PYRROLIDINYL AND PYRROLINYL ETHYLAMINE COMPOUNDS AS KAPPA AGONISTS

Technical Field

This invention relates to novel pyrrolidinyl and pyrrolinyl ethylamine compounds and their pharmaceutically acceptable salts, and to pharmaceutical compositions containing them. The pharmaceutically active compounds of this invention can be used as a selective kappa-receptor agonist.

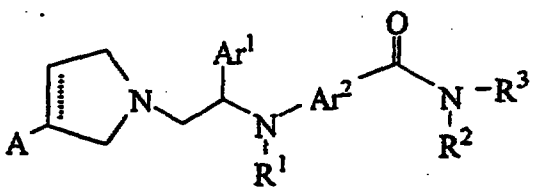
Background Art

Opioid analgesics such as morphine are therapeutically useful, but their usage is strictly limited because of their side effects such as drug dependency and abuse. Thus, analgesics with high usefulness and reduced tendency to cause drug dependency are desired. Considerable pharmacological and biochemical studies have been carried out to discover the opioid peptides and opioid receptors, and the discovery of the subtype of opioid receptor such as mu (μ), delta (δ), kappa (κ) in a variety of species, including human, has made a beginning towards creating new analgesics. As it is thought that opioid analgesics such as morphine act as a mu-receptor agonist, separating the action based on a kappa-receptor agonist from the action based on mu-receptor agonist has been investigated. Recently kappa-selective agonists (kappa-agonists) have been reported from the above viewpoint for example, EMD-61753: A. Barber *et al.*, *Br. J. Pharmacol.*, Vol. 113, pp. 1317-1327, 1994. Some of them actually have been studied in clinical trials (*Med. Res. Rev.*, Vol. 12, p. 525, 1992).

European Patent No. EP 0254545 B1 discloses a variety of ethylenediamine compounds. European Patent No. EP 0483580 A2 discloses a variety of pyrrolidine compounds as analgesics. International Publication WO 96/30339 discloses a wide variety of pyrrolidinyl hydroxamic acid compounds as selective kappa-receptor agonists.

Brief Disclosure of the Invention

The present invention provides a compound of the following formula:



(I)

and the salts thereof, wherein

A is hydrogen, halo, hydroxy, C_1-C_6 (preferably C_1-C_4) alkyl, halo C_1-C_6 (preferably C_1-C_4) alkyl, C_1-C_6 (preferably C_1-C_4) alkoxy, halo C_1-C_6 (preferably C_1-C_4) alkoxy, oxo, OY wherein Y is a hydroxy protecting group, or absent;

the broken line represents an optional double bond with proviso that if the broken line is a double bond, then A is absent;

Ar^1 is phenyl optionally substituted by one or more (preferably one to two) substituents selected from halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy-C_1-C_4 alkoxy, CF_3, carboxy-C_1-C_4 alkoxy and C_1-C_4 alkoxy-carbonyl-C_1-C_4 alkoxy;

Ar^2 is aryl or heteroaryl selected from phenyl, naphthyl, pyridyl, thienyl, furyl, pyrrolyl and pyrimidyl, the aryl or heteroaryl being optionally substituted by one or more (preferably one to two) substituents selected from halo, hydroxy, amino, nitro, carboxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylamino, di C_1-C_4 alkylamino, halo C_1-C_4 alkyl, C_1-C_4 alkylthio and sulfonyl methyl;

R^1 is hydrogen, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy or OY wherein Y is a hydroxy protecting group; and

R^2 and R^3 are independently selected from hydrogen, hydroxy, C_1-C_7 alkyl optionally substituted by one or more (preferably one to five) hydroxy or halo, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_7 (preferably C_1-C_5) alkoxy, phenyl optionally substituted by halo (preferably substituted by one or two halogen atoms), phenyl C_1-C_7 (preferably C_1-C_5) alkyl, halo substituted phenyl C_1-C_7 alkyl, and (CH_2)nX-R^4 wherein n is one or two, X is O, NH or S and R^4 is C_1-C_3 alkyl, or when Ar^2 is phenyl, -Ar^2-C(=O)-N(R^2)- is a phthalimide group and R^3 is C_1-C_7 alkyl, or

R^2 and R^3, together with the nitrogen atom to which they are attached, form a pyrrolidine, piperidine or morpholine ring, optionally substituted by C_1-C_3 alkyl or halo.

When Ar^2 is phenyl, R^2R^3N-C(=O)- is preferably at the meta or para position on the phenyl ring with respect to 2-(A-pyrrolydinyl)-1-Ar^1-ethyl-N(R^1)-. When oxo is selected as "A" group, it is apparent that the oxygen atom should be attached to the pyrrolidinyl group through a double bond.

The pyrrolidinyl and pyrrolynyl ethylamine compounds of the present invention of formula (I) exhibit good kappa-receptor agonist activity, and thus are useful as an analgesic, anesthetic, anti-inflammatory or neuroprotective agent, and also useful in the treatment of arthritis, stroke or functional bowel disease such as abdominal pain, for the

treatment of a mammalian subject, especially a human subject. Specifically, these compounds are useful as an analgesic for acute and chronic pain. Especially, these compounds are useful as an analgesic at central nervous system in the mammalian subject. Also, these compounds are useful as an analgesic for peripheral mediated inflammatory pain caused, for example by burns (induced by a contact with heat, acid or the other agents), scald (induced by a contact by hot liquid or steam), rheumatism or the like, in the said subject.

Accordingly, the present invention provides a pharmaceutical composition, which is useful as an analgesic, anesthetic, anti-inflammatory or neuroprotective agent, and also useful in the treatment of the above-mentioned diseases, which comprises a therapeutically effective amount of the compound of the formula (I), and a pharmaceutically inert carrier.

The present invention also provides a method for the treatment of a medical condition for which agonist activity toward opioid kappa-receptor is needed, in a mammalian subject, which comprises administering to said subject a therapeutically effective amount of the compound of the formula (I).

Detailed Disclosure of the Invention

In this specification, the term "hydroxy protecting group" means a functional group to protect a hydroxy group against undesirable reactions during synthetic procedures, including, but not limited to benzyl, benzoyl, methoxymethyl, tetrahydropyranyl and trialkylsilyl.

The term "C_1-C_6 alkyl" is used herein means a straight or branched alkyl including but not limited to methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl and the like.

The term "C_1-C_6 alkoxy" is used herein to mean a straight or branched -OR (R is C_1-C_6 alkyl) including, but not limited to, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, *iso*-butoxy, *tert*-butoxy and the like.

The term "halo" means F, Cl, Br or I, preferably F or Cl.

The term "halo C_1-C_6 alkyl" means a straight or branched, halo-substituted alkyl of 1 to 6 carbon atoms including, but not limited to methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl and *tert*-butyl, substituted by 1 to 13 (preferably one to five) halogen atoms.

The term "halo C_1-C_6 alkoxy" means C_1-C_6 alkoxy substituted by 1 to 13

(preferably one to three) halogen atoms.

The term "halo substituted phenyl C_1-C_7 alkyl" means C_1-C_7 alkyl having a phenyl group attached to its terminal carbon atom, the phenyl group being substituted by one to five (preferably one to two) halogen atoms.

A preferred group of compounds of this invention includes the compounds of the formula (I) wherein

A is hydrogen, halo, hydroxy, oxo or OY; or if the broken line is a double bond then A is absent;

Ar^1 is phenyl optionally substituted by one to three substituents selected from halo, hydroxy, C_1-C_4 alkoxy, carboxy C_1-C_4 alkoxy and C_1-C_4 alkoxy-carbonyl-C_1-C_4 alkoxy;

Ar^2 is phenyl, pyridyl or thienyl, optionally substituted by one to two halo or C_1-C_4 alkoxy;

R^1 is hydrogen, hydroxy or C_1-C_4 alkyl; and

R^2 and R^3 are independently selected from hydrogen, C_1-C_7 alkyl optionally substituted by one or more hydroxy or halo, C_3-C_6 (preferably C_3-C_4) cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 (preferably C_2-C_3) alkynyl, C_1-C_4 alkoxy phenyl and halo substituted phenyl C_1-C_7 alkyl, when Ar^2 is phenyl, -Ar^2-C(=O)-N(R^2)- is a phthalimide group and R^3 is C_1-C_7 alkyl, or

R^2 and R^3, together with the nitrogen atom to which they are attached, form a pyrrolidine or morpholine ring.

A more preferred group of this invention includes the compounds of the formula (I) wherein

A is hydrogen, fluorine, chlorine, hydroxy or OY wherein Y is methoxymethyl or tetrahydropyranyl; or if the broken line is a double bond then A is absent or;

Ar^1 is phenyl optionally substituted by chlorine, hydroxy, methoxy or carboxymethoxy;

Ar^2 is phenyl, pyridyl or thienyl, optionally substituted by chlorine, fluorine or methoxy;

R^1 is C_1-C_4 alkyl;

R^2 is C_1-C_7 (preferably C_1-C_5) alkyl optionally substituted by hydroxy or fluorine, C_2-C_6 (preferably C_2-C_3) alkenyl, halo substituted phenylmethyl or phenyl; and

R^3 is hydrogen or methyl; or

R^2 and R^3, together with the nitrogen atom to which they are attached, form a pyrrolidine or morpholine ring.

A more preferred group of this invention includes the compounds of the formula (I) wherein

A is hydroxy, fluorine or chlorine; or if the broken line is a double bond, then A is absent; Ar^1 is phenyl optionally substituted by carboxymethoxy; Ar^2 is phenyl optionally substituted by methoxy or pyridyl; R^1 is C_1-C_4 alkyl; R^2 is C_1-C_7 alkyl optionally substitute by hydroxy; and R^3 is hydrogen.

Preferred individual compounds are:

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-2-methoxy-N'-propylbenzamide;

6-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylnicotinamide;

4-{N-[1-(S)-(3-carboxymethoxyphenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(S)-hydroxypropyl)benzamide;

5-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylpicolinamide;

4-{N-methylamino-N-[2-(3-pyrrolin-1-yl)-1-(S)-phenylethyl]}-N'-propylbenzamide; and

4-{N-[2-(3-(S)-chloropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(S)-hydroxypropyl)benzamide.

Other preferred individual compounds are:

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-isopropylbenzamide;

3-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

2-chloro-4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-

methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-3-methoxy-N'-propylbenzamide;

3-chloro-4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[1-(S)-(3-hydroxyphenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-(3-methoxyphenyl)-ethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[1-(S)-phenyl-2-(pyrrolidin-1-yl)ethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[1-(S)-(3-chlorophenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(R)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-pyrrolidinebenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-morpholinebenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(R)-hydroxypropyl)benzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-isobutylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-allylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(3,3,3,-trifluoropropyl)benzamide;

3-fluoro-4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2,2,3,3,3,-pentafluoropropyl)benzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-tert-amylbenzamide;

5-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylpicolinamide;

4-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(S)-hydroxypropyl)benzamide;

2-chloro-4-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide; and

4-{N-[2-(3-(S)-chloropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide.

Other preferred compounds are:

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-methylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-ethylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-butylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-pentylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-phenylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-chlorobenzyl)benzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N',N'-dimethylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-methyl-N'-propylbenzamide;

5-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propyl-2-thiophenecarboxamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]amino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylphthalimide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-ethoxybenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(3-hydroxypropyl)benzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-cyclopropylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(S)-sec-butylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(R)-sec-butylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propargylbenzamide;

4-{N-[1-(R)-(3-carboxymethoxyphenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-tert-butylbenzamide;

4-{N-hydroxy-N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]amino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-hydroxyamino}-N'-propylbenzamide;

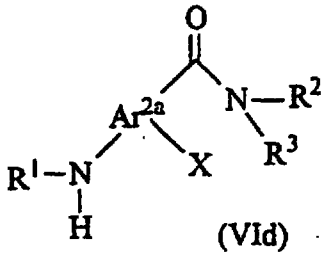
4-{N-[2-(3-(R)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(R)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-chloropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(R)-hydroxypropyl)benzamide; and

4-{N-[2-(3-oxopyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide.

Further, the present invention provides a compound of the following formula:



(VId)

wherein

Ar^{2a} is phenyl, pyridyl or thienyl;

X is hydrogen, halo or C_1-C_7 alkoxy;

R^1 is hydrogen, optionally protected hydroxy or C_1-C_4 alkyl; and

R^2 and R^3 are independently hydrogen or C_1-C_7 alkyl optionally substituted by hydroxy or halo.

Preferred individual compounds of the formula (VId) are:

4-methylamino-N'-propylbenzamide;

5-N-methylamino-N'-propylpicolinamide;

2-chloro-4-methylamino-N'-propylbenzamide;

4-methylamino-N'-(2-(S)-hydroxypropyl)benzamide;

4-methylamino-N'-(2-(R)-hydroxypropyl)benzamide;

4-methylamino-N'-(2,2,3,3,3-pentafluoropropyl)benzamide; and

4-methylamino-N'-tert-amylbezamide.

Further, the present invention provides compounds selected from

2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethanol;

2-(3-(S)-fluoropyrrolidin-1-yl)-2-(R)-phenylethanol;

2-(R)-phenyl-2-(3-pyrroline-1-yl)ethanol;

2-(3-(R)-fluoropyrrolidin-1-yl)-1-(S)-phenylethanol;

2-(3-(R)-fluoropyrrolidin-1-yl)-2-(R)-phenylethanol;

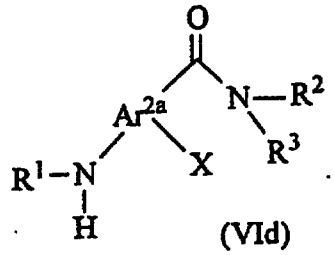
2-(3-(S)-fluoropyrrolidin-1-yl)-1-(R)-phenylethanol;

2-(3-(S)-fluoropyrrolidin-1-yl)-2-(S)-phenylethanol

2-(3-(S)-chloropyrrolidin-1-yl)-1-(S)-phenylethanol; and

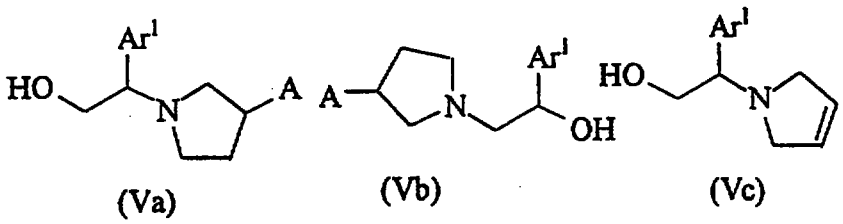
2-(3-(S)-chloropyrrolidin-1-yl)-2-(R)-phenylethanol.

