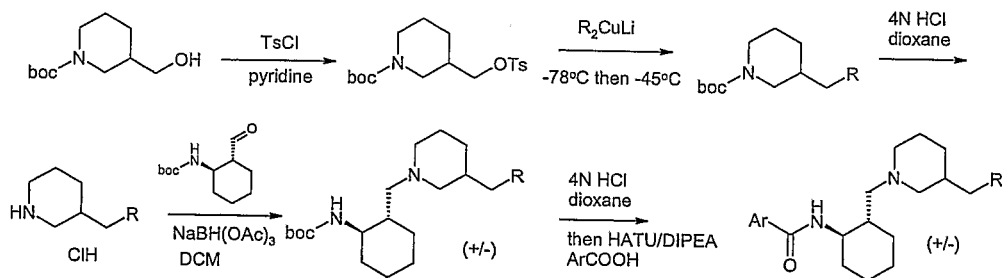
Scheme 5. (Examples 131-145, 192, 193)

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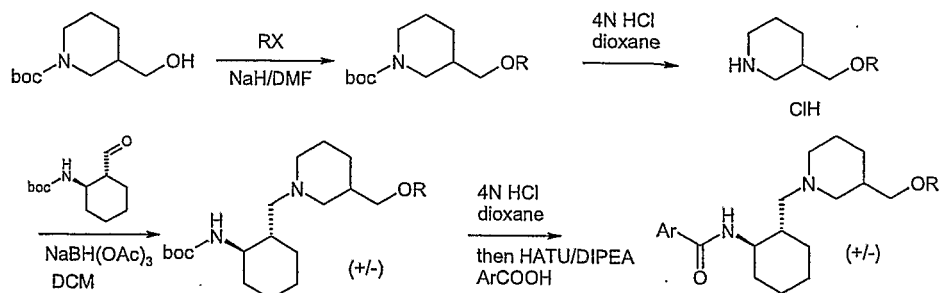


Scheme 6. (Examples 101-106)

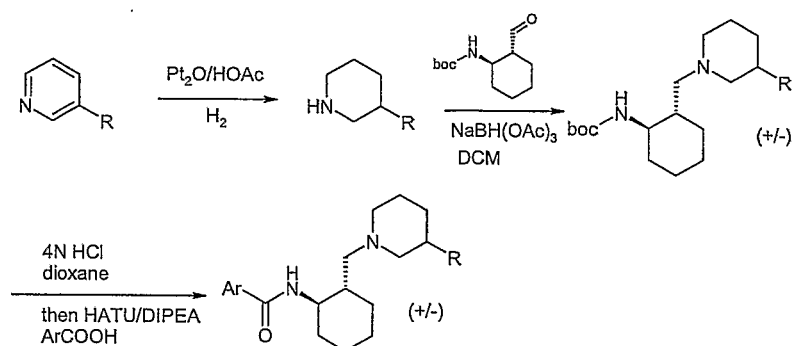
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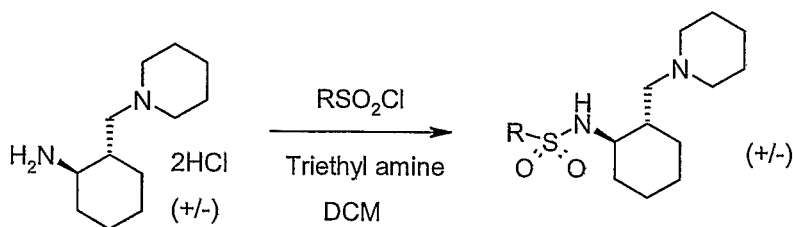
Scheme 7. (Examples 97-100 and 118-128, 168-170, 180)



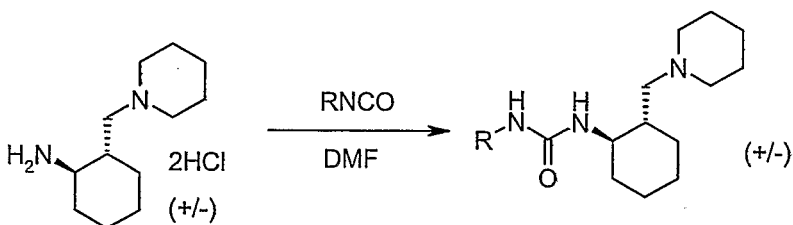
Scheme 8. (Examples 107-115, 163-167, 172-179)



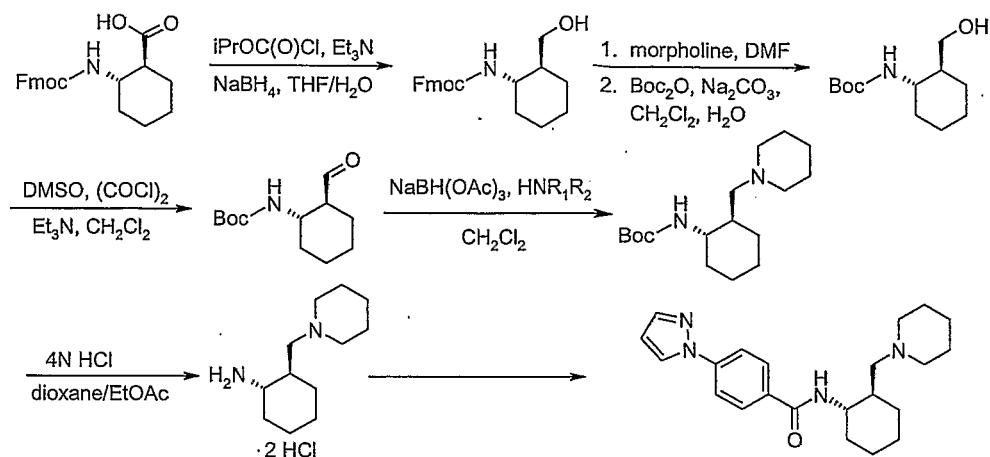
5 Scheme 9. (Examples 159-162)



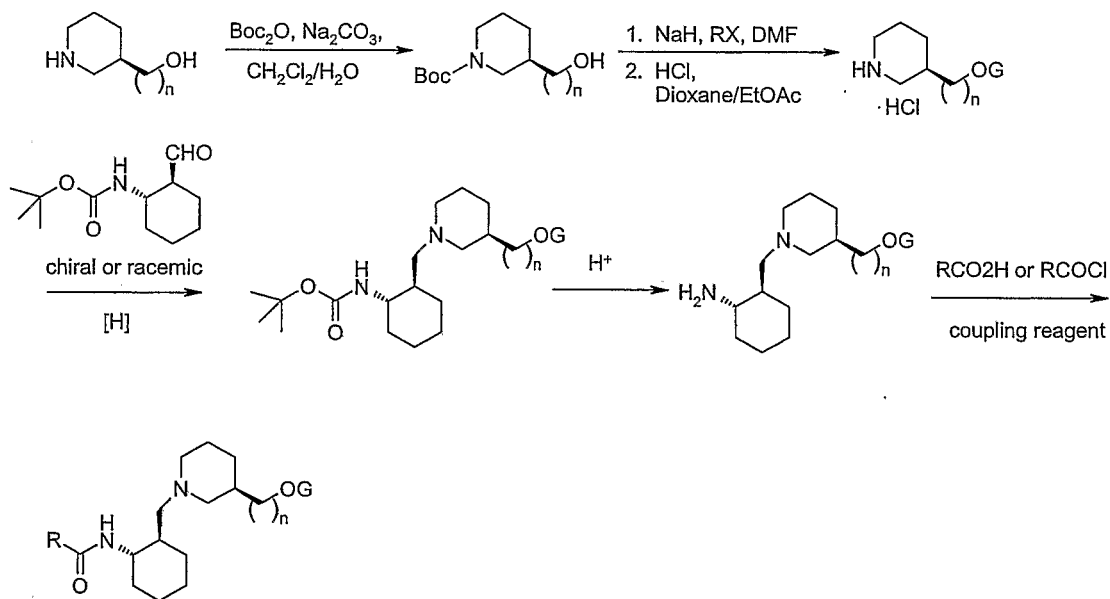
Scheme 10. (Examples 156-158)



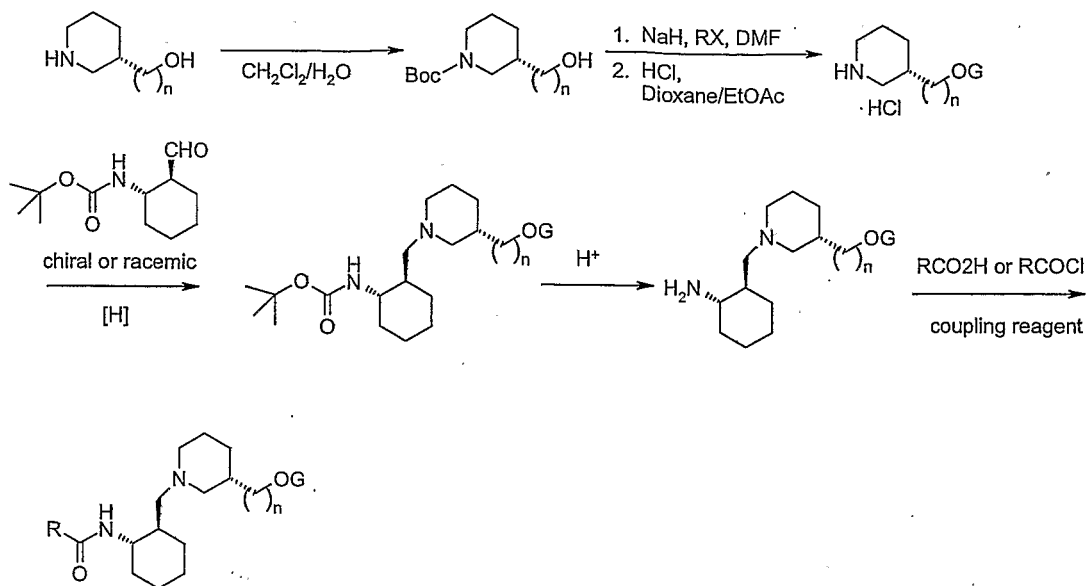
Scheme 11 (Example 200)



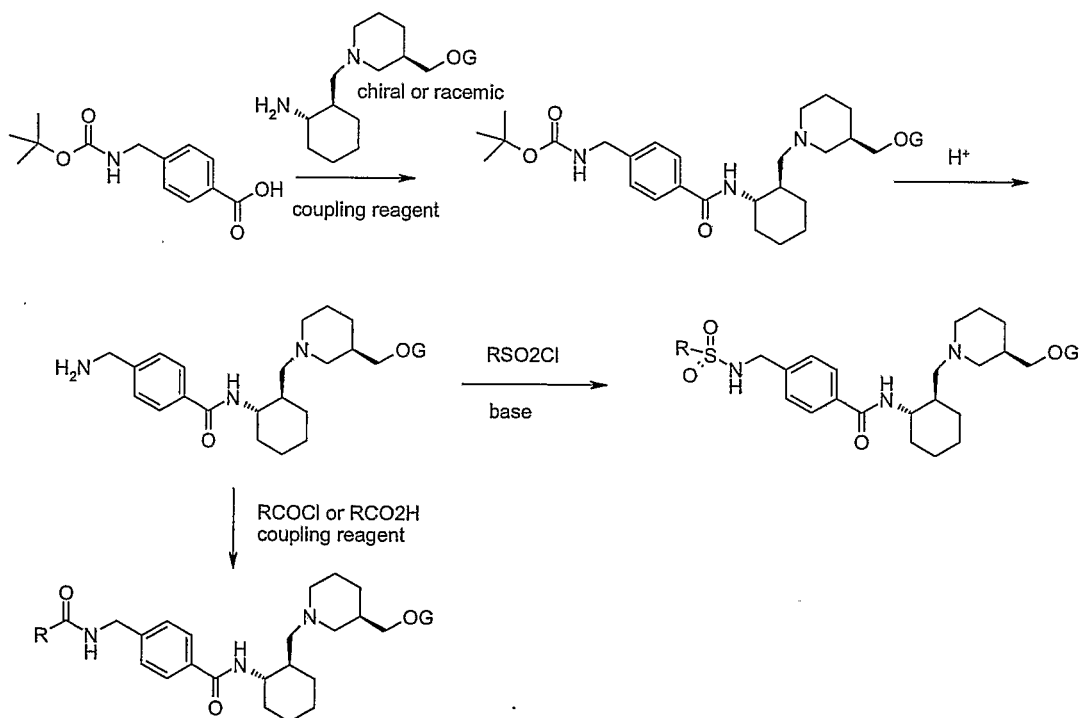
5 Scheme 12 (Example 129, 183-191, 194-198, 201-203, 209-231).



10 Scheme 13 (Example 130, 204-206, 208)

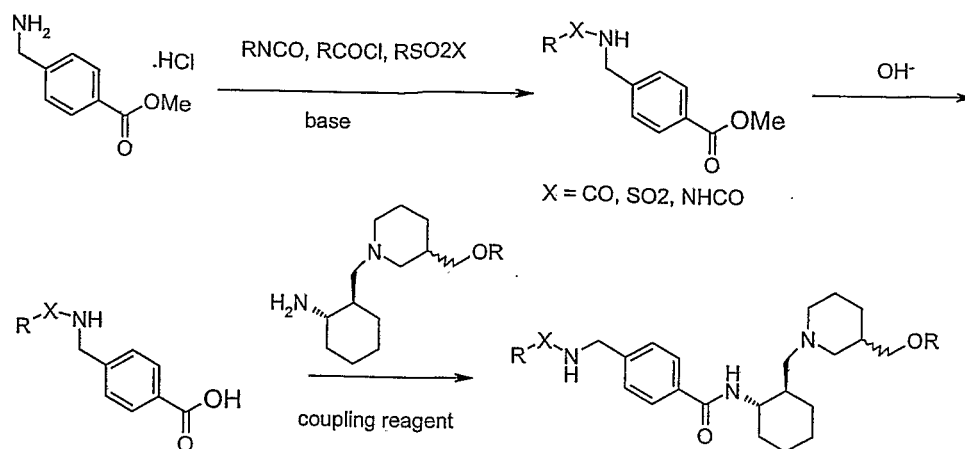


Scheme 14 (Example 171, 232-235)

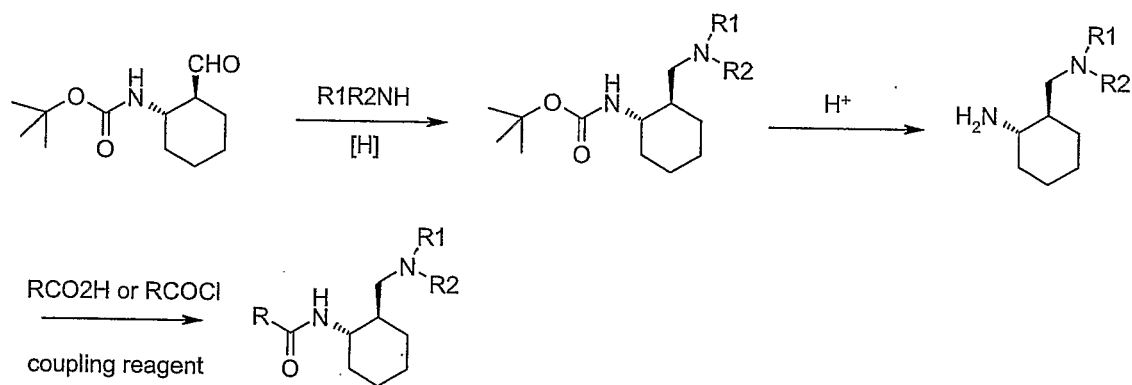


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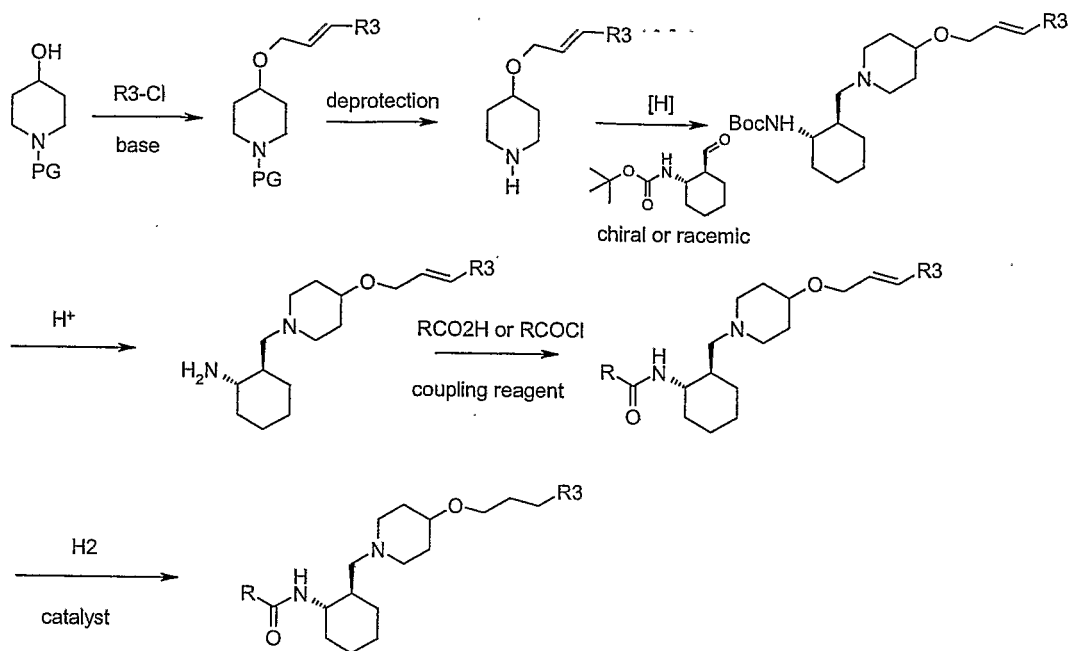
Scheme 15 (Example 207, 236-239)



Scheme 16 (Example 240, 241)



Scheme 17 (Example 116, 117, 181, 182)



Biological Evaluation

Human M1, rat M1, human M3 and human M5 calcium mobilization FLIPR™ assay

The compound activity in the present invention (EC_{50} or IC_{50}) was measured using a 384 plate-based imaging assay that monitors drug induced intracellular Ca^{2+} release in whole cells. Activation of hM1 (human Muscarinic receptor subtype 1, gene bank access NM_000738), rM1 (rat Muscarinic receptor subtype 1, gene bank access NM_080773), hM3 (human Muscarinic receptor subtype 3, gene bank access NM_000740NM_000740) and hM5 (human Muscarinic receptor subtype 5, gene bank access NM_0121258) receptors expressed in CHO cells (chinese hamster ovary cells, ATCC) was quantified in a Molecular Devices FLIPR II™ instrument as an increase in fluorescent signal. Inhibition of hM3 and hM5 by compounds was determined by the decrease in fluorescent signal in response to 2 nM acetylcholine activation.

CHO cells were plated in 384-black polylysine coated plate (Costar) at 8000 cells/well/50 μ l for 24 hours or 4000 cells/well for 48 hours in a humidified incubator (5% CO_2 and 37°C) in DMEM/F12 medium without selection agent. Prior to the experiment the cell culture medium was removed from the plates by inversion. A loading solution of 30 μ l of Hank's balanced salt solution, 10 mM Hepes and 2.5 mM Probenicid at Ph 7.4 (Cat no. 311-520-VL, Wisent) with 2 μ M calcium indicator dye

(FLUO-3AM, Molecular Probes F14202) was added to each well. Plates were incubated at 37°C for 60 minutes prior to start the experiment. The incubation was terminated by washing the cells four times in assay buffer, leaving a residual 25µl buffer per well. Cell plates were then transferred to the FLIPR, ready for compound additions.

The day of experiment, acetylcholine and compounds were diluted in three-fold concentration range (10 points serial dilution) for addition by FLIPR instrument. For all calcium assays, a baseline reading was taken for 30 seconds followed by the addition of 12.5µl (25µl for hM1 and rM1) of compounds, resulting in a total well volume of 37.5µl (50µl for hM1 and rM1). Data were collected every 1.6 seconds for 300 seconds. For hM3 and hM5 an additional 12.5µl of acetylcholine (2 nM final) was added at 300 seconds. After this addition of acetylcholine (producing a final volume of 50µl), the FLIPR continued to collect data every 2 seconds for 240 seconds. The fluorescence emission was read using filter 1 (emission 520-545 nm) by the FLIPR on board CCD camera.

Calcium mobilization output data were calculated as the maximal relative fluorescence unit (RFU) minus the minimal value for both compound and agonist reading frame (except for hM1 and rM1 using only the maximal RFU). Data were analyzed using sigmoidal fits of a non-linear curve-fitting program (XLfit version 5.0.6 from ID Business Solutions Limited, Guildford, UK). All EC₅₀ and IC₅₀ values are reported as geometric means of 'n' independent experiments. Using the above-mentioned assays, the IC₅₀ and EC₅₀ towards human hM1, ratM1, hM3 and hM5 receptors for most compounds is measured to be in the range 1->30000 nM. The E_{max} (maximal effect, agonism or antagonist inhibition) towards human hM1, ratM1, hM3 and hM5 receptors for most compounds is measured to be in the range of 0 - 110 %.

hM2 receptor GTPγS binding

Membranes produced from Chinese hamster ovary cells (CHO) expressing the cloned human M2 receptor (human Muscarinic receptor subtype 2, gene bank access NM_000739), were obtained from Perkin-Elmer (RBHM2M). The membranes were thawed at 37 °C, passed 3 times through a 23-gauge blunt-end needle, diluted in the GTPγS binding buffer (50 mM Hepes, 20 mM NaOH, 100 mM NaCl, 1 mM EDTA, 5 mM MgCl₂, pH 7.4, 100µM DTT). The EC₅₀, IC₅₀ and E_{max} of the compounds of the invention were evaluated from 10-point dose-response curves (three fold concentration range) done in 60µl in 384-well non-specific binding surface plate

(Corning). Ten microliters from the dose-response curves plate (5X concentration) were transferred to another 384 well plate containing the following: 10µg of hM2 membranes, 500µg of Flashblue beads (Perkin-Elmer) and GDP in a 25µl volume. An additional 15µl containing 3.3X (55000 dpm) of GTPγ³⁵S (0.4 nM final) were added to the wells resulting in a total well volume of 50µl. Basal and maximal stimulated GTPγ³⁵S binding was determined in absence and presence of 30 µM of acetylcholine agonist. The membranes/beads mix were pre-incubated for 15 minutes at room temperature with 25 µM GDP prior to distribution in plates (12.5 µM final). The reversal of acetylcholine-induced stimulation (2µM final) of GTPγ³⁵S binding was used to assay the antagonist properties (IC₅₀) of the compounds. The plates were incubated for 60 minutes at room temperature with shaking, then centrifuged at 2000rpm for 5 minutes. The radioactivity (cpm) was counted in a Trilux (Perkin-Elmer).

Values of EC₅₀, IC₅₀ and E_{max} were obtained using sigmoidal fits of a non-linear curve-fitting program (XLfit version 5.0.6 from ID Business Solutions Limited, Guildford, UK) of percent-stimulated GTPγ³⁵S binding vs. log (molar ligand).

All EC₅₀ and IC₅₀ values are reported as geometric means of 'n' independent experiments. Based on the above assays, the EC₅₀ towards human M2 receptors for most compounds of the invention is measured to be in the range of about between 200 and >30000 nM. The E_{max} (maximal effect, agonism or antagonist inhibition) towards human M2 receptors for most compounds of the invention were measured to be in the range of about 0-120 %. The IC₅₀ was the concentration of the compound of the invention at which 50% inhibition of acetylcholine GTPγ³⁵S binding stimulation has been observed. The IC₅₀ towards human M2 receptors for most compounds of the invention was measured to be in the range of between 40 and >90000 nM.

hM4 receptor GTPγS binding

Membranes produced from Chinese hamster ovary cells (CHO) expressing the cloned human M4 receptor (human Muscarinic receptor subtype 4, gene bank access NM_000741), were obtained from Perkin-Elmer (RBHM4M). The membranes were thawed at 37 °C, passed 3 times through a 23-gauge blunt-end needle, diluted in the GTPγS binding buffer (50 mM Hepes, 20 mM NaOH, 100 mM NaCl, 1 mM

EDTA, 5 mM MgCl₂, pH 7.4, 100μM DTT). The EC₅₀, IC₅₀ and E_{max} of the compounds of the invention were evaluated from 10-point dose-response curves (three fold concentration range) done in 60μl in 384-well non-specific binding surface plate (Corning). Ten microliters from the dose-response curves plate (5X concentration) were transferred to another 384 well plate containing the following: 10μg of hM4 membranes, 500μg of Flashblue beads (Perkin-Elmer) and GDP in a 25μl volume. An additional 15μl containing 3.3X (55000 dpm) of GTPγ³⁵S (0.4 nM final) were added to the wells resulting in a total well volume of 50μl. Basal and maximal stimulated GTPγ³⁵S binding was determined in absence and presence of 30 μM of acetylcholine agonist. The membranes/beads mix were pre-incubated for 15 minutes at room temperature with 40 μM GDP prior to distribution in plates (20 μM final). The reversal of acetylcholine-induced stimulation (10μM final) of GTPγ³⁵S binding was used to assay the antagonist properties (IC₅₀) of the compounds. The plates were incubated for 60 minutes at room temperature with shaking, then centrifuged at 2000rpm for 5 minutes. The radioactivity (cpm) was counted in a Trilux (Perkin-Elmer).

Values of EC₅₀, IC₅₀ and E_{max} were obtained using sigmoidal fits of a non-linear curve-fitting program (XLfit version 5.0.6 from ID Business Solutions Limited, Guildford, UK) of percent-stimulated GTPγ³⁵S binding vs. log (molar ligand).

All EC₅₀ and IC₅₀ values are reported as geometric means of 'n' independent experiments. Based on the above assays, the EC₅₀ towards human M4 receptors for most compounds of the invention is measured to be in the range of between 300 and >30000 nM. The E_{max} (maximal effect, agonism or antagonist inhibition) towards human M4 receptors for most compounds of the invention were measured to be in the range of about 0-120 %. The IC₅₀ was the concentration of the compound of the invention at which 50% inhibition of acetylcholine GTPγ³⁵S binding stimulation has been observed. The IC₅₀ towards human M4 receptors for most compounds of the invention was measured to be in the range of between 3000 and >30000 nM.

Certain compounds of the invention were tested using one or more above assays. Some of the results are summarized in Table 1 below.

Table 1. Certain biological properties for certain compounds of the invention

Compound	hM1EC50(nM)	hM1Emax(%)	hM2_EC50 (nM)	hM2 Emax (%)
Trans-(+/-)-N-[2-[(3-butyl-1-piperidyl)methyl]cyclohexyl]-3-(4-chlorophenyl)propanamide	174	86	1233	38
Trans-(+/-)-N-[2-[[3-(ethoxymethyl)-1-piperidyl]methyl]cyclohexyl]-4-1,3-oxazol-5-yl-benzamide	17	97	5481	25
trans-(+/-)-N-{2-[(3-Butylpiperidin-1-yl)methyl]cyclohexyl}-4-[(diethylamino)methyl]benzamide	103	94	165	2
Trans-(±)-N-[2-({3-[(Allyloxy)methyl]piperidin-1-yl)methyl}cyclohexyl)-4-[(4-methylpiperazin-1-yl)methyl]benzamide	49	80	390	19
N-[(1S,2R)-2-({(3R)-3-[(allyloxy)methyl]piperidin-1-yl)methyl}cyclohexyl)-6-(1H-imidazol-1-yl)nicotinamide	5	95	216	22

N-[(1S,2R)-2-(piperidin-1-ylmethyl)cyclohexyl]-6-(1H-pyrazol-1-yl)nicotinamide	26	82	>30000	0
(N-((1S,2R)-2-[(3R)-3-ethoxypiperidin-1-yl]methyl)cyclohexyl)pyrazine-2-carboxamide	1504	76	Not tested	Not tested
N-((1S,2R)-2-[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl)cyclohexyl)-6-pyrrolidin-1-yl)nicotinamide	41	91	107	60
N-[(1S,2R)-2-(azepan-1-ylmethyl)cyclohexyl]-4-(1H-pyrazol-1-yl)benzamide	130	70	>30000	>12
N-((1S,2R)-2-[(3R)-3-(allyloxy)piperidin-1-yl]methyl)cyclohexyl)-6-(1H-pyrazol-1-yl)nicotinamide	33	97	4446	50
N-((1S,2R)-2-[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl)cyclohexyl)-4-[[[(methylsulfonyl)amino]methyl]benzamide	20	95	1344	34

4-[(diacetylamino)methyl]-N-((1S,2R)-2-[[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl]benzamide	103	91	3305	18
N-((1S,2R)-2-[[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl]benzamide	119	74	1905	34
N-((1S,2R)-2-[[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl]cyclohexanecarboxamide	157	75	1075	30
N-((1S,2R)-2-[[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl]chromane-2-carboxamide	55	98	570	54
N-((1S,2R)-2-[[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4,6-dimethylnicotinamide	504	54	Not tested	Not tested
N ² -acetyl-N ¹ -((1S,2R)-2-[[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl]glycinamide	322	91	Not tested	Not tested
N-((1S,2R)-2-[[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-5,7-dimethylpyrazolo[1,5-a]pyrimidine-2-carboxamid	22	82	>30000	0

N-((1S,2R)-2-[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-methyl-3,4-dihydro-2H-1,4-benzoxazine-7-carboxamide	152	85	>30000	0
N-((1S,2R)-2-[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-(1H-tetrazol-1-yl)benzamide	9	95	1211	27
N-[(1S,2R)-2-[(3-phenyl-1-piperidyl)methyl]cyclohexyl]-6-pyrazol-1-yl-pyridine-3-carboxamide	393.3	105.1	Not tested	Not tested
4-[[(cyclopropylsulfonylamino)methyl]-N-[(1S,2R)-2-[[(3R)-3-(ethoxymethyl)-1-piperidyl]methyl]cyclohexyl]benzamide	11	102	1431	40

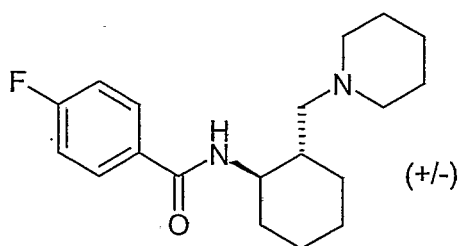
EXAMPLES

The invention will further be described in more detail by the following

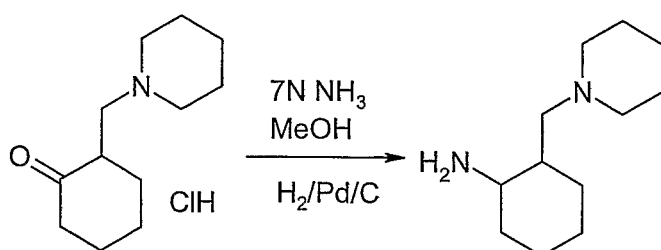
- 5 Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

Example 1. *trans*-(+/-)-4-fluoro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide

10



Step A. The preparation of [2-(piperidin-1-ylmethyl)cyclohexyl]amine

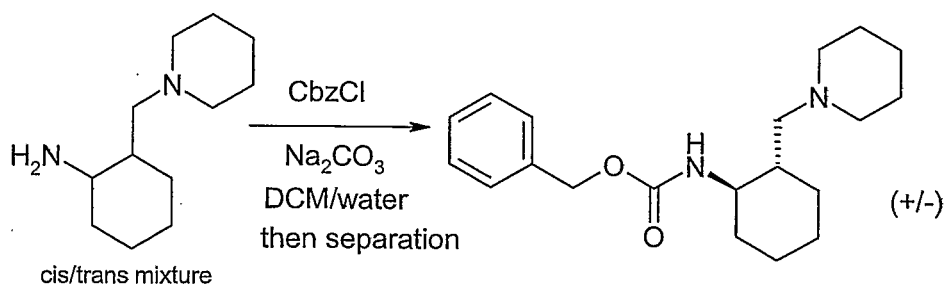


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To a solution of 2-(piperidin-1-ylmethyl)cyclohexanone hydrochloride (5.0 g, 21.6 mmol) in 7N NH₃ in MeOH (50 mL) was added 10% Pd/C (0.5 g) and the mixture was hydrogenated at 40 psi overnight. Filtration of catalyst and concentration of MeOH afforded a cis/trans mixture of [2-(piperidin-1-ylmethyl)cyclohexyl]amine (3.94 g, 93%), which was used without further purification.

10

Step B. The preparation of *trans*-(+/-)-benzyl [2-(piperidin-1-ylmethyl)cyclohexyl]carbamate



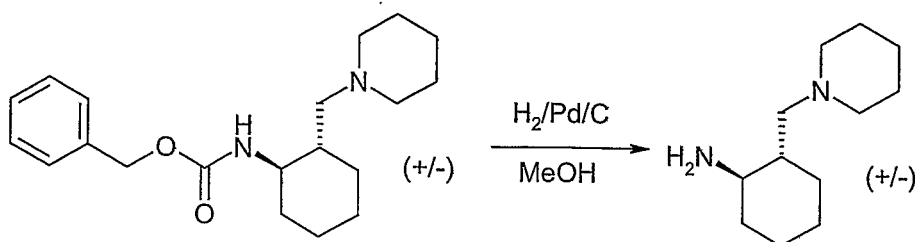
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To a solution of [2-(piperidin-1-ylmethyl)cyclohexyl]amine (crude from Step A, 3.94 g, 20.1 mmol) in dichloromethane (80 mL) was added a solution of Na₂CO₃ (4.0 g) in water (100 mL), then benzyl chloroformate (3.44 g, 20.1 mmol) was added slowly in 5 min. The reaction mixture was stirred at room temperature for 1 h. The organic phase was separated, washed with water (50 mL) and brine (50 mL), dried over Na₂SO₄,

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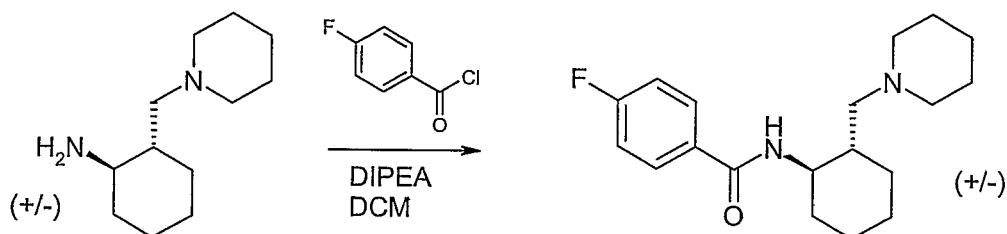
yielded crude product as *cis/trans* mixture (~ 1:3 ratio, 6.3 g), which was separated by using reverse phase HPLC to yield *trans*-(+/-)-isomer 4.8 g (54%) as its TFA salt. MS (M+1): 331.1.

5 Step C. The preparation of *trans*-(+/-)-[2-(piperidin-1-ylmethyl)cyclohexyl]amine



To a solution of *trans*-(+/-)-benzyl [2-(piperidin-1-ylmethyl)cyclohexyl]carbamate TFA salt (8.85 g, 20.0 mmol) in MeOH (50 mL) was added 10% Pd/C (1.0 g) and the mixture was hydrogenated at 40 psi for 6h. Filtration of catalyst and concentration of MeOH afforded *trans*-(+/-)-[2-(piperidin-1-ylmethyl)cyclohexyl]amine as its TFA salt (6.18 g, 99%), which was used without further purification.

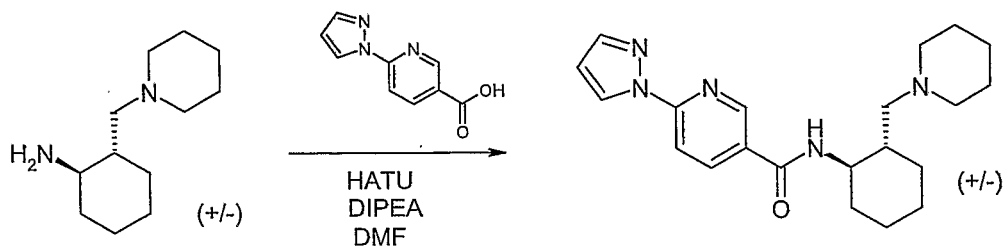
15 Step D. The preparation of *trans*-(+/-)-4-fluoro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide



To the solution of *trans*-(+/-)-[2-(piperidin-1-ylmethyl)cyclohexyl]amine (0.4 mmol) in dry DCM (5 mL) was added 4-fluorobenzoyl chloride (0.5 mmol) followed by diisopropylethylamine (1.0 mmol), the mixture was stirred at room temperature for 1 h, and the reaction was quenched with water (5 mL). DCM (10 mL) was added and washed with saturated NaHCO₃ (5 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified with reverse phase HPLC to yield *trans*-(+/-)-4-fluoro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide (84 mg, 49%) as its TFA salt. MS (M+1): 319.3. ¹H NMR (400 MHz, METHANOL-D₄): δppm 1.17 - 1.30 (m, 1 H), 1.31 - 1.41 (m, 2 H), 1.41 - 1.57 (m, 2 H), 1.71 - 1.88 (m, 6 H), 1.91 - 2.00 (m, 2 H), 2.02 - 2.11

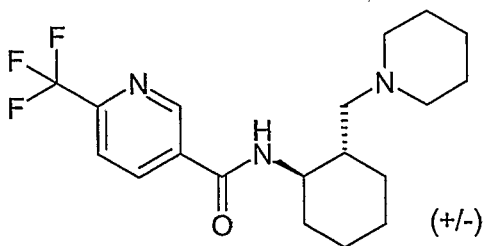
(m, 1 H), 2.72 - 2.85 (m, 1 H), 2.91 - 3.05 (m, 2 H), 3.11 - 3.23 (m, 1 H), 3.37 - 3.47 (m, 1 H), 3.53 - 3.61 (m, 1 H), 3.65 - 3.79 (m, 2 H), 7.18 (t, J=8.79 Hz, 2 H), 7.84 - 7.95 (m, 2 H).

5 **Example 2. *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide**



To the solution of *trans*-(+/-)-[2-(piperidin-1-ylmethyl)cyclohexyl]amine hydrochloride (116 mg, 0.5 mmol) in dry DMF (5 mL) was added 6-(1*H*-pyrazol-1-yl)nicotinic acid (113 mg, 0.6 mmol) followed by HATU (228 mg, 0.6 mmol) and diisopropylethylamine (0.18 mL, 1.0 mmol). The mixture was stirred at room temperature for 1 h, and the reaction was quenched with water (5 mL). The solvent was removed in vacuo. DCM (15 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL),
 15 dried over Na₂SO₄. The crude product was purified with reverse phase HPLC to yield *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide (156 mg, 71%) as its HCl salt. MS (M+1): 368.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.20 - 1.62 (m, 5 H), 1.72 - 1.93 (m, 7 H), 1.95 - 2.15 (m, 3 H), 2.76 - 2.90 (m, 1 H), 2.94 - 3.06 (m, 2 H), 3.16 - 3.24 (m, 1 H), 3.39 - 3.50 (m, 1 H), 3.59 (d, J=11.33 Hz, 1 H), 3.74 - 3.85 (m, 1 H), 6.55 (d, J=1.76 Hz, 1 H), 7.79 (s, 1 H), 8.01 (d, J=8.59 Hz, 1 H), 8.38 (dd, J=8.59, 2.34 Hz, 1 H), 8.64 (d, J=2.54 Hz, 1 H), 8.91 (d, J=1.95 Hz, 1 H).
 20

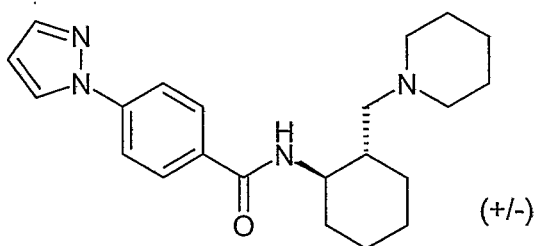
25 **Example 3. *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-6-(trifluoromethyl)nicotinamide**



Following the same procedure as Example 2, yielded *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-6-(trifluoromethyl)nicotinamide (143 mg, 65%) as its HCl salt.

MS (M+1): 370.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.17 - 1.62 (m, 5 H), 1.71 - 1.93 (m, 8 H), 1.95 - 2.11 (m, 2 H), 2.81 (s, 1 H), 2.94 - 3.08 (m, 2 H), 3.15 - 3.24 (m, 1 H), 3.39 - 3.49 (m, 1 H), 3.54 - 3.63 (m, 1 H), 3.75 - 3.86 (m, 1 H), 7.93 (d, J=8.20 Hz, 1 H), 8.44 (dd, J=8.20, 1.47 Hz, 1 H), 9.12 (s, 1 H).

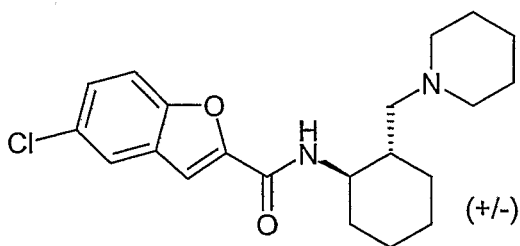
Example 4. *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide



Following the same procedure as Example 2, yielded *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide (121 mg, 66%) as its free base.

MS (M+1): 367.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.99 - 1.18 (m, 1 H), 1.26 - 1.46 (m, 4 H), 1.47 - 1.62 (m, 4 H), 1.65 - 1.83 (m, 3 H), 1.94 (d, J=12.69 Hz, 1 H), 2.06 - 2.23 (m, 2 H), 2.31 - 2.53 (m, 6 H), 3.54 - 3.64 (m, 1 H), 6.54 (s, 1 H), 7.74 (s, 1 H), 7.83 - 7.89 (m, 2 H), 7.91 - 7.98 (m, 2 H), 8.31 (d, J=2.34 Hz, 1 H).

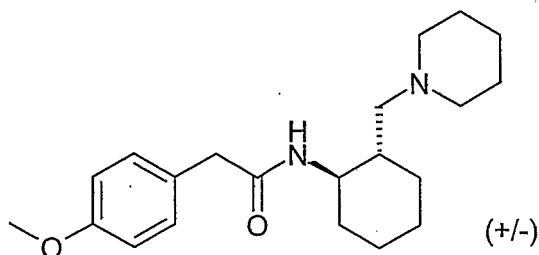
Example 5. *trans*-(+/-)-5-chloro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1-benzofuran-2-carboxamide



Following the same procedure as Example 2, yielded *trans*-(+/-)-5-chloro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1-benzofuran-2-carboxamide (93 mg, 62%) as its free base. MS (M+1): 375.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.01 - 1.15 (m, 1 H), 1.25 - 1.38 (m, 3 H), 1.39 - 1.49 (m, 2 H), 1.50 - 1.63 (m, 4 H), 1.66 - 1.80 (m, 3 H), 1.86 (d, J=13.28 Hz, 1 H), 2.12 (dd, J=12.79, 5.18 Hz, 1 H), 2.21 (d,

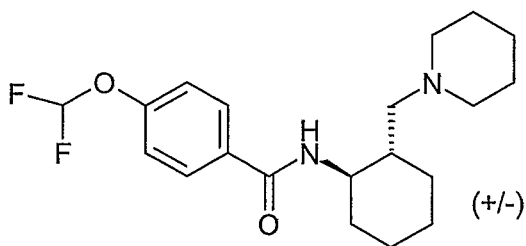
J=11.33 Hz, 1 H), 2.27 - 2.52 (m, 5 H), 3.47 - 3.59 (m, 1 H), 7.37 - 7.46 (m, 2 H), 7.48 - 7.55 (m, 1 H), 7.73 (d, J=1.95 Hz, 1 H).

Example 6. *trans*-(+/-)-2-(4-methoxyphenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide



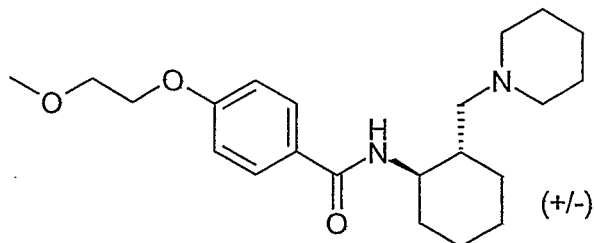
Following the same procedure as Example 2, yielded *trans*-(+/-)-2-(4-methoxyphenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide (94 mg, 68%) as its free base. MS (M+1): 345.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.90 - 1.05 (m, 1 H), 1.13 - 1.31 (m, 3 H), 1.33 - 1.46 (m, 3 H), 1.46 - 1.58 (m, 4 H), 1.61 - 1.76 (m, 2 H), 1.82 - 1.91 (m, 1 H), 1.92 - 2.04 (m, 2 H), 2.07 - 2.19 (m, 3 H), 2.21 - 2.36 (m, 2 H), 3.31 - 3.36 (m, 1 H), 3.37 (s, 2 H), 3.74 (s, 3 H), 6.84 (d, J=8.59 Hz, 2 H), 7.21 (d, J=8.59 Hz, 2 H).

Example 7. *trans*-(+/-)-4-(difluoromethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide



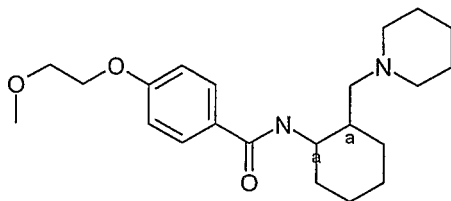
Following the same procedure as Example 2, yielded *trans*-(+/-)-4-(difluoromethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide (163 mg, 67%) as its HCl salt. MS (M+1): 367.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.00 - 1.15 (m, 1 H), 1.24 - 1.45 (m, 5 H), 1.44 - 1.59 (m, 4 H), 1.58 - 1.69 (m, 1 H), 1.69 - 1.82 (m, 2 H), 1.93 (d, J=13.09 Hz, 1 H), 2.05 - 2.18 (m, 2 H), 2.28 - 2.46 (m, 5 H), 3.49 - 3.61 (m, 1 H), 6.92 (t, J=73.63 Hz, 1 H), 7.20 (d, J=8.79 Hz, 2 H), 7.85 (d, J=8.79 Hz, 2 H).

Example 8. *trans*-(+/-)-4-(2-methoxyethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide



Following the same procedure as Example 2, yielded *trans*-(+/-)-4-(2-methoxyethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide (194 mg, 47%) as its HCl salt. MS (M+1): 375.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.17 - 1.60 (m, 5 H), 1.70 - 1.96 (m, 8 H), 2.00 - 2.17 (m, 2 H), 2.81 (t, J=11.13 Hz, 1 H), 2.88 - 3.03 (m, 2 H), 3.13 (d, J=12.50 Hz, 1 H), 3.39 (s, 3 H), 3.41 (d, J=11.71 Hz, 1 H), 3.56 (d, J=11.71 Hz, 1 H), 3.68 - 3.79 (m, 3 H), 4.10 - 4.20 (m, 2 H), 6.99 (d, J=8.59 Hz, 2 H), 7.87 (d, J=8.59 Hz, 2 H).

Example 9. *trans*-(+)-4-(2-methoxyethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide (Isomer 1)

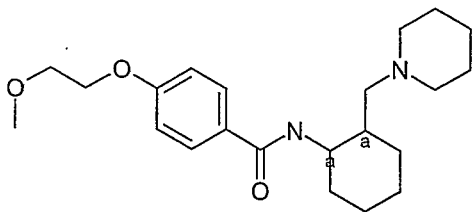


a = unknown absolute

ISOMER 1

The racemic product from Example 8 (98 mg, HCl salt) was separated by chiral AD column (15% IPA in Hexanes) to yield *trans*-(+)-4-(2-methoxyethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide (27 mg, 31%) as its free base. $[\alpha]_D^{20} +35.3$ (c2.0, MeOH). MS (M+1): 375.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.17 - 1.60 (m, 5 H), 1.70 - 1.96 (m, 8 H), 2.00 - 2.17 (m, 2 H), 2.81 (t, J=11.13 Hz, 1 H), 2.88 - 3.03 (m, 2 H), 3.13 (d, J=12.50 Hz, 1 H), 3.39 (s, 3 H), 3.41 (d, J=11.71 Hz, 1 H), 3.56 (d, J=11.71 Hz, 1 H), 3.68 - 3.79 (m, 3 H), 4.10 - 4.20 (m, 2 H), 6.99 (d, J=8.59 Hz, 2 H), 7.87 (d, J=8.59 Hz, 2 H).

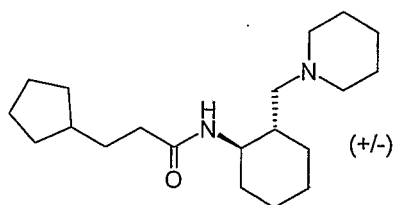
Example 10. *trans*-(-)-4-(2-methoxyethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide (Isomer 1)



a = unknown absolute
ISOMER 2

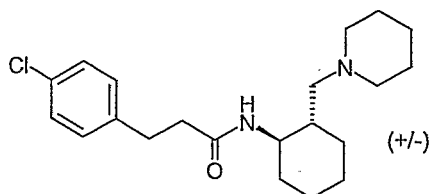
- 5 The racemic product from Example 8 (98 mg, HCl salt) was separated by chiral AD column (15% IPA in Hexanes) to yield *trans*-(-)-4-(2-methoxyethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide (29 mg, 33%) as its free base. $[\alpha]_D^{20} -31.5$ (c2.0, MeOH). MS (M+1): 375.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.17 - 1.60 (m, 5 H), 1.70 - 1.96 (m, 8 H), 2.00 - 2.17 (m, 2 H), 2.81 (t, J=11.13 Hz, 1 H), 2.88 - 3.03 (m, 2 H), 3.13 (d, J=12.50 Hz, 1 H), 3.39 (s, 3 H), 3.41 (d, J=11.71 Hz, 1 H), 3.56 (d, J=11.71 Hz, 1 H), 3.68 - 3.79 (m, 3 H), 4.10 - 4.20 (m, 2 H), 6.99 (d, J=8.59 Hz, 2 H), 7.87 (d, J=8.59 Hz, 2 H).

Example 11. *trans*-(+/-)-3-cyclopentyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide



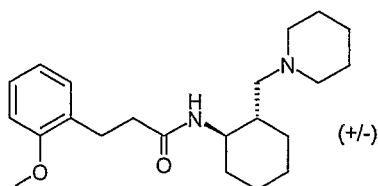
- Following the same procedure as Example 2, yielded *trans*-(+/-)-3-cyclopentyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide (117 mg, 82%) as its HCl salt. MS (M+1): 321.3; ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.09 - 1.41 (m, 5 H), 1.46 - 1.66 (m, 7 H), 1.71 - 2.02 (m, 14 H), 2.19 - 2.26 (m, 2 H), 2.76 - 2.85 (td, J=12.35, 3.03 Hz, 1 H), 2.92 (dd, J=13.48, 9.57 Hz, 1 H), 2.97 (td, J=11.91, 3.91 Hz, 1 H), 3.06 (dd, J=13.28, 2.93 Hz, 1 H), 3.39 - 3.45 (m, J=12.50 Hz, 1 H), 3.47 - 3.59 (m, 2 H).

Example 12. *trans*-(+/-)-3-(4-chlorophenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide



Following the same procedure as Example 2, yielded *trans*-(+/-)-3-(4-chlorophenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide (76 mg, 46%) as its HCl salt. MS (M+1): 363.1; ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.09 - 1.36 (m, 4 H), 1.45 - 1.56 (m, 1 H), 1.62 - 1.94 (m, 10 H), 2.48 (td, *J*=12.69, 2.93 Hz, 1 H), 2.52 (t, *J*=7.23 Hz, 2 H), 2.66 - 2.75 (m, 2 H), 2.79 (dd, *J*=13.28, 9.57 Hz, 1 H), 2.84 - 2.98 (m, 2 H), 3.30 - 3.35 (m, *J*=13.09 Hz, 1 H), 3.40 - 3.48 (m, 2 H), 7.22 (d, *J*=8.59 Hz, 2 H), 7.29 (d, *J*=8.59 Hz, 2 H).

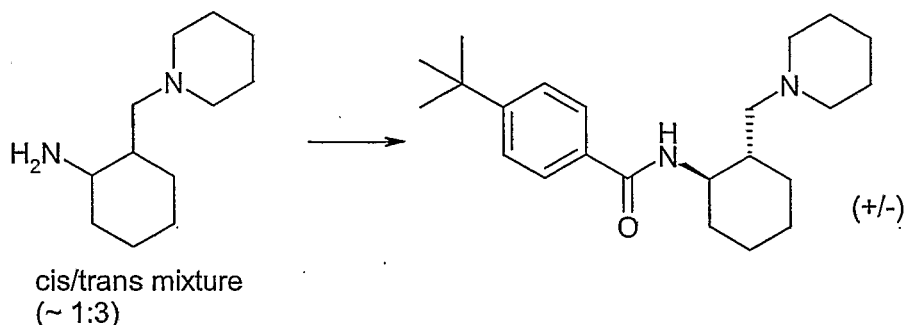
10 **Example 13. *trans*-(+/-)-3-(2-methoxyphenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide**



Following the same procedure as Example 2, yielded *trans*-(+/-)-3-(4-chlorophenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide (109 mg, 69%) as its HCl salt. MS (M+1): 359.3; ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.10 - 1.35 (m, 4 H), 1.43 - 1.52 (m, 1 H), 1.64 - 1.89 (m, 9 H), 1.94 - 2.01 (m, 1 H), 2.43 - 2.58 (m, 3 H), 2.77 - 2.83 (m, 3 H), 2.84 - 2.97 (m, 2 H), 3.30 - 3.35 (m, 1 H), 3.40 - 3.49 (m, 2 H), 3.81 (s, 3 H), 6.84 (td, *J*=7.37, 1.07 Hz, 1 H), 6.92 (d, *J*=8.20 Hz, 1 H), 7.13 (dd, *J*=7.42, 1.56 Hz, 1 H), 7.19 (td, *J*=7.81, 1.76 Hz, 1 H).

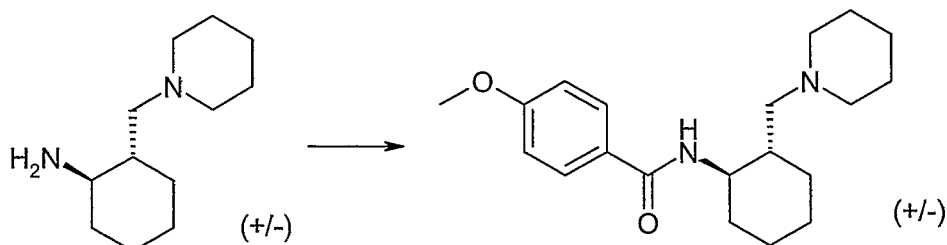
20

Example 14. *trans*-(+/-)-4-*tert*-butyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide



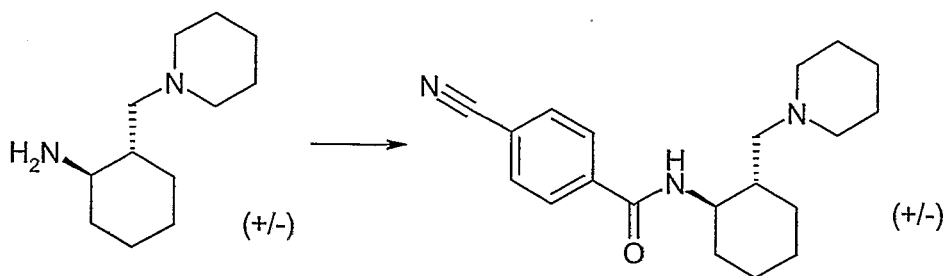
Following the same procedure as Example 2, but used *cis/trans* mixture of [2-(piperidin-1-ylmethyl)cyclohexyl]amine (~ 1:3 ratio, 0.35 mmol). After the same work-up, the crude product was purified with reverse phase HPLC to yielded *trans*-(+/-)-4-*tert*-butyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide (34 mg, 21%) as its TFA salt. MS (M+1): 357.0. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.32 (s, 9 H), 1.30 - 1.59 (m, 6 H), 1.67 - 1.89 (m, 6 H), 1.90 - 2.01 (m, 2 H), 2.03-2.08 (m, 1 H), 2.72 - 2.84 (m, 1 H), 2.90 - 3.04 (m, 2 H), 3.06 - 3.19 (m, 1 H), 3.40 (d, J=12.01 Hz, 1 H), 3.57 (d, J=12.01 Hz, 1 H), 3.70 - 3.81 (m, 1 H), 7.50 (d, J=8.40 Hz, 2 H), 7.77 (d, J=8.40 Hz, 2 H).

Example 15. *trans*-(+/-)-4-methoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide



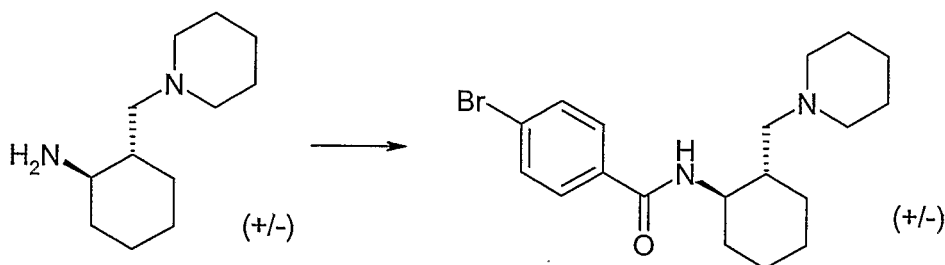
Following the same procedure as Example 1 (step D), yielded *trans*-(+/-)-4-methoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide (134 mg, 82%) as its HCl salt. MS (M+1): 331.2. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.17 - 1.59 (m, 5 H), 1.68 - 1.89 (m, 7 H), 1.90 - 1.99 (m, 2 H), 2.05 (d, J=12.30 Hz, 1 H), 2.73 - 2.84 (m, 1 H), 2.93 - 3.04 (m, 2 H), 3.13 (dd, J=13.28, 2.73 Hz, 1 H), 3.40 (d, J=12.30 Hz, 1 H), 3.58 (d, J=12.30 Hz, 1 H), 3.71 - 3.80 (m, 1 H), 3.84 (s, 3 H), 6.98 (d, J=8.89 Hz, 2 H), 7.81 (d, J=8.89 Hz, 2 H).

Example 16. *trans*-(+/-)-4-cyano-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide



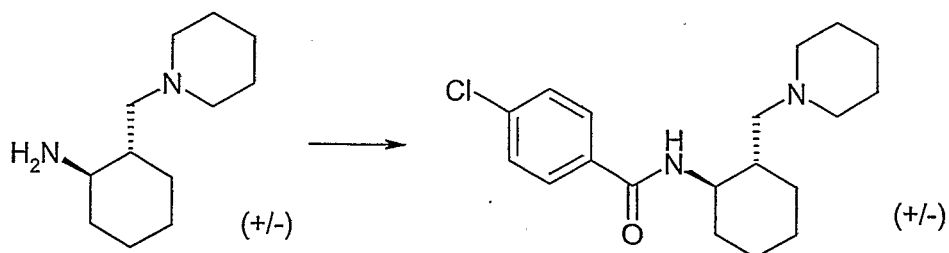
Following the same procedure as Example 1 (step D), yielded *trans*-(+/-)-4-cyano-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide (198 mg, 74%) as its HCl salt. MS (M+1): 326.0. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.18 - 1.59 (m, 5 H), 1.71 - 2.00 (m, 8 H), 2.01 - 2.18 (m, 2 H), 2.76 - 2.90 (m, 1 H), 2.92 - 3.07 (m, 2 H), 3.17 (d, J=11.91 Hz, 1 H), 3.44 (d, J=12.11 Hz, 1 H), 3.58 (d, J=12.11 Hz, 1 H), 3.71 - 3.84 (m, 1 H), 7.84 (d, J=8.20 Hz, 2 H), 8.04 (d, J=8.20 Hz, 2 H).

Example 17. *trans*-(+/-)-4-bromo-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide



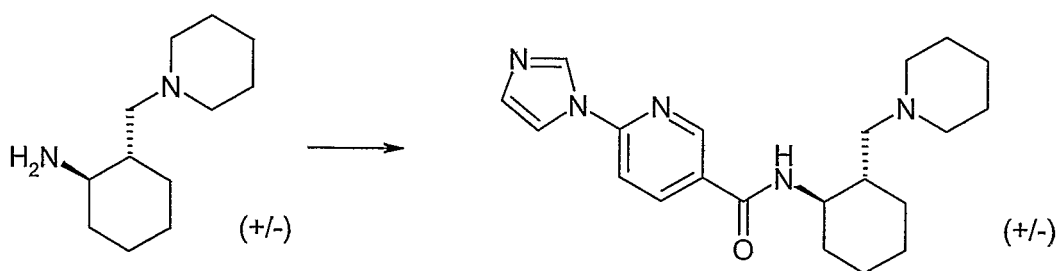
Following the same procedure as Example 1 (step D), yielded *trans*-(+/-)-4-bromo-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide (123 mg, 74%) as its HCl salt. MS (M+1): 379.0. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.15 - 1.61 (m, 6 H), 1.73 - 1.92 (m, 6 H), 1.93 - 2.18 (m, 3 H), 2.70 - 2.88 (m, 1 H), 2.95 - 3.06 (m, 2 H), 3.16 (dd, J=13.28, 2.73 Hz, 1 H), 3.55 - 3.70 (m, 2 H), 3.72 - 3.84 (m, 1 H), 7.66 (d, J=8.59 Hz, 2 H), 7.78 (d, J=8.59 Hz, 2 H).

Example 18. *trans*-(+/-)-4-chloro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide



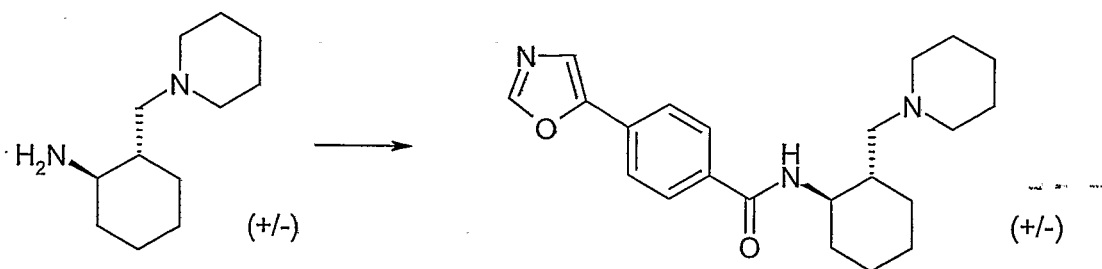
Following the same procedure as Example 1 (step D), yielded *trans*-(+/-)-4-chloro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide (93 mg, 42%) as its HCl salt. MS (M+1): 335.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.23 - 1.60 (m, 6 H), 1.73 - 1.92 (m, 7 H), 1.93 - 2.12 (m, 2 H), 2.74 - 2.89 (m, 1 H), 2.94 - 3.08 (m, 2 H), 3.16 (dd, J=13.28, 2.73 Hz, 1 H), 3.38 - 3.50 (m, 1 H), 3.56 - 3.64 (m, 1 H), 3.72 - 3.83 (m, 1 H), 7.50 (d, J=8.59 Hz, 2 H), 7.85 (d, J=8.59 Hz, 2 H).

Example 19. *trans*-(+/-)-6-(1*H*-imidazol-1-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]nicotinamide



Following the same procedure as Example 2, yielded *trans*-(+/-)-6-(1*H*-imidazol-1-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]nicotinamide (94 mg, 51%) as white solids. MS (M+1): 368.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.99 - 1.18 (m, 1 H), 1.26 - 1.45 (m, 4 H), 1.45 - 1.62 (m, 4 H), 1.61 - 1.70 (m, 1 H), 1.70 - 1.82 (m, 2 H), 1.90 - 1.99 (m, 1 H), 2.07 - 2.17 (m, 2 H), 2.23 - 2.49 (m, 6 H), 3.54 - 3.66 (m, 1 H), 7.16 (s, 1 H), 7.80 (d, J=8.59 Hz, 1 H), 7.95 (s, 1 H), 8.34 (dd, J=8.50, 2.25 Hz, 1 H), 8.60 (d, 1 H), 8.91 (d, J=1.95 Hz, 1 H).

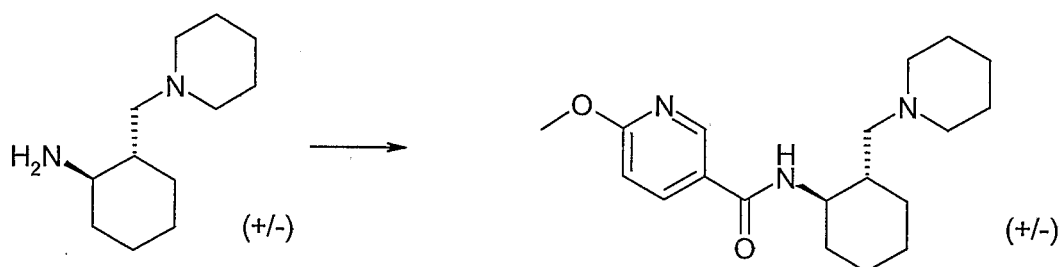
Example 20. *trans*-(+/-)-4-(1,3-oxazol-5-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide



Following the same procedure as Example 2, yielded *trans*-(+/-)- 4-(1,3-oxazol-5-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide (123 mg, 67%) as white solids. MS

- 5 (M+1): 368.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.02 - 1.19 (m, 1 H), 1.24 - 1.44 (m, 4 H), 1.44 - 1.60 (m, 4 H), 1.61 - 1.71 (m, 1 H), 1.71 - 1.82 (m, 2 H), 1.88 - 1.99 (m, 1 H), 2.07 - 2.18 (m, 2 H), 2.24 - 2.48 (m, 6 H), 3.51 - 3.63 (m, 1 H), 7.64 (s, 1 H), 7.77 - 7.85 (m, 2 H), 7.88 - 7.94 (m, 2 H), 8.29 (s, 1 H).

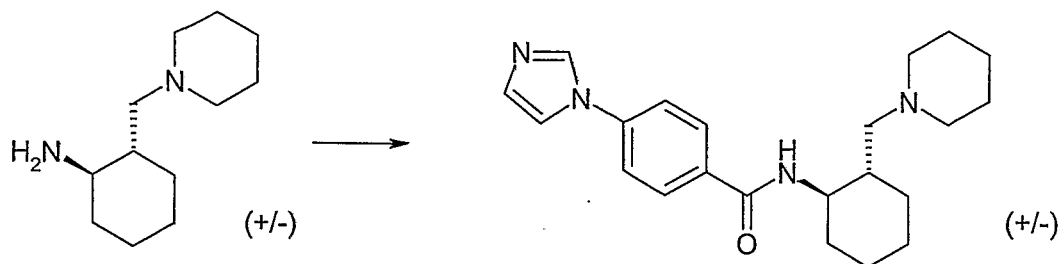
- 10 **Example 21.** *trans*-(+/-)- 6-methoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]nicotinamide



- 15 Following the same procedure as Example 2, yielded *trans*-(+/-)- 6-methoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]nicotinamide (56 mg, 42%) as white solids. MS (M+1): 332.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.96 - 1.19 (m, 1 H), 1.27 - 1.41 (m, 3 H), 1.43 - 1.51 (m, 2 H), 1.54 - 1.68 (m, 4 H), 1.70 - 1.85 (m, 3 H), 1.90 - 2.09 (m, 2 H), 2.30 - 2.46 (m, 1 H), 2.50 - 2.81 (m, 5 H), 3.56 - 3.67 (m, 1 H), 3.94 (s, 3 H), 6.84 (d, J=8.79 Hz, 1 H), 8.07 (dd, J=8.69, 2.44 Hz, 1 H), 8.62 (d, J=2.34 Hz, 1 H).
- 20

Example 22. *trans*-(+/-)- 4-(1*H*-imidazol-1-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide

25



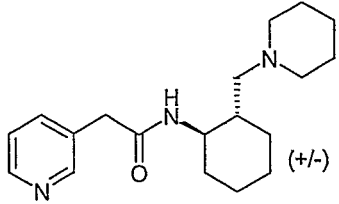
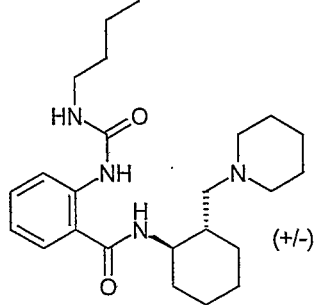
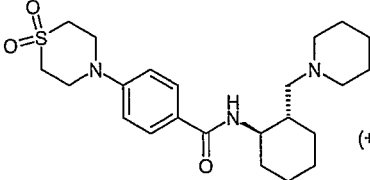
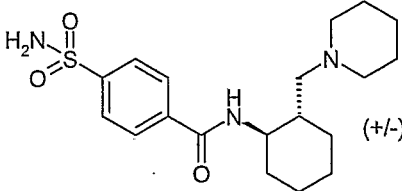
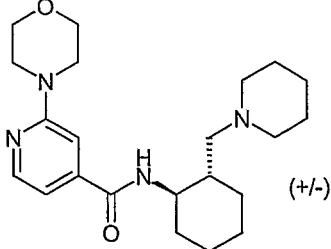
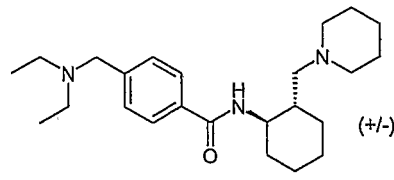
Following the same procedure as Example 2, yielded *trans*-(+/-)-4-(1*H*-imidazol-1-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide (56 mg, 42%) as white solids.

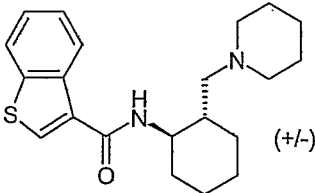
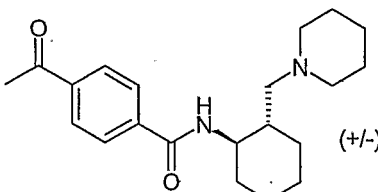
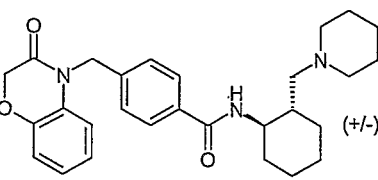
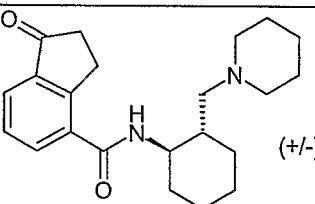
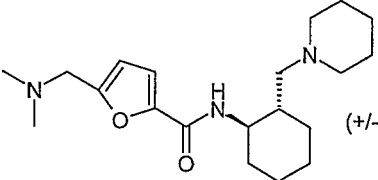
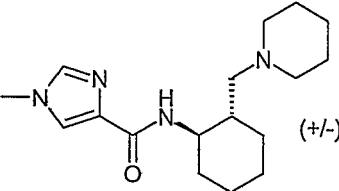
- 5 MS (M+1): 367.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.00 - 1.23 (m, 1 H), 1.24 - 1.50 (m, 6 H), 1.50 - 1.66 (m, 5 H), 1.66 - 1.86 (m, 3 H), 1.89 - 2.22 (m, 2 H), 2.28 - 2.77 (m, 4 H), 3.51 - 3.70 (m, 1 H), 7.16 (s, 1 H), 7.60 - 7.73 (m, 3 H), 7.98 (d, *J*=8.79 Hz, 2 H), 8.25 (s, 1 H).