Further, the present invention provides processes for producing a compound of formula (I), which comprises reacting an amide compound of the formula (VId):



(VId)

with an ethanol compound selected from compounds (Va), (Vb) and (Vc), and a mixture of compounds (Va) and (Vb):



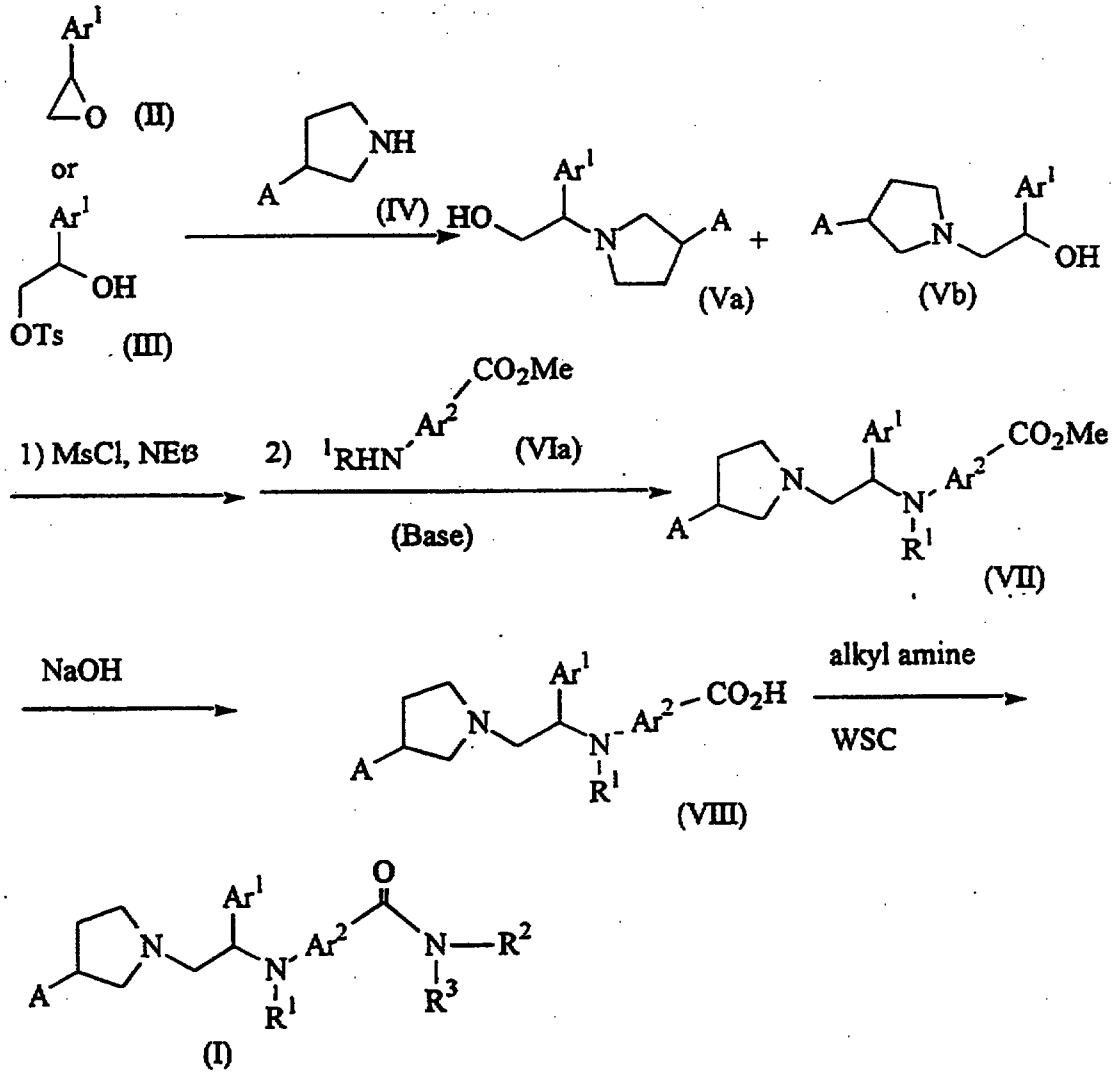
(Va) (Vb) (Vc)

in the absence or presence of a base in a reaction inert solvent.

General Synthesis

The kappa agonists (kappa-receptor agonists) of formula (I) of this invention can be prepared as described in the following schemes. Unless otherwise indicated, in the reaction schemes that follow, A, Ar^1, Ar^2, R^1, R^2 and R^3 are defined as above.

Scheme 1a



In the above Scheme 1a, an optionally substituted styrene oxide (II) or an optionally substituted phenyl-1,2-ethanediol 2-tosylate (III) can be reacted with a pyrrolidine compound (IV) in the absence or presence of a base such as K_2CO_3 to form a mixture of substituted pyrrolidinyl ethanols (Va) and (Vb) . This reaction may be carried out in the absence or presence of a reaction inert solvent (e.g., methanol (MeOH), ethanol (EtOH), isopropylalcohol, tetrahydrofuran (THF), dioxane, N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), methylene chloride (CH_2Cl_2), water, benzene, toluene, n-hexane or cyclohexane). This reaction can be carried out at a temperature from -78°C to the reflux temperature of the solvent, preferably at from room temperature to a reflux temperature of the solvent for 5 minutes to 48 hours, preferably from 0.5 to 12 hours. The compound (Va) or the mixture of the compounds (Va) and (Vb), can be treated with methanesulfonyl chloride in the presence of a base such as triethylamine in a proper solvent such as dichloroethane, followed by coupling with a methyl ester compound of formula (VIa) to give an intermediate compound (VII). This coupling reaction can be carried out, in the absence or presence of a base such as sodium hydride (NaH), in a suitable polar solvent such as water, EtOH or DMF, at from room temperature to reflux temperature of the solvent, for 15 minutes to 6 hours.

Then, the intermediate compound (VII) may be treated with a base such as NaOH in a reaction inert solvent such as methanol, at a temperature from 0 to 100°C for 5 minutes to 12 hours to give a carboxylic acid compound (VIII).

The carboxylic acid (VIII) can be reacted with an alkyl amine in the presence of a carbodiimide compound to give the pyrrolydinyl ethylamine compound (I). A convenient carbodiimide compound is 1-ethyl-3-(3-dimeythylaminopropyl)carbodiimide (WSC). This reaction may be carried out by contacting substantially equivalent amounts of the carboxylic acid and alkylamine with a small excess amount of the carbodiimide in an appropriate solvent. Appropriate solvents are inert aromatic hydrocarbons, ethers, halogenated hydrocarbons, especially dichloromethane. The reaction may take place at a temperature in the range from -30 to 100°C, usually from 0 to 30°C for 30 minutes to 24 hours, usually 12 to 16 hours at room temperature. The resulting product can be isolated and purified by standard techniques.

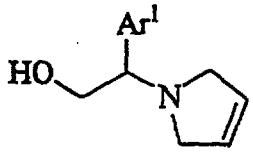
If required, the hydroxy protecting group in A of the compound (I) obtained (i.e., Y of -OY), can be removed by the appropriate method for the particular protecting group chosen. For example, a typical protecting group methoxymethyl, can be

removed by acid catalyzed hydrolysis in the presence of acid catalyst such as HCl. A further convenient protecting group in A is the tetrahydropyranyl group (THP). This can be also removed by acid-catalyzed hydrolysis. Appropriate acid catalysts are organic acids, inorganic acids, or Lewis acids such as acetic acid (AcOH), *p*-toluenesulfonic acid (*p*-TsOH), hydrochloric acid (HCl), and dimethylaluminium chloride (Me_2AlCl). Preferred acid catalyst is HCl.

An optically inactive compound (I) wherein Ar^1 is optionally substituted phenyl, can be prepared by subjecting a corresponding optically inactive 1-phenyl-1,2-ethanediol 2-tosylate of the formula (III) or 1-phenyl-2-pyrrolidinylethanol (Vb) to the reactions described in Scheme 1a. Optically inactive compounds (III), wherein Ar^1 is optionally substituted phenyl, may be prepared according to the procedures described in for example *Tetrahedron*, Vol. 47, pp. 9861-9866, 1991, *Cehm. Rev.*, Vol. 80, pp. 187-213, 1980 or *J. Org. Chem.*, Vol. 47, pp. 1229-1232, 1982, followed by tosylation such as reaction with *p*-toluanesulfonyl chloride in pyridine at 0°C. Optically inactive (Vb) can be prepared according to the procedures described for example in *Tetrahedron Lett.*, Vol. 35, pp. 1511-1514, 1994 followed by a conventional reduction.

A compound of the formula (I) wherein A is hydroxy, R^2 is alkoxy and R^3 is hydrogen, can be obtained from a methylbenzoate of formula (VII) wherein A is hydroxy. First the hydroxy group of the methylbenzoate compound may be protected with a suitable protecting group such as *tert*-butyldimethysilyl group. Second the hydroxy-protected methyl ester compound can be subjected to hydrolysis to give the corresponding carboxylic acid. Then the carboxylic acid can be subjected to amidation to give the compound (I). The hydroxy protection can be conducted by subjecting the compound of the formula (VII) in DMF to a reaction with *tert*-butyldimethylsilylchloride and immidazole solution at about 0 °C for 1 to 6 hours. The hydrolysis can be carried out in the presence of a base such as sodium hydroxide in a polar solvent such as methanol at about the reflux temperature of the solvent for from 1 to 10 hours. The amidation can be carried out with a desired O-alkylhydroxylamine in the presence of a carbodiimide such as WSC at room temperature for from 1 to 24 hours. If deprotection is required, a conventional procedures can be employed. For example, when the hydroxy group is protected with *tert*-butyldimethylsilyl group, the amide compound can be treated with tetrabutylammonium fluoride in a proper solvent such as THF at room temperature.

A compound of formula (I), wherein A is absent and the broken line is a double bond, can be also prepared by subjecting a 2-phenyl-2-(3-pyrrolin-1-yl)ethanol compound (Vc) and a benzamide compound to the coupling reactions illusrated in Scheme 1a.

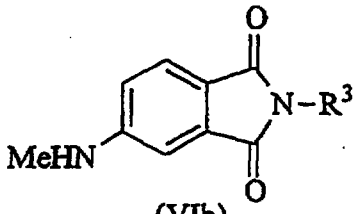


(Vc)

The ethanol coompound (Vc) can be prepared by reacting a corresponding phenylglicinol and 1,4-dichlorobutene in the presence of base such as Et_3N in a reaction inert solvent such as ethanol at the reflux temperature of the solvent for 1 to 24 hours.

A compound of the formula (I) wherein A is oxo (=O), can be prepared by oxidation of the corresponding pyrrolidinol compound. A suitable oxidation is Swern oxidation.

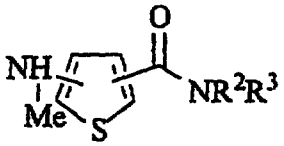
Further, the compounds of the formula (I) wherein $-Ar^2-C(=O)-N(R^2)-$, is a phthalimide group, can be prepared by using a compound of the formula (VIb):



(VIb)

instead of the compound (VIa) in the above-mentioned Scheme 1a.

Compounds of the formula (I) wherein Ar^2 is thienyl, can be prepared by using a methylaminothiophenecarboxamide of the formula (VIc):



(VIc)

instead of the compound (VIa) in the above-mentioned Scheme 1a. Compounds (VIc) can be prepared, first, by reacting a nitrothiophenecarboxaldehyde with the Jones reagent to give a nitrothiophenecarboxylic acid. Then, the carboxylic acid obtained can be subjected to condensation with a compound of the formula: NHR^2R^3, and then to

reduction of the nitro group with iron powder and ammonium chloride, followed by methylation of the amino group.

The compounds of formula (II), (III) and (IV) are either known compounds, which can be made by the known methods, or they are analogs of known compounds, which can be prepared by methods analogous to the known methods.

According to the well known procedures or the following procedures, R, S configuration of compounds (Va) and (Vb) can be selectively determined by subjecting a 3-pyrrolidinol with the corresponding R,S configuration.

Compounds of the fromula (Va) and (Vb) wherein A is fluorine and Ar^1 is phenyl, can be prepared from a commercially available 1-benzyl-3-pyrrolidinol. First, hydroxy group of the pyrrolidinol can be converted to an appropriate leaving group such as *p*-toluenesulfonate. The conversion can be achieved by subjecting the ptrrolidinol to the reaction with *p*-toluenesulfonyl chloride in pyridine. Second, the leaving group may be replaced by fluorine by a reaction with a suitable fluorinating agent such as tetrabutylammonium fluoride in a reaction inert solvent such as THF. Then, the 3-fluoropyrrolidine can be subjected to hydrogenation followed by a coupling with a stylene oxide of formula (II). The hydrogenation can be carried out in the presence of a suitable catalyst such as palladium hydroxide on carbon under hydrogen atmosphere in a reaction inert solvents such as EtOH at from 0°C to a room temperature for 5 minutes to 48 hours preferably 12 to 36 hours. The coupling reaction can take place in the absence or presence of a reaction inert solvent such as EtOH.

Compounds of the fromula (Va) and (Vb) wherein A is chlorine and Ar^1 is phenyl, can also be prepared from 1-benzyl-3-pyrrolidinol. For example, the 1-benzyl-3-pyrrolidinol can be subjected to chlorination to give 1-benzyl-3-chloropyrrolidine. The benzyl group of the 1-benzyl-3-chloropyrrolidine can be removed by treating the 1-benzyl-3-chloropyrrolidine with 1-chloroethyl chloroformate followed by coupling with styreneoxide of the formula (II). The chlorination 1-benzyl-3-pyrrolidinol can be carried out under a conventional condition, for example in the presence of a suitable reagent such as triphenylphosphine in a suitable solvent such as CCl_4 at room temperature. The debenzylation can be carried out accroding to the well known methods. The debenzylation is typically carried out in a reaction inert solvent such as dichloroethane at the reflux temperature of the solvent for 5 minutes to 3 hours. Then the solvent may be evapolated and the residue can be subjected to the coupling reaction

with styrene oxide in a suitable solvent such as EtOH at the reflux temperature of the solvent for 5 minutes to 4 hours.

Compounds (Va) and (Vb) wherein A is halo and Ar^1 is a optionally substituted phenyl, can be prepared from a desired N-protected 3-pyrrolidinol compound via the corresponding N-protected 3-halopyrrolidine. First, 1-benzyl-3-pyrrolidinol can be treated with a suitable halogenation reagent in a reaction inert solvent for example, triphenylphosphine in CCl_4 at the reflux temperature of the solvent for from 3 to 36 hours. Second, the 1-benzyl-3-chloropyrrolidine can be purified, and deprotection can be carried out under conditions known to skilled in the art (e.g., with 1-chloroethyl chloroformate in dichloroethane at 0°C for 30 minutes to 6 hours). Third, the 3-chloropyrrolidine can be treated with a styreneoxide compound to give the ethanols (Va) and (Vb) according to the procedures illustrated in Scheme 1a.

Methyl ester compounds of the formula (VIa), wherein Ar^2 is optionally substituted phenyl, are known compounds or can be prepared by treating a substituted 4-aminobenzoic acid compound with an alkylhalide in the presence of a base such as NaH or Na_2CO_3 in a reaction inert solvent such as DMF.

More specifically, the compounds of the formula (VIa) can be prepared by the following methods.

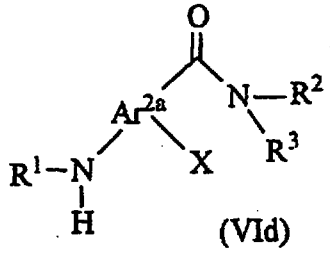
A: Methyl 3-methylaminobenzoate of the formula (VIa) can be prepared by first subjecting 3-acetamidebenzoic acid to methylation in the presence of a base such as NaH in a reaction inert solvent such as DMF, followed by deacetylation in the presence of an acid catalyst such as conc. sulfuric acid (H_2SO_4).

B: A compound of the formula (VIa) wherein Ar^2 is substituted by fluorine and R^1 is hydrogen, can be prepared from a nitrobenzoic acid by subjecting the nitrobenzoic acid to esterification followed by reduction. The esterification can be achieved in the presence of acid catalyst such as sulfuric acid in MeOH at the reflux temperature of the solvent for 1 to 12 hours. The reduction can be carried out in the presence of a reducing agent such as iron powder in a suitable solvent such as acetic acid at from room temperature to 60 °C for 0.5 to 6 hours. If desired, the amino group can be alkylated by a well known method. For example, first the methyl ester can be treated with trifluoroacetic anhydride in the presence of base such as Na_2CO_3 in a suitable solvent such as

CH_2Cl_2, then can be alkylated with a suitable alkylating agent such as iodomethane. A compound of the formula (VIa) wherein Ar^2 is substituted by chlorine and R^1 is alkyl, can be prepared from a chlorobenzoic acid by alkylation . The alkylation can be take place in the presence of a base such as NaH with a suitable alkyl halide in a reaction inert solvent such as DMF at about 0 °C for 1 to 24 hours.

C: A compound of the formula (VIa), wherein Ar^2 is pyridyl; the methylester group is on the 3-position and the R^1HN- is on the 6-position of the pyridine ring respectively, can be prepared by esterification of a 6-aminonicotic acid. The crude residue of the methyl ester obtained may be subjected to methylation of the amino group. A suitable esterificating agent is, for example, trimethylsilyldiazomethane. The methylation of the amino group can be carried out according to the same procedures of the above mentioned preparation of compounds (VIa).

Alternatively, an amide compound of the general formula (VId)



(VId)

wherein Ar^{2a}, X, R^1, R^2 and R^3 are defined as above, can be subjected to the coupling reaction with compounds (Va) and (Vb) to directly give a compound (I). This coupling reaction can be carried out in the absence or presence of a base such as NaH in a reaction inert solvent. The preferred solvents include EtOH and DMF. The reaction can be carried out at a temperature in the range of -78 °C to the reflux temperature of the solvent, preferably from room temperature to the reflux temperature, for 5 minutes to 48 hours, preferably 0.5 to 24 hours.

The amide compounds of the formula (VId) can be prepared according to the procedures described below.

A: A compound of the formula (VId) wherein Ar^{2a} is phenyl; R^1 is hydroxy and X is hydrogen, can be obtained by reduction of a known nitro N-alkylbenzamide compound. Suitable reducing agents include for example,

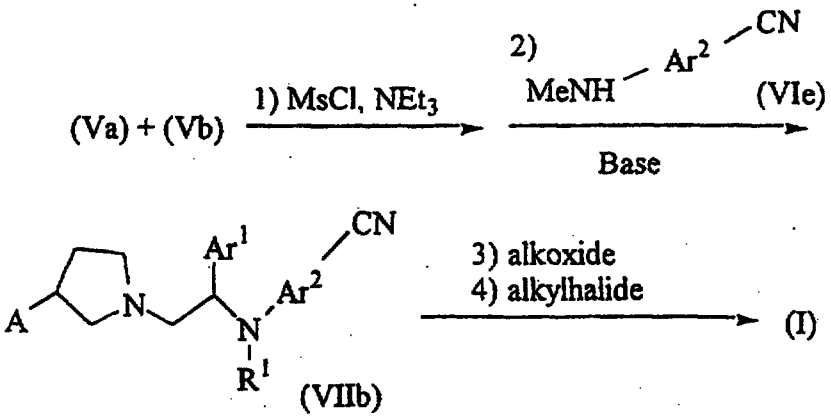
zinc powder. This reduction can be carried out by adding the reducing agent to a mixture of the nitro N-alkylbenzamide compound and ammonium chloride at about room temperature (e.g., 20-25°C) for from 1 to 3 hours.

B: A compound of the formula (VId) wherein Ar^{2a} is phenyl; R^1 is hydrogen or C_1-C_4 alkyl; R^2 is C_1-C_7 alkyl optionally substituted by hydroxy; R^3 is hydrogen and X is hydrogen or halo, may be prepared from a known amino benzoic acid compound, wherein the phenyl ring is optionally substituted by halo. The benzoic acid can be subjected to amidation under the similar conditions to those illustrated in Scheme 1a. If desired, the amino group of the benzamide compound obtained can be alkylated. For example, preferable alkylating agent is alkylhalide, and this alkylation can be carried out in the presence of base such as potassium carbonate at about room temperature for 12 to 24 hours.

C: An amide compound (VId) wherein Ar^{2a} is pyridyl, and -NHR^1 group is on the 5-position and the amide group is on the 2-position of the pyridine ring respectively, can be prepared by treating an amino-protected picolinic acid with oxalyl chloride followed by amidation with an desired alkyl amine. The treatment of the 5-protected-amino picolic acid and oxalyl chloride can be performed in a reaction inert solvent such as CH_2Cl_2 or DMF/CH_2Cl_2 in the presence of a base such as triethylamine at room temperature. The amidation can be carried out in the presence of a base in a reaction inert solvent. The base is preferably triethylamine and the reaction may be conducted in a suitable solvent, e.g., dichloroethane at about 15 °C. If required, the amino protecting group can be removed by the procedures known to those skilled in the art.

An alternative method to prepare the compounds of the formula (I) is illustrated in the following Scheme 1b.

Scheme 1b



The mixture of the compounds (Va) and (Vb) can be treated with methanesulfonyl chloride in a similar way as shown in Scheme 1a, followed by coupling with a cyano compound (VIe) to give the compound of the formula (VIIb). This coupling reaction can be carried out in a reaction inert solvent such as DMF or ethanol, in the presence or absence of base such as NaH, $NaNH_2$ or 2,6-lutidine. This reaction may take place at from room temperature to the reflux temperature of the solvent for 30 minutes to 12 hours.

Then, the compound (VIIb) may be reacted with a suitable alkoxide such as *t*-BuOK in the presence of water, in a polar solvent such as *t*-BuOH. This reaction may take place at reflux temperature of the solvent for 5 minutes to 6 hours. Then, a proper alkyl halide can be added to the resulting reaction mixture. The mixture thus obtained is refluxed for 5 minutes to 5 hours. The target compound (I) can be isolated and purified from a resulting reaction mixture by standard techniques.

Cyano compounds of the formula (VIe), wherein Ar^2 is a substituted phenyl can be prepared by treating known substituted 4-aminobenzonitrile compounds with NaH or K_2CO_3, followed by alkylation with an alkylhalide in a reaction inert solvent such as DMF.

The compounds of formula (I) of this invention are basic, and therefore they will form acid-addition salts. All such salts are within the scope of this invention. However, it is necessary to use an acid addition salts which is pharmaceutically-acceptable for administration to a mammal. The acid-addition salts can be prepared by standard methods, e.g., by contacting the basic and acidic compounds in substantially equivalent proportions in water or an organic solvent such as methanol or ethanol, or a mixture thereof. The salts can be isolated by evaporation of the solvent. Typical salts which can be formed are the hydrochloride, nitrate, sulfate, bisulfate, phosphate, acetate,

lactate, citrate, tartrate, succinate, malate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, p-toluenesulfonate, oxalate and pamoate (1,1'-methylene-bis-(2-hydroxy-3-naphtoate)) salts.

The compounds of formula (I) of this invention, wherein Ar^1 is phenyl substituted by carboxy-C_1-C_4 alkoxy are acidic, and they will form base salts. All such salts are within the scope of this invention. However, it is necessary to use a base salt which is pharmaceutically-acceptable for administration to a mammal. The base salts can be prepared by standard methods, e.g., by contacting the acidic and basic compounds in substantially equivalent proportions in water or an organic solvent such as methanol or ethanol, or a mixture thereof. The salts can be formed are the sodium, potassium, calcium and magnesium salts, and also salts with ammonia and amines, such as ethylamine, diethylamine, cyclohexylamine, piperidine or morpholine salts.

Also included within the scope of this invention are bioprecursors (also called as pro-drugs) of the kappa agonist compounds of the formula (I). A bioprecursor of a kappa agonist of formula (I) is a chemical derivative thereof which is readily converted back into the parent compound of formula (I) in biological systems. In particular, a bioprecursor of a kappa agonist of formula (I) is converted back to the parent compound of formula (I) after the bioprecursor has been administered to, and absorbed by, a mammalian subject, e.g., a human subject. For example, it is possible to make a bioprecursor of a kappa agonist of the invention of formula (I) in which one or both of A and R^1 is hydroxy groups by making an ester of the hydroxy group. When only one of A and R^1 is a hydroxy group, only mono-esters are possible. When both A and R^1 are hydroxy, mono- and di-esters (which can be the same or different) can be made. Typical esters are simple alkanoate esters, such as acetate, propionate, butyrate, etc. In addition, when A or R^1 is a hydroxy group, bioprecursors can be made by converting the hydroxy group to an acyloxymethyl derivative (e. g., a pivaloyloxymethyl derivative) by reaction with an acyloxymethyl halide (e. g., pivaloyloxymethyl chloride).

The kappa agonists compounds of the present invention of formula (I) exhibit significant agonist activity toward opioid kappa-receptor and are thus useful as an analgesic, anesthetic, anti-inflammatory agent or neuroprotective agent, and also useful in the treatment of arthritis, stroke or functional bowel disease such as abdominal pain, for the treatment of a mammalian subject, especially a human subject.

The activity of the kappa-agonists compounds of formula (I) of the present

invention, is demonstrated by the opioid receptor binding activity. Such activity may be determined in homogenate from guinea pig whole brain, as described by Regina, A. *et al.*,. in *J. Receptor Res.*, Vol. 12: pp. 171-180, 1992. In summary, tissue homogenate is incubated at 25°C for 30 min in the presence of labelled ligand and test compounds. The mu-sites are labelled by 1 nM of (3H)-[D-Ala2,MePhe4,Gly-ol5]enkephalin (DAMGO), the delta-sites by 1 nM of (3H)-[D-Pen2,5]enkephalin (DPDPE) and the kappa-sites by 0.5 nM (3H)-CI-977. The non specific binding is measured by use of 1μM CI-977 (kappa), 1μM (DAMGO) (mu), 1μM (DPDPE) (delta). Data are expressed as the IC_{50} values obtained by a non-linear fitting program using the Cheng and Prusoff equation. Some compounds prepared in the Examples showed a potent IC_{50} value against kappa receptor in the range of 0.01 to 100 nM.

The analgesic activity of the kappa-agonist compounds at the central nervous system can also be demonstrated by the Formalin Test as described by Wheeler-Aceto, H. *et al.* in *Psychopharmacology*, Vol. 104: pp. 35-44, 1991. In this testing, male SD rats (80-100 g) are injected s.c. with a test compound dissolved in 0.1% methyl cellulose saline or vehicle. After 30 min., 50μl of a 2% formalin are injected into a hind paw. The number of licking the injected paw per observation period is measured 15-30 min. after the injection of formalin and expressed as % inhibition compared to the respective vehicle group. Some compounds prepared in the Examples showed a potent ED_{50} value in the range of less than 25 mg/kg p.o.

The activity of the kappa agonists, against peripheral acute-pain, can be demonstrated by the Randall-Selitto assay (M. E. Planas, *Pain*, Vol.60, pp. 67-71, 1995). In this testing, Male SD rats (100-120 g) were used and the nociceptive threshold at the right paw was measured by Randall-Selitto (Ugo Basile) method. After three days of acclimation of assay condition, experiments were carried out. Hyperalgesia was induced by the intraplantar injection of a 0.1 ml/right paw of 1% solution of carrageenin. Painful pressure were delivered to the right plantar via a wedge-shaped piston and the level of response were measured at 3.5 and 4.5 hr later the carrageenin injection. Some compounds, prepared in the working examples as described below, were tested in accordance with the above procedures, and showed good activity against acute-pain (i.e., ED_{50} value of less than 10 mg/kg p.o.).

The activity of the kappa agonists, against chronic pain at the periphery, can be demonstrated by the adjuvant-induced hyperalgesia, according to the procedure

described by Judith S. Waker *et al.*, as reported in *Life Sciences*, Vol. 57, PP. 371-378, 1995. In this testing, male SD rats, weighing 180-230 g at the time of inoculation, were used. To produce adjuvant arthritis, rats were anesthetized with ether and inoculated intradermally into the footpad of the right hindpaw with 0.05 ml of Mycobacterium butyricum suspended in paraffin oil (2 mg/ml). Nociceptive threshold was evaluated by paw pressure test, using same procedures of the Randall-Selitto assay (as being described above), and edema was measured as the width of foot. Assays were done through the whole period.

The sedation function of kappa agonists can be determined by the Rotarod Test as described by Hayes, A.G. *et al.* in *Br. J. Pharmacol.*, Vol. 79, pp. 731-736, 1983. In this testing, a group of 6-10 male SD rats (100-120 g) are selected for their ability to balance on a rotating rod (diameter 9 cm, rate of rotation 5 r.p.m.). The selected rats are then injected s.c. with a test compound dissolved in 0.1% methyl cellulose saline. The animals are tested again 30 min. after treatment; a rat falling off the bar more than twice within 150 seconds is considered to be showing motor impairment and the animal's performance (i.e., time on the rotarod) are recorded. The ED_{50} value, defined as the dose of the drug which have the performance time is observed in the control group. Some compounds, prepared in the working examples as described below, were tested in accordance with the above procedures.

The diuresis function of the kappa agonists can be determined according to the procedure described by A. Barber *et al.*, (*Br. J. Pharmacol.*, Vol. 111, pp. 843-851, 1994). Some compounds, prepared in the working examples as described below, were tested in accordance with the above procedures.

The kappa agonists compounds of formula (I) of this invention can be administered via either the oral, parenteral or topical routes to mammals. A preferable dosage level may be in a range of from 0.01 mg to 10 mg per kg of body weight per day, although variations will necessarily occur depending upon the weight and condition of the subject being treated, the disease state being treated and the particular route of administration chosen. However, a dosage level that is in the range of from 0.01 mg to 1 mg per kg of body weight per day, single or divided dosage is most desirably employed in humans for the treatment of pain in a postoperative patient and a pain like hyperalgesia caused by chronic diseases.