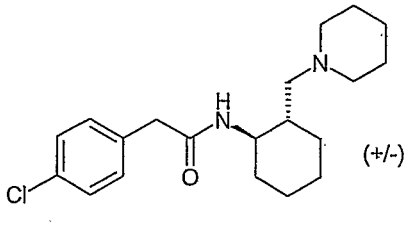
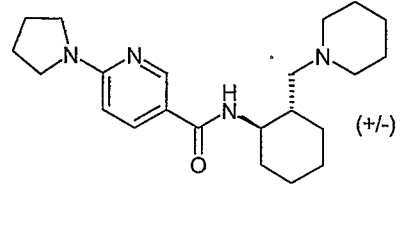
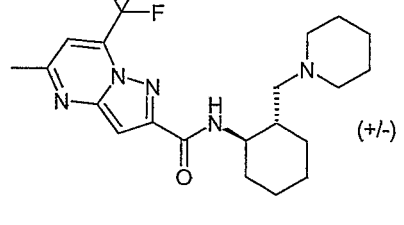
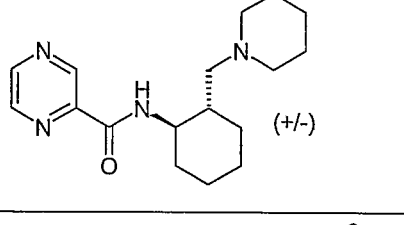
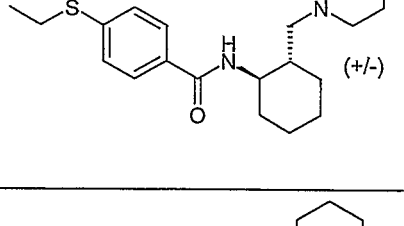
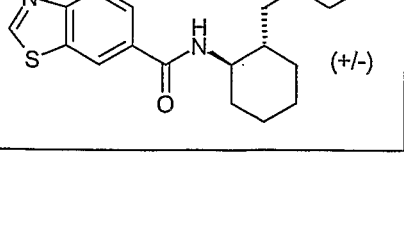
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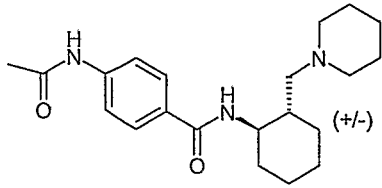
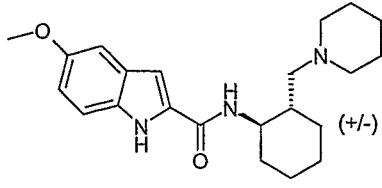
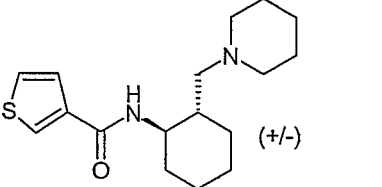
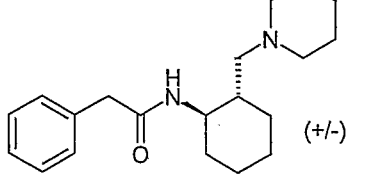
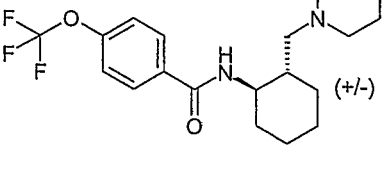
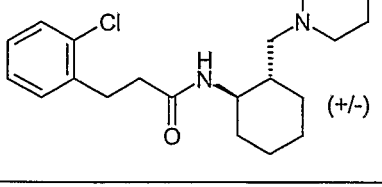
Examples 23-88: Compounds listed in the following table were prepared as described in Example 2:

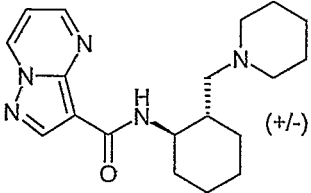
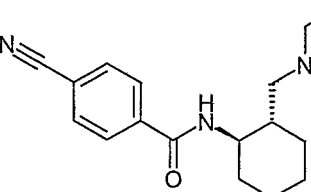
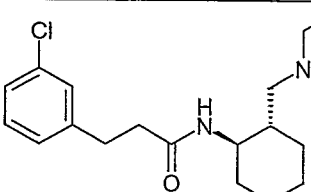
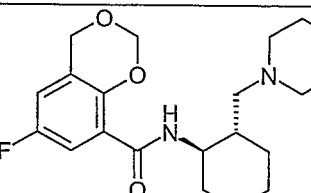
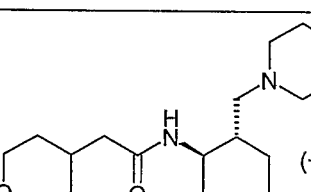
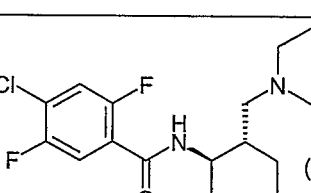
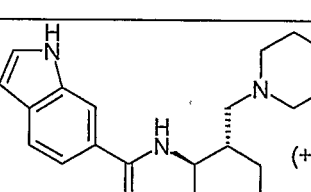
Ex p. No	Structure	Name	MS (M+1)	R et en tio n ti m e (m in)
23		<i>trans</i> -(+/-)-4-[(4-oxopiperidin-1-yl)carbonyl]- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	426.42	1.37

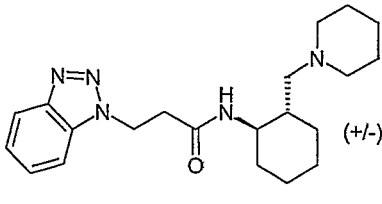
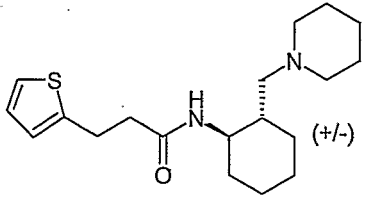
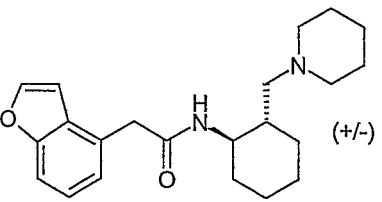
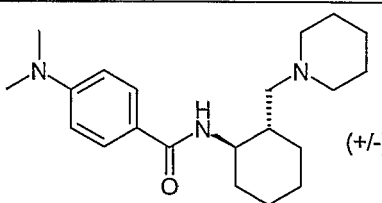
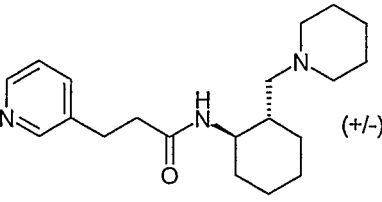
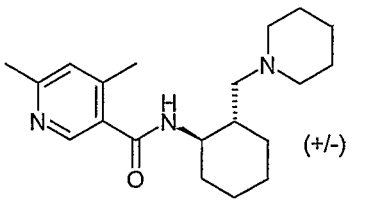
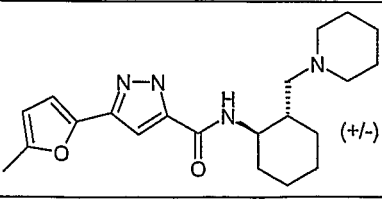
24		<i>trans</i> -(+/-)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-2-pyridin-3-ylacetamide	315.97	1.17
25		<i>trans</i> -(+/-)-2-[[[(butylamino)carbonyl]amino]- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	414.96	1.98
26		<i>trans</i> -(+/-)-4-(1,1-dioxidothiomorpholin-4-yl)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	433.88	1.46
27		<i>trans</i> -(+/-)-4-(aminosulfonyl)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	379.91	1.33
28		<i>trans</i> -(+/-)-2-morpholin-4-yl- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]isonicotinamide	386.95	1.54
29		<i>trans</i> -(+/-)-4-[(diethylamino)methyl]- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	386	1.94

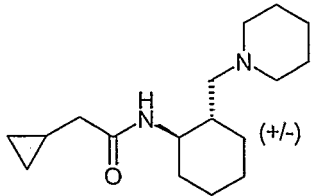
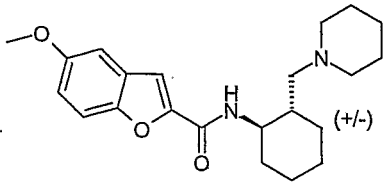
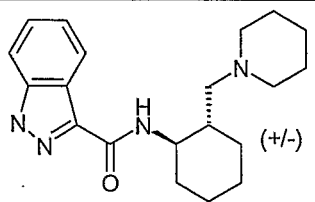
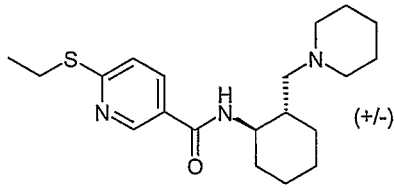
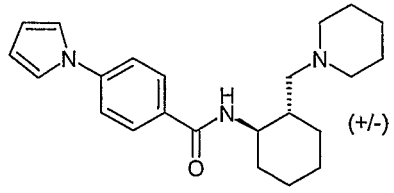
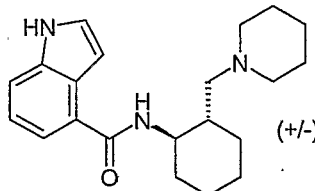
30		<i>trans</i> -(+/-)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-1-benzothiophene-3-carboxamide	356.91	1.97
31		<i>trans</i> -(+/-)-4-acetyl- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	342.95	1.62
32		<i>trans</i> -(+/-)-4-[(3-oxo-2,3-dihydro-4 <i>H</i> -1,4-benzoxazin-4-yl)methyl]- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	461.89	1.85
33		<i>trans</i> -(+/-)-1-oxo- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]indane-4-carboxamide	354.94	1.55
34		<i>trans</i> -(+/-)-5-[(dimethylamino)methyl]- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-2-furamide	348.01	1.43
35		<i>trans</i> -(+/-)-1-methyl- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-1 <i>H</i> -imidazole-4-carboxamide	304.98	1.15

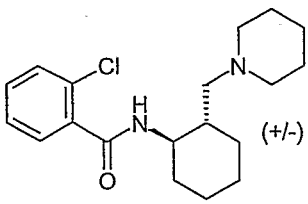
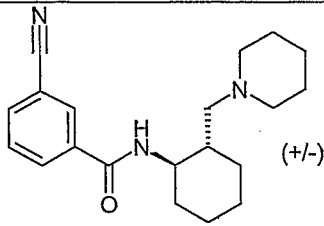
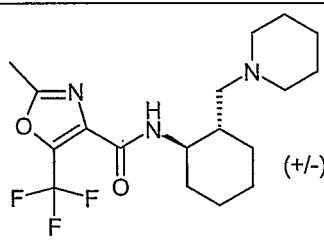
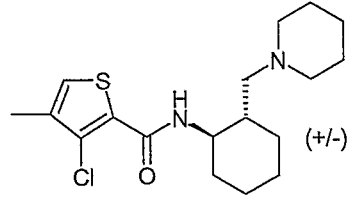
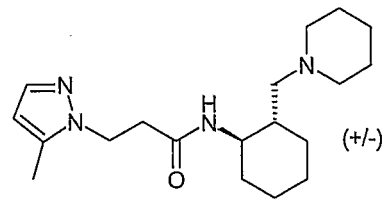
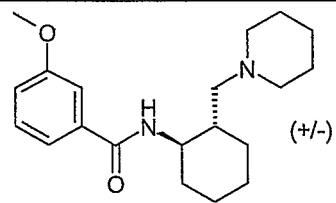
36		<i>trans</i> -(+/-)-2-(4-chlorophenyl)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide	348.92	1.68
37		<i>trans</i> -(+/-)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-6-pyrrolidin-1-ylnicotinamide	371	1.61
38		<i>trans</i> -(+/-)-5-methyl- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-7-(trifluoromethyl)pyrazolo[1,5- <i>a</i>]pyrimidine-2-carboxamide	424.44	1.79
39		<i>trans</i> -(+/-)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]pyrazine-2-carboxamide	303.02	1.46
40		<i>trans</i> -(+/-)-4-(ethylthio)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	360.94	1.99
41		<i>trans</i> -(+/-)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-1,3-benzothiazole-6-carboxamide	357.96	1.6

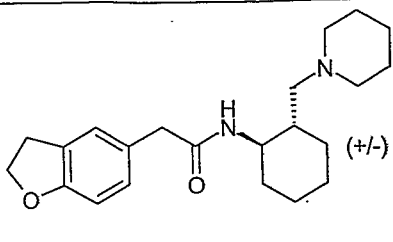
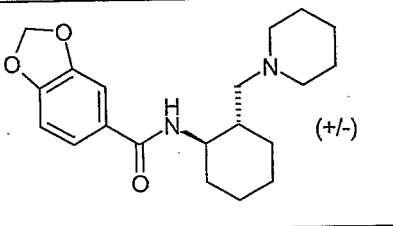
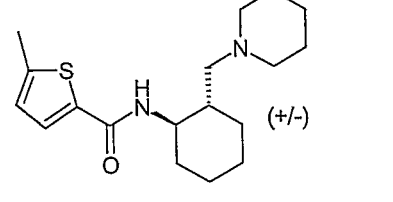
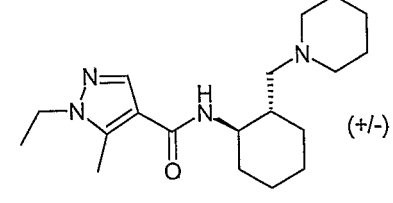
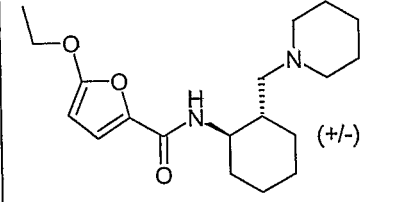
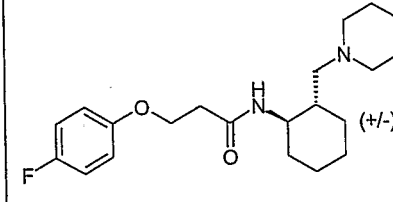
42		<i>trans</i> -(+/-)-4-(acetylamino)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	357.96	1.36
43		<i>trans</i> -(+/-)-5-methoxy- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-1 <i>H</i> -indole-2-carboxamide	370	1.75
44		<i>trans</i> -(+/-)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]thiophene-3-carboxamide	306.97	1.58
45		<i>trans</i> -(+/-)-2-phenyl- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide	314.98	1.53
46		<i>trans</i> -(+/-)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-4-(trifluoromethoxy)benzamide	384.87	2.04
47		<i>trans</i> -(+/-)-3-(2-chlorophenyl)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide	362.9	1.82

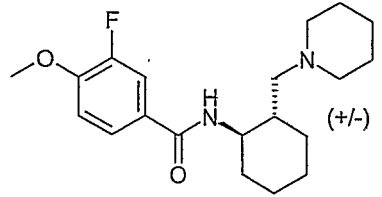
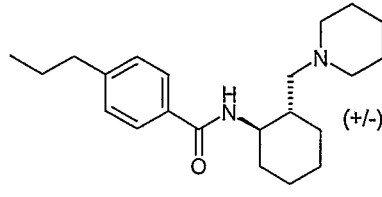
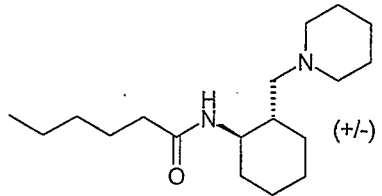
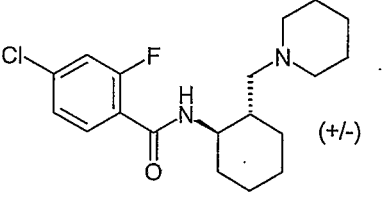
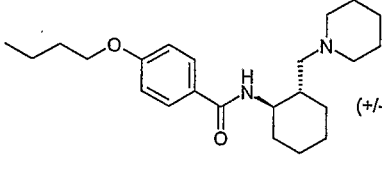
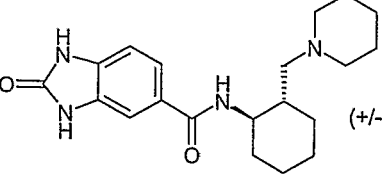
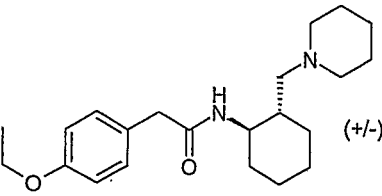
48		<i>trans</i> -(+/-)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]pyrazolo[1,5-a]pyrimidine-3-carboxamide	341.93	1.32
49		<i>trans</i> -(+/-)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-4-cyano benzamide	324.93	1.86
50		<i>trans</i> -(+/-)-3-(3-chlorophenyl)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide	362.89	1.81
51		<i>trans</i> -(+/-)-6-fluoro- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-4 <i>H</i> -1,3-benzodioxine-8-carboxamide	376.88	1.67
52		<i>trans</i> -(+/-)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-2-(tetrahydro-2 <i>H</i> -pyran-4-yl)acetamide	322.97	1.24
53		<i>trans</i> -(+/-)-4-chloro-2,5-difluoro- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	370.84	2.05
54		<i>trans</i> -(+/-)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-1 <i>H</i> -indole-6-carboxamide	339.92	1.68

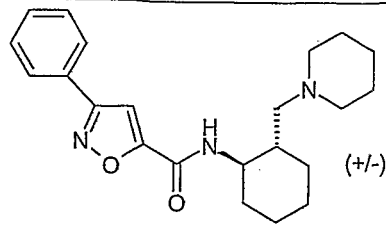
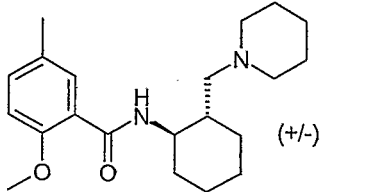
55		<i>trans</i> -(+/-)-3-(1 <i>H</i> -1,2,3-benzotriazol-1-yl)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide	369.97	1.34
56		<i>trans</i> -(+/-)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-3-(2-thienyl)propanamide	334.95	1.62
57		<i>trans</i> -(+/-)-2-(1-benzofuran-4-yl)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide	354.92	1.62
58		<i>trans</i> -(+/-)-4-(dimethylamino)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	343.97	1.75
59		<i>trans</i> -(+/-)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-3-pyridin-3-ylpropanamide	329.99	1.21
60		<i>trans</i> -(+/-)-4,6-dimethyl- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]nicotinamide	329.94	1.39
61		<i>trans</i> -(+/-)-3-(5-methyl-2-furyl)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-1 <i>H</i> -pyrazole-5-carboxamide	370.89	1.66

62		<i>trans</i> -(+/-)-2-cyclopropyl-N-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide	279.01	1.37
63		<i>trans</i> -(+/-)-5-methoxy-N-[2-(piperidin-1-ylmethyl)cyclohexyl]-1-benzofuran-2-carboxamide	370.89	2.02
64		<i>trans</i> -(+/-)-N-[2-(piperidin-1-ylmethyl)cyclohexyl]-1H-indazole-3-carboxamide	340.91	1.57
65		<i>trans</i> -(+/-)-6-(ethylthio)-N-[2-(piperidin-1-ylmethyl)cyclohexyl]nicotinamide	361.92	1.85
66		<i>trans</i> -(+/-)-N-[2-(piperidin-1-ylmethyl)cyclohexyl]-4-(1H-pyrrol-1-yl)benzamide	365.93	1.94
67		<i>trans</i> -(+/-)-N-[2-(piperidin-1-ylmethyl)cyclohexyl]-1H-indole-4-carboxamide	339.91	1.61

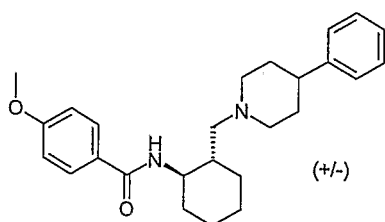
68		<i>trans</i> -(+/-)-2-chloro- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	334.87	1.74
69		<i>trans</i> -(+/-)-3-cyano- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	325.92	1.73
70		<i>trans</i> -(+/-)-2-methyl- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-5-(trifluoromethyl)-1,3-oxazole-4-carboxamide	373.86	1.95
71		<i>trans</i> -(+/-)-3-chloro-4-methyl- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]thiophene-2-carboxamide	354.82	2.04
72		<i>trans</i> -(+/-)-3-(5-methyl-1 <i>H</i> -pyrazol-1-yl)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide	332.95	1.27
73		<i>trans</i> -(+/-)-3-methoxy- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	330.92	1.74

74		<i>trans</i> -(+/-)-2-(2,3-dihydro-1-benzofuran-5-yl)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide	356.96	1.48
75		<i>trans</i> -(+/-)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-1,3-benzodioxole-5-carboxamide	344.93	1.69
76		<i>trans</i> -(+/-)-5-methyl- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]thiophene-2-carboxamide	320.89	1.76
77		<i>trans</i> -(+/-)-1-ethyl-5-methyl- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-1 <i>H</i> -pyrazole-4-carboxamide	332.94	1.34
78		<i>trans</i> -(+/-)-5-ethoxy- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-2-furamide	334.95	1.77
79		<i>trans</i> -(+/-)-3-(4-fluorophenoxy)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide	362.95	1.66

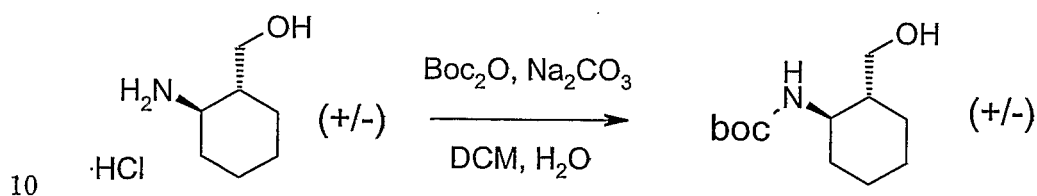
80		<i>trans</i> -(+/-)-3-fluoro-4-methoxy- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	348.93	1.76
81		<i>trans</i> -(+/-)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-4-propylbenzamide	342.96	2.12
82		<i>trans</i> -(+/-)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]hexanamide	295.04	1.68
83		<i>trans</i> -(+/-)-4-chloro-2-fluoro- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	352.85	1.96
84		<i>trans</i> -(+/-)-4-butoxy- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	372.94	2.15
85		<i>trans</i> -(+/-)-2-oxo- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]-2,3-dihydro-1 <i>H</i> -benzimidazole-5-carboxamide	356.9	1.24
86		<i>trans</i> -(+/-)-2-(4-ethoxyphenyl)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide	358.98	1.62

		mide		
87		<i>trans</i> -(+/-)- 3-phenyl- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]isoxazole-5-carboxamide	367.88	2.10
88		<i>trans</i> -(+/-)- 2-methoxy-5-methyl- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide	344.92	1.73

Example 89. *trans*-(+/-)-4-methoxy-*N*-{2-[(4-phenyl)piperidin-1-yl)methyl]cyclohexyl}benzamide



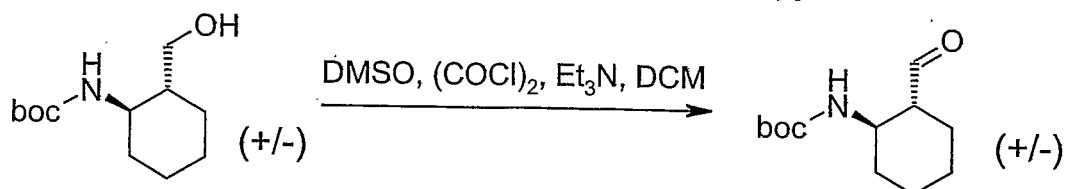
Step A. The preparation of *trans*-(+/-)-*tert*-butyl [2-(hydroxymethyl)cyclohexyl]carbamate



A solution of sodium carbonate (1.26 g, 12.2 mmol) in water (20 ml) was added to a suspension of *trans*-(+/-)-[2-aminocyclohexyl]methanol hydrochloride salt (1.00 g, 6.10 mmol) in dichloromethane (25 ml). The reaction was stirred at room temperature for 2 days. The solution was diluted with water (20 ml). The phases were separated and the aqueous was extracted with dichloromethane (2x75ml). The

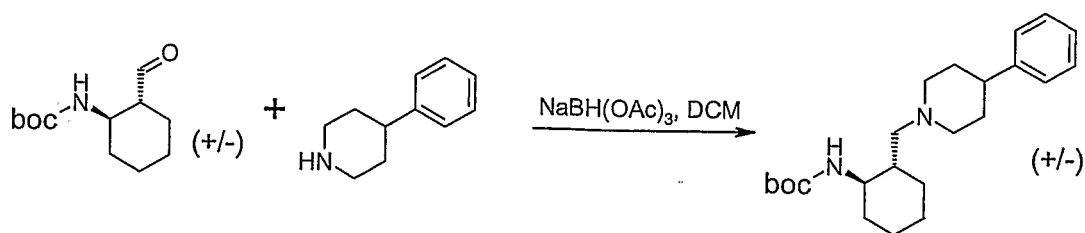
combined organic phases were washed with brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. A white solid was obtained (1.45g). The product was used directly for the next step without further purification.

- 5 Step B. The preparation of *trans*-(+/-)- *tert*-butyl [2-formylcyclohexyl]carbamate



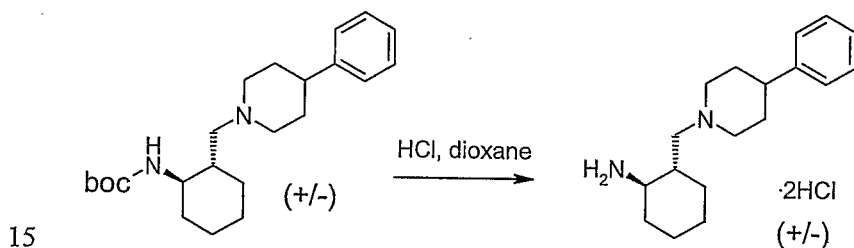
- A 2M solution of oxalyl chloride in dichloromethane (4.57 ml, 9.14 mmol) was cooled to -78°C under nitrogen and added to a solution of dimethylsulfoxide (1.30 ml, 18.3 mmol) in dichloromethane (6 ml) at -78°C under nitrogen via cannula. After 10 minutes, a solution of the product from step A *trans*-(+/-)- (*tert*-butyl [2-(hydroxymethyl)cyclohexyl]carbamate, 6.10 mmol) in dichloromethane (6 ml) at -78°C under nitrogen was added to the reaction mixture via cannula. The mixture was stirred at -78°C under nitrogen for 10 minutes and then triethylamine (3.40 ml, 24.4 mmol) was added dropwise. The reaction was stirred at -78°C under nitrogen for 20 minutes, then allowed to warm up to 0°C over 1 hour. The reaction was quenched with water (25 ml) and diluted with dichloromethane (50 ml). The phases were separated and the aqueous was extracted with dichloromethane (2x75ml). The combined organic phases were washed with saturated aqueous ammonium chloride, brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. A yellow solid was obtained (1.34g, 97%). ^1H NMR (400 MHz, CHLOROFORM-D): δ ppm 1.12 - 1.27 (m, 2 H), 1.29 - 1.52 (m, 2 H), 1.40 (s, 9 H), 1.70 - 1.82 (m, 3 H), 1.96 - 2.10 (m, 2 H), 3.68 - 3.80 (m, 1 H), 4.42 - 4.49 (m, 1 H), 9.56 (d, $J=4.10$ Hz, 1 H).

- 25 Step C. The preparation of *trans*-(+/-)-*tert*-butyl {2-[(4-phenylpiperidin-1-yl)methyl]cyclohexyl}carbamate



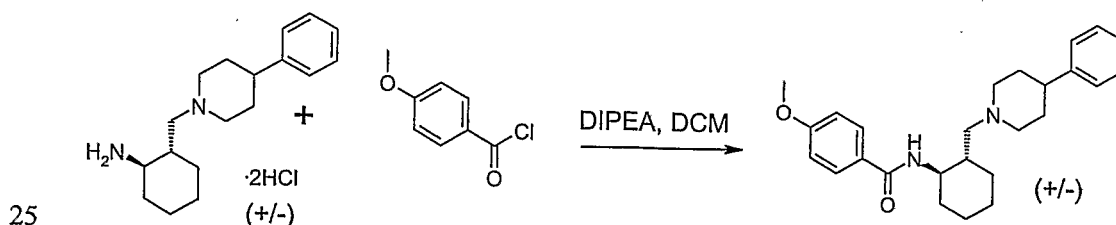
4-Phenylpiperidine (97 mg, 0.60 mmol) was added to a solution of *trans*-(+/-)-*tert*-butyl [2-formylcyclohexyl]carbamate (114 mg, 0.50 mmol) in dichloromethane (4 ml). The reaction was stirred at room temperature for 30 minutes, and then sodium triacetoxymethylborohydride (212 mg, 1.00 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 12 hours, and then cooled to 0°C. Water (1 ml) was added dropwise. A 1N sodium hydroxide solution (10 ml) and dichloromethane (30 ml) were added to the mixture. The phases were separated and the aqueous was extracted with dichloromethane (2x15ml). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Yellow oil was obtained (200 mg). The product was used directly for the next step without further purification.

Step D. The preparation of *trans*-(+/-)- {2-[(4-phenylpiperidin-1-yl)methyl]cyclohexyl}amine hydrochloride salt



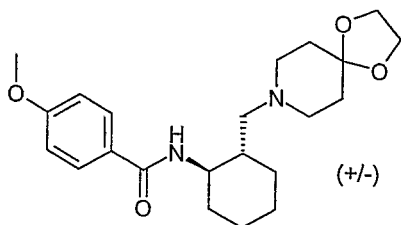
A 4N solution of hydrochloric acid in dioxane (2.0 ml, 8.0 mmol) was added to a solution of the crude product from step C *trans*-(+/-)- *tert*-butyl {2-[(4-phenylpiperidin-1-yl)methyl]cyclohexyl}carbamate (0.50 mmol) in dioxane (5 ml). The reaction was stirred at room temperature for 3 days. The mixture was concentrated *in vacuo*. The product was used directly for the next step without further purification. MS (M+1): 273.2.

Step E. The preparation of *trans*-(+/-)- 4-methoxy-*N*-{2-[(4-phenylpiperidin-1-yl)methyl]cyclohexyl}benzamide



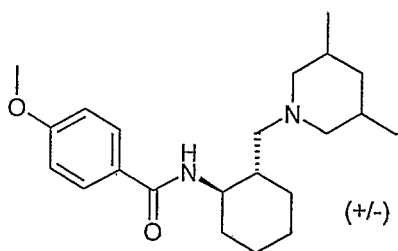
- 4-Methoxybenzoyl chloride (94 mg, 0.55 mmol) was added to a solution of the crude product from step D *trans*-(+/-)- {2-[(4-phenylpiperidin-1-yl)methyl]cyclohexyl}amine hydrochloride salt (0.50 mmol) and diisopropylethylamine (0.348 ml, 2.0 mmol) in dichloromethane (3 ml). The reaction was stirred at room temperature for 12 hours.
- 5 The reaction mixture was diluted with dichloromethane. The solution was washed with saturated aqueous sodium bicarbonate, brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by reverse phase HPLC. The combined pure fractions were concentrated *in vacuo*. The residue was dissolved in dioxane (2 ml) and a 4N solution of hydrochloric acid in dioxane (0.5 ml, 2.0 mmol)
- 10 was added. The solution was concentrated *in vacuo*. The product was lyophilized. The HCl salt of the title compound was obtained as a white solid in a 68% yield over 3 steps (149 mg). MS (M+1): 407.3; ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.23 - 1.61 (m, 4 H), 1.83 (dd, 2 H), 1.92 - 2.17 (m, 7 H), 2.84 (tt, *J*=11.69, 4.44, 4.20 Hz, 1 H), 2.99 (td, *J*=12.35, 4.20 Hz, 1 H), 3.07 (dd, *J*=13.28, 9.37 Hz, 1 H), 3.14 -
- 15 3.23 (m, 2 H), 3.53 - 3.60 (m, 1 H), 3.71 - 3.76 (m, 1 H), 3.79 (td, *J*=10.94, 3.91 Hz, 1 H), 3.83 (s, 3 H), 6.99 (d, *J*=8.98 Hz, 2 H), 7.12 - 7.25 (m, 3 H), 7.26 - 7.33 (m, 2 H), 7.86 (d, *J*=8.98 Hz, 2 H).

20 **Example 90. *trans*-(+/-)- *N*-[2-(1,4-dioxo-8-azaspiro[4.5]dec-8-ylmethyl)cyclohexyl]-4-methoxybenzamide**



- Following the procedure described in Example 89 (steps C to E), the HCl salt of the title compound was obtained as a white solid in a 24% yield over 3 steps (50 mg).
- MS (M+1): 389.3; ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.21 - 1.58 (m, 4 H),
- 25 1.75 - 2.17 (m, 9 H), 2.99 - 3.08 (m, 1 H), 3.15 - 3.25 (m, 1 H), 3.45 - 3.53 (m, 1 H), 3.58 - 3.80 (m, 4 H), 3.83 (s, 3 H), 3.92 - 3.98 (m, 4 H), 6.98 (d, *J*=8.79 Hz, 2 H), 7.84 (d, *J*=8.98 Hz, 2 H).

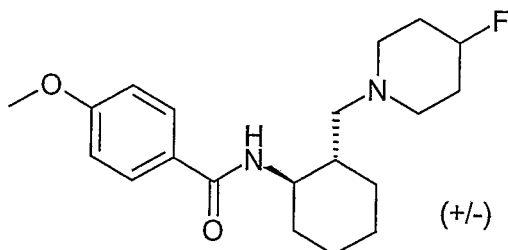
30 **Example 91. *trans*-(+/-)- *N*-[2-[(3,5-dimethylpiperidin-1-yl)methyl]cyclohexyl]-4-methoxybenzamide**



Following the procedure described in Example 89 (steps C to E), the HCl salt of the title compound was obtained as a white solid in a 43% yield over 3 steps (84 mg).

MS (M+1): 359.3; ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.82 (q, *J*=12.43 Hz, 1 H), 0.89 - 0.97 (m, 6 H), 1.15 - 1.66 (m, 5 H), 1.75 - 2.13 (m, 7 H), 2.33 (t, *J*=12.21 Hz, 1 H), 2.55 (t, *J*=12.11 Hz, 1 H), 3.01 (s, 1 H), 3.09 - 3.15 (m, 1 H), 3.30 - 3.39 (m, 1 H), 3.48 (s, *J*=11.91 Hz, 1 H), 3.75 (td, *J*=10.89, 4.00 Hz, 1 H), 3.83 (s, 3 H), 6.98 (d, *J*=8.79 Hz, 2 H), 7.84 (s, 2 H).

10 **Example 92. *trans*-(+/-)- *N*-(2-[(4-fluoropiperidin-1-yl)methyl]cyclohexyl)-4-methoxybenzamide**

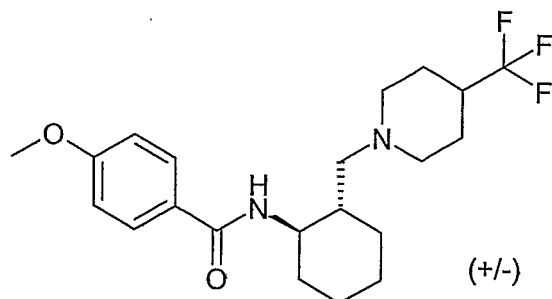


Following the procedure described in Example 89 (steps C to E), the title compound was obtained as a white solid in a 59% yield over 3 steps (51 mg). MS (M+1): 349.3.

15 ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.99 - 1.17 (m, 1 H), 1.23 - 1.45 (m, 3 H), 1.58 - 1.87 (m, 7 H), 1.91 - 2.00 (m, 1 H), 2.03 - 2.11 (m, 1 H), 2.17 (dd, *J*=12.79, 6.54 Hz, 1 H), 2.26 - 2.40 (m, 2 H), 2.44 (dd, *J*=12.69, 5.47 Hz, 1 H), 2.49 - 2.62 (m, 2 H), 3.54 - 3.64 (m, 1 H), 3.84 (s, 3 H), 4.49 - 4.68 (m, 1 H), 6.98 (d, *J*=8.79 Hz, 2 H), 7.78 (d, *J*=8.79 Hz, 2 H).

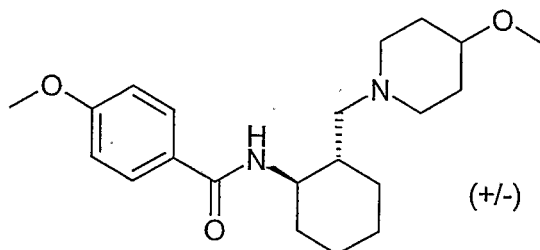
20

Example 93. *trans*-(+/-)- 4-methoxy-*N*-(2-[[4-(trifluoromethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide



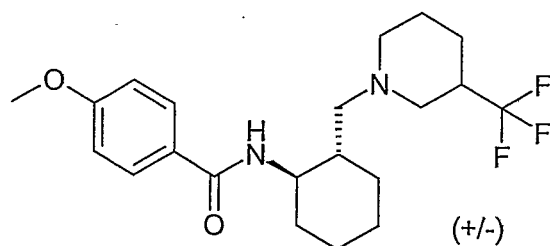
Following the procedure described in Example 89 (steps C to E), the title compound was obtained as a white solid in a 48% yield over 3 steps (48 mg). MS (M+1): 399.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.20 - 1.64 (m, 4 H), 1.74 - 1.91 (m, 3 H), 1.92 - 2.05 (m, 3 H), 2.06 - 2.20 (m, 3 H), 2.49 - 2.69 (m, 1 H), 2.94 (t, J=12.50 Hz, 1 H), 3.05 - 3.20 (m, 3 H), 3.60 (d, J=11.13 Hz, 1 H), 3.73 - 3.82 (m, 2 H), 3.83 - 3.87 (m, 3 H), 7.00 (d, J=8.40 Hz, 2 H), 7.88 (d, J=8.40 Hz, 2 H).

Example 94. *trans*-(+/-)- 4-methoxy-N-{2-[(4-methoxypiperidin-1-yl)methyl]cyclohexyl}benzamide



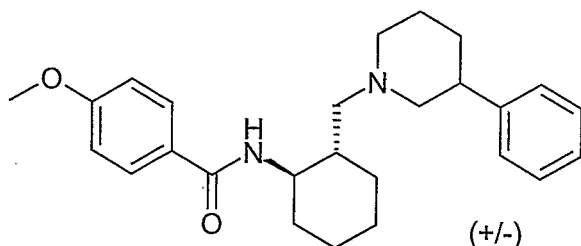
Following the procedure described in Example 89 (steps C to E), the title compound was obtained as a white solid in a 58% yield over 3 steps (52 mg). MS (M+1): 361.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.98 - 1.17 (m, 1 H), 1.22 - 1.48 (m, 4 H), 1.51 - 1.68 (m, 2 H), 1.70 - 1.99 (m, 5 H), 2.04 - 2.19 (m, 4 H), 2.42 (dd, J=12.69, 5.47 Hz, 1 H), 2.62 - 2.82 (m, 2 H), 3.15 - 3.26 (m, 1 H), 3.30 (s, 3H), 3.51 - 3.61 (m, 1 H), 3.84 (s, 3 H), 6.98 (d, J=8.79 Hz, 2 H), 7.78 (d, J=8.79 Hz, 2 H).

Example 95. *trans*-(+/-)- 4-methoxy-N-(2-{[3-(trifluoromethyl)piperidin-1-yl]methyl}cyclohexyl)benzamide



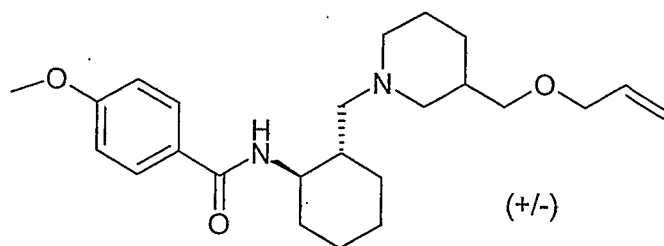
Following the procedure described in Example 89 (steps C to E), the title compound was obtained as a white solid in a 73% yield over 3 steps (58 mg). MS (M+1): 399.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.21 - 1.65 (m, 6 H), 1.76 - 1.91 (m, 3 H), 1.90 - 2.15 (m, 5 H), 2.76 - 2.88 (m, 1 H), 2.95 - 3.18 (m, 2 H), 3.19 - 3.26 (m, 1 H), 3.45 - 3.67 (m, 1 H), 3.66 - 3.81 (m, 2 H), 3.83 (s, 3 H), 6.98 (d, J=8.89 Hz, 2 H), 7.80 (dd, J=8.89, 2.34 Hz, 2 H).

Example 96. *trans*-(+/-)- 4-methoxy-N-[2-[(3-phenylpiperidin-1-yl)methyl]cyclohexyl]benzamide

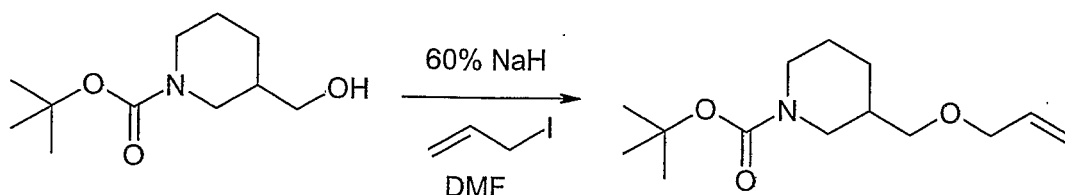


Following the procedure described in Example 89 (steps C to E), the title compound was obtained as a white solid in a 77% yield over 3 steps (63 mg). MS (M+1): 407.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.21 - 1.58 (m, 5 H) 1.66 - 1.86 (m, 3 H) 1.86 - 2.03 (m, 5 H) 2.03 - 2.15 (m, 1 H) 2.79 - 2.98 (m, 1 H) 3.00 - 3.12 (m, 2 H) 3.13 - 3.24 (m, 2 H) 3.66 - 3.80 (m, 2 H) 3.83 (d, J=0.98 Hz, 3 H) 6.91 - 7.00 (m, 2 H) 7.19 - 7.35 (m, 5 H) 7.73 (d, J=8.79 Hz, 1 H) 7.80 (d, J=8.79 Hz, 1 H).

Example 97. *trans*-(+/-)- N-[2-[(3-[(allyloxy)methyl]piperidin-1-yl)methyl]cyclohexyl]-4-methoxybenzamide

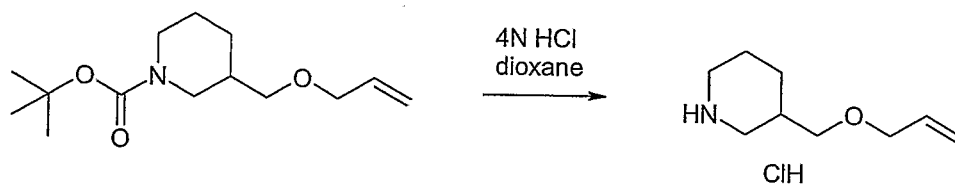


Step A: The preparation of *tert*-butyl 3-[(allyloxy)methyl]piperidine-1-carboxylate



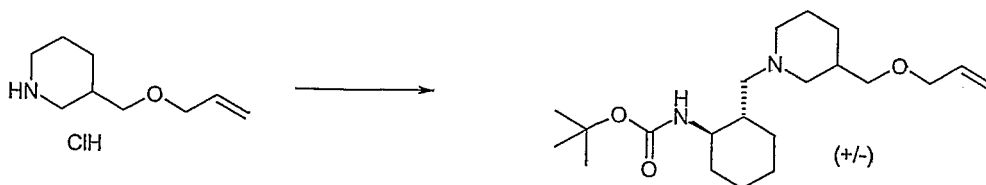
- 5 To a solution of *tert*-butyl 3-(hydroxymethyl)piperidine-1-carboxylate (0.86 g, 4.0 mmol) in dry DMF (15 mL) was added NaH (60% , 0.24 g, 6.0 mmol) at 0°C under nitrogen and the suspension was stirred at room temperature for 30 min. Allyl iodide (1.51 g, 9.0 mmol) was added to the reaction mixture and stirred over night at room temperature. The solvent was removed in vacuo and the residue was dissolved in
- 10 dichloromethane (50 mL), washed with water (30 mL), dried over Na₂SO₄. Removal of solvent gave the crude product, which was used for the next step without further purification.

Step B: The preparation of 3-[(allyloxy)methyl]piperidine hydrochloride



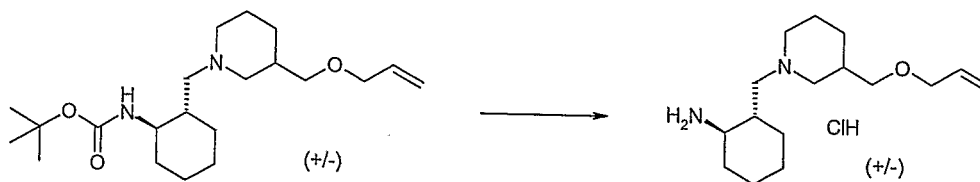
- 15 The crude *tert*-butyl 3-[(allyloxy)methyl]piperidine-1-carboxylate from step A was stirred in 4N HCl in dioxane (10 mL) at room temperature for 4 h. The solvent was removed in vacuo and the residue was added diethyl ether to form solid, filtered to give 3-[(allyloxy)methyl]piperidine hydrochloride as yellow powders (0.62 g, 81% for
- 20 two steps).

Step C: The preparation of *trans*-(+/-)-*tert*-butyl [2-((3-[(allyloxy)methyl]piperidin-1-yl)methyl)cyclohexyl]carbamate



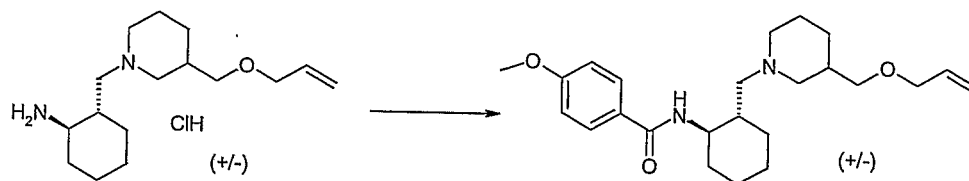
Following the procedure described in Example 89 (steps C), 3-[(allyloxy)methyl]piperidine hydrochloride (0.25 mmol) was added to a solution of *trans*-(+/-)-*tert*-butyl [2-formylcyclohexyl]carbamate (57 mg, 0.25 mmol) in dichloromethane (4 ml). The reaction was stirred at room temperature for 30 minutes, and then sodium triacetoxyborohydride (106 mg, 0.5 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 12 hours, and then cooled to 0°C. After the same work-up, the yellow oil was used directly for the next step without further purification.

Step D: The preparation of *trans*-(+/-)-2-({3-[(allyloxy)methyl]piperidin-1-yl)methyl)cyclohexyl]amine hydrochloride



Following the procedure described in Example 89 (steps D), the HCl salt was obtained and used for the next step without further purification.

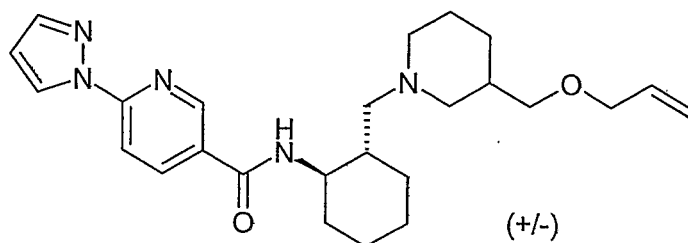
Step E: The preparation of *trans*-(+/-)-*N*-[2-({3-[(allyloxy)methyl]piperidin-1-yl)methyl)cyclohexyl]-4-methoxybenzamide



Following the procedure described in Example 1 (step D), the TFA salt of the title compound was obtained as a white solid in a 37% yield over 3 steps (48 mg). MS ($M+1$): 401.3. ^1H NMR (400 MHz, METHANOL- D_4): δ ppm 1.22 - 1.60 (m, 5 H), 1.74 - 1.87 (m, 4 H), 1.90 - 2.01 (m, 3 H), 2.02 - 2.23 (m, 2 H), 2.55 - 2.97 (m, 2 H), 3.00 -

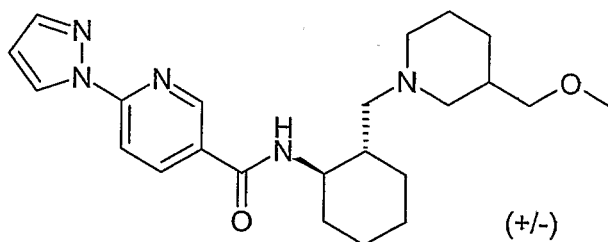
3.08 (m, 1 H), 3.11 - 3.18 (m, 1 H), 3.22 - 3.27 (m, 1 H), 3.36 - 3.52 (m, 2 H), 3.59 - 3.68 (m, 1 H), 3.71 - 3.80 (m, 1 H), 3.83 (s, 3 H), 3.88 - 3.98 (m, 2 H), 5.07 - 5.29 (m, 2 H), 5.78 - 5.94 (m, 1 H), 6.98 (d, J=8.79 Hz, 2 H), 7.81 (d, J=8.79 Hz, 2 H).

5 **Example 98. *trans*-(+/-)- *N*-[2-({3-[(allyloxy)methyl]piperidin-1-yl)methyl}cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide**



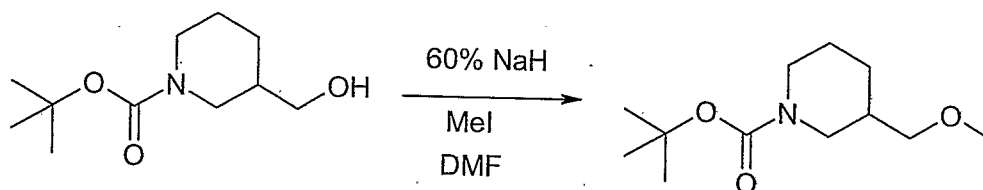
Following the procedure described in Example 2, the title compound was obtained as a white solid in a 29% yield over 3 steps (32 mg). MS (M+1): 438.0. ¹H NMR (400
10 MHz, METHANOL-D₄): δ ppm 0.83 - 1.00 (m, 1 H), 1.01 - 1.17 (m, 1 H), 1.25 - 1.43 (m, 4 H), 1.53 - 1.79 (m, 6 H), 1.77 - 1.99 (m, 3 H), 2.04 - 2.19 (m, 2 H), 2.34 - 2.47 (m, 1 H), 2.68 - 3.04 (m, 2 H), 3.07 - 3.26 (m, 2 H), 3.55 - 3.66 (m, 1 H), 3.78 (d, J=5.47 Hz, 1 H), 3.88 - 3.94 (m, 1 H), 4.98 - 5.28 (m, 2 H), 5.61 - 5.98 (m, 1 H), 6.54 (s, 1 H), 7.78 (s, 1 H), 8.00 (d, J=8.59 Hz, 1 H), 8.26 - 8.34 (m, 1 H), 8.63 (d, J=2.15
15 Hz, 1 H), 8.85 (d, J=1.76 Hz, 1 H).

Example 99. *trans*-(+/-)- *N*-(2-({3-(methoxymethyl)piperidin-1-yl)methyl}cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide



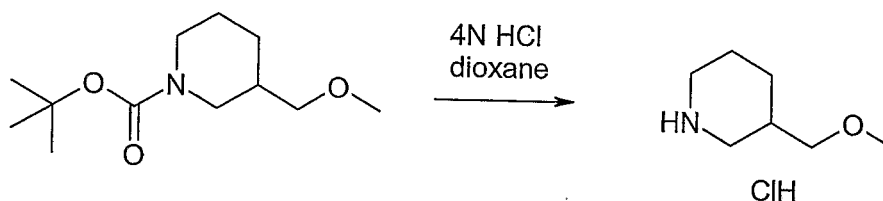
20

Step A: The preparation of *tert*-butyl 3-[(methoxy)methyl]piperidine-1-carboxylate



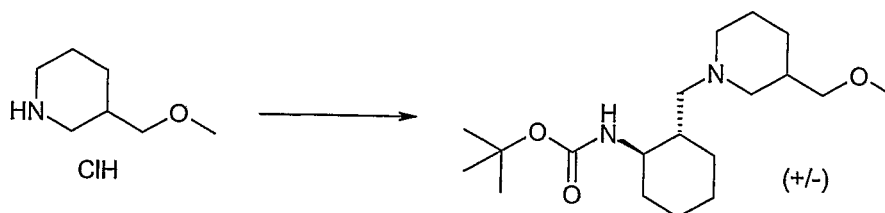
Following the same procedure as Example 97 (step A): To a solution of *tert*-butyl 3-(hydroxymethyl)piperidine-1-carboxylate (1.72 g, 8.0 mmol) in dry DMF (30 mL) was added NaH (60% , 0.48 g, 12.0 mmol) at 0°C under nitrogen and the suspension was stirred at room temperature for 30 min. Methyl iodide (12.0 mmol) was added to the reaction mixture and stirred over night at room temperature. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (80 mL), washed with water (50 mL), dried over Na₂SO₄. Removal of solvent gave the crude product (1.75 g, 95%), which was used for the next step without further purification.

Step B: The preparation of 3-[(methoxy)methyl]piperidine hydrochloride



Following the same procedure as Example 97 (step B), the crude *tert*-butyl 3-[(methoxy)methyl]piperidine-1-carboxylate from step A was treated with 4N HCl in dioxane to give 3-[(methoxy)methyl]piperidine hydrochloride as white powders (1.18 g, 94%).

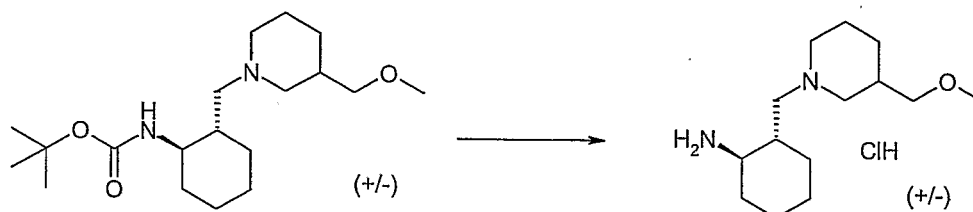
Step C: The preparation of *trans*-(+/-)-*tert*-butyl [2-({3-[(methoxy)methyl]piperidin-1-yl)methyl}cyclohexyl]carbamate



Following the procedure described in Example 89 (steps C)): 3-[(methoxy)methyl]piperidine hydrochloride (0.2 mmol) was added to a solution of *trans*-(+/-)-*tert*-butyl [2-formylcyclohexyl]carbamate (0.2 mmol) in dichloromethane (4

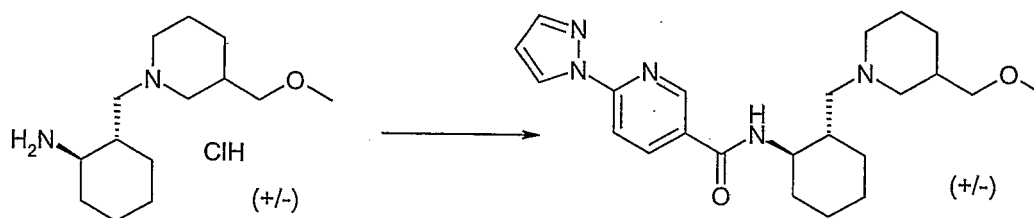
ml). The reaction was stirred at room temperature for 30 minutes, and then sodium triacetoxyborohydride (85 mg, 0.4 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 12 hours, and then cooled to 0°C. After the same work-up, the yellow oil was used directly for the next step without further purification.

Step D: The preparation of *trans*-(+/-)-2-({3-[(methoxy)methyl]piperidin-1-yl)methyl)cyclohexyl]amine hydrochloride



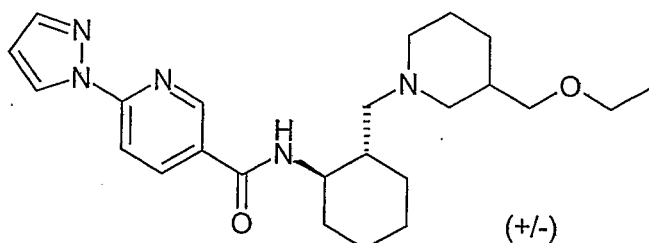
Following the procedure described in Example 89 (steps D), the HCl salt was obtained and used for the next step without further purification.

Step E: The preparation of *trans*-(+/-)-N-(2-({3-(methoxymethyl)piperidin-1-yl)methyl}cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide

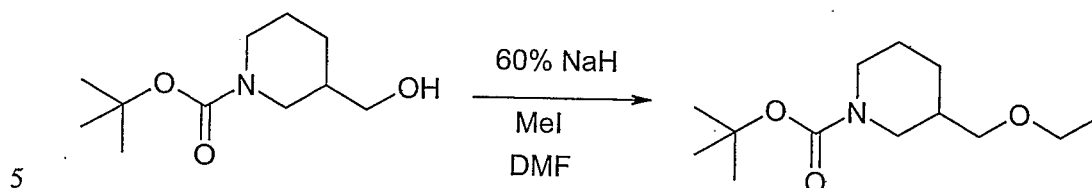


Following the procedure described in Example 2, the title compound was obtained as a white solid in a 51% yield over 3 steps (42 mg). MS (M+1): 412.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.82 - 0.98 (m, 1 H), 1.01 - 1.14 (m, 1 H), 1.30 - 1.43 (m, 3 H), 1.53 - 1.81 (m, 7 H), 1.83 - 1.90 (m, 1 H), 1.91 - 2.01 (m, 1 H), 2.06 - 2.18 (m, 2 H), 2.36 - 2.48 (m, 1 H), 2.71 - 3.00 (m, 2 H), 3.04 - 3.11 (m, 1 H), 3.11 - 3.15 (m, 1 H), 3.16 (s, 3 H), 3.21 - 3.26 (m, 1 H), 3.50 - 3.70 (m, 1 H), 6.54 (s, 1 H), 7.78 (s, 1 H), 8.00 (d, J=8.59 Hz, 1 H), 8.30 (d, J=8.40 Hz, 1 H), 8.63 (s, 1 H) 8.84 (s, 1 H).

Example 100. *trans*-(+/-)- *N*-(2-[[3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide



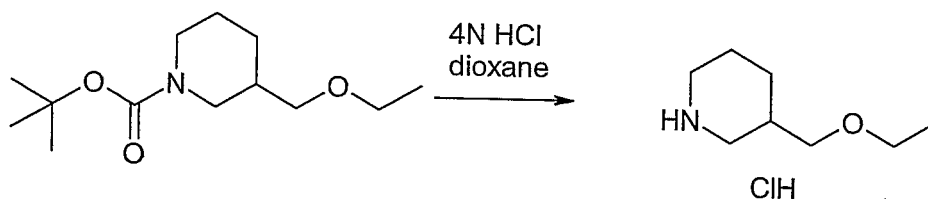
Step A: The preparation of *tert*-butyl 3-[(ethoxy)methyl]piperidine-1-carboxylate



Following the same procedure as Example 97 (step A): To a solution of *tert*-butyl 3-(hydroxymethyl)piperidine-1-carboxylate (1.72 g, 8.0 mmol) in dry DMF (30 mL) was added NaH (60% , 0.48 g, 12.0 mmol) at 0°C under nitrogen and the suspension was stirred at room temperature for 30 min. ethyl iodide (12.0 mmol) was added to the reaction mixture and stirred over night at room temperature. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (80 mL), washed with water (50 mL), dried over Na₂SO₄. Removal of solvent gave the crude product (1.86 g, 95%), which was used for the next step without further purification.

15

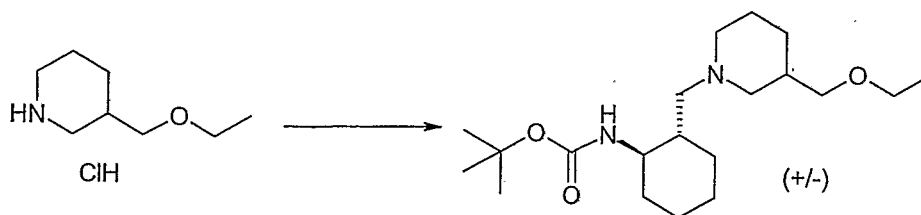
Step B: The preparation of 3-[(ethoxy)methyl]piperidine hydrochloride



Following the same procedure as Example 97 (step B), the crude *tert*-butyl 3-[(ethoxy)methyl]piperidine-1-carboxylate from step A was treated with 4N HCl in dioxane to give 3-[(ethoxy)methyl]piperidine hydrochloride as white powders (1.31 g, 96%).

20

Step C: The preparation of *trans*-(+/-)-*tert*-butyl [2-({3-[(ethoxy)methyl]piperidin-1-yl}methyl)cyclohexyl]carbamate

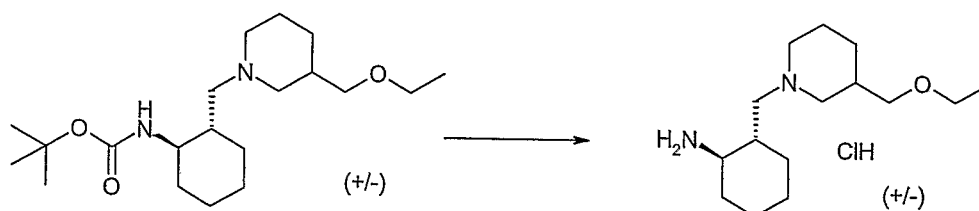


Following the procedure described in Example 89 (steps C), 3-[(ethoxy)methyl]piperidine hydrochloride (0.2 mmol) was added to a solution of *trans*-(+/-)-*tert*-butyl [2-formylcyclohexyl]carbamate (0.2 mmol) in dichloromethane (4 ml).

- 5 The reaction was stirred at room temperature for 30 minutes, and then sodium triacetoxyborohydride (85 mg, 0.4 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 12 hours, and then cooled to 0°C. After the same work-up, the yellow oil was used directly for the next step without further purification.

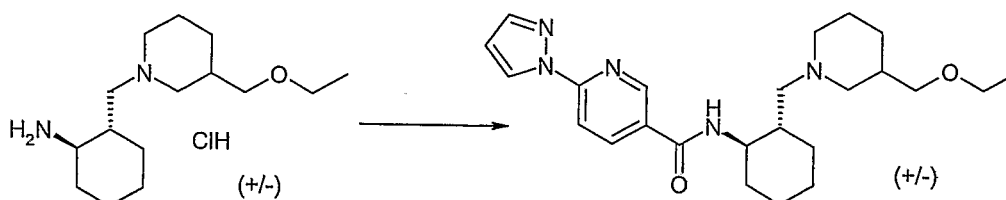
10

Step D: The preparation of *trans*-(+/-)- 2-({3-[(ethoxy)methyl]piperidin-1-yl)methyl}cyclohexyl)amine hydrochloride



- 15 Following the procedure described in Example 89 (steps D), the HCl salt was obtained and used for the next step without further purification.

Step E: The preparation of *trans*-(+/-)- *N*-(2-{[3-(ethoxymethyl)piperidin-1-yl]methyl}cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide

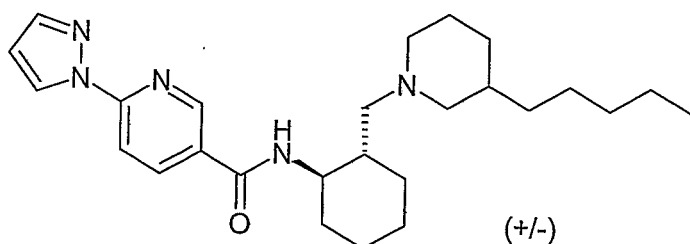


20

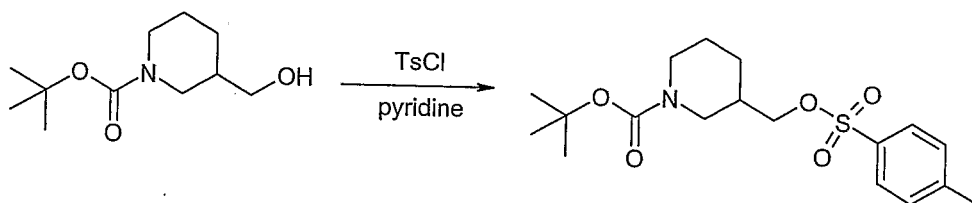
Following the procedure described in Example 2, the title compound was obtained as a white solid in a 45% yield over 3 steps (38 mg). MS ($M+1$): 426.2. ^1H NMR (400 MHz, METHANOL- D_4): δ ppm 0.85 - 0.96 (m, 1 H), 1.03 (t, $J=6.93$ Hz, 2 H), 1.06 -

1.11 (m, 1 H), 1.14 (t, $J=7.03$ Hz, 2 H), 1.25 - 1.45 (m, 4 H), 1.54 - 1.82 (m, 6 H), 1.83 - 1.99 (m, 3 H), 2.05 - 2.20 (m, 2 H), 2.38 - 2.49 (m, 1 H), 2.71 - 3.03 (m, 2 H), 3.07 - 3.24 (m, 2 H), 3.36 - 3.49 (m, 1 H), 3.54 - 3.67 (m, 1 H), 6.55 (d, $J=1.95$ Hz, 1 H), 7.78 (s, 1 H), 8.00 (d, $J=8.59$ Hz, 1 H), 8.30 (dd, $J=8.59, 1.37$ Hz, 1 H), 8.63 (s, 1 H), 8.85 (s, 1 H).

Example 101. *trans*-(+/-)- *N*-{2-[(3-pentylpiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-pyrazol-1-yl)nicotinamide

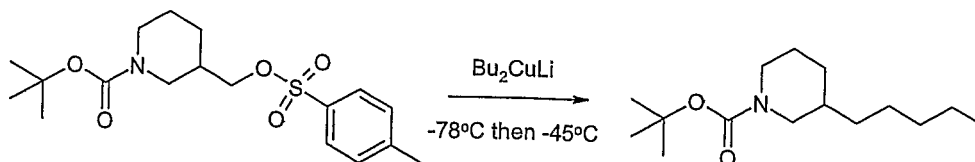


10 Step A: The preparation of *tert*-butyl 3-([(4-methylphenyl)sulfonyl]oxy)methyl)piperidine-1-carboxylate



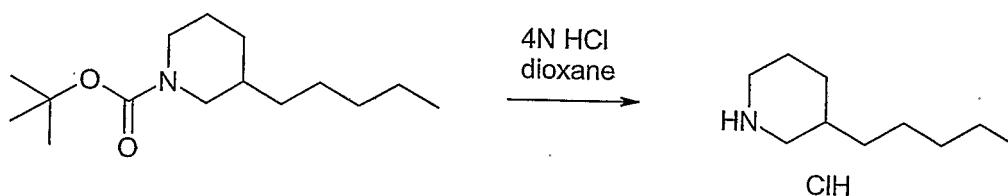
15 To a solution of *tert*-butyl 3-(hydroxymethyl)piperidine-1-carboxylate (2.15 g, 10.0 mmol) in dry pyridine (15 mL) was added Tosyl chloride (2.29 g, 12.0 mmol) at 0°C, the reaction mixture was stirred at 0°C for 5 h and then at room temperature for 48h. Ice water was added, extracted with DCM (50 mL), dried over Na₂SO₄. After removal of the solvent, the residue was purified with flash chromatography to give the title
20 product as white solids (3.24 g, 88%).

Step B: The preparation of *tert*-butyl 3-pentylpiperidine-1-carboxylate



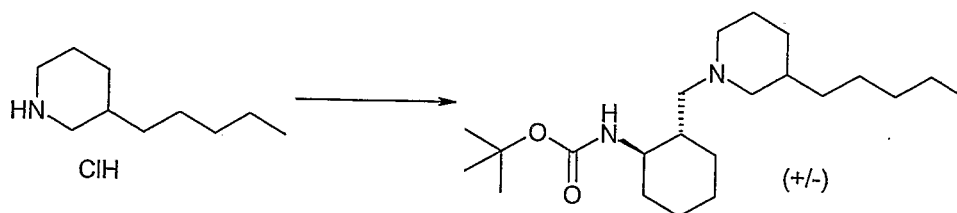
n-BuLi (1.6M in Hexanes, 18.8 mL, 30mmol) was added dropwise to a stirred slurry of CuI (2.83g, 15 mmol) in dry Et₂O (30 mL) at -78°C, then warmed up to -45°C and stirred for 40 min to give a homogeneous solution. The temperature was lowered to -78°C and to the mixture was slowly added a solution of *tert*-butyl 3-(((4-methylphenyl)sulfonyl]oxy)methyl)piperidine-1-carboxylate (from step A, 1.11g, 3.0 mmol) in Et₂O (3 mL), then then warmed up to -45°C and stirred for 20 min, poured into saturated aq. NH₄Cl (30 mL). NH₄OH (28%, 10 mL) was added, extracted with Et₂O (3 x 50 mL), the organic phase was separated, dried over Na₂SO₄, concentrated to give the crude product (570 mg, 74%), which was used without further purification.

Step C: The preparation of 3-pentylpiperidine hydrochloride



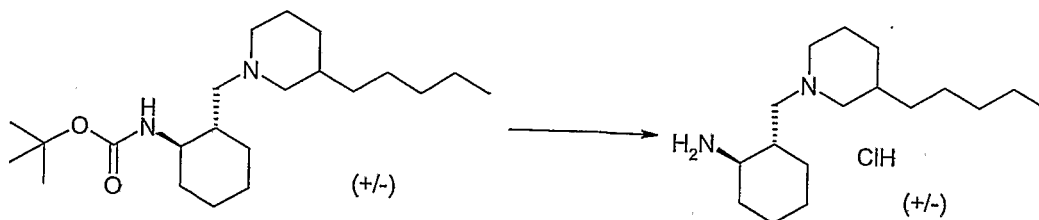
Following the same procedure as Example 97 (step B), the crude *tert*-butyl 3-pentylpiperidine-1-carboxylate from step B was treated with 4N HCl in dioxane to give 3-pentylpiperidine hydrochloride as white powders (423mg, 99%).

Step D: The preparation of *trans*-(+/-)- *tert*-butyl {2-[(3-pentylpiperidin-1-yl)methyl]cyclohexyl}carbamate



Following the procedure described in Example 89 (steps C), 3-pentylpiperidine hydrochloride (2.2 mmol) was added to a solution of *trans*-(+/-)-*tert*-butyl [2-formylcyclohexyl]carbamate (2.2 mmol) in dichloromethane (30 ml). The reaction was stirred at room temperature for 30 minutes, and then sodium triacetoxyborohydride (935 mg, 4.4 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 12 hours, and then cooled to 0°C. After the same work-up, the yellow oil (746mg, 92%) was used directly for the next step without further purification.

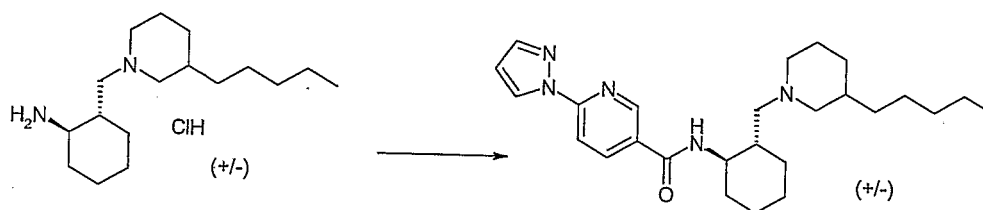
Step E: The preparation of *trans*-(+/-)- 2-[(3-pentylpiperidin-1-yl)methyl]cyclohexylamine hydrochloride



5

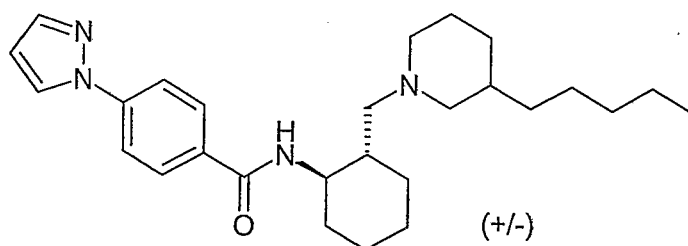
Following the procedure described in Example 89 (steps D), the crude *trans*-(+/-)-tert-butyl {2-[(3-pentylpiperidin-1-yl)methyl]cyclohexyl}carbamate from step D was treated with 4N HCl in dioxane, the HCl salt (2.0 mmol) was obtained and its stock solution in DMF (0.1M) was made to used for the next step.