The compounds of the present invention may be administered alone or in

combination with pharmaceutically acceptable carriers or diluents by either of the above routes previously indicated, and such administration can be carried out in single or multiple doses. More particularly, the novel therapeutic agents of the invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, trochees, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various nontoxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging 5% to 70% by weight, preferably 10% to 50% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dipotassium phosphate and glycine may be employed along with various disintegrants such as starch and preferably corn, potato or tapioca starch, alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatine capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene grycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of a compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH>8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intra-articular, intra-muscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques

well-known to those skilled in the art. Additionally, it is also possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

Examples and Preparations

The present invention is illustrated by the following examples and preparations. However, it should be understood that the invention is not limited to the specific details of these examples and preparations. Melting points were taken with a Buchi micro melting point apparatus and uncorrected. Infrared Ray absorption spectra (IR) were measured by a Shimadzu infrared spectrometer (IR-470). ^{1}H and ^{13}C nuclear magnetic resonance spectra (NMR) were measured in $CDCl_3$ by a JEOL NMR spectrometer (JNM-GX270, 270MHz) unless otherwise indicated and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane. The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad.

Preparation 1

2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol

To a stirred solution of (S)-(-)-1,2,4-butanetriol (10.61g, 0.1mol) in pyridine (50ml) was added *p*-toluenesulfonyl chloride (38.13g, 0.2mol) by portions at 0°C. After 14h stirring, the reaction mixture was poured into conc. HCl aqueous solution including ice and acidified to pH2. The mixture was extracted with ether (100ml x 3). The extract combined was washed with brine, dried (Na_2SO_4), and concentrated to give 18.58g of colorless oil. To a stirred solution of this crude ditosylate (18.58g, 45.7mmol) and dimethoxymethane (50ml) in CH_2Cl_2 (50ml) was added P_2O_5 by portions at rt (room temperature) and stirred for 26h. The CH_2Cl_2 layer was separated and the P_2O_5 (50g) solid was washed with CH_2Cl_2 (50ml x 4). The CH_2Cl_2 layer combined was washed with saturated $NaHCO_3$ aqueous solution and brine. After dry (Na_2SO_4), the solvent was evaporated to afford 18.01g of brown viscous oil. A mixture of this oil (18.00g,40mmol), R-(-)-2-phenylglycinol (4.80g, 35mmol), and Et_3N (11.3ml, 80mmol) in ethanol (20ml) was refluxed with stirring for 8h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (200ml). This solution was washed with saturated $NaHCO_3$ aqueous solution and brine, dried (Na_2SO_4), and concentrated to give 16.69g of brown viscous oil, which was purified by column chromatography (silica gel 200g, CH_2Cl_2/MeOH: 20/1) to afford 5.13g (20.4%, over all yield) of clear brown viscous oil.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.40-7.25 (5H, m), 4.62 (1H, d, J=7.0Hz), 4.58(1H, d, J=7.0Hz), 4.25-4.15 (1H, m), 3.88 (1H, dd, J=5.9, 10.6Hz), 3.80 (1H, dd, J=5.9, 10.6Hz), 3.50 (1H, t, J=5.9Hz), 3.33 (3H, s), 2.76 (1H, dt, J=6.2, 8.4Hz), 2.71 (1H, dd, J=5.9, 10.3Hz), 2.63 (1H, dd, J=3.3, 10.3Hz), 2.45 (1H, dt, J=6.2, 8.1Hz), 2.18 (1H, br. s), 2.16-2.02 (1H, m), 1.87-1.75 (1H, m).

IR(neat) : 3450cm^{-1} .

Preparation 2

2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol

A mixture of 3-(S)-methoxymethoxypyrrolidine (4.37g, 33.3mmol) and (S)-(-)-styrene oxide (4.00g, 33.3mmol) in EtOH (40ml) was refluxed with stirring for 2h. After evaporation of the solvent, the residue was purified by column chromatography (slicagel: 120g, CH_2Cl_2:MeOH=40:1-20:1) to give 4.91g (58.7%) of pale yellow oil as 0.65 to 0.35 mixture of title compounds.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.40-7.27 (5H, m), 4.68-4.63 (2.65H, m), 4.35-4.15 (1H, m), 3.90-3.75 (0.7H, m), 3.49 (0.35H, t, J=5.9Hz), 3.38 (1.95H,s), 3.32 (1.05H, s), 3.10-2.90 (1.3H, m), 2.80-2.40 (4H, m), 2.20-2.00 (1H, m), 1.95-1.75 (2H, m)

Preparation 3

2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol

A mixture of 3-(S)-methoxymethoxypyrrolidine (6.10g, 46.5mmol), (S)-(+)-1-phenyl-1,2-ethanediol-2-tosylate (13.6g, 46.5mmol) and K_2CO_3 (7.06g, 51.1mmol) in EtOH (80ml) was refluxed with stirring for 4.5h. After evaporation of the solvent, CH_2Cl_2 was added to the residue and washed with saturated $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4), and concentrated to give 14.94g of crude products, which was purified by column chromatography (slicagel: 150g, CH_2Cl_2/MeOH=50:1-20:1) to afford 7.75g (66.4%) of brown oil as 0.65 to 0.35 mixture of title compounds.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.40-7.27 (5H, m), 4.68-4.63 (2.65H, m), 4.35-4.15 (1H,

m), 3.90-3.75 (0.7H, m), 3.49 (0.35H, t, J=5.9Hz), 3.38 (1.95H,s), 3.32 (1.05H, s), 3.10-2.90 (1.3H, m), 2.80-2.40 (4H, m), 2.20-2.00 (1H, m), 1.95-1.75 (2H, m)

Preparation 4

2-(R)-Phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)ethanol and 1-(S)-Phenyl-2-(3-(S)- tetrahydropyran-2-yloxypyrrolidin-1-yl)ethanol

This was prepared from 3-(S)-tetrahydropyranyloxypyrrolidine (3.00g, 17.5mmol) and (S)-(-)-styrene oxide (2.10g, 17.5mmol) in 50% yield as 0.35 to 0.65 mixture of title compounds according to a procedure similar to that described in Preparation 2.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.50-7.20 (5H, m), 4.71 (0.65H, dd, J=3.3, 10.6Hz), 4.65-4.50 (1H, m), 4.45-4.25 (1H, m), 3.95-3.75 (1.7H, m), 3.60 - 3.42 (1.35H, m), 3.20-2.40 (5.3H, m), 2.25-1.45 (9H, m).

Preparation 5

2-(R)-Phenyl-2-pyrrolidin-1-yl-ethanol and 1-(S)-Phenyl-2-pyrrolidin-1-yl-ethanol

This was prepared from pyrrolidine (592mg, 8.32mmol) and (S)-(-)-styrene oxide (1.00g, 8.32mmol) in 96% yield as 0.3 to 0.7 mixture of title compounds according to a procedure similar to that described in Preparation 2.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.45-7.27 (5H, m), 4.70 (0.7H, dd, J=3.3, 10.6Hz), 3.87 (0.3H, dd, J=5.9, 10.6Hz), 3.81 (0.3H, dd, J=5.9, 10.6Hz), 3.47 (0.3H, t, J=5.9Hz), 2.90-2.70 (1.4H, m), 2.65-2.40 (4H, m), 1.90-1.60(5H, m).

Preparation 6

Methyl 3-methoxy -4-methylaminobenzoate

To a suspension of NaH (2.43g, 60.7mmol) in DMF (20ml) was added a solution of 4-amino-3-hydroxybenzoic acid (3.00g, 19.6mmol) in DMF(20ml) at 0°C. After stirring at room temperature for 1H, iodomethane (3.78ml, 60.7mmol) was added to this mixture at 0°C and stirred at room temperature for 16h. The mixture was poured into ice water and extracted with nHex : AcOEt : Et_2O =1 : 1: 1 (300ml). The extract was washed with water, brine, dried (Na_2SO_4), and concentrated to give brown

oil, which was purified by column chromato-graphy (silica gel 190g, nHex/AcOEt=10/1 and silica gel 35g, CH_2Cl_2 only) to afford 481mg (13%) of title compound.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.66 (1H, dd, J=1.8, 8.4Hz), 7.40 (1H, d, J=1.8Hz), 6.52 (1H, d, J=8.4Hz), 4.72 (1H, br. s), 3.89 (3H, s), 3.86 (3H, s), 2.91 (3H, d, J=5.1Hz).

Preparation 7

Methyl 2-methoxy -4-methylaminobenzoate

This was prepared from 4-amino-2-hydroxybenzoic acid (3.00g, 19.6mmol) in 22% yield according to a procedure similar to that described in Preparation 6.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.77 (1H, d, J=8.8Hz), 6.16 (1H, dd, J=2.2, 8.8Hz), 6.08 (1H, d, J=1.8Hz), 4.19 (1H, br. s), 3.88 (3H, s), 3.82 (3H, s), 2.89 (3H, d, J=5.1Hz).

Preparation 8

Methyl 2-chloro-4-methylaminobenzoate

This was prepared from 4-amino-2-chlorobenzoic acid (2.00g, 11.7mmol) in 13% yield according to a procedure similar to that described in Preparation 6.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.80 (1H, d, J=8.8Hz), 6.59 (1H, d, J=2.6Hz), 6.44 (1H, dd, J=2.6, 8.8Hz), 4.21 (1H, br. s), 3.86 (3H, s), 2.87 (3H, d, J=5.1Hz).

Preparation 9

3-Chloro-4-methylaminobenzonitrile

This was prepared from 4-amino-3-chlorobenzonitrile (2.00g, 13.1mmol) in 42% yield according to a procedure similar to that described in Preparation 6.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.50 (1H, d, J=1.8Hz), 7.43 (1H, dd, J=1.8, 8.4Hz), 6.61 (1H, d, J=8.4Hz),4.92 (1H, br. s), 2.96 (3H, d, J=5.1Hz).

Preparation 10

Methyl 6-methylaminonicotinate

To a suspension of 6-aminonicotinic acid (1.00g, 7.24mmol) in MeOH (20ml)

and MeCN (10ml) was added 10% solution of trimethylsilyldiazomethane in CH_2Cl_2 (25ml) at room temperature. After stirring at room temperature for 0.5 h, the solvent was evaporated to give crude methyl 6-aminonicotinate as a yellow solid. Title compound was prepared from this crude methyl 6-aminonicotinate in 17% yield according to a procedure similar to that described in Preparation 6.

^{1}H NMR (270MHz, $CDCl_3$) δ 8.75(1H, d, J=2.2Hz), 8.01(1H, dd, J=2.2, 8.8Hz), 6.36(1H, d, J=9.2Hz), 5.11(1H, br. s), 3.87(3H, s), 2.99(3H, d, J=5.5Hz).

Preparation 11

Methyl 3-methylaminobenzoate

To a suspension of NaH (1.54g, 38.5mmol) in DMF (20ml) was added a solution of 3-acetamidebenzoic acid (3.00g, 16.7mmol) in DMF (20ml) at 0°C. After stirring at room temperature for 0.5 h, iodomethane (2.40ml, 38.5mmol) was added to this mixture at 0°C and stirred at room temperature for 1.5 h. The mixture was poured into ice 6N-HCl aqueous solution and extracted with AcOEt : toluene = 2 : 1 (200 ml x 3). The extract was washed with water, brine, dried (Na_2SO_4), and concentrated to give 3.08g of brown oil. A mixture of this brown oil and cH_2SO_4 (5ml) in MeOH (30ml) was refluxed with stirring for 7h. After cooling down to room temperature, the solvent was evaporated. The residue was basified with saturated $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2. The extracted was washed with water, brine, dried (Na_2SO_4), and concentrated to give 2.31g (84 %) of brown oil.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.37 (1H, dt, J=1.4, 7.5Hz), 7.28-7.20 (2H, m), 6.78 (1H, ddd, J=0.73, 2.6, 8.1Hz), 3.89 (3H, s), 2.87 (3H, s).

Preparation 12

4-Amino-N'-propylphthalimide

To a suspension of NaH (493g, 12.3mmol) in DMF (10ml) was added a solution of 4-aminophthalimide (2.00g, 12.3mmol) in DMF (10ml) at 0°C. After stirring at room temperature for 1 h, iodopropane (1.20ml, 12.3mmol) was added to this mixture at 0°C and stirred at room temperature for 28 h. The mixture was poured into water and extracted with AcOEt : toluene = 2 : 1 (150ml x 3). The extract was washed

with water, brine, dried (Na_2SO_4), and concentrated to give yellow solid, which was purified by column chromatography (silica gel: 130g, CH_2Cl_2 only to CH_2Cl_2/MeOH=75/1) to give 1.14g (45%) of yellow solid.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.59 (1H, d, J=8.1Hz), 7.03 (1H, d, J=2.2Hz), 6.81 (1H, dd, J=2.2, 8.1Hz), 4.32 (2H, br. s), 3.65-3.55 (2H, m), 1.80-1.60 (2H, m), 0.93(3H,t, J=7.3Hz).

Preparation 13

4-Methylamino-N'-propylphthalimide

This was prepared from 4-amino-N'-propylphthalimide in 11% yield according to a procedure similar to that described in Preparation 12.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.59 (1H, d, J=8.4Hz), 6.96 (1H, d, J=2.2Hz), 6.71 (1H, dd, J=2.2, 8.4Hz), 4.50 (1H, br. s), 3.65-3.55 (2H, m), 2.95 (3H, d, J=5.1Hz), 1.80-1.60 (2H, m), 0.93 (3H,t, J=7.3Hz).

Preparation 14

5-Nitro-2-thiophenecarboxylic acid

To a solution of 5-nitro-2-thiophenecarboxaldehyde (1.00g, 6.24mmol) in acetone (50ml) was added Jones reagent (8N in acetone, 8.12ml, 65mmol) at -20°C. After stirring for 1H, 30ml of isopropanol was added to the mixture. H_2O was added to the mixture and extracted with CH_2Cl_2. The extract was washed with water, brine, dried (Na_2SO_4), and concentrated to give 967mg (90%) of yellow amorphous.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.88 (1H, d, J=4.4Hz), 7.66 (1H, d, J=4.0Hz), 5.14 (1H, br. s).

Preparation 15

5-Nitro-N-propyl-2-thiophenecarboxamide

To a solution of 5-nitro-2-thiophenecarboxylic acid (967mg, 5.59mmol) in DMF (0.745ml) and CH_2Cl_2 (4ml) was added oxalyl chloride at 0°C. After stirring for 0.5h at rt (room temperature), the solvent was evaporated below 30°C to give yellow oil

and solid. To a solution of n-propylamine (0.551ml, 6.71mmol) in Et_3N (1.87ml, 13.4mmol) and CH_2Cl_2 (25ml) was added a solution of crude acid chloride in CH_2Cl_2 (10ml) below 20°C. After stirring for 4h at rt, the mixture was washed with water, saturated $NaHCO_3$ aqueous solution, water, brine, dried (Na_2SO_4), and concentrated to give brown solid, which was purified by column chromatography (silica gel 50g, CH_2Cl_2/MeOH=100/1-30/1) to afford 815mg (68%) of white solid.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.85 (1H, d, J=4.0Hz), 7.35 (1H, d, J=4.4Hz), 6.12 (1H, br. s), 3.50-3.35 (2H, m), 1.75-1.55 (2H, m), 0.99 (3H,t, J=7.3Hz).