10 Step F: The preparation of *trans*-(+/-)- *N*-{2-[(3-pentylpiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-pyrazol-1-yl)nicotinamide



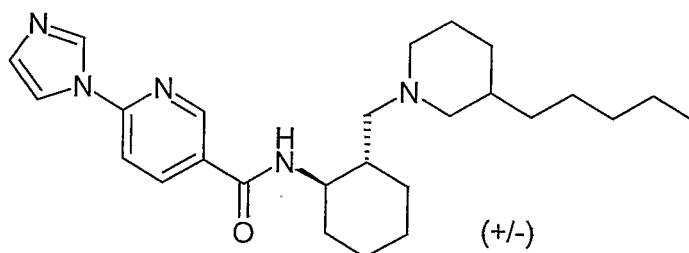
15 Following the procedure described in Example 2, the title compound was obtained as white solids (98 mg, 56%). MS (*M*+1): 438.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.72 (t, *J*=7.23 Hz, 2 H), 0.84 (t, *J*=6.93 Hz, 2 H), 0.92 - 1.15 (m, 6 H), 1.16 - 1.39 (m, 7 H), 1.49 - 1.57 (m, 2 H), 1.59 - 1.78 (m, 6 H), 1.82 - 2.00 (m, 1 H), 2.02 - 2.19 (m, 2 H), 2.31 - 2.45 (m, 1 H), 2.60 - 3.02 (m, 2 H), 3.45 - 3.70 (m, 1 H), 6.49 - 6.56 (m, 1 H), 7.76 (s, 1 H), 7.99 (d, *J*=8.59 Hz, 1 H), 8.29 (dd, *J*=8.59, 2.34 Hz, 1 H),
20 8.61 (d, *J*=2.15 Hz, 1 H), 8.84 (d, *J*=1.95 Hz, 1 H).

Example 102. *trans*-(+/-)- *N*-{2-[(3-pentylpiperidin-1-yl)methyl]cyclohexyl}-4-(1*H*-pyrazol-1-yl)benzamide



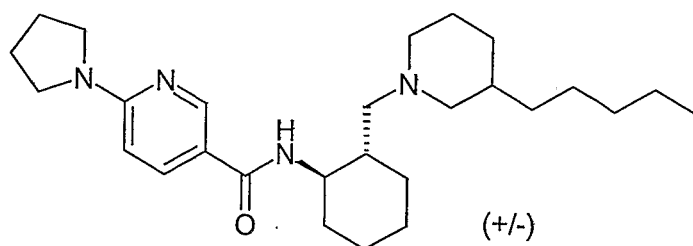
Following the procedure described in Example 2, the title compound was obtained as white solids (93 mg, 53%). MS (M+1): 437.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.68 - 0.90 (m, 4 H), 0.94 - 1.17 (m, 6 H), 1.19 - 1.40 (m, 7 H), 1.48 - 1.56 (m, 2 H), 1.61 - 1.80 (m, 6 H), 1.89 (m, 1 H), 2.02 - 2.21 (m, 2 H), 2.32 - 2.44 (m, 1 H), 2.61 - 3.02 (m, 2 H), 3.45 - 3.64 (m, 1 H), 6.53 (s, 1 H), 7.73 (s, 1 H), 7.80 - 7.88 (m, 2 H), 7.90 - 7.95 (m, 2 H), 8.31 (d, J=2.54 Hz, 1 H).

Example 103. *trans-(+/-)- 6-(1H-imidazol-1-yl)-N-{2-[(3-pentylpiperidin-1-yl)methyl]cyclohexyl}nicotinamide*



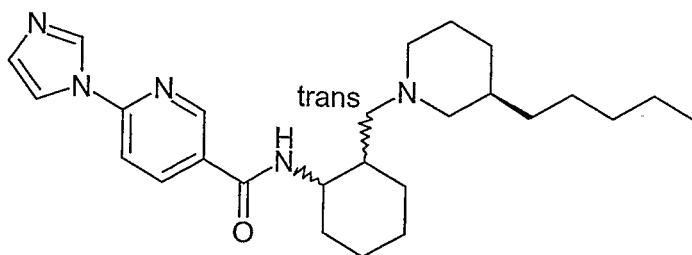
Following the procedure described in Example 2, the title compound was obtained as white solids (84 mg, 48%). MS (M+1): 438.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.71 - 0.90 (m, 4 H), 0.96 - 1.17 (m, 6 H), 1.20 - 1.41 (m, 7 H), 1.46 - 1.60 (m, 2 H), 1.60 - 1.81 (m, 6 H), 1.82 - 2.00 (m, 1 H), 2.03 - 2.19 (m, 2 H), 2.29 - 2.45 (m, 1 H), 2.62 - 3.02 (m, 2 H), 3.51 - 3.68 (m, 1 H), 7.16 (s, 1 H), 7.80 (dd, J=8.50, 4.78 Hz, 1 H), 7.95 (s, 1 H), 8.30 - 8.37 (m, 1 H), 8.60 (s, 1 H), 8.90 (d, J=1.95 Hz, 1 H).

Example 104. *trans-(+/-)- N-{2-[(3-pentylpiperidin-1-yl)methyl]cyclohexyl}-6-pyrrolidin-1-ylnicotinamide*

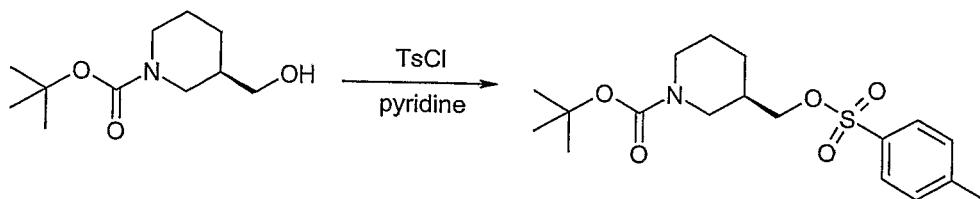


Following the procedure described in Example 2, the title compound was obtained as white solids (79 mg, 45%). MS (M+1): 441.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.76 - 0.90 (m, 4 H), 0.95 - 1.15 (m, 6 H), 1.16 - 1.35 (m, 8 H), 1.36 - 1.48 (m, 1 H), 1.51 - 1.65 (m, 3 H), 1.66 - 1.79 (m, 4 H), 1.81 - 1.96 (m, 1 H), 1.98 - 2.06 (m, 4 H), 2.06 - 2.16 (m, 1 H), 2.28 - 2.41 (m, 1 H), 2.64 - 3.01 (m, 2 H), 3.40-3.52 (m, 4 H), 3.49 - 3.60 (m, 1 H), 6.47 (d, J=8.79 Hz, 1 H), 7.89 (dd, J=8.89, 1.86 Hz, 1 H), 8.51 (d, J=1.95 Hz, 1 H).

10 **Example 105. trans-(±)-6-(1H-imidazol-1-yl)-N-(-2-[[[(3R)-3-pentylpiperidin-1-yl]methyl]cyclohexyl]nicotinamide**

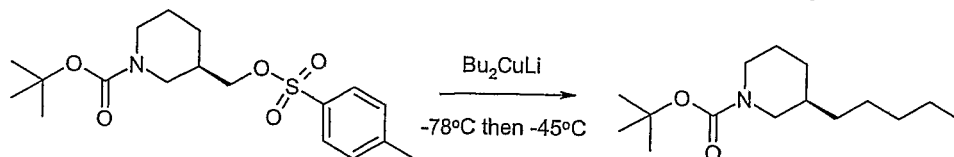


15 **Step A: The preparation of *tert*-butyl (3R)-3-([(4-methylphenyl)sulfonyl]oxy)methyl)piperidine-1-carboxylate**



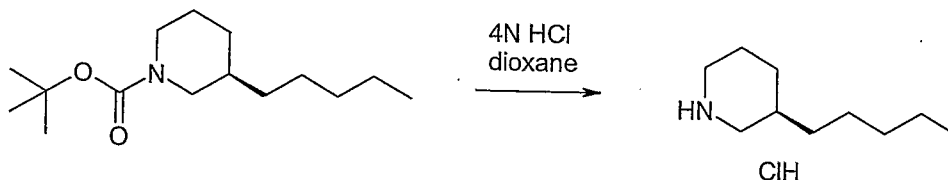
Following the same procedure as Example 101 (step A), the title product was obtained as white solids (820 mg, 96%).

Step B: The preparation of *tert*-butyl (3*R*)-3-pentylpiperidine-1-carboxylate



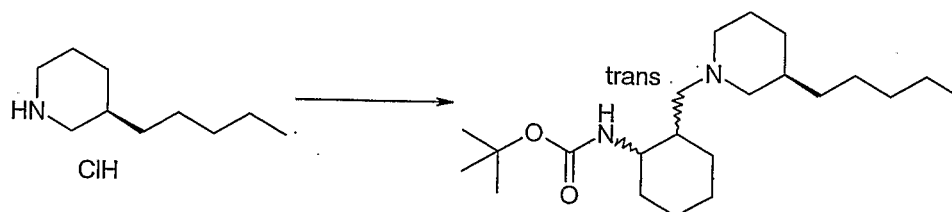
- 5 Following the same procedure as Example 101 (step B), the title product was obtained as a crude oil (460 mg, 81%).

Step C: The preparation of (3*R*)-3-pentylpiperidine hydrochloride



- 10 Following the same procedure as Example 97 (step B), the title product was obtained as a crude HCl salt (307 mg, 89%).

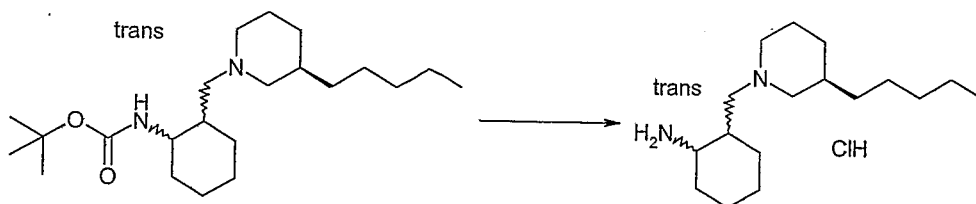
Step D: The preparation of *trans*-(±)-*tert*-butyl (2-[(3*R*)-3-pentylpiperidin-1-yl]methyl)cyclohexylcarbamate



- 15 Following the procedure described in Example 89 (steps C), yielded title compound as a crude oil, which was used for the next step without further purification.

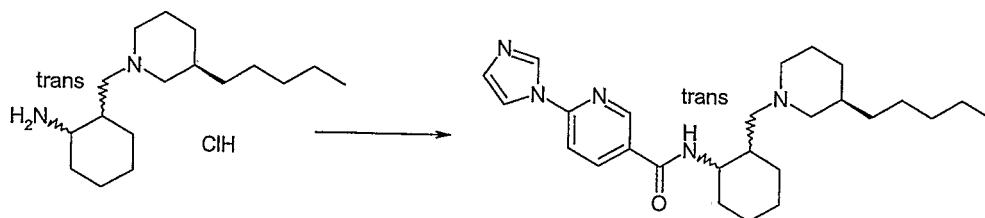
Step E: The preparation of *trans*-(±)(2-[(3*R*)-3-pentylpiperidin-1-yl]methyl)cyclohexylaminehydrochloride

- 20



Following the procedure described in Example 89 (steps D), the crude trans (±)-*tert*-butyl (2-((3*R*)-3-pentylpiperidin-1-yl)methyl)cyclohexylcarbamate from step D was treated with 4N HCl in dioxane, the HCl salt (~1.6 mmol) was obtained and its stock solution in DMF (0.1M) was made to used for the next step.

Step F: The preparation of trans-(±)-6-(1*H*-imidazol-1-yl)-*N*-(2-((3*R*)-3-pentylpiperidin-1-yl)methyl)cyclohexyl)nicotinamide



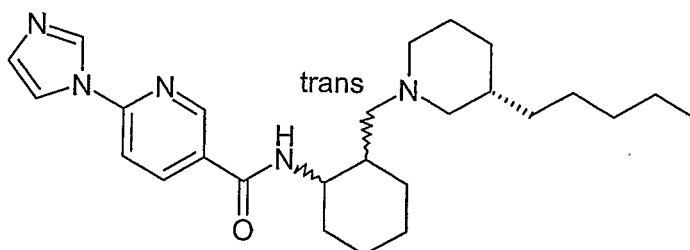
10

Following the procedure described in Example 2, the title compound was obtained as white solids (43 mg, 39% over 3 steps). MS ($M+1$): 438.3. ^1H NMR (400 MHz, METHANOL- D_4): δ ppm 0.69 - 0.90 (m, 4 H), 0.94 - 1.19 (m, 6 H), 1.22 - 1.40 (m, 6 H), 1.47 - 1.60 (m, 2 H), 1.60 - 1.83 (m, 6 H), 1.83 - 2.00 (m, 1 H), 2.04 - 2.20 (m, 2 H), 2.32 - 2.48 (m, 1 H), 2.63 - 2.87 (m, 1 H), 2.88 - 3.06 (m, 2 H), 3.51 - 3.69 (m, 1 H), 7.16 (s, 1 H), 7.81 (dd, $J=8.50, 4.98$ Hz, 1 H), 7.95 (s, 1 H), 8.29 - 8.38 (m, 1 H), 8.60 (s, 1 H), 8.88 - 8.94 (m, 1 H).

15

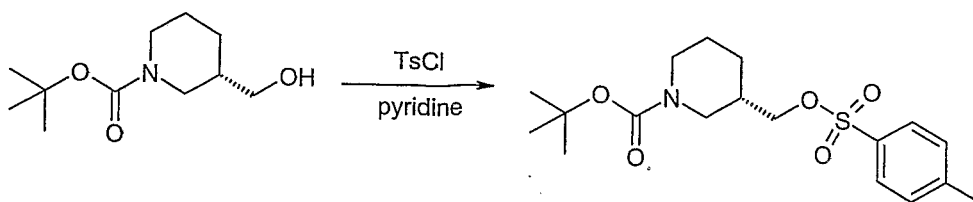
Example 106. Trans (±)-6-(1*H*-imidazol-1-yl)-*N*-(2-((3*S*)-3-pentylpiperidin-1-yl)methyl)cyclohexyl)nicotinamide

20



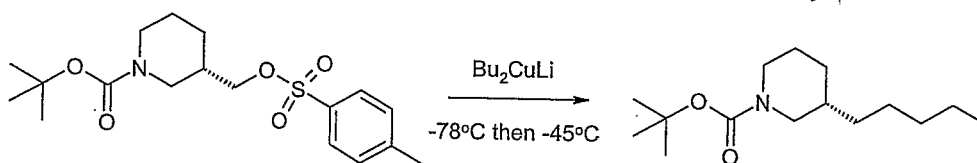
Step A: The preparation of *tert*-butyl (3*S*)-3-((4-methylphenyl)sulfonyl)oxy)methyl)piperidine-1-

carboxylate.



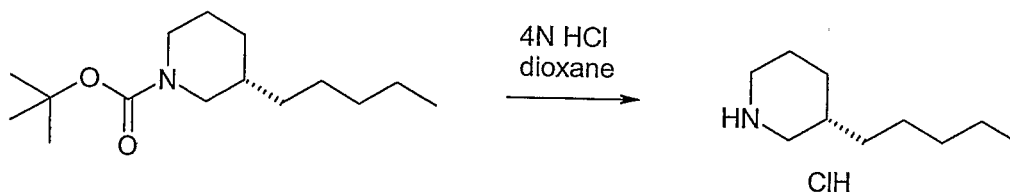
Following the same procedure as Example 101 (step A), the title product was
 5 obtained as white solids (818 mg, 96%).

Step B: The preparation of *tert*-butyl (3*S*)-3-pentylpiperidine-1-carboxylate



10 Following the same procedure as Example 101 (step B), the title product was
 obtained as a crude oil (510 mg, 90%).

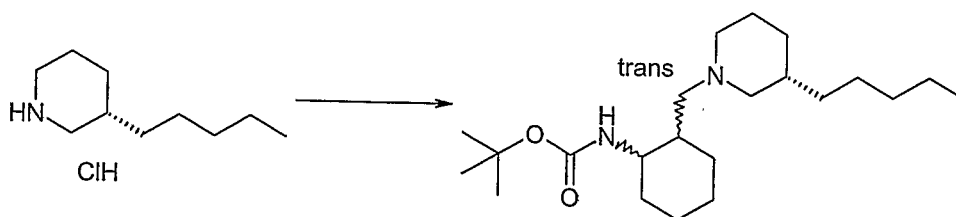
Step C: The preparation of (3*S*)-3-pentylpiperidine hydrochloride



15

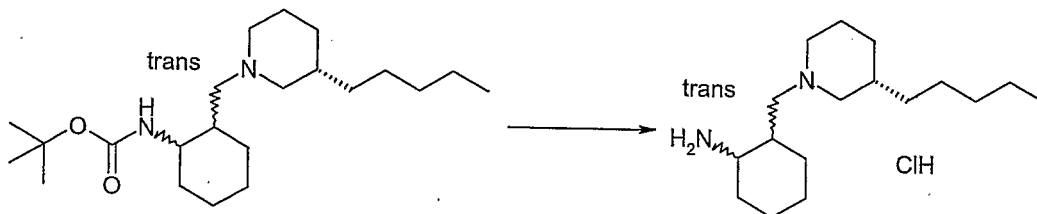
Following the same procedure as Example 97 (step B), the title product was obtained
 as a crude HCl salt (345 mg, 90%).

20 Step D: The preparation of *trans*-(±)-*tert*-butyl (2-((3*S*)-3-pentylpiperidin-1-yl)methyl)cyclohexyl)carbamate



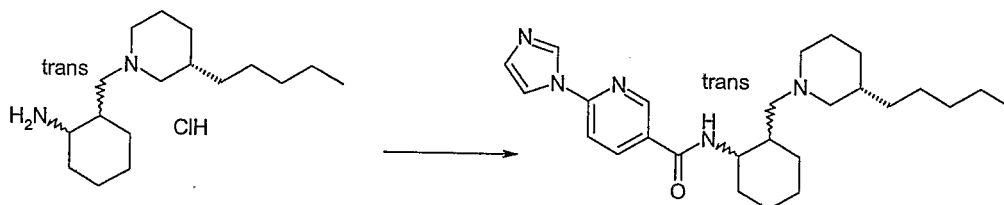
Following the procedure described in Example 89 (steps C), yielded title compound as a crude oil, which was used for the next step without further purification.

Step E: The preparation of *trans*-($\pm$)-2-[[*(3S)*-3-pentylpiperidin-1-yl]methyl]cyclohexylaminehydrochloride



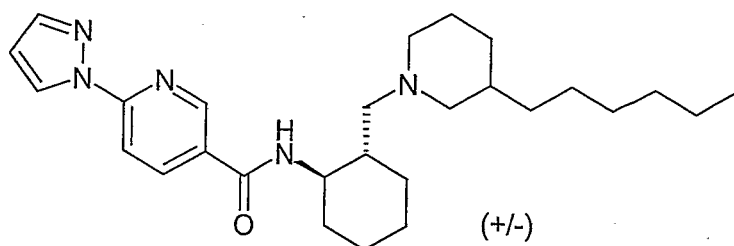
Following the procedure described in Example 89 (steps D), the crude *trans*-($\pm$)-*tert*-butyl 2-[[*(3R)*-3-pentylpiperidin-1-yl]methyl]cyclohexylcarbamate from step D was treated with 4N HCl in dioxane, the HCl salt (~1.8 mmol) was obtained and its stock solution in DMF (0.1M) was made to used for the next step.

Step F: The preparation of *trans*-($\pm$)-6-(1*H*-imidazol-1-yl)-*N*-(2-[[*(3S)*-3-pentylpiperidin-1-yl]methyl]cyclohexyl)nicotinamide

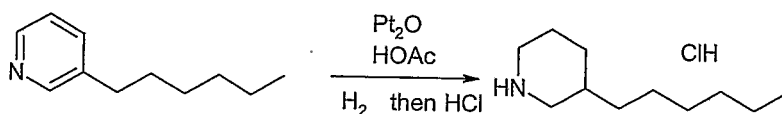


Following the procedure described in Example 2, the title compound was obtained as white solids (38 mg, 35% over 3 steps). MS (*M*+1): 438.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.68 - 0.89 (m, 4 H), 0.96 - 1.17 (m, 6 H), 1.20 - 1.43 (m, 6 H), 1.41 - 1.60 (m, 2 H), 1.61 - 1.82 (m, 6 H), 1.82 - 2.02 (m, 1 H), 2.04 - 2.21 (m, 2 H), 2.32 - 2.49 (m, 1 H), 2.59 - 2.87 (m, 1 H), 2.90 - 3.10 (m, Hz, 2 H), 3.52 - 3.69 (m, 1 H), 7.16 (s, 1 H), 7.81 (dd, *J*=8.50, 4.98 Hz, 1 H), 7.95 (s, 1 H), 8.29 - 8.37 (m, 1 H), 8.60 (s, 1 H), 8.83 - 8.95 (m, 1 H).

Example 107. *trans*-($\pm$)-*N*-{(2-[[*(3S)*-3-hexylpiperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide



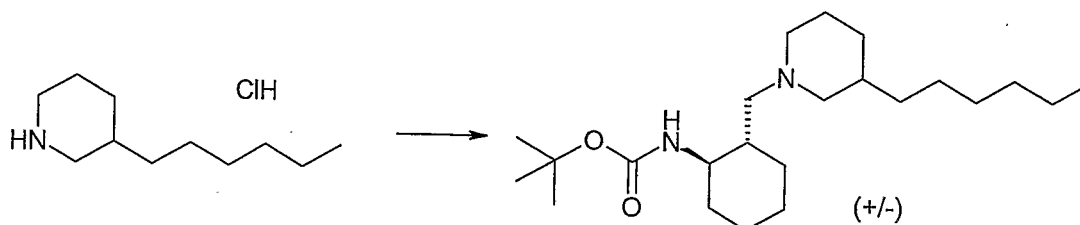
Step A: The preparation of 3-hexylpiperidine hydrochloride



- 5 To a solution of 3-hexylpyridine (2.28g, 14.0 mmol) in HOAc (40 mL) was added Pt₂O (0.15g) and the mixture was hydrogenated at room temperature (40 psi) for 5 h. After being filtered and concentrated, 40% aq. NaOH (20 mL) was added, extracted with EtOAc (3 x 30 mL), dried over Na₂SO₄, then treated with 4N HCl in dioxane, evaporated to give the HCl salt as white powders (2.54g, 88%).

10

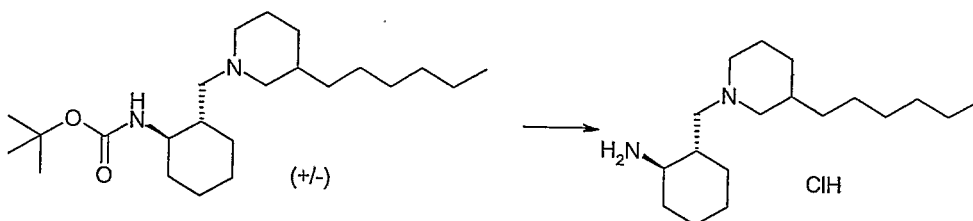
Step B: The preparation of *trans*-(+/-)- *tert*-butyl {2-[(3-hexylpiperidin-1-yl)methyl]cyclohexyl}carbamate



- 15 Following the procedure described in Example 89 (steps C), yielded title compound as a crude oil (635mg, 93%), which was used for the next step without further purification.

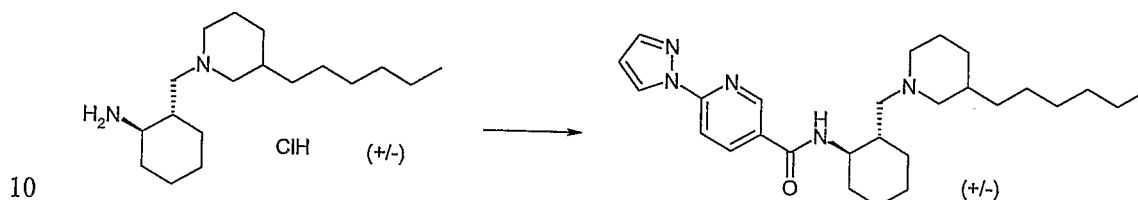
Step C: The preparation of *trans*-(+/-)- *tert*-butyl {2-[(3-hexylpiperidin-1-yl)methyl]cyclohexyl}carbamate

20



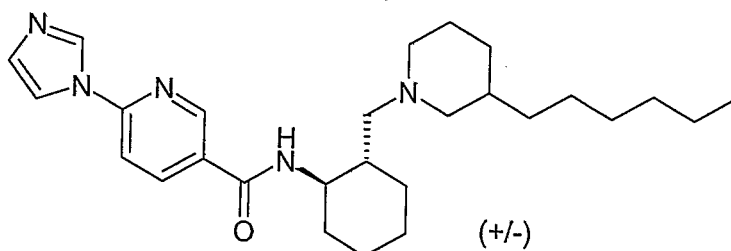
Following the procedure described in Example 89 (steps D), the crude *trans*-(+/-)-*tert*-butyl {2-[(3-hexylpiperidin-1-yl)methyl]cyclohexyl}carbamate from step B was treated with 4N HCl in dioxane, the HCl salt (505mg, 100%) was obtained and its stock solution in DMF (0.1M) was made to used for the next step.

Step D: The preparation of *trans*-(+/-)- *N*-{2-[(3-hexylpiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-pyrazol-1-yl)nicotinamide



Following the procedure described in Example 2, the title compound was obtained as white solids (108 mg, 60%). MS (M+1): 452.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.74 - 0.90 (m, 4 H), 0.97 - 1.19 (m, 8 H), 1.21 - 1.44 (m, 8 H), 1.50 - 1.81 (m, 6 H), 1.82 - 2.01 (m, 2 H), 2.05 - 2.22 (m, 2 H), 2.33 - 2.49 (m, 1 H), 2.63 - 3.01 (m, 2 H), 3.46 - 3.69 (m, 1 H), 6.53 - 6.56 (m, 1 H), 7.78 (s, 1 H), 8.01 (dd, J=8.59, 0.78 Hz, 1 H), 8.26 - 8.33 (m, 1 H), 8.63 (d, J=2.54 Hz, 1 H), 8.82 - 8.87 (m, 1 H).

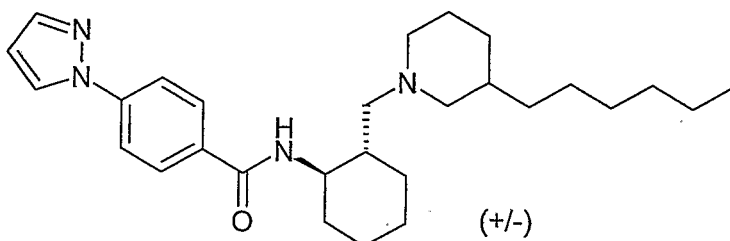
Example 108. *trans*-(+/-)- *N*-{2-[(3-hexylpiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-imidazol-1-yl)nicotinamide



Following the procedure described in Example 2, the title compound was obtained as white solids (104 mg, 57%). MS (M+1): 452.3. ¹H NMR (400 MHz, METHANOL-D₄):

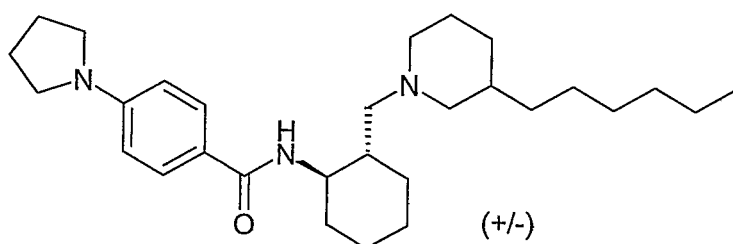
δ ppm 0.73 - 0.88 (m, 4 H), 0.95 - 1.17 (m, 7 H), 1.19 - 1.29 (m, 5 H), 1.31 - 1.41 (m, 3 H), 1.47 - 1.58 (m, 2 H), 1.61 - 1.80 (m, 6 H), 1.81 - 2.00 (m, 1 H), 2.03 - 2.21 (m, 2 H), 2.32 - 2.45 (m, 1 H), 2.61 - 3.03 (m, 2 H), 3.51 - 3.68 (m, 1 H), 7.16 (s, 1 H), 7.80 (dd, J=8.50, 4.98 Hz, 1 H), 7.95 (s, 1 H), 8.33 (d, J=8.40 Hz, 1 H), 8.60 (s, 1 H), 8.90 (s, 1 H).

Example 109. *trans*-(+/-)- *N*-{2-[(3-hexylpiperidin-1-yl)methyl]cyclohexyl}-4-(1*H*-pyrazol-1-yl)benzamide



Following the procedure described in Example 2, the title compound was obtained as white solids (113 mg, 63%). MS (M+1): 451.2. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.72 - 0.91 (m, 4 H), 0.95 - 1.18 (m, 7 H), 1.19 - 1.41 (m, 8 H), 1.49-1.56 (m, 2 H), 1.61 - 1.80 (m, 6 H), 1.81 - 1.98 (m, 1 H), 2.02 - 2.24 (m, 2 H), 2.31 - 2.43 (m, 1 H), 2.60 - 3.01 (m, 2 H), 3.47 - 3.63 (m, 1 H), 6.50 - 6.56 (m, 1 H), 7.73 (s, 1 H), 7.82 - 7.89 (m, 2 H), 7.90 - 7.94 (m, 2 H), 8.31 (d, J=2.15 Hz, 1 H).

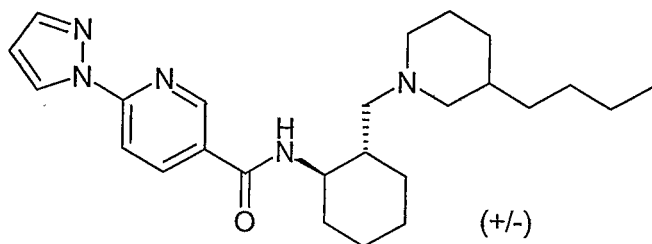
Example 110. *trans*-(+/-)- *N*-{2-[(3-hexylpiperidin-1-yl)methyl]cyclohexyl}-4-pyrrolidin-1-ylbenzamide



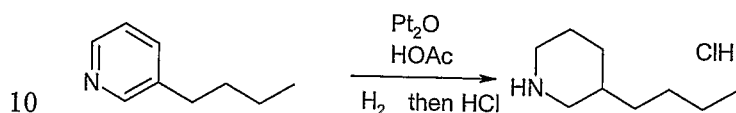
Following the procedure described in Example 2, the title compound was obtained as white solids (99 mg, 54%). MS (M+1): 455.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.74 - 0.92 (m, 4 H), 0.99 - 1.16 (m, 6 H), 1.19 - 1.34 (m, 8 H), 1.34 - 1.49 (m, 2 H), 1.51 - 1.67 (m, 4 H), 1.68 - 1.80 (m, 4 H), 1.81 - 1.97 (m, 1 H), 1.99 - 2.06 (m, 4 H), 2.08 - 2.17 (m, 1 H), 2.26 - 2.44 (m, 1 H), 2.63 - 3.00 (m, 2 H), 3.42 - 3.62 (m, 5

H), 6.49 (d, J=8.98 Hz, 1 H), 7.90 (dd, J=8.98, 2.34 Hz, 1 H), 8.51 (d, J=2.34 Hz, 1 H).

5 **Example 111. *trans*-(+/-)- *N*-{(2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-pyrazol-1-yl)nicotinamide**

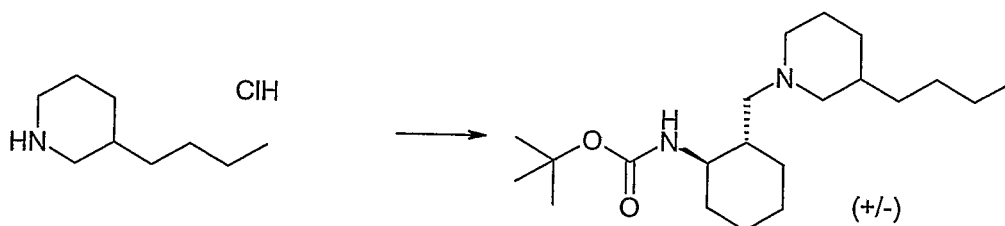


Step A: The preparation of 3-butylpiperidine hydrochloride



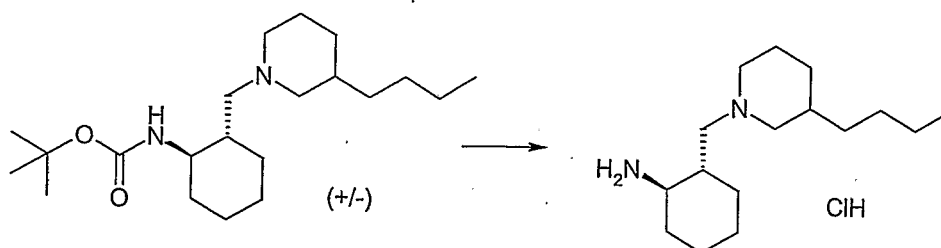
To a solution of 3-butylpyridine (1.35g, 10.0 mmol) in HOAc (30 mL) was added Pt₂O (0.12g) and the mixture was hydrogenated at room temperature (40 psi) for 5 h. After being filtered and concentrated, 40% aq. NaOH (20 mL) was added, extracted with EtOAc (3 x 30 mL), dried over Na₂SO₄, then treated with 4N HCl in dioxane, evaporated to give the HCl salt as white powders (1.68g, 94%).

Step B: The preparation of *trans*-(+/-)- *tert*-butyl {2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}carbamate



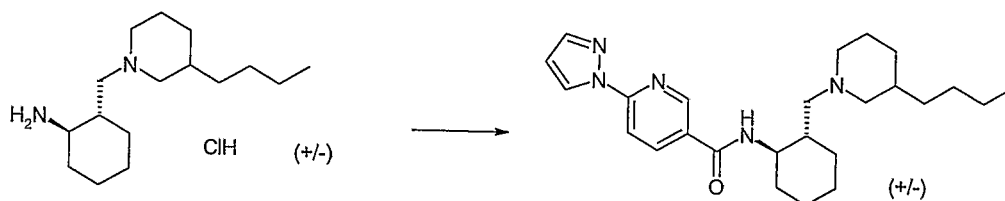
Following the procedure described in Example 89 (steps C), yielded title compound as a crude oil (597mg, 94%), which was used for the next step without further purification.

Step C: The preparation of *trans*-(+/-)- *tert*-butyl {2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}carbamate



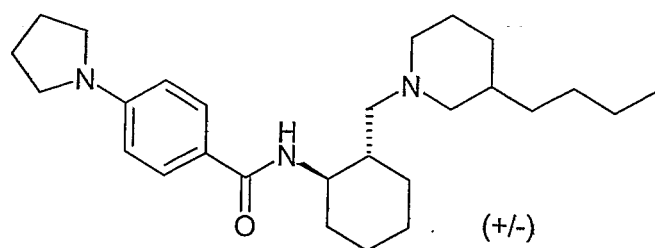
Following the procedure described in Example 89 (steps D), the crude *trans*-(+/-)- *tert*-butyl {2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}carbamate from step B was treated with 4N HCl in dioxane, the HCl salt (490mg, 100%) was obtained and its stock solution in DMF (0.1M) was made to used for the next step.

Step D: The preparation of *trans*-(+/-)- *N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-pyrazol-1-yl)nicotinamide



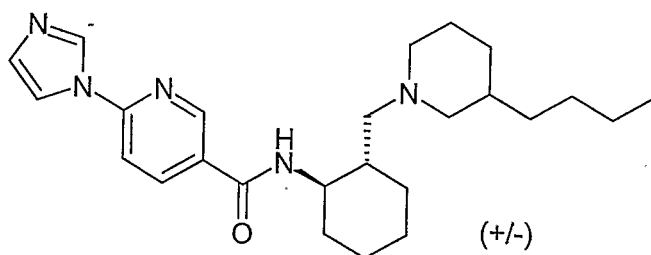
Following the procedure described in Example 2, the title compound was obtained as white solids (73 mg, 49%). MS (M+1): 424.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.64 - 0.89 (m, 4 H), 0.97 - 1.16 (m, 5 H), 1.24 - 1.40 (m, 6 H), 1.47 - 1.60 (m, 2 H), 1.62 - 1.80 (m, 6 H), 1.82 - 2.00 (m, 1 H), 2.03 - 2.23 (m, 2 H), 2.31 - 2.45 (m, 1 H), 2.64 - 3.05 (m, 2 H), 3.49 - 3.69 (m, 1 H), 6.51 - 6.59 (m, 1 H), 7.78 (s, 1 H), 8.00 (dd, J=8.59, 1.95 Hz, 1 H), 8.30 (dd, J=8.59, 2.15 Hz, 1 H), 8.63 (d, J=2.73 Hz, 1 H), 8.85 (d, J=2.15 Hz, 1 H).

Example 112. *trans*-(+/-)- *N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-4-pyrrolidin-1-ylbenzamide



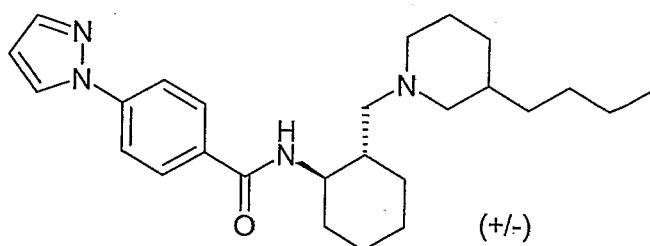
Following the procedure described in Example 2, the title compound was obtained as white solids (86 mg, 58%). MS (M+1): 427.2. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.72 - 0.89 (m, 4 H), 0.96 - 1.20 (m, 6 H), 1.22 - 1.36 (m, 6 H), 1.48 - 1.66 (m, 3 H), 1.67 - 1.80 (m, 4 H), 1.82 - 1.98 (m, 1 H), 2.00 - 2.07 (m, 5 H), 2.08 - 2.17 (m, 1 H), 2.30 - 2.44 (m, 1 H), 2.59 - 3.00 (m, 2 H), 3.38 - 3.62 (m, 5 H), 6.49 (d, J=8.98 Hz, 1 H), 7.89 (dd, J=8.98, 2.15 Hz, 1 H), 8.51 (s, 1 H).

Example 113. *trans*-(+/-)-N-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-6-(1H-imidazol-1-yl)nicotinamide



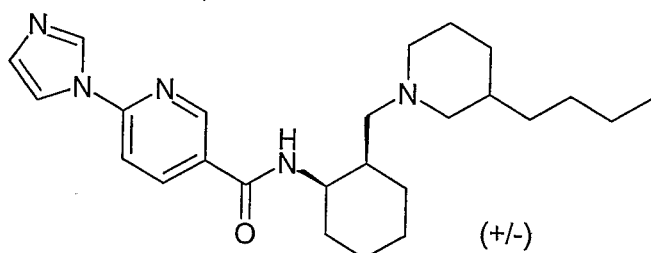
Following the procedure described in Example 2, the title compound was obtained as white solids (69 mg, 47%). MS (M+1): 424.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.65 - 0.92 (m, 4 H), 0.96 - 1.20 (m, 6 H), 1.21 - 1.40 (m, 6 H), 1.41 - 1.60 (m, 3 H), 1.61 - 1.81 (m, 6 H), 1.83 - 2.00 (m, 1 H), 2.04 - 2.21 (m, 2 H), 2.33 - 2.43 (m, 1 H), 2.58 - 3.04 (m, 2 H), 3.51 - 3.69 (m, 1 H), 7.16 (s, 1 H), 7.81 (dd, J=8.50, 5.37 Hz, 1 H), 7.95 (s, 1 H), 8.30 - 8.38 (m, 1 H), 8.60 (s, 1 H), 8.87 - 8.93 (m, 1 H).

Example 114. *trans*-(+/-)-N-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-4-(1H-pyrazol-1-yl)benzamide

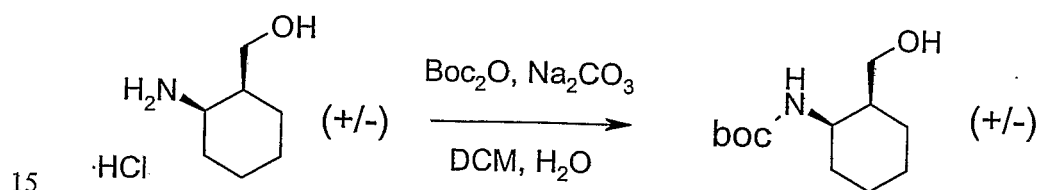


Following the procedure described in Example 2, the title compound was obtained as white solids (76 mg, 51%). MS (M+1): 423.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.66 - 0.91 (m, 4 H), 0.97 - 1.10 (m, 4 H), 1.19 - 1.38 (m, 6 H), 1.41 - 1.56 (m, 3 H), 1.61 - 1.81 (m, 6 H), 1.80 - 1.98 (m, 1 H), 2.03 - 2.22 (m, 2 H), 2.32 - 2.43 (m, 1 H), 2.58 - 3.05 (m, 2 H), 3.46 - 3.70 (m, 1 H), 6.53 (s, 1 H), 7.73 (s, 1 H), 7.82 - 7.89 (m, 2 H), 7.89 - 7.95 (m, 2 H), 8.31 (d, J=2.34 Hz, 1 H).

Example 115. *cis*-(+/-)- *N*-[2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl]-6-(1*H*-imidazol-1-yl)nicotinamide

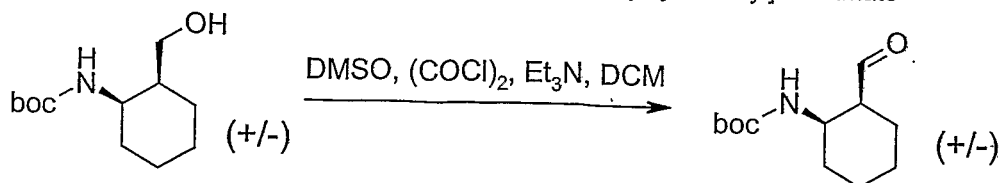


Step A. The preparation of *cis*-(+/-)-*tert*-butyl [2-(hydroxymethyl)cyclohexyl]carbamate



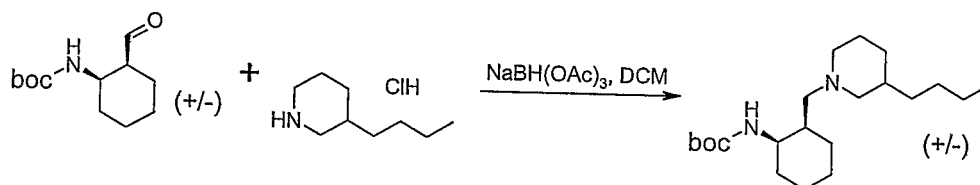
Following the same procedure as Example 89 (step A), the title compound was obtained as white solids (386 mg, 96%) and was used directly for the next step without further purification.

Step B. The preparation of *cis*-(+/-)- *tert*-butyl [2-formylcyclohexyl]carbamate



Following the same procedure as Example 89 (step B), the title compound was obtained as white solids (365 mg, 99%) and was used directly for the next step without further purification.

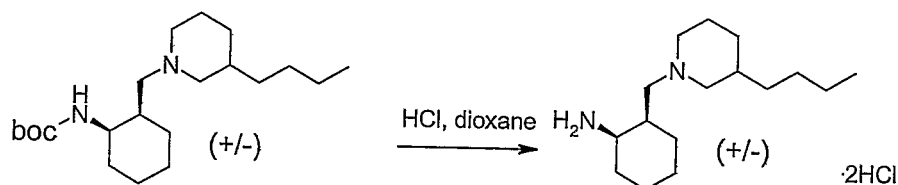
Step C. The preparation of *cis*-(+/-)- *tert*-butyl {2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}carbamate



Following the same procedure as Example 89 (step C), the title compound was obtained as colorless oils (543 mg, 96%) and was used directly for the next step without further purification.

The product was used directly for the next step without further purification.

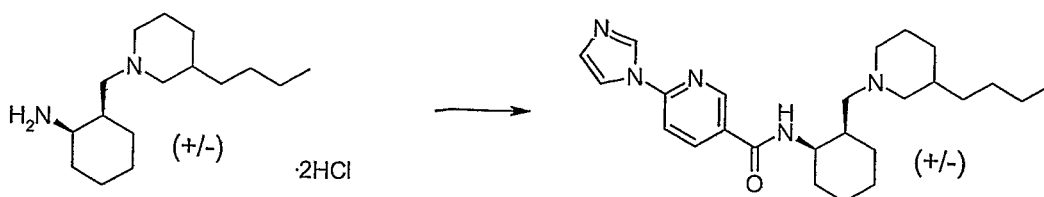
Step D. The preparation of *trans*-(+/-)- {2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}amine hydrochloride



Following the same procedure as Example 89 (step D), the title compound was obtained as HCl salt (389 mg, 79%) and was used directly for the next step without further purification.

The product was used directly for the next step without further purification.

Step E. The preparation of *cis*-(+/-)- *N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-imidazol-1-yl)nicotinamide

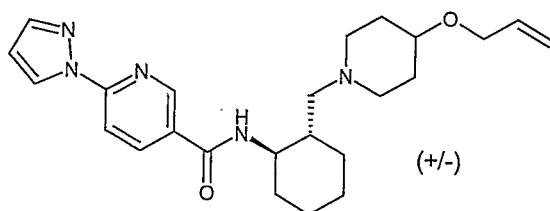


Following the same procedure as Example 2, yielded the title compound 92 mg

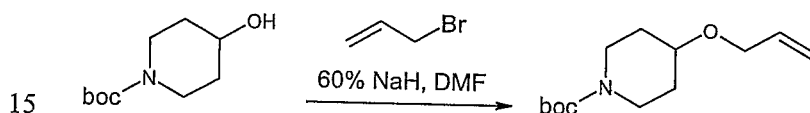
(54%). MS (M+1): 424.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.71 - 0.94

- 5 (m, 4 H), 0.99 - 1.35 (m, 8 H), 1.41 - 1.65 (m, 6 H), 1.69 - 1.94 (m, 8 H), 2.21 - 2.38 (m, 1 H), 2.79 - 3.12 (m, 2 H), 4.04 - 4.31 (m, 1 H), 7.17 (s, 1 H), 7.81 (dd, *J*=8.59, 2.54 Hz, 1 H), 7.95 (d, *J*=1.17 Hz, 1 H), 8.32 (d, *J*=8.20 Hz, 1 H), 8.60 (s, 1 H) 8.88 (s, 1 H).

- 10 **Example 116. *trans*-(+/-)-*N*-(2-[[4-(Allyloxy)piperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide**



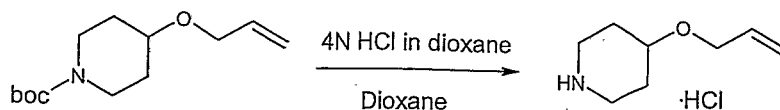
Step A: The preparation of *tert*-butyl 4-(allyloxy)piperidin-1-carboxylate



- To a solution of *tert*-butyl 4-(hydroxy)piperidin-1-carboxylate (1.0 g, 5.0 mmol) in dry DMF (20 mL) was added NaH (60%, 0.38 g, 10 mmol) at 0°C under nitrogen and the suspension was stirred at room temperature for 30 min. Allyl bromide (0.52 mL, 6.0 mmol) was added to the reaction mixture and stirred over night at room temperature. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (50 mL), washed with water (30 mL), dried over Na₂SO₄. Removal of solvent gave the crude product, which was used for the next step without further purification.

25

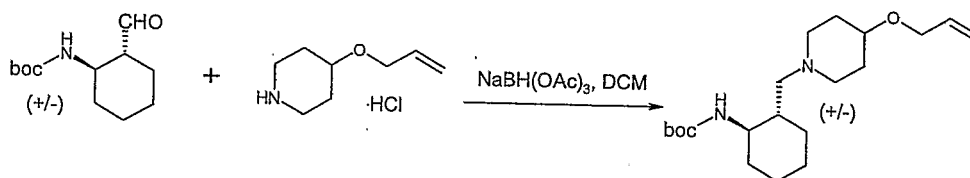
Step B: The preparation of 4-(allyloxy)piperidine hydrochloride



Following the same procedure as Example 97 Step B, the title compound was obtained as a white solid in a 61% yield over 2 steps (545mg).

5

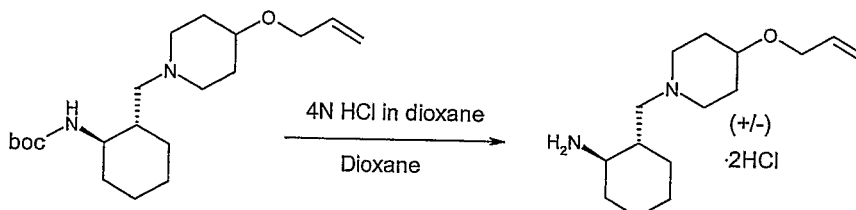
Step C: The preparation of *trans*-(+/-)-*tert*-butyl (2-([4-(allyloxy)piperidin-1-yl]methyl)cyclohexyl)carbamate



- 10 The title compound was prepared following the same procedure as Example 89 Step C. The product was used directly for the next step without further purification.

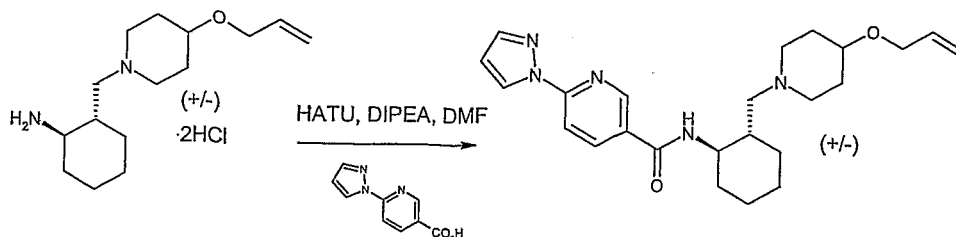
Step D: The preparation of *trans*-(+/-)-(2-([4-(allyloxy)piperidin-1-yl]methyl)cyclohexyl)amine hydrochloride

15



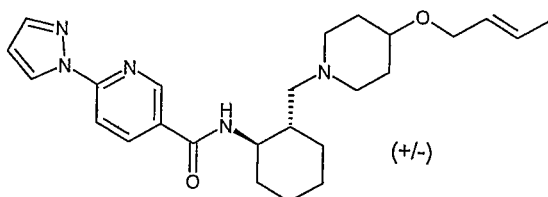
The title compound was prepared following the same procedure as Example 89 Step D. The product was used directly for the next step without further purification.

- 20 Step E: The preparation of *trans*-(+/-)-*N*-(2-([4-(Allyloxy)piperidin-1-yl]methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide

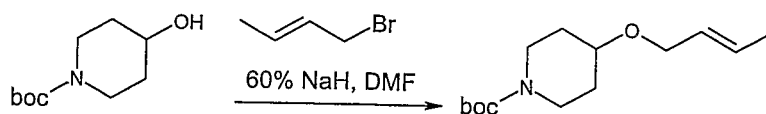


Following the procedure described in Example 2, the HCl salt of the title compound was obtained as a yellow solid in a 34% yield over 3 steps (75 mg). MS (M+1): 424.0. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.23 - 1.58 (m, 4 H), 1.69 - 2.25 (m, 9 H), 2.89 - 3.14 (m, 2 H), 3.18 - 3.30 (m, 2 H), 3.42 - 3.83 (m, 4 H), 3.95 - 4.04 (m, 2 H), 5.07 - 5.15 (m, 1 H), 5.21 - 5.28 (m, 1 H), 5.82 - 5.93 (m, 1 H), 6.56 (s, 1 H), 7.79 (s, 1 H), 8.02 (d, J=8.59 Hz, 1 H), 8.37 (dd, J=8.59, 2.15 Hz, 1 H), 8.64 (d, J=2.15 Hz, 1 H), 8.91 (s, 1 H). Anal. Calcd for C₂₄H₃₃N₅O₂ · 2 HCl · 0.55 C₄H₈O₂ C, 57.75; H, 7.29; N, 12.85. Found: C, 58.07; H, 7.63; N, 13.10.

Example 117. *trans*-(+/-)-N-[2-((4-[(*2E*)-but-2-en-1-yloxy]piperidin-1-yl)methyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide

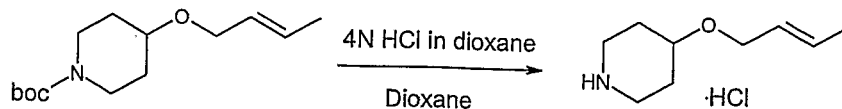


Step A: The preparation of *tert*-butyl 4-[(*2E*)-but-2-en-1-yloxy]piperidin-1-carboxylate



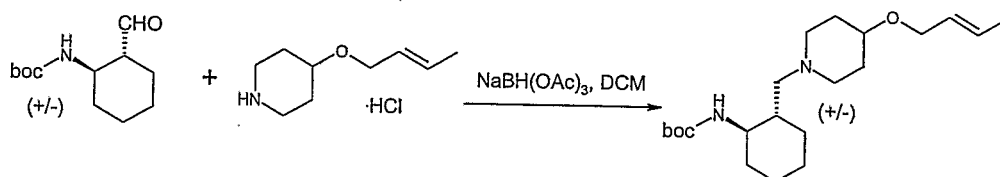
The title compound was prepared following the same procedure as Example 115 (Step A). The product was used directly for the next step without further purification.

Step B: The preparation of 4-[(*2E*)-but-2-en-1-yloxy]piperidine hydrochloride



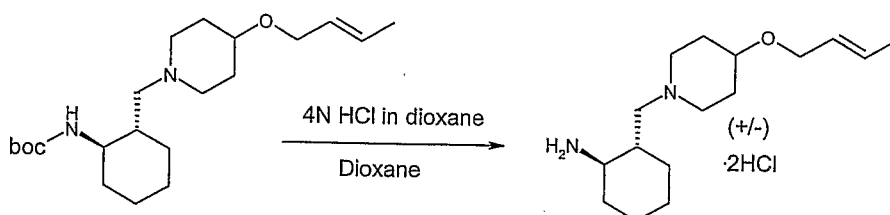
Following the same procedure as 97 Step B, the hydrochloride salt of the title compound was obtained as a white solid in a 76% yield over 2 steps (725mg).

Step C: The preparation of *trans*-(+/-)-*tert*-butyl (2-[4-[(2*E*)-but-2-en-1-yloxy]piperidin-1-yl]methyl)cyclohexyl)carbamate



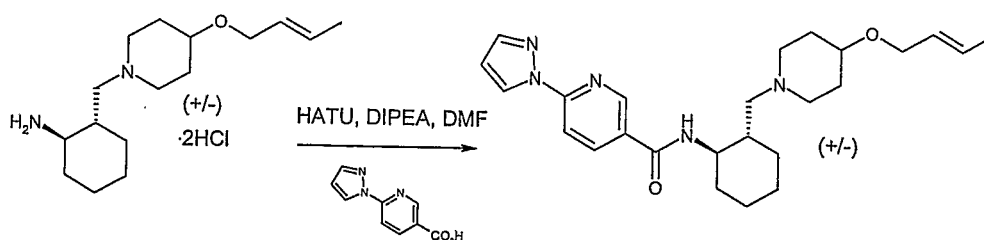
The title compound was prepared following the same procedure as Example 89 Step C. The product was used directly for the next step without further purification.

Step D: The preparation of *trans*-(+/-)-(2-[4-[(2*E*)-but-2-en-1-yloxy]piperidin-1-yl]methyl)cyclohexyl)amine hydrochloride



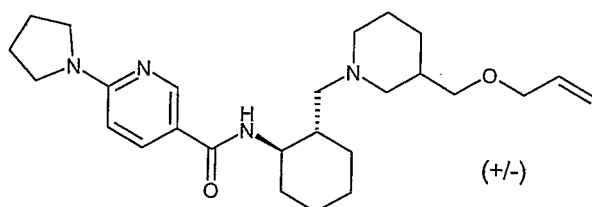
The title compound was prepared following the same procedure as Example 89 Step D. The product was used directly for the next step without further purification. MS (M+1): 267.0.

Step E: The preparation of *trans*-(+/-)-*N*-(2-[4-[(2*E*)-but-2-en-1-yloxy]piperidin-1-yl]methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide



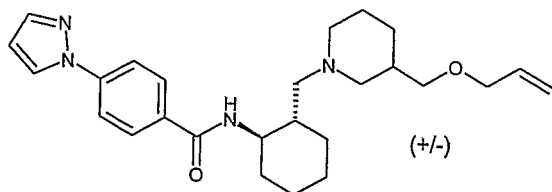
Following the procedure described in Example 2, the HCl salt of the title compound was obtained as a white solid in a 40% yield over 3 steps (75 mg). MS (M+1): 438.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.22 - 2.19 (m, 16 H), 2.97 - 3.12 (m, 2 H), 3.17 - 3.26 (m, J=13.28, 13.28, 1.95 Hz, 1 H), 3.42 - 3.83 (m, 5 H), 3.88 - 3.96 (m, 2 H), 5.47 - 5.58 (m, 1 H), 5.64 - 5.74 (m, 1 H), 6.56 (dd, J=2.54, 1.76 Hz, 1 H), 7.79 (d, J=1.37 Hz, 1 H), 8.02 (d, J=8.59 Hz, 1 H), 8.34 - 8.39 (m, 1 H), 8.64 (d, J=2.34 Hz, 1 H), 8.90 (s, 1 H). Anal. Calcd for C₂₅H₃₅N₅O₂ · 2.55 HCl · 0.7 C₄H₈O₂ C, 56.38; H, 7.34; N, 11.83. Found: C, 56.18; H, 7.70; N, 12.18.

10 **Example 118. *trans*-(+/-)-N-[2-({3-[(Allyloxy)methyl]piperidin-1-yl)methyl}cyclohexyl]-6-pyrrolidin-1-yl]nicotinamide**



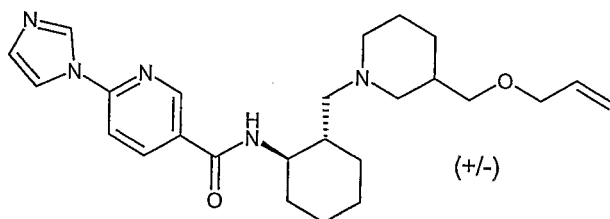
Following the procedure described in Example 2, the HCl salt of the title compound was obtained as a white solid in a 40% yield over 3 steps (101 mg). MS (M+1): 441.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.20 - 1.55 (m, 5 H), 1.74 - 1.85 (m, 3 H), 1.91 - 2.00 (m, 2 H), 2.03 - 2.24 (m, 6 H), 2.68 - 2.88 (m, 1 H), 2.92 - 3.00 (m, 2 H), 3.19 - 3.27 (m, 1 H), 3.42 (dd, J=9.28, 4.59 Hz, 1 H), 3.47 - 3.70 (m, 8 H), 3.75 (td, J=10.40, 2.44 Hz, 1 H), 3.90 - 3.95 (m, 2 H), 5.09 - 5.15 (m, 1 H), 5.20 (dq, J=5.49, 1.68 Hz, 1 H), 5.24 (dq, J=5.42, 1.71 Hz, 1 H), 5.79 - 5.91 (m, 1 H), 7.14 (d, J=9.57 Hz, 1 H), 8.40 - 8.45 (m, 1 H), 8.52 (dd, J=6.45, 1.56 Hz, 1 H).

25 **Example 119. *trans*-(+/-)-N-[2-({3-[(Allyloxy)methyl]piperidin-1-yl)methyl}cyclohexyl]-4-(1H-pyrazol-1-yl)benzamide**



Following the procedure described in Example 2, the free base of the title compound was obtained as a white solid in a 61% yield over 3 steps (80 mg). MS (M+1): 437.3. ¹H NMR (400 MHz, CHLOROFORM-D): δ ppm 0.83 - 1.02 (m, 1 H), 1.02 - 1.18 (m, 2 H), 1.23 - 1.52 (m, 3 H), 1.56 - 1.84 (m, 8 H), 1.86 - 1.99 (m, 1 H), 2.07 (dd, J=12.60, 6.15 Hz, 1 H), 2.37 - 2.48 (m, 1 H), 2.56 - 2.74 (m, 2 H), 3.03 - 3.27 (m, 2 H), 3.30 - 3.49 (m, 2 H), 3.69 (dt, J=5.47, 1.37 Hz, 1 H), 3.98 (dt, J=5.66, 1.37 Hz, 1 H), 5.00 - 5.11 (m, 1 H), 5.22 (dq, J=10.35, 1.51, 1.27 Hz, one diast 1 H), 5.30 (dq, J=17.28, 1.59 Hz, one diast 1 H), 5.71 (ddt, J=17.19, 10.35, 5.66 Hz, one diast 1 H), 5.94 (ddt, J=17.38, 10.55, 5.66 Hz, one diast 1 H), 6.46 - 6.55 (m, 1 H), 7.73 - 7.78 (m, 3 H), 7.95 (dd, J=8.69, 3.42 Hz, 2 H), 7.99 (dd, J=5.96, 2.05 Hz, 1 H), 8.93 (s, one diast 1 H), 9.03 (s, one diast 1 H).

Example 120. *trans*-(+/-)-N-[2-({3-[(Allyloxy)methyl]piperidin-1-yl)methyl}cyclohexyl)-6-(1*H*-imidazol-1-yl)nicotinamide

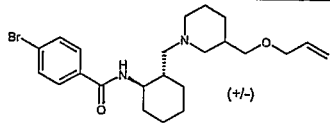
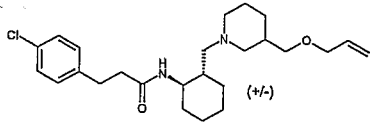


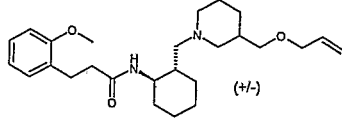
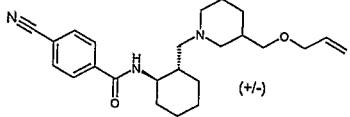
15

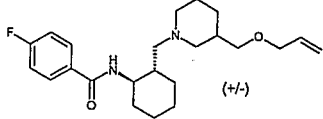
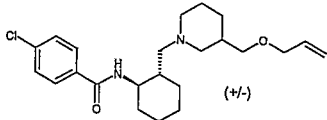
Following the procedure described in Example 2, the free base of the title compound was obtained as a white solid in a 45% yield over 3 steps (59 mg). MS (M+1): 438.3. ¹H NMR (400 MHz, CHLOROFORM-D): δ ppm 0.86 - 1.01 (m, 1 H), 1.03 - 1.19 (m, 2 H), 1.23 - 1.84 (m, 11 H), 1.90 - 1.99 (m, 1 H), 2.09 (dd, J=12.79, 4.39 Hz, 1 H), 2.43 (t, J=11.43 Hz, 1 H), 2.55 - 2.75 (m, 2 H), 3.03 - 3.28 (m, 2 H), 3.31 - 3.48 (m, 2 H), 3.71 (d, J=5.47 Hz, 1 H), 4.00 (dt, J=5.81, 1.29 Hz, 1 H), 5.02 - 5.10 (m, 1 H), 5.23 (dq, J=10.35, 1.46, 1.17 Hz, one diast 1 H), 5.30 (dq, J=17.19, 1.63 Hz, one diast 1 H), 5.70 (ddt, J=17.19, 10.35, 5.47 Hz, one diast 1 H), 5.95 (ddt, J=17.19, 10.35, 5.66 Hz, one diast 1 H), 7.21 - 7.24 (m, 1 H), 7.39 (ddd, J=8.50, 1.66, 0.78 Hz, 1 H), 7.68 (dt, J=6.25, 1.46 Hz, 1 H), 8.30 (ddd, J=8.40, 3.52, 2.34 Hz, 1 H), 8.41 (dt, J=7.62, 0.98 Hz, 1 H), 8.89 (s, 1 H), 9.21 (s, one diast 1 H), 9.29 (s, one diast 1 H).

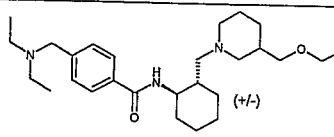
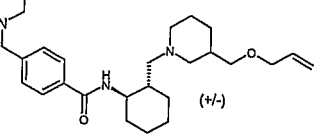
Example 121-128

The same procedure described in Example 120 was followed to prepare Examples 121-128

Example No.	Structure	Name	Data
121		trans-(±)- N-2-({3- [(Allyloxy) methyl]piperidin-1- yl)methyl} cyclohexyl]-4- bromoben zamide	¹ H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.85 - 2.15 (m, 16 H), 2.32 - 2.71 (m, 3 H), 3.03 - 3.48 (m, 4 H), 3.69 - 3.77 (m, J=5.52, 2.78, 1.51, 1.51 Hz, 1 H), 3.98 (dt, J=5.81, 1.39 Hz, 1 H), 5.09 - 5.33 (m, 2 H), 5.73 - 6.00 (m, 1 H), 7.52 - 7.56 (m, 2 H), 7.71 (dd, J=8.50, 1.66 Hz, 2 H), 8.92 (s, 1 H one isomer), 9.00 (s, 1 H one isomer). MS: 449.3 (M+1).
122		Trans-(±)- (N-2-({3- [(Allyloxy) methyl]piperidin-1- yl)methyl} cyclohexyl]-3-(4- chlorophe nyl)propan amide	¹ H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.85 - 1.07 (m, 3 H), 1.15 - 1.95 (m, 13 H), 1.95 - 2.06 (m, 1 H), 2.19 - 2.49 (m, 4 H), 2.64 - 3.35 (m, 6 H), 3.87 - 4.00 (m, 2 H), 5.13 - 5.31 (m, 2 H), 5.80 - 5.98 (m, 1 H), 7.11 - 7.18 (m, 2 H), 7.21 - 7.25 (m, 2 H), 7.99 (s, 1 H), 8.02 (s, 1 H). MS: 433.3 (M+1).

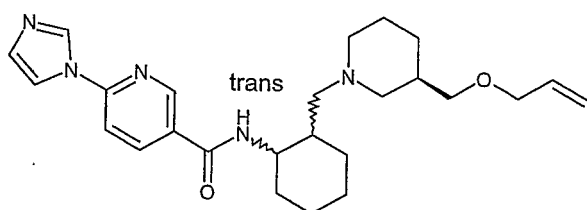
123		<i>Trans-(±)-</i> <i>N</i> -[2-({3- [(Allyloxy) methyl]pip eridin-1- yl}methyl) cyclohexyl]-3-(2- methoxyp henyl)prop anamide	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.86 - 1.07 (m, 3 H), 1.16 - 2.05 (m, 15 H), 2.22 - 2.47 (m, 4 H), 2.56 (d, $J=11.52$ Hz, 1 H one isomer), 2.70 (dd, $J=5.37, 2.83$ Hz, 1 H one isomer), 2.80 - 2.86 (m, 1 H one isomer), 2.91 - 2.98 (m, 2 H), 3.08 (d, $J=10.94$ Hz, 1 H one isomer), 3.19 - 3.33 (m, 3 H), 3.81 (s, 3 H one isomer), 3.82 (s, 3 H one isomer), 3.89 (dq, $J=5.54, 1.34$ Hz, 1 H), 3.95 (dt, $J=5.66, 1.37$ Hz, 1 H), 5.11 - 5.30 (m, 2 H), 5.79 - 5.96 (m, 1 H), 6.81 - 6.90 (m, 2 H), 7.15 - 7.20 (m, 2 H), 7.70 (d, $J=3.91$ Hz, 1 H one isomer), 7.84 (s, 1 H one isomer). MS: 429.3 (M+1).
124		<i>Trans-(±)-</i> <i>N</i> -[2-({3- [(Allyloxy) methyl]pip eridin-1- yl}methyl) cyclohexyl]-4- cyanoben zamide	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.82 - 1.17 (m, 3 H), 1.23 - 1.97 (m, 12 H), 2.08 (dd, $J=12.79, 3.22$ Hz, 1 H), 2.34 - 2.74 (m, 3 H), 3.02 - 3.26 (m, 2 H), 3.29 - 3.48 (m, 2 H), 3.76 (dt, $J=5.47, 1.37$ Hz, 1 H), 3.99 (dt, $J=5.66, 1.37$ Hz, 1 H), 5.10 - 5.34 (m, 2 H), 5.72 - 6.01 (m, 1 H), 7.68 - 7.73 (m, 2 H), 7.92 (dd, $J=7.91, 4.79$ Hz, 2 H), 9.16 (s, 1 H one isomer), 9.26 (s, 1

			H one isomer). MS: 396.3 (M+1).
125		<i>Trans-(±)-</i> <i>N</i> -[(2-{3- [(Allyloxy) methyl]pip eridin-1- yl)methyl] cyclohexyl]-4- fluorobenz amide	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.08 (d, J=10.94 Hz, 3 H), 1.23 - 1.84 (m, 11 H), 1.85 - 1.97 (m, 1 H), 1.98 - 2.13 (m, 1 H), 2.34 - 2.49 (m, 1 H), 2.50 - 2.70 (m, 2 H), 3.02 - 3.50 (m, 4 H), 3.74 (d, J=5.47 Hz, 2 H one isomer), 3.98 (dt, J=5.66, 1.27 Hz, 2 H one isomer), 5.08 - 5.34 (m, 2 H), 5.72 - 6.00 (m, 1 H), 7.04 - 7.12 (m, 2 H), 7.83 (t, J=5.66 Hz, 2 H), 8.87 (s, 1 H one isomer), 8.95 (s, 1 H one isomer). MS: 389.3 (M+1).
126		<i>Trans-(±)-</i> <i>N</i> -[(2-{3- [(Allyloxy) methyl]pip eridin-1- yl)methyl] cyclohexyl]-4- chloroben zamide	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.82 - 1.18 (m, 3 H), 1.22 - 1.44 (m, 2 H), 1.44 - 1.85 (m, 9 H), 1.91 (t, J=10.84 Hz, 1 H), 2.06 (dd, J=12.79, 6.74 Hz, 1 H), 2.34 - 2.46 (m, 1 H), 2.50 - 2.73 (m, 2 H), 3.04 - 3.47 (m, 4 H), 3.73 (dq, J=5.44, 1.57 Hz, 2 H one isomer), 3.98 (dt, J=5.66, 1.37 Hz, 2 H one isomer), 5.09 - 5.34 (m, 2 H), 5.73 - 6.00 (m, 1 H), 7.35 - 7.40 (m, 2 H), 7.78 (dd, J=8.59, 2.15 Hz, 2 H), 8.92 (s, 1 H one isomer), 9.00 (s, 1 H one

127		<i>Trans-(±)-</i> <i>N</i> -[2-({3- [(Allyloxy) methyl]piperidin-1- yl}methyl) cyclohexyl]-4- [(diethyla mino)meth yl]benzam ide	isomer). MS: 405.3 (M+1). 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.82 - 1.00 (m, 1 H), 1.03 (t, J=7.13 Hz, 6 H), 1.06 - 1.51 (m, 4 H), 1.52 - 1.95 (m, 10 H), 2.04 (ddd, J=12.94, 8.35, 1.56 Hz, 1 H), 2.35 - 2.45 (m, 1 H), 2.50 (q, J=7.23 Hz, 4 H), 2.54 - 2.67 (m, 2 H), 3.03 (d, J=11.72 Hz, 1 H one isomer), 3.12 (d, J=6.25 Hz, 1 H), 3.22 (dd, J=9.18, 7.81 Hz, 1 H one isomer), 3.26 (d, J=10.35 Hz, 1 H one isomer), 3.34 (dd, J=9.18, 5.08 Hz, 1 H one isomer), 3.38 - 3.48 (m, 1 H), 3.59 (s, 2 H), 3.72 (dt, J=5.47, 1.37 Hz, 2 H one isomer), 3.98 (dt, J=5.66, 1.37 Hz, 2 H one isomer), 5.06 - 5.35 (m, 2 H), 5.71 - 6.00 (m, 1 H), 7.37 (d, J=7.81 Hz, 2 H), 7.77 (d, J=8.20 Hz, 2 H), 8.76 (s, 1 H one isomer), 8.86 (s, 1 H one isomer). MS: 456.3 (M+1).
128		<i>Trans-(±)-</i> <i>N</i> -[2-({3- [(Allyloxy) methyl]piperidin-1- yl}methyl) cyclohexyl]-4-[(4- methylpiperidin-1-yl)methyl]benzam ide	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.82 - 1.51 (m, 6 H), 1.52 - 1.93 (m, 9 H), 2.00 - 2.09 (m, 2 H), 2.28 (s, 3 H), 2.35 - 2.68 (m, 10 H), 3.04 (d, J=10.16 Hz, 1 H one isomer), 3.11 (d, J=6.25 Hz, 1 H), 3.23 (dd,

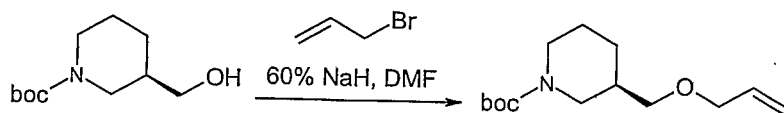
		methylpiperazin-1-yl)methyl]benzamide	J=9.18, 7.81 Hz, 1 H one isomer), 3.27 (d, J=9.96 Hz, 1 H one isomer), 3.34 (dd, J=9.28, 5.18 Hz, 1 H one isomer), 3.38 - 3.47 (m, 1 H), 3.52 (s, 2 H one isomer), 3.53 (s, 2 H one isomer), 3.72 (dt, J=5.47, 1.46 Hz, 2 H one isomer), 3.98 (dt, J=5.66, 1.37 Hz, 2 H one isomer), 5.07 - 5.34 (m, 2 H), 5.71 - 6.00 (m, 1 H), 7.36 (d, J=8.40 Hz, 2 H), 7.77 (d, J=8.20 Hz, 2 H), 8.76 (d, J=2.54 Hz, 1 H one isomer), 8.85 (d, J=2.73 Hz, 1 H one isomer). MS: 483.3 (M+1).
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Example 129. *Trans-(±)*- [2-({(3*R*)-3-[(allyloxy)methyl]piperidin-1-yl)methyl)cyclohexyl]-6-(1*H*-imidazol-1-yl)nicotinamide



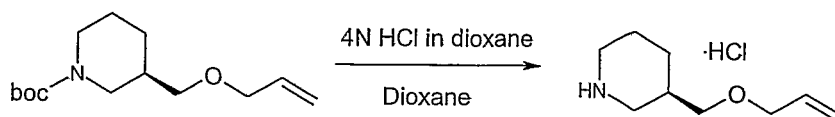
5

Step A: The preparation of *tert*-butyl (3*R*)-3-[(allyloxy)methyl]piperidin-1-carboxylate



10 The title compound was prepared following the same procedure as Example 115 (Step A). The product was used directly for the next step without further purification.