Preparation 16

5-Amino-N'-propyl-2-thiophenecarboxamide

A mixture of 5-nitro-N-propyl-2-thiophenecarboxamide (815mg, 3.81mmol), iron powder (1.06g, 19.0mmol) and NH_4Cl (102mg, 1.90mmol) in EtOH (12ml) and H_2O (6ml) was refluxed with stirring for 2h. The reaction mixture was filtered and washed with EtOH. The combined filtrate was evaporated. The residue was dissolved in AcOEt and washed with water, brine, dried (Na_2SO_4), and concentrated to give brown amorphous, which was purified by column chromatography (silica gel 40g, CH_2Cl_2/MeOH=40/1) to afford 411mg (59%) of brown amorphous.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.09 (1H, d, J=3.7Hz), 6.07 (1H, d, J=4.0Hz), 5.80-5.60 (1H, m), 4.14 (2H, br. s), 3.40-3.25 (2H, m), 1.70-1.50 (2H, m), 0.96 (3H,t, J=7.3Hz).

Preparation 17

5-Methylamino-N'-propyl-2-thiophenecarboxamide

To a solution of 5-amino-N'-propyl-2-thiophenecarboxamide (411mg, 2.23mmol) in CH_2Cl_2(12ml) was added Na_2CO_3 (710mg, 6.70mmol) and trifluoroacetic anhydride (0.631ml, 4.47mmol) at rt. After stirring for 5h, the solid was filtered off. The filtrate was washed with water and brine, dried (Na_2SO_4) and concentrated to give 396mg of yellow oil. To a solution of this oil in DMF (6.5ml) was added Na_2CO_3 (2.35g, 22.2mmol) and iodomethane (2.90ml, 46.6mmol) at rt. After stirring for 22h, the mixture was poured into ice 1N-HCl and extracted with AcOEt : toluene = 2 : 1. The extract was washed with water, brine, dried(Na_2SO_4), and concentrated to give

298mg of orange solid. To a solution of this solid in MeOH (3.5ml) was added 7% K_2CO_3 aqueous solution (1.8ml) at rt. After stirring for 18h, the solvent was evaporated. The residue was dissolved in AcOEt and water. The organic layer was washed with water, brine, dried (Na_2SO_4), and concentrated to give brown oil, which was purified by column chromatography(silica gel 15g, CH_2Cl_2/MeOH=60/1-40/1) to afford 122.5mg (44%) of title compound.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.16 (1H, d, J=4.0Hz), 5.89 (1H, d, J=4.4Hz), 5.68 (1H, br. s), 4.32 (1H, br. s), 3.40-3.30 (2H, m), 2.91 (3H, d, J=5.1Hz), 1.70-1.50 (2H, m), 0.96 (3H,t, J=7.3Hz).

Preparation 18

(S)-1-(3-Methoxymethoxyphenyl)-1,2-ethanediol

A mixture of 3-methoxymethoxystyrene (prepared by methoxymethylation of 3-hydroxystyrene in a standard manner) (1.54g, 9.39mmol), and AD-mix-α (13.18g, 9.41mmol) in water (48ml) and *t*-BuOH (48ml) was stirred at 0°C for 6.5h. To this reaction mixture was added Na_2SO_3 (14.13g) and the mixture was stirred at rt for 1H. The reaction mixture was extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4), and concentrated to give light brown oil, which was purified by column chromatography (silica gel: 90g, ethyl acetate/hexane:1/2-3/1) to afford 1.69g (91%) of desired product as colorless oil.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.25 (1H, dd, J=7.7, 8.1Hz), 7.03 (1H, d, J=1.8Hz), 6.98-6.92 (2H, m), 5.15 (2H, s), 4.74 (1H, dd, J=3.3, 8.1Hz), 3.71 (1H, br.d, J=9.9Hz), 3.65-3.55 (2H, m, including 1H, dd, J=8.1, 11.0Hz at 3.61ppm, CHCH2OH), 3.44 (3H, s), 3.14 (1H, br.s, OH).

Preparation 19

(S)-1-(3-Methoxymethoxyphenyl)-1,2-ethanediol-2-tosylate

To a stirred solution of (S)-1-(3-methoxymethoxyphenyl)-1,2-ethanediol (1.69g, 8.54mmol) in pyridine (20ml) was added p-toluenesulfonyl chloride (1.63g, 8.54mmol) and 4-dimethylaminopyridine (1.04g, 8.54mmol) at 0°C and the reaction mixture was stirred at 0°C to rt for 16h at 60°C for 1h. The reaction mixture was

acidified with 2N HCl aqueous solution and extracted with ethyl acetate. The extract was washed with water and brine, dried (Na_2SO_4), and concentrated to give brown oil, which was purified by column chromatography (silica gel: 150g, ethyl acetate/hexane:1/2 to 2/1) to afford 2.01g (67%) of desired product as colorless oil. Its optical purity was 98%ee by HPLC.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.77 (2H, d, J=8.4Hz), 7.34 (2H, d, J=8.1Hz), 7.25 (1H, dd, J=7.7, 8.4Hz), 7.00-6.92 (3H, m), 5.15 (2H, s), 4.95 (1H, ddd, J=3.3, 3.3, 8.4Hz), 4.15 (1H, dd, J=3.3, 10.3Hz), 4.03 (1H, dd, J=8.4, 10.3Hz), 3.46 (3H, s), 2.65 (1H, d, J=3.3Hz), 2.45 (3H, s).

Preparation 20

2-(R)-(3-Methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)ethanol and 1-(S)-(3-Methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)ethanol

This was prepared from (S)-1-(3-methoxymethyloxyphenyl)-1,2-ethanediol-2-tosylate in 79% yield as 0.25 to 0.75 mixture of title compounds according to a procedure similar to that described in Preparation 3.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.29-7.21 (1H, m), 7.09-6.91 (3H, m), 5.22-5.13 (2H, m), 4.80-4.55 (2.75H, m), 4.33-4.15 (1H, m), 3.90-3.72 (0.5H, m), 3.51-3.45 (0.25H, m), 3.48 (3H, s), 3.38 (2.25H, s), 3.33 (0.75H, s), 3.05-2.90 (1.5H, m), 2.80-2.43 (4H, m), 2.23-2.02 (1H, m), 1.95-1.70 (2H, m).

Preparation 21

(S)-1-(3-Chlorophenyl)-1,2-ethanediol

This was prepared from 3-chlorostyrene in 100% yield according to a procedure similar to that described in Preparation 18.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.40-7.20 (4H, m), 4.90-4.75 (1H, m), 3.85-3.75 (1H, m), 3.75-3.60 (1H, m), 2.66 (1H, d, J=2.9Hz), 2.20-2.05 (1H, m).

Preparation 22

(S)-1-(3-Chlorophenyl)-1,2-ethanediol-2-tosylate

This was prepared from (S)-1-(3-chlorophenyl)-1,2-ethanediol in 74% yield according to a procedure similar to that described in Preparation 19. Its optical purity was 98%ee by HPLC.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.76 (2H, d, J=8.1Hz), 7.32 (2H, d, J=8.4Hz), 7.31-7.17 (4H, m), 5.00-4.92 (1H, m), 4.14 (1H, dd, J=3.3, 10.6Hz), 4.02 (1H, dd, J=8.4, 10.6Hz), 2.63 (1H, d, J=3.7Hz), 2.46 (3H, s).

Preparation 23

2-(R)-(3-Chlorophenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)ethanol and 1-(S)-(3-Chlorophenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)ethanol

This was prepared from (S)-1-(3-chlorophenyl)-1,2-ethanediol-2-tosylate in 62% yield as 0.15 to 0.85 mixture of title compounds according to a procedure similar to that described in Preparation 3.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.40-7.20 (4H, m), 4.80-4.57 (2.85H, m), 4.32-4.15 (1H, m), 3.85-3.80 (0.3H, m), 3.48-3.40 (0.15H, m), 3.38 (2.55H, s), 3.34 (0.45H, s), 3.05-2.92 (1.7H, m), 2.80-2.62 (2H, m), 2.58-2.40 (2H, m), 2.23-2.05 (1H, m), 1.95-1.80 (1H, m).

Preparation 24

(R)-1-Benzyl-3-pyrrolidinol-tosylate

To a stirred solution of (R)-1-benzyl-3-pyrrolidinol (1.77g, 10mmol) in pyridine(30ml) was added p-toluenesulfonyl chloride (9.53g, 50mmol) by portions at 0°C. After 90h stirring at room temperature, water was added to the reaction mixture and the mixture was extracted with ether (150ml). The extract was washed with water, brine, dried(Na_2SO_4), and concentrated to give 3.06g (92%) of brown oil.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.76 (2H, d, J=8.4Hz), 7.31 (2H, d, J=8.4Hz), 7.35-7.20 (5H, m), 5.05-4.90 (1H, m), 3.61 (1H, d, J=12.8Hz), 3.54 (1H, d, J=12.8Hz), 2.76 (1H, dd, J=6.0, 11.2Hz), 2.75-2.60 (1H, m), 2.55-2.35 (2H, m), 2.44(3H, s), 2.12-2.05 (1H, m), 2.03-1.90 (1H, m).

Preparation 25

(S)-1-Benzyl-3-fluoropyrrolidine

To a solution of (R)-1-benzyl-3-pyrrolidinol-tosylate (3.06g, 9.24mmol) in THF (30 ml) was added 1.0M solution of tetrabutylammonium fluoride in THF (37.0 ml, 37.0 mmol) at room temperature. After 1.5h stirring at reflux temperature, water (150ml) was added to the reaction mixture and the mixture was extracted with ethyl acetate (100mlx2). The combined extract was washed with water, brine, dried (Na_2SO_4), and concentrated to give brown oil, which was purified by column chromatography (silica gel: 80g, CH_2Cl_2/MeOH:50/1) to afford 1.18g (71%) of brown oil.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.45-7.20 (5H, m), 5.29-5.00 (1H, m), 3.68 (1H, d, J=13.2Hz), 3.63 (1H, d, J=12.8Hz), 2.95-2.60 (3H, m), 2.55-2.38 (1H, m), 2.30-1.90 (2H, m).

Preparation 26

2-(3-(S)-Fluoropyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-Fluoropyrrolidin-1-yl)-2-(R)-phenylethanol

A suspension mixture of (S)-1-benzyl-3-fluoropyrrolidine (1.18g, 6.58mmol) and 20% palladium hydroxide on carbon (354mg) in EtOH (20ml) was stirred under hydrogen atmosphere at room temperature for 21.5h. After removal of the catalyst by Celite filtration, to this solution was added a solution of (S)-(-)-styrene oxide (791mg, 6.58mmol) in EtOH (5ml). The mixture was refluxed with stirring for 3.5h. After evaporation of the solvent, the residue was purified by column chromatography (slicagel: 80g, CH_2Cl_2:MeOH=40:1-30:1) to give 713mg (51.8%) of yellow oil as 0.7 to 0.3 mixture of title compounds.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.45-7.20 (5H, m), 5.35-5.05 (0.7H, m), 5.25-4.95 (0.3H, m), 4.71 (0.7H, dd, J=3.3, 10.6Hz), 3.95-3.75 (0.6H, m), 3.52 (0.3H, t, J=5.9Hz), 3.15-2.40 (5.4H, m), 2.30-1.80 (3H, m).

Preparation 27

2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(R)-phenylethanol and 2-(3-(S)-

Methoxymethoxypyrrolidin-1-yl)-2-(S)-phenylethanol

This was prepared from 3-(S)-methoxymethoxypyrrolidine and (R)-(-)-styrene oxide in 53% yield as 0.7 to 0.3 mixture of title compounds according to a procedure similar to that described in Preparation 2.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.40-7.20 (5H, m), 4.72 (0.7H, dd, J=3.3, 10.6Hz), 4.66 (0.7H, d, J=7.0Hz), 4.63 (0.7H, d, J=7.0Hz),4.63-4.56 (0.6H, m), 4.35-4.17 (1H, m), 3.92-3.77 (0.6H, m), 3.50 (0.3H, t, J=5.5Hz), 3.37 (2.1H,s), 3.33 (0.9H, s), 3.10-2.50 (5.4H, m), 2.25-2.00 (1H, m), 1.95-1.70 (2H, m)

Preparation 28

(R)-1-(3-Methoxymethoxyphenyl)-1,2-ethanediol

This was prepared from 3-methoxymethoxystyrene and AD-mix-β in 100% yield according to the procedures similar to those described in Preparation 18.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.31-7.25 (1H, m), 7.06-6.96 (3H, m), 5.18 (2H, s), 4.80 (1H, dd, J=3.7, 8.1Hz), 3.78 (1H, dd, J=3.7, 11.4Hz), 3.66 (1H, dd, J=8.1, 11.4Hz), 3.48 (3H, s).

Preparation 29

(R)-1-(3-Methoxymethoxyphenyl)-1,2-ethanediol-2-tosylate

This was prepared from (R)-1-(3-methoxymethoxyphenyl)-1,2-ethanediol in 77% yield according to the procedures similar to those described in Preparation 19.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.77 (2H, d, J=8.4Hz), 7.33 (2H, d, J=7.7Hz), 7.28-7.18 (1H, m), 7.00-6.92 (3H, m), 5.15 (2H, s), 5.00-4.90 (1H, m), 4.20-4.00(2H, m), 3.46 (3H, s), 2.80-2.60 (1H, m), 2.45 (3H, s).

97%ee(by HPLC)

Preparation 30

2-(R)-Phenyl-2-(3-pyrroline-1-yl)ethanol

This was prepared from R-(-)-2-phenylglycinol and cis-1,4-dichloro-2-butene

in 58% yield according to the procedures similar to those described in Preparation 1.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.36-7.29(5H, m), 5.77(2H, s), 3.83(2H, d, J=5.9Hz), 3.66(1H,m), 3.50(4H, s).

Preparation 31

(S)-1-Benzyl-3-pyrrolidinol-tosylate

This was prepared from (S)-1-benzyl-3-pyrrolidinol and p-toluenesulfonyl chloride in 98% yield according to the procedures similar to those described in Preparation 24.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.76(2H, d, J=8.4Hz), 7.33-7.26(7H, m), 4.97(1H, t, J=2.9Hz), 3.69-3.58(2H, m), 2.89-2.83(1H, m), 2.73-2.68(2H, m), 2.58-2.55(1H, m), 2.44(3H, s), 2.20-2.12(1H, m), 1.99-1.93(1H, m).

Preparation 32

(R)-1-Benzyl-3-fluoropyrrolidine

This was prepared from (S)-1-benzyl-3-pyrrolidinol-tosylate in 61% yield according to the procedures similar to those described in Preparation 25.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.33-7.23(5H, m), 5.28-5.04(1H, m), 3.71-3.61(2H, m), 2.91-2.67(3H, m), 2.50-2.42(1H, m), 2.24-2.00(2H, m).

Preparation 33

2-(3-(R)-Fluoropyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(R)-Fluoropyrrolidin-1-yl)-2-(R)-phenylethanol

This was prepared (R)-1-benzyl-3-fluoropyrrolidine in 76% over all yield as 0.6 to 0.4 mixture of title compounds according to the procedures similar to those described in Preparation 26.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.40-7.24(5H, m), 5.32-5.27(0.3H, m), 5.25-5.21(0.2H, m), 5.11-5.07(0.3H, m), 5.07-5.01(0.2H, m), 4.71(0.6H, dd, J=3.3, 10.3Hz), 3.90-3.78(0.6H, m), 3.55-3.51(0.4H, m), 3.13-2.44(5.4H, m), 2.23-1.94(2H, m).

Preparation 34

2-(3-(S)-Fluoropyrrolidin-1-yl)-1-(R)-phenylethanol and 2-(3-(S)-Fluoropyrrolidin-1-yl)-2-(S)-phenylethanol

This was prepared from 3-(S)-fluoropyrrolidine and (R)-(+)-styreneoxide in 72% yield as 0.7 to 0.3 mixture of the title compounds according to the procedures similar to those described in Preparation 26.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.39-7.24(5H, m), 5.31-5.28(0.35H, m), 5.28-5.22(0.15H, m), 5.12-5.07(0.35H, m), 5.06-5.01(0.15H, m), 4.73-4.68(0.7H, m), 3.88-3.79(0.7H, m), 3.54-3.50(0.3H, m), 3.13-2.44(5.3H, m), 2.20-1.93(2H, m).

Preparation 35

(S)-1-Benzyl-3-chloropyrrolidine

To a stirred solution of (R)-1-benzyl-3-pyrrolidinol (886mg, 5.0mmol) in CCl_4(20ml) was added triphenylphosphine(1.574g, 6.0mmol) at rt. After 20h stirring at reflux temperature, the solvent was evapolated. Saturated $NaHCO_3$ aqueous solution and water was added to the residue, and the mixture was extracted with AcOEt. The extract was brine, dried(Na_2SO_4), and concentrated to give brown oil, which was purified by column chromatography (silica gel; 100g, CH_2Cl_2/MeOH: 50/1-45/1) to give 706mg(72%) of pale yellow oil.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.33-7.23(5H, m), 4.42-4.33(1H, m), 3.73-3.61(2H, m), 3.09(1H, dd, J=6.6, 10.6Hz), 2.81-2.61(3H, m), 2.48-2.35(1H, m), 2.13-2.03(1H, m).

Preparation 36

2-(3-(S)-Chloropyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-Chloropyrrolidin-1-yl)-2-(R)-phenylethanol

To a stirred solution of (S)-1-benzyl-3-chloropyrrolidine(695mg, 3.55mmol) in dichloroethane(10ml) was added 1-chloroethyl chloroformate(0.38ml, 3.55mmol) at 0°C. The mixture was stirred at 0°C for 10min and refluxed for 1.5h. After cooling down to rt, the solvent was evapolated. The residue was dissolved in MeOH(5ml) and refluxed for 1h. After cooling down to rt, the solvent was evapolated to give 787mg of

brown solid.

Title compounds were prepared from the above solid and (S)-(-)-styreneoxide in 39% over all yield as 0.67 to 0.33 mixture of the title compounds according to the procedures similar to those described in Preparation 2.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.39-7.27(5H, m), 4.70(0.67H, dd, J=3.3, 10.3Hz), 4.45-4.40(0.67H, m), 4.38-4.32(0.33H, m), 3.91-3.02(2.33H, m), 2.88-2.56(4H, m), 2.50-2.31(1H, m), 2.17-2.03(1H, m).

Preparation 37

Methlyl 3-fluoro-4-nitrobenzoate

A mixture of 3-fluoro-4-nitrobenzoic acid(2.07g, 11.2mmol) and cH_2SO_4(0.5ml) in MeOH(10ml) was refluxed for 8h. The solvent was evapolated. The residue was dissolved in AcOEt and washed with saturated $NaHCO_3$ aqueous solution, water, brine, dried (Na_2SO_4), and concentrrated to give 2.14g(96%) of ivory solid.

^{1}H NMR (270MHz, $CDCl_3$) δ 8.15-8.07(1H, m), 7.99-7.96(1H, m), 7.95-7.92(1H, m), 3.99(3H, S).

Preparation 38

Methlyl 4-amino-3-fluorobenzoate

A mixture of methlyl 3-fluoro-4-nitrobenzoate(2.14g, 10.8mmol) and iron powder(2.63g) in acetic acid(22ml) was stirred at 50°C for 2.5h. After cooling down to room temperature, CH_2Cl_2(100ml) and water(300ml) was added to the mixture and filtered to remove iron powder. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2(70mlx2). The CH_2Cl_2 solution was combined, washed with water, brine, dried(Na_2SO_4), and concentrated to give 1.77g(97%) of pale brown solid.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.70-7.62(2H, m), 6.79-6.70(1H, m), 4.13(2H, br. s), 3.86(3H, S).

Preparation 39

Methlyl 3-fluoro-4-methylaminobenzoate

To a solution of methlyl 4-amino-3-fluorobenzoate(1.77g, 10.5mmol) in CH_2Cl_2(50ml) was added Na_2CO_3(3.33g, 31.4mmol) and trifluoroacetic anhydride(2.96ml, 20.9mmol) at room temperature. After stirring for 2.5h, the solid was filtered off. The filtrate was washed with water, brine, dried(Na_2SO_4), and concentrated to give 2.70g(97%) of white solid. To a solution of this solid(2.70g, 10.2mmol) in DMF(48ml) was added Na_2CO_3(16.9g, 160mmol) and iodomethane(20.8ml, 334mmol) at 0°C. After stirring for 2h at 0°C, for 1h at room temperature, the mixture was poured into 2NHCl with ice and extracted with AcOEt: toluene = 2:1(200mlx2). The extract was washed with water, brine, dried(Na_2SO_4), and concentrated to give 3.06g(quant) of brown oil. This oil was dissolved in MeOH(25ml) and 7%K_2CO_3 solution(12.5ml) was added at 0°C. After stirring for 2h at 0°C, for 4h at room temperature, 7%K_2CO_3 solution(12.5ml) was added. After stirring for 1.5h at room temperature, the mixture was acidified with 5NHCl and MeOH was evapolated. The residue was extracted with AcOEt. The extract was washed with water, brine, dried(Na_2SO_4), and concentrated to give 1.83g(98%) of pale brown solid.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.80-7.72(1H, m), 7.62(1H, dd, J=1.8, 12.5Hz), 6.63(1H, t, J=8.6Hz), 4.40(1H, br. s), 3.86(3H, S), 2.94(3H, d, J=5.1Hz).

Preparation 40

5-[N-(tert-Butoxycarbonyl)-N-methylamino]-N'-propylpicolinamide

To a solution of 5-[N-(tert-butoxycarbonyl)-N-methylamino]picolinic acid(1.93g, 7.66mmol) and triethylamine(1.60ml, 11.5mmol) in DMF(0.678ml) and CH_2Cl_2(14ml) was added oxalyl chloride(0.989ml, 11.3mmol) dropwise at room temperature. After stirring for 30min at room temperature, the solvent was evapolated. The residue was dissolved in CH_2Cl_2(14ml). This solution was added dropwise to a stirried, cooled solution of n-propylamine(0.756ml, 9.19mmol) and triethylamine(3.20ml, 23.0mmol) in CH_2Cl_2(28ml) while the temperature was kept below 15°C. After stirring for 15h at room temperature, the mixture was washed with water, brine, dried(Na_2SO_4), and concentrated to give brown oil, which was purified by column chromatography (silica gel; 100g, CH_2Cl_2/MeOH: 60/1) to give 1.82g(81%) of pale brown oil.

^{1}H NMR (270MHz, $CDCl_3$) δ 8.49(1H, d, J=2.6Hz), 8.16(1H, d, J=8.4Hz), 7.95(1H, br. s), 7.71(1H, dd, J=2.6, 8.4Hz), 3.50-3.40(2H, m), 3.32(3H, S), 1.75-1.55(2H, m), 1.48(9H, s), 1.00(3H, t, J=7.3Hz).

Preparation 41

5-N-Methylamino-N'-propylpicolinamide

A solution of 5-[N-(tert-butoxycarbonyl)-N-methylamino]-N'-propylpicolinamide(1.82g, 6.21mmol) in trifluoroacetic acid(30ml) was stirred at 0°C for 2h. After removal of the solvent, the residue was dissolved in CH_2Cl_2 and 25% ammonia solution. The organic layer was separated and washed with brine, dried(Na_2SO_4), and concentrated to give 1.20g(100%) of brown solid.

^{1}H NMR (270MHz, $CDCl_3$) δ 8.01(1H, d, J=8.4Hz), 7.88(1H, d, J=2.9Hz), 7.78(1H, br. s), 6.90(1H, dd, J=2.9, 8.4Hz), 4.17(1H, br. s), 3.45-3.35(2H, m), 2.91(3H, d, J=5.1Hz), 1.75-1.55(2H, m), 0.98(3H, t, J=7.3Hz).

Preparation 42

4-N-Hydroxyamino-N'-propylbenzamide

To a solution of 4-nitro-N-propylbenzamide(2.75g,13.2mmol) and ammonium chloride(812mg, 15.2mmol) in EtOH(20ml) and water(10ml) was added zinc powder(1.70g, 26.0mmol) portionwise with water cooling. After stirring for 30min at room temperature, zinc powder(0.50g, 7.65mmol) was added to the mixture and stirred for 30min at room temperature. The solid was removed through celite and washed with MeOH. The filtrate and washings were combined and concentrated to give yellow solid, which was purified by column chromatography (silica gel; 130g, CH_2Cl_2/MeOH: 25/1-10/1) to give 2.06g(80%) of ivory solid.

^{1}H NMR (270MHz, $CDCl_3$-DMSO-d6) δ 8.32(1H, d, J=2.2Hz), 7.72(2H, d, J=8.4Hz), 7.25-7.10(1H, m), 6.95(2H, d, J=8.8Hz), 3.45-3.30(2H, m), 2.91(1H, s), 1.70-1.55(2H, m), 0.96(3H, t, J=7.3Hz).

Preparation 43

4-Amino-2-chloro-N'-propylbenzamide

A mixture of 4-amino-2-chlorobenzoic acid(3.00g, 17.5mmol), n-propylamine(2.88ml, 35.0mmol) and WSC(6.71g, 35.0mmol) in CH_2Cl_2(35ml) was stirred at room temperature for 16h. The mixture was washed with water, brine, dried(Na_2SO_4), and concentrated to give brown oil, which was purified by column chromatography (silica gel; 180g, CH_2Cl_2/MeOH: 30/1-10/1) to give 2.32g(62%) of pale ivory solid.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.64(1H, d, J=8.4Hz), 6.64(1H, d, J=2.6Hz), 6.57(1H, dd, J=2.6, 8.4Hz), 6.44(1H, br. s), 3.97(2H, br. s), 3.50-3.30(2H, m), 1.75-1.55(2H, m), 0.99(3H, t, J=7.3Hz).

Preparation 44

2-Chloro-4-methylamino -N'-propylbenzamide

A mixture of 4-amino-2-chloro-N'-propylbenzamide(2.32g, 10.9mmol), iodomethane(0.68ml, 10.9mmol) and K_2CO_3(1.51g, 10.9mmol) in DMF(50ml) was stirred at room temperature for 20h. Water was added to the mixture and extracted with AcOEt : toluene=1 : 1. The extract was washed with water, brine, dried(Na_2SO_4), and concentrated to give pale brown solid, which was purified by column chromatography (silica gel; 120g, CH_2Cl_2/MeOH: 40/1) to give 887mg(36%) of pale brown solid.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.57(1H, d, J=8.4Hz), 6.80(1H, br. s), 6.53(1H, d, J=2.2Hz), 6.50(1H, dd, J=2.2, 8.4Hz), 5.00-4.80(1H, m), 3.45-3.30(2H, m), 2.82(3H, d, J=5.1Hz), 1.75-1.55(2H, m), 0.99(3H, t, J=7.3Hz).

Preparation 45

4-Methylamino -N'-(2-(S)-hydroxypropyl)benzamide

This was prepared from 4-(methylamino)benzoic acid and (S)-(+)-1-amino-2-propanol in 22% yield according to the procedures similar to those described in Preparation 43.

^{1}H NMR (270MHz, $CDCl_3$-DMSO-d6) δ 7.69(2H, d, J=8.4Hz), 7.14(1H, br. s),

6.56(2H, d, J=8.8Hz), 4.60-4.30(2H, m), 3.98-3.94(1H, m), 3.64-3.55(1H, m), 3.28-3.18(1H, m), 2.85(3H, s), 1.20(3H, d, J=6.2Hz).

Preparation 46

4-Methylamino -N'-(2-(R)-hydroxypropyl)benzamide

This was prepared from 4-(methylamino)benzoic acid and (R)-(-)-1-amino-2-propanol in 41% yield according to the procedures similar to those described in Preparation 43.

^{1}H NMR (270MHz, $CDCl_3$-DMSO-d6) δ 7.68(2H, dd, J=1.8, 7.0Hz), 7.12(1H, br. s), 6.55(2H, dd, J=1.8, 7.0Hz), 4.50(1H, br. s), 4.37(1H, br. s), 3.98-3.93(1H, m), 3.64-3.55(1H, m), 3.28-3.18(1H, m), 2.85(3H, d, J=4.8Hz), 1.20(3H, d, J=6.2Hz).

Preparation 47

4-Methylamino -N'-propylbenzamide

This was prepared from 4-(methylamino)benzoic acid and n-propylamine in 82% yield according to the procedures similar to those described in Preparation 43.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.63(2H, d, J=8.8Hz), 6.56(2H, d, J=8.8Hz), 6.05(1H, br. s), 4.11(1H, br. s), 3.45-3.30(2H, m), 2.86(3H, s), 1.70-1.50(2H, m), 0.97(3H, t, J=7.3Hz).