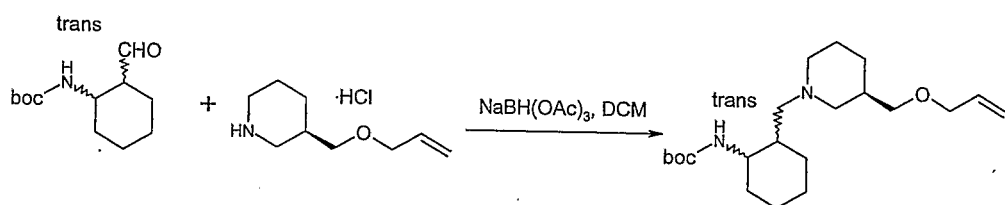
Step B: The preparation of (3*R*)-3-[(allyloxy)methyl]piperidine hydrochloride



Following the same procedure as Example 97 Step B, the hydrochloride salt of the title compound was obtained as a white solid in a 80% yield over 2 steps (397mg).

5

Step C: The preparation of *Trans-(±)-tert-butyl [2-((3*R*)-3-[(allyloxy)methyl]piperidin-1-yl)methyl]cyclohexyl]carbamate*

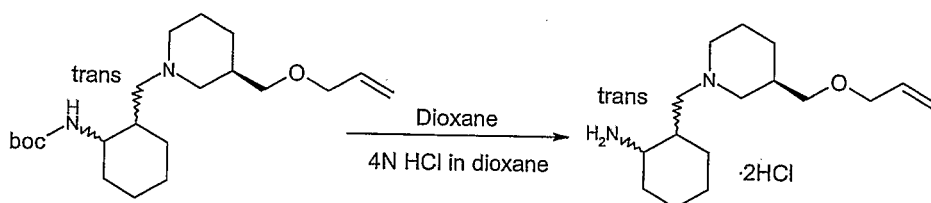


10

The title compound was prepared following the same procedure as Example 89 Step C. The product was used directly for the next step without further purification.

Step D: The preparation of *Trans-(±)-[2-((3*R*)-3-[(allyloxy)methyl]piperidin-1-yl)methyl]cyclohexyl]amine hydrochloride*

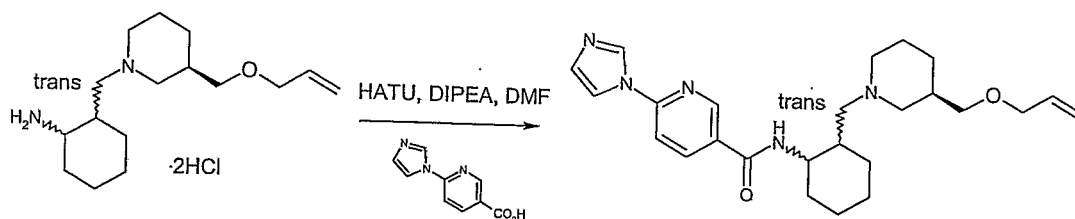
15



The title compound was prepared following the same procedure as Example 89 Step D. The product was used directly for the next step without further purification. MS (M+1): 267.2.

20

Step E: The preparation of *trans-(±) [2-((3*R*)-3-[(allyloxy)methyl]piperidin-1-yl)methyl]cyclohexyl]-6-(1*H*-imidazol-1-yl)nicotinamide*

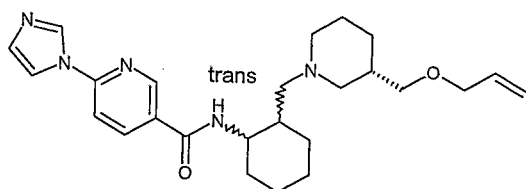


Following the procedure described in Example 2, the free base of the title compound was obtained as a white solid in a 36% yield over 3 steps (130 mg). MS (M+1):

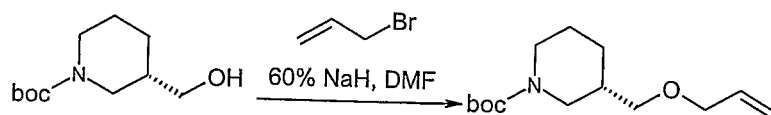
- 5 438.3. ¹H NMR (400 MHz, CHLOROFORM-D): δ ppm 0.86 - 1.02 (m, 1 H), 1.08 - 1.80 (m, 13 H), 1.94 (t, J=10.74 Hz, 1 H), 2.10 (dd, J=13.28, 4.88 Hz, 1 H), 2.42 (t, J=10.25 Hz, 1 H), 2.56 - 2.75 (m, 2 H), 3.06 - 3.18 (m, 1 H and one diast 1 H) 3.24 (dd, J=9.18, 8.01 Hz, one diast 1 H), 3.32 - 3.48 (m, 1 H), 3.38 (dd, J=9.28, 4.98 Hz, 1 H), 3.71 (d, J=5.47 Hz, 1 H), 3.99 (dt, J=5.81, 1.29 Hz, 1 H), 5.01 - 5.11 (m, 1 H),
 10 5.22 (dq, J=10.35, 1.46, 1.17 Hz, one diast 1 H), 5.30 (dq, J=17.26, 1.60 Hz, one diast 1 H), 5.70 (ddt, J=17.19, 10.55, 5.47 Hz, one diast 1 H), 5.94 (ddt, J=17.19, 10.35, 5.66 Hz, one diast 1 H), 7.22 (s, 1 H), 7.39 (ddd, J=8.59, 1.76, 0.78 Hz, 1 H), 7.68 (dt, J=6.05, 1.17 Hz, 1 H), 8.28 - 8.32 (m, 1 H), 8.41 (d, J=7.42 Hz, 1 H), 8.89 (s, 1 H), 9.21 (s, one diast 1 H), 9.29 (s, one diast 1 H).

15

Example 130. Trans-(±)- [2-((3S)-3-[(Allyloxy)methyl]piperidin-1-yl)methyl)cyclohexyl]-6-(1H-imidazol-1-yl)nicotinamide

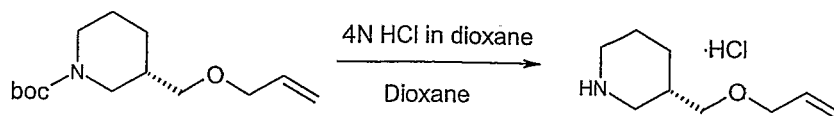


- 20 Step A: The preparation of *tert*-butyl (3S)-3-[(allyloxy)methyl]piperidine-1-carboxylate



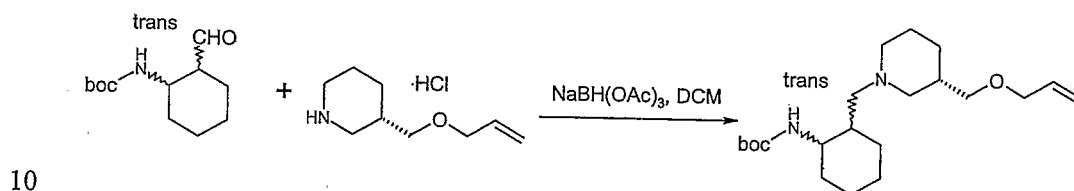
- 25 The title compound was prepared following the same procedure as Example 115 (Step A). The product was used directly for the next step without further purification.

Step B: The preparation of (3*S*)-3-[(allyloxy)methyl]piperidine hydrochloride



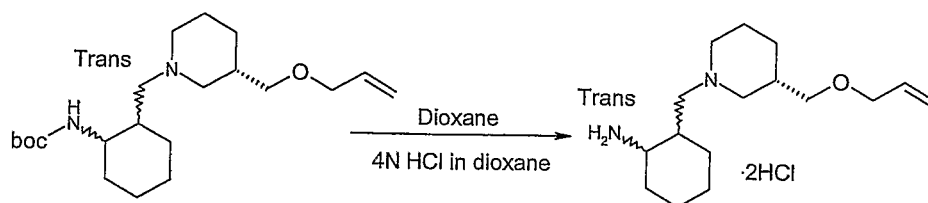
Following the same procedure as Example 97 Step B, the hydrochloride salt of the title compound was obtained as a white solid in a 75% yield over 2 steps (372mg).

Step C: The preparation of *trans*-(±)-*tert*-butyl [2-((3*S*)-3-[(allyloxy)methyl]piperidin-1-yl)methyl)cyclohexyl]carbamate



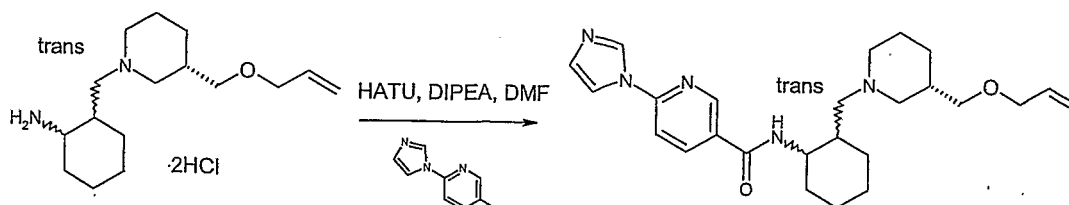
The title compound was prepared following the same procedure as Example 89 Step C. The product was used directly for the next step without further purification.

Step D: The preparation of *trans*-(±) [2-((3*S*)-3-[(allyloxy)methyl]piperidin-1-yl)methyl)cyclohexyl]amine hydrochloride



The title compound was prepared following the same procedure as Example 89 Step D. The product was used directly for the next step without further purification. MS (M+1): 267.2.

Step E: The preparation of *trans*-(±) [2-((3*S*)-3-[(allyloxy)methyl]piperidin-1-yl)methyl)cyclohexyl]-6-(1*H*-imidazol-1-yl)nicotinamide

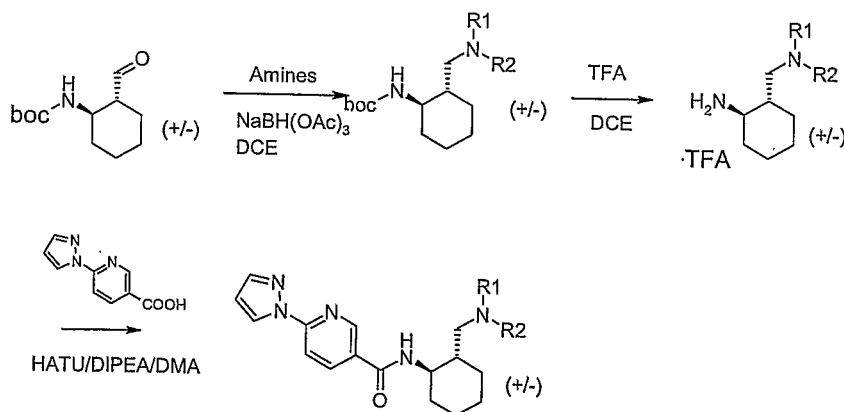


Following the procedure described in Example 2, the free base of the title compound was obtained as a white solid in a 41% yield over 3 steps (205 mg). MS (M+1):

- 5 438.3. MS (M+1): 438.3. ¹H NMR (400 MHz, CHLOROFORM-D): δ ppm 0.86 - 1.02 (m, 1 H), 1.08 - 1.80 (m, 13-H), 1.94 (t, J=10.74 Hz, 1 H), 2.10 (dd, J=13.28, 4.88 Hz, 1 H), 2.42 (t, J=10.25 Hz, 1 H), 2.56 - 2.75 (m, 2 H), 3.06 - 3.18 (m, 1 H and one diast 1H) 3.24 (dd, J=9.18, 8.01 Hz, one diast 1 H), 3.32 - 3.48 (m, 1 H), 3.38 (dd, J=9.28, 4.98 Hz, 1 H), 3.71 (d, J=5.47 Hz, 1 H), 3.99 (dt, J=5.81, 1.29 Hz, 1 H), 5.01 - 5.11
- 10 (m, 1 H), 5.22 (dq, J=10.35, 1.46, 1.17 Hz, one diast 1 H), 5.30 (dq, J=17.26, 1.60 Hz, one diast 1 H), 5.70 (ddt, J=17.19, 10.55, 5.47 Hz, one diast 1 H), 5.94 (ddt, J=17.19, 10.35, 5.66 Hz, one diast 1 H), 7.22 (s, 1 H), 7.39 (ddd, J=8.59, 1.76, 0.78 Hz, 1 H), 7.68 (dt, J=6.05, 1.17 Hz, 1 H), 8.28 - 8.32 (m, 1 H), 8.41 (d, J=7.42 Hz, 1 H), 8.89 (s, 1 H), 9.21 (s, one diast 1 H), 9.29 (s, one diast 1 H).

15

Examples 131-145



Procedure:

20

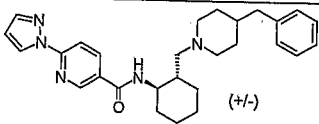
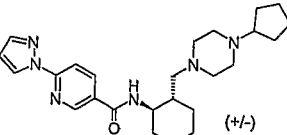
In a plate format, a 0.30M solution of amine in dichloroethane (0.80 ml, 0.22 mmol) was added to a 0.40M solution of *trans*-(+/-)- *tert*-butyl [2-formylcyclohexyl]carbamate in dichloroethane (0.50 ml, 0.20 mmol). Solid sodium triacetoxymethylborohydride (85 mg,

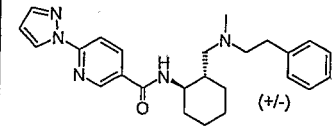
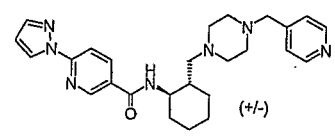
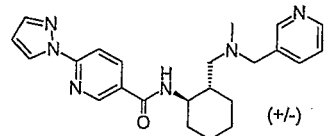
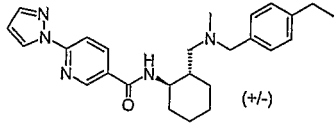
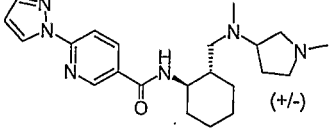
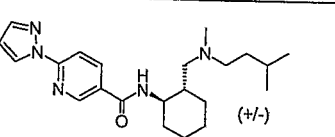
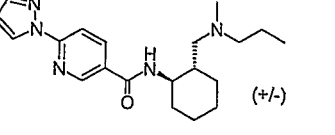
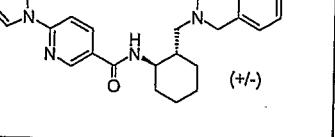
0.40 mmol) was added to the reaction mixtures. The mixtures were stirred at room temperature for 72 hours. A 1N sodium hydroxide solution (0.45 ml, 0.45 mmol) was added. The mixtures were filtered on Hydromatrix and washed with dichloromethane. The mixtures were concentrated.

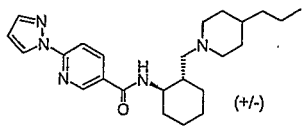
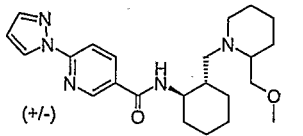
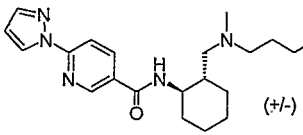
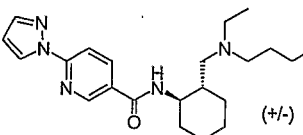
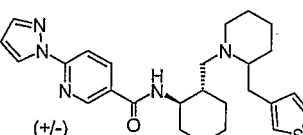
- 5 The crude compounds were dissolved in dichloroethane (0.80 ml) and trifluoroacetic acid (0.15 ml) was added. The reactions were stirred at room temperature for 8 hours and concentrated.

- 10 A 0.2M solution of 6-(1*H*-pyrazol-1-yl)-nicotinic acid in dimethylacetamide (1.1 ml, 0.22 mmol) was added to the crude compounds, followed by diisopropylethylamine (0.14 ml, 0.8 mmol) and a 0.55M solution of HATU in dimethylacetamide (0.41 ml, 0.22 mmol). The reactions were stirred at room temperature for 16 hours and concentrated. The crude compounds were dissolved in 0.60 ml dichloromethane. A 1N sodium hydroxide solution (0.20 ml) was added. The mixtures were filtered on
- 15 Hydromatrix and washed three times with dichloromethane. The mixtures were concentrated.

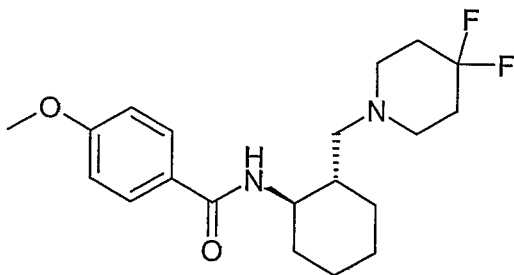
The compounds were purified by high pH reverse phase prep LC-MS.

Exp No.	Structure	Name	MS (M+1)	Retention time (min)
131		<i>trans</i> -(+/-)- <i>N</i> -{2-[(4-benzylpiperidin-1-yl)methyl]cyclohexyl}-6-(1 <i>H</i> -pyrazol-1-yl)nicotinamide	457.87	2.19
132		<i>trans</i> -(+/-)- <i>N</i> -{2-[(4-cyclopentylpiperazin-1-yl)methyl]cyclohexyl}-6-(1 <i>H</i> -pyrazol-1-yl)nicotinamide	436.89	1.57

133		<i>trans</i> -(+/-)- <i>N</i> -(2-([methyl(2-phenylethyl)amino]methyl)cyclohexyl)-6-(1 <i>H</i> -pyrazol-1-yl)nicotinamide	417.88	1.87
134		<i>trans</i> -(+/-)-6-(1 <i>H</i> -pyrazol-1-yl)- <i>N</i> -(2-([4-(pyridin-4-ylmethyl)piperazin-1-yl]methyl)cyclohexyl)nicotinamide	459.92	1.34
135		<i>trans</i> -(+/-)- <i>N</i> -(2-([methyl(pyridin-3-ylmethyl)amino]methyl)cyclohexyl)-6-(1 <i>H</i> -pyrazol-1-yl)nicotinamide	404.86	1.36
136		<i>trans</i> -(+/-)- <i>N</i> -(2-([4-ethylbenzyl](methyl)amino]methyl)cyclohexyl)-6-(1 <i>H</i> -pyrazol-1-yl)nicotinamide	431.88	2.07
137		<i>trans</i> -(+/-)- <i>N</i> -(2-([methyl(1-methylpyrrolidin-3-yl)amino]methyl)cyclohexyl)-6-(1 <i>H</i> -pyrazol-1-yl)nicotinamide	396.89	1.27
138		<i>trans</i> -(+/-)- <i>N</i> -(2-([methyl(3-methylbutyl)amino]methyl)cyclohexyl)-6-(1 <i>H</i> -pyrazol-1-yl)nicotinamide	383.91	1.92
139		<i>trans</i> -(+/-)- <i>N</i> -(2-([methyl(propyl)amino]methyl)cyclohexyl)-6-(1 <i>H</i> -pyrazol-1-yl)nicotinamide	355.95	1.64
140		<i>trans</i> -(+/-)- <i>N</i> -(2-([benzyl(methyl)amino]methyl)cyclohexyl)-6-(1 <i>H</i> -pyrazol-1-yl)nicotinamide	403.86	1.83

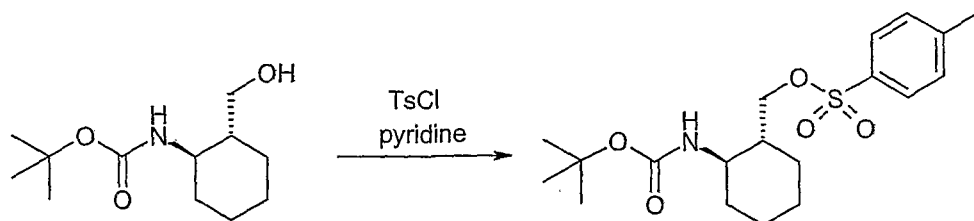
141		<i>trans</i> -(+/-)- <i>N</i> -{2-[(4-propylpiperidin-1-yl)methyl]cyclohexyl}-6-(1 <i>H</i> -pyrazol-1-yl)nicotinamide	409.9	2.24
142		<i>trans</i> -(+/-)- <i>N</i> -(2-{[2-(methoxymethyl)piperidin-1-yl]methyl}cyclohexyl)-6-(1 <i>H</i> -pyrazol-1-yl)nicotinamide	411.88	1.78
143		<i>trans</i> -(+/-)- <i>N</i> -(2-{[butyl(methyl)amino]methyl}cyclohexyl)-6-(1 <i>H</i> -pyrazol-1-yl)nicotinamide	369.91	1.8
144		<i>trans</i> -(+/-)- <i>N</i> -(2-{[butyl(ethyl)amino]methyl}cyclohexyl)-6-(1 <i>H</i> -pyrazol-1-yl)nicotinamide	383.93	1.96
145		<i>trans</i> -(+/-)-6-(1 <i>H</i> -pyrazol-1-yl)- <i>N</i> -(2-{[2-(3-thienylmethyl)piperidin-1-yl]methyl}cyclohexyl)nicotinamide	463.81	2.09

Example 146. *trans*-(+/-)-*N*-{2-[(4,4-difluoropiperidin-1-yl)methyl]cyclohexyl}-4-methoxybenzamide



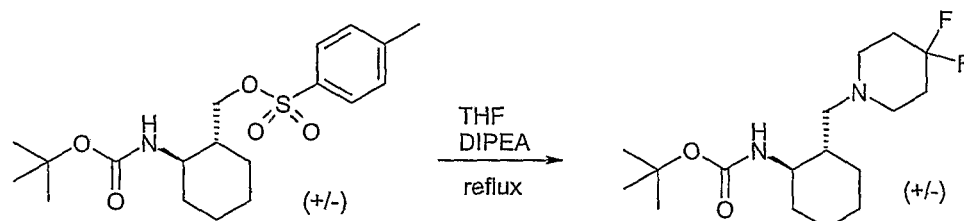
102213-1 WO

Step A: The preparation of *trans*-(+/-)-2-[(*tert*-butoxycarbonyl)amino]cyclohexyl)methyl 4-methylbenzenesulfonate



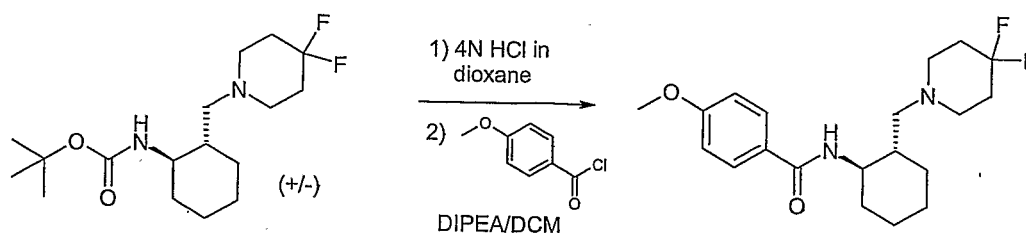
- 5 To a solution of 2.41 g (10.6 mmol) of *trans*-(+/-)-*tert*-butyl [2-(hydroxymethyl)cyclohexyl]carbamate (Example 89, step A) in dry pyridine (20 mL) was added Tosyl chloride (2.53 g, 13.25 mmol) at 0°C, the reaction mixture was stirred at 0°C for 5 h and then at room temperature for 48h. Ice water was added, extracted with DCM (50 mL), dried over Na₂SO₄. After removal of the solvent, the residue was purified with flash chromatography to give the title product as white solids (4.02 g, 87%).

Step B: The preparation of *trans*-(+/-)-*tert*-butyl {2-[(4,4-difluoropiperidin-1-yl)methyl]cyclohexyl}carbamate



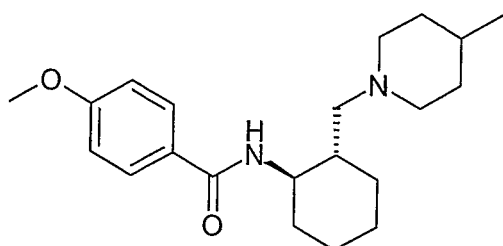
- 15 To a solution of *trans*-(+/-)-2-[(*tert*-butoxycarbonyl)amino]cyclohexyl)methyl 4-methylbenzenesulfonate (192 mg, 0.5 mmol) in THF (5 mL) was added 4,4-difluoropiperidine hydrochloride (95 mg, 0.6 mmol) followed by DIPEA (1.5 mmol). The solution was refluxed for 5h. After being cooled to room temperature, DCM (30 mL) was added, extracted with 1N NaOH (10 mL), dried over Na₂SO₄. After removal of the solvent, the crude product was used for the next step without further purification.

Step C: The preparation of *trans*-(+/-)-*N*-{2-[(4,4-difluoropiperidin-1-yl)methyl]cyclohexyl}-4-methoxybenzamide



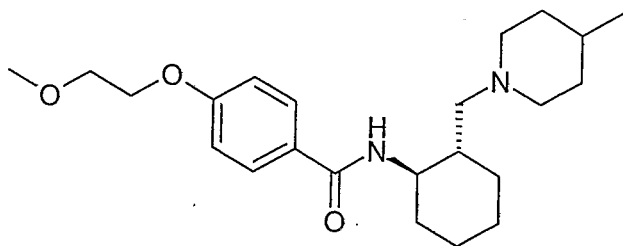
Following the procedure described in Example 89 (steps D to E), the title compound was obtained in as a white solid in a 27% yield over 2 steps (32 mg, TFA salt). MS (M+1): 367.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.22 - 1.63 (m, 4 H), 1.78 - 1.90 (m, 2 H), 1.93 - 2.03 (m, 2 H), 2.04 - 2.12 (m, 1 H), 2.26 - 2.45 (m, 4 H), 3.10 - 3.20 (m, 2 H), 3.25 - 3.29 (m, 1 H), 3.33 - 3.45 (m, 1 H), 3.54 - 3.68 (m, 1 H), 3.73 - 3.83 (m, 2 H), 3.85 (s, 3 H), 7.00 (d, J=8.79 Hz, 2 H), 7.83 (d, J=8.79 Hz, 2 H).

Example 147. *trans*-(+/-)-4-methoxy-N-{2-[(4-methylpiperidin-1-yl)methyl]cyclohexyl}benzamide



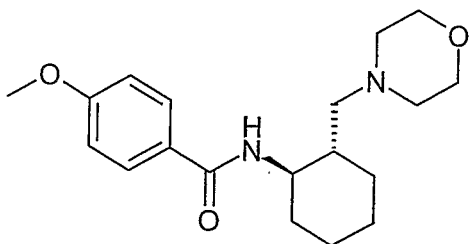
Following the same procedure as described in Example 146 (steps B to C), the title compound was obtained as its TFA salt (18 mg, 16% for 3 steps). MS (M+1): 345.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.99 (d, J=6.45 Hz, 3 H), 1.21 - 1.56 (m, 6 H), 1.60 - 1.73 (m, 1 H), 1.77 - 1.90 (m, 4 H), 1.91 - 2.01 (m, 2 H), 2.01 - 2.10 (m, 1 H), 2.73 - 2.87 (m, 1 H), 2.95 - 3.17 (m, 3 H), 3.37 - 3.47 (m, 1 H), 3.59 - 3.67 (m, 1 H), 3.73 - 3.82 (m, 1 H), 3.85 (s, 3 H), 7.00 (d, J=8.79 Hz, 2 H), 7.82 (d, J=8.79 Hz, 2 H).

Example 148. *trans*-(+/-)-4-(2-methoxyethoxy)-N-{2-[(4-methylpiperidin-1-yl)methyl]cyclohexyl}benzamide



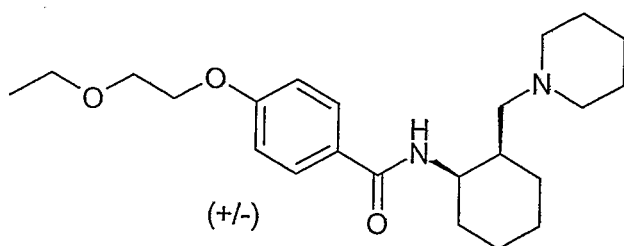
Following the same procedure as described in Example 146 (steps B to C), the title compound was obtained as its TFA salt (14 mg, 11% for 3 steps). MS (M+1): 389.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.99 (d, J=6.44 Hz, 3 H), 1.22 - 1.58 (m, 6 H), 1.62 - 1.74 (m, 1 H), 1.76 - 1.91 (m, 4 H), 1.91 - 2.01 (m, 2 H), 2.02 - 2.12 (m, 1 H), 2.71 - 2.86 (m, 1 H), 2.97 - 3.17 (m, 3 H), 3.38 - 3.48 (m, 1 H), 3.41 - 3.44 (m, 3 H), 3.58 - 3.69 (m, 1 H), 3.73 - 3.83 (m, 3 H), 4.11 - 4.22 (m, 2 H), 7.02 (d, J=8.79 Hz, 2 H), 7.82 (d, J=8.79 Hz, 2 H).

10 **Example 149. *trans*-(+/-)-4-methoxy-N-[2-(morpholin-4-ylmethyl)cyclohexyl]benzamide**

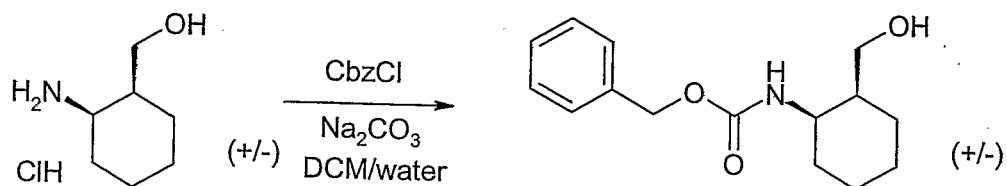


Following the same procedure as described in Example 146 (steps B to C), the title compound was obtained as its TFA salt (42 mg, 31% for 3 steps). MS (M+1): 333.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.20 - 1.61 (m, 4 H), 1.78 - 1.91 (m, 2 H), 1.93 - 2.03 (m, 2 H), 2.04 - 2.13 (m, 1 H), 2.97 - 3.14 (m, 2 H), 3.15 - 3.27 (m, 2 H), 3.39 (d, J=12.20 Hz, 1 H), 3.57 (d, J=12.20 Hz, 1 H), 3.73 - 3.84 (m, 3 H), 3.85 (s, 3 H), 3.94 - 4.08 (m, 2 H), 7.00 (d, J=8.89 Hz, 2 H), 7.83 (d, J=8.89 Hz, 2 H).

20 **Example 150. *cis*-(+/-)-4-(2-ethoxyethoxy)-N-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide**

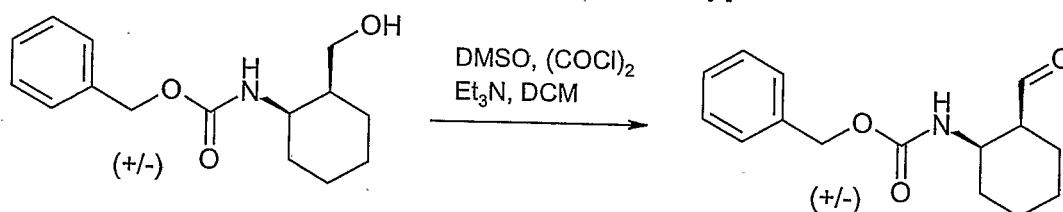


Step A. The preparation of *cis*-(+/-)-benzyl [2-(hydroxymethyl)cyclohexyl]carbamate



- 5 Following the same procedure as Example 1 (Step B), 612 mg of (+/-) *cis*-[2-aminocyclohexyl]methanol hydrochloride (3.69 mmol) was treated with Na_2CO_3 and benzyl chloroformate to yield crude *cis*-(+/-)-benzyl [2-(hydroxymethyl)cyclohexyl]carbamate 0.95 g (98%).

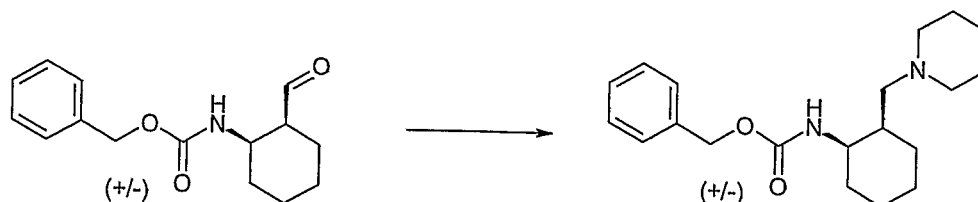
- 10 Step B. The preparation of *cis*-(+/-)-benzyl [2-formylcyclohexyl]carbamate



Following the same procedure as Example 89 (step B), yielded crude *cis*-(+/-)-benzyl [2-formylcyclohexyl]carbamate 923 mg (98%), which was used for the next step

- 15 without further purification.

Step C. The preparation of *cis*-(+/-)-benzyl [2-(piperidin-1-ylmethyl)cyclohexyl]carbamate

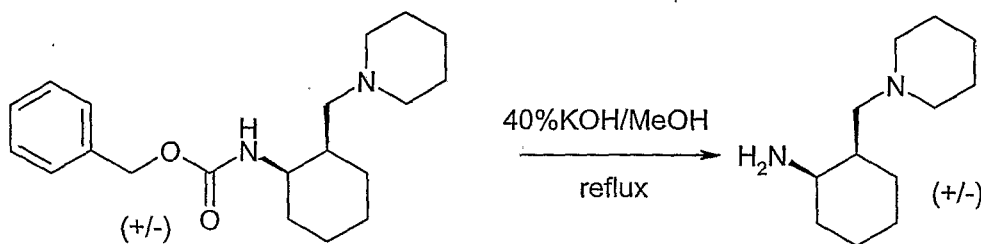


102213-1 WO

Following the same procedure as Example 89 (step C), *cis*-(+/-)-benzyl [2-formylcyclohexyl]carbamate from step B (1.8 mmol) was treated with NaBH(OAc)₃ to yielded *cis*-(+/-)-benzyl [2-(piperidin-1-ylmethyl)cyclohexyl]carbamate 520 mg (88%), which was used for the next step without further purification.

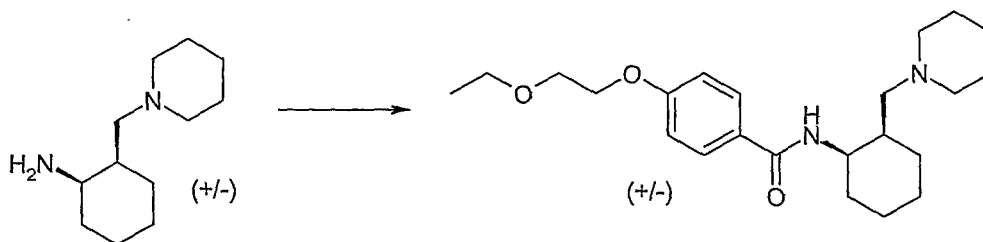
5

Step D. The preparation of *cis*-(+/-)- [2-(piperidin-1-ylmethyl)cyclohexyl]amine



- 10 The solution of crude *cis*-(+/-)-benzyl [2-(piperidin-1-ylmethyl)cyclohexyl]carbamate (0.3 mmol) in 40% KOH/MeOH (8 mL, 1:1 v/v) was stirred at reflux for 5h. The reaction mixture was cooled to room temperature, extracted with DCM (3 x 10 mL), dried over Na₂SO₄, concentrated to yield crude *cis*-(+/-)- [2-(piperidin-1-ylmethyl)cyclohexyl]amine (50 mg, 85%), which was used for the next step without
- 15 further purification.

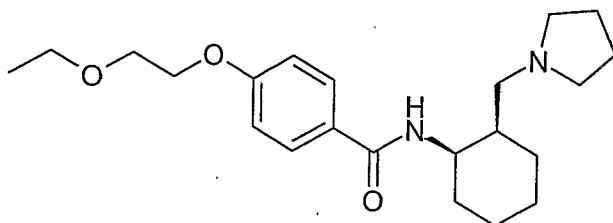
Step E. The preparation of *cis*-(+/-)-4-(2-ethoxyethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide



- 20 Following the same procedure as Example 2, the crude *cis*-(+/-)- [2-(piperidin-1-ylmethyl)cyclohexyl]amine from step D was converted to amide to yield *cis*-(+/-)-4-(2-ethoxyethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide (49 mg, 38%). MS (M+1): 389.0. ¹H NMR (400 MHz, CHLOROFORM-D): δ ppm 1.25 (t, J=6.95 Hz, 3 H), 1.31 - 1.61 (m, 4 H), 1.63 - 1.78 (m, 4 H), 1.82 - 2.02 (m, 6 H), 2.30 - 2.44 (m, 1 H), 2.73 - 2.90 (m, 2 H), 2.91 - 3.02 (m, 2 H), 3.36 - 3.49 (m, 1 H), 3.54 - 3.60 (m, 1
- 25 H), 7.23 - 7.30 (m, 2 H), 7.31 - 7.38 (m, 2 H), 7.39 - 7.46 (m, 2 H).

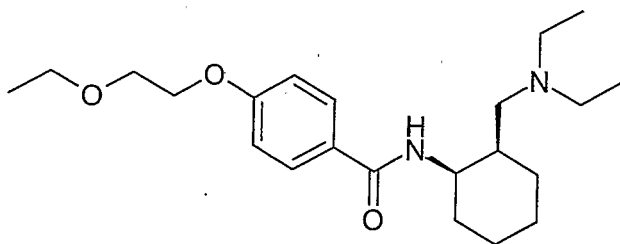
H), 3.61 (q, J=6.95 Hz, 2 H), 3.78 - 3.85 (m, 2 H), 4.14 - 4.20 (m, 2 H), 4.23 - 4.31 (m, 1 H), 6.97 (d, J=8.40 Hz, 2 H), 7.09 (d, J=7.03 Hz, 1 H), 7.80 (d, J=8.40 Hz, 2 H).

Example 151. *cis*-(+/-)-4-(2-ethoxyethoxy)-*N*-[2-(pyrrolidin-1-ylmethyl)cyclohexyl]benzamide



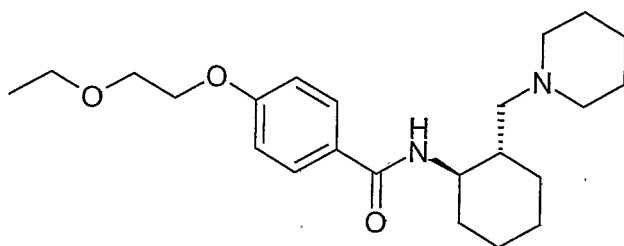
Following the same procedure as Example 150 (from step C to step E), yielded *cis*-(+/-)-4-(2-ethoxyethoxy)-*N*-[2-(pyrrolidin-1-ylmethyl)cyclohexyl]benzamide (38 mg, 27% for 3 steps) as its TFA salt. MS (M+1): 375.0. ¹H NMR (400 MHz, CHLOROFORM-D): δ ppm 1.25 (t, J=6.99 Hz, 3 H), 1.29 - 1.58 (m, 3 H), 1.64 - 1.82 (m, 4 H), 1.83 - 1.94 (m, 1 H), 2.02 - 2.19 (m, 4 H), 2.18 - 2.29 (m, 1 H), 2.95 - 3.14 (m, 4 H), 3.61 (q, J=6.99 Hz, 2 H), 3.66 - 3.78 (m, 2 H), 3.79 - 3.85 (m, 2 H), 4.14 - 4.21 (m, 2 H), 4.27 - 4.38 (m, 1 H), 6.86 (d, J=8.01 Hz, 1 H), 6.97 (d, J=8.79 Hz, 2 H), 7.76 (d, J=8.79 Hz, 2 H).

Example 152. *cis*-(+/-)-*N*-[2-[(diethylamino)methyl]cyclohexyl]-4-(2-ethoxyethoxy)benzamide



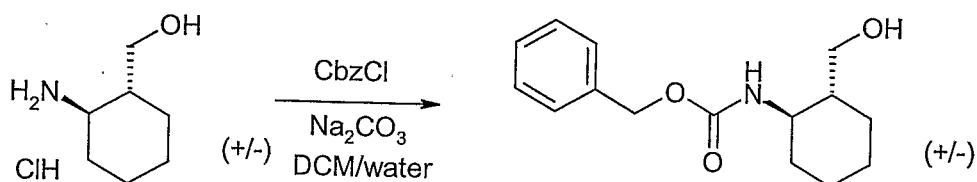
Following the same procedure as Example 150 (from step C to step E), yielded *cis*-(+/-)-*N*-[2-[(diethylamino)methyl]cyclohexyl]-4-(2-ethoxyethoxy)benzamide (24 mg, 16% for 3 steps) as its TFA salt. MS (M+1): 377.0. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.20 (t, J=7.03 Hz, 3 H) 1.24 - 1.37 (m, 7 H) 1.43 - 1.56 (m, 2 H) 1.61 - 1.71 (m, 1 H) 1.74 - 1.91 (m, 4 H) 2.20 - 2.31 (m, J=3.71 Hz, 1 H) 2.73 - 2.88 (m, 1 H) 2.92 - 3.01 (m, 1 H) 3.05 - 3.16 (m, 1 H) 3.18 - 3.26 (m, 2 H) 3.36 - 3.47 (m, 1 H) 3.58 (q, J=6.97 Hz, 2 H) 3.75 - 3.81 (m, 2 H) 4.11 - 4.21 (m, 2 H) 4.24 - 4.32 (m, 1 H) 7.02 (d, J=8.79 Hz, 2 H) 7.84 (d, J=8.79 Hz, 2 H)

Example 153. *trans*-(+/-)- 4-(2-ethoxyethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide



5

Step A. The preparation of *trans*-(+/-)-benzyl [2-(hydroxymethyl)cyclohexyl]carbamate

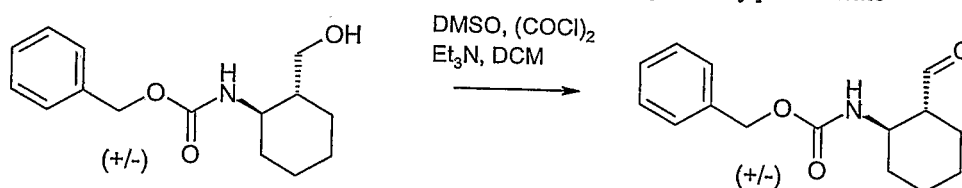


10

Following the same procedure as Example 150 (Step A), 612 mg of *trans*-(+/-)-[2-aminocyclohexyl]methanol hydrochloride (3.69 mmol) was treated with Na_2CO_3 and benzyl chloroformate to yield crude *trans*-(+/-)-benzyl [2-(hydroxymethyl)cyclohexyl]carbamate 0.92 g (95%).

15

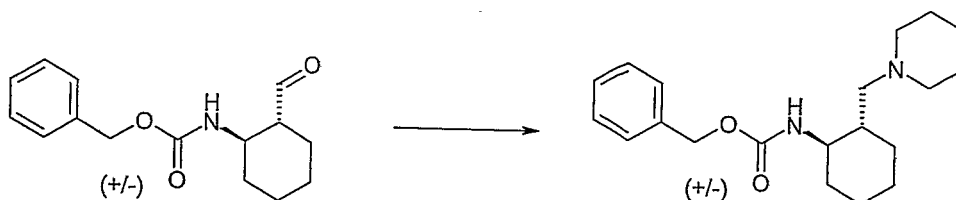
Step B. The preparation of *trans*-(+/-)-benzyl [2-formylcyclohexyl]carbamate



Following the same procedure as Example 89 (step B), yielded crude *trans*-(+/-)-benzyl [2-formylcyclohexyl]carbamate 890 mg (97%), which was used for the next step without further purification.

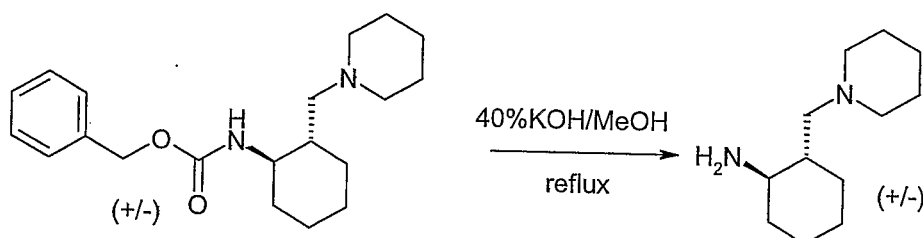
20

Step C. The preparation of *trans*-(+/-)-benzyl [2-(piperidin-1-ylmethyl)cyclohexyl]carbamate



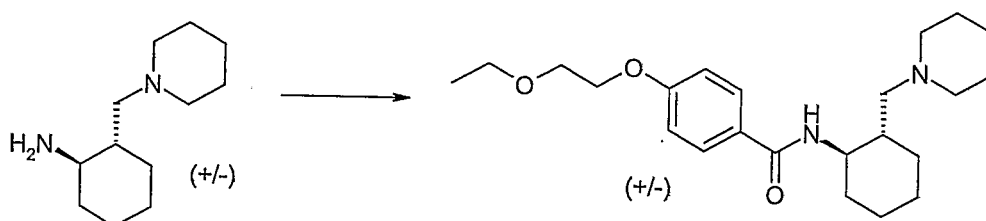
Following the same procedure as Example 89 (step C), the aldehyde from step B (1.8 mmol) was treated with $\text{NaBH}(\text{OAc})_3$ to yield crude *trans*-(+/-)-benzyl [2-(piperidin-1-ylmethyl)cyclohexyl]carbamate 543 mg (92%), which was used for the next step without further purification.

Step D. The preparation of *trans*-(+/-)-[2-(piperidin-1-ylmethyl)cyclohexyl]amine



The solution of crude *trans*-(+/-)-benzyl [2-(piperidin-1-ylmethyl)cyclohexyl]carbamate (0.25 mmol) in 40% KOH/MeOH (6 mL, 1:1 v/v) was stirred at reflux for 5h. The reaction mixture was cooled to room temperature, extracted with DCM (3 x 10 mL), dried over Na_2SO_4 , concentrated to yield crude *trans*-(+/-)-[2-(piperidin-1-ylmethyl)cyclohexyl]amine, which was used for the next step without further purification.

Step E. The preparation of *trans*-(+/-)-4-(2-ethoxyethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide

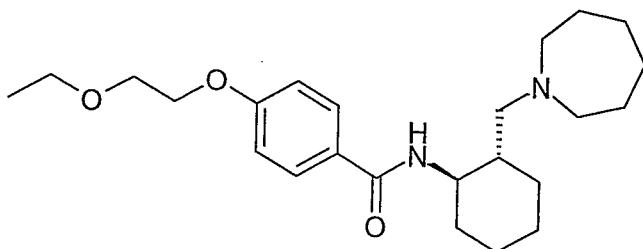


20

Following the same procedure as Example 2, the crude *trans*-(+/-)-[2-(piperidin-1-ylmethyl)cyclohexyl]amine from step D was converted to amide to yield *trans*-(+/-)-*N*-

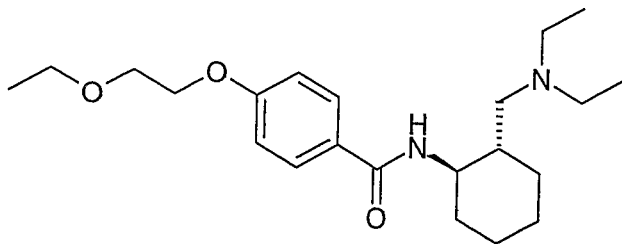
{2-[(diethylamino)methyl]cyclohexyl}-4-(2-ethoxyethoxy)benzamide (33 mg, 26% for 2 steps) as its TFA salt. MS (M+1): 389.0. ¹H NMR (400 MHz, CHLOROFORM-D): δ ppm 1.25 (t, J=6.95 Hz, 3 H), 1.29 - 1.45 (m, 4 H), 1.69 - 1.90 (m, 6 H), 1.93 - 2.05 (m, 2 H), 2.06 - 2.16 (m, 2 H), 2.53 - 2.66 (m, 2 H), 3.18 - 3.35 (m, 4 H), 3.61 (q, J=6.95 Hz, 2 H), 3.64 - 3.70 (m, 1 H), 3.77 - 3.83 (m, 2 H), 3.84 - 3.92 (m, 1 H), 4.14 - 4.19 (m, 2 H), 6.94 (d, J=8.79 Hz, 2 H), 7.93 (d, J=8.79 Hz, 2 H), 7.96 (d, J=7.03 Hz, 1 H).

Example 154. *trans*-(+/-)-N-[2-(azepan-1-ylmethyl)cyclohexyl]-4-(2-ethoxyethoxy)benzamide



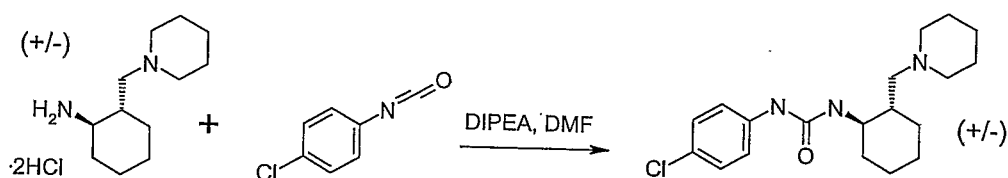
Following the same procedure as Example 153 (from step C to step E), yielded *trans*-(+/-)-N-[2-(azepan-1-ylmethyl)cyclohexyl]-4-(2-ethoxyethoxy)benzamide (32 mg, 21% for 3 steps) as its TFA salt. MS (M+1): 403.0. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.19 (t, J=7.03 Hz, 3 H), 1.26 - 1.54 (m, 4 H), 1.60 - 1.72 (m, 4 H), 1.75 - 1.91 (m, 7 H), 1.91 - 1.99 (m, 1 H), 2.05 (d, J=11.72 Hz, 1 H), 2.92 - 3.01 (m, 1 H), 3.10 - 3.20 (m, 2 H), 3.22 - 3.27 (m, 1 H), 3.39 - 3.49 (m, 2 H), 3.58 (q, J=7.03 Hz, 2 H), 3.70 - 3.76 (m, 1 H), 3.76 - 3.81 (m, 2 H), 4.12 - 4.20 (m, 2 H), 7.01 (d, J=8.79 Hz, 2 H), 7.80 (d, J=8.79 Hz, 2 H).

Example 155. *trans*-(+/-)-N-[2-[(diethylamino)methyl]cyclohexyl]-4-(2-ethoxyethoxy)benzamide



Following the same procedure as Example 153 (from step C to step E), yielded *trans*-(+/-)-*N*-{2-[(diethylamino)methyl]cyclohexyl}-4-(2-ethoxyethoxy)benzamide (28 mg, 19% for 3 steps) as its TFA salt. MS (M+1): 377.0. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 1.16 - 1.24 (m, 6 H), 1.28 (t, J=7.13 Hz, 3 H), 1.30 - 1.61 (m, 4 H), 1.76 - 1.89 (m, 3 H), 1.90 - 1.98 (m, 1 H), 2.05 (d, J=11.91 Hz, 1 H), 2.95 - 3.05 (m, 1 H), 3.10 - 3.26 (m, 5 H), 3.58 (q, J=7.13 Hz, 2 H), 3.71 - 3.81 (m, 3 H), 4.11 - 4.20 (m, 2 H), 7.00 (d, J=8.79 Hz, 2 H), 7.80 (d, J=8.79 Hz, 2 H).

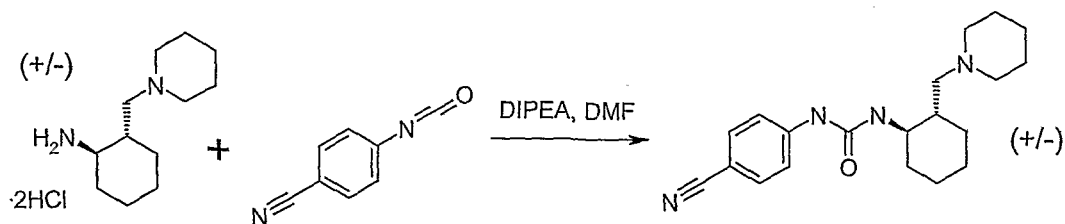
Example 156. *trans*-(+/-)-*N*-(4-chlorophenyl)-*N'*-[2-(piperidin-1-ylmethyl)cyclohexyl]urea



Diisopropylethylamine (0.127 ml, 0.732 mmol) was added to a suspension of *trans*-(+/-)-[2-(piperidin-1-ylmethyl)cyclohexyl]amine hydrochloride salt (98 mg, 0.37 mmol) in DMF (2 ml). The reaction mixture was added to 1-chloro-4-isocyanatobenzene (54 mg, 0.36 mmol). The reaction was stirred at room temperature under nitrogen for 12 hours. The solution was concentrated *in vacuo*. The product was purified by preparative LC/MS at high pH (water and acetonitrile buffered at pH10 with ammonium bicarbonate and ammonium hydroxide). The pure product crystallized out of the fractions obtained after preparative LC/MS. The free base of the title compound was obtained as white needles (30 mg, 24% yield). MS (M+1): 350.3; ¹H NMR (400 MHz, CHLOROFORM-D): δ ppm 0.95 - 1.11 (m, 2 H), 1.18 - 1.38 (m, 2 H), 1.37 - 1.53 (m, 7 H), 1.55 - 1.76 (m, 5 H), 2.06 (dd, J=12.89, 2.15 Hz, 1 H), 2.23 (s, 1 H), 2.35 (dd, J=12.99, 9.67 Hz, 1 H), 2.39 - 2.44 (m, 1 H), 2.51 (s, 1 H), 3.21 (td, J=10.79, 3.22 Hz, 1 H), 6.03 (s, 1 H), 7.21 - 7.32 (m, 4 H), 7.85 (s, 1 H).

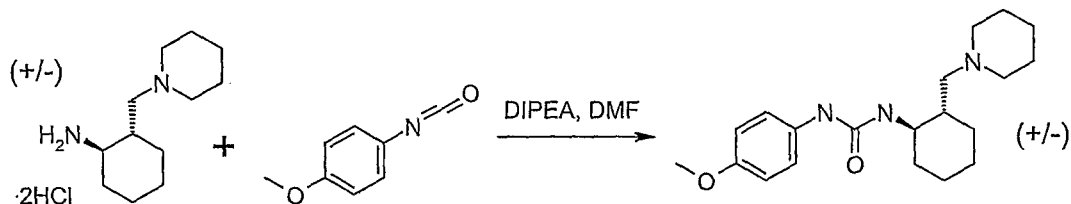
Example 157. *trans*-(+/-)-*N*-(4-cyanophenyl)-*N'*-[2-(piperidin-1-ylmethyl)cyclohexyl]urea

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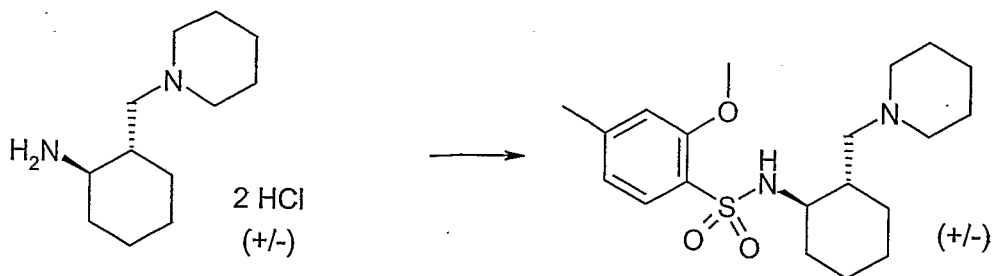
The procedure described in Example 156 was followed. The fractions from preparative LC/MS had to be evaporated as the product did not crystallize out. The free base of *trans*-(+/-)-*N*-(4-cyanophenyl)-*N'*-[2-(piperidin-1-ylmethyl)cyclohexyl]urea was obtained as a white solid (47 mg, 66% yield). MS (*M*+1): 341.3; ¹H NMR (400 MHz, CHLOROFORM-*D*): δ ppm 1.02 - 1.12 (m, 2 H), 1.21 - 1.38 (m, 2 H), 1.43 - 1.77 (m, 12 H), 2.14 (d, *J*=11.72 Hz, 1 H), 2.27 - 2.42 (m, 2 H), 2.43 - 2.51 (m, 1 H), 3.24 (td, *J*=10.89, 3.61 Hz, 1 H), 3.24 (td, *J*=10.89, 3.61 Hz, 1 H), 6.54 (s, 1 H), 7.44 - 7.51 (m, 2 H), 7.51 - 7.57 (m, 2 H), 8.05 (s, 1 H).

Example 158. *trans*-(+/-)-*N*-(4-methoxyphenyl)-*N'*-[2-(piperidin-1-ylmethyl)cyclohexyl]urea



Following the same procedure as Example 156, yielded the free base of *trans*-(+/-)-*N*-(4-methoxyphenyl)-*N'*-[2-(piperidin-1-ylmethyl)cyclohexyl]urea (40 mg, 34%) as white needles. MS (*M*+1): 346.3; ¹H NMR (400 MHz, CHLOROFORM-*D*): δ ppm 0.95 - 1.10 (m, 2 H), 1.17 - 1.32 (m, 2 H), 1.31 - 1.44 (m, 7 H), 1.55 - 1.73 (m, 5 H), 2.02 (dd, *J*=12.79, 2.64 Hz, 1 H), 2.19 (s, 1 H), 2.35 (dd, *J*=12.79, 9.08 Hz, 1 H), 2.37 - 2.47 (m, 2 H), 3.24 (s, 1 H), 3.78 (s, 3H), 5.91 (s, 1 H), 6.81 - 6.88 (d, *J*=8.98 Hz, 2 H), 7.22 (d, *J*=8.98 Hz, 2 H), 7.29 (s, 1 H).

Example 159. *trans*-(+/-)-2-methoxy-4-methyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzenesulfonamide

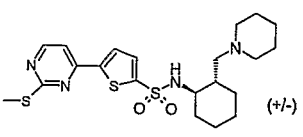
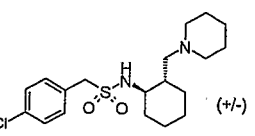


- To a solution of *trans*-(+/-)- [2-(piperidin-1-ylmethyl)cyclohexyl]amine hydrochloride (81 mg, 0.3 mmol) in dichloromethane (4 mL) was added 2-methoxy-4-methylbenzenesulfonyl chloride (66 mg, 0.3 mmol) followed by triethylamine (37mg, 0.36 mmol). The mixture was stirred at room temperature for 5 h, quenched with water (5 mL), extracted with saturated aq. NaHCO₃, dried over Na₂SO₄, concentrated to yield crude product which was purified with reverse phase HPLC. The title compound was obtained as white solids (84 mg, 74%). MS (M+1): 381.3. ¹H NMR (400 MHz, METHANOL-D₄): δ ppm 0.82 - 0.95 (m, 1 H), 1.00 - 1.25 (m, 3 H), 1.40 - 1.50 (m, 3 H), 1.52 - 1.64 (m, 7 H), 1.69 - 1.84 (m, 2 H), 2.02 (dd, *J*=11.91, 6.25 Hz, 1 H), 2.22 - 2.35 (m, 2 H), 2.40 (s, 3 H), 2.41 - 2.49 (m, 2 H), 2.69 - 2.79 (m, 1 H), 3.92 (s, 3 H), 6.87 (d, *J*=7.81 Hz, 1 H), 7.01 (s, 1 H), 7.67 (d, *J*=7.81 Hz, 1 H).

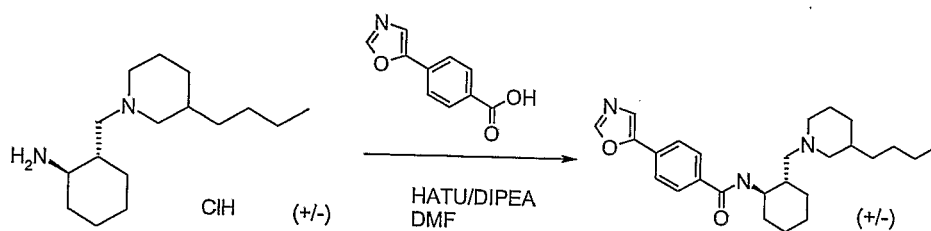
15 Example 160- 162

The same procedure described in Example 151 was followed to make Examples 160-162.

Exp No.	Structure	Name	MS (M+1)	Retention time (min)
160		<i>trans</i> -(+/-)- methyl 3-([2-(piperidin-1-ylmethyl)cyclohexyl]amino)sulfonylthiophene-2-carboxylate	400.8	1.88

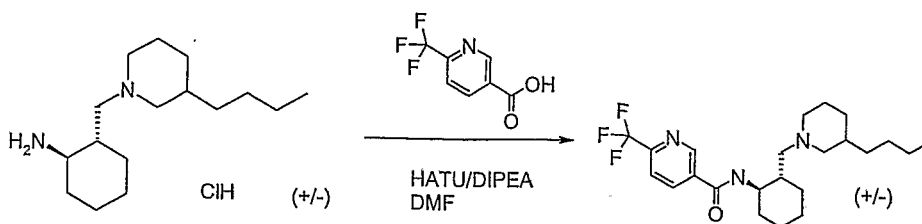
161		<i>trans</i> -(+/-)-5-[2-(methylthio)pyrimidin-4-yl]- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]thiophene-2-sulfonamide	466.7	2.2
162		<i>trans</i> -(+/-)-1-(4-chlorophenyl)- <i>N</i> -[2-(piperidin-1-ylmethyl)cyclohexyl]methanesulfonamide	384.79	2.12

Example 163. *trans*-(+/-)-*N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-4-(1,3-oxazol-5-yl)benzamide



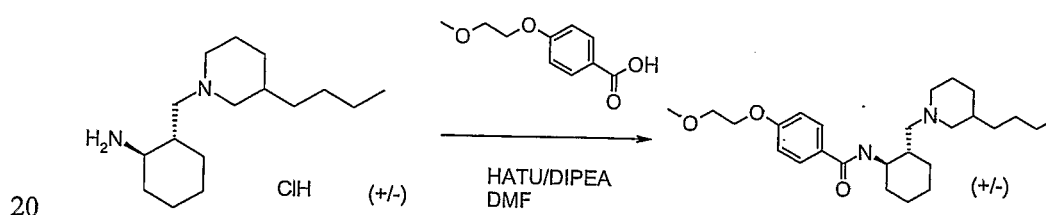
- 5 To a solution of *trans*-(+/-)- 2-[(3-butylpiperidin-1-yl)methyl]cyclohexylamine hydrochloride (72 mg, 0.25 mmol) in dry DMF (3 mL) was added 4-(1,3-oxazol-5-yl)benzoic acid (56 mg, 0.3 mmol) followed by HATU (114 mg, 0.3 mmol) and diisopropylethylamine (0.10 mL, 0.5 mmol). The mixture was stirred at room temperature for 1 h, and the reaction was quenched with water (5 mL). The solvent
- 10 was removed *in vacuo*. DCM (15 mL) was added and the mixture was washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified with reverse phase HPLC to yield *trans*-(+/-)- *N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-4-(1,3-oxazol-5-yl)benzamide (52 mg, 49%) as white powders. MS (M+1): 424.3. ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 0.68 - 0.90 (m, 4 H),
- 15 0.98 - 1.17 (m, 4 H), 1.22 - 1.46 (m, 7 H), 1.50 - 1.62 (m, 2 H), 1.64 - 1.81 (m, 5 H), 1.81 - 2.01 (m, 2 H), 2.02 - 2.27 (m, 2 H), 2.34 - 2.53 (m, 1 H), 2.63 - 3.08 (m, 2 H), 3.48 - 3.69 (m, 1 H), 7.64 (s, 1 H), 7.79 - 7.85 (m, 2 H), 7.86 - 7.92 (m, 2 H), 8.29 (d, J=1.56 Hz, 1 H).

- 20 **Example 164. *trans*-(+/-)-*N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-6-(trifluoromethyl)nicotinamide**



To a solution of *trans*-(+/-)- 2-[(3-butylpiperidin-1-yl)methyl]cyclohexylamine hydrochloride (72 mg, 0.25 mmol) in dry DMF (3 mL) was added 6-(trifluoromethyl)nicotinic acid (57 mg, 0.3 mmol) followed by HATU (114 mg, 0.3 mmol) and diisopropylethylamine (0.10 mL, 0.5 mmol). The mixture was stirred at room temperature for 1 h, and the reaction was quenched with water (5 mL). The solvent was removed *in vacuo*. DCM (15 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified with reverse phase HPLC to yield *trans*-(+/-)- *N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-6-(trifluoromethyl)nicotinamide (66 mg, 62%) as a white powder. MS (M+1): 426.2. ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 0.75 - 0.82 (m, 2 H), 0.83 - 0.92 (m, 2 H), 0.98 - 1.18 (m, 5 H), 1.22 - 1.41 (m, 6 H), 1.46 - 1.59 (m, 2 H), 1.61 - 1.81 (m, 5 H), 1.82 - 1.99 (m, 1 H), 2.02 - 2.19 (m, 2 H), 2.33 - 2.46 (m, 1 H), 2.63 - 3.01 (m, 2 H), 3.52 - 3.69 (m, 1 H), 7.92 (d, J=8.20 Hz, 1 H), 8.34 - 8.44 (m, 1 H), 9.08 (d, J=4.10 Hz, 1 H).

Example 165. *trans*-(+/-)- *N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-4-(2-methoxyethoxy)benzamide

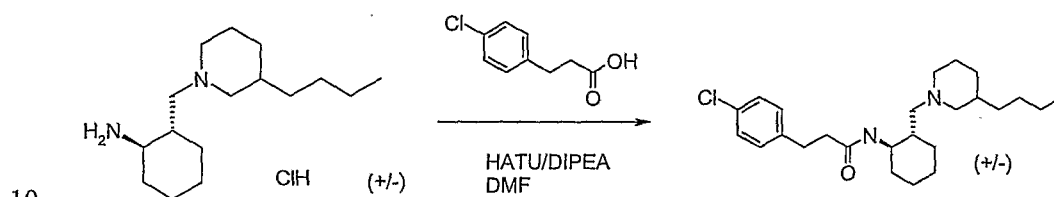


To a solution of *trans*-(+/-)- 2-[(3-butylpiperidin-1-yl)methyl]cyclohexylamine hydrochloride (72 mg, 0.25 mmol) in dry DMF (3 mL) was added 4-(2-methoxyethoxy)benzoic acid (58 mg, 0.3 mmol) followed by HATU (114 mg, 0.3 mmol) and diisopropylethylamine (0.10 mL, 0.5 mmol). The mixture was stirred at room temperature for 1 h, and the reaction was quenched with water (5 mL). The solvent was removed *in vacuo*. DCM (15 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified with reverse phase HPLC to yield *trans*-(+/-)- *N*-{2-[(3-butylpiperidin-1-

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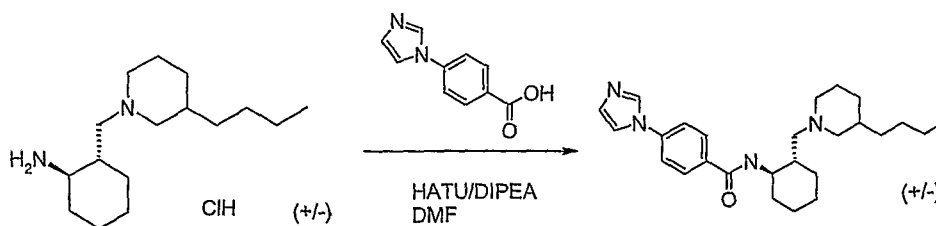
yl)methyl]cyclohexyl}-4-(2-methoxyethoxy)benzamide (76 mg, 71%) as a white powder. MS (M+1): 431.3. ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 0.77 - 0.92 (m, 4 H), 0.96 - 1.07 (m, 2 H), 1.07 - 1.19 (m, 4 H), 1.20 - 1.41 (m, 5 H), 1.46 - 1.64 (m, 4 H), 1.66 - 1.81 (m, 4 H), 1.82 - 1.98 (m, 1 H), 2.04 - 2.19 (m, 2 H), 2.29 - 2.43 (m, 1 H), 2.64 - 2.79 (m, 1 H), 2.81 - 2.98 (m, 1 H), 3.40 (s, 3 H), 3.45 - 3.62 (m, 1 H), 3.69 - 3.77 (m, 2 H), 4.14 (s, 2 H), 6.98 (d, J=8.59 Hz, 2 H), 7.76 (d, J=7.62 Hz, 2 H).

Example 166. *trans*-(+/-)-*N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-3-(4-chlorophenyl)propanamide



To a solution of *trans*-(+/-)-2-[(3-butylpiperidin-1-yl)methyl]cyclohexylamine hydrochloride (72 mg, 0.25 mmol) in dry DMF (3 mL) was added 3-(4-chlorophenyl)propanoic acid (55 mg, 0.3 mmol) followed by HATU (114 mg, 0.3 mmol) and diisopropylethylamine (0.10 mL, 0.5 mmol). The mixture was stirred at room temperature for 1 h, and the reaction was quenched with water (5 mL). The solvent was removed *in vacuo*. DCM (15 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified with reverse phase HPLC to yield *trans*-(+/-)-*N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-3-(4-chlorophenyl)propanamide (65 mg, 62%) as white powders. MS (M+1): 419.3. ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 0.83 - 1.02 (m, 6 H), 1.05 - 1.20 (m, 4 H), 1.21 - 1.41 (m, 8 H), 1.48 - 1.62 (m, 2 H), 1.61 - 1.77 (m, 4 H), 1.79 - 1.88 (m, 1 H), 1.91 - 2.10 (m, 2 H), 2.39 - 2.49 (m, 2 H), 2.65 - 2.79 (m, 2 H), 2.80 - 3.00 (m, 2 H), 3.30 - 3.38 (m, 1 H), 7.11 - 7.31 (m, 4 H).

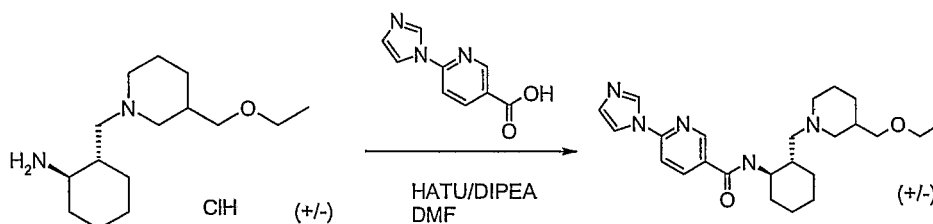
Example 167. *trans*-(+/-)-*N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-4-(1*H*-imidazol-1-yl)benzamide



EXAMPLE 167

To a solution of *trans*-(+/-)- 2-[(3-butylpiperidin-1-yl)methyl]cyclohexylamine hydrochloride (72 mg, 0.25 mmol) in dry DMF (3 mL) was added 4-(1*H*-imidazol-1-yl)benzoic acid (56 mg, 0.3 mmol) followed by HATU (114 mg, 0.3 mmol) and diisopropylethylamine (0.10 mL, 0.5 mmol). The mixture was stirred at room temperature for 1 h, and the reaction was quenched with water (5 mL). The solvent was removed *in vacuo*. DCM (15 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified with high pH HPLC to yield *trans*-(+/-)- *N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-4-(1*H*-imidazol-1-yl)benzamide (52 mg, 49%) as a white powder. MS (M+1): 423.3. ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 0.66 - 0.96 (m, 5 H), 0.98 - 1.18 (m, 5 H), 1.21 - 1.44 (m, 6 H), 1.48 - 1.62 (m, 2 H), 1.64 - 1.85 (m, 5 H), 1.82 - 2.03 (m, 1 H), 2.05 - 2.23 (m, 2 H), 2.29 - 2.47 (m, 1 H), 2.62 - 3.01 (m, 2 H), 3.50 - 3.63 (m, 1 H), 7.17 (s, 1 H), 7.67 (s, 1 H), 7.70 (dd, J=8.30, 4.39 Hz, 2 H), 7.97 (d, J=8.40 Hz, 2 H), 8.26 (s, 1 H).

Example 168. *trans*-(+/-)- *N*-(2-[[3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-imidazol-1-yl)nicotinamide

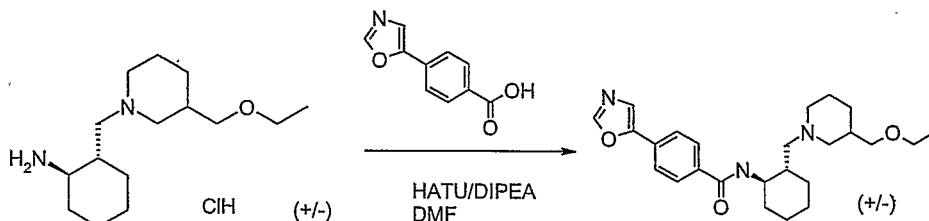


To a solution of *trans*-(+/-)- 2-([3-(ethoxy)methyl]piperidin-1-yl)methyl]cyclohexyl]amine hydrochloride (73 mg, 0.25 mmol) in dry DMF (3 mL) was added 6-(1*H*-imidazol-1-yl)nicotinic acid (57 mg, 0.3 mmol) followed by HATU (114 mg, 0.3 mmol) and diisopropylethylamine (0.10 mL, 0.5 mmol). The mixture was stirred at room temperature for 1 h, and the reaction was quenched with water (5 mL). The solvent was removed *in vacuo*. DCM (15 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified with high pH HPLC to yield *trans*-(+/-)- *N*-(2-[[3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-imidazol-1-yl)nicotinamide (67 mg, 63%) as a white powder. MS (M+1): 426.2. ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 0.83 - 0.97 (m, 1 H), 1.00 - 1.20 (m, 4 H), 1.27 - 1.45 (m, 3 H), 1.51 - 1.81 (m, 6 H), 1.83 - 2.00 (m, 2 H), 2.04 - 2.19 (m, 2 H), 2.32 - 2.49 (m, 1 H), 2.70 - 3.01 (m, 2 H), 3.07 - 3.25 (m, 2 H), 3.38 - 3.50 (m, 1 H), 3.56 - 3.69 (m, 1 H), 4.49 - 4.71 (m, 3 H), 7.17 (s, 1 H),

102215-1 WVO

7.80 (d, J=8.59 Hz, 1 H), 7.95 (s, 1 H), 8.29 - 8.39 (m, 1 H), 8.60 (s, 1 H), 8.90 (s, 1 H).

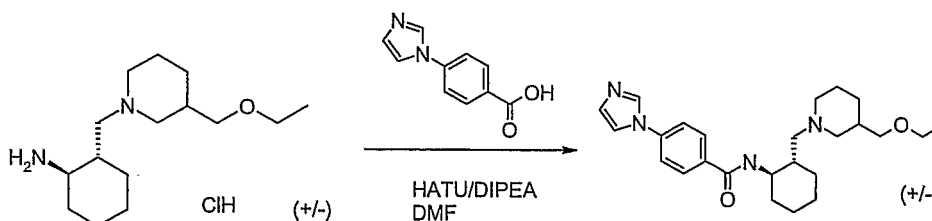
Example 169. *trans*-(+/-)-*N*-(2-([3-(ethoxymethyl)piperidin-1-yl]methyl)cyclohexyl)-4-(1,3-oxazol-5-yl)benzamide



To a solution of *trans*-(+/-)- 2-([3-(ethoxymethyl)piperidin-1-yl]methyl)cyclohexyl]amine hydrochloride (73 mg, 0.25 mmol) in dry DMF (3 mL) was added 4-(1,3-oxazol-5-yl)benzoic acid (56 mg, 0.3 mmol) followed by HATU (114 mg, 0.3 mmol) and diisopropylethylamine (0.10 mL, 0.5 mmol). The mixture was stirred at room temperature for 1 h, and the reaction was quenched with water (5 mL). The solvent was removed *in vacuo*. DCM (15 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified with high pH HPLC to yield *trans*-(+/-)-*N*-(2-([3-(ethoxymethyl)piperidin-1-yl]methyl)cyclohexyl)-4-(1,3-oxazol-5-yl)benzamide (62 mg, 58%) as a white powder.

MS (M+1): 426.2. ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 0.92 (s, 1 H), 1.00 - 1.19 (m, 4 H), 1.24 - 1.44 (m, 4 H), 1.51 - 1.81 (m, 8 H), 1.84 - 1.97 (m, 2 H), 2.06 - 2.20 (m, 2 H), 2.36 - 2.48 (m, 1 H), 2.69 - 2.88 (m, 1 H), 2.88 - 3.04 (m, 1 H), 3.07 - 3.24 (m, 2 H), 3.37 - 3.48 (m, 1 H), 3.53 - 3.64 (m, 1 H), 7.64 (s, 1 H), 7.80 - 7.85 (m, 2 H), 7.87 - 7.94 (m, 2 H), 8.29 (s, 1 H).

Example 170. *trans*-(+/-)- *N*-(2-([3-(ethoxymethyl)piperidin-1-yl]methyl)cyclohexyl)-4-(1*H*-imidazol-1-yl)benzamide

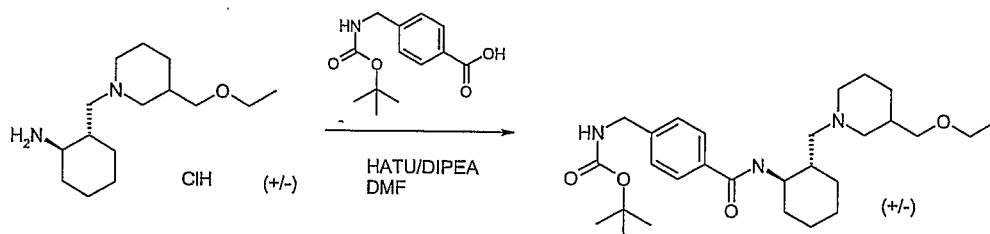


To a solution of *trans*-(+/-)- 2-([3-(ethoxymethyl)piperidin-1-yl]methyl)cyclohexyl]amine hydrochloride (73 mg, 0.25 mmol) in dry DMF (3 mL) was added 4-(1*H*-imidazol-1-yl)benzoic acid (56 mg, 0.3 mmol) followed by HATU (114

mg, 0.3 mmol) and diisopropylethylamine (0.10 mL, 0.5 mmol). The mixture was stirred at room temperature for 1 h, and the reaction was quenched with water (5 mL). The solvent was removed *in vacuo*. DCM (15 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified with high pH HPLC to yield *trans*-(+/-)- *N*-(2-([3-(ethoxymethyl)piperidin-1-yl)methyl]cyclohexyl)-4-(1*H*-imidazol-1-yl)benzamide (56 mg, 53%) as a white powder. MS (M+1): 425.3. ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 0.86 - 0.99 (m, 1 H), 1.02 - 1.21 (m, 5 H), 1.24 - 1.48 (m, 4 H), 1.57 - 1.82 (m, 8 H), 1.88 - 2.01 (m, 2 H), 2.04 - 2.25 (m, 2 H), 2.33 - 2.54 (m, 1 H), 2.73 - 3.03 (m, 1 H), 3.10 - 3.24 (m, 2 H), 3.38 - 3.49 (m, 1 H), 3.54 - 3.66 (m, 1 H), 7.17 (s, 1 H), 7.67 (s, 1 H), 7.70 (d, J=8.20 Hz, 2 H), 7.91 - 8.00 (m, 2 H), 8.25 (s, 1 H).

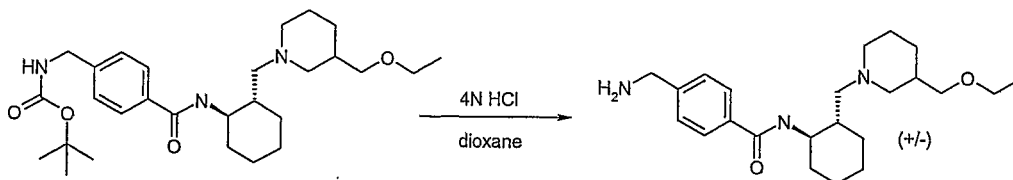
Example 171. *trans*-(+/-)- *N*-2-([3-(ethoxymethyl)piperidin-1-yl)methyl]cyclohexyl)-4-[(methylsulfonyl)amino]methyl]benzamide

Step A: The preparation of *trans*-(+/-)- *tert*-butyl (4-([(2-([3-(ethoxymethyl)piperidin-1-yl)methyl]cyclohexyl)amino]carbonyl)benzyl)carbamate



To a solution of *trans*-(+/-)- 2-([3-(ethoxy)methyl]piperidin-1-yl)methyl]cyclohexyl]amine hydrochloride (147 mg, 0.5 mmol) in dry DMF (5 mL) was added 4-[(*tert*-butoxycarbonyl)amino]methyl]benzoic acid (126 mg, 0.5 mmol) followed by HATU (190 mg, 0.5 mmol) and diisopropylethylamine (0.10 mL, 0.5 mmol). The mixture was stirred at room temperature for 1 h, and the reaction was quenched with water (5 mL). The solvent was removed *in vacuo*. DCM (15 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product *trans*-(+/-)- *tert*-butyl (4-([(2-([3-(ethoxymethyl)piperidin-1-yl)methyl]cyclohexyl)amino]carbonyl)benzyl)carbamate (240 mg, 98%) was used for the next step without further purification. MS (M+1): 488.36.

Step B: The preparation of *trans*-(+/-)- 4-(aminomethyl)-*N*-(2-[[3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide HCl salt

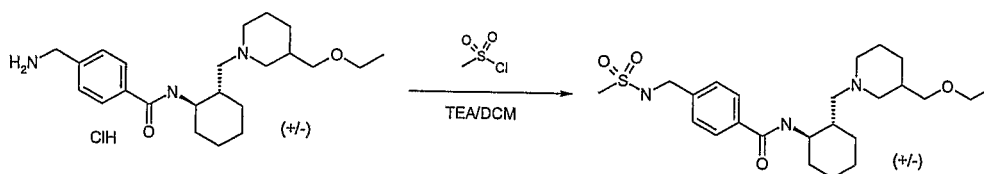


5

The crude product from step A (*trans*-(+/-)- *tert*-butyl 4-[[2-[[3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl]amino]carbonyl]benzyl)carbamate, 122 mg, 0.25 mmol) was treated with 4N HCl in dioxane (5 mL), the reaction mixture was stirred at room temperature for 5h. Removal of solvent afforded the desired intermediate *trans*-(+/-)- 4-(aminomethyl)-*N*-(2-[[3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide as its HCl salt .

10

Step C: The preparation of *trans*-(+/-)- *N*-2-[[3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-[[[(methylsulfonyl)amino]methyl]benzamide

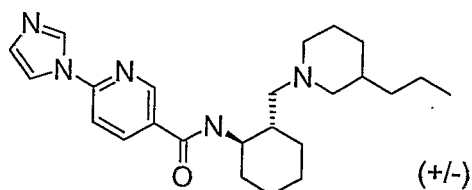


15

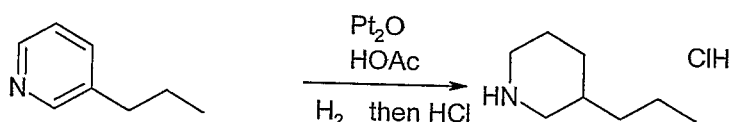
The crude product from step B (*trans*-(+/-)- 4-(aminomethyl)-*N*-(2-[[3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide HCl salt, ~ 0.25 mmol) was taken up into dichloromethane (5 mL), triethyl amine (0.14 mL, 1.0 mmol) was added followed by methyl sulfonyl chloride (0.3 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction was quenched with water (5 mL). DCM (30 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified with high pH to yield the title compound (68 mg, 59%) as a white powder. MS (M+1): 466.3. ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 0.84 - 1.03 (m, 1 H), 1.05 - 1.19 (m, 4 H), 1.26 - 1.45 (m, 4 H), 1.51 - 1.71 (m, 6 H), 1.83 - 1.98 (m, 3 H), 2.06 - 2.22 (m, 2 H), 2.38 - 2.52 (m, 1 H), 2.67 - 2.80 (m, 1 H), 2.87 (d, J=1.37 Hz, 3 H), 2.93 - 3.07 (m, 1 H), 3.09 - 3.26 (m, 2 H), 3.33 (q, J=7.23 Hz, 1 H), 3.39 - 3.49 (m, 1 H), 3.52 - 3.65 (m, 1 H), 4.29 (s, 2 H), 7.47 (d, J=7.81 Hz, 2 H), 7.79 (dd, J=8.10, 1.66 Hz, 2 H).

25
30

Example 172. *trans*-(+/-)- *N*-(2-[[3-propylpiperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-imidazol-1-yl)nicotinamide

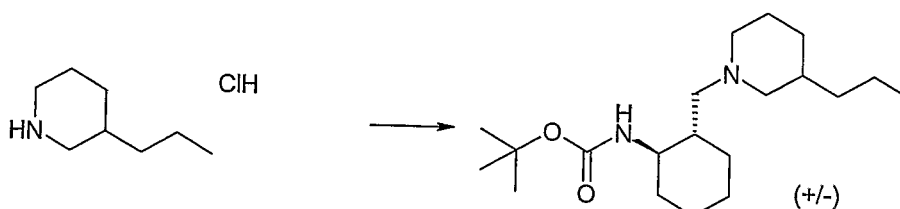


- 5 Step A. The preparation of 3-propylpiperidine hydrochloride



- To a solution of 3-propylpyridine (5.0 g, 41.3 mmol) in HOAc (60 mL) was added Pt₂O (0.5 g) and the mixture was hydrogenated at room temperature (40 psi) for 5 h.
- 10 After being filtered and concentrated, 40% aq. NaOH (50 mL) was added, extracted with EtOAc (3 x 50 mL), dried over Na₂SO₄, then treated with 4N HCl in dioxane, evaporated to give the HCl salt as white powders (6.56 g, 97%).

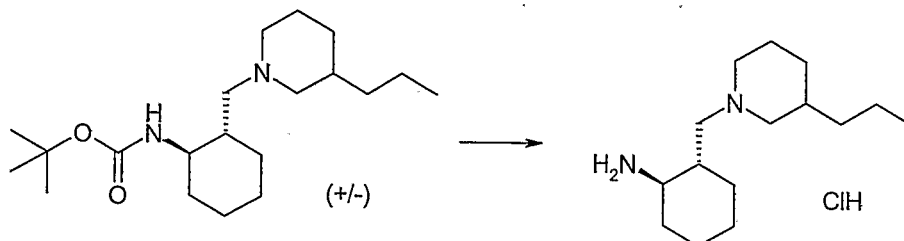
- Step B: The preparation of *trans*-(+/-)- *tert*-butyl {2-[(3-propylpiperidin-1-yl)methyl]cyclohexyl}carbamate
- 15



- The HCl salt from step A (3-propylpiperidine hydrochloride, 328 mg, 2.0 mmol) was added to a solution of *trans*-(+/-)-*tert*-butyl [2-formylcyclohexyl]carbamate (454 mg, 2.0 mmol) in dichloromethane (16 ml). The reaction was stirred at room temperature
- 20 for 30 minutes, and then sodium triacetoxyborohydride (636 mg, 3.00 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 12 hours, and then cooled to 0°C. Water (1 ml) was added dropwise. A 1N sodium hydroxide solution (20 ml) and dichloromethane (80 ml) were added to the mixture. The phases were separated and the aqueous was extracted with dichloromethane
- 25 (2x30ml). The combined organic phases were washed with brine, dried over

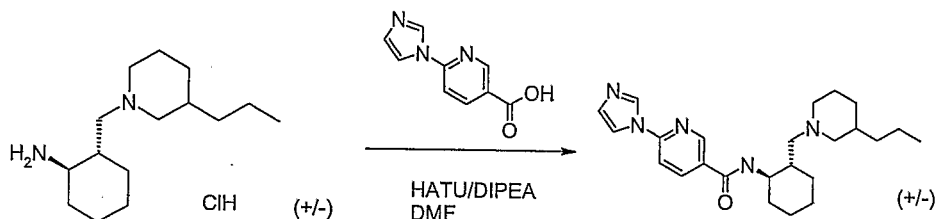
Na₂SO₄, filtered, and concentrated *in vacuo*. The title compound was obtained as a crude oil (554mg, 82%), which was used for the next step without further purification.

Step C: The preparation of *trans*-(+/-)- *tert*-butyl 2-[(3-propylpiperidin-1-yl)methyl]cyclohexyl]carbamate



The crude product from steps B was treated with 4N HCl in dioxane (10 mL), stirred at room temperature for 3 h. After concentrated, the title compound was obtained as its HCl salt (520mg, 95%), which was used for the next step without further purification.

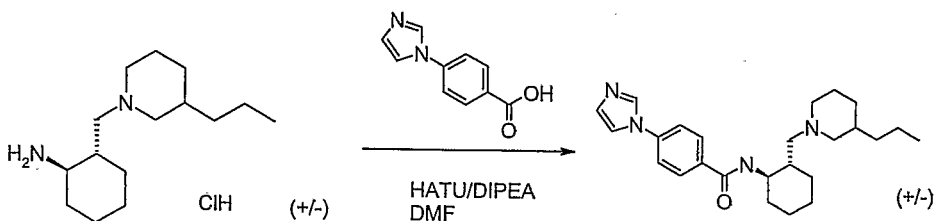
Step D. The preparation of *trans*-(+/-)- *N*-(2-[(3-propylpiperidin-1-yl)methyl]cyclohexyl)-6-(1*H*-imidazol-1-yl)nicotinamide



To a solution of *trans*-(+/-)- 2-[(3-propylpiperidin-1-yl)methyl]cyclohexyl]amine hydrochloride (69 mg, 0.25 mmol) in dry DMF (3 mL) was added 6-(1*H*-imidazol-1-yl)nicotinic acid (57 mg, 0.3 mmol) followed by HATU (114 mg, 0.3 mmol) and diisopropylethylamine (0.10 mL, 0.5 mmol). The mixture was stirred at room temperature for 1 h, and the reaction was quenched with water (5 mL). The solvent was removed *in vacuo*. DCM (15 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified with high pH HPLC to yield *trans*-(+/-)- *N*-(2-[(3-propylpiperidin-1-yl)methyl]cyclohexyl)-6-(1*H*-imidazol-1-yl)nicotinamide (65 mg, 63%) as a white powder. MS (*M*+1): 410.3. ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 0.65 - 0.91 (m, 5 H), 1.00 - 1.18 (m, 4 H), 1.22 - 1.43 (m, 5 H), 1.52 - 1.61 (m, 2 H), 1.63 - 1.84 (m, 5 H), 1.86 - 2.01 (m, 1 H), 2.06 - 2.21 (m, 2 H), 2.31 - 2.49 (m, 1 H), 2.66 - 3.01

(m, 2 H), 3.55 - 3.70 (m, 1 H), 7.17 (s, 1 H), 7.81 (dd, J=8.59, 2.15 Hz, 1 H), 7.95 (s, 1 H), 8.34 (dd, J=8.59, 1.56 Hz, 1 H), 8.60 (s, 1 H), 8.91 (s, 1 H).

Example 173. *trans*-(+/-)- 4-(1*H*-imidazol-1-yl)-*N*-(2-[(3-propylpiperidin-1-yl)methyl]cyclohexyl)benzamide



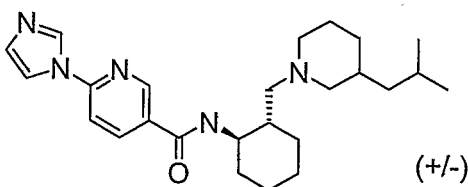
To a solution of *trans*-(+/-)- 2-[(3-propylpiperidin-1-yl)methyl]cyclohexylamine hydrochloride (69 mg, 0.25 mmol) in dry DMF (3 mL) was added 4-(1*H*-imidazol-1-yl)benzoic acid (56 mg, 0.3 mmol) followed by HATU (114 mg, 0.3 mmol) and

diisopropylethylamine (0.10 mL, 0.5 mmol). The mixture was stirred at room temperature for 1 h, and the reaction was quenched with water (5 mL). The solvent was removed in vacuo. DCM (15 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was

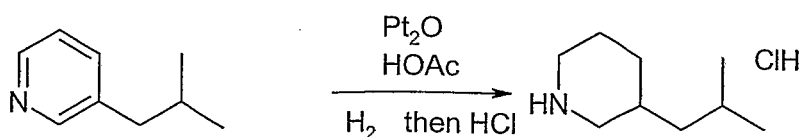
purified with high pH HPLC to yield *trans*-(+/-)- 4-(1*H*-imidazol-1-yl)-*N*-(2-[(3-propylpiperidin-1-yl)methyl]cyclohexyl)benzamide (74 mg, 72%) as a white powder.

MS (M+1): 409.3. ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 0.65 - 0.91 (m, 5 H), 0.97 - 1.06 (m, 1 H), 1.06 - 1.20 (m, 3 H), 1.21 - 1.45 (m, 5 H), 1.53 - 1.83 (m, 7 H), 1.87 - 2.00 (m, 1 H), 2.06 - 2.24 (m, 2 H), 2.36 - 2.51 (m, 1 H), 2.64 - 3.01 (m, 2 H), 3.50 - 3.66 (m, 1 H), 7.17 (s, 1 H), 7.62 - 7.68 (m, 1 H), 7.70 (d, J=7.62 Hz, 2 H), 7.97 (d, J=8.01 Hz, 2 H), 8.24 (d, J=2.93 Hz, 1 H).

Example 174. *trans*-(+/-)- *N*-(2-[(3-isobutylpiperidin-1-yl)methyl]cyclohexyl)-6-(1*H*-imidazol-1-yl)nicotinamide

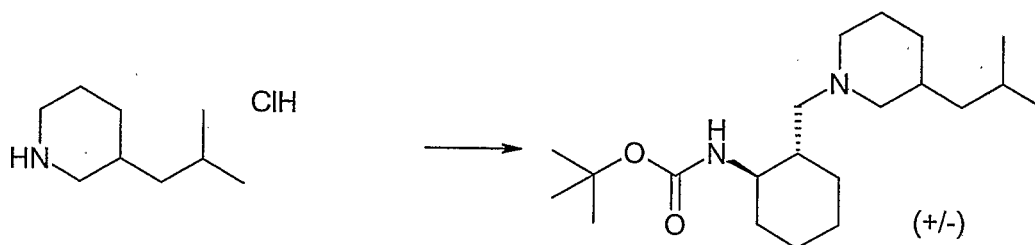


Step A. The preparation of 3-isobutylpiperidine hydrochloride



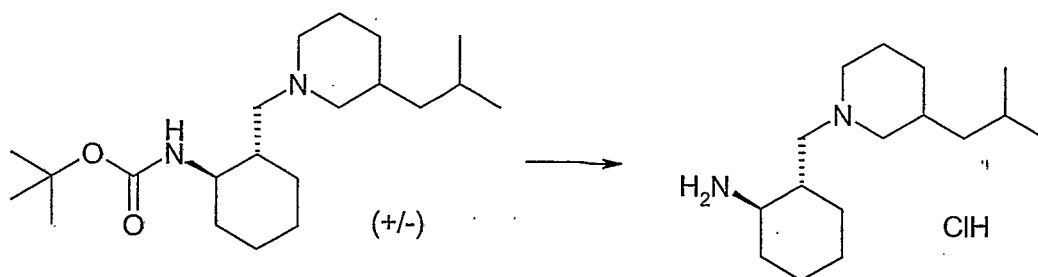
To a solution of 3-isobutylpyridine (2.5 g, 18.5 mmol) in HOAc (40 mL) was added Pt₂O (0.2 g) and the mixture was hydrogenated at room temperature (40 psi) for 5 h. After being filtered and concentrated, 40% aq. NaOH (30 mL) was added, extracted with EtOAc (3 x 40 mL), dried over Na₂SO₄, then treated with 4N HCl in dioxane, evaporated to give the HCl salt as white powders (2.92 g, 89%).

Step B: The preparation of *trans*-(+/-)- *tert*-butyl {2-[(3-isobutylpiperidin-1-yl)methyl]cyclohexyl}carbamate



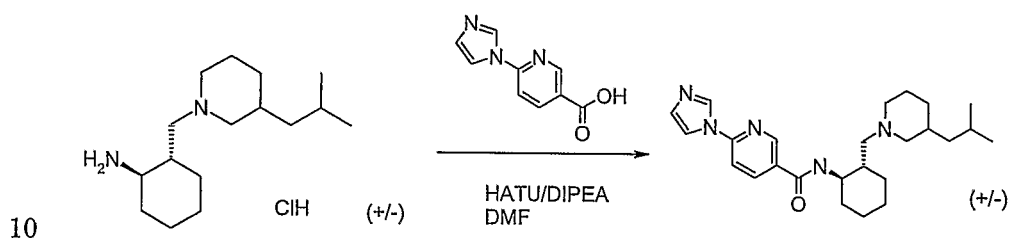
The HCl salt from step A (3-isobutylpiperidine hydrochloride, 356 mg, 2.0 mmol) was added to a solution of *trans*-(+/-)-*tert*-butyl [2-formylcyclohexyl]carbamate (454 mg, 2.0 mmol) in dichloromethane (16 ml). The reaction was stirred at room temperature for 30 minutes, and then sodium triacetoxyborohydride (636 mg, 3.00 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 12 hours, and then cooled to 0°C. Water (1 ml) was added dropwise. A 1N sodium hydroxide solution (20 ml) and dichloromethane (80 ml) were added to the mixture. The phases were separated and the aqueous was extracted with dichloromethane (2x30ml). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The title compound was obtained as a crude oil (624mg, 89%), which was used for the next step without further purification.

Step C: The preparation of *trans*-(+/-)- *tert*-butyl {2-[(3-isobutylpiperidin-1-yl)methyl]cyclohexyl}carbamate



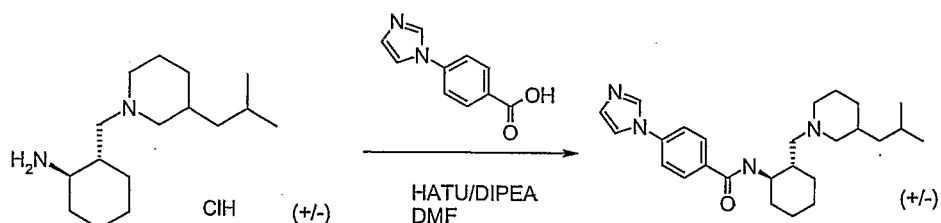
The crude product from steps B was treated with 4N HCl in dioxane (10 mL), stirred at room temperature for 3 h. After concentrated, the title compound was obtained as its HCl salt (543mg, 94%), which was used for the next step without further purification.

Step D. The preparation of *trans*-(+/-)- *N*-(2-([3-isobutylpiperidin-1-yl]methyl)cyclohexyl)-6-(1*H*-imidazol-1-yl)nicotinamide



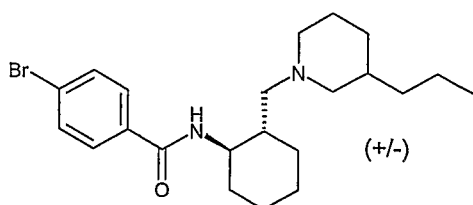
To a solution of *trans*-(+/-)- 2-([3-isobutylpiperidin-1-yl]methyl)cyclohexyl]amine hydrochloride (73 mg, 0.25 mmol) in dry DMF (3 mL) was added 6-(1*H*-imidazol-1-yl)nicotinic acid (57 mg, 0.3 mmol) followed by HATU (114 mg, 0.3 mmol) and diisopropylethylamine (0.10 mL, 0.5 mmol). The mixture was stirred at room temperature for 1 h, and the reaction was quenched with water (5 mL). The solvent was removed in vacuo. DCM (15 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified with high pH HPLC to yield *trans*-(+/-)- *N*-(2-([3-isobutylpiperidin-1-yl]methyl)cyclohexyl)-6-(1*H*-imidazol-1-yl)nicotinamide (62 mg, 58%) as a white powder. MS (M+1): 424.3. ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 0.65 (dd, J=5.96, 2.44 Hz, 3 H), 0.76 - 0.97 (m, 5 H), 0.99 - 1.16 (m, 2 H), 1.23 - 1.51 (m, 5 H), 1.59 - 1.86 (m, 8 H), 1.85 - 2.04 (m, 1 H), 2.06 - 2.27 (m, 2 H), 2.36 - 2.54 (m, 1 H), 2.62 - 3.09 (m, 2 H), 3.54 - 3.71 (m, 1 H), 7.17 (s, 1 H), 7.78 - 7.85 (m, 1 H), 7.95 (s, 1 H), 8.36 (dd, J=5.66, 2.93 Hz, 1 H), 8.61 (s, 1 H), 8.84 - 8.97 (m, 1 H).

Example 175. *trans*-(+/-)- 4-(1*H*-imidazol-1-yl)-*N*-{2-[(3-isobutylpiperidin-1-yl)methyl]cyclohexyl}benzamide



To a solution of *trans*-(+/-)- 2-[(3-isobutylpiperidin-1-yl)methyl]cyclohexylamine hydrochloride (73 mg, 0.25 mmol) in dry DMF (3 mL) was added 4-(1*H*-imidazol-1-yl)benzoic acid (56 mg, 0.3 mmol) followed by HATU (114 mg, 0.3 mmol) and diisopropylethylamine (0.10 mL, 0.5 mmol). The mixture was stirred at room temperature for 1 h, and the reaction was quenched with water (5 mL). The solvent was removed in vacuo. DCM (15 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified with high pH HPLC to yield *trans*-(+/-)- 4-(1*H*-imidazol-1-yl)-*N*-{2-[(3-isobutylpiperidin-1-yl)methyl]cyclohexyl}benzamide (74 mg, 72%) as a white powder. MS (M+1): 423.3. ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 0.60 - 0.69 (m, 3 H), 0.78 - 0.97 (m, 5 H), 0.97 - 1.19 (m, 2 H), 1.23 - 1.51 (m, 5 H), 1.56 - 1.82 (m, 8 H), 1.82 - 2.11 (m, 2 H), 2.10 - 2.28 (m, 1 H), 2.37 - 2.57 (m, 1 H), 2.72 - 3.15 (m, 2 H), 3.51 - 3.70 (m, 1 H), 7.17 (s, 1 H), 7.66 (s, 1 H), 7.70 (dd, J=8.50, 1.46 Hz, 2 H), 7.97 (d, J=8.40 Hz, 2 H), 8.25 (s, 1 H).

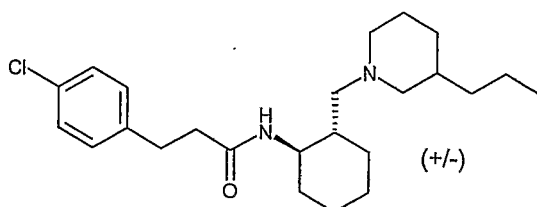
Example 176. *trans*-(+/-)-4-Bromo-*N*-{2-[(3-propylpiperidin-1-yl)methyl]cyclohexyl}benzamide



Following the HATU coupling procedure described in Example 173: The title compound was obtained as a white solid in a 50% yield (111 mg). MS (M+1): 421.3. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.68 (dd, J=7.13 Hz, 3 H one isomer), 0.74 - 0.86 (m, 1 H), 0.93 (t, J=7.32 Hz, 3 H one isomer), 0.96 - 1.92 (m, 18 H), 2.04 (dd, J=12.79, 3.61 Hz, 1 H), 2.30 - 2.67 (m, 3 H), 3.10 (d, J=10.35 Hz, 1 H), 3.39 (t,

J=10.06 Hz, 1 H), 7.50 - 7.57 (m, 2 H), 7.71 (t, J=7.71 Hz, 2 H), 9.18 (d, J=17.58 Hz, 1 H).

Example 177. *trans*-(+/-)-3-(4-Chlorophenyl)-N-{2-[(3-propylpiperidin-1-yl)methyl]cyclohexyl}propanamide

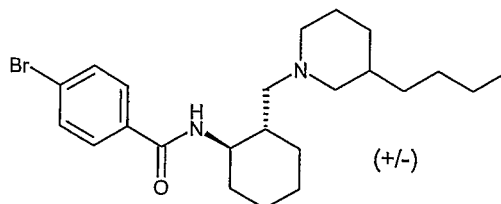


5

Following the procedure described in Example 173, the title compound was obtained as a white solid in a 52% yield (112 mg). MS (M+1): 405.3. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.77 - 1.06 (m, 3 H), 0.85 (t, J=7.23 Hz, 3 H one isomer), 0.89 (t, J=7.32 Hz, 3 H one isomer), 1.08 - 1.47 (m, 9 H), 1.52 - 2.03 (m, 8 H), 2.16 - 2.59 (m, 5 H), 2.82 - 3.03 (m, 3 H), 3.15 - 3.25 (m, 1 H), 7.10 - 7.16 (m, 2 H), 7.19 - 7.25 (m, 2 H), 8.16 (amide NH, one isomer), 8.23 (amide NH, one isomer).

10

Example 178. *trans*-(+/-)-4-Bromo-N-{2-[(3-butylpiperidin-1-

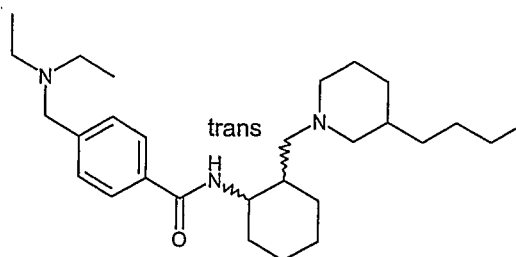


yl)methyl]cyclohexyl}benzamide

Following the procedure described in Example 165: the title compound was obtained as a white solid in a 52% yield (80 mg). MS (M+1): 435.3. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.72 - 1.46 (m, 15 H), 1.48 - 1.87 (m, 8 H), 1.99 - 2.25 (m, 2 H), 2.37 - 2.86 (m, 3 H), 3.20 (s, 1 H), 3.51 (s, 1 H), 7.48 - 7.59 (m, 2 H), 7.77 (d, J=7.42 Hz, 2 H), 9.03 (s, 1 H).

20

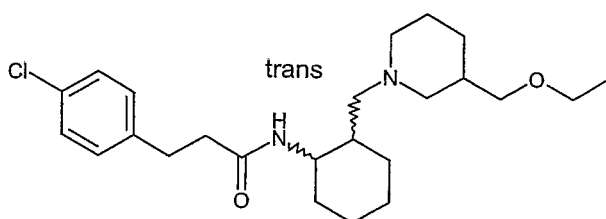
Example 179. *trans*-(+/-)-N-{2-[(3-Butylpiperidin-1-yl)methyl]cyclohexyl}-4-



[(diethylamino)methyl]benzamide

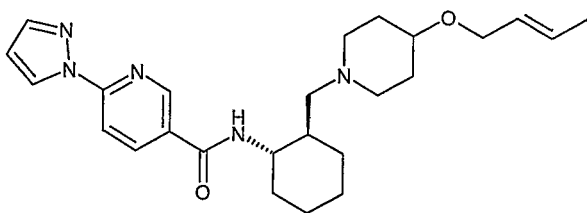
Following the procedure described in Example 165: the title compound was obtained as a yellow solid in a 12% yield (18 mg). MS (M+1): 442.3. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.72 - 0.95 (m, 5 H), 0.96 - 1.46 (m, 17 H), 1.50 - 1.95 (m, 7 H), 2.03 - 2.46 (m, 3 H), 2.47 - 2.65 (m, 5 H), 2.75 (s, 1 H), 3.26 (s, 1 H), 3.47 - 3.76 (m, 3 H), 7.35 - 7.48 (m, 2 H), 7.89 (s, 2 H), 8.80 (s, 1 H).

Example 180. *trans*-(+/-)-3-(4-Chlorophenyl)-N-(2-[[3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)propanamide



Following the procedure described in Example 2: the title compound was obtained as a white solid in a 50% yield (111 mg). MS (M+1): 421.3. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.85 - 1.05 (m, 3 H), 1.16 (dd, J=7.03 Hz, 3 H one isomer), 1.21 (t, J=7.03 Hz, 3 H one isomer), 1.22 - 2.03 (m, 13 H), 2.17 - 2.47 (m, 5 H), 2.83 - 3.01 (m, 3 H), 3.15 - 3.32 (m, 3 H), 3.37 - 3.50 (m, 2 H), 7.11 - 7.18 (m, 2 H), 7.21 - 7.25 (m, 2 H), 8.04 (br s, 1H). Anal. Calcd for C₂₄ H₃₇ Cl N₂ O₂: C, 68.47; H, 8.86; N, 6.65. Found: C, 68.03; H, 8.63; N, 6.57.

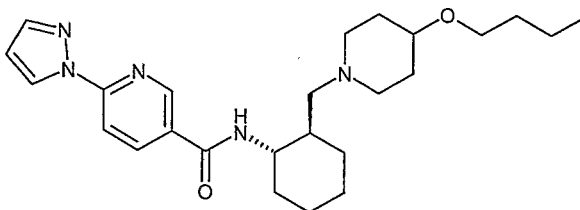
Example 181. *N*-[(1*S*,2*R*)-2-({4-[(2*E*)-But-2-en-1-yloxy]piperidin-1-yl)methyl]cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide



trans-(+/-)-*N*-[2-({4-[(2*E*)-But-2-en-1-yloxy]piperidin-1-yl)methyl]cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide from Example 117 was separated on chiral AD column (10% ethanol in hexanes), and the second fraction was collected to yield the title compound as a pure enantiomer. MS (M+1): 438.3. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.05 - 1.16 (m, 2 H), 1.25 - 1.47 (m, 2 H), 1.58 (s, 3 H), 1.59 - 1.67 (m, 3 H), 1.71 (dq, J=6.27, 1.29 Hz, 2 H), 1.73 - 1.81 (m, 3 H), 2.03 (t, J=9.37 Hz, 1 H), 2.10 (d, J=12.50 Hz, 1 H), 2.38 (s, 1 H), 2.43 (dd, J=12.89, 9.57 Hz,

1 H), 2.50 (s, 1 H), 2.63 (dd, J=12.69, 2.34 Hz, 1 H), 2.89 (s, 1 H), 3.35 - 3.48 (m, 2 H), 3.88 (dt, J=6.01, 1.10 Hz, 2 H), 5.51 - 5.61 (m, 1 H), 5.64 - 5.74 (m, 1 H), 6.49 (dd, J=2.64, 1.66 Hz, 1 H), 7.76 (dd, J=1.66, 0.68 Hz, 1 H), 8.03 (dd, J=8.50, 0.68 Hz, 1 H), 8.24 (dd, J=8.59, 2.34 Hz, 1 H), 8.62 (dd, J=2.64, 0.68 Hz, 1 H), 8.87 (dd, J=2.25, 0.68 Hz, 1 H), 9.11 (s, 1 H). Anal. Calcd for C₂₅H₃₅N₅O₂ · 0.55 H₂O: C, 67.10; H, 8.13; N, 15.65. Found: C, 67.14; H, 8.19; N, 15.56. Chiralpak AD column, 4.6 x 250mm column 10%isopropanol/90%hexane, 1 peak at 11.423min, K': 1.75 >99%(215nm), >99%(254nm), >99%(280nm).

10 **Example 182. *N*-{(1*S*,2*R*)-2-[(4-Butoxypiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-**



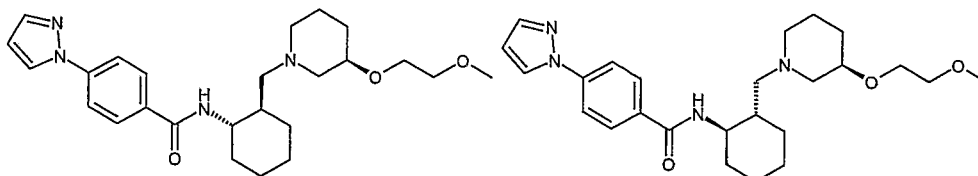
pyrazol-1-yl)nicotinamide

The title compound was obtained from the hydrogenation of *N*-[(1*S*,2*R*)-2-[(4-[(2*E*)-But-2-en-1-yloxy]piperidin-1-yl)methyl]cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide from Example 181. MS (M+1): 440.3. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm

15 0.91 (t, J=7.32 Hz, 3 H), 1.06 - 1.24 (m, 2 H), 1.24 - 1.45 (m, 4 H), 1.44 - 1.58 (m, 3 H), 1.60 - 1.94 (m, 8 H), 2.05 - 2.31 (m, 2 H), 2.41 - 2.70 (m, 3 H), 2.87 - 3.04 (m, 1 H), 3.31 - 3.44 (m, 1 H), 3.38 (t, J=6.54 Hz, 2 H), 3.46 - 3.55 (m, 1 H), 6.48 (dd, J=2.64, 1.66 Hz, 1 H), 7.76 (d, J=0.98 Hz, 1 H), 8.03 (d, J=8.40 Hz, 1 H), 8.29 (d, J=7.81 Hz, 1 H), 8.62 (d, J=2.73 Hz, 1 H), 8.90 (s, 1 H), 9.09 (s, 1 H).

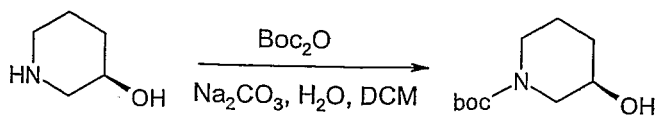
20

Example 183 and 184. *N*-(1*S*,2*R*)-2-[(3*R*)-3-(2-Methoxyethoxy)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrazol-1-yl)benzamide and *N*-(1*R*,2*S*)-2-[(3*R*)-3-(2-Methoxyethoxy)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrazol-1-yl)benzamide



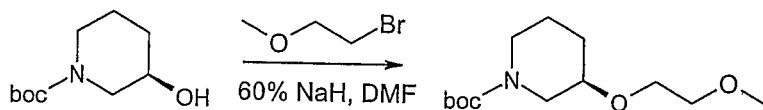
25

Step A: The preparation of *tert*-butyl (3*R*)-3-hydroxypiperidin-1-carboxylate



To a solution of the hydrochloric salt of (3R)-3-hydroxypiperidine (2.0 g, 14.6 mmol) in water (50 mL) and dichloromethane (40 mL) were added sodium carbonate (4.12 g, 29 mmol) and di-*tert*-butyl dicarbonate (3.5 g, 16 mmol). The reaction was stirred at room temperature overnight. The reaction was diluted with water (50 mL) and dichloromethane (50 mL). The phases were separated and the aqueous was extracted with dichloromethane (2x30ml). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The product was purified by column chromatography (30% to 50% heptane in ethyl acetate). The product was obtained as colourless oil (2.32 g, 79%). ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.42 - 1.54 (m, 2 H), 1.46 (s, 9 H), 1.69 - 1.80 (m, 1 H), 1.86 - 1.93 (m, 1 H), 2.20 - 2.72 (m, 1 H), 2.99 - 3.16 (m, 2 H), 3.56 (d, *J*=4.49 Hz, 1 H), 3.50-3.60 (d, *J*=1.56 Hz, 1 H), 3.73 - 3.84 (m, 1 H).

Step B: The preparation of *tert*-butyl (3R)-3-(2-methoxyethoxy)piperidine-1-carboxylate

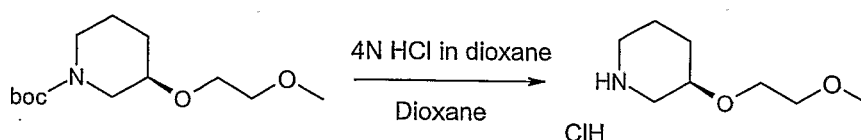


To a solution of *tert*-butyl (3R)-3-hydroxypiperidine-1-carboxylate (300 mg, 1.5 mmol) in dry DMF (5 mL) was added sodium hydride (60%, 115 mg, 3.0 mmol) at 0°C under nitrogen and the suspension was stirred at room temperature for 30 min. 1-Bromo-2-methoxyethane (0.17 mL, 1.8 mmol) was added to the reaction mixture and stirred over night at room temperature. The reaction mixture was heated at 50°C and Sodium hydride (60%, 58 mg, 1.5 mmol) was added, then 1-bromo-2-methoxyethane (0.17 mL, 1.8 mmol). The reaction mixture was stirred at 50°C for 2 hours. Sodium hydride (60%, 58 mg, 1.5 mmol) was added, then 1-bromo-2-methoxyethane (0.17 mL, 1.8 mmol). The reaction was stirred at 50°C for 2 hours and then cooled to room temperature. The reaction was quenched with water (1 mL) at 0°C. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (30 mL) and water (25 mL). The phases were separated and the aqueous was extracted with dichloromethane (2x30ml). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The product was purified by

column chromatography (50% heptane in ethyl acetate). The product was obtained as colourless oil (328 mg, 84%). ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.38 - 1.53 (m, 4 H), 1.46 (s, 9 H), 1.68 - 1.79 (m, 1 H), 1.93 - 2.03 (m, 1 H), 2.89 - 3.00 (m, 2 H), 3.27 - 3.35 (m, 1 H), 3.39 (s, 3 H), 3.51 - 3.56 (m, 2 H), 3.59 - 3.73 (m, 2 H).

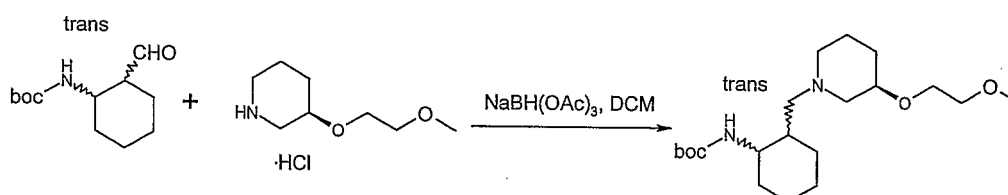
5

Step C: The preparation of (3*R*)-3-(2-methoxyethoxy)piperidine hydrochloride



10 *tert*-butyl (3*R*)-3-(2-methoxyethoxy)piperidine-1-carboxylate from step A was stirred in 4N HCl in dioxane (3 mL) and dioxane (10 mL) at room temperature overnight. The solvent was removed *in vacuo*. The product was used directly for next step.

Step D: The preparation of trans (±)-*tert*-butyl (2-[(3*R*)-3-(2-methoxyethoxy)piperidin-1-yl]methyl)cyclohexyl)carbamate

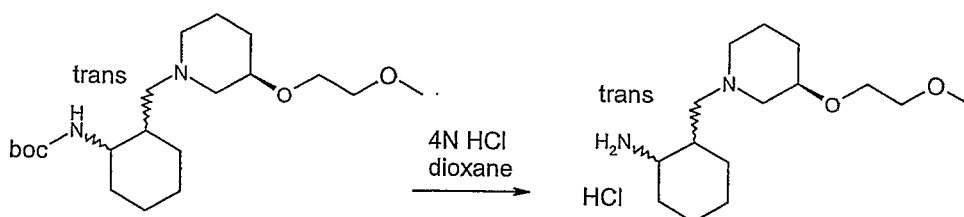


15

The product from step C was added to a solution of trans-(±)-*tert*-butyl [2-formylcyclohexyl]carbamate (290 mg, 4.40 mmol) in dichloromethane (13 ml). The reaction was stirred at room temperature for 30 minutes, and then sodium triacetoxyborohydride (530 mg, 2.54 mmol) was added portionwise to the reaction mixture. The reaction was stirred at room temperature overnight, and then cooled to 0°C. Water (5 ml) was added dropwise. A 1N sodium hydroxide solution (40 ml) and dichloromethane (50 ml) were added to the mixture. The phases were separated and the aqueous was extracted with dichloromethane (2x30ml). The combined organic phases were washed with brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The product was used directly for the next step without further purification.

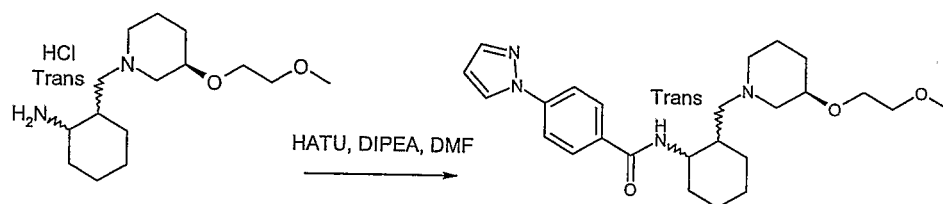
25

Step E: The preparation of trans(±)-(2-[(3*R*)-3-(2-methoxyethoxy)piperidin-1-yl]methyl)cyclohexyl)amine hydrochloride



A 4N solution of hydrochloric acid in dioxane (6.0 ml, 24.0 mmol) was added to a solution of the crude product from step D trans($\pm$)-*tert*-butyl (2-[[*(3R)*-3-(2-methoxyethoxy)piperidin-1-yl]methyl]cyclohexyl)carbamate (1.27 mmol) in dioxane (20 ml). The reaction was stirred at room temperature overnight. The solvent was removed *in vacuo*. MS ($M+1$): 271.2.

Step F: The preparation of trans($\pm$)-*N*-(2-[[*(3R)*-3-(2-methoxyethoxy)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrazol-1-yl)benzamide

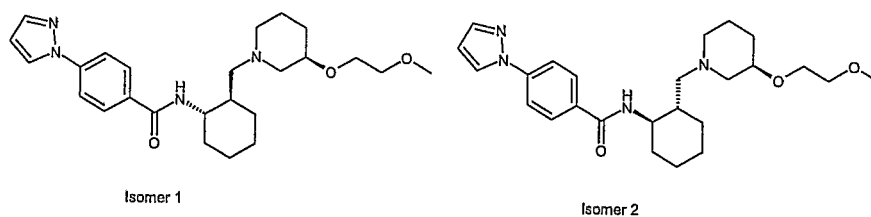


10

To the solution of trans($\pm$)-2-[[*(3R)*-3-(2-methoxyethoxy)piperidin-1-yl]methyl]cyclohexylamine hydrochloride (161 mg, 0.47 mmol) in dry DMF (10 mL) at 0°C was added 6-(1*H*-imidazol-1-yl)benzoic acid (98 mg, 0.52 mmol) followed by diisopropylethylamine (0.33 mL, 1.88 mmol) and HATU (198 mg, 0.52 mmol). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*. A 1N sodium hydroxide solution (20 ml) and dichloromethane (30 ml) were added to the mixture. The phases were separated and the aqueous was extracted with dichloromethane (2x30ml). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*.

20

Step G: Separation of two diastereoisomers

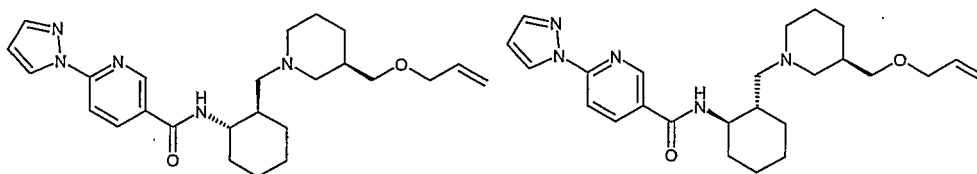


The diastereoisomer mixtures from Step F were separated with high pH reverse phase HPLC to yield both diastereoisomers.

Isomer 1 (*N*-(1*S*,2*R*)-2-[[*(3R)*-3-(2-methoxyethoxy)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrazol-1-yl)benzamide, white solid (41 mg, 20%): MS (*M*+1): 441.3. ¹H NMR (400 MHz, CHLOROFORM-*D*) δ ppm 1.03 - 1.48 (m, 5 H), 1.53 - 1.68 (m, 3 H), 1.68 - 1.80 (m, 3 H), 1.84 (br s, 1 H), 1.96 (t, *J*=11.03 Hz, 1 H), 2.02 - 2.14 (m, 2 H), 2.43 - 2.55 (m, 2 H), 2.60 (d, *J*=10.35 Hz, 1 H), 3.33 (d, *J*=8.59 Hz, 1 H), 3.40 (s, 3 H), 3.43 - 3.50 (m, 2 H), 3.51 - 3.57 (m, 2 H), 3.60 - 3.68 (m, 1 H), 3.69 - 3.77 (m, 1 H), 6.51 (dd, *J*=2.54, 1.76 Hz, 1 H), 7.72 - 7.79 (m, 3 H), 7.93 (d, *J*=8.40 Hz, 2 H), 8.00 (d, *J*=2.54 Hz, 1 H), 8.74 (s, 1 H). Anal. Calcd for C₂₅H₃₆N₄O₃ · 0.7 H₂O: C, 66.26; H, 8.32; N, 12.36. Found: C, 66.96; H, 8.32; N, 12.36.

Isomer 2 (*N*-(1*R*,2*S*)-2-[[*(3R)*-3-(2-Methoxyethoxy)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrazol-1-yl)benzamide: White solid (37 mg, 18%), MS (*M*+1): 441.3. ¹H NMR (400 MHz, CHLOROFORM-*D*) δ ppm 1.03 - 1.16 (m, 2 H), 1.25 - 1.50 (m, 4 H), 1.53 - 1.82 (m, 7 H), 1.99 - 2.09 (m, 1 H), 2.10 (d, *J*=12.69 Hz, 1 H), 2.41 (dd, *J*=12.01, 9.86 Hz, 2 H), 2.56 - 2.69 (m, 2 H), 3.20 (s, 1 H), 3.23 (br s, 3 H), 3.35 - 3.51 (m, 5 H), 6.50 (dd, *J*=2.54, 1.76 Hz, 1 H), 7.74 - 7.77 (m, 2 H), 7.77 - 7.80 (m, 1 H), 8.00 (d, *J*=2.15 Hz, 1 H), 8.05 (d, *J*=8.40 Hz, 2 H), 8.96 (br s, 1 H).

Example 185 and 186: *N*-[(1*S*,2*R*)-2-[[*(3R)*-3-[(Allyloxy)methyl]piperidin-1-yl]methyl]cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide and *N*-[(1*R*,2*S*)-2-[[*(3R)*-3-[(Allyloxy)methyl]piperidin-1-yl]methyl]cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide



Following the HATU coupling procedure described in Example 129, Step E: the diastereo-mixture *trans*(±)-*N*-[2-[[*(3R)*-3-[(Allyloxy)methyl]piperidin-1-yl]methyl]cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide were prepared from *trans*(±)-[2-[[*(3R)*-3-[(allyloxy)methyl]piperidin-1-yl]methyl]cyclohexyl]amine hydrochloride, then

the diastereomeric mixture was separated by chiral AD column (15% isopropanol in hexanes) to yield diastereo-isomeric pure compounds.

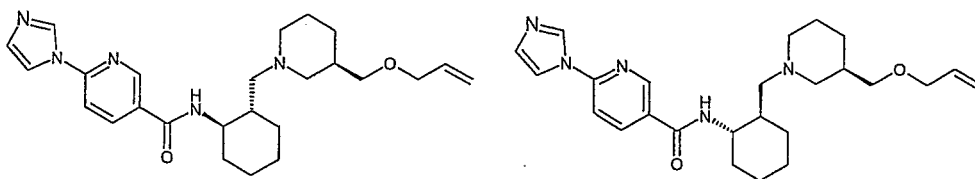
Fraction 1: (*N*-[(1*R*,2*S*)-2-({(3*R*)-3-[(Allyloxy)methyl]piperidin-1-yl)methyl]cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide): MS (*M*+1): 438.3. ¹H NMR (400 MHz,

5 CHLOROFORM-*D*) δ ppm 0.88 - 1.03 (m, 1 H), 1.04 - 1.17 (m, 2 H), 1.24 - 1.48 (m, 2 H), 1.53 - 1.87 (m, 10 H), 2.09 (d, *J*=12.69 Hz, 1 H), 2.43 (dd, *J*=12.89, 9.77 Hz, 1 H), 2.60 - 2.74 (m, 2 H), 3.03 - 3.18 (m, 3 H), 3.43 (tt, *J*=10.55, 3.12 Hz, 1 H), 3.69 (d, *J*=5.47 Hz, 2 H), 4.98 - 5.10 (m, 2 H), 5.62 - 5.75 (dddd, *J*=17.24, 10.55, 5.57, 5.32 Hz, 1 H), 6.49 (dd, *J*=2.54, 1.56 Hz, 1 H), 7.76 (d, *J*=0.78 Hz, 1 H), 8.01 (d, *J*=8.59
10 Hz, 1 H), 8.24 (dd, *J*=8.50, 2.25 Hz, 1 H), 8.61 (d, *J*=2.54 Hz, 1 H), 8.86 (d, *J*=1.76 Hz, 1 H), 9.14 (s, 1 H). Anal. Calcd for C₂₅H₃₅N₅O₂: C, 68.62; H, 8.06; N, 16.00. Found: C, 68.30; H, 7.89; N, 15.93. Chiralpak AD column, 4.6 x 250mm column 10%isopropanol/90%hexane, 1 peak at 8.163min, *K'*: 0..97 >99%(215nm), >99%(254nm), >99%(280nm)

15

Fraction 2: (*N*-[(1*S*,2*R*)-2-({(3*R*)-3-[(Allyloxy)methyl]piperidin-1-yl)methyl]cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide): MS (*M*+1): 438.3. ¹H NMR (400 MHz, CHLOROFORM-*D*) δ ppm 0.90 (qd, *J*=12.40, 3.81 Hz, 1 H), 1.01 - 1.18 (m, 2 H), 1.19 - 1.44 (m, 3 H), 1.45 - 1.57 (m, 2 H), 1.59 - 1.82 (m, 5 H), 1.94 (dd, 2 H), 2.07 (d, *J*=12.89 Hz, 1 H), 2.43 (dd, *J*=12.50, 10.16 Hz, 1 H), 2.61 (t, *J*=11.23 Hz, 2 H), 3.23 (t, *J*=8.50 Hz, 1 H), 3.31 - 3.47 (m, 3 H), 3.99 (d, *J*=5.47 Hz, 2 H), 5.18 - 5.35 (m, 2 H), 5.94 (ddd, *J*=22.61, 10.60, 5.66 Hz, 1 H), 6.49 (s, 1 H), 7.77 (s, 1 H), 8.01 (d, *J*=8.59 Hz, 1 H), 8.25 (dd, *J*=8.59, 2.15 Hz, 1 H), 8.62 (d, *J*=2.15 Hz, 1 H), 8.87 (d, *J*=1.56 Hz, 1 H), 9.21 (s, 1 H). Anal. Calcd for C₂₅H₃₅N₅O₂: C, 68.82; H, 8.06; N, 16.00. Found: C, 68.30; H, 7.83; N, 15.73. Chiralpak AD column, 4.6 x 250mm
25 column 10%isopropanol, 1 peak at 12.653min, *K'*: 2.05 >99%(215nm), >99%(254nm), >99%(280nm)

30 **Example 187 and 188.** *N*-[(1*R*,2*S*)-2-({(3*R*)-3-[(Allyloxy)methyl]piperidin-1-yl)methyl]cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide and *N*-[(1*S*,2*R*)-2-({(3*R*)-3-[(Allyloxy)methyl]piperidin-1-yl)methyl]cyclohexyl]-6-(1*H*-imidazol-1-yl)nicotinamide

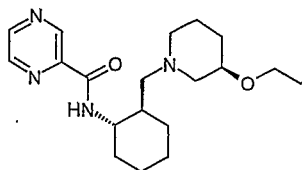


The diastereo mixture *trans*($\pm$)-*N*-[2-((3*R*)-3-[(allyloxy)methyl]piperidin-1-yl)methyl)cyclohexyl]-6-(1*H*-imidazol-1-yl)nicotinamide from Example 129 was separated by chiral AD column (10% ethanol in hexanes) to produce two pure diastereoisomers.

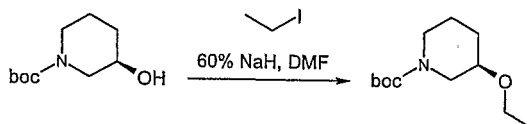
Fraction 1: (*N*-[(1*R*,2*S*)-2-((3*R*)-3-[(Allyloxy)methyl]piperidin-1-yl)methyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide): MS (*M*+1): 438.3. ¹H NMR (400 MHz, CHLOROFORM-*D*) δ ppm 0.96 (qd, *J*=12.11, 3.32 Hz, 1 H), 1.05 - 1.18 (m, 2 H), 1.26 - 1.48 (m, 2 H), 1.52 - 1.89 (m, 10 H), 2.10 (d, *J*=13.28 Hz, 1 H), 2.44 (t, *J*=10.84 Hz, 1 H), 2.67 (dd, *J*=3 5.74, 10.94 Hz, 2 H), 3.03 - 3.18 (m, 3 H), 3.44 (t, *J*=10.16 Hz, 1 H), 3.71 (d, *J*=5.47 Hz, 2 H), 5.00 - 5.12 (m, 2 H), 5.62 - 5.78 (m, *J*=17.31, 10.67, 5.47, 5.22 Hz, 1 H), 7.22 (t, 1 H), 7.39 (dd, *J*=8.40, 0.78 Hz, 1 H), 7.67 (t, *J*=1.37 Hz, 1 H), 8.30 (dd, *J*=8.50, 2.25 Hz, 1 H), 8.40 (s, 1 H), 8.89 (d, *J*=1.95 Hz, 1 H), 9.21 (s, 1 H). Chiralpak OD column, 4.6 x 250mm column 10%Ethanol/90%hexane, 1 peak at 10.672min, *K'*: 1.57, >99%(215nm), >99%(254nm), >99%(280nm)

Fraction 2: ((*N*-[(1*S*,2*R*)-2-((3*R*)-3-[(Allyloxy)methyl]piperidin-1-yl)methyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide (MS (*M*+1): 438.3. ¹H NMR (400 MHz, CHLOROFORM-*D*) δ ppm 0.85 - 0.99 (m, 1 H), 1.02 - 1.58 (m, 6 H), 1.59 - 1.84 (m, 6 H), 1.95 (t, *J*=10.35 Hz, 2 H), 2.09 (d, *J*=13.09 Hz, 1 H), 2.43 (t, *J*=10.84 Hz, 1 H), 2.60 (s, 2 H), 3.24 (dd, *J*=9.08, 7.91 Hz, 1 H), 3.31 - 3.48 (m, 3 H), 4.00 (dt, *J*=5.71, 1.34 Hz, 2 H), 5.20 - 5.34 (m, 2 H), 5.89 - 6.00 (ddt, *J*=17.16, 10.42, 5.74 Hz, 1 H), 7.22 (s, 1 H), 7.39 (dd, *J*=8.50, 0.68 Hz, 1 H), 7.69 (s, 1 H), 8.31 (dd, *J*=8.40, 2.34 Hz, 1 H), 8.42 (s, 1 H), 8.89 (d, *J*=1.76 Hz, 1 H), 9.29 (s, 1 H). Chiralpak OD column, 4.6 x 250mm column 10%Ethanol/90%hexane, 1 peak at 13.684min, *K'*: 2.30, >99%(215nm), >99%(254nm), >99%(280nm)

Example 189. (*N*-[(1*S*,2*R*)-2-[(3*R*)-3-ethoxypiperidin-1-yl)methyl]cyclohexyl)pyrazine-2-carboxamide

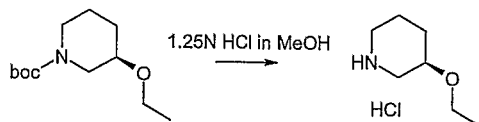


Step A. The preparation of *tert*-butyl 3*R*-(ethoxy)piperidin-1-carboxylate



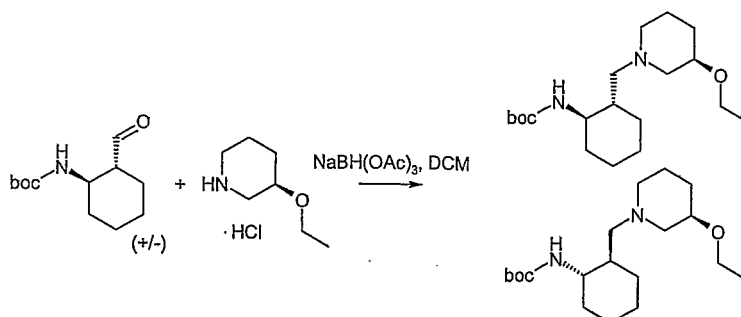
- 5 To a solution of *tert*-butyl 3*R*-(hydroxy)piperidin-1-carboxylate (145 mg, 0.72 mmol) in dry DMF (3 mL) was added NaH (60% , 55 mg, 1.44 mmol) at 0°C under nitrogen and the suspension was stirred at room temperature for 30 min. ethyl iodide (0.07 mL, 0.86 mmol) was added to the reaction mixture and stirred over night at room temperature. Quenched with water. Extracted with dichloromethane (3 x 20 mL), washed with brine, dried over Na₂SO₄. Removal of solvent gave 146 mg of crude product, which was used for the next step without further purification. MS (M+1): 230.1 (m-55): 174.0
- 10

Step B. The preparation of 3*R*-(ethoxy)piperidine hydrochloride salt



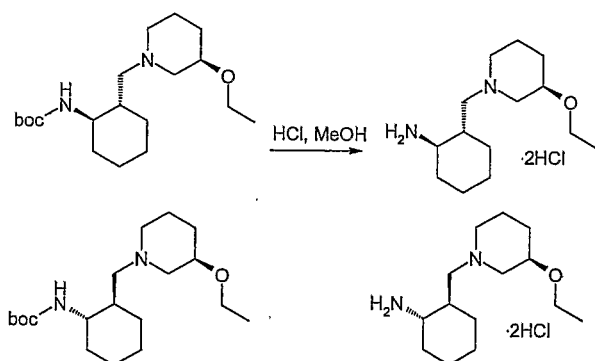
- 15 A 1.25N solution of hydrochloric acid in MeOH (8.0 mL, 10.0 mmol) was added to a solution of the crude product from step A *tert*-butyl 3*R*-(ethoxy)piperidin-1-carboxylate (0.72 mmol). The reaction was stirred at room temperature for 3 days. The mixture was concentrated *in vacuo* to get 153 mg crude. The product was used directly for the next step without further purification. MS (M+1): 130.0.
- 20

Step C. The preparation of *tert*-butyl ((1*R*^{*}, 2*S*^{*})-2-[[3*R*-(3-ethoxypiperidin-1-yl)methyl]cyclohexyl)carbamate



Crude product from step B (3R)-3-ethoxypiperidine hydrochloride salt (153 mg, 0.60 mmol) was added to a solution of tert-butyl *trans*-(+/-)- [2-formylcyclohexyl]carbamate (136 mg crude, 0.72 mmol) in dichloromethane (4 mL). The reaction was stirred at room temperature for 30 minutes, and then sodium triacetoxyborohydride (254 mg, 1.2 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 12Hours. Water (1 mL) was added dropwise. A 2N sodium hydroxide solution (10 mL) and dichloromethane (30 mL) were added to the mixture. The phases were separated and the aqueous was extracted with dichloromethane (2x15mL). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to get 167 mg crude product. MS (m+1): 341.3. The product was used directly for the next step without further purification.

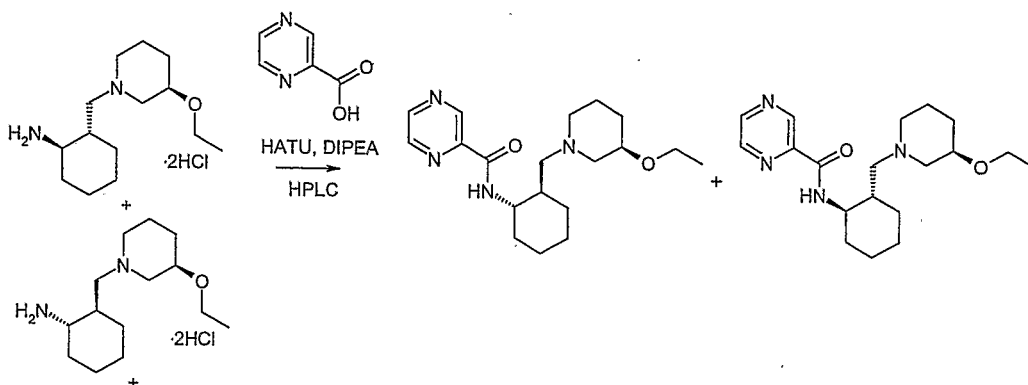
Step D. The preparation of *trans*-2-[[[(3R)-3-ethoxypiperidin-1-yl]methyl]cyclohexyl]amine hydrochloride salt



A 1.25N solution of hydrochloric acid in MeOH (8.0 mL, 10.0 mmol) was added to a solution of the crude product from step C *trans*-tert-butyl (2-[[[(3R)-3-ethoxypiperidin-1-yl]methyl]cyclohexyl]carbamate (0.50 mmol). The reaction was stirred at room temperature for overnight. 1.25N solution of hydrochloric acid in MeOH was added until full conversion if reaction not completed. The mixture was concentrated *in*

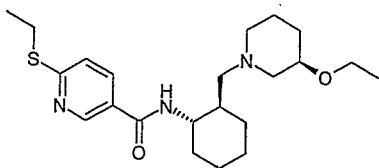
vacuo. The product was used directly for the next step without further purification. MS (M+1): 241.2

Step E. The preparation of *N*-((1*S*,2*R*)-2-[[*(3R)*-3-ethoxypiperidin-1-yl]methyl]cyclohexyl)pyrazine-2-carboxamide



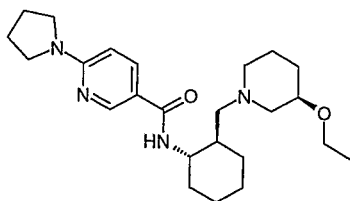
A solution of pyrazine-2-carboxylic acid (75 mg, 0.6 mmol), HATU (228 mg, 0.6 mmol) and diisopropylethylamine (0.18 mL, 1.0 mmol) in dry DMF (5 mL) was stirred at room temperature for 10 minutes. *Trans*-(+/-)-2-[[*(3R)*-3-ethoxypiperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt crude (143 mg, 0.5 mmol) was added to the solution. The mixture was stirred at room temperature for overnight, but no full conversion. Then 1.2 eq of carboxylic acid, 1.2 eq of HATU and 4 eq DIPEA were added to the mixture, which was stirred for 3 days. The solvent was removed in *vacuo*. DCM (15 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. Removal of solvent gave the crude *trans*(±)-*N*-(2-[[*(3R)*-3-ethoxypiperidin-1-yl]methyl]cyclohexyl)pyrazine-2-carboxamide diastereomeric mixtures. The diastereoisomeric mixtures were separated with preparative high pH HPLC. The first fraction was collected to afford the title compound (*N*-((1*S*,2*R*)-2-[[*(3R)*-3-ethoxypiperidin-1-yl]methyl]cyclohexyl)pyrazine-2-carboxamide as its free base (15 mg). MS (M+1): 347.3 ¹H NMR (400 MHz, CDCl₃) δ ppm 0.98 - 1.18 (m, 3H), 1.21 (t, *J* = 6.93 Hz, 3H), 1.24 - 1.51 (m, 3H), 1.51 - 1.82 (m, 6H), 1.87 (t, *J* = 10.64 Hz, 1H), 1.98 - 2.09 (m, 1H), 2.09 - 2.19 (m, 1H), 2.34 - 2.50 (m, 2H), 2.56 (d, *J* = 9.96 Hz, 1H), 3.20 (s, 1H), 3.39 - 3.69 (m, 4H), 8.51 (s, 1H), 8.73 (d, *J* = 2.34 Hz, 1H), 9.13 (s, 1H), 9.40 (s, 1H)

Example 190. *N*-((1*S*,2*R*)-2-[[*(3R)*-3-ethoxypiperidin-1-yl]methyl]cyclohexyl)-6-(ethylthio)nicotinamide



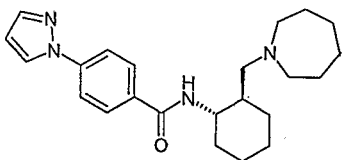
A solution of 6-(ethylthio)nicotinic acid (81 mg, 0.44 mmol), HATU (168 mg, 0.44 mmol) and diisopropylethylamine (0.12 mL, 0.88 mmol) in dry DMF (5 mL) was stirred at room temperature for 10 minutes. *Trans*-2-(((3*R*)-3-ethoxypiperidin-1-yl)methyl)cyclohexylamine hydrochloride salt described in Example 189 Step D (68 mg, 0.22 mmol) was added to the solution. The mixture was stirred at room temperature for overnight, but no full conversion. Then 1.2 eq of carboxylic acid, 1.2 eq of HATU and 4 eq DIPEA were added to the mixture, which was stirred for 3 days. The solvent was removed in vacuo. DCM (15 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was subjected to separation on high pH preparative LC-MS. The first fraction was collected to yield the title compound *N*-((1*S*,2*R*)-2-(((3*R*)-3-ethoxypiperidin-1-yl)methyl)cyclohexyl)-6-(ethylthio)nicotinamide (15 mg) as its free base. MS (*M*+1): 406.1. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.99 - 1.42 (m, 5H), 1.18 (t, *J* = 6.93 Hz, 3H), 1.36 (t, *J* = 7.32 Hz, 3H), 1.48 - 1.82 (m, 4H), 1.88 - 2.16 (m, *J* = 20.70 Hz, 4H), 2.33 - 2.64 (m, 3H), 3.07 - 3.31 (m, 4H), 3.40 (d, *J* = 5.86 Hz, 2H), 3.47 - 3.66 (m, 3H), 7.17 (d, *J* = 8.20 Hz, 1H), 7.91 (s, 1H), 8.79 (d, *J* = 18.75 Hz, 2H).