Preparation 48

4-[N-(Benzyloxycarbonyl)-N-methylamino]-N'-(2,2,3,3,3,-pentafluoropropyl)benzamide

To a solution of 4-[N-(benzyloxycarbonyl)-N-methylamino]benzoic acid (100mg, 0.351mmol) in CH_2Cl_2(1ml) was added oxalyl chloride(0.122ml, 1.40mmol) and DMF(0.026ml) at room temperature. After stirring for 4h at room temperature, the solvent was evapolated. The residue was dissolved in CH_2Cl_2(10ml). To this solution was added 2,2,3,3,3-pentafluoropropylamine(523mg, 3.51mmol) and triethylamine(0.372ml, 2.67mmol) at room temperature. After stirring for 18h at room temperature, saturated $NaHCO_3$ aqueous solution was added to the mixture and extracted with CH_2Cl_2. The extract was washed with brine, dried(Na_2SO_4), and

concentrated to give brown oil, which was purified by column chromatography (silica gel; 30g, CH_2Cl_2 only-CH_2Cl_2/MeOH: 50/1) to give 532mg(72%) of title compound.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.75(2H, d, J=8.8Hz), 7.39-7.31(7H, m), 6.42-6.31(1H, m), 5.19(2H, s), 4.17(2H, ddd, J=6.2, 14.7, 14.7Hz), 3.36(3H, s).

Preparation 49

4-[N-(Benzyloxycarbonyl)-N-methylamino]-N'- tert-amylbenzamide

This was prepared from 4-[N-(benzyloxycarbonyl)-N-methylamino]benzoic acid and tert-amylamine in 22% yield according to the procedures similar to those described in Preparation 48.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.69 (2H, d, J=8.4Hz), 7.32-7.29 (7H, m), 5.86-5.75 (1H, m), 5.17(2H, s), 3.33(3H, s), 1.88-1.80(2H, m), 1.40(6H, s), 0.89(3H, t, J=7.3Hz).

Preparation 50

4-[N-(Benzyloxycarbonyl)-N-methylamino]-N'- tert-butylbenzamide

This was prepared from 4-[N-(benzyloxycarbonyl)-N-methylamino]benzoic acid and tert-butylamine in 93% yield according to the procedures similar to those described in Preparation 48.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.69 (2H, d, J=8.8Hz), 7.32-7.29 (7H, m), 5.89 (1H, br. s), 5.17(2H, s), 3.33(3H, s), 1.46(9H, s).

Preparation 51

4-Methylamino-N'-(2,2,3,3,3,-pentafluoropropyl)benzamide

A suspension mixture of 4-[N-(benzyloxycarbonyl)-N-methylamino]-N'-(2,2,3,3,3,-pentafluoropropyl)benzamide(532mg, 1.28mmol) and 10% palladium carbon(41mg) in MeOH(5ml) was stirred under hydrogen atmosphere at room temperature for 6h. The catalyst was removed through Celite and washed with MeOH. The filtrate and washings were combined and concentrated to give 345mg(96%) of title compound.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.66 (2H, d, J=8.4Hz), 6.58 (2H, d, J=8.4Hz), 6.15-6.12(1H, m), 4.23-4.09(3H, m), 2.89(3H, d, J=4.4Hz).

Preparation 52

4-Methylamino-N'-tert-amylbenzamide

This was prepared from 4-[N-(benzyloxycarbonyl)-N-methylamino]-N'-tert-amylbenzamide in 88% yield according to the procedures similar to those described in Preparation 51.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.58(2H, d, J=8.4Hz), 6.56(2H, d, J=8.8Hz), 5.70(1H, br. s), 4.00(1H, br. s), 2.87(3H, s), 1.83(2H, q, J=7.7Hz), 1.39(6H, s), 0.89(3H, t, J=7.7Hz).

Preparation 53

4-Methylamino-N'-tert-butylbenzamide

This was prepared from 4-[N-(benzyloxycarbonyl)-N-methylamino]-N'-tert-butylbenzamide in 100% yield according to the procedures similar to those described in Preparation 51.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.58(2H, d, J=8.4Hz), 6.56(2H, d, J=8.8Hz), 5.78(1H, br. s), 2.86(3H, s), 1.45(9H, s).

Example 1

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

(i) Methyl 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoate

To a stirred solution of the mixture of 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol (2.01g, 8.00mmol) and triethylamine (1.34ml, 9.60mmol) in CH_2Cl_2 (35ml) was added methanesulfonyl chloride (0.744ml, 9.60mmol) dropwise at 0°C (ice bath). After 5.5h stirring at room temperature, the reaction mixture was washed with saturated $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4), and concentrated to give

2.16g of brown viscous oil. To this oil was added Methyl 4-methylaminobenzoate (1.45g, 8.80mmol) and ethanol (16ml) and the mixture was stirred at reflux temperature for 1.5h. The solvent was evaporated. The residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ aqueous solution and brine, dried (Na_2SO_4), and concentrated to give brown oil, which was purified by column chromato-graphy (silica gel 150g, CH_2Cl_2/MeOH: 100/1-35/1) to afford 1.99g(62.5%) of brown oil.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.89 (2H, d, J = 9.2Hz), 7.35-7.20 (5H, m), 6.78 (2H, d, J=9.2Hz), 5.17 (1H, dd, J = 6.6, 8.1Hz), 4.59 (1H, d, J = 7.0Hz), 4.55 (1H, d, J = 7.0Hz), 4.22-4.12 (1H, m), 3.85 (3H, s), 3.30 (3H, s), 3.10 (1H, dd, J = 6.2, 12.8Hz), 3.03 (1H, dd, J = 8.4, 12.8Hz), 2.86 (3H, s), 2.85-2.80 (1H, m), 2.77-2.67 (1H, m), 2.65-2.53(2H, m), 2.05 (1H, ddd, J = 7.5, 13.9, 13.9Hz), 1.83-1.70(1H, m).

(ii) 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid

A mixture of methyl 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoate (1.99g, 5.00mmol) and 4N-NaOH (12.5ml, 50.0mmol) in MeOH (35ml) was stirred at 75°C for 3h. The mixture was neutrallized with 5N-HCl at 0°C. The solvent was removed in vacuo. CH_2Cl_2 was added to the residue and insoluble solid was removed by filtration. The filtrate was concentrated to give 2.04g (quant) of pale brown amorphous.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.93 (2H, d, J = 8.8Hz), 7.40-7.10 (5H, m), 6.81 (2H, d, J = 9.2Hz), 5.85 (1H, br. s), 5.26 (1H, dd, J = 6.2, 8.1Hz), 4.60 (1H, d, J = 7.0Hz), 4.56 (1H, d, J = 7.0Hz), 4.25-4.15 (1H, m), 3.30 (3H, s), 3.20-3.05 (2H, m), 2.97 (1H, dd, J = 6.2, 9.9Hz), 2.87 (3H, s), 2.80-2.65 (3H, m), 2.15-2.00 (1H, m), 1.90-1.75 (1H, m)

(iii) 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

To a stirred solution of 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid (2.04g, 5.00mmol) and n-propylamine (0.822ml, 10.0mmol) in CH_2Cl_2 (35ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.92g, 10mmol) at room temperature.

After 15.5hr stirring, the reaction mixture was washed with water and brine, dried(Na_2SO_4), and concentrated to give brown oil, which was purified by column chromatography (silica gel; 100g, CH_2Cl_2/MeOH: 25/1) to give 1.52g(72%) of pale brown amorphous.

^1H NMR (270MHz, $CDCl_3$) δ 7.65 (2H, d, J = 8.8Hz), 7.35-7.20 (5H, m), 6.79 (2H, d, J = 9.2Hz), 6.05-5.90 (1H, m), 5.14 (1H, dd, J = 6.6, 8.1Hz), 4.59 (1H, d, J = 7.0Hz), 4.55 (1H, d, J = 7.0Hz), 4.24-4.10 (1H,m), 3.39 (2H, dd, J=6.6, 13.9Hz), 3.30 (3H, s), 3.14-2.96 (2H, m), 2.90-2.80 (1H, m), 2.85 (3H, s), 2.78-2.52 (3H, m), 2.14-1.96 (1H, m), 1.84-1.70 (1H, m), 1.68-1.56 (2H, m), 0.97 (3H, t, J=7.3Hz)

Example 2

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

A mixture of 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide (1.52g, 3.58mmol) and 10% HCl in MeOH (25ml) was stirred at room temperature for 6h. The solvent was evaporated. The residue was basified with 25% ammonium hydroxide, extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4) and concentrated to give pale brown amorphous, which was purified by column chromatography (silica gel; 65g, CH_2Cl_2/MeOH: 20/1-15/1) to give 1.21g (89%) of pale brown amorphous.

^1H NMR (270MHz, free amine, $CDCl_3$) δ 7.66 (2H, d, J=9.2Hz), 7.40-7.20 (5H, m), 6.81 (2H, d, J=9.2Hz), 6.05-5.90 (1H, m), 5.15 (1H, dd, J=5.9, 9.2Hz), 4.28-4.16 (1H, m), 3.46-3.32 (2H, m), 3.13 (1H, dd, J=9.2, 12.8Hz), 3.03 (1H, dd, J=5.9, 12.8Hz), 2.90 (1H, ddd, J=5.0, 8.5, 8.5Hz), 2.84 (3H, s), 2.73 (1H, d, J=9.9Hz), 2.56 (1H, dd, J=4.6, 9.7Hz), 2.32 (1H, ddd, J=6.1, 9.0, 9.0Hz), 2.18-2.00 (1H, m), 1.90-1.50 (4H, m), 0.98 (3H, t, J=7.3Hz)

600mg of this amorphous was dissolved in 10% HCl in MeOH (10ml). The solvent was concentrated to give 625mg of HCl salt as pale brown amorphous.

IR(KBr) : 3300, 1610cm^{-1}.

MS m/z: 382(M+H)$^+$

Anal. Calcd for $C_{23}H_{31}N_3O_2 \cdot HCl \cdot 1.5H_2O$: C, 62.08 ; H, 7.93; N, 9.44.

Found : C, 62.29 ; H, 8.01 ; N, 9.42 .

Example 3

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-methylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and methylamine hydrochloride in 26% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.64 (2H, d, J=8.8Hz), 7.40-7.20 (5H, m), 6.79(2H, d, J=8.8Hz), 6.02 (1H, br. s), 5.13 (1H, dd, J=6.6, 8.1Hz), 4.59 (1H, d, J=7.0Hz), 4.55 (1H, d, J=6.6Hz), 4.20-4.13 (1H, m), 3.30 (3H, s), 3.15-3.00 (2H, m), 2.97 (3H, d, J=5.1Hz), 2.90-2.80 (1H, m), 2.83 (3H, s), 2.75-2.55 (3H, m), 2.05 (1H, ddd, J=7.7, 14.3, 13.9Hz), 1.90-1.70 (1H, m)

Example 4

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-methylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-methylbenzamide in 82% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.66 (2H, d, J=9.2Hz), 7.40-7.20 (5H, m), 6.81 (2H, d, J=8.8Hz), 6.00-5.95 (1H, m), 5.15 (1H, dd, J=6.0, 9.0Hz), 4.25-4.20 (1H, m), 3.13 (1H, dd, J=9.2, 12.8Hz), 3.03 (1H, dd, J=5.9, 12.8Hz), 2.98 (3H, d, J=5.1Hz), 2.95-2.80 (1H, m), 2.83 (3H, s), 2.74 (1H, d, J=9.9Hz), 2.55 (1H, dd, J=4.6, 9.7Hz), 2.35-2.25 (1H, m), 2.17-2.05 (1H, m), 1.80-1.60 (2H, m)

HCl salt: amorphous solid.

1R(KBr) : 3350, 1610cm^{-1}.

Anal. Calcd for $C_{21}H_{27}N_3O_2 \cdot HCl \cdot 1.2H_2O$: C, 61.29 ; H, 7.45 ; N, 10.21

Found : C,61.68 ; H, 7.84 ; N,10.20.

Example 5

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-ethylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and ethylamine hydrochloride in 33% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.64 (2H, d, J=8.8Hz), 7.34-7.24 (5H, m), 6.79 (2H, d, J=8.8Hz), 5.95-5.83 (1H, m), 5.13 (1H, dd, J=7.0, 7.5Hz), 4.59 (1H, d, J=7.0Hz), 4.55 (1H, d, J=6.6Hz), 4.25-4.14 (1H, m), 3.52-3.42 (2H, m), 3.30 (3H, s), 3.10-3.01 (2H, m), 2.89-2.80 (1H, m), 2.83 (3H, s), 2.75-2.53 (3H, m), 2.11-2.01 (1H, m), 1.80-1.74 (1H, m), 1.23 (3H, t, J=7.1Hz)

Example 6

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-ethylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-ethylbenzamide in 43% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.65 (2H, d, J=8.8Hz), 7.34-7.23 (5H, m), 6.80 (2H, d, J=8.8Hz), 6.01 (1H, br.s), 5.14 (1H, dd, J=6.2, 8.8Hz), 4.22-4.18 (1H, m), 3.50-3.40 (2H, m), 3.11 (1H, dd, J=8.8, 12.8Hz), 3.02 (1H, dd, J=5.9, 12.8Hz), 2.92-2.85 (1H, m), 2.82 (3H, s), 2.70 (1H, d, J=9.5Hz), 2.57 (1H, dd, J=4.8, 9.9Hz), 2.37-2.29 (1H, m), 2.12-2.01 (2H, m), 1.68-1.60 (1H,m), 1.21 (3H, t, J=7.3Hz)

HCl salt: amorphous solid.

IR(KBr) : 3350, 1610cm^{-1}.

Anal. Calcd for $C_{22}H_{29}N_3O_2 \cdot HCl \cdot 4H_2O$: C, 55.72 ; H, 7.70; N, 8.97

Found : C, 55.51 ; H, 8.05 ; N, 8.83.

Example 7

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-butylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and *n*-butylamine in 40% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.63 (2H, d, J=9.2Hz), 7.34-7.24 (5H, m), 6.79 (2H, d, J=9.2Hz), 6.00-5.85 (1H, m), 5.12 (1H, dd, J=6.6, 7.1Hz), 4.59 (1H, d, J=6.6Hz), 4.55 (1H, d, J=6.6Hz), 4.19-4.15 (1H, m), 3.50-3.40 (2H, m), 3.29 (3H, s), 3.07-3.02 (2H, m), 2.90-2.80 (1H, m), 2.84 (3H, s), 2.72-2.57 (3H, m), 2.08-2.01 (1H, m), 1.78-1.60 (1H, m), 1.58-1.36 (4H, m), 0.94 (3H, t, J=7.3Hz)

Example 8

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-butylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-butylbenzamide in 59% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.65 (2H, d, J=8.8Hz), 7.35-7.24 (5H, m), 6.80 (2H, d, J=8.8Hz), 5.82-5.78 (1H, m), 5.15 (1H, dd, J=5.9, 8.8Hz), 4.26-4.24 (1H.m), 3.43 (2H, dd, J=7.0, 12.8Hz), 3.13 (1H, dd, J=8.8, 12.8Hz), 3.03 (1H, dd, J=6.2, 12.8Hz), 2.93-2.85 (1H, m), 2.84 (3H, s), 2.73 (1H, d, J=9.5Hz), 2.56 (1H, dd, J=4.8, 9.5Hz), 2.37-2.28 (1H, m), 2.10-2.06 (1H, m), 1.72-1.52 (4H, m), 1.47-1.25 (2H, m), 0.95 (3H, t, J=7.3Hz)

HCl salt: amorphous solid.