Example 191. *N*-((1*S*,2*R*)-2-(((3*R*)-3-ethoxypiperidin-1-yl)methyl)cyclohexyl)-6-pyrrolidin-1-yl nicotinamide

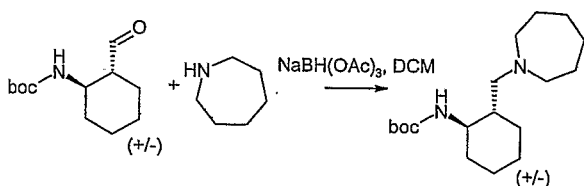


Following the same procedure as Example 189: *N*-((1*S*,2*R*)-2-(((3*R*)-3-ethoxypiperidin-1-yl)methyl)cyclohexyl)-6-pyrrolidin-1-yl nicotinamide (16 mg, 33 %) was obtained as its free base. MS (*M*+1): 415.3. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.12 (d, *J* = 21.09 Hz, 2H), 1.20 (t, *J* = 6.54 Hz, 3H), 1.24 - 1.47 (m, 5H), 1.48 - 1.85 (m, 7H), 1.86 - 2.18 (m, 7H), 2.21 - 2.85 (m, 3H), 3.06 - 3.40 (m, *J* = 56.44 Hz, 1H), 3.50 (s, 3H), 3.62 (d, 2H), 3.80 - 4.07 (m, 1H), 6.32 (d, *J* = 8.98 Hz, 1H), 7.87 (s, 1H), 8.22 (s, 1H), 8.46 - 9.02 (m, 1H)

Example 192. *N*-[(1*S*,2*R*)-2-(azepan-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide

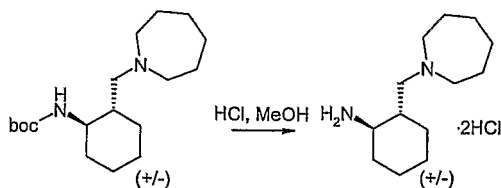


Step A. *trans*-(+/-)-*tert*-butyl-[2-(azepan-1-ylmethyl)cyclohexyl]carbamate



5
 Azepane (0.27 mL, 2.40 mmol) was added to a solution of *trans*-(+/-)-*tert*-butyl [2-formylcyclohexyl]carbamate from Elise Balaux (273 mg crude, 1.2 mmol) in dichloromethane (12 mL). The reaction was stirred at room temperature for 30 minutes, and then sodium triacetoxyborohydride (254 mg, 1.2 mmol) was added to
 10 the reaction mixture. The reaction was stirred at room temperature for 12 hours. Water (1 mL) was added dropwise. A 2N sodium hydroxide solution (15 mL) and dichloromethane (30 mL) were added to the mixture. The phases were separated and the aqueous was extracted with dichloromethane (2x20 mL). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and
 15 concentrated *in vacuo*. MS (m+1): 311.3. 421 mg was obtained. The product was used directly for the next step without further purification.

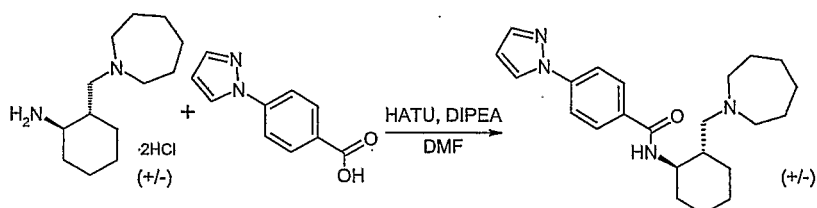
Step B. The preparation of *trans*-(+/-)-[2-(azepan-1-ylmethyl)-1-ethylpentyl]amine hydrochloride salt



20
 A 1.25N solution of hydrochloric acid in MeOH (6.0 mL, 7.20 mmol) was added to a solution of the crude product from step A *trans*-(+/-)-*tert*-butyl [2-(azepan-1-ylmethyl)cyclohexyl]carbamate (1.20 mmol). The reaction was stirred at room temperature for 3 days. Reaction was not completed. 3 mL of 1.25N solution of
 25 hydrochloric acid in MeOH was added and the mixture stirred 4 hours. Still not completed, excess of 1.25N solution of hydrochloric acid in MeOH was added and

stirred at room temperature for 12Hours. The mixture was concentrated *in vacuo* to get 563.6 mg crude. The product was used directly for the next step without further purification. MS (M+1): 211.1.

- 5 Step C. The preparation of *trans*-(+/-)-*N*-[2-(azepan-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide

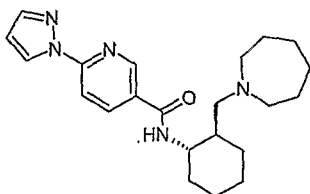


- A solution of pyrazine-2-carboxylic acid (135 mg, 0.72 mmol), HATU (273 mg, 0.72 mmol) and diisopropylethylamine (0.42 mL, 2.4 mmol) in dry DMF (5 mL) was stirred at room temperature for 10 minutes. *trans*-(+/-)-[2-(azepan-1-ylmethyl)-1-ethylpentyl]amine hydrochloride salt crude (0.6 mmol) was added to the solution. The mixture was stirred at room temperature for overnight, but no full conversion. Then 1.2 eq of carboxylic acid, 1.2 eq of HATU and 4 eq DIPEA were added to the mixture, which was stirred for 3 days. The solvent was removed in *vacuo*. DCM (15 mL) was added and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified with reverse phase HPLC High pH to get the *trans*-(+/-)-*N*-[2-(azepan-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide. MS (M+1): 381.2

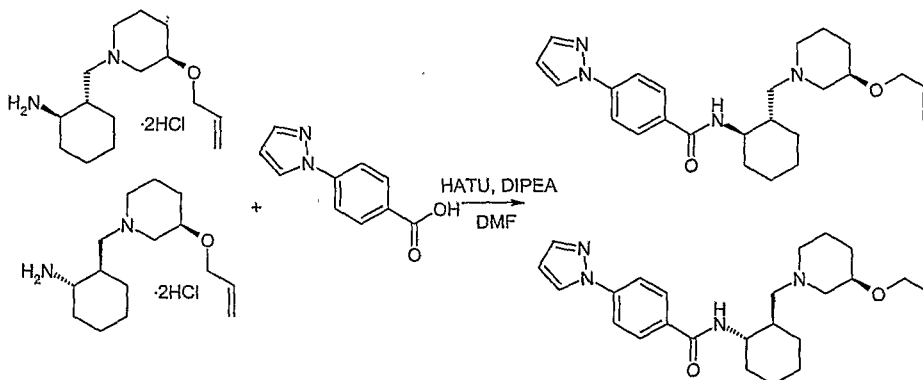
- 20 Step D: The preparation of *N*-[(1*S*,2*R*)-2-(azepan-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide

- The racemic mixture from step C was separated by chiral AD column with 10% EtOH/Hex. as eluent to get the yielded *N*-[(1*S*,2*R*)-2-(azepan-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide (10 mg, 9 % two steps) as its free base. MS (M+1): 381.3. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.06 (d, *J* = 7.42Hz, 2H), 1.20 - 1.47 (m, 4H), 1.47 - 1.67 (m, 6H), 1.67 - 1.80 (m, 3H), 2.25 - 2.34 (m, 1H), 2.35 - 2.45 (m, 1H), 2.47 - 2.57 (m, 2H), 2.63 (d, *J* = 11.91 Hz, 4H), 3.36 - 3.50 (m, 1H), 6.47 - 6.52 (m, 1H), 7.70 - 7.78 (m, 3H), 7.92 (d, *J* = 8.20 Hz, 2H), 7.98 (d, *J* = 2.34 Hz, 1H), 9.20 (s, 1H).

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Example 193. *N*-[(1*S*,2*R*)-2-(azepan-1-ylmethyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide

Following the same procedure as example 192, the racemic mixture of the *trans-N*-[2-(azepan-1-ylmethyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide was obtained and separated on AD column with 10% EtOH/Hex. as eluent. The first fraction was collected to yield *N*-[(1*S*,2*R*)-2-(azepan-1-ylmethyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide 15 mg (13 % two steps) as its free base. MS (*M*+1) : 382.3 ¹H NMR (400 MHz, CDCl₃) δ ppm 0.95 - 1.19 (m, 3H), 1.22 - 1.47 (m, 3H), 1.49 - 1.61 (m, *J* = 6.84 Hz, 1H), 1.61 (s, 3H), 1.69 - 1.81 (m, 3H), 2.27 - 2.45 (m, 3H), 2.48 - 2.58 (m, 3H), 2.64 (d, *J* = 13.28 Hz, 4H), 3.38 - 3.49 (m, *J* = 10.45, 10.45 Hz, 1H), 6.48 (m, 1H), 7.76 (d, *J* = 0.78 Hz, 1H), 8.00 (d, *J* = 8.59 Hz, 1H), 8.20 (m, 1H), 8.60 (d, *J* = 2.54 Hz, 1H), 8.84 (s, 1H), 9.44 (s, 1H)

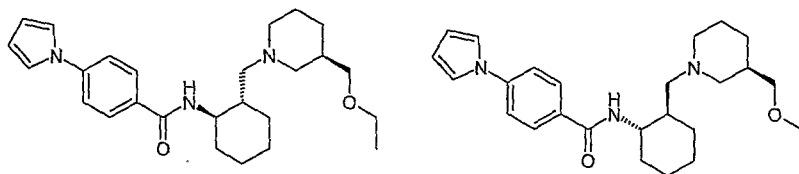
Example 194: *N*-[(1*S*,2*R*)-2-[(3*R*)-3-(allyloxy)piperidin-1-yl]methyl]cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide

A solution of pyrazine-2-carboxylic acid (120 mg, 0.64 mmol), HATU (304 mg, 0.80 mmol) and diisopropylethylamine (0.28 mL, 1.60 mmol) in dry DMF (5 mL) was stirred at room temperature for 10 minutes. The *trans*-(+/-)-2-[(3*R*)-3-(allyloxy)piperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt (100 mg, 0.31 mmol) was added to the solution. The mixture was stirred at room temperature for overnight. Then 1.2 eq of pyrazine-2-carboxylic acid, 1.2 eq of HATU and 4 eq DIPEA were added to the mixture, which was stirred for 3 days. The solvent was

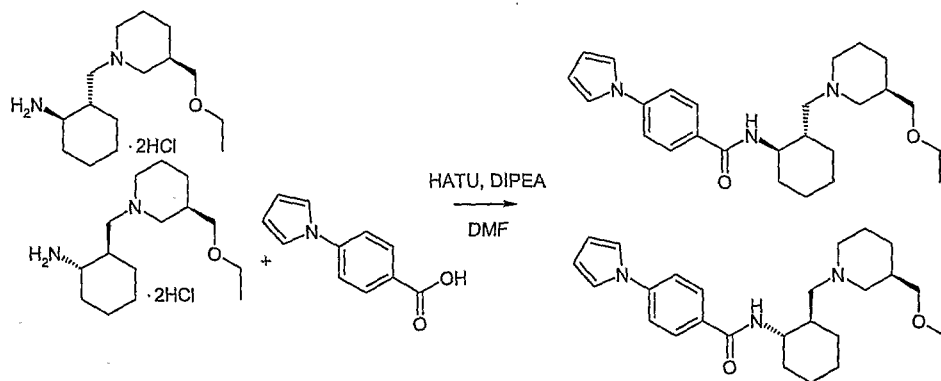
102213-1 WO

removed in vacuo. DCM (15 mL) was added and washed with saturated NaHCO_3 (10 mL) and brine (10 mL), dried over Na_2SO_4 . The crude product was purified with High pH LC-MS to separate two diastereoisomers. The first fraction was collected to yield The title compound *N*-((1*S*,2*R*)-2-[[*(3R)*-3-(allyloxy)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrazol-1-yl)benzamide 16 mg (25 %) as its free base. MS ($M+1$) : 423.3. ^1H NMR (400 MHz, CDCl_3) δ ppm 0.99 - 1.49 (m, 6H), 1.49 - 1.68 (m, 4H), 1.73 (q, J = 9.96 Hz, 3H), 1.91 - 2.06 (m, 2H), 2.09 (d, J = 12.89 Hz, 1H), 2.39 - 2.55 (m, 2H) 2.61 (d, J = 10.94 Hz, 1H), 3.26 (d, J = 9.37 Hz, 1H), 3.37 - 3.52 (m, 2H), 4.05 (ddd, J = 31.10, 12.55, 5.57 Hz, 2H), 5.18 (dd, J = 10.35, 0.98 Hz, 1H), 5.29 (dd, J = 17.19, 1.56 Hz, 1H), 5.85 - 5.98 (m, 1H), 6.45 - 6.54 (m, 1H), 7.70 - 7.79 (m, 2H), 7.91 (d, J = 8.59 Hz, 2H), 7.99 (d, J = 2.34 Hz, 1H), 8.71 (s, 1H).

Example 195 and 196. *N*-((1*R*,2*S*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrrol-1-yl)benzamide and *N*-((1*S*,2*R*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrrol-1-yl)benzamide



Step A. The preparation of *trans*-*N*-(2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrrol-1-yl)benzamide



A solution 4-(1*H*-pyrrol-1-yl)benzoic acid (94 mg, 0.50 mmol), HATU (190 mg, 0.50 mmol) and a few drop of diisopropylethylamine in dry DMF (5 mL) was stirred at room temperature for 10 minutes. Crude *trans*($\pm$)- (2-[[*(3R)*-3-ethoxypiperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt (162 mg, 0.50 mmol) was added to the solution. The mixture was stirred at room temperature for overnight. The solvent was

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removed in vacuo. Residue was dissolved in DCM (15 mL) and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified by prep LC-MS High pH to yield the diastereomeric mixtures *trans*-(±)-*N*-(2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrrol-1-yl)benzamide as its free base. MS(*M*+1): 424.3

Step B. Chiral Separation of *trans*-*N*-(2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrrol-1-yl)benzamide

- 10 The diastereo mixture *trans*-*N*-(2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrrol-1-yl)benzamide was separated on chiral AD column, eluent 10% *i*-PrOH/Hexane to obtain two isomers.

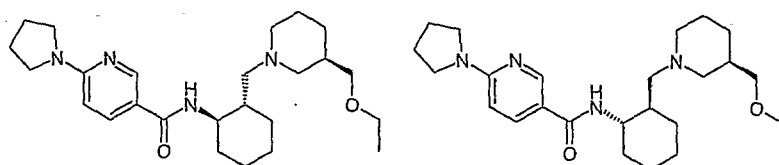
Isomer 1 (64 mg): *N*-((1*R*,2*S*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrrol-1-yl)benzamide as its free base. MS (*M*+1): 424.3. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.83 - 0.96 (m, 1H), 1.00 (t, *J* = 6.93 Hz, 3H), 1.03 - 1.16 (m, 2H), 1.20 - 1.48 (m, 2H), 1.49 - 1.67 (m, 5H), 1.73 (d, *J* = 9.57 Hz, 5H), 2.05 (d, *J* = 12.69 Hz, 1H), 2.41 (dd, *J* = 12.21, 10.06 Hz, 1H), 2.51 - 2.72 (m, 2H), 2.97 - 3.11 (m, 3H), 3.11 - 3.23 (m, 2H), 3.42 (t, *J* = 10.45 Hz, 1H), 6.36 (t, 2H), 7.12 (t, *J* = 2.15 Hz, 2H), 7.41 (d, *J* = 8.40 Hz, 2H), 7.88 (d, *J* = 8.40 Hz, 2H), 8.90 (s, 1H)

Isomer 2: *N*-((1*S*,2*R*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrrol-1-yl)benzamide 68 mg was obtained as its free base. MS (*M*+1): 424.3. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.78 - 0.98 (m, 1H), 1.01 - 1.17 (m, 2H), 1.24 (t, *J* = 7.03 Hz, 3H), 1.27 - 1.44 (m, 2H), 1.42 - 1.53 (m, 2H), 1.53 - 1.70 (m, 4H), 1.70 - 1.81 (m, 2H), 1.84 - 1.98 (m, 2H), 2.05 (d, *J* = 12.69 Hz, 1H), 2.41 (dd, *J* = 12.69, 9.77 Hz, 1H), 2.59 (t, *J* = 11.52 Hz, 2H), 3.21 (t, *J* = 8.50 Hz, 1H), 3.25 - 3.38 (m, 2H), 3.38 - 3.55 (m, 3H), 6.36 - 6.40 (m, 2H), 7.15 (t, *J* = 2.15 Hz, 2H), 7.42 (d, *J* = 8.59 Hz, 2H), 7.90 (d, *J* = 8.59 Hz, 2H), 8.98 (s, 1H)

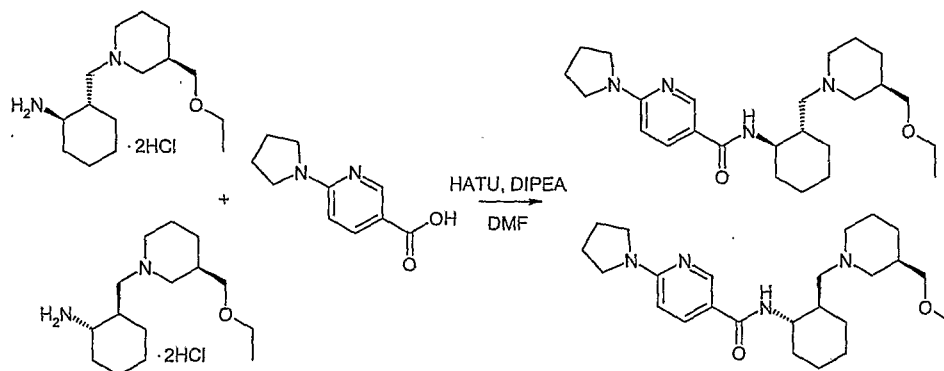
30

Examples 197 and 198. *N*-((1*R*,2*S*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-6-pyrrolidin-1-ylnicotinamide and *N*-((1*S*,2*R*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-6-pyrrolidin-1-ylnicotinamide

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Step A. The preparation of *trans*-*N*-(2-((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-6-pyrrolidin-1-ynicotinamide



- 5 A solution 6-pyrrolidin-1-ynicotinic acid (96 mg, 0.50 mmol), HATU (190 mg, 0.50 mmol) and a few drop of diisopropylethylamine in dry DMF (5 mL) was stirred at room temperature for 10 minutes. Crude *trans*(±)- (2-((3*R*)-3-ethoxypiperidin-1-yl)methyl)cyclohexyl)amine hydrochloride salt (162 mg, 0.50 mmol) was added to the solution. The mixture was stirred at room temperature for overnight. The solvent was removed in vacuo. Residue was dissolved in DCM (15 mL) and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified by prep LC-MS High pH to afford the diastereomeric mixture *trans*-*N*-(2-((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-6-pyrrolidin-1-ynicotinamide 123 mg (57 %) as its free base. MS(*M*+1): 429.3

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Step B. Chiral separation of of *trans*-*N*-(2-((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-6-pyrrolidin-1-ynicotinamide

- The diastereo mixture of the *trans*-*N*-(2-((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-(1*H*-pyrrol-1-yl)benzamide 123 mg (57 %) was separated on chiral AD column, eluent 10% *i*-PrOH/Hexane to afford two isomers:
- 20 **Isomer 1:** *N*-((1*R*,2*S*)-2-((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-6-pyrrolidin-1-ynicotinamide 5 mg (8 %) as its free base. MS(*M*+1): 429.3. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.80 - 1.15 (m, 2H), 1.03 (t, *J* = 7.03 Hz, 3H), 1.14 - 1.51 (m, 2H), 1.49 - 1.67 (m, 4H), 1.67 - 1.79 (m, 6H), 1.94 - 2.08 (m, 4H), 2.38 (dd, *J* =
- 25

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12.60, 9.28 Hz, 1H), 2.53 (d, J = 11.33 Hz, 1H), 2.63 (d, J = 6.45 Hz, 1H), 3.03 (d, J = 10.35 Hz, 1H), 3.12 (d, J = 5.08 Hz, 2H), 3.14 - 3.26 (m, 3H), 3.37 - 3.53 (m, 6H), 6.29 (d, J = 8.79 Hz, 1H), 7.86 (dd, J = 8.79, 2.15 Hz, 1H), 8.45 (s, 1H), 8.62 (d, J = 1.76 Hz, 1 H)

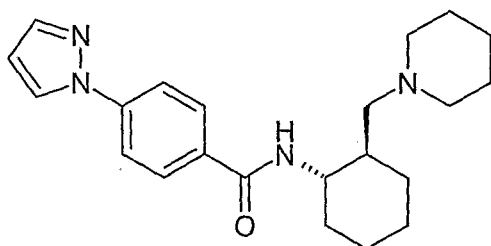
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Isomer 2: *N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-6-pyrrolidin-1-yl)nicotinamide 10 mg (16 %) was obtained as its free base. MS ($M+1$): 429.3. ^1H NMR (400 MHz, CDCl_3) δ ppm 0.77 - 0.99 (m, 1H), 1.00 - 1.16 (m, 2H), 1.21 (t, J = 6.74 Hz, 3H), 1.26 - 1.57 (m, 6H), 1.60 - 1.79 (m, 6H), 1.82 - 1.98 (m, 2H), 1.95 - 2.07 (m, 4H), 2.28 - 2.46 (m, 1H), 2.46 - 2.65 (m, 2H), 3.12 - 3.39 (m, 3H), 3.38 - 3.55 (m, 6H), 6.29 (d, J = 8.79 Hz, 1H), 7.86 (d, J = 7.23 Hz, 1H), 8.55 (s, 1H), 8.64 (s, 1 H)

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Example 199. *N*-[(1*S*,2*R*)-2-(piperidin-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide

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A solution of *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide (0.050 g, 0.14 mmol) in EtOH (2.5 mL) was subjected to preparative scale chiral phase HPLC (ChiralPak AD column, 21 x 250 mm; 20 μm , 15%

20 EtOH/85% Hexanes with 0.1% diethylamine modifier, 18 mL/min flow rate).

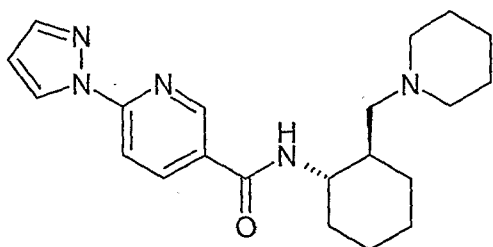
Fractions of the first eluting enantiomer were collected, concentrated, and lyophilized from $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ to give the title compound as a white solid (23 mg, 45%). MS

($M+1$): 367.3. ^1H NMR (400 MHz, $\text{METHANOL}-D_4$) δ ppm 1.04 - 1.15 (m, 1 H), 1.24 - 1.84 (m, 13 H), 1.90 - 1.99 (m, 1 H), 2.08 - 2.21 (m, 2 H), 2.28 - 2.50 (m, 4 H), 3.59

25 (td, J =10.7, 4.1 Hz, 1 H), 6.56 (dd, J =2.5, 2.0 Hz, 1 H), 7.73 - 7.78 (m, 1 H), 7.85 - 7.90 (m, 2 H), 7.92 - 7.99 (m, 2 H), 8.33 (dd, J =2.7, 0.6 Hz, 1 H).

Example 200. *N*-[(1*S*,2*R*)-2-(piperidin-1-ylmethyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide

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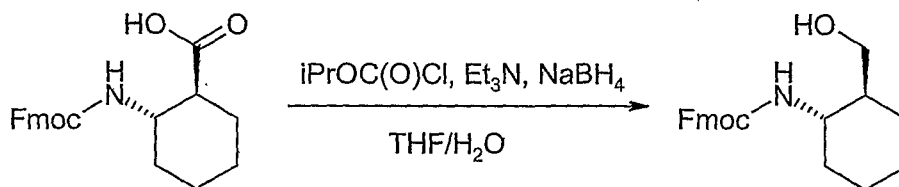
Method 1: Chiral Separation approach

A solution of *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide (0.10 g, 0.27 mmol) in EtOH (2.5 mL) was subjected to preparative scale chiral phase HPLC (ChiralPak AD column, 21 x 250 mm, 20 μ m, 15% EtOH/85% Hexanes with 0.1% diethylamine modifier, 18 mL/min flow rate).

Fractions of the first eluting enantiomer were collected, concentrated, and lyophilized from CH₃CN/H₂O to give the title compound as an off-white solid (0.0372 g, 37%).

MS (*M*+1): 368.3. ¹H NMR (400 MHz, METHANOL-*D*₄) δ ppm 1.01 - 1.17 (m, 1 H), 1.23 - 1.85 (m, 13 H), 1.89 - 2.01 (m, 1 H), 2.06 - 2.23 (m, 2 H), 2.29 - 2.55 (m, 4 H), 3.62 (td, *J*=10.7, 3.8 Hz, 1 H), 6.56 (dd, *J*=2.6, 1.7 Hz, 1 H), 7.79 (d, *J*=1.0 Hz, 1 H), 8.02 (dd, *J*=8.6, 0.6 Hz, 1 H), 8.32 (dd, *J*=8.8, 2.3 Hz, 1 H), 8.65 (dd, *J*=2.5, 0.6 Hz, 1 H), 8.87 (dd, *J*=2.2, 0.7 Hz, 1 H). Anal. Calcd for C₂₁H₂₉N₅O·0.4 H₂O: C, 67.32; H, 8.02; N, 18.69. Found: C, 67.34; H, 7.81; N, 18.52.

Method 2: Synthetic approach from chiral starting material

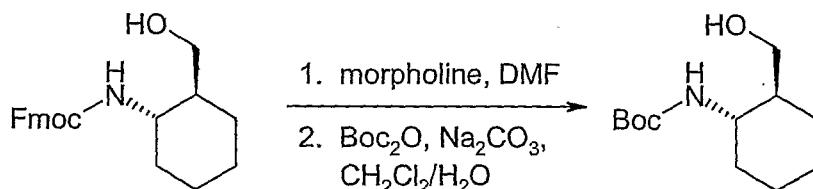
Step A: 9*H*-fluoren-9-ylmethyl [(1*S*,2*S*)-2-(hydroxymethyl)cyclohexyl]carbamate

A solution of (1*S*,2*S*)-2-[[9*H*-fluoren-9-ylmethoxy)carbonyl]amino)cyclohexanecarboxylic acid (0.948 g, 2.59 mmol) in THF (18 mL) was cooled to 0 °C, and Et₃N (1.1 mL, 7.9 mmol) and isopropyl chloroformate (4.9 mL of 1M in toluene, 4.9 mmol) were added. The resulting solution was stirred for 10 min, and then a solution of NaBH₄ (0.353 g, 9.33 mmol) in H₂O (3.5 mL) was added. The mixture was stirred for 5 h, and additional NaBH₄ (0.050 g, 1.3 mmol) in H₂O (0.5 mL) was added. After stirring for an additional 30 min, a final portion of NaBH₄ (0.030 g, 0.79 mmol) in H₂O (0.3 mL) was added and the reaction stirred for a further 30 min. The reaction was

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then diluted with H₂O (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (95:5 CH₂Cl₂:MeOH) to provide the title compound as a white solid (0.711 g, 78%). MS (M+1): 352.2. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.00 - 1.37 (m, 3 H), 1.44 - 1.53 (m, 1 H), 1.60 - 1.82 (m, 4 H), 1.90 - 2.00 (m, 1 H), 3.08 - 3.20 (m, 1 H), 3.24 - 3.37 (m, 1 H), 3.38 - 3.51 (m, 1 H), 3.57 - 3.67 (m, 1 H), 4.20 (t, J=6.4 Hz, 1 H), 4.40 (dd, J=10.7, 6.4 Hz, 1 H), 4.53 (dd, J=10.7, 6.6 Hz, 1 H), 4.60 (d, J=9.2 Hz, 1 H), 7.32 (td, J=7.4, 1.2 Hz, 2 H), 7.36 - 7.45 (m, 2 H), 7.58 (d, J=7.6 Hz, 2 H), 7.71 - 7.80 (m, 2 H).

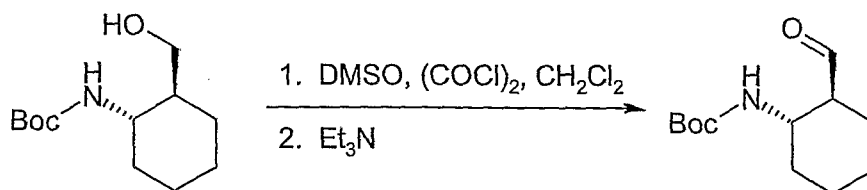
Step B: *tert*-butyl [(1*S*,2*S*)-2-(hydroxymethyl)cyclohexyl]carbamate



A mixture of 9*H*-fluoren-9-ylmethyl [(1*S*,2*S*)-2-(hydroxymethyl)cyclohexyl]carbamate (0.700 g, 1.99 mmol) and morpholine (11 mL) in DMF (11 mL) was stirred at room temperature for 30 min. The mixture was poured into H₂O (300 mL) in a separatory funnel and washed with hexanes (4 x 150 mL). The aqueous phase was then extracted with CH₂Cl₂ (4 x 150 mL). The combined CH₂Cl₂ extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ (5 mL), and Na₂CO₃ (0.208 g, 1.96 mmol) dissolved in H₂O (10 mL) was added, followed by di-*tert*-butyl dicarbonate (0.393 g, 1.8 mmol) and additional CH₂Cl₂ (3 mL). The resulting mixture was stirred for 22 h. The layers were separated, and the aqueous phase was extracted with CH₂Cl₂ (3x15 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (95:5 CH₂Cl₂:MeOH) to provide the title compound as a white solid (0.363 g, 79% over 2 steps). MS (M+1): 230.1. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.98 - 1.39 (m, 4 H), 1.44 (s, 9 H), 1.47 - 1.58 (m, 1 H), 1.61 - 1.82 (m, 3 H), 1.87 - 2.01 (m, 1 H), 3.23 - 3.46 (m, 2 H), 3.49 - 3.60 (m, 1 H), 3.69 - 3.80 (m, 1 H), 4.43 (d, J=8.0 Hz, 1 H).

Step C: *tert*-butyl [(1*S*,2*S*)-2-formylcyclohexyl]carbamate

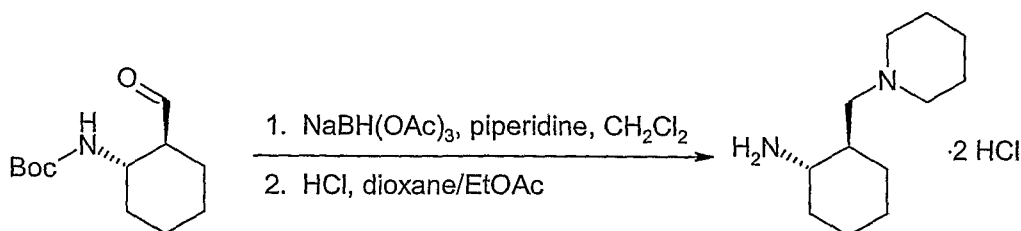
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Oxalyl chloride (0.084 mL, 0.96 mmol) was added dropwise to a solution of dry DMSO (0.14 mL, 2.0 mmol) in dry CH₂Cl₂ (2 mL) cooled in a -78°C cold bath. The resulting mixture was stirred for 10 min, and then a solution of *tert*-butyl [(1*S*,2*S*)-2-(hydroxymethyl)cyclohexyl]carbamate (0.148 g, 0.64 mmol) in CH₂Cl₂ (0.6 mL + 2 x 0.3 mL) was added dropwise. After stirring an additional 10 min, Et₃N (0.36 mL, 2.6 mmol) was added dropwise. The reaction was stirred for 20 min at -78 °C and 1.5 h at 0 °C. H₂O (5 mL) and CH₂Cl₂ (5 mL) were then added, the layers separated, and the aqueous phase was extracted with additional CH₂Cl₂ (3 x 5 mL). The combined organic layers were washed successively with a saturated solution of NH₄Cl (10 mL) and then brine (10 mL) before being dried over Na₂SO₄, filtered, and concentrated *in vacuo* to provide a sample of the title compound as a yellow solid (0.174 g, quantitative). The compound was used in subsequent steps without further purification. MS (M+1): 228.1.

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Step D: [(1*S*,2*R*)-2-(piperidin-1-ylmethyl)cyclohexyl]amine hydrochloride salt



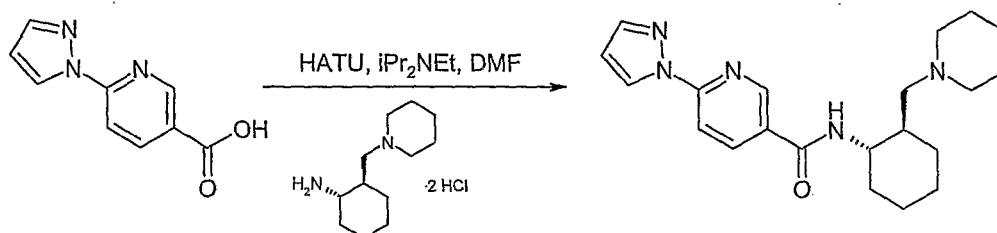
A mixture of crude *tert*-butyl [(1*S*,2*S*)-2-formylcyclohexyl]carbamate (0.081 g, ~0.30 mmol) and piperidine (0.035 mL, 0.35 mmol) in dry CH₂Cl₂ (6 mL) was stirred for 30 min at 5 °C. NaBH(OAc)₃ (0.127 g, 0.60 mmol) was added to the reaction and the resulting mixture was allowed to slowly warm to room temperature and stir for 14 h. The reaction was cooled to 0 °C, and water (3 mL) was added, followed by 1 N NaOH (3 mL) and CH₂Cl₂ (10 mL). The layers were separated, and the aqueous phase was extracted with additional CH₂Cl₂ (2 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in EtOAc (0.75 mL), and 4 N HCl in dioxane (0.75 mL, 3 mmol) was added. The mixture was stirred for 3 h and then concentrated *in vacuo* to provide the title

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compound. The compound was used in subsequent steps without further purification. MS (M+1): 197.1.

Step E: *N*-[(1*S*,2*R*)-2-(piperidin-1-ylmethyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotin-
5 amide



A mixture of 6-(1*H*-pyrazol-1-yl)nicotinic acid (0.0622 g, 0.33 mmol), HATU (0.125 g, 0.33 mmol), and diisopropylethylamine (0.073 mL, 0.42 mmol) in dry DMF (1 mL)

was stirred at 0 °C for 10 min. A suspension of crude [(1*S*,2*R*)-2-(piperidin-1-ylmethyl)cyclohexyl]amine hydrochloride salt (~0.30 mmol) and diisopropylethylamine (0.14 mL, 0.80 mmol) in DMF (0.5 mL + 2 x 0.5 mL) was then added to the reaction, and the resulting mixture was stirred at 0 °C for 30 min and then warmed to room

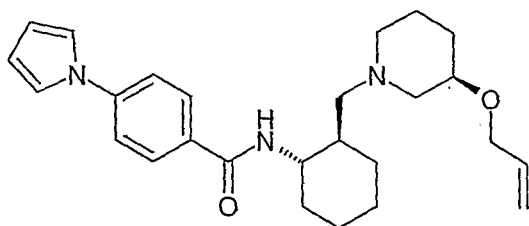
temperature and stirred for an additional 16h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH₂Cl₂ (5 mL) and a saturated solution of NaHCO₃ in water (5 mL). The mixture was passed through a Varian Chem Elut™ extraction cartridge, and the cartridge was washed with additional CH₂Cl₂ (3 x 5 mL).

The organic extract was concentrated *in vacuo*, and the residue was purified by preparative scale reverse phase LC/MS (gradient 55-75% CH₃CN in H₂O containing 10 mM NH₄HCO₃) to provide the title compound as a light yellow solid (0.0574 g,

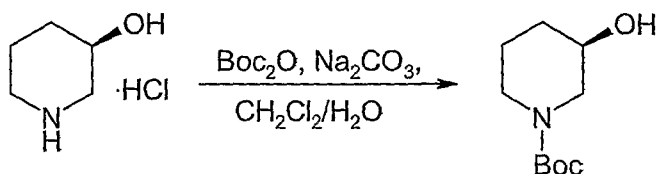
52% over 3 steps) following lyophilization from CH₃CN/H₂O. MS (M+1): 368.3. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.00 - 1.16 (m, 2 H), 1.21 - 1.81 (m, 13 H), 2.02 - 2.25 (m, 3 H), 2.38 (dd, *J*=13.1, 10.0 Hz, 1 H), 2.44 - 2.71 (m, 2 H), 3.33 - 3.46 (m, 1 H), 6.48 (dd, *J*=2.6, 1.7 Hz, 1 H), 7.76 (dd, *J*=1.7, 0.7 Hz, 1 H), 8.00 (dd, *J*=8.6, 0.8 Hz, 1 H), 8.25 (dd, *J*=8.6, 2.3 Hz, 1 H), 8.61 (dd, *J*=2.7, 0.8 Hz, 1 H), 8.89 (dd, *J*=2.3, 0.8 Hz, 1 H), 9.41 (s, 1 H)

Example 201. *N*-[(1*S*,2*R*)-2-[(3*R*)-3-(allyloxy)piperidin-1-yl]methyl]cyclohexyl]-4-(1*H*-pyrrol-1-yl)benzamide

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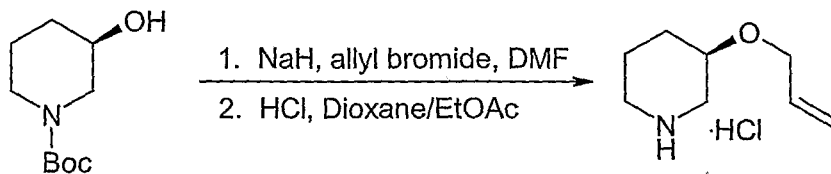


Step A: *tert*-butyl (3*R*)-3-hydroxypiperidine-1-carboxylate



A suspension of (3*R*)-piperidin-3-ol hydrochloride salt (3.17 g, 0.023 mol) in CH₂Cl₂ (40 mL) was treated with Na₂CO₃ (5.13 g, 0.048 mol) dissolved in H₂O (80 mL), followed by di-*tert*-butyl dicarbonate (5.53 g, 0.025 mol) and additional CH₂Cl₂ (24 mL). The resulting mixture was stirred for 21 h. The layers were separated, and the aqueous phase was extracted with CH₂Cl₂ (3x50 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (9:1 CH₂Cl₂:MeOH) to provide the title compound as a colorless oil (5.07 g, quantitative). MS (M+1): 202.0. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.40 - 1.56 (m, 2 H), 1.44 (s, 9 H), 1.67 - 1.80 (m, 1 H), 1.80 - 1.93 (m, 1 H), 2.95 - 3.22 (m, 2 H), 3.47 (d, *J*=5.1 Hz, 1 H), 3.51 (br s, 1 H), 3.64 - 3.78 (m, 2 H).

Step B: (3*R*)-3-(allyloxy)piperidine hydrochloride salt

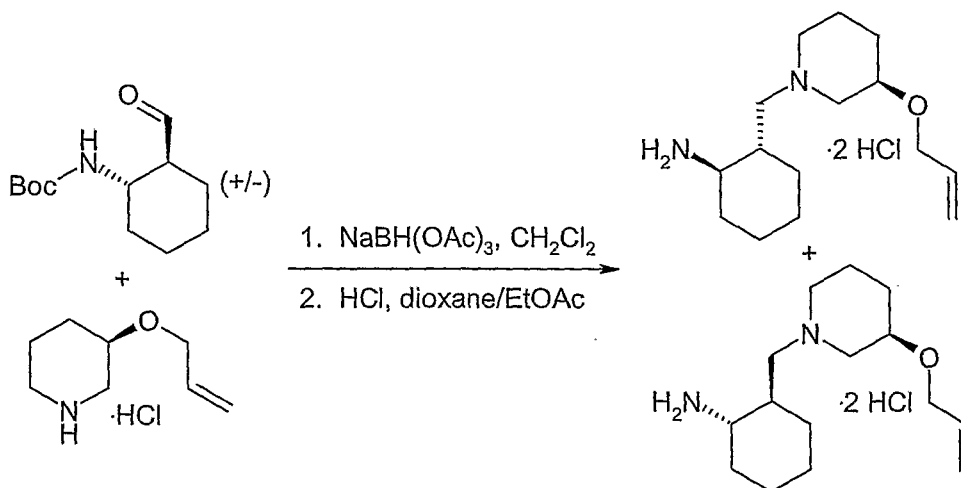


NaH (0.60 g of 60% in oil, 15 mmol) was washed with hexanes (2 x 10 mL), and then suspended in dry DMF (12 mL) and cooled to 0 °C. A solution of *tert*-butyl (3*R*)-3-hydroxypiperidine-1-carboxylate (1.51 g, 7.5 mmol) in dry DMF (6 mL + 2 x 2 mL) was slowly added, and the resulting mixture was stirred for 30 min at 0 °C. Allyl bromide (0.78 mL, 9.0 mmol) was added, and the reaction was allowed to warm to room temperature and stir for 13 h. The reaction was cooled to 0 °C, H₂O (2 mL) was added, and then the reaction was concentrated *in vacuo*. The residue was partitioned between CH₂Cl₂ (50 mL) and H₂O (25 mL). The layers were separated,

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and the aqueous layer was extracted with additional CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with brine (2 x 25 mL) and then dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was dissolved in EtOAc (9 mL), and 4 N HCl in dioxane (8.9 mL, 36 mmol) was added. The mixture was stirred for 3 h and then concentrated *in vacuo*. The resulting solid was washed with Et_2O and dried *in vacuo* to provide the title compound (1.19 g, 89% over 2 steps) as a hygroscopic light orange solid. The compound was used in subsequent steps without further purification. MS (M+1): 142.0.

- 10 Step C: ((1*R*,2*S*)-2-[[*(3R)*-3-(allyloxy)piperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt and ((1*S*,2*R*)-2-[[*(3R)*-3-(allyloxy)piperidin-1-yl]methyl]cyclohexyl)-amine hydrochloride salt

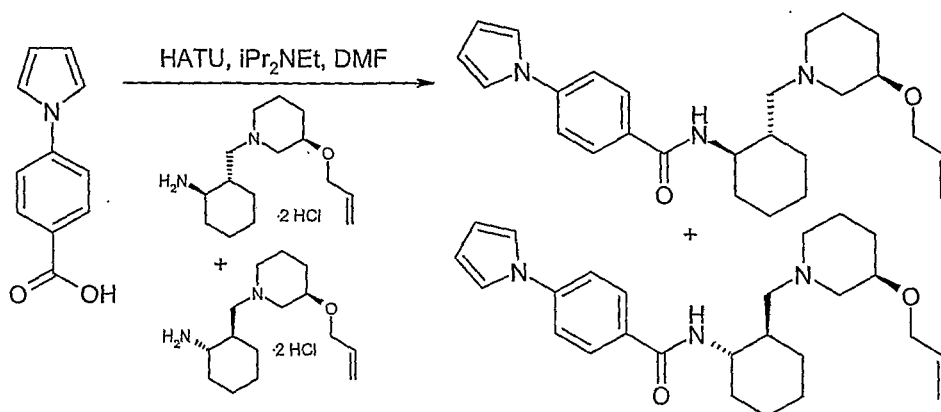


- A mixture of crude *tert*-butyl [*trans*-(+/-)-2-formylcyclohexyl]carbamate (1.38 g, ~6.1 mmol) and (*3R*)-3-(allyloxy)piperidine hydrochloride salt (1.19 g, 6.7 mmol) in dry CH_2Cl_2 (60 mL) was stirred for 30 min at room temperature. $\text{NaBH}(\text{OAc})_3$ (2.58 g, 12 mmol) was added to the reaction and the resulting mixture was stirred for 16 h. The reaction was cooled to 0 °C, and water (25 mL) was added, followed by 1 N NaOH (25 mL) and CH_2Cl_2 (60 mL). The layers were separated, and the aqueous phase was extracted with additional CH_2Cl_2 (2 x 60 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was dissolved in EtOAc (14 mL), and 4 N HCl in dioxane (14 mL, 56 mmol) was added. The mixture was stirred for 2 h and then concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 and hexanes and concentrated *in vacuo* to give a light yellow foam. The foam was triturated with Et_2O twice and dried *in vacuo* to provide the title compound

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(1.89 g, 95% over two steps) as a yellow solid. The compound was used in subsequent steps without further purification. MS (M+1): 253.0.

Step D: *N*-((1*R*,2*S*)-2-[[*(3R)*-3-(allyloxy)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrrol-1-yl)benzamide and *N*-((1*S*,2*R*)-2-[[*(3R)*-3-(allyloxy)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrrol-1-yl)benzamide

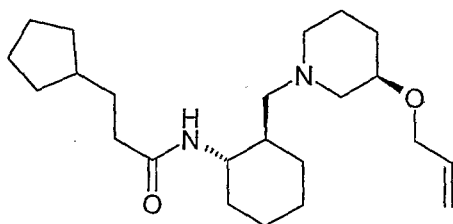


A mixture of 4-(1*H*-pyrrol-1-yl)benzoic acid (0.144 g, 0.77 mmol), HATU (0.293 g, 0.77 mmol), and diisopropylethylamine (0.17 mL, 0.98 mmol) in dry DMF (2 mL) was stirred at 0 °C for 10 min. A solution of a mixture of crude ((1*R*,2*S*)-2-[[*(3R)*-3-(allyloxy)piperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt and ((1*S*,2*R*)-2-[[*(3R)*-3-(allyloxy)piperidin-1-yl]methyl]cyclohexyl)-amine hydrochloride salt (0.228 g, ~0.7 mmol) and diisopropylethylamine (0.32 mL, 1.8 mmol) in DMF (1 + 2 x 1 mL) was then added to the reaction, and the resulting mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for an additional 15h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH₂Cl₂ (8 mL) and a saturated solution of NaHCO₃ in water (8 mL). The mixture was passed through a Varian Chem ElutTM extraction cartridge, and the cartridge was washed with additional CH₂Cl₂ (3 x 12 mL). The organic extract was concentrated *in vacuo*, and the residue was purified by preparative scale reverse phase LC/MS (gradient 55-75% CH₃CN in H₂O containing 10 mM NH₄HCO₃). The first stereoisomer of the product to elute, *N*-((1*S*,2*R*)-2-[[*(3R)*-3-(allyloxy)piperidin-1-yl]methyl]cyclohexyl)-4-(1*H*-pyrrol-1-yl)benzamide, was obtained as a white solid (0.0577 g, 20%) following lyophilization from CH₃CN/H₂O. MS (M+1): 422.2. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.02 - 1.49 (m, 6 H), 1.54 - 1.83 (m, 6 H), 1.94 - 2.06 (m, 2 H), 2.11 (dd, *J*=13.0, 1.5 Hz, 1 H), 2.47 (dd, *J*=12.9, 9.2 Hz, 2 H), 2.57 - 2.65 (m, 1 H), 3.20 - 3.30 (m, 1 H), 3.38 - 3.54 (m, 2 H), 3.95 - 4.15 (m, 2 H), 5.20 (ddd, *J*=10.4,

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3.1, 1.4 Hz, 1 H), 5.30 (ddd, $J=17.2, 3.4, 1.7$ Hz, 1 H), 5.85 - 6.01 (m, 1 H), 6.34 - 6.43 (m, 2 H), 7.10 - 7.18 (m, 2 H), 7.37 - 7.45 (m, 2 H), 7.83 - 7.92 (m, 2 H), 8.66 (d, $J=2.9$ Hz, 1 H).

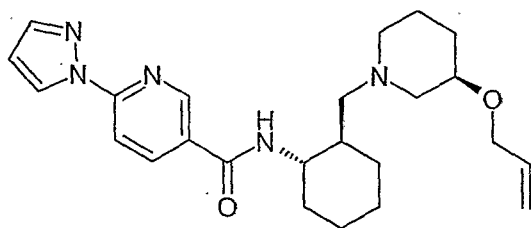
5 **Example 202.** *N*-((1*S*,2*R*)-2-[[*(3R)*-3-(allyloxy)piperidin-1-yl]-methyl]cyclohexyl)-3-cyclopentylpropanamide



A mixture of 3-cyclopentylpropanoic acid (0.11 mL, 0.77 mmol), HATU (0.293 g, 0.77 mmol), and diisopropylethylamine (0.17 mL, 0.98 mmol) in dry DMF (2 mL) was stirred at 0 °C for 10 min. A solution of a mixture of crude ((1*R*,2*S*)-2-[[*(3R)*-3-(allyloxy)piperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt and ((1*S*,2*R*)-2-[[*(3R)*-3-(allyloxy)piperidin-1-yl]methyl]cyclohexyl)-amine hydrochloride salt (0.228 g, ~0.7 mmol) and diisopropylethylamine (0.32 mL, 1.8 mmol) in DMF (1 + 2 x 1 mL) was then added to the reaction, and the resulting mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for an additional 15h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH₂Cl₂ (8 mL) and a saturated solution of NaHCO₃ in water (8 mL). The mixture was passed through a Varian Chem ElutTM extraction cartridge, and the cartridge was washed with additional CH₂Cl₂ (3 x 12 mL). The organic extract was concentrated *in vacuo*, and the residue was purified by preparative scale reverse phase LC/MS (gradient 65-85% CH₃CN in H₂O containing 10 mM NH₄HCO₃). The first stereoisomer of the product to elute, *N*-((1*S*,2*R*)-2-[[*(3R)*-3-(allyloxy)piperidin-1-yl]-methyl]cyclohexyl)-3-cyclopentylpropanamide, was obtained as a slightly yellow oil (0.0361 g, 14%) following lyophilization from CH₃CN/H₂O. MS ($M+1$): 377.5. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.87 - 1.88 (m, 23 H), 1.93 - 2.21 (m, 5 H), 2.32 - 2.46 (m, 2 H), 2.50 - 2.62 (m, 1 H), 3.02 - 3.13 (m, 1 H), 3.21 - 3.33 (m, 1 H), 3.35 - 3.46 (m, 1 H), 3.96 - 4.12 (m, 2 H), 5.18 (ddd, $J=10.4, 2.9, 1.4$ Hz, 1 H), 5.29 (ddd, $J=17.2, 3.4, 1.7$ Hz, 1 H), 5.82 - 6.00 (m, 1 H), 7.54 (s, 1 H).

30 **Example 203.** *N*-((1*S*,2*R*)-2-[[*(3R)*-3-(allyloxy)piperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide

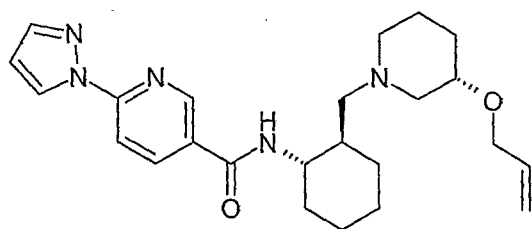
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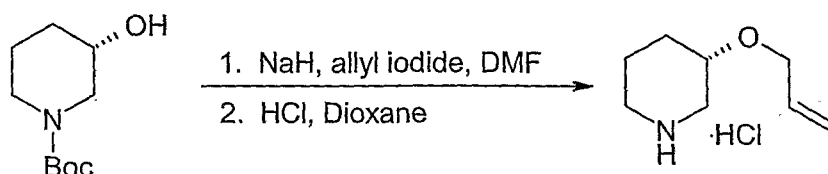
- A mixture of 6-(1*H*-pyrazol-1-yl)nicotinic acid (0.146 g, 0.77 mmol), HATU (0.293 g, 0.77 mmol), and diisopropylethylamine (0.17 mL, 0.98 mmol) in dry DMF (2 mL) was stirred at 0 °C for 10 min. A solution of a mixture of crude ((1*R*,2*S*)-2-(((3*R*)-3-(allyloxy)piperidin-1-yl)methyl)cyclohexyl)amine hydrochloride salt and ((1*S*,2*R*)-2-(((3*R*)-3-(allyloxy)piperidin-1-yl)methyl)cyclohexyl)-amine hydrochloride salt (0.228 g, ~0.7 mmol) and diisopropylethylamine (0.32 mL, 1.8 mmol) in DMF (1 + 2 x 1 mL) was then added to the reaction, and the resulting mixture was stirred at 0 °C for 20 min and then warmed to room temperature and stirred for an additional 14h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH₂Cl₂ (8 mL) and a saturated solution of NaHCO₃ in water (8 mL). The mixture was passed through a Varian Chem ElutTM extraction cartridge, and the cartridge was washed with additional CH₂Cl₂ (3 x 12 mL). The organic extract was concentrated *in vacuo*, and the residue was purified by preparative scale reverse phase LC/MS (gradient 55-75% CH₃CN in H₂O containing 10 mM NH₄HCO₃). The first stereoisomer of the product to elute, *N*-((1*S*,2*R*)-2-(((3*R*)-3-(allyloxy)piperidin-1-yl)methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide, was obtained as a slightly orange solid (0.0627 g, 21%) following lyophilization from CH₃CN/H₂O. MS (*M*+1): 424.3. ¹H NMR (400 MHz, CHLOROFORM-*D*) δ ppm 1.00 - 1.48 (m, 6 H), 1.52 - 1.85 (m, 6 H), 1.89 - 2.18 (m, 3 H), 2.34 - 2.53 (m, 2 H), 2.62 (d, *J*=10.7 Hz, 1 H), 3.19 (d, *J*=8.6 Hz, 1 H), 3.36 - 3.53 (m, 2 H), 3.86 - 4.15 (m, 2 H), 5.16 (d, *J*=10.4 Hz, 1 H), 5.27 (dd, *J*=17.1, 1.3 Hz, 1 H), 5.80 - 5.98 (m, *J*=22.6, 10.7, 5.8 Hz, 1 H), 6.42 - 6.54 (m, 1 H), 7.76 (d, *J*=0.8 Hz, 1 H), 7.99 (d, *J*=8.6 Hz, 1 H), 8.21 (dd, *J*=8.5, 2.1 Hz, 1 H), 8.60 (d, *J*=2.3 Hz, 1 H), 8.84 (d, *J*=1.6 Hz, 1 H), 8.90 (s, 1 H). Anal. Calcd for C₂₄H₃₃N₅O₂· 0.1 H₂O: C, 67.77; H, 7.87; N, 16.46. Found: C, 67.84; H, 7.79; N, 16.43.

Example 204. *N*-((1*S*,2*R*)-2-(((3*S*)-3-(allyloxy)piperidin-1-yl)methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide

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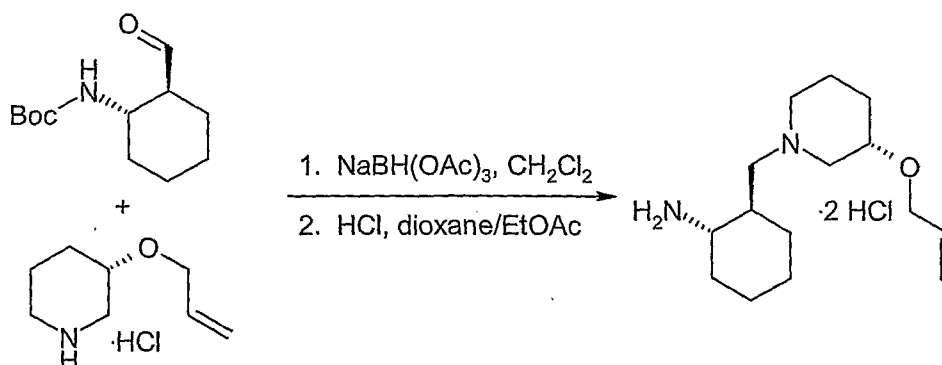
Step A: (3S)-3-(allyloxy)piperidine hydrochloride salt



NaH (0.20 g of 60% in oil, 5.0 mmol) was added in portions to a solution of *tert*-butyl
 5 (3S)-3-hydroxypiperidine-1-carboxylate (0.514 g, 2.6 mmol) dissolved in dry DMF.
 The resulting mixture was stirred for 30 min, and then allyl iodide (0.3 mL, 2.5 mmol)
 was added, and the reaction was stirred for 2 h. The reaction was cooled to 0 °C,
 H₂O was added, and then the reaction was concentrated *in vacuo*. The residue was
 partitioned between CH₂Cl₂ and H₂O. The layers were separated, and the aqueous
 10 layer was extracted with additional CH₂Cl₂. The combined organic layers were dried
 over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in 4 N
 HCl in dioxane (3.8 mL, 15 mmol). The mixture was stirred for 16 h and then
 concentrated *in vacuo*. The compound was used in subsequent steps without further
 purification. MS (M+1): 142.1.

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Step B: ((1S,2R)-2-(((3S)-3-(allyloxy)piperidin-1-yl)methyl)cyclohexyl)amine hydrochloride salt

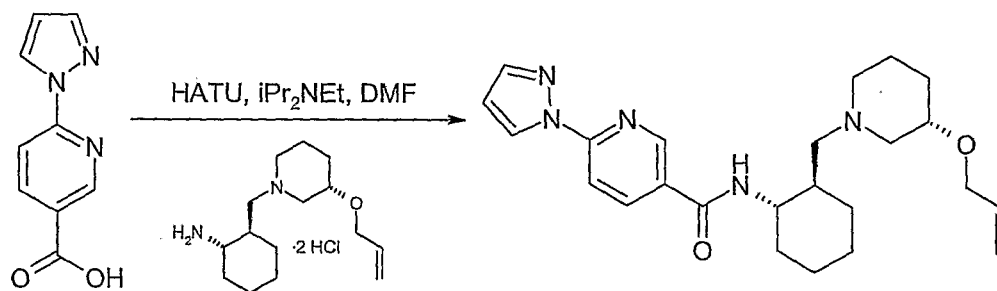


A mixture of crude *tert*-butyl [(1S,2S)-2-formylcyclohexyl]carbamate (0.0770 g, ~0.3
 20 mmol) and (3S)-3-(allyloxy)piperidine hydrochloride salt (0.0640 g, 0.36 mmol) in dry

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CH₂Cl₂ (6 mL) was stirred for 30 min at 5 °C. NaBH(OAc)₃ (0.127 g, 0.6 mmol) was added to the reaction and the resulting mixture was allowed to warm to room temperature and stirred for 14 h. The reaction was cooled to 0 °C, and water (3 mL) was added, followed by 1 N NaOH (3 mL) and CH₂Cl₂ (10 mL). The layers were separated, and the aqueous phase was extracted with additional CH₂Cl₂ (2 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in EtOAc (0.75 mL), and 4 N HCl in dioxane (0.75 mL, 3 mmol) was added. The mixture was stirred for 1.5 h and then concentrated *in vacuo* to provide the title compound, which was used in subsequent steps without further purification. MS (M+1): 253.2.

Step C: *N*-((1*S*,2*R*)-2-(((3*S*)-3-(allyloxy)piperidin-1-yl)methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide

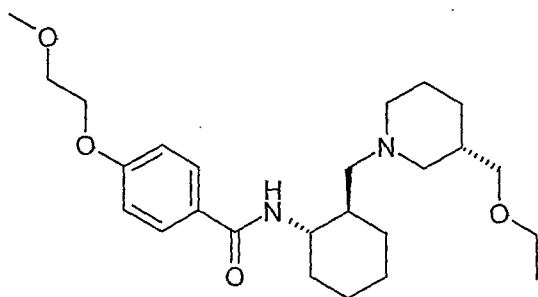


A mixture of 6-(1*H*-pyrazol-1-yl)nicotinic acid (0.0624 g, 0.33 mmol), HATU (0.126 g, 0.33 mmol), and diisopropylethylamine (0.073 mL, 0.42 mmol) in dry DMF (1 mL) was stirred at 0 °C for 10 min. A solution of crude ((1*S*,2*R*)-2-(((3*S*)-3-(allyloxy)piperidin-1-yl)methyl)cyclohexyl)amine hydrochloride salt (~0.3 mmol) and diisopropylethylamine (0.14 mL, 0.8 mmol) in DMF (0.5 + 2 x 0.5 mL) was then added to the reaction, and the resulting mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for an additional 21h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH₂Cl₂ (4 mL) and a saturated solution of NaHCO₃ in water (4 mL). The mixture was passed through a Varian Chem ElutTM extraction cartridge, and the cartridge was washed with additional CH₂Cl₂ (3 x 8 mL). The organic extract was concentrated *in vacuo*, and the residue was purified by preparative scale reverse phase LC/MS (gradient 55-75% CH₃CN in H₂O containing 10 mM NH₄HCO₃) to provide the title compound as a white solid (0.0656 g, 52% over 3 steps) following lyophilization from CH₃CN/H₂O. MS (M+1): 424.3. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.94 - 1.85 (m, 12 H),

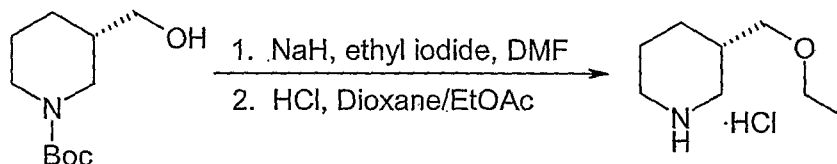
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1.97 - 2.79 (m, 7 H), 3.17 - 3.58 (m, 2 H), 3.73 - 4.04 (m, 2 H), 4.99 (d, $J=10.4$ Hz, 1 H), 5.13 (d, $J=17.4$ Hz, 1 H), 5.67 - 5.93 (m, 1 H), 6.47 (dd, $J=2.6, 1.7$ Hz, 1 H), 7.75 (d, $J=1.0$ Hz, 1 H), 7.98 (dd, $J=8.6, 0.4$ Hz, 1 H), 8.37 (dd, $J=8.7, 1.9$ Hz, 1 H), 8.60 (dd, $J=2.5, 0.6$ Hz, 1 H), 8.95 (d, $J=1.0$ Hz, 1 H), 9.27 (s, 1 H). Anal. Calcd for $C_{24}H_{33}N_5O_2 \cdot 0.2 H_2O$: C, 67.48; H, 7.88; N, 16.39. Found: C, 67.46; H, 7.65; N, 16.26.

Example 205. *N*-((1*S*,2*R*)-2-[[*(3S)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-(2-methoxyethoxy)benzamide



Step A: (*3S*)-3-(ethoxymethyl)piperidine hydrochloride salt



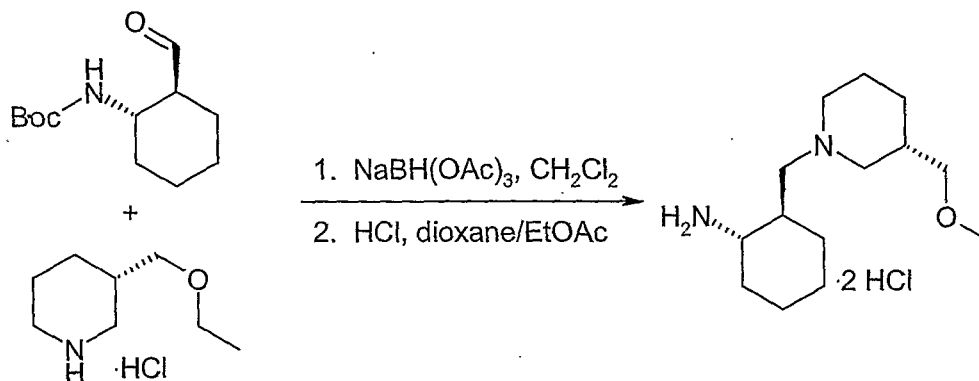
NaH (0.271 g of 60% in oil, 6.8 mmol) was washed with hexanes (2 x 10 mL), and then suspended in dry DMF (6 mL) and cooled to 0 °C. A solution of *tert*-butyl (*3S*)-3-(hydroxymethyl)piperidine-1-carboxylate (0.730 g, 3.4 mmol) in dry DMF (3 mL + 2 x 1 mL) was slowly added, and the resulting mixture was stirred for 30 min at 0 °C. Ethyl iodide (0.33 mL, 4.1 mmol) was added, and the reaction was allowed to warm to room temperature and stir for 40 h. The reaction was cooled to 0 °C, H₂O (1 mL) was added, and then the reaction was concentrated *in vacuo*. The residue was partitioned between CH₂Cl₂ (25 mL) and H₂O (15 mL). The layers were separated, and the aqueous layer was extracted with additional CH₂Cl₂ (2 x 15 mL). The combined organic layers were washed with brine (2 x 15 mL) and then dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in EtOAc (5 mL), and 4 N HCl in dioxane (4.3 mL, 17 mmol) was added. The mixture was stirred for 16 h and then concentrated *in vacuo*. The resulting solid was washed with Et₂O and dried *in vacuo* to provide the title compound (0.725 g, quantitative over 2 steps)

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as a white solid. The compound was used in subsequent steps without further purification. MS (M+1): 144.1.

Step B: ((1*S*,2*R*)-2-[[*(3S)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)amine

5 hydrochloride salt

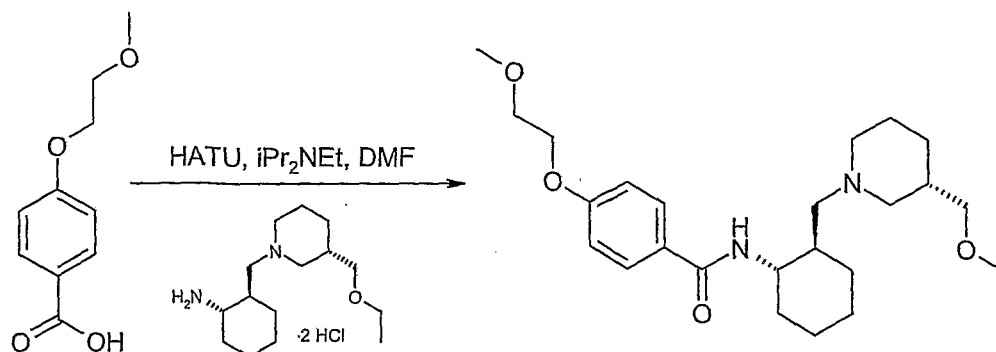


A mixture of crude *tert*-butyl [(1*S*,2*S*)-2-formylcyclohexyl]carbamate (0.316 g, ~1.2 mmol) and *(3S)*-3-(ethoxymethyl)piperidine hydrochloride salt (0.315 g, ~1.5 mmol) in dry CH₂Cl₂ (24 mL) was stirred for 30 min at 5 °C. NaBH(OAc)₃ (0.521 g, 2.5 mmol) was added to the reaction and the resulting mixture was allowed to warm to room temperature and stirred for 15 h. The reaction was cooled to 0 °C, and water (12 mL) was added, followed by 1 N NaOH (12 mL) and CH₂Cl₂ (40 mL). The layers were separated, and the aqueous phase was extracted with additional CH₂Cl₂ (2 x 40 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in EtOAc (3 mL), and 4 N HCl in dioxane (3 mL, 12 mmol) was added. The mixture was stirred for 6 h and then concentrated *in vacuo* to provide the title compound, which was used in subsequent steps without further purification. MS (M+1): 255.2.

20

Step C: *N*-((1*S*,2*R*)-2-[[*(3S)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclo-hexyl)-4-(2-methoxyethoxy)benzamide

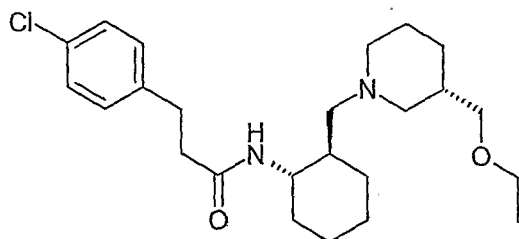
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A mixture of 4-(2-methoxyethoxy)benzoic acid (0.0669 g, 0.34 mmol), crude ((1S,2R)-2-[(3S)-3-(ethoxymethyl)piperidin-1-yl]methyl)cyclohexyl)amine hydrochloride salt (~0.31 mmol), and diisopropylethylamine (0.14 mL, 0.80 mmol) in dry DMF (2 mL) was cooled to 0 °C, and HATU (0.130 g, 0.34 mmol) in dry DMF (0.5 mL) was added. Additional diisopropylethylamine (0.073 mL, 0.42 mmol) was then added, and the resulting mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for an additional 15h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH₂Cl₂ (4 mL) and a saturated solution of NaHCO₃ in water (4 mL). The mixture was passed through a Varian Chem Elut™ extraction cartridge, and the cartridge was washed with additional CH₂Cl₂ (3 x 8 mL). The organic extract was concentrated *in vacuo*, and the residue was purified by preparative scale reverse phase LC/MS (gradient 55-75% CH₃CN in H₂O containing 10 mM NH₄HCO₃) to provide the title compound as a slightly yellow oil (0.0410 g, 31% over 3 steps) following lyophilization from CH₃CN/H₂O. MS (M+1): 433.3. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.84 - 0.98 (m, 1 H), 0.98 - 1.12 (m, 4 H), 1.14 - 1.45 (m, 2 H), 1.47 - 1.82 (m, 11 H), 2.02 (dd, J=12.8, 1.7 Hz, 1 H), 2.39 (dd, J=12.9, 9.4 Hz, 1 H), 2.49 - 2.67 (m, 2 H), 2.96 - 3.28 (m, 5 H), 3.34 - 3.43 (m, 1 H), 3.44 (s, 3 H), 3.71 - 3.78 (m, 2 H), 4.09 - 4.17 (m, 2 H), 6.87 - 6.94 (m, 2 H), 7.73 - 7.80 (m, 2 H), 8.68 (d, J=2.3 Hz, 1 H). Anal. Calcd for C₂₅H₄₀N₂O₄·0.5 H₂O: C, 68.00; H, 9.36; N, 6.34. Found: C, 67.93; H, 9.28; N, 6.64.

Example 206. 3-(4-chlorophenyl)-N-((1S,2R)-2-[(3S)-3-(ethoxymethyl)piperidin-1-yl]methyl)cyclohexyl)propanamide

102213-1 WO

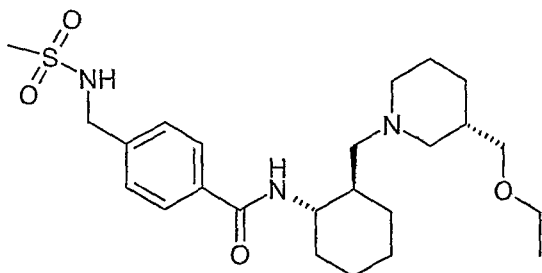


- A mixture of 3-(4-chlorophenyl)propanoic acid (0.0630 g, 0.34 mmol), crude ((1S,2R)-2-(((3S)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)amine hydrochloride salt (~0.31 mmol), and diisopropylethylamine (0.14 mL, 0.80 mmol) in dry DMF (2 mL) was cooled to 0 °C, and HATU (0.130 g, 0.34 mmol) in dry DMF (0.5 mL) was added. Additional diisopropylethylamine (0.073 mL, 0.42 mmol) was then added, and the resulting mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for an additional 15h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH₂Cl₂ (4 mL) and a saturated solution of NaHCO₃ in water (4 mL). The mixture was passed through a Varian Chem Elut™ extraction cartridge, and the cartridge was washed with additional CH₂Cl₂ (3 x 8 mL). The organic extract was concentrated *in vacuo*, and the residue was purified by preparative scale reverse phase LC/MS (gradient 65-85% CH₃CN in H₂O containing 10 mM NH₄HCO₃) to provide the title compound as a slightly yellow oil (0.0455 g, 35% over 3 steps) following lyophilization from CH₃CN/H₂O. MS (M+1): 421.3. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.83 - 1.06 (m, 3 H), 1.14 (t, J=7.0 Hz, 3 H), 1.17 - 1.89 (m, 12 H), 1.98 (dd, J=12.5, 1.8 Hz, 1 H), 2.25 (dd, J=12.7, 9.2 Hz, 1 H), 2.32 - 2.46 (m, 3 H), 2.65 (d, J=8.6 Hz, 1 H), 2.77 - 2.98 (m, 3 H), 3.13 - 3.26 (m, 3 H), 3.33 - 3.44 (m, 2 H), 7.10 - 7.17 (m, 2 H), 7.18 - 7.24 (m, 2 H), 8.03 (d, J=2.9 Hz, 1 H). Anal. Calcd for C₂₄H₃₇ClN₂O₂: C, 68.47; H, 8.86; N, 6.65. Found: C, 68.21; H, 8.88; N, 6.41.

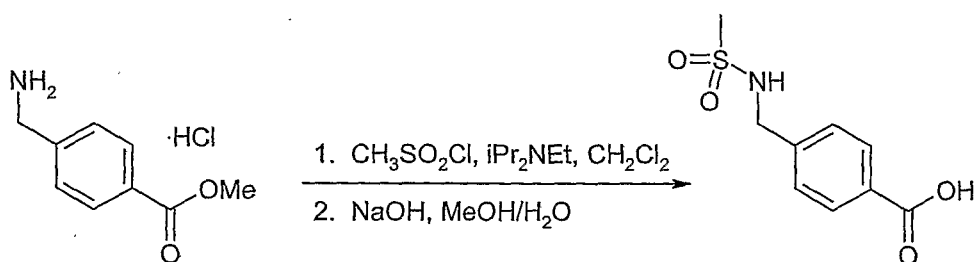
Example 207. N-((1S,2R)-2-(((3S)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-((methylsulfonyl)amino)methylbenzamide

25

102213-1 WO



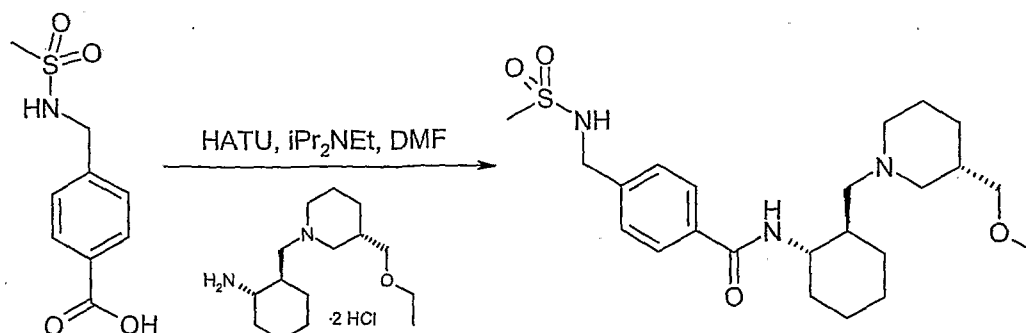
Step A: 4-((methylsulfonyl)amino)methyl}benzoic acid



- A suspension of methyl 4-(aminomethyl)benzoate hydrochloride salt (0.541 g, 2.7 mmol) in dry CH_2Cl_2 (7 mL) was cooled to 0 °C, and methanesulfonyl chloride (0.48 mL, 6.2 mmol) and diisopropylethylamine (1.5 mL, 8.8 mmol) were added. The resulting mixture was allowed to warm to room temperature and stir for 15 h. The reaction was then diluted with CH_2Cl_2 (10 mL) and washed with H_2O (10 mL), a saturated aqueous solution of NaHCO_3 (10 mL), and brine (10 mL) successively.
- The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was dissolved in MeOH (14 mL), and NaOH (1.29 g, 32 mmol) dissolved in H_2O (7 mL) was added. The reaction was stirred for 16 h and was then concentrated *in vacuo*. The residue was dissolved in H_2O (10 mL) and acidified to pH 1 with 3 N HCl. The aqueous phase was extracted with EtOAc (3 x 50 mL), and the combined organic phases were dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to provide the title compound as a slightly yellow powder (0.60 g, 98% over 2 steps), which was used in subsequent steps without further purification. ^1H NMR (400 MHz, DMSO- D_6) δ ppm 2.88 (s, 3 H), 4.22 (d, $J=6.2$ Hz, 2 H), 7.45 (d, $J=8.6$ Hz, 2 H), 7.65 (t, $J=6.3$ Hz, 1 H), 7.86 - 7.95 (m, 2 H), 12.91 (s, 1 H)

Step B: *N*-((1*S*,2*R*)-2-(((3*S*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-((methylsulfonyl)amino)methyl}benzamide

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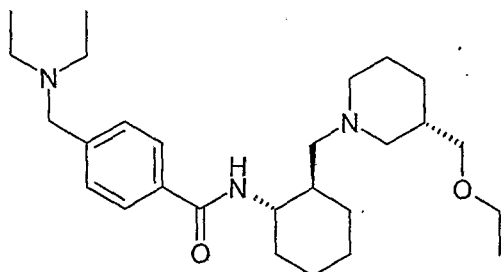


A mixture of 4-[[[(methylsulfonyl)amino]methyl]benzoic acid (0.0782 g, 0.34 mmol), crude ((1S,2R)-2-[[[(3S)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt (~0.31 mmol), and diisopropylethylamine (0.14 mL, 0.80 mmol) in dry DMF (2 mL) was cooled to 0 °C, and HATU (0.130 g, 0.34 mmol) in dry DMF (0.5 mL) was added. Additional diisopropylethylamine (0.073 mL, 0.42 mmol) was then added, and the resulting mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for an additional 15h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH₂Cl₂ (4 mL) and a saturated solution of NaHCO₃ in water (4 mL). The mixture was passed through a Varian Chem Elut™ extraction cartridge, and the cartridge was washed with additional CH₂Cl₂ (3 x 8 mL). The organic extract was concentrated *in vacuo*, and the residue was purified by preparative scale reverse phase LC/MS (gradient 45-65% CH₃CN in H₂O containing 10 mM NH₄HCO₃) to provide the title compound as a white solid (0.0453 g, 31% over 3 steps) following lyophilization from CH₃CN/H₂O. MS (M+1): 466.3. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.73 - 0.94 (m, 1 H), 0.97 - 1.14 (m, 5 H), 1.18 - 1.81 (m, 13 H), 2.03 (dd, *J*=12.9, 1.2 Hz, 1 H), 2.35 (dd, *J*=12.9, 9.8 Hz, 1 H), 2.46 - 2.64 (m, 2 H), 2.88 (s, 3 H), 2.93 - 3.10 (m, 3 H), 3.25 (q, *J*=7.0 Hz, 2 H), 3.39 (tt, *J*=10.6, 3.6 Hz, 1 H), 4.21 - 4.42 (m, 2 H), 7.38 (d, *J*=8.2 Hz, 2 H), 7.73 - 7.83 (m, 2 H), 8.94 (d, *J*=2.1 Hz, 1 H).

Example 208. 4-[(diethylamino)methyl]-N-((1S,2R)-2-[[[(3S)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide

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102213-1 WO

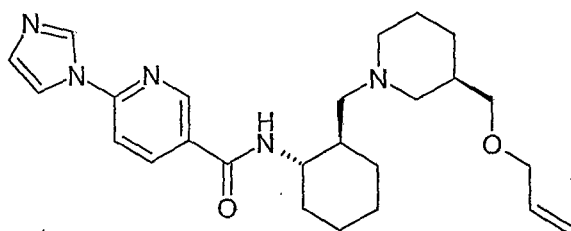


A mixture of 4-[(diethylamino)methyl]benzoic acid (0.0707 g, 0.34 mmol), crude ((1S,2R)-2-[(3S)-3-(ethoxymethyl)piperidin-1-yl]methyl)cyclohexylamine hydrochloride salt (~0.31 mmol), and diisopropylethylamine (0.14 mL, 0.80 mmol) in dry DMF (2 mL) was cooled to 0 °C, and HATU (0.130 g, 0.34 mmol) in dry DMF (0.5 mL) was added. Additional diisopropylethylamine (0.073 mL, 0.42 mmol) was then added, and the resulting mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for an additional 15h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH₂Cl₂ (4 mL) and a saturated solution of NaHCO₃ in water (4 mL). The mixture was passed through a Varian Chem ElutTM extraction cartridge, and the cartridge was washed with additional CH₂Cl₂ (3 x 8 mL). The organic extract was concentrated *in vacuo*, and the residue was purified by preparative scale reverse phase LC/MS (gradient 65-85% CH₃CN in H₂O containing 10 mM NH₄HCO₃) to provide the title compound as a yellow solid (0.0501 g, 36% over 3 steps) following lyophilization from CH₃CN/H₂O. MS (M+1): 444.5. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.84 - 0.98 (m, 1 H), 0.98 - 1.14 (m, 10 H), 1.16 - 1.82 (m, 13 H), 2.04 (dd, J=12.9, 1.4 Hz, 1 H), 2.39 (dd, J=12.9, 9.4 Hz, 1 H), 2.49 (q, J=7.1 Hz, 4 H), 2.60 (t, J=9.8 Hz, 2 H), 3.02 (d, J=10.9 Hz, 1 H), 3.08 (d, J=6.4 Hz, 2 H), 3.10 - 3.24 (m, 2 H), 3.34 - 3.49 (m, 1 H), 3.52 - 3.65 (m, 2 H), 7.35 (d, J=8.4 Hz, 2 H), 7.75 (d, J=8.4 Hz, 2 H), 8.77 (s, 1 H). Anal. Calcd for C₂₇H₄₅N₃O₂·0.3 H₂O: C, 72.21; H, 10.23; N, 9.36. Found: C, 72.39; H, 10.21; N, 9.08.

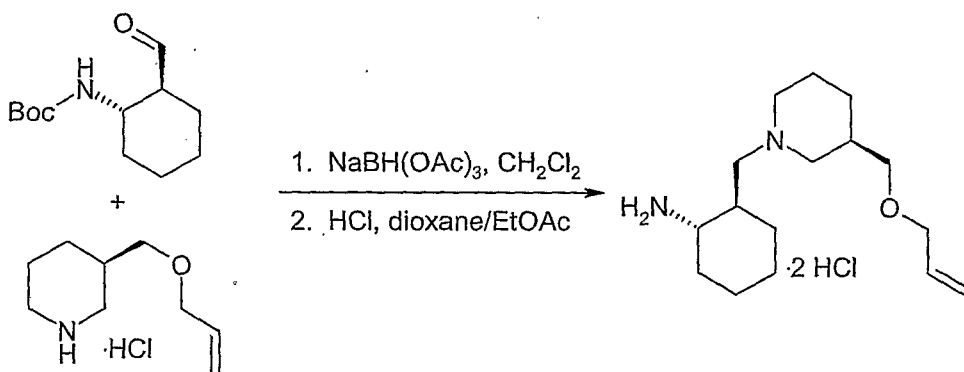
Example 209. N-[(1S,2R)-2-[(3R)-3-[(allyloxy)methyl]piperidin-1-yl]methyl]cyclohexyl]-6-(1H-imidazol-1-yl)nicotinamide

25

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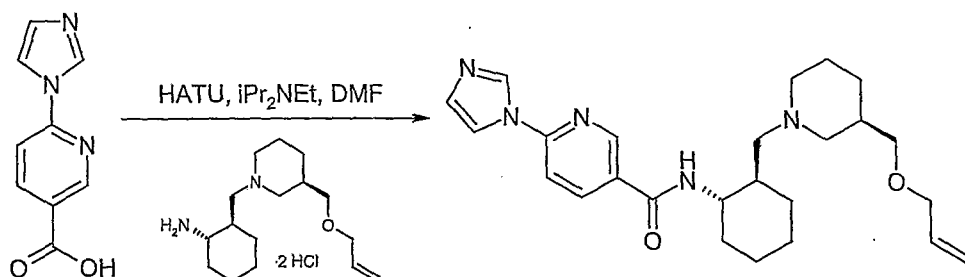
Step A: [(1S,2R)-2-({(3R)-3-[(allyloxy)methyl]piperidin-1-yl)methyl}cyclohexyl)amine hydrochloride salt



- 5 A mixture of crude *tert*-butyl [(1S,2S)-2-formylcyclohexyl]carbamate (1.95 g, 8.6 mmol) and (3R)-3-[(allyloxy)methyl]piperidine hydrochloride salt (2.08 g, 11 mmol) in dry CH₂Cl₂ (180 mL) was stirred for 30 min at 5 °C. NaBH(OAc)₃ (3.64 g, 17 mmol) was added to the reaction and the resulting mixture was allowed to warm to room temperature and stirred for 15 h. The reaction was cooled to 0 °C, and water (50 mL)
- 10 was added, followed by 1 N NaOH (50 mL). The layers were separated, and the aqueous phase was extracted with additional CH₂Cl₂ (3 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The intermediate, *tert*-butyl [(1S,2R)-2-({(3R)-3-[(allyloxy)methyl]piperidin-1-yl)methyl}cyclohexyl]carbamate, was obtained as a yellow oil (2.46 g, 78%) following
- 15 purification by column chromatography (9:1 CH₂Cl₂:MeOH). MS (M+1): 367.3. The *tert*-butyl [(1S,2R)-2-({(3R)-3-[(allyloxy)methyl]piperidin-1-yl)methyl}cyclohexyl]carbamate obtained above was dissolved in EtOAc (17 mL), and 4 N HCl in dioxane (17 mL, 68 mmol) was added. The mixture was stirred for 1.5 h and then concentrated *in vacuo* to provide the title compound (2.41 g, quantitative), which was
- 20 used in subsequent steps without further purification. MS (M+1): 267.2.

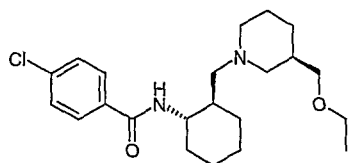
Step B: N-[(1S,2R)-2-({(3R)-3-[(allyloxy)methyl]piperidin-1-yl)methyl}cyclohexyl)-6-(1H-imidazol-1-yl)nicotinamide

102213-1 WO



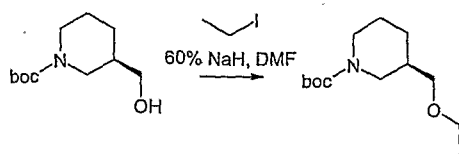
A mixture of 6-(1H-imidazol-1-yl)nicotinic acid (1.39 g, 7.4 mmol) and crude [(1S,2R)-2-((3R)-3-[(allyloxy)methyl]piperidin-1-yl)methyl)cyclohexyl]amine hydrochloride salt (2.41 g, ~6.7 mmol) in dry DMF (40 mL) was cooled to 0 °C, and HATU (2.80 g, 7.4 mmol) and diisopropylethylamine (4.7 mL, 27 mmol) were added. The resulting mixture was allowed to slowly warm to room temperature and stirred for an additional 16h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH₂Cl₂ (80 mL) and a saturated solution of NaHCO₃ in water (80 mL). The layers were separated, and the aqueous phase was extracted with additional CH₂Cl₂ (3 x 60 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (9:1 CH₂Cl₂:MeOH), and the product was then dissolved in CH₂Cl₂ and treated with 1 N HCl in ether (8 mL) to provide the title compound as its HCl salt (1.46 g, 43%) following lyophilization from H₂O. MS (M+1): 438.3. ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 1.16 - 2.37 (m, 14 H), 2.75 - 2.91 (m, 1 H), 2.96 - 3.09 (m, 1 H), 3.15 - 3.29 (m, 2 H), 3.42 (dd, J=9.6, 4.9 Hz, 1 H), 3.48 - 3.76 (m, 3 H), 3.76 - 3.87 (m, 1 H), 3.89 - 4.05 (m, 2 H), 5.08 - 5.19 (m, 1 H), 5.20 - 5.30 (m, 1 H), 5.78 - 5.95 (m, 1 H), 7.78 - 7.84 (m, 1 H), 8.06 (d, J=8.2 Hz, 1 H), 8.39 - 8.48 (m, 1 H), 8.62 (dd, J=8.6, 2.3 Hz, 1 H), 9.10 (d, J=2.0 Hz, 1 H), 9.86 (s, 1 H).

Example 210. 4-chloro-N-((1S,2R)-2-((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide



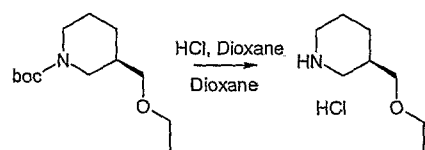
Step A. The preparation of *tert*-butyl (3R)-3-(ethoxymethyl)piperidine-1-carboxylate

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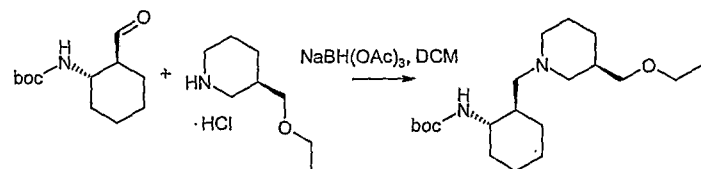
To a solution of *tert*-butyl (3*R*)-3-(hydroxymethyl)piperidine-1-carboxylate (568 mg, 2.63 mmol) in dry DMF (10 mL) was added NaH (60% , 200 mg, 5.26 mmol) at 0°C under nitrogen and the suspension was stirred at room temperature for 30 min. ethyl iodide (0.51 mL, 6.32 mmol) was added to the reaction mixture and stirred over night at room temperature. Quenched with water. Extracted with dichloromethane (3 x 20 mL), washed with brine, dried over Na₂SO₄. Removal of solvent gave the crude product, which was used for the next step without further purification. MS (M+1): 244.2

Step B: The preparation of (3*R*)-3-(ethoxymethyl)piperidine hydrochloride salt



A 4N solution of hydrochloric acid in Dioxane (4.5 mL, 18.0 mmol) was added to a solution of the crude product from step A *tert*-butyl (3*R*)-3-(ethoxymethyl)piperidine-1-carboxylate (2.63 mmol) in Dioxane (5 mL). The reaction was stirred at room temperature for 5 hours. The mixture was concentrated *in vacuo*. The product was used directly for the next step without further purification. MS (M+1): 144.1 m: 477 mg

Step C. The preparation of *tert*-butyl ((1*S*,2*R*)-2-[(3*R*)-3-(ethoxymethyl)piperidin-1-yl]methyl)cyclohexyl)carbamate

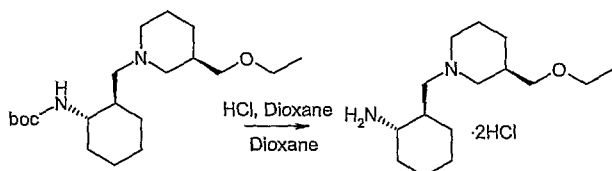


Crude product from step B (3*R*)-3-(ethoxymethyl)piperidine hydrochloride salt (340 mg, 1.89 mmol) was added to a solution of *tert*-butyl [(1*S*,2*S*)-2-formylcyclohexyl]carbamate (341 mg crude, 1.5 mmol) in dichloromethane (5 mL) at 0°C. The reaction was stirred at 0°C for 30 min. and then sodium triacetoxymethylborohydride (636 mg, 3.0 mmol) was added to the reaction mixture. The

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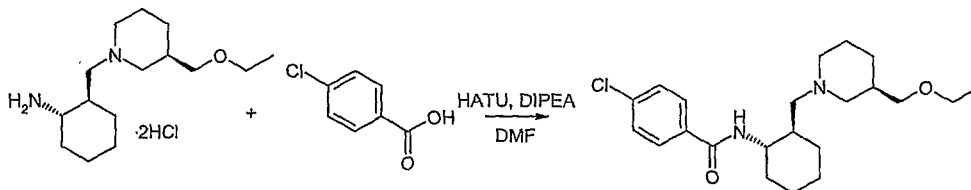
reaction was stirred at 0°C to room temperature, and stirred at room temperature for 3.5 h. Water (5 mL) was added dropwise. A 2N sodium hydroxide solution (10 mL) and dichloromethane (30 mL) were added to the mixture. The phases were separated and the aqueous was extracted with dichloromethane (2x15mL). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. MS (m+1): 355.4 The product was used directly for the next step without further purification.

Step D. The preparation of ((1*S*,2*R*)-2-[[*(3R)*-3-ethoxypiperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt



A 4N solution of hydrochloric acid in Dioxane (2.25 mL, 9.0 mmol) was added to a solution of the crude product from step C *tert*-butyl ((1*S*,2*R*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)carbamate (1.50 mmol) in Dioxane (5 mL). The reaction was stirred at room temperature for overnight. The mixture was concentrated *in vacuo*. The product was used directly for the next step without further purification. 572 mg MS (M+1): 255.3

Step E. The preparation of 4-chloro-*N*-((1*S*,2*R*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide

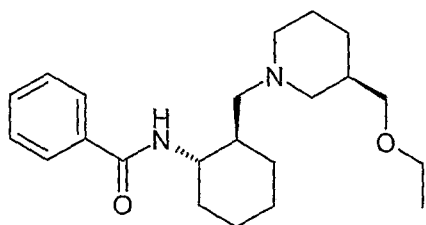


A solution of 4-chlorobenzoic acid (47 mg, 0.30 mmol), HATU (114 mg, 0.3 mmol) and diisopropylethylamine (0.07 mL, 0.40 mmol) in dry DMF (3 mL) was stirred at room temperature for 10 minutes. Crude ((1*S*,2*R*)-2-[[*(3R)*-3-ethoxypiperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt from step D (0.30 mmol) was added to the solution. The mixture was stirred at room temperature for overnight. The solvent was removed *in vacuo*. Residue was dissolved in DCM (15 mL) and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was purified with reverse phase HPLC High pH to yield 4-chloro-*N*-((1*S*,2*R*)-2-[[*(3R)*-

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3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide 17.3 mg (15%) as its free base. MS (M+1): 393.3 ¹H NMR (400 MHz, CDCl₃) δ ppm 0.82 - 0.98 (m, *J* = 9.37 Hz, 1H) 0.98 - 1.15 (m, *J* = 9.18 Hz, 2H), 1.23 (t, *J* = 7.03 Hz, 3H), 1.27 - 1.55 (m, 4H), 1.57 - 1.80 (m, 6H), 1.80 - 1.97 (m, 2H), 2.05 (d, *J* = 11.91 Hz, 1H), 2.40 (s, 1H), 2.57 (s, 2H), 3.20 (t, *J* = 8.50 Hz, 1H), 3.24 - 3.32 (m, *J* = 10.16 Hz, 1H), 3.34 (dd, *J* = 9.28, 5.18 Hz, 1H), 3.37 - 3.44 (m, *J* = 11.72 Hz, 1H), 3.44 - 3.55 (m, 2H), 7.38 (d, *J* = 8.40 Hz, 2H), 7.78 (d, *J* = 7.81 Hz, 2H), 9.00 (s, 1H)

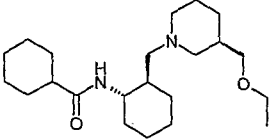
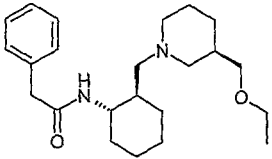
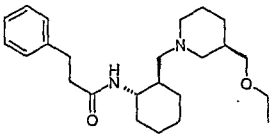
Example 211. *N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide



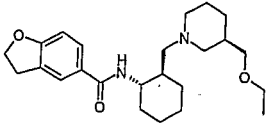
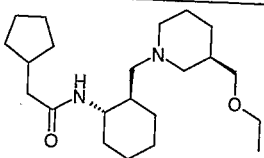
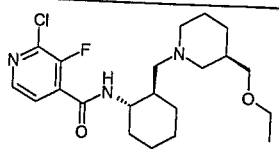
A mixture of benzoic acid (0.0148 g, 0.12 mmol) and crude ((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)amine hydrochloride salt (0.0351 g, ~0.11 mmol) in dry DMF (1 mL) was cooled to 0 °C, and HATU (0.0460 g, 0.12 mmol) and diisopropylethylamine (0.077 mL, 0.44 mmol) were added. The resulting mixture was allowed to slowly warm to room temperature and stirred for an additional 16h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH₂Cl₂ (2 mL) and a saturated solution of NaHCO₃ in water (2 mL). The mixture was passed through a Varian Chem ElutTM extraction cartridge, and the cartridge was washed with additional CH₂Cl₂ (3 x 6 mL). The organic extract was concentrated *in vacuo*, and the residue was purified by preparative scale reverse phase LC/MS (gradient 55-75% CH₃CN in H₂O containing 10 mM NH₄HCO₃) to provide the title compound as a yellow gum (0.0234 g, 59%) following lyophilization from CH₃CN/H₂O. MS (M+1): 359.4. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.77 - 1.17 (m, 3 H), 1.22 (t, *J*=7.0 Hz, 3 H), 1.25 - 1.78 (m, 10 H), 1.79 - 1.97 (m, *J*=11.3, 11.3 Hz, 2 H), 2.02 (d, *J*=12.5 Hz, 1 H), 2.39 (dd, *J*=12.1, 9.8 Hz, 1 H), 2.48 - 2.66 (m, 2 H), 3.18 (dd, *J*=9.3, 7.9 Hz, 1 H), 3.25 (d, *J*=10.7 Hz, 1 H), 3.31 (dd, *J*=9.4, 5.3 Hz, 1 H), 3.36 - 3.54 (m, 3 H), 7.33 - 7.50 (m, 3 H), 7.82 (d, *J*=7.0 Hz, 2 H), 8.89 (s, 1 H). Anal. Calcd for C₂₂H₃₄N₂O₂ · 0.6 H₂O: C, 71.55; H, 9.61; N, 7.58. Found: C, 71.74; H, 9.63; N, 7.36.

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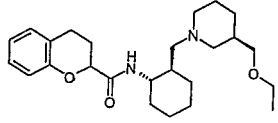
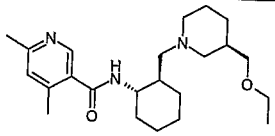
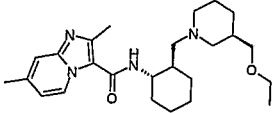
Examples 212-231: Compounds listed in the following table were prepared as described in Example 212:

Example No.	Structure	Name	Data
212		<i>N</i> -((1 <i>S</i> ,2 <i>R</i>)-2-(((3 <i>R</i>)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)cyclohexanecarboxamide	¹ H NMR (400 MHz, CHLOROFORM- <i>D</i>) δ ppm 0.84 - 1.09 (m, 3 H), 1.13 - 2.03 (m, 27 H), 2.32 (dd, <i>J</i> =12.8, 9.1 Hz, 1 H), 2.36 - 2.45 (m, 1 H), 2.63 - 2.75 (m, 1 H), 3.07 - 3.26 (m, 3 H), 3.26 - 3.36 (m, 1 H), 3.41 - 3.55 (m, 2 H), 7.76 (s, 1 H). MS: 365.3 (M+1).
213		<i>N</i> -((1 <i>S</i> ,2 <i>R</i>)-2-(((3 <i>R</i>)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-2-phenylacetamide	¹ H NMR (400 MHz, CHLOROFORM- <i>D</i>) : δ ppm 0.84 - 1.06 (m, 3 H), 1.19 (t, <i>J</i> =6.9 Hz, 3 H), 1.22 - 1.92 (m, 12 H), 2.00 (dd, <i>J</i> =12.7, 2.9 Hz, 1 H), 2.20 - 2.39 (m, 2 H), 2.61 (d, <i>J</i> =11.1 Hz, 1 H), 3.02 (d, <i>J</i> =11.5 Hz, 1 H), 3.15 - 3.25 (m, 1 H), 3.24 - 3.35 (m, 2 H), 3.39 - 3.53 (m, 4 H), 7.17 - 7.36 (m, 5 H), 7.61 (s, 1 H). MS: 373.3 (M+1).
214		<i>N</i> -((1 <i>S</i> ,2 <i>R</i>)-2-(((3 <i>R</i>)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-3-phenylpropanamide	¹ H NMR (400 MHz, CHLOROFORM- <i>D</i>) δ ppm 0.77 - 1.06 (m, 3 H), 1.19 (t, <i>J</i> =7.0 Hz, 3 H), 1.22 - 2.01 (m, 13 H), 2.15 - 2.50 (m, 5 H), 2.82 - 3.03 (m, 2 H), 3.07 (d, <i>J</i> =9.6 Hz, 1 H), 3.13 - 3.32 (m, 3 H), 3.37 - 3.51 (m, 2 H), 7.11 - 7.21 (m, 3

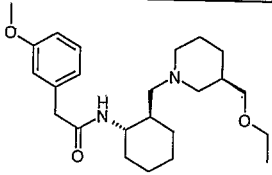
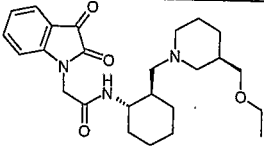
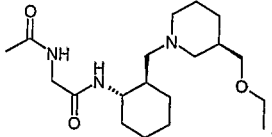
102213-1 WO

		amide	H), 7.22 - 7.30 (m, 2 H), 8.00 (s, 1 H). MS: (M+1) 387.3.
215		N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-2,3-dihydro-1-benzofuran-5-carboxamide	¹ H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.80 - 0.96 (m, 1 H), 0.97 - 1.13 (m, 2 H), 1.21 (t, J=7.0 Hz, 3 H), 1.24 - 1.77 (m, 10 H), 1.81 - 1.96 (m, 2 H), 2.01 (d, J=12.3 Hz, 1 H), 2.29 - 2.45 (m, 1 H), 2.56 (d, J=11.1 Hz, 2 H), 3.11 - 3.54 (m, 8 H), 4.61 (t, J=8.8 Hz, 2 H), 6.74 (d, J=8.4 Hz, 1 H), 7.60 (d, J=8.0 Hz, 1 H), 7.73 (s, 1 H), 8.75 (s, 1 H). MS: (M+1) 401.4.
216		2-cyclopentyl-N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)acetamide	¹ H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.83 - 2.13 (m, 29 H), 2.16 - 2.28 (m, 1 H), 2.33 (dd, J=12.7, 9.2 Hz, 1 H), 2.37 - 2.47 (m, 1 H), 2.69 (d, J=11.1 Hz, 1 H), 3.10 (d, J=10.9 Hz, 1 H), 3.16 - 3.27 (m, 2 H), 3.27 - 3.35 (m, 1 H), 3.40 - 3.54 (m, 2 H), 7.84 (s, 1 H). MS: (M+1) 365.3.
217		2-chloro-N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-2-fluorobenzamide	¹ H NMR (400 MHz, METHANOL-D4) δ ppm 1.11 - 1.21 (m, 3 H), 1.21 - 1.58 (m, 5 H), 1.71 - 2.17 (m, 8 H), 2.17 - 2.34 (m, 1 H), 2.70 - 2.91 (m, 2 H), 2.98 - 3.32 (m, 3 H), 3.38 - 3.60 (m, 4 H), 3.65 (d, J=10.9

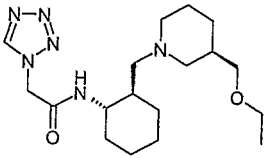
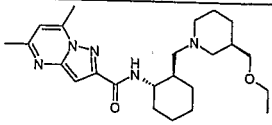
102213-1 WO

		clohexyl)-3-fluoroisonicotinamide hydrochloride salt	Hz, 1 H), 3.70 - 3.81 (m, 1 H), 7.56 - 7.65 (m, 1 H), 8.28 - 8.35 (m, 1 H). MS: (M+1) 412.3.
218		<i>N</i> -((1 <i>S</i> ,2 <i>R</i>)-2-(((3 <i>R</i>)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)chromane-2-carboxamide	¹ H NMR (400 MHz, METHANOL-D ₄) δ ppm 0.99 - 1.59 (m, 8 H), 1.62 - 2.56 (m, 12 H), 2.68 - 3.15 (m, 5 H), 3.23 - 3.29 (m, 1 H), 3.32 - 3.72 (m, 6 H), 4.52 - 4.59 (m, 0.5 H), 4.65 - 4.74 (m, 0.5 H), 6.82 - 7.01 (m, 2 H), 7.02 - 7.20 (m, 2 H). MS: (M+1) 415.3.
219		<i>N</i> -((1 <i>S</i> ,2 <i>R</i>)-2-(((3 <i>R</i>)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4,6-dimethylnicotinamide	¹ H NMR (400 MHz, METHANOL-D ₄) δ ppm 1.12 - 1.22 (m, 3 H), 1.22 - 1.59 (m, 5 H), 1.73 - 2.14 (m, 9 H), 2.19 - 2.34 (m, 1 H), 2.68 (s, 3 H), 2.77 (s, 3 H), 2.84 - 2.97 (m, 2 H), 2.99 - 3.11 (m, 1 H), 3.24 - 3.65 (m, 6 H), 3.70 - 3.82 (m, 1 H), 7.85 (s, 1 H), 8.86 - 8.91 (m, 1 H). MS: (M+1) 388.3.
220		<i>N</i> -((1 <i>S</i> ,2 <i>R</i>)-2-(((3 <i>R</i>)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-7-methyl-1 <i>H</i> -benzotriazole-4-carboxamide	¹ H NMR (400 MHz, METHANOL-D ₄) δ ppm 1.11 - 1.19 (m, 3 H), 1.22 - 1.70 (m, 5 H), 1.74 - 2.34 (m, 9 H), 2.61 (s, 3 H), 2.76 (s, 3 H), 2.77 - 2.90 (m, 2 H), 3.02 - 3.12 (m, 1 H), 3.24 - 3.29 (m, 1 H), 3.32 -

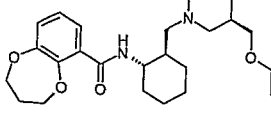
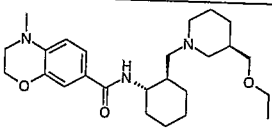
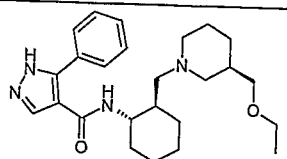
102213-1 WO

		2,7-dimethylimidazo[1,2-a]pyridine-3-carboxamide	3.67 (m, 6 H), 3.85 (td, $J=10.9$, 3.9 Hz, 1 H), 7.38 - 7.44 (m, 1 H), 7.66 - 7.73 (m, 1 H), 9.02 - 9.09 (m, 1 H). MS: (M+1) 427.2.
221		<i>N</i> -((1 <i>S</i> ,2 <i>R</i>)-2-((3 <i>R</i>)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-2-(3-methoxyphenyl)acetamide	^1H NMR (400 MHz, METHANOL- D_4) δ ppm 1.12 - 1.19 (m, 3 H), 1.20 - 1.56 (m, 5 H), 1.63 - 2.24 (m, 9 H), 2.39 (t, $J=12.3$ Hz, 1 H), 2.64 - 3.00 (m, 3 H), 3.24 (dd, $J=9.6$, 6.8 Hz, 1 H), 3.33 - 3.55 (m, 8 H), 3.80 (s, 3 H), 6.78 - 6.89 (m, 1 H), 6.90 - 7.02 (m, 2 H), 7.26 (t, $J=7.8$ Hz, 1 H). MS: (M+1) 403.3.
222		2-(2,3-dioxo-2,3-dihydro-1 <i>H</i> -indol-1-yl)- <i>N</i> -((1 <i>S</i> ,2 <i>R</i>)-2-((3 <i>R</i>)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)acetamide	^1H NMR (400 MHz, METHANOL- D_4) δ ppm 1.13 - 1.20 (m, 3 H), 1.20 - 1.50 (m, 5 H), 1.71 - 2.07 (m, 9 H), 2.11 - 2.27 (m, 1 H), 2.62 - 3.21 (m, 3 H), 3.34 - 3.68 (m, 7 H), 4.41 - 4.54 (m, 2 H), 7.07 - 7.23 (m, 2 H), 7.58 - 7.72 (m, 2 H). MS: (M+1) 442.3.
223		<i>N</i> ² -acetyl- <i>N</i> ¹ -((1 <i>S</i> ,2 <i>R</i>)-2-((3 <i>R</i>)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)acetamide	^1H NMR (400 MHz, METHANOL- D_4) δ ppm 1.12 - 1.19 (m, 3 H), 1.19 - 1.48 (m, 5

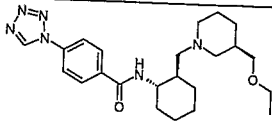
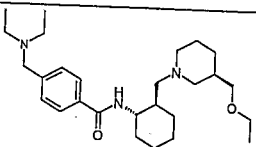
102213-1 WO

		(ethoxymethyl)piperidin-1-yl)methyl}cyclohexylglycinamide	¹ H, 1.68 - 2.11 (m, 9 H), 2.03 (s, 3 H), 2.17 - 2.32 (m, 1 H), 2.74 - 2.95 (m, 3 H), 3.16 (dd, $J=13.3, 2.7$ Hz, 1 H), 3.25 - 3.33 (m, 1 H), 3.38 - 3.66 (m, 6 H), 3.70 - 3.77 (m, 1 H), 3.78 - 3.87 (m, 1 H). MS: (M+1) 354.2.
224		<i>N</i> -((1 <i>S</i> ,2 <i>R</i>)-2-(((3 <i>R</i>)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-2-(1 <i>H</i> -tetrazol-1-yl)acetamide	¹ H NMR (400 MHz, METHANOL-D ₄) δ ppm 1.12 - 1.18 (m, 3 H), 1.21 - 1.50 (m, 5 H), 1.70 - 2.10 (m, 9 H), 2.15 - 2.33 (m, 1 H), 2.76 - 2.90 (m, 2 H), 2.95 (dd, $J=13.3, 9.8$ Hz, 1 H), 3.16 - 3.24 (m, 1 H), 3.25 - 3.33 (m, 1 H), 3.38 - 3.71 (m, 5 H), 5.26 - 5.34 (m, 1 H), 5.36 - 5.45 (m, 1 H), 9.25 (s, 1 H). MS: (M+1) 365.2.
225		<i>N</i> -((1 <i>S</i> ,2 <i>R</i>)-2-(((3 <i>R</i>)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-5,7-dimethylpyrazolo[1,5- <i>a</i>]pyrimidine-2-carboxamide	¹ H NMR (400 MHz, METHANOL-D ₄) δ ppm 1.06 - 1.17 (m, 3 H), 1.16 - 1.54 (m, 4 H), 1.57 - 1.71 (m, 1 H), 1.72 - 2.30 (m, 9 H), 2.64 (s, 3 H), 2.68 - 2.88 (m, 4 H), 2.97 - 3.27 (m, 3 H), 3.32 - 3.57 (m, 5 H), 3.67 (d, $J=11.3$ Hz, 1 H), 3.82 (td, $J=10.8, 4.1$ Hz, 1 H), 7.02 - 7.05 (m, 1 H), 7.07 (s, 1 H). MS: (M+1) 428.3.

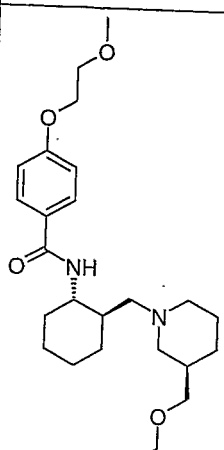
102213-1 WO

226		<i>N</i> -((1 <i>S</i> ,2 <i>R</i>)-2-(((3 <i>R</i>)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-3,4-dihydro-2 <i>H</i> -1,5-benzodioxepine-6-carboxamide	¹ H NMR (400 MHz, METHANOL-D ₄) δ ppm 1.11 - 1.19 (m, 3 H), 1.19 - 1.65 (m, 5 H), 1.72 - 2.35 (m, 11 H), 2.67 - 2.87 (m, 2 H), 2.98 - 3.29 (m, 3 H), 3.33 - 3.59 (m, 4 H), 3.65 (d, <i>J</i> =11.3 Hz, 1 H), 3.76 (td, <i>J</i> =10.6, 4.1 Hz, 1 H), 4.11 - 4.26 (m, 2 H), 4.26 - 4.34 (m, 2 H), 6.97 - 7.04 (m, 1 H), 7.07 - 7.13 (m, 1 H), 7.24 - 7.32 (m, 1 H). MS: (M+1) 431.3.
227		<i>N</i> -((1 <i>S</i> ,2 <i>R</i>)-2-(((3 <i>R</i>)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-methyl-3,4-dihydro-2 <i>H</i> -1,4-benzoxazin-7-carboxamide	¹ H NMR (400 MHz, METHANOL-D ₄) δ ppm 1.10 - 1.20 (m, 3 H), 1.20 - 1.63 (m, 5 H), 1.69 - 2.32 (m, 9 H), 2.66 - 2.84 (m, 2 H), 2.91 - 3.03 (m, 1 H), 3.05 (s, 3 H), 3.08 - 3.17 (m, 1 H), 3.24 (dd, <i>J</i> =9.6, 7.2 Hz, 1 H), 3.34 - 3.55 (m, 6 H), 3.62 (d, <i>J</i> =11.7 Hz, 1 H), 3.74 (td, <i>J</i> =10.8, 4.1 Hz, 1 H), 4.25 - 4.34 (m, 2 H), 6.84 - 6.94 (m, 1 H), 7.28 - 7.35 (m, 1 H), 7.41 - 7.51 (m, 1 H). MS: (M+1) 430.2.
228		<i>N</i> -((1 <i>S</i> ,2 <i>R</i>)-2-(((3 <i>R</i>)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-6-phenyl-1 <i>H</i> -benzotriazole-4-carboxamide	¹ H NMR (400 MHz, METHANOL-D ₄) δ ppm 1.11 - 1.20 (m, 3 H), 1.21 - 1.47 (m, 5 H), 1.68 - 2.27 (m, 9 H), 2.61 (td, <i>J</i> =12.8, 3.3 Hz, 1 H), 2.74

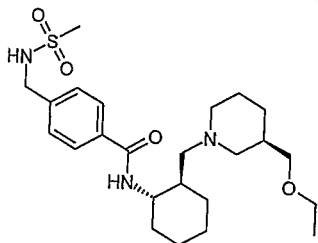
102213-1 WO

		yl)methyl}cy clohexyl)-5- phenyl-1 <i>H</i> - pyrazole-4- carboxamid e	(t, $J=12.3$ Hz, 1 H), 2.91 - 3.14 (m, 2 H), 3.26 (dd, $J=9.4$, 7.0 Hz, 1 H), 3.35 - 3.51 (m, 4 H), 3.55 (d, $J=12.9$ Hz, 1 H), 3.67 (td, $J=10.4$, 4.1 Hz, 1 H), 7.40 - 7.51 (m, 3 H), 7.61 - 7.71 (m, 2 H), 8.13 - 8.19 (m, 1 H). MS: ($M+1$) 425.2.
229		<i>N</i> -((1 <i>S</i> ,2 <i>R</i>)- 2-(((3 <i>R</i>)-3- (ethoxymeth yl)piperidin- 1- yl)methyl}cy clohexyl)-4- (1 <i>H</i> -tetrazol- 1- yl)benzamid e	^1H NMR (400 MHz, METHANOL- D_4) δ ppm 1.08 - 1.21 (m, 3 H), 1.21 - 1.68 (m, 5 H), 1.73 - 2.31 (m, 9 H), 2.71 - 2.92 (m, 2 H), 3.00 - 3.28 (m, 3 H), 3.36 - 3.61 (m, 4 H), 3.66 (d, $J=11.3$ Hz, 1 H), 3.81 (td, $J=10.8$, 4.1 Hz, 1 H), 7.94 - 8.07 (m, 2 H), 8.11 - 8.18 (m, 2 H), 9.83 - 9.90 (m, 1 H). MS: ($M+1$) 427.2.
230		4- [[[(diethylami no)methyl]- <i>N</i> -((1 <i>S</i> ,2 <i>R</i>)- 2-(((3 <i>R</i>)-3- (ethoxymeth yl)piperidin- 1- yl)methyl}cy clohexyl)be nzamide	MS ($M+1$): 444.5 ^1H NMR (400 MHz, CDCl_3) δ ppm 0.76 - 0.96 (m, 1H), 1.03 (t, $J = 7.13$ Hz, 6H), 1.06 - 1.20 (m, 2H), 1.23 (t, $J = 7.03$ Hz, 3H), 1.27 - 1.51 (m, 4H), 1.53 - 1.69 (m, 5H), 1.69 - 1.79 (m, 2H), 1.88 (t, $J =$ 11.33 Hz, 2H), 2.03 (d, $J =$ 12.89 Hz, 1H), 2.39 (dd, $J =$ 12.60, 9.67 Hz, 1H), 2.50 (q, J $= 7.10$ Hz, 4H), 2.55 - 2.65 (m, 1H), 3.17 - 3.23 (m, 1H), 3.26 (d, $J = 10.55$ Hz, 1H), 3.33 (dd, $J = 9.28$, 5.18 Hz, 1H), 3.37 -

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			3.44 (m, 1H), 3.46 – 3.54 (m, 2H), 3.59 (s, 2H), 7.37 (d, $J = 8.01$ Hz, 2H), 7.77 (d, $J = 8.01$ Hz, 2H), 8.85 (s, 1H)
231		<i>N</i> -((1 <i>S</i> ,2 <i>R</i>)-2-(((3 <i>R</i>)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-((2-methoxyethyl)benzamide	. MS ($M+1$): 433.3 ^1H NMR (400 MHz, CDCl_3) δ ppm 1.17 (t, $J = 6.35$ Hz, 3H), 1.21 - 1.35 (m, 2H), 1.34 - 1.50 (m, 3H), 1.58 - 1.83 (m, 8H), 1.83 - 2.00 (m, 1H), 2.02 - 2.19 (m, 1H), 2.30 - 2.72 (m, 3H), 3.10 (dd, $J = 7.42, 3.91$ Hz, 1H), 3.13 - 3.24 (m, 1H), 3.28 (dd, $J = 9.57, 5.08$ Hz, 1H), 3.35 - 3.53 (m, 4H), 3.45 (s, 3H), 3.52 - 3.72 (m, 1H), 3.73 - 3.79 (m, 2H), 3.79 - 3.93 (m, 1H), 6.97 (d, $J = 8.79$ Hz, 2H), 8.20 (d, $J = 1.17$ Hz, 2H), 8.45 (d, $J = 3.71$ Hz, 1H)

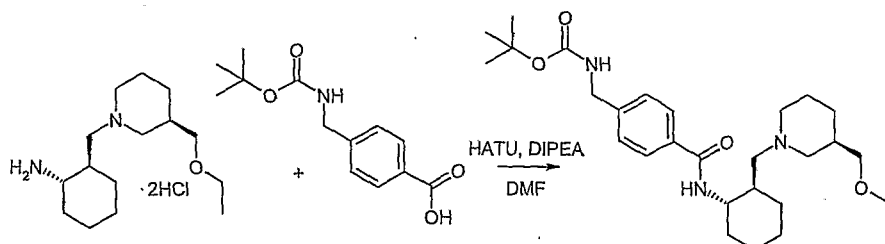
Example 232. *N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-(((methylsulfonyl)amino)methyl)benzamide



5

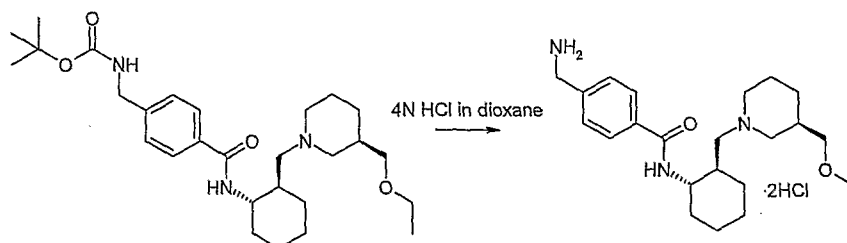
Step A. The preparation of *tert*-butyl 4-(((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)amino)carbonyl)benzyl)carbamate

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A solution 4-[[*tert*-butoxycarbonyl]amino]methyl]benzoic acid (75 mg, 0.30 mmol), HATU (114 mg, 0.30 mmol) and a few drop of diisopropylethylamine in dry DMF (3 mL) was stirred at room temperature for 10 minutes. Crude ((1*R*,2*S*)-2-[[*(3R)*-3-ethoxypiperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt (87mg, 0.30 mmol) was added to the solution. The mixture was stirred at room temperature for overnight. The solvent was removed in vacuo. Residue was dissolved in DCM (15 mL) and washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄. The crude product was used for the next step without further purification. MS(M+1): 488.5

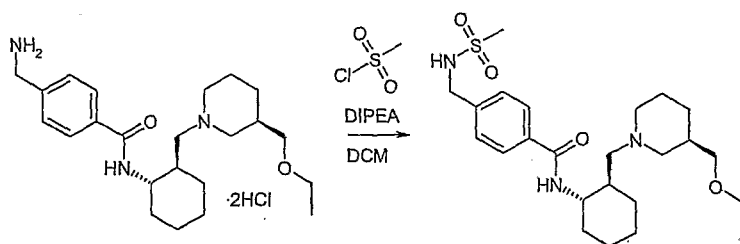
Step B The preparation of 4-(aminomethyl)-*N*-((1*S*,2*R*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide hydrochloride salt



A 4N solution of hydrochloric acid in Dioxane (4.5 mL, 18.0 mmol) was added to a solution of the crude product from step A *tert*-butyl (4-[[[(1*S*,2*R*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl]amino]carbonyl]benzyl)carbamate (0.30 mmol) in Dioxane (5 mL). The reaction was stirred at room temperature for 6 hours. The mixture was concentrated *in vacuo*. The product was used directly for the next step without further purification. MS (M+1): 388.4

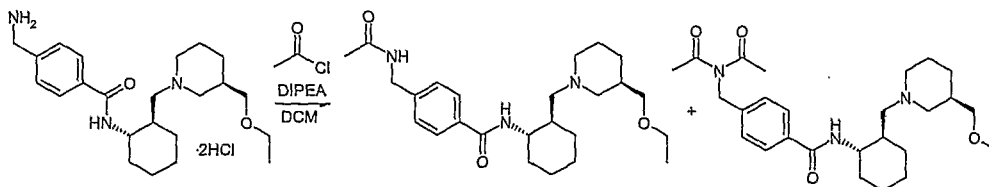
Step C. The preparation of *N*-((1*S*,2*R*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-[[*(methylsulfonyl)*amino]methyl]benzamide

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To a solution of crude 4-(aminomethyl)-*N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide hydrochloride salt (0.3 mmol) from step B and diisopropylethylamine (few drop) was added 0.05 mL in DCM (5 mL), 0.60 mmol methanesulfonyl chloride. The mixture was stirred overnight at room temperature. Aqueous solution of NaHCO₃ sat. was added (10 mL), then mixture of both layers poured into VARIAN CHEM ELUTTM cartridges. The column was rinsed with DCM (2x20 mL). Organic layer was concentrated in *vacuo*. The crude product was purified by prep LC-MS High pH to yield the title compound *N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-(((methylsulfonyl)amino)methyl)benzamide (42 mg, 30%) as its free base. MS (*M*+1): 466.3 ¹H NMR (400 MHz, CDCl₃) δ ppm 0.79 - 0.96 (m, 1H), 0.98 - 1.21 (m, 2H), 1.24 (t, *J* = 6.93 Hz, 3H), 1.28 - 1.40 (m, 2H), 1.40 - 1.51 (m, 2H), 1.50 - 1.70 (m, 3H), 1.69 - 1.79 (m, 3H), 1.90 (t, *J* = 10.64 Hz, 2H), 2.04 (d, *J* = 12.69 Hz, 1H), 2.40 (dd, *J* = 11.52, 10.55 Hz, 1H), 2.58 (dd, *J* = 15.23, 13.67 Hz, 2H), 2.88 (s, 3H), 3.20 (t, *J* = 8.50 Hz, 1H), 3.25 - 3.32 (m, 1H), 3.34 (dd, *J* = 9.18, 5.08 Hz, 1H), 3.37 - 3.46 (m, 1H), 3.45 - 3.55 (m, 2H), 4.37 (s, 2H), 4.62 (s, 1H), 7.39 (d, *J* = 8.01 Hz, 2H), 7.85 (d, *J* = 7.81 Hz, 2H), 8.99 (s, 1H)

Example 233. 4-[(acetylamino)methyl]-*N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide



To a solution of crude 4-(aminomethyl)-*N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide hydrochloride salt (0.3 mmol) from example 13 step B and diisopropylethylamine (few drop) was added 0.05 mL in DCM (5 mL), 0.60 mmol acetyl chloride. The mixture was stirred overnight at room temperature. Aqueous solution of NaHCO₃ sat. was added (10 mL), then

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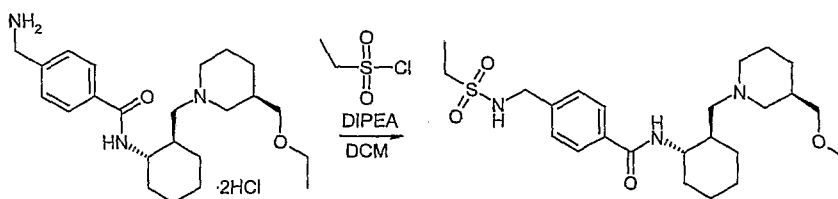
mixture of both layers poured into VARIAN CHEM ELUT™ cartridges. The column was rinsed with DCM (2x20 mL). Organic layer was concentrated in *vacuo*. The crude product was purified by prep LC-MS High pH to obtain two fractions, and the fraction 1 is the title compound 4-[(acetylamino)methyl]-*N*-((1*S*,2*R*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide 10 mg as its free base.

MS (*M*+1): 430.2 ¹H NMR (400 MHz, CDCl₃) δ ppm 1.18 (s, 3H), 1.21 - 1.89 (m, 9H), 1.89 - 2.23 (m, 3H), 2.05 (s, 3H), 2.29 - 2.70 (m, 3H), 2.74 - 3.17 (m, *J* = 82.22 Hz, 1H), 3.27 (s, 3H), 3.35 - 3.53 (m, 3H), 3.54 - 3.72 (m, *J* = 5.66 Hz, 1H), 3.76 - 3.97 (m, 1H), 4.47 (d, *J* = 5.66 Hz, 2H), 5.81 (s, 1H), 7.32 (d, *J* = 8.01 Hz, 2H), 7.95 (s, 2H), 8.25 (s, 1H), 11.41 (s, 1H)

Example 234: 4-[(diacetylamino)methyl]-*N*-((1*S*,2*R*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide

Fraction 2 of Example 233: 4-[(diacetylamino)methyl]-*N*-((1*S*,2*R*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide 15 mg as its free base. MS (*M*+1): 472.3 ¹H NMR (400 MHz, CDCl₃) δ ppm 1.17 (t, *J* = 6.93 Hz, 3H), 1.35 (t, 5H), 1.71 - 2.20 (m, 9H), 2.42 (s, 6H), 2.44 - 2.54 (m, 2H), 2.54 - 2.62 (m, 1H), 3.23 - 3.38 (m, 3H), 3.38 - 3.53 (m, 3H), 3.63 (d, *J* = 9.57 Hz, 1H), 3.80 - 3.94 (m, 1H), 5.00 (s, 2H), 7.20 (d, *J* = 8.20 Hz, 2H), 7.95 (d, *J* = 8.20 Hz, 2H), 8.14 (t, *J* = 9.67 Hz, 1H)

Example 235. *N*-((1*S*,2*R*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-[(ethylsulfonyl)amino]methyl]benzamide

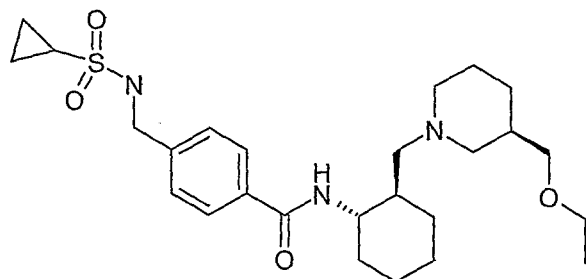


To a solution of crude 4-(aminomethyl)-*N*-((1*S*,2*R*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide hydrochloride salt (0.3 mmol) and diisopropylethylamine (few drop) was added 0.05 mL in DCM (5 mL), ethanesulfonyl chloride (0.6 mmol). The mixture was stirred overnight at room temperature. Aqueous solution of saturated NaHCO₃ was added (10 mL), then mixture of both layers poured into VARIAN CHEM ELUT™ cartridges. The column was rinsed with DCM (2x20 mL). Organic layer was concentrated in *vacuo*. The crude product was purified by prep LC-MS Low pH to yield *N*-((1*S*,2*R*)-2-[[*(3R)*-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-[(ethylsulfonyl)amino]methyl]benzamide

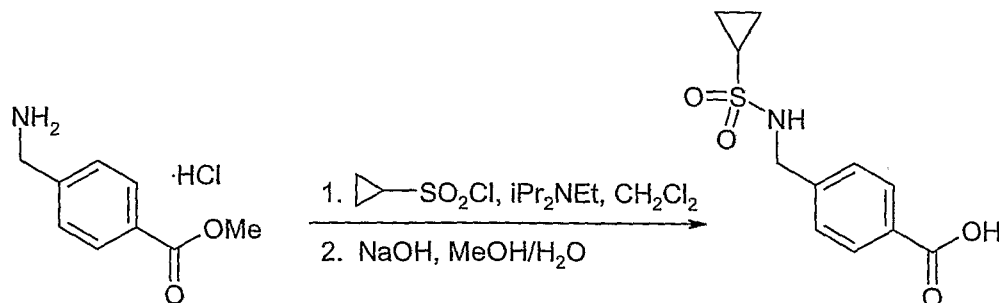
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{{[(ethylsulfonyl)amino]methyl}benzamide 32 mg (15 %) as TFA salt. MS (M+1): 480.4. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.17 (t, *J* = 7.03 Hz, 3H), 1.23 - 1.50 (m, 5H), 1.34 (t, *J* = 7.42 Hz, 3H), 1.65 - 1.87 (m, 3H), 1.86 - 2.17 (m, 4H), 2.37 - 2.63 (m, 4H), 2.98 (t, *J* = 7.42 Hz, 2H), 3.22 - 3.33 (m, 3H), 3.39 - 3.52 (m, 3H), 3.63 (d, *J* = 6.64 Hz, 1H), 3.79 - 3.97 (m, 1H), 4.35 (d, *J* = 5.86 Hz, 2H), 4.57 (t, *J* = 5.57 Hz, 1H), 7.40 (d, *J* = 8.20 Hz, 2H), 7.98 (d, *J* = 8.01 Hz, 2H), 8.27 (t, *J* = 8.79 Hz, 1H), 11.23 (s, 1 H)

Example 236. 4-[[[(cyclopropylsulfonyl)amino]methyl]-*N*-((1*S*,2*R*)-2-[[[(3*R*)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide



Step A: 4-[[[(cyclopropylsulfonyl)amino]methyl]benzoic acid



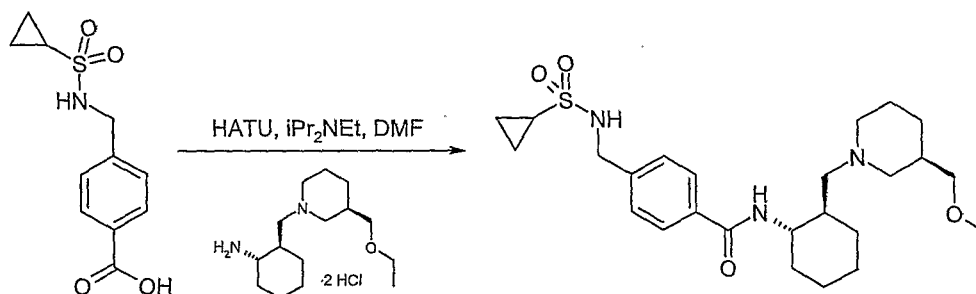
A suspension of methyl 4-(aminomethyl)benzoate hydrochloride salt (0.395 g, 2.0 mmol) in dry CH₂Cl₂ (5 mL) was cooled to 0 °C, and cyclopropanesulfonyl chloride (0.46 mL, 4.5 mmol) and diisopropylethylamine (1.1 mL, 6.3 mmol) were added. The resulting mixture was allowed to warm to room temperature and stir for 89 h. The reaction was then diluted with CH₂Cl₂ (10 mL) and washed with H₂O (10 mL), a saturated aqueous solution of NaHCO₃ (10 mL), and brine (10 mL) successively. The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in MeOH (10 mL), and NaOH (0.94 g, 24 mmol) dissolved in H₂O (5 mL) was added. The reaction was stirred for 20 h and was then concentrated *in vacuo*. The residue was dissolved in H₂O (7 mL) and acidified to pH 1 with 3 N HCl. The resulting precipitate was collected by filtration and washed with H₂O to

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provide the title compound as a tan solid (0.46 g, 93% over 2 steps), which was used in subsequent steps without further purification. ^1H NMR (400 MHz, METHANOL- D_4) δ ppm 0.88 - 0.96 (m, 2 H), 0.99 - 1.05 (m, 2 H), 2.40 - 2.48 (m, 1 H), 4.35 (s, 2 H), 7.46 - 7.52 (m, 2 H), 7.97 - 8.02 (m, 2 H).

5

Step B: 4-[[[(cyclopropylsulfonyl)amino]methyl]-*N*-((1*S*,2*R*)-2-[[[(3*R*)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide

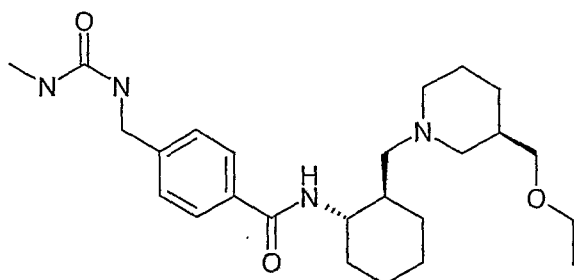


- 10 A mixture of 4-[[[(cyclopropylsulfonyl)amino]methyl]benzoic acid (0.0842 g, 0.33 mmol) and crude ((1*S*,2*R*)-2-[[[(3*R*)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt (~0.30 mmol) in dry DMF (3 mL) was cooled to 0 °C, and HATU (0.126 g, 0.33 mmol) and diisopropylethylamine (0.21 mL, 1.2 mmol) were added. The resulting mixture was stirred at 0 °C for 30 min and then warmed to room
- 15 temperature and stirred for an additional 16h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH_2Cl_2 (4 mL) and a saturated solution of NaHCO_3 in water (4 mL). The mixture was passed through a Varian Chem ElutTM extraction cartridge, and the cartridge was washed with additional CH_2Cl_2 (3 x 8 mL). The organic extract was concentrated *in vacuo*, and the residue was purified by
- 20 preparative scale reverse phase LC/MS (gradient 55-75% CH_3CN in H_2O containing 10 mM NH_4HCO_3) to provide the title compound as a white solid (0.0706 g, 48% over 3 steps) following lyophilization from $\text{CH}_3\text{CN}/\text{H}_2\text{O}$. MS ($\text{M}+1$): 492.3. ^1H NMR (400 MHz, CHLOROFORM- D) δ ppm 0.79 - 0.97 (m, 3 H), 0.99 - 1.18 (m, 4 H), 1.23 (t, $J=7.0$ Hz, 3 H), 1.26 - 1.49 (m, 4 H), 1.50 - 1.79 (m, 7 H), 1.89 (t, $J=10.7$ Hz, 2 H),
- 25 1.99 - 2.07 (m, 1 H), 2.26 - 2.46 (m, 2 H), 2.49 - 2.65 (m, 2 H), 3.12 - 3.23 (m, 1 H), 3.23 - 3.54 (m, 4 H), 4.38 (d, $J=2.3$ Hz, 2 H), 4.52 - 4.64 (m, 1 H), 7.35 - 7.43 (m, 2 H), 7.78 - 7.86 (m, 2 H), 8.97 (s, 1 H). Anal. Calcd for $\text{C}_{26}\text{H}_{41}\text{N}_3\text{O}_4\text{S}\cdot 0.1 \text{ H}_2\text{O}$: C, 63.28; H, 8.42; N, 8.51. Found: C, 63.25; H, 8.80; N, 8.41.

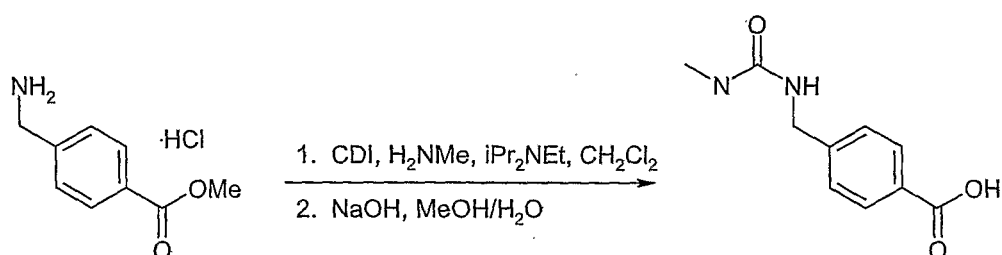
Example 237. *N*-((1*S*,2*R*)-2-[[[(3*R*)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-[[[(methylamino)carbonyl]amino]methyl]benzamide

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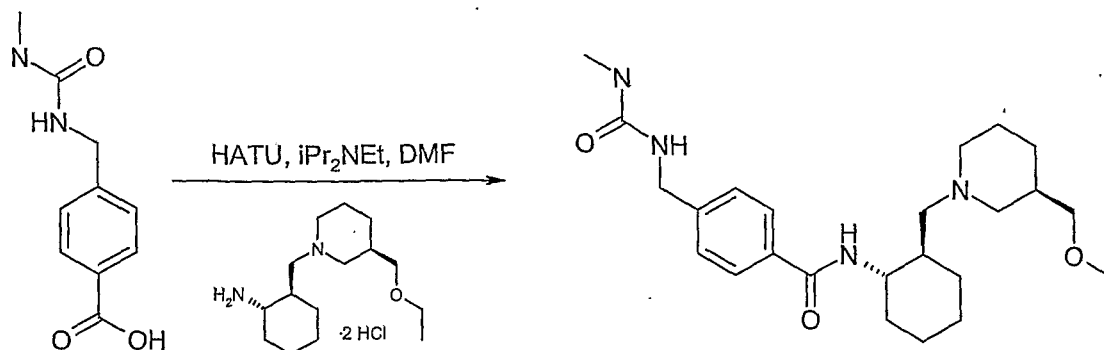
Step A: 4-(((methylamino)carbonyl)amino)methyl)benzoic acid



- A suspension of methyl 4-(aminomethyl)benzoate hydrochloride salt (0.257 g, 1.3 mmol) in dry CH_2Cl_2 (5 mL) was treated with diisopropylethylamine (0.67 mL, 3.8 mmol) and 1,1'-carbonyldiimidazole (0.207 g, 1.3 mmol). The resulting mixture was stirred for 15 min, and then methyl amine (1.3 mL of 2M in MeOH, 2.6 mmol) was added and the reaction was stirred for an additional 132 h. Water (5 mL) was added, and the mixture was passed through a Varian Chem ElutTM extraction cartridge. The cartridge was washed with additional CH_2Cl_2 (3 x 8 mL), and the organic extract was concentrated *in vacuo*. The residue was dissolved in MeOH (7 mL), and NaOH (0.61 g, 15 mmol) dissolved in H_2O (3.5 mL) was added. The reaction was stirred for 20 h and was then concentrated *in vacuo*. The residue was dissolved in H_2O (5 mL) and acidified to pH 1 with 3 N HCl. The resulting precipitate was collected by filtration and washed with H_2O to provide the title compound as a white solid (0.22 g, 82% over 2 steps), which was used in subsequent steps without further purification. ^1H NMR (400 MHz, METHANOL- D_4) δ ppm 2.71 (s, 3 H), 4.37 (s, 2 H), 7.38 (d, $J=4.7$ Hz, 2 H), 7.97 (d, $J=5.5$ Hz, 2 H).

- Step B: *N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-(((methylamino)carbonyl)amino)methyl)benzamide

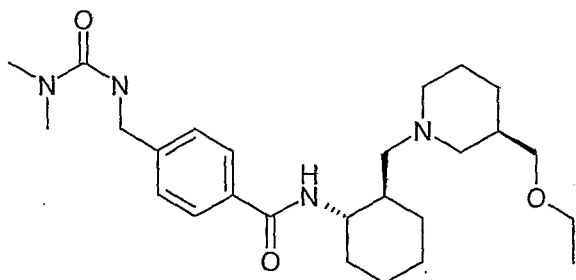
102213-1 WO



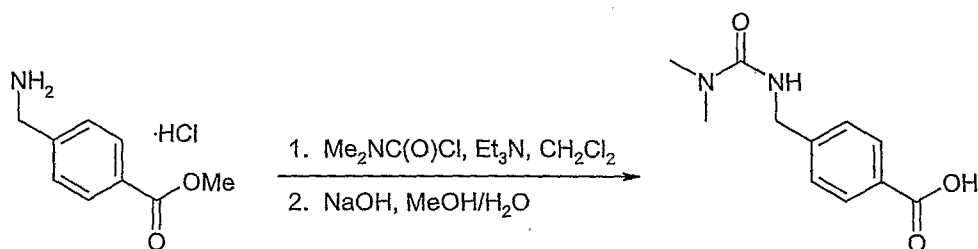
A mixture of 4-((methylamino)carbonylamino)methylbenzoic acid (0.0687 g, 0.33 mmol) and crude ((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)amine hydrochloride salt (~0.30 mmol) in dry DMF (3 mL) was cooled to 0 °C, and HATU (0.126 g, 0.33 mmol) and diisopropylethylamine (0.21 mL, 1.2 mmol) were added. The resulting mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for an additional 16h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH₂Cl₂ (4 mL) and a saturated solution of NaHCO₃ in water (4 mL). The mixture was passed through a Varian Chem ElutTM extraction cartridge, and the cartridge was washed with additional CH₂Cl₂ (3 x 8 mL). The organic extract was concentrated *in vacuo*, and the residue was purified by preparative scale reverse phase LC/MS (gradient 45-65% CH₃CN in H₂O containing 10 mM NH₄HCO₃) to provide the title compound as a white solid (0.0630 g, 47% over 3 steps) following lyophilization from CH₃CN/H₂O. MS (M+1): 445.2. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.74 - 0.93 (m, 1 H), 0.96 - 1.18 (m, 2 H), 1.21 (t, J=7.0 Hz, 3 H), 1.24 - 1.49 (m, 4 H), 1.51 - 1.79 (m, 6 H), 1.79 - 1.93 (m, 2 H), 2.02 (d, J=12.9 Hz, 1 H), 2.36 (dd, J=13.1, 9.6 Hz, 1 H), 2.46 - 2.58 (m, 2 H), 2.79 (d, J=5.1 Hz, 3 H), 3.16 (dd, J=9.4, 8.2 Hz, 1 H), 3.21 - 3.29 (m, 1 H), 3.29 - 3.41 (m, 2 H), 3.42 - 3.53 (m, 2 H), 4.40 (d, J=5.5 Hz, 2 H), 5.02 (d, J=4.3 Hz, 1 H), 5.32 (t, J=5.7 Hz, 1 H), 7.22 (d, J=8.6 Hz, 2 H), 7.58 - 7.66 (m, 2 H), 9.00 (d, J=2.7 Hz, 1 H). Anal. Calcd for C₂₅H₄₀N₄O₃·0.3 H₂O: C, 66.72; H, 9.09; N, 12.45. Found: C, 66.63; H, 8.77; N, 12.73.

Example 238. 4-(((dimethylamino)carbonylamino)methyl)-N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide

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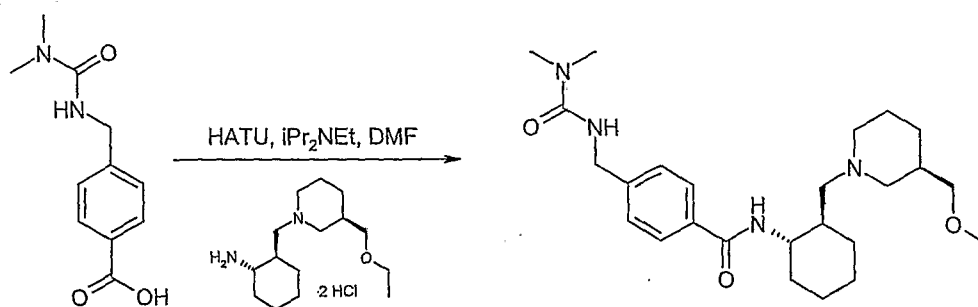
Step A: 4-({[(dimethylamino)carbonyl]amino}methyl)benzoic acid



- A suspension of methyl 4-(aminomethyl)benzoate hydrochloride salt (0.266 g, 1.3 mmol) in dry CH_2Cl_2 (5 mL) was treated with triethylamine (0.92 mL, 6.6 mmol) and dimethylcarbamoyl chloride (0.13 mL, 1.4 mmol). The resulting mixture was stirred for 132 h. Water (5 mL) was added, and the mixture was passed through a Varian Chem ElutTM extraction cartridge. The cartridge was washed with additional CH_2Cl_2 (3 x 8 mL), and the organic extract was concentrated *in vacuo*. The residue was dissolved in MeOH (7 mL), and NaOH (0.63 g, 16 mmol) dissolved in H_2O (3.5 mL) was added. The reaction was stirred for 20 h and was then concentrated *in vacuo*. The residue was dissolved in H_2O (5 mL) and acidified to pH 1 with 3 N HCl. The resulting precipitate was collected by filtration and washed with H_2O to provide the title compound as a white solid (0.20 g, 70% over 2 steps), which was used in subsequent steps without further purification. ^1H NMR (400 MHz, METHANOL- D_4) δ ppm 2.93 (s, 6 H), 4.40 (s, 2 H), 7.38 (d, $J=8.2$ Hz, 2 H), 7.93 - 7.98 (m, 2 H)

Step B: 4-({[(dimethylamino)carbonyl]amino}methyl)-N-((1S,2R)-2-((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide

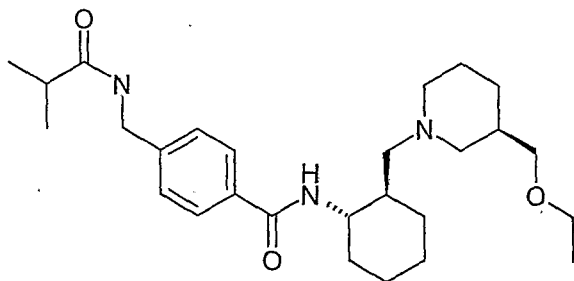
102213-1 WO



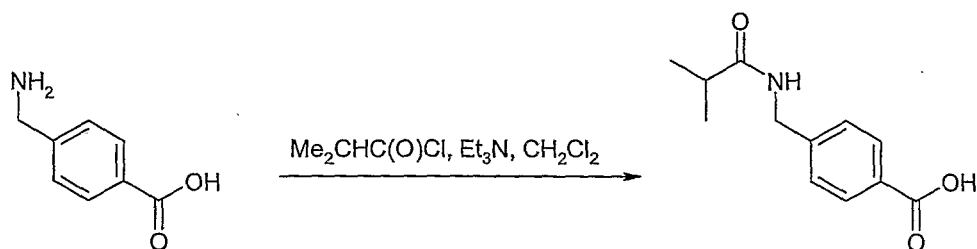
A mixture of 4-((dimethylamino)carbonyl)aminomethylbenzoic acid (0.0733 g, 0.33 mmol) and crude ((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)amine hydrochloride salt (~0.30 mmol) in dry DMF (3 mL) was cooled to 0 °C, and HATU (0.126 g, 0.33 mmol) and diisopropylethylamine (0.21 mL, 1.2 mmol) were added. The resulting mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for an additional 16h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH₂Cl₂ (4 mL) and a saturated solution of NaHCO₃ in water (4 mL). The mixture was passed through a Varian Chem ElutTM extraction cartridge, and the cartridge was washed with additional CH₂Cl₂ (3 x 8 mL). The organic extract was concentrated *in vacuo*, and the residue was purified by preparative scale reverse phase LC/MS (gradient 45-65% CH₃CN in H₂O containing 10 mM NH₄HCO₃) to provide the title compound as a white solid (0.0722 g, 52% over 3 steps) following lyophilization from CH₃CN/H₂O. MS (M+1): 459.2. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.78 - 0.93 (m, 1 H), 0.95 - 1.19 (m, 2 H), 1.22 (t, J=7.0 Hz, 3 H), 1.24 - 1.50 (m, 4 H), 1.51 - 1.78 (m, 6 H), 1.81 - 1.95 (m, 2 H), 2.01 (d, J=12.9 Hz, 1 H), 2.38 (dd, J=12.9, 9.4 Hz, 1 H), 2.50 - 2.63 (m, 2 H), 2.89 - 2.96 (m, 6 H), 3.19 (dd, J=9.4, 7.8 Hz, 1 H), 3.25 (dd, J=10.7, 2.9 Hz, 1 H), 3.32 (dd, J=9.2, 5.3 Hz, 1 H), 3.35 - 3.53 (m, 3 H), 4.36 - 4.55 (m, 2 H), 4.65 (t, J=5.9 Hz, 1 H), 7.33 (d, J=8.2 Hz, 2 H), 7.75 - 7.82 (m, 2 H), 8.84 (d, J=2.7 Hz, 1 H). Anal. Calcd for C₂₆H₄₂N₄O₃·0.4 H₂O: C, 67.04; H, 9.26; N, 12.03. Found: C, 67.13; H, 9.24; N, 11.86.

Example 239. N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-((isobutylamino)methyl)benzamide

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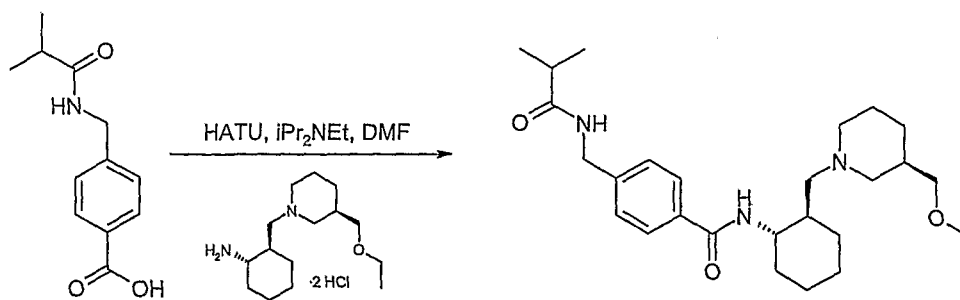
Step A: 4-[(isobutyrylamino)methyl]benzoic acid



- A suspension of 4-(aminomethyl)benzoic acid (0.214 g, 1.4 mmol) in dry CH_2Cl_2 (10 mL) was treated with triethylamine (0.98 mL, 7.0 mmol) and 2-methylpropanoyl chloride (0.16 mL, 1.5 mmol). The resulting mixture was stirred for 132 h. Water (5 mL) and EtOAc (10 mL) were added, and the aqueous layer was acidified to pH 1 with 1 N HCl. The layers were separated, and the aqueous phase was extracted with additional EtOAc (3 x 10 mL). The combined organic phases were dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to provide the title compound as a slightly yellow solid (0.318 g, quantitative), which was used in subsequent steps without further purification. ^1H NMR (400 MHz, METHANOL- D_4) δ ppm 1.14 (d, $J=7.0$ Hz, 6 H), 2.37 - 2.60 (m, 1 H), 4.33 - 4.47 (m, 2 H), 7.36 (d, $J=8.6$ Hz, 2 H), 7.97 (d, $J=8.6$ Hz, 2 H).

15

Step B: *N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-[(isobutyrylamino)methyl]benzamide



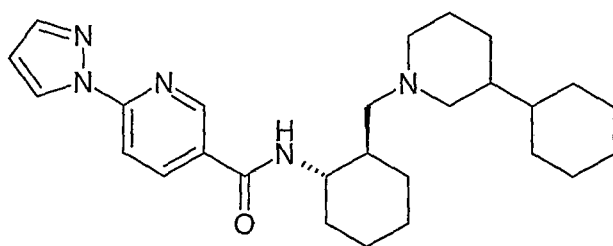
102213-1 WO

A mixture of 4-[(isobutrylamino)methyl]benzoic acid (0.0730 g, 0.33 mmol) and crude ((1*S*,2*R*)-2-[[3-(3-ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt (~0.30 mmol) in dry DMF (3 mL) was cooled to 0 °C, and HATU (0.126 g, 0.33 mmol) and diisopropylethylamine (0.21 mL, 1.2 mmol) were added.

- 5 The resulting mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for an additional 16h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH₂Cl₂ (4 mL) and a saturated solution of NaHCO₃ in water (4 mL). The mixture was passed through a Varian Chem Elut™ extraction cartridge, and the cartridge was washed with additional CH₂Cl₂ (3 x 8 mL).
- 10 The organic extract was concentrated *in vacuo*, and the residue was purified by preparative scale reverse phase LC/MS (gradient 45-65% CH₃CN in H₂O containing 10 mM NH₄HCO₃) to provide the title compound as a white solid (0.0534 g, 36% over 3 steps) following lyophilization from CH₃CN/H₂O. MS (M+1): 458.3. ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 1.10 - 1.16 (m, 9 H), 1.16 - 1.65 (m, 5 H), 1.69 - 1.91 (m, 4 H), 1.91 - 2.27 (m, 5 H), 2.41 - 2.58 (m, 1 H), 2.66 - 2.85 (m, 2 H), 2.95 - 3.19 (m, 2 H), 3.20 - 3.27 (m, 1 H), 3.36 - 3.57 (m, 4 H), 3.63 (d, *J*=12.1 Hz, 1 H), 3.77 (td, *J*=10.8, 4.1 Hz, 1 H), 4.40 (s, 2 H), 7.38 (d, *J*=8.2 Hz, 2 H), 7.78 - 7.86 (m, 2 H).
- 15 Anal. Calcd for C₂₇H₄₃N₃O₃·2.1 HCl: C, 60.70; H, 8.51; N, 7.87. Found: C, 60.75; H, 8.25; N, 8.10.

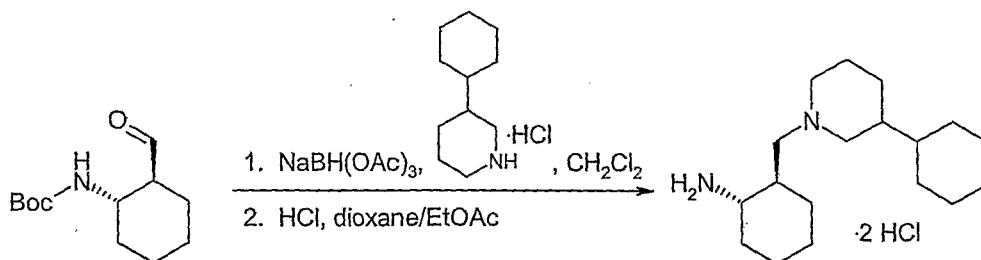
20

Example 240. *N*-((1*S*,2*R*)-2-[[3-cyclohexylpiperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide



- 25 Step A: ((1*S*,2*R*)-2-[[3-cyclohexylpiperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt

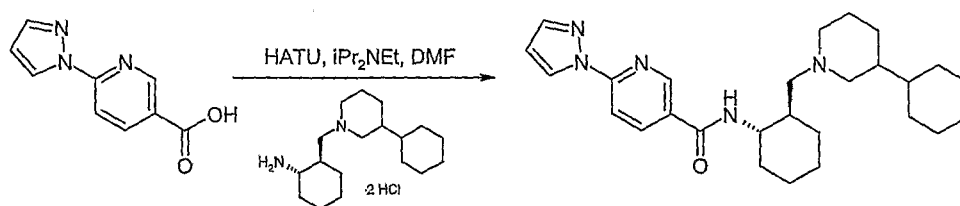
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- A mixture of crude *tert*-butyl [(1*S*,2*S*)-2-formylcyclohexyl]carbamate (0.136 g, ~0.60 mmol) and 3-cyclohexylpiperidine hydrochloride salt (0.147 g, 0.72 mmol) in dry
- 5 CH₂Cl₂ (12 mL) was stirred for 30 min at 5 °C. NaBH(OAc)₃ (0.254 g, 1.2 mmol) was added to the reaction and the resulting mixture was allowed to slowly warm to room temperature and stir for 16 h. The reaction was cooled to 0 °C, and water (6 mL) was added, followed by 1 N NaOH (6 mL) and CH₂Cl₂ (20 mL). The layers were separated, and the aqueous phase was extracted with additional CH₂Cl₂ (2 x 20 mL).
- 10 The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in EtOAc (1.5 mL), and 4 N HCl in dioxane (1.5 mL, 6 mmol) was added. The mixture was stirred for 1 h and then concentrated *in vacuo* to provide the title compound. The compound was used in subsequent steps without further purification. MS (*M*+1): 279.2.

15

Step B: *N*-((1*S*,2*R*)-2-[[3-cyclohexylpiperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide



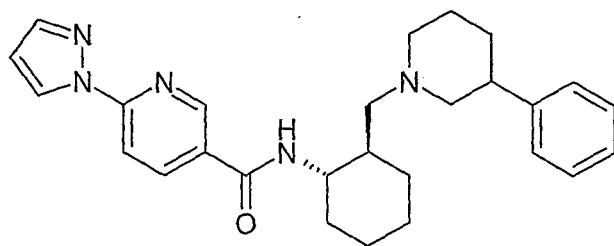
- A mixture of crude ((1*S*,2*R*)-2-[[3-cyclohexylpiperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt (~0.6 mmol) and 6-(1*H*-pyrazol-1-yl)nicotinic acid (0.125 g, 0.66 mmol) in dry DMF (5 mL) was cooled to 0 °C. HATU (0.251 g, 0.66 mmol) and diisopropylethylamine (0.42 mL, 2.4 mmol) were then added to the reaction, and the resulting mixture was stirred at 0 °C for 30 min and then warmed to room
- 20 temperature and stirred for an additional 63h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH₂Cl₂ (8 mL) and a saturated solution of NaHCO₃ in water (8 mL). The mixture was passed through a Varian Chem Elut™ extraction cartridge, and the cartridge was washed with additional CH₂Cl₂ (2 x 12

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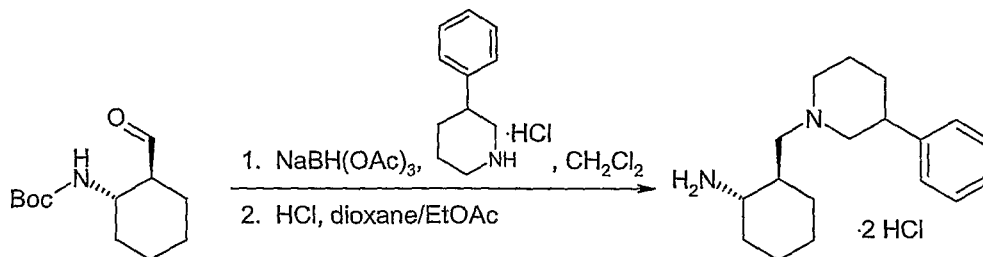
mL). The organic extract was concentrated *in vacuo*, and the residue was purified by preparative scale reverse phase LC/MS (gradient 75-100% CH₃CN in H₂O containing 10 mM NH₄HCO₃) to provide a mixture of the title compounds as a white solid (0.0414 g, 15% over 3 steps) following lyophilization from CH₃CN/H₂O. MS (M+1):

5 450.2. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.38 - 1.91 (m, 26 H), 2.05 (d, J=13.3 Hz, 1 H), 2.27 - 2.45 (m, 1 H), 2.47 - 2.73 (m, 2 H), 3.03 - 3.22 (m, 1 H), 3.34 - 3.48 (m, 1 H), 6.43 - 6.50 (m, 1 H), 7.72 - 7.79 (m, 1 H), 7.94 - 8.05 (m, 1 H), 8.17 - 8.29 (m, 1 H), 8.56 - 8.66 (m, 1 H), 8.79 - 8.92 (m, 1 H), 9.29 - 9.47 (m, 1 H).

10 **Example 241. N-((1S,2R)-2-[[3-phenylpiperidin-1-yl]methyl]cyclohexyl)-6-(1H-pyrazol-1-yl)nicotinamide**



Step A: ((1S,2R)-2-[[3-phenylpiperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt



15

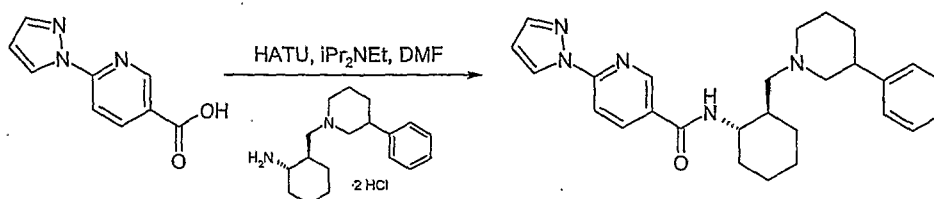
A mixture of crude *tert*-butyl [(1S,2S)-2-formylcyclohexyl]carbamate (0.136 g, ~ 0.60 mmol) and 3-phenylpiperidine (0.116 g, 0.72 mmol) in dry CH₂Cl₂ (12 mL) was stirred for 30 min at 5 °C. NaBH(OAc)₃ (0.254 g, 1.2 mmol) was added to the reaction and the resulting mixture was allowed to slowly warm to room temperature and stir for 16 h. The reaction was cooled to 0 °C, and water (6 mL) was added, followed by 1 N NaOH (6 mL) and CH₂Cl₂ (20 mL). The layers were separated, and the aqueous phase was extracted with additional CH₂Cl₂ (2 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in EtOAc (1.5 mL), and 4 N HCl in dioxane (1.5 mL, 6 mmol) was added. The mixture was stirred for 1 h and then concentrated *in vacuo* to provide the title

25

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compound. The compound was used in subsequent steps without further purification. MS (M+1): 273.2.

Step B: *N*-((1*S*,2*R*)-2-[[3-phenylpiperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide

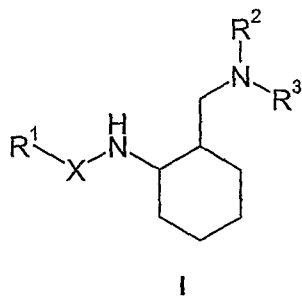


A mixture of crude ((1*S*,2*R*)-2-[[3-phenylpiperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt and ((1*S*,2*R*)-2-[[3-phenylpiperidin-1-yl]methyl]cyclohexyl)amine hydrochloride salt (~0.6 mmol) and 6-(1*H*-pyrazol-1-yl)nicotinic acid (0.125 g, 0.66 mmol) in dry DMF (5 mL) was cooled to 0 °C. HATU (0.251 g, 0.66 mmol) and diisopropylethylamine (0.42 mL, 2.4 mmol) were then added to the reaction, and the resulting mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for an additional 63h. The reaction was concentrated *in vacuo*, and the residue was taken up into CH₂Cl₂ (8 mL) and a saturated solution of NaHCO₃ in water (8 mL). The mixture was passed through a Varian Chem ElutTM extraction cartridge, and the cartridge was washed with additional CH₂Cl₂ (2 x 12 mL). The organic extract was concentrated *in vacuo*, and the residue was purified by preparative scale reverse phase LC/MS (gradient 65-85% CH₃CN in H₂O containing 10 mM NH₄HCO₃) to provide a mixture of the title compounds as a white solid (0.131 g, 49% over 3 steps) following lyophilization from CH₃CN/H₂O. MS (M+1): 444.2. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.00 - 1.51 (m, 5 H), 1.51 - 2.19 (m, 9 H), 2.34 - 2.53 (m, 2 H), 2.56 - 2.88 (m, 3 H), 3.18 - 3.33 (m, 1 H), 3.37 - 3.51 (m, 1 H), 6.45 - 6.52 (m, *J*=2.1, 2.1 Hz, 1 H), 6.86 (dd, *J*=7.6, 1.8 Hz, 1 H), 7.05 - 7.16 (m, 2 H), 7.20 - 7.38 (m, 2 H), 7.74 - 7.80 (m, 1 H), 8.01 - 8.09 (m, 1 H), 8.22 - 8.34 (m, *J*=8.8, 8.8, 2.3 Hz, 1 H), 8.63 (d, *J*=2.7 Hz, 1 H), 8.85 - 8.95 (m, 1 H), 9.16 (d, *J*=3.9 Hz, 1 H). Anal. Calcd for C₂₇H₃₃N₅O: C, 73.11; H, 7.50; N, 15.79. Found: C, 72.93; H, 7.50; N, 15.89.

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What is claimed is:

1. A compound of formula I, a pharmaceutically acceptable salt thereof, diastereomer, enantiomer, or mixture thereof:



wherein

R¹ is selected from C₆₋₁₀aryl, C₂₋₉heteroaryl, C₃₋₅heterocycloalkyl, C₆₋₁₀aryl-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₅heterocycloalkyl-C₁₋₃alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₃alkyl, and C₁₋₆alkyl, wherein said C₆₋₁₀aryl, C₂₋₉heteroaryl, C₆₋₁₀aryl-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₃alkyl, and C₁₋₆alkyl are optionally substituted with one or more group selected from C₆₋₁₀aryl, C₁₋₉heteroaryl, C₃₋₅heterocycloalkyl, C₆₋₁₀aryl-C₁₋₃alkyl, C₆₋₁₀aryl-O-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₅heterocycloalkyl-C₁₋₃alkyl, -CN, -SR, -OR, -O(CH₂)_m-OR, R, -C(=O)-R, -CO₂R, -SO₂R, -SO₂NR₂, halogen, -NO₂, -NR₂, -(CH₂)_mNR₂, - (CH₂)_mNHC(=O)-NR₂, -NHC(=O)-R, -N[C(=O)R]₂, -(CH₂)_mNHS(=O)₂-R, - (CH₂)_mNHC(=O)-R, -(CH₂)_mN[C(=O)-R]₂, and -C(=O)-NR₂;

R² and R³ are independently selected from C₁₋₆alkyl, C₂₋₆alkenyl, and C₁₋₆alkoxy wherein said C₁₋₆alkyl, C₂₋₆alkenyl, and C₁₋₆alkoxy are optionally substituted by one or more groups selected from amino, halogen, C₁₋₆alkoxy and -CN; or R² and R³ together with the nitrogen connected thereto form a heterocycloalkyl, wherein said heterocycloalkyl is optionally substituted with one or more group selected from C₆₋₁₀aryl, C₂₋₉heteroaryl, C₃₋₆cycloalkyl, C₃₋₅heterocycloalkyl, C₆₋₁₀aryl-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₅heterocycloalkyl-C₁₋₃alkyl, -CN, -SR, -OR, -(CH₂)_mOR, R, -CO₂R; -SO₂R; -SO₂NR₂, halogen, -NO₂, -NR₂, -(CH₂)_mNR₂, and -C(=O)-NR₂;

each R is independently hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl or halogenated C₁₋₆alkyl; and

X is selected from -C(=O)-, -C(=O)-NH-, -C(=O)-O- and -S(=O)₂-,

with a proviso that

when X is -C(=O)- and R² and R³ together with the nitrogen connected thereto form said piperdiny; R¹ is not 4-amino-5-chloro-2-alkoxyphenyl, 4-amino-5-chloro-2-cycloalkoxyphenyl, 4-amino-5-chloro-2-cycloalkyl-alkoxy-phenyl, 4-

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butoxyphenyl, 3-butoxyphenyl, 4-pentyloxyphenyl, 4-isobutoxyphenyl, 4-benzyloxyphenyl and 7-(2,3-dihydro)benzofuranyl.

2. A compound as claimed in claim 1, wherein
 5 said R^2 and R^3 together with the nitrogen connected thereto form a heterocycloalkyl, wherein said heterocycloalkyl is optionally substituted with one or more group selected from C_{6-10} aryl, C_{2-9} heteroaryl, C_{3-6} cycloalkyl, C_{3-5} heterocycloalkyl, C_{6-10} aryl- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, -CN, -SR, -OR, $-(CH_2)_mOR$, R, $-CO_2R$; $-SO_2R$; $-SO_2NR_2$, halogen, $-NO_2$, $-NR_2$, $-(CH_2)_mNR_2$, and $-C(=O)-NR_2$.
 10
3. A compound as claimed in claim 1, wherein
 said R^2 and R^3 together with the nitrogen connected thereto form a group selected from piperdiny, 1,4-dioxo-8-azaspiro[4,5]dec-8-yl, piperaziny, methyl(2-phenylethyl)amino, methyl(pyridin-3-ylmethyl)amino, (4-ethylbenzyl)(methyl)amino,
 15 methyl(1-methylpyrrolidin-3-yl)amino, methyl(3-methylbutyl)amino, methyl(propyl)amino, methyl(butyl)amino, butyl(ethyl)amino, diethylamino, benzyl(methyl)amino, morpholin-4-yl, pyrrolidin-1-yl, and azepan-1-yl, wherein said piperdiny, 1,4-dioxo-8-azaspiro[4,5]dec-8-yl, piperaziny, methyl(2-phenylethyl)amino,
 20 methyl(pyridin-3-ylmethyl)amino, (4-ethylbenzyl)(methyl)amino, methyl(1-methylpyrrolidin-3-yl)amino, methyl(3-methylbutyl)amino, methyl(propyl)amino, methyl(butyl)amino, butyl(ethyl)amino, diethylamino, benzyl(methyl)amino, morpholin-4-yl, pyrrolidin-1-yl, and azepan-1-yl are optionally substituted with one or more group selected from C_{6-10} aryl, C_{2-9} heteroaryl, C_{3-6} cycloalkyl, C_{3-5} heterocycloalkyl, C_{6-10} aryl- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, -CN, -SR, -OR, $-(CH_2)_mOR$, R, $-CO_2R$; $-SO_2R$; $-SO_2NR_2$, halogen, $-NO_2$, $-NR_2$, $-(CH_2)_mNR_2$, and $-C(=O)-NR_2$.
 25
4. A compound as claimed in claim 1, wherein
 30 said R^1 is selected from 2-cyclopentylethyl, cyclopropylmethyl, methyl, cyclohexyl, cyclopentylmethyl, chromanyl, ethyl, pentyl, 2-phenylethyl, phenyl, benzyl, pyridinyl, pyridinylethyl, 1-benzofuranyl, benzothienyl, furyl, imidazolyl, pyrazolo[1,5-a]pyrimidinyl, pyrazinyl, 1,3-benzothiazolyl, indolyl, indazolyl, thienyl, 1,3-benzodioxinyl, tetrahydro-2H-pyran-4-ylmethyl, 1-H-1,2,3-benzotriazol-1-yl, 2-(thien-2-yl)ethyl, (1-benzofuran-4-yl)methyl, 1,3-oxazolyl, 1H-pyrazol-1-yl, 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 2-oxo-2,3-dihydro-2H-

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benzimidazolyl, isoxazolyl, imidazo[1,2,a]pyridinyl, 2-3-dioxo-2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-2H-1,4-benzoxazinyl; pyrazolyl, 1H-tetrazol-1-yl-methyl, and 3,4-dihydro-2H-1,5-benzodioxepinyl, optionally substituted by 1H-pyrazol-1-yl, fluoro, chloro, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, t-butyl, cyano, bromo, 1,3-oxazol-5-yl, 1H-imidazol-1-yl, (4-oxopiperidin-1-yl)carbonyl, pyridin-3-ylmethyl, [(butylamino)carbonyl]amino, 1,1,-dioxidothiomorpholin-4-yl, aminosulfonyl, morpholin-4-yl, diethylaminomethyl, acetyl, (3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)methyl, 1-oxo-indan-4-yl, dimethylaminomethyl, methyl, pyrrolidin-1-yl, ethylthio, acetylamino, dimethylamino, 1H-pyrrol-1-yl, ethyl, ethoxy, fluorophenoxy, propyl, phenyl, methoxycarbonyl, diacetylamino, (methylsulfonylamino)methyl, (cyclopropylsulfonylamino)methyl, 1H-tetrazol-1-yl, pyrazolyl, methylaminocarbonylamino, dimethylaminocarbonylamino, and (methylthio)pyrimidin-4-yl.

5. A compound as claimed in claim 1, wherein said R^2 and R^3 together with the nitrogen connected thereto form a group selected from piperdinyl, 1,4-dioxo-8-azaspiro[4,5]dec-8-yl, piperazinyl, methyl(2-phenylethyl)amino, methyl(pyridin-3-ylmethyl)amino, (4-ethylbenzyl)(methyl)amino, methyl(1-methylpyrrolidin-3-yl)amino, methyl(3-methylbutyl)amino, methyl(propyl)amino, methyl(butyl)amino, butyl(ethyl)amino, diethylamino, benzyl(methyl)amino, morpholin-4-yl, pyrrolidin-1-yl, and azepan-1-yl, wherein said piperdinyl, 1,4-dioxo-8-azaspiro[4,5]dec-8-yl, piperazinyl, methyl(2-phenylethyl)amino, methyl(pyridin-3-ylmethyl)amino, (4-ethylbenzyl)(methyl)amino, methyl(1-methylpyrrolidin-3-yl)amino, methyl(3-methylbutyl)amino, methyl(propyl)amino, methyl(butyl)amino, butyl(ethyl)amino, diethylamino, benzyl(methyl)amino, morpholin-4-yl, pyrrolidin-1-yl, and azepan-1-yl are optionally substituted with one or more group selected from phenyl, benzyl, methyl, fluoro, trifluoromethyl, methoxy, allyloxy, (2E)-but-2-en-1-yloxy, (allyloxy)methyl, methoxymethyl, ethoxymethyl, propyl, butyl, pentyl, hexyl, cyclopentyl, pyridin-4-ylmethyl, ethoxy, butoxy, 2-methoxyethoxy, cyclohexyl, and thienylmethyl.

6. A compound as claimed in claim 1, wherein said R^2 and R^3 together with the nitrogen connected thereto form a group selected from piperdinyl, wherein said piperdinyl is optionally substituted with one or more group selected from phenyl, benzyl, methyl, fluoro, trifluoromethyl, methoxy, allyloxy, (2E)-but-2-en-1-yloxy, (allyloxy)methyl, methoxymethyl, ethoxymethyl, propyl, butyl, pentyl, hexyl,

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cyclopentyl, pyridin-4-ylmethyl, ethoxy, butoxy, 2-methoxyethoxy, cyclohexyl, and thienylmethyl.

7. A compound selected from

- 5 *trans*-(+/-)-4-fluoro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
trans-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-6-(trifluoromethyl)nicotinamide;
trans-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide;
trans-(+/-)-5-chloro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1-benzofuran-2-
10 carboxamide;
trans-(+/-)-2-(4-methoxyphenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide;
trans-(+/-)-4-(difluoromethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-4-(2-methoxyethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+)-4-(2-methoxyethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
15 *trans*-(+)-4-(2-methoxyethoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-3-cyclopentyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide;
trans-(+/-)-3-(4-chlorophenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide;
trans-(+/-)-3-(2-methoxyphenyl)-*N*-[2-(piperidin-1-
ylmethyl)cyclohexyl]propanamide;
20 *trans*-(+/-)-4-*tert*-butyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-4-methoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-4-cyano-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-4-bromo-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-4-chloro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
25 *trans*-(+/-)-6-(1*H*-imidazol-1-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]nicotinamide;
trans-(+/-)-4-(1,3-oxazol-5-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-6-methoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]nicotinamide;
trans-(+/-)-4-(1*H*-imidazol-1-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-4-[(4-oxopiperidin-1-yl)carbonyl]-*N*-[2-(piperidin-1-
30 ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-2-pyridin-3-ylacetamide;
trans-(+/-)-2-[[butylamino]carbonyl]amino-*N*-[2-(piperidin-1-
ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-4-(1,1-dioxidothiomorpholin-4-yl)-*N*-[2-(piperidin-1-
35 ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-4-(aminosulfonyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;

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- trans*-(+/-)-2-morpholin-4-yl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]isonicotinamide;
trans-(+/-)-4-[(diethylamino)methyl]-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1-benzothiophene-3-
 5 carboxamide;
trans-(+/-)-4-acetyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-4-[(3-oxo-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)methyl]-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-1-oxo-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]indane-4-carboxamide;
 10 *trans*-(+/-)-5-[(dimethylamino)methyl]-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-2-furamide;
trans-(+/-)-1-methyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1*H*-imidazole-4-carboxamide;
trans-(+/-)-2-(4-chlorophenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide;
 15 *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-6-pyrrolidin-1-ylnicotinamide;
trans-(+/-)-5-methyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide;
trans-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]pyrazine-2-carboxamide;
trans-(+/-)-4-(ethylthio)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
 20 *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1,3-benzothiazole-6-carboxamide;
trans-(+/-)-4-(acetylamino)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-5-methoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1*H*-indole-2-carboxamide;
 25 *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]thiophene-3-carboxamide;
trans-(+/-)-2-phenyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide;
trans-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-4-(trifluoromethoxy)benzamide;
trans-(+/-)-3-(2-chlorophenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide;
trans-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidine-3-
 30 carboxamide;
trans-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-4-cyano benzamide;
trans-(+/-)-3-(3-chlorophenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide;
trans-(+/-)-6-fluoro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-4*H*-1,3-benzodioxine-8-carboxamide;
 35 *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-2-(tetrahydro-2*H*-pyran-4-yl)acetamide;

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- trans*-(+/-)-4-chloro-2,5-difluoro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1*H*-indole-6-carboxamide;
trans-(+/-)-3-(1*H*-1,2,3-benzotriazol-1-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide;
5 *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-3-(2-thienyl)propanamide;
trans-(+/-)-2-(1-benzofuran-4-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide;
trans-(+/-)-4-(dimethylamino)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-3-pyridin-3-ylpropanamide;
trans-(+/-)-4,6-dimethyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]nicotinamide;
10 *trans*-(+/-)-3-(5-methyl-2-furyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1*H*-pyrazole-5-carboxamide;
trans-(+/-)-2-cyclopropyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide;
trans-(+/-)-5-methoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1-benzofuran-2-carboxamide;
15 *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1*H*-indazole-3-carboxamide;
trans-(+/-)-6-(ethylthio)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]nicotinamide;
trans-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrrol-1-yl)benzamide;
trans-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1*H*-indole-4-carboxamide;
trans-(+/-)-2-chloro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
20 *trans*-(+/-)-3-cyano-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-2-methyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-5-(trifluoromethyl)-1,3-oxazole-4-carboxamide;
trans-(+/-)-3-chloro-4-methyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]thiophene-2-carboxamide;
25 *trans*-(+/-)-3-(5-methyl-1*H*-pyrazol-1-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide;
trans-(+/-)-3-methoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
trans-(+/-)-2-(2,3-dihydro-1-benzofuran-5-yl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide;
30 *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1,3-benzodioxole-5-carboxamide;
trans-(+/-)-5-methyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]thiophene-2-carboxamide;
trans-(+/-)-1-ethyl-5-methyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide;
35 *trans*-(+/-)-5-ethoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-2-furamide;

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- trans*-(+/-)-3-(4-fluorophenoxy)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]propanamide;
- trans*-(+/-)-3-fluoro-4-methoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-4-propylbenzamide;
- 5 *trans*-(+/-)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]hexanamide;
- trans*-(+/-)-4-butoxy-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-4-chloro-2-fluoro-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-2-oxo-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]-2,3-dihydro-1*H*-benzimidazole-5-carboxamide;
- 10 *trans*-(+/-)-2-(4-ethoxyphenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]acetamide;
- trans*-(+/-)-3-phenyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]isoxazole-5-carboxamide;
- trans*-(+/-)-2-methoxy-5-methyl-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]benzamide;
- trans*-(+/-)-4-methoxy-*N*-{2-[(4-phenylpiperidin-1-yl)methyl]cyclohexyl}benzamide;
- 15 *trans*-(+/-)-*N*-[2-(1,4-dioxo-8-azaspiro[4.5]dec-8-ylmethyl)cyclohexyl]-4-methoxybenzamide;
- trans*-(+/-)-*N*-{2-[(3,5-dimethylpiperidin-1-yl)methyl]cyclohexyl}-4-methoxybenzamide;
- trans*-(+/-)-*N*-{2-[(4-fluoropiperidin-1-yl)methyl]cyclohexyl}-4-methoxybenzamide;
- 20 *trans*-(+/-)-4-methoxy-*N*-(2-[(4-(trifluoromethyl)piperidin-1-yl)methyl]cyclohexyl)benzamide; .
- trans*-(+/-)-4-methoxy-*N*-{2-[(4-methoxypiperidin-1-yl)methyl]cyclohexyl}benzamide;
- trans*-(+/-)-4-methoxy-*N*-(2-[(3-(trifluoromethyl)piperidin-1-yl)methyl]cyclohexyl)benzamide;
- 25 *trans*-(+/-)-4-methoxy-*N*-{2-[(3-phenylpiperidin-1-yl)methyl]cyclohexyl}benzamide;
- trans*-(+/-)-*N*-[2-(3-[(allyloxy)methyl]piperidin-1-yl)methyl]cyclohexyl]-4-methoxybenzamide;
- 30 *trans*-(+/-)-*N*-[2-(3-[(allyloxy)methyl]piperidin-1-yl)methyl]cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-(2-[[3-(methoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-(2-[[3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 35

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- trans*-(+/-)- *N*-{2-[(3-pentylpiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)- *N*-{2-[(3-pentylpiperidin-1-yl)methyl]cyclohexyl}-4-(1*H*-pyrazol-1-yl)benzamide;
- 5 *trans*-(+/-)- 6-(1*H*-imidazol-1-yl)-*N*-{2-[(3-pentylpiperidin-1-yl)methyl]cyclohexyl}nicotinamide;
- trans*-(+/-)- *N*-{2-[(3-pentylpiperidin-1-yl)methyl]cyclohexyl}-6-pyrrolidin-1-ylnicotinamide;
- trans*(±)-6-(1*H*-imidazol-1-yl)-*N*-{2-[(3*R*)-3-pentylpiperidin-1-yl]methyl}cyclohexyl}nicotinamide;
- 10 *trans*(±)-6-(1*H*-imidazol-1-yl)-*N*-{2-[(3*S*)-3-pentylpiperidin-1-yl]methyl}cyclohexyl}nicotinamide;
- trans*-(+/-)- *N*-{2-[(3-hexylpiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 15 *trans*-(+/-)- *N*-{2-[(3-hexylpiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-imidazol-1-yl)nicotinamide;
- trans*-(+/-)- *N*-{2-[(3-hexylpiperidin-1-yl)methyl]cyclohexyl}-4-(1*H*-pyrazol-1-yl)benzamide;
- trans*-(+/-)- *N*-{2-[(3-hexylpiperidin-1-yl)methyl]cyclohexyl}-4-pyrrolidin-1-ylbenzamide;
- 20 *trans*-(+/-)- *N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)- *N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-4-pyrrolidin-1-ylbenzamide;
- 25 *trans*-(+/-)- *N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-imidazol-1-yl)nicotinamide;
- trans*-(+/-)- *N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-4-(1*H*-pyrazol-1-yl)benzamide;
- cis*-(+/-)- *N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-imidazol-1-yl)nicotinamide;
- 30 *trans*-(+/-)-*N*-{2-[[4-(Allyloxy)piperidin-1-yl]methyl]cyclohexyl}-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-{2-[[4-(2*E*)-But-2-en-1-yloxy]piperidin-1-yl]methyl}cyclohexyl}-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 35 *trans*-(+/-)-*N*-{2-[[3-(Allyloxy)methyl]piperidin-1-yl]methyl}cyclohexyl}-6-pyrrolidin-1-ylnicotinamide;

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- trans*-(+/-)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide;
- trans*-(+/-)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-6-(1*H*-imidazol-1-yl)nicotinamide;
- 5 *trans*-(±)-*N*-2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-4-bromobenzamide;
- Trans*-(±)-(*N*-2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-3-(4-chlorophenyl)propanamide
- Trans*-(±)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-3-(2-methoxyphenyl)propanamide
- 10 *Trans*-(±)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-4-cyanobenzamide
- Trans*-(±)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-4-fluorobenzamide
- 15 *Trans*-(±)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-4-chlorobenzamide
- Trans*-(±)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-4-[(diethylamino)methyl]benzamide
- Trans*-(±)-*N*-[2-({3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-4-[(4-methylpiperazin-1-yl)methyl]benzamide;
- 20 *trans*(±)- [2-({(3*R*)-3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-6-(1*H*-imidazol-1-yl)nicotinamide;
- trans*(±)- [2-({(3*S*)-3-[(Allyloxy)methyl]piperidin-1-yl}methyl)cyclohexyl]-6-(1*H*-imidazol-1-yl)nicotinamide;
- 25 *trans*-(+/-)-*N*-{2-[(4-benzylpiperidin-1-yl)methyl]cyclohexyl}-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-{2-[(4-cyclopentylpiperazin-1-yl)methyl]cyclohexyl}-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-(2-{[methyl(2-phenylethyl)amino]methyl}cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 30 *trans*-(+/-)-6-(1*H*-pyrazol-1-yl)-*N*-(2-{[4-(pyridin-4-ylmethyl)piperazin-1-yl]methyl}cyclohexyl)nicotinamide;
- trans*-(+/-)-*N*-(2-{[methyl(pyridin-3-ylmethyl)amino]methyl}cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 35 *trans*-(+/-)-*N*-(2-{[(4-ethylbenzyl)(methyl)amino]methyl}cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;

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- trans*-(+/-)-*N*-(2-([methyl(1-methylpyrrolidin-3-yl)amino]methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-(2-([methyl(3-methylbutyl)amino]methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 5 *trans*-(+/-)-*N*-(2-([methyl(propyl)amino]methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-(2-([benzyl(methyl)amino]methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-(2-([4-propylpiperidin-1-yl]methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 10 *trans*-(+/-)-*N*-(2-([2-(methoxymethyl)piperidin-1-yl]methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-*N*-(2-([butyl(methyl)amino]methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 15 *trans*-(+/-)-*N*-(2-([butyl(ethyl)amino]methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- trans*-(+/-)-6-(1*H*-pyrazol-1-yl)-*N*-(2-([2-(3-thienylmethyl)piperidin-1-yl]methyl)cyclohexyl)nicotinamide;
- trans*-(+/-)-*N*-(2-([4,4-difluoropiperidin-1-yl]methyl)cyclohexyl)-4-
- 20 methoxybenzamide;
- trans*-(+/-)-4-methoxy-*N*-(2-([4-methylpiperidin-1-yl]methyl)cyclohexyl)benzamide;
- trans*-(+/-)-4-(2-methoxyethoxy)-*N*-(2-([4-methylpiperidin-1-yl]methyl)cyclohexyl)benzamide;
- trans*-(+/-)-4-methoxy-*N*-(2-(morpholin-4-ylmethyl)cyclohexyl)benzamide;
- 25 *cis*-(+/-)-4-(2-ethoxyethoxy)-*N*-(2-(piperidin-1-ylmethyl)cyclohexyl)benzamide;
- cis*-(+/-)-4-(2-ethoxyethoxy)-*N*-(2-(pyrrolidin-1-ylmethyl)cyclohexyl)benzamide;
- cis*-(+/-)-*N*-(2-([diethylamino]methyl)cyclohexyl)-4-(2-ethoxyethoxy)benzamide;
- trans*-(+/-)-4-(2-ethoxyethoxy)-*N*-(2-(piperidin-1-ylmethyl)cyclohexyl)benzamide;
- trans*-(+/-)-*N*-(2-(azepan-1-ylmethyl)cyclohexyl)-4-(2-ethoxyethoxy)benzamide;
- 30 *trans*-(+/-)-*N*-(2-([diethylamino]methyl)cyclohexyl)-4-(2-ethoxyethoxy)benzamide;
- trans*-(+/-)-*N*-(4-chlorophenyl)-*N'*-(2-(piperidin-1-ylmethyl)cyclohexyl)urea;
- trans*-(+/-)-*N*-(4-cyanophenyl)-*N'*-(2-(piperidin-1-ylmethyl)cyclohexyl)urea;
- trans*-(+/-)-*N*-(4-methoxyphenyl)-*N'*-(2-(piperidin-1-ylmethyl)cyclohexyl)urea;
- trans*-(+/-)-2-methoxy-4-methyl-*N*-(2-(piperidin-1-
- 35 ylmethyl)cyclohexyl]benzenesulfonamide;

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- trans*-(+/-)- methyl 3-({[2-(piperidin-1-ylmethyl)cyclohexyl]amino}sulfonyl)thiophene-2-carboxylate;
trans-(+/-)-5-[2-(methylthio)pyrimidin-4-yl]-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]thiophene-2-sulfonamide;
 5 *trans*-(+/-)-1-(4-chlorophenyl)-*N*-[2-(piperidin-1-ylmethyl)cyclohexyl]methanesulfonamide;
trans-(+/-)- *N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-4-(1,3-oxazol-5-yl)benzamide;
trans-(+/-)- *N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-6-
 10 (trifluoromethyl)nicotinamide;
trans-(+/-)- *N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-4-(2-methoxyethoxy)benzamide;
trans-(+/-)-*N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-3-(4-chlorophenyl)propanamide;
 15 *trans*-(+/-)- *N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}-4-(1*H*-imidazol-1-yl)benzamide;
trans-(+/-)- *N*-(2-{[3-(ethoxymethyl)piperidin-1-yl]methyl}cyclohexyl)-6-(1*H*-imidazol-1-yl)nicotinamide;
trans-(+/-)-*N*-(2-{[3-(ethoxymethyl)piperidin-1-yl]methyl}cyclohexyl)-4-(1,3-oxazol-
 20 5-yl)benzamide;
trans-(+/-)- *N*-(2-{[3-(ethoxymethyl)piperidin-1-yl]methyl}cyclohexyl)-4-(1*H*-imidazol-1-yl)benzamide;
trans-(+/-)- *N*-2-{[3-(ethoxymethyl)piperidin-1-yl]methyl}cyclohexyl)-4-
 {[(methylsulfonyl)amino]methyl}benzamide;
 25 *trans*-(+/-)- *N*-(2-{[3-propylpiperidin-1-yl]methyl}cyclohexyl)-6-(1*H*-imidazol-1-yl)nicotinamide;
trans-(+/-)- 4-(1*H*-imidazol-1-yl)-*N*-{2-[(3-propylpiperidin-1-yl)methyl]cyclohexyl}benzamide;
trans-(+/-)- *N*-(2-{[3-isobutylpiperidin-1-yl]methyl}cyclohexyl)-6-(1*H*-imidazol-1-
 30 yl)nicotinamide;
trans-(+/-)- 4-(1*H*-imidazol-1-yl)-*N*-{2-[(3-isobutylpiperidin-1-yl)methyl]cyclohexyl}benzamide;
trans-(+/-)-4-Bromo-*N*-{2-[(3-propylpiperidin-1-yl)methyl]cyclohexyl}benzamide;
trans-(+/-)-3-(4-Chlorophenyl)-*N*-{2-[(3-propylpiperidin-1-
 35 yl)methyl]cyclohexyl}propanamide;
trans-(+/-)-4-Bromo-*N*-{2-[(3-butylpiperidin-1-yl)methyl]cyclohexyl}benzamide;

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- trans*-(+/-)-*N*-[2-[(3-Butylpiperidin-1-yl)methyl]cyclohexyl]-4-[(diethylamino)methyl]benzamide;
- trans*-(+/-)-3-(4-Chlorophenyl)-*N*-(2-[[3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)propanamide;
- 5 *N*-[(1*S*,2*R*)-2-[(4-[(2*E*)-But-2-en-1-yloxy]piperidin-1-yl)methyl]cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
- N*-[(1*S*,2*R*)-2-[(4-Butoxypiperidin-1-yl)methyl]cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
- N*-(1*S*,2*R*)-2-[[[(3*R*)-3-(2-Methoxyethoxy)piperidin-1-yl]methyl]cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide;
- 10 *N*-(1*R*,2*S*)-2-[[[(3*R*)-3-(2-Methoxyethoxy)piperidin-1-yl]methyl]cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide;
- N*-[(1*S*,2*R*)-2-[(3*R*)-3-[(Allyloxy)methyl]piperidin-1-yl]methyl]cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 15 *N*-[(1*R*,2*S*)-2-[(3*R*)-3-[(Allyloxy)methyl]piperidin-1-yl]methyl]cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
- N*-[(1*R*,2*S*)-2-[(3*R*)-3-[(Allyloxy)methyl]piperidin-1-yl]methyl]cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 20 *N*-[(1*S*,2*R*)-2-[(3*R*)-3-[(Allyloxy)methyl]piperidin-1-yl]methyl]cyclohexyl]-6-(1*H*-imidazol-1-yl)nicotinamide;
- (*N*-[(1*S*,2*R*)-2-[(3*R*)-3-ethoxypiperidin-1-yl]methyl]cyclohexyl)pyrazine-2-carboxamide;
- N*-[(1*S*,2*R*)-2-[(3*R*)-3-ethoxypiperidin-1-yl]methyl]cyclohexyl]-6-(ethylthio)nicotinamide;
- 25 *N*-[(1*S*,2*R*)-2-[(3*R*)-3-ethoxypiperidin-1-yl]methyl]cyclohexyl]-6-pyrrolidin-1-yl)nicotinamide;
- N*-[(1*S*,2*R*)-2-(azepan-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide;
- N*-[(1*S*,2*R*)-2-(azepan-1-ylmethyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
- N*-[(1*S*,2*R*)-2-[[[(3*R*)-3-(allyloxy)piperidin-1-yl]methyl]cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide;
- 30 *N*-[(1*R*,2*S*)-2-[[[(3*R*)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl]-4-(1*H*-pyrrol-1-yl)benzamide;
- N*-[(1*S*,2*R*)-2-[[[(3*R*)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl]-4-(1*H*-pyrrol-1-yl)benzamide;
- 35 *N*-[(1*R*,2*S*)-2-[[[(3*R*)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl]-6-pyrrolidin-1-yl)nicotinamide;

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- N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-6-pyrrolidin-1-yl nicotinamide;
- N*-[(1*S*,2*R*)-2-(piperidin-1-ylmethyl)cyclohexyl]-4-(1*H*-pyrazol-1-yl)benzamide;
- N*-[(1*S*,2*R*)-2-(piperidin-1-ylmethyl)cyclohexyl]-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 5 *N*-((1*S*,2*R*)-2-(((3*R*)-3-(allyloxy)piperidin-1-yl)methyl)cyclohexyl)-4-(1*H*-pyrrol-1-yl)benzamide;
- N*-((1*S*,2*R*)-2-(((3*R*)-3-(allyloxy)piperidin-1-yl)-methyl)cyclohexyl)-3-cyclopentylpropanamide;
- N*-((1*S*,2*R*)-2-(((3*R*)-3-(allyloxy)piperidin-1-yl)methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- 10 *N*-((1*S*,2*R*)-2-(((3*S*)-3-(allyloxy)piperidin-1-yl)methyl)cyclohexyl)-6-(1*H*-pyrazol-1-yl)nicotinamide;
- N*-((1*S*,2*R*)-2-(((3*S*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-(2-methoxyethoxy)benzamide;
- 15 3-(4-chlorophenyl)-*N*-((1*S*,2*R*)-2-(((3*S*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)propanamide;
- N*-((1*S*,2*R*)-2-(((3*S*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-(((methylsulfonyl)amino)methyl)benzamide;
- 4-[(diethylamino)methyl]-*N*-((1*S*,2*R*)-2-(((3*S*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide;
- 20 *N*-[(1*S*,2*R*)-2-(((3*R*)-3-(allyloxy)methyl)piperidin-1-yl)methyl)cyclohexyl]-6-(1*H*-imidazol-1-yl)nicotinamide;
- 4-chloro-*N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide;
- 25 *N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide;
- N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)cyclohexanecarboxamide;
- N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-2-phenylacetamide;
- 30 *N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-3-phenylpropanamide;
- N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-2,3-dihydro-1-benzofuran-5-carboxamide;
- 2-cyclopentyl-*N*-((1*S*,2*R*)-2-(((3*R*)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)acetamide;
- 35

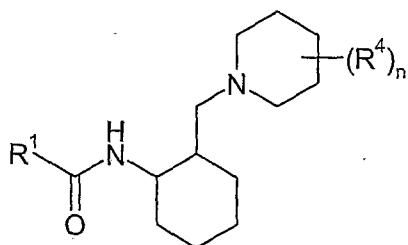
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- 2-chloro-N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-3-fluoroisonicotinamide;
- N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)chromane-2-carboxamide;
- 5 N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4,6-dimethylnicotinamide;
- N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-2,7-dimethylimidazo[1,2-a]pyridine-3-carboxamide hydrochloride salt;
- N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-2-(3-methoxyphenyl)acetamide;
- 10 2-(2,3-dioxo-2,3-dihydro-1H-indol-1-yl)-N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)acetamide hydrochloride salt;
- N2-acetyl-N1-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)glycinamide;
- 15 N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-2-(1H-tetrazol-1-yl)acetamide;
- N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-5,7-dimethylpyrazolo[1,5-a]pyrimidine-2-carboxamide;
- N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-3,4-dihydro-2H-1,5-benzodioxepine-6-carboxamide;
- 20 N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-methyl-3,4-dihydro-2H-1,4-benzoxazine-7-carboxamide;
- N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-5-phenyl-1H-pyrazole-4-carboxamide;
- 25 N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-(1H-tetrazol-1-yl)benzamide;
- 4-((diethylamino)methyl)-N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide;
- N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-(2-methoxyethoxy)benzamide;
- 30 N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)-4-(((methylsulfonyl)amino)methyl)benzamide;
- 4-((acetylamino)methyl)-N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide;
- 35 4-((diacetylamino)methyl)-N-((1S,2R)-2-(((3R)-3-(ethoxymethyl)piperidin-1-yl)methyl)cyclohexyl)benzamide;

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- $N-((1S,2R)-2-[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-[[(ethylsulfonyl)amino]methyl]benzamide;$
 $4-[[(cyclopropylsulfonyl)amino]methyl]-N-((1S,2R)-2-[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide;$
 5 $N-((1S,2R)-2-[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-[[(methylamino)carbonyl]amino]methyl]benzamide;$
 $4-[[(dimethylamino)carbonyl]amino]methyl]-N-((1S,2R)-2-[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)benzamide;$
 $N-((1S,2R)-2-[[(3R)-3-(ethoxymethyl)piperidin-1-yl]methyl]cyclohexyl)-4-[[(isobutylamino)methyl]benzamide;$
 10 $N-((1S,2R)-2-[[3-cyclohexylpiperidin-1-yl]methyl]cyclohexyl)-6-(1H-pyrazol-1-yl)nicotinamide;$
 $N-((1S,2R)-2-[[3-phenylpiperidin-1-yl]methyl]cyclohexyl)-6-(1H-pyrazol-1-yl)nicotinamide;$
 15 and pharmaceutically acceptable salts thereof.

8. A compound of formula V, a pharmaceutically acceptable salt thereof, diastereomer, enantiomer, or mixture thereof:



20 V
 wherein

- R^1 is selected from C_{6-10} aryl, C_{2-9} heteroaryl, C_{3-5} heterocycloalkyl, C_{6-10} aryl- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-3} alkyl, and C_{1-6} alkyl, wherein said C_{6-10} aryl, C_{2-9} heteroaryl, C_{6-10} aryl- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-3} alkyl, and C_{1-6} alkyl are optionally substituted with one or more group selected from C_{6-10} aryl, C_{1-9} heteroaryl, C_{3-5} heterocycloalkyl, C_{6-10} aryl- C_{1-3} alkyl, C_{6-10} aryl-O- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, -CN, -SR, -OR, -O(CH₂)_m-OR, R, -C(=O)-R, -CO₂R, -SO₂R, -SO₂NR₂, halogen, -NO₂, -NR₂, -(CH₂)_mNR₂, -
 25 (CH₂)_mNHC(=O)-NR₂, -NHC(=O)-R, -N[C(=O)R]₂, -(CH₂)_mNHC(=O)-R, -
 30 (CH₂)_mN[C(=O)-R]₂, -(CH₂)_mNHS(=O)₂-R, and -C(=O)-NR₂; and

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R⁴ is selected from C₆₋₁₀aryl, C₂₋₉heteroaryl, C₃₋₆cycloalkyl, C₃₋₅heterocycloalkyl, C₆₋₁₀aryl-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₅heterocycloalkyl-C₁₋₃alkyl, -CN, -SR, -OR, -(CH₂)_mOR, -O(CH₂)_mOR, -O(CH₂)_mNR₂, -(CH₂)_mO(CH₂)_nOR, -(CH₂)_mO(CH₂)_nNR₂, R, -CO₂R, -SO₂R, -SO₂NR₂, halogen, -NO₂, -NR₂, -(CH₂)_mNR₂, and -C(=O)-NR₂;

each R is independently hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl or halogenated C₁₋₆alkyl;

with a proviso that

R¹ is not 4-amino-5-chloro-2-alkoxyphenyl, 4-amino-5-chloro-2-cycloalkoxyphenyl, 4-amino-5-chloro-2-cycloalkyl-alkoxy-phenyl, 4-butoxyphenyl, 3-butoxyphenyl, 4-pentyloxyphenyl, 4-isobutoxyphenyl, 4-benzyloxyphenyl and 7-(2,3-dihydro)benzofuranyl.

9. A compound as claimed in claim 1, wherein

R¹ is selected from C₆₋₁₀aryl, C₂₋₉heteroaryl, C₃₋₅heterocycloalkyl, C₆₋₁₀aryl-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₅heterocycloalkyl-C₁₋₃alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₃alkyl, and C₃₋₆alkyl, wherein said C₆₋₁₀aryl, C₂₋₉heteroaryl, C₆₋₁₀aryl-C₁₋₃alkyl, C₆₋₁₀aryl-O-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₃alkyl, and C₃₋₆alkyl are optionally substituted by one or more groups selected from 1H-pyrazol-1-yl, fluoro, chloro, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, t-butyl, cyano, bromo, 1,3-oxazol-5-yl, 1H-imidazol-1-yl, (4-oxopiperidin-1-yl)carbonyl, pyridin-3-ylmethyl, [(butylamino)carbonyl]amino, 1,1-dioxidothiomorpholin-4-yl, aminosulfonyl, morpholin-4-yl, diethylaminomethyl, acetyl, (3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)methyl, 1-oxo-indan-4-yl, dimethylaminomethyl, methyl, pyrrolidin-1-yl, ethylthio, acetylamino, dimethylamino, 1H-pyrrol-1-yl, ethyl, ethoxy, fluorophenoxy, propyl, phenyl, methoxycarbonyl, diacetylamino, (methylsulfonylamino)methyl, (cyclopropylsulfonylamino)methyl, 1H-tetrazol-1-yl, pyrazolyl, methylaminocarbonylamino, dimethylaminocarbonylamino, and (methylthio)pyrimidin-4-yl.

10. A compound as claimed in claim 8, wherein said R¹ is selected from 2-cyclopentylethyl, cyclopropylmethyl, ethyl, methyl, cyclohexyl, cyclopentylmethyl, chromanyl, pentyl, 2-phenylethyl, phenyl, benzyl, pyridinyl, pyridinylethyl, 1-benzofuranyl, benzothienyl, furyl, imidazolyl, pyrazolo[1,5-a]pyrimidinyl, pyrazinyl, 1,3-benzothiazolyl, indolyl, indazolyl, thienyl, 1,3-benzodioxinyl, tetrahydro-2H-pyran-

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4-ylmethyl, 1-H-1,2,3,-benzotriazol-1-yl, 2-(thien-2-yl)ethyl, (1-benzofuran-4-yl)methyl, 1,3-oxazolyl, 1H-pyrazol-1-yl, 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 2-oxo-2,3-dihydro-2H-benzimidazolyl, isoxazolyl, imidazo[1,2,a]pyridinyl, 2-3-dioxo-2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-2H-1,4-benzoxazinyl; pyrazolyl, 1H-tetrazol-1-yl-methyl, and 3,4-dihydro-2H-1,5-benzodioxepinyl, which are optionally substituted by one or more groups selected from C₆₋₁₀aryl, C₂₋₉heteroaryl, C₃₋₅heterocycloalkyl, C₆₋₁₀aryl-C₁₋₃alkyl, C₆₋₁₀aryl-O-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₅heterocycloalkyl-C₁₋₃alkyl, -CN, -SR, -OR, -O(CH₂)_m-OR, R, -C(=O)-R, -CO₂R, -SO₂R, -SO₂NR₂, halogen, -NO₂, -NR₂, -

10 (CH₂)_mNR₂, -(CH₂)_mNHC(=O)-NR₂, -NHC(=O)-R, -N[C(=O)R]₂, -(CH₂)_mNHC(=O)-R, -(CH₂)_mN[C(=O)-R]₂, -(CH₂)_mNHS(=O)₂-R, and -C(=O)-NR₂.

11. A compound as claimed in claim 8, wherein said R¹ is selected from 2-cyclopentylethyl, cyclopropylmethyl, ethyl, methyl, cyclohexyl, cyclopentylmethyl, chromanyl, pentyl, 2-phenylethyl, phenyl, benzyl, pyridinyl, pyridinylethyl, 1-benzofuranyl, benzothienyl, furyl, imidazolyl, pyrazolo[1,5-a]pyrimidinyl, pyrazinyl, 1,3-benzothiazolyl, indolyl, indazolyl, thienyl, 1,3-benzodioxinyl, tetrahydro-2H-pyran-4-ylmethyl, 1-H-1,2,3,-benzotriazol-1-yl, 2-(thien-2-yl)ethyl, (1-benzofuran-4-yl)methyl, 1,3-oxazolyl, 1H-pyrazol-1-yl, 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 2-oxo-2,3-dihydro-2H-benzimidazolyl, isoxazolyl, imidazo[1,2,a]pyridinyl, 2-3-dioxo-2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-2H-1,4-benzoxazinyl; pyrazolyl, 1H-tetrazol-1-yl-methyl, and 3,4-dihydro-2H-1,5-benzodioxepinyl, which are optionally substituted by one or more groups selected from 1H-pyrazol-1-yl, fluoro, chloro, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, t-butyl, cyano, bromo, 1,3-oxazol-5-yl, 1H-imidazol-1-yl, (4-oxopiperidin-1-yl)carbonyl, pyridin-3-ylmethyl, [(butylamino)carbonyl]amino, 1,1,-dioxidothiomorpholin-4-yl, aminosulfonyl, morpholin-4-yl, diethylaminomethyl, acetyl, (3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)methyl, 1-oxo-indan-4-yl, dimethylaminomethyl, methyl, pyrrolidin-1-yl, ethylthio, acetylamino, dimethylamino, 1H-pyrrol-1-yl, ethyl, ethoxy, fluorophenoxy, propyl, phenyl, methoxycarbonyl, diacetylamino, (methylsulfonylamino)methyl, (cyclopropylsulfonylamino)methyl, 1H-tetrazol-1-yl, pyrazolyl, methylaminocarbonylamino, dimethylaminocarbonylamino, and (methylthio)pyrimidin-4-yl.

35

12. A compound as claimed in claim 8, wherein

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R⁴ is selected from phenyl, benzyl, methyl, fluoro, trifluoromethyl, methoxy, allyloxy, (2E)-but-2-en-1-yloxy, (allyloxy)methyl, methoxymethyl, ethoxymethyl, propyl, butyl, pentyl, hexyl, cyclopentyl, pyridin-4-ylmethyl, ethoxy, butoxy, 2-methoxyethoxy, cyclohexyl, and thienylmethyl.

5

13. A compound according to any one of claims 1-12 for use as a medicament.

14. The use of a compound according to any one of claims 1-12 in the manufacture of a medicament for the therapy of pain.

10

15. The use of a compound according to any one of claims 1-12 in the manufacture of a medicament for the treatment of Alzheimer's disease.

15

16. The use of a compound according to any one of claims 1-12 in the manufacture of a medicament for the treatment of schizophrenia.

17. A pharmaceutical composition comprising a compound according to any one of claims 1-12 and a pharmaceutically acceptable carrier.

20

18. A method for the therapy of pain in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-12.

25

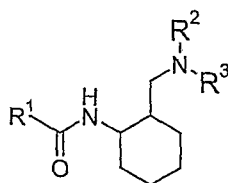
19. A method for the therapy of Alzheimer's disease in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-12.

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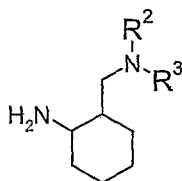
20. A method for the therapy of schizophrenia in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-12.

21. A process for preparing a compound of Formula II, comprising:

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II

reacting a compound of Formula III with a compound of R^1 -COCl or R^1 -COOH,

III

5

wherein

R^1 is selected from C_{6-10} aryl, C_{2-9} heteroaryl, C_{3-5} heterocycloalkyl, C_{6-10} aryl- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-3} alkyl, and C_{1-6} alkyl, wherein said C_{6-10} aryl, C_{2-9} heteroaryl, C_{6-10} aryl- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-3} alkyl, and C_{1-6} alkyl are optionally substituted with one or more group selected from C_{6-10} aryl, C_{2-9} heteroaryl, C_{3-5} heterocycloalkyl, C_{6-10} aryl- C_{1-3} alkyl, C_{6-10} aryl- O - C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, -CN, -SR, -OR, - $O(CH_2)_m$ -OR, R, -C(=O)-R, -CO₂R, -SO₂R, -SO₂NR₂, halogen, -NO₂, -NR₂, -(CH₂)_mNR₂, -
 10 (CH₂)_mNHC(=O)-NR₂, -NHC(=O)-R, -N[C(=O)R]₂, -(CH₂)_mNHC(=O)-R, -
 15 (CH₂)_mN[C(=O)-R]₂, -(CH₂)_mNHS(=O)₂-R, and -C(=O)-NR₂;

R^2 and R^3 are independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and C_{1-6} alkoxy wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{1-6} alkoxy are optionally substituted by one or more groups selected from amino, halogen, C_{1-6} alkoxy and -CN; or R^2 and R^3 together with the nitrogen connected thereto form a heterocycloalkyl, wherein said heterocycloalkyl is optionally substituted with one or more group selected from C_{6-10} aryl, C_{2-9} heteroaryl, C_{3-6} cycloalkyl, C_{3-5} heterocycloalkyl, C_{6-10} aryl- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, -CN, -SR, -OR, -(CH₂)_mOR, R, -CO₂R; -SO₂R; -SO₂NR₂, halogen, -NO₂, -NR₂, -(CH₂)_mNR₂, and -C(=O)-NR₂;
 20 each R is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or halogenated C_{1-6} alkyl; and

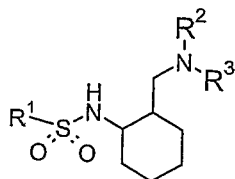
with a proviso that

when R^2 and R^3 together with the nitrogen connected thereto form said piperdiny; R^1 is not 4-amino-5-chloro-2-alkoxyphenyl, 4-amino-5-chloro-2-

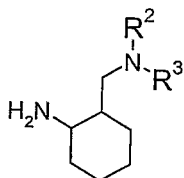
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cycloalkoxyphenyl, 4-amino-5-chloro-2-cycloalkyl-alkoxy-phenyl, 4-butoxyphenyl, 3-butoxyphenyl, 4-pentyloxyphenyl, 4-isobutoxyphenyl, 4-benzyloxyphenyl and 7-(2,3-dihydro)benzofuranyl.

22. A process for preparing a compound of Formula IV, comprising:

**IV**

reacting a compound of Formula III with a compound of R^1SO_2Cl ,

**III**

wherein

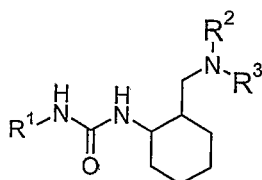
- R^1 is selected from C_{6-10} aryl, C_{2-9} heteroaryl, C_{3-5} heterocycloalkyl, C_{6-10} aryl- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-3} alkyl, and C_{1-6} alkyl, wherein said C_{6-10} aryl, C_{2-9} heteroaryl, C_{6-10} aryl- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-3} alkyl, and C_{1-6} alkyl are optionally substituted with one or more group selected from C_{6-10} aryl, C_{2-9} heteroaryl, C_{3-5} heterocycloalkyl, C_{6-10} aryl- C_{1-3} alkyl, C_{6-10} aryl-O- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, -CN, -SR, -OR, -O(CH₂)_m-OR, R, -C(=O)-R, -CO₂R, -SO₂R, -SO₂NR₂, halogen, -NO₂, -NR₂, -(CH₂)_mNR₂, -
- (CH₂)_mNHC(=O)-NR₂, -NHC(=O)-R, -N[C(=O)R]₂, -(CH₂)_mNHC(=O)-R, -
- (CH₂)_mN[C(=O)-R]₂, -(CH₂)_mNHS(=O)₂-R, and -C(=O)-NR₂;

- R^2 and R^3 are independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and C_{1-6} alkoxy wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{1-6} alkoxy are optionally substituted by one or more groups selected from amino, halogen, C_{1-6} alkoxy and -CN; or R^2 and R^3 together with the nitrogen connected thereto form a heterocycloalkyl, wherein said heterocycloalkyl is optionally substituted with one or more group selected from C_{6-10} aryl, C_{2-9} heteroaryl, C_{3-6} cycloalkyl, C_{3-5} heterocycloalkyl, C_{6-10} aryl- C_{1-3} alkyl, C_{2-9} heteroaryl- C_{1-3} alkyl, C_{3-5} heterocycloalkyl- C_{1-3} alkyl, -CN, -SR, -OR, -(CH₂)_mOR, R, -CO₂R, -SO₂R, -SO₂NR₂, halogen, -NO₂, -NR₂, -(CH₂)_mNR₂, and -C(=O)-NR₂; and

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each R is independently hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl or halogenated C₁₋₆alkyl.

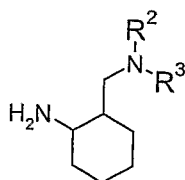
23. A process for preparing a compound of Formula VI, comprising



5

VI

reacting a compound of Formula III with R¹NCO,

III

10 wherein

R¹ is selected from C₆₋₁₀aryl, C₂₋₉heteroaryl, C₃₋₅heterocycloalkyl, C₆₋₁₀aryl-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₅heterocycloalkyl-C₁₋₃alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₃alkyl, and C₁₋₆alkyl, wherein said C₆₋₁₀aryl, C₂₋₉heteroaryl, C₆₋₁₀aryl-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₅heterocycloalkyl-C₁₋₃alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₃alkyl, and C₁₋₆alkyl are optionally substituted with one or more group selected from C₆₋₁₀aryl, C₂₋₉heteroaryl, C₃₋₅heterocycloalkyl, C₆₋₁₀aryl-C₁₋₃alkyl, C₆₋₁₀aryl-O-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₅heterocycloalkyl-C₁₋₃alkyl, -CN, -SR, -OR, -O(CH₂)_m-OR, R, -C(=O)-R, -CO₂R, -SO₂R, -SO₂NR₂, halogen, -NO₂, -NR₂, -(CH₂)_mNR₂, -(CH₂)_mNHC(=O)-NR₂, -NHC(=O)-R, -N[C(=O)R]₂, -(CH₂)_mNHC(=O)-R, -(CH₂)_mN[C(=O)-R]₂, -(CH₂)_mNHS(=O)₂-R, and -C(=O)-NR₂;

R² and R³ are independently selected from C₁₋₆alkyl, C₂₋₆alkenyl, and C₁₋₆alkoxy wherein said C₁₋₆alkyl, C₂₋₆alkenyl, and C₁₋₆alkoxy are optionally substituted by one or more groups selected from amino, halogen, C₁₋₆alkoxy and -CN; or R² and R³ together with the nitrogen connected thereto form a heterocycloalkyl, wherein said heterocycloalkyl is optionally substituted with one or more group selected from C₆₋₁₀aryl, C₂₋₉heteroaryl, C₃₋₆cycloalkyl, C₃₋₅heterocycloalkyl, C₆₋₁₀aryl-C₁₋₃alkyl, C₂₋₉heteroaryl-C₁₋₃alkyl, C₃₋₅heterocycloalkyl-C₁₋₃alkyl, -CN, -SR, -OR, -(CH₂)_mOR, R, -CO₂R; -SO₂R; -SO₂NR₂, halogen, -NO₂, -NR₂, -(CH₂)_mNR₂, and -C(=O)-NR₂; and

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each R is independently hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl or halogenated C₁₋₆alkyl.

24. A method for the therapy of anxiety in a warm-blooded animal, comprising the
5 step of administering to said animal in need of such therapy a therapeutically
effective amount of a compound according to any one of claims 1-12.
25. A method for the therapy of depression in a warm-blooded animal, comprising
the step of administering to said animal in need of such therapy a therapeutically
10 effective amount of a compound according to any one of claims 1-12.