IR(KBr) : 3350, 1610cm^{-1}.

MS m/z: 396$(M+H)^+$.

Anal. Calcd for $C_{24}H_{33}N_3O_2 \cdot HCl \cdot 1.4H_2O$: C, 63.05; 8.11; N, 9.19

Found : C, 63.06 ; H, 8.04 ; N, 8.98.

Example 9

Preparation of 4-{N-[1-(S)-Phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)-

ethyl]-N-methylamino}-N'-pentylbenzamide

This was prepared from 2-(R)-phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)ethanol and 1-(S)- phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)ethanol in 33% over all yield according to a procedure similar to that described in Example 1 (i)-(iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.70-7.60 (2H, m), 7.40-7.20 (5H, m), 6.79 (2H, d, J=8.8Hz), 6.00-5.90 (1H, m), 5.20-5.10 (1H, m), 4.60-4.55 (0.6H, m), 4.50-4.40 (0.4H, m), 4.35-4.20 (1H, m), 3.90-3.72 (1H, m), 3.50-3.35 (3H, m), 3.15-2.90 (3H, m), 2.84 (1.8H, s), 2.83 (1.2H, s), 2.80-2.50 (3H, m), 2.20-1.95 (1H, m), 1.90-1.25 (13H,m), 0.91 (3H, t, J=7.0Hz).

Example 10

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-pentylbenzamide

This was prepared from 4-{N-[1-(S)-phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)ethyl]-N-methylamino}-N'-pentylbenzamide in 98% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.65 (2H, d, J=9.2Hz), 7.40-7.20 (5H, m), 6.81 (2H, d, J=8.8Hz), 6.00-5.90 (1H, m), 5.16 (1H, dd, J=6.0, 9.0Hz), 4.26-4.18 (1H.m), 3.50-3.37 (2H, m), 3.13 (1H, dd, J=9.2, 12.8Hz), 3.03 (1H, dd, 6.3, 12.8Hz). 2.93-2.80 (1H, m), 2.84 (3H, s), 2.73 (1H, d, J=9.2Hz), 2.56 (1H, dd, J=4.8, 9.5Hz), 2.37-2.28 (1H, m), 2.17-2.00 (1H, m), 1.90-1.55 (4H, m), 1.50-1.30 (4H, m), 0.93 (3H, t, J=7.3Hz)

HCl salt: amorphous solid.

1R(KBr) : 3350, 1610cm^{-1}.

Anal. Calcd for $C_{25}H_{35}N_3O_2 \cdot HCl \cdot 0.25H_2O$: C, 66.65 ; H, 8.17; N, 9.33

Found : C, 66.57 ; H, 8.47 ; N,9.31.

Example 11

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-isopropylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and isopropylamine in 15% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.63 (2H, d, J=9.2Hz), 7.34-7.21 (5H, m), 6.78 (2H, d, J=9.6Hz), 5.75-5.72 (1H, m), 5.12 (1H, dd, J=6.2, 8.8Hz), 4.59 (1H, d, J=6.6Hz), 4.55 (1H, d, J=6.6Hz), 4.30-4.23 (1H, m), 4.18-4.14 (1H, m), 3.30 (3H, s), 3.06-3.03 (2H, m), 2.90-2.80 (1H,m), 2.85 (3H, s), 2.81-2.72 (1H, m), 2.66-2.57 (2H, m), 2.08-2.01 (1H, m), 1.79-1.76 (1H, m), 1.23 (6H, d, J=6.6Hz)

Example 12

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-isopropylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-isopropylbenzamide in 80% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.64 (2H, d, J=8.8Hz), 7.34-7.22 (5H, m), 6.80 (2H, d, J=8.8Hz), 5.79-5.77 (1H, m), 5.15 (1H, dd, J=6.2, 8.8Hz), 4.30-4.19 (2H, m), 3.13 (1H, dd, J=9.2, 12.8Hz), 3.03 (1H, dd, J=6.2, 12.8Hz), 2.93-2.84 (1H, m), 2.82 (3H, s), 2.72 (1H, d, J=9.5Hz), 2.57 (1H, dd, J=4.8, 9.9Hz), 2.38-2.29 (1H, m), 2.14-2.02 (2H, m), 1.68-1.58 (1H, m), 1.23 (6H, d, J=6.6Hz)

HCl salt: amorphous solid.

1R(KBr) : 3350, 1610cm^{-1}.

MS m/z: 382$(M+H)^+$.

Anal. Calcd for $C_{23}H_{31}N_3O_2 \cdot HCl \cdot 1.9H_2O$: C, 61.09 ; H, 7.98; N, 9.29

Found : C, 61.16 ; H, 7.61 ; N, 9.12.

Example 13

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-phenylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and aniline in 48% yield according to a

procedure similar to that described in Example 1(iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.63 (2H, d, J=8.8Hz), 7.69 (1H, br. s), 7.62 (2H, d, J=7.7Hz), 7.40-7.24 (7H, m), 7.11 (1H, t, J=7.3Hz), 6.88-6.80 (2H, m), 5.18 (1H, dd, J=7.7, 15.0Hz), 4.60 (1H, d, J=7.0Hz), 4.56 (1H, d, J=7.0Hz), 4.25-4.10 (1H, m), 3.31 (3H, s), 3.15-3.05 (2H, m), 2.89 (3H, s), 2.95-2.80 (1H, m), 2.80-2.55 (3H, m), 2.15-2.00 (1H, m), 1.90-1.70 (1H, m)

Example 14

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-phenylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-phenylbenzamide in 16% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.84 (1H, br. s), 7.76 (2H, d, J=8.8Hz), 7.66-7.60 (2H, m), 7.40-7.24 (7H, m), 7.10 (1H, t, J=7.3Hz), 6.84 (2H, d, J=9.2Hz), 5.18 (1H, dd, J=6.2, 8.8Hz), 4.30-4.17 (1H, m), 3.15 (1H, dd, J=9.2, 12.8Hz), 3.05 (1H, dd, J=5.9, 12.8Hz), 3.00-2.85 (1H, m), 2.85 (3H, s), 2.74 (1H, d, J=9.5Hz), 2.59 (1H, dd, J=4.8, 9.5Hz), 2.45-2.30 (1H, m), 2.25 (1H, br. s), 2.15-2.00 (1H, m), 1.80-1.60 (1H, m)

HCl salt: amorphous solid.

1R(KBr) : 3400, 1600cm^{-1}.

Anal. Calcd for $C_{26}H_{29}N_3O_2 \cdot HCl \cdot H_2O$: C, 66.44 ; H, 6.86; N, 8.94

Found : C, 66.33 ; H, 7.16 ; N, 8.86.

Example 15

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-chlorobenzyl)benzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and 2-chlorobenzylamine in 88% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.68 (2H, d, J=9.2Hz), 7.50-7.20 (9H, m), 6.80 (2H, d, J=9.2Hz), 6.50-6.40 (1H, m), 5.13 (1H, dd, J=6.6, 8.1Hz), 4.71 (2H, d, J=5.9Hz), 4.59 (1H, d, J=7.0Hz), 4.54 (1H, d, J=7.0Hz), 4.22-4.10 (1H, m), 3.29 (3H, s), 3.15-2.97 (2H, m), 2.87-2.80 (1H, m), 2.85 (3H, s), 2.75-2.52 (3H, m), 2.13-1.98 (1H, m), 1.85-1.70(1H, m)

Example 16

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-chlorobenzyl)benzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-chlorobenzyl)benzamide in 98% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.68 (2H, d, J=8.8Hz), 7.50-7.20 (9H, m), 6.79 (2H, d, J=8.8Hz), 6.50-6.40 (1H, m), 5.14 (1H, dd, J=6.0, 9.0Hz), 4.71 (2H, d, J=5.9Hz), 4.25-4.20 (1H, m), 3.12 (1H, dd, J=8.8, 12.8Hz), 3.03 (1H, dd, J=6.2, 12.8Hz), 2.95-2.80 (1H, m), 2.84 (3H, s), 2.72 (1H,d, J=9.9Hz), 2.56 (1H, dd, J=4.4, 9.9Hz), 2.40-2.32 (1H, m), 2.16-2.00 (1H, m), 1.80-1.55 (2H, m)
HCl salt: amorphous solid.
1R(KBr) : 3300, 1630, 1605cm^{-1}.
Anal. Calcd for $C_{27}H_{30}N_3O_2Cl \cdot HCl \cdot H_2O \cdot 0.3C_3H_8O$: C, 62.46 ; H, 6.65; N, 7.83
Found : C, 62.51 ; H, 7.02 ; N, 7.94.

Example 17

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N',N'-dimethylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and dimethylamine hydrochloride in 71% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.50-7.20 (7H, m), 7.00-6.75 (2H, m), 5.35-5.25 (1H,m), 4.62 (1H, d, J=7.0Hz), 4.58 (1H, d, J=6.6Hz), 4.35-4.20 (1H, m), 3.40-3.20 (2H, m), 3.32 (3H, s), 3.15-3.30 (1H, m), 3.07 (6H, s), 2.95-2.70 (2H, m), 2.81 (3H, s), 2.25-

2.05 (1H,m), 2.00-1.80 (1H, m), 1.80-1.55 (1H, m)

Example 18

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N',N'-dimethylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N',N'-dimethylbenzamide in 88% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.37 (2H, d, J=8.8Hz), 7.35-7.20 (5H, m), 6.79 (2H, d, J=9.2Hz), 5.13 (1H,dd, J=6.0, 9.0Hz), 4.25-4.17 (1H, m), 3.18-2.98 (2H, m), 3.07 (6H, s), 2.91 (1H, ddd, J=5.1, 8.4, 8.4Hz), 2.81 (3H, s), 2.74 (1H,d, J=9.2Hz), 2.55 (1H, dd, J=4.8, 9.5Hz), 2.37-2.25 (1H, m), 2.20-2.00 (1H, m), 1.80-1.55 (2H, m)

HCl salt: amorphous solid.

1R(KBr) : 3400, 1610cm^{-1}.

Anal. Calcd for $C_{22}H_{29}N_3O_2 \cdot HCl \cdot H_2O$: C, 62.62 ; H, 7.64; N,9.96

Found : C, 62.52 ; H, 7.86 ; N, 9.98.

Example 19

Preparation of 4-{N-[1-(S)-Phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-methyl-N'-propylbenzamide

This was prepared from 2-(R)-phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)ethanol and 1-(S)-phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)ethanol in 32% over all yield according to a procedure similar to that described in Example 1 (i)-(iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.40-7.20 (7H, m), 6.77 (2H, d, J=8.8Hz), 5.11 (1H, dd, J=7.0, 7.7Hz), 4.60-4.55 (0.6H, m), 4.53-4.47 (0.4H, m), 4.38-4.25 (1H, m), 3.90-3.75 (1H, m), 3.55-3.30 (3H, m), 3.15-2.92 (2H, m), 3.03 (3H, s), 2.81 (1.8H, s), 2.80 (1.2H, s), 2.80-2.70 (1H, m), 2.68-2.50 (3H, m), 2.15-1.95 (1H, m), 1.90-1.45 (9H, m), 1.00-0.80 (3H, m).

Example 20

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-methyl-N'-propylbenzamide

This was prepared from 4-{N-[1-(S)-phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)ethyl]-N-methylamino}-N'-methyl-N'-propylbenzamide in 83% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.40-7.20 (7H, m), 6.79 (2H, d, J=8.8Hz), 5.11 (1H, dd, J=6.2, 8.8Hz), 4.28-4.16 (1H, m), 3.46-3.32 (2H, m), 3.18-2.98 (1H, m), 3.03 (3H, s), 2.90 (1H, ddd, J=5.1, 8.4, 8.5Hz), 2.81 (3H, s), 2.78-2.70 (1H, m), 2.56 (1H, dd, J=4.6, 9.7Hz), 2.32 (1H, ddd, J=6.2, 9.2, 9.2Hz), 2.18-2.00 (1H, m), 1.90-1.50 (4H, m), 1.00-0.80 (3H,m)

HCl salt: amorphous solid.

1R(KBr) : 3350, 1610cm^{-1}.

Anal. Calcd for $C_{24}H_{33}N_3O_2 \cdot HCl \cdot 0.75H_2O$: C, 64.70 ; H, 8.03; N,9.43

Found : C, 64.68 ; H, 8.39 ; N, 9.49.

Example 21

Preparation of 3-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

(i) Methyl-3-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoate

This was prepared from 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol and methyl 3-methylaminobenzoate in 78% yield according to a procedure similar to that described in Example 1 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.51-7.48 (1H, m), 7.39-7.34 (1H, m), 7.33-7.20 (6H, m), 7.04-6.98 (1H, m), 5.15-5.05 (1H, m), 4.59 (1H, d, J = 7.0Hz), 4.55 (1H, d, J=7.0Hz), 4.20-4.10 (1H, m), 3.89 (3H, s), 3.30 (3H, s), 3.15-2.97 (2H, m), 2.90-2.80 (1H, m), 2.82 (3H, s), 2.77-2.55 (3H, m), 2.12-1.98 (1H,m), 1.83-1.60 (1H, m)

(ii) 3-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid

This was prepared from methyl 3-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-

yl)-1-(S)-phenylethyl]-N-methylamino}benzoate in 100% yield according to a procedure similar to that described in Example 1 (ii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.98 (1H, br. s), 7.47 (1H, d, J=7.7Hz), 7.30-7.10 (6H, m), 6.82 (1H, d, J=2.2, 8.4Hz), 5.70-5.60 (1H, m), 4.63 (1H, d, J = 6.6Hz), 4.59 (1H, d, J=6.6Hz), 4.40-4.30 (1H, m), 4.04 (1H, br. s), 3.77 (1H, dd, J=5.9, 11.7Hz), 3.68-3.58 (1H, m), 3.48-3.28 (2H, m), 3.32 (3H, s), 3.12-3.00 (1H, m), 2.96-2.84 (1H, m), 2.71 (3H, s), 2.26-2.12 (1H, m), 2.06-1.92 (1H,m)

(iii) 3-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 3-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and n-propylamine in 78% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.34-7.19 (7H, m), 6.98 (1H, d, J=7.3Hz), 6.91 (1H, dd, J=2.2, 8.1Hz), 6.22 (1H, br. s), 5.16-5.06 (1H, m), 4.57 (1H, d, J = 6.6Hz), 4.53 (1H, d, J=6.6Hz), 4.22-4.12 (1H, m), 3.46-3.32 (2H, m), 3.28 (3H, s), 3.16-2.96 (1H, m), 2.81 (3H, s), 2.86-2.52 (4H, m), 2.14-1.98 (1H,m), 1.82-1.56 (4H, m), 0.98 (3H, t, J=7.3Hz)

Example 22

Preparation of 3-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 3-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide in 90% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.42-7.37 (1H, m), 7.36-7.19 (6H, m), 6.97 (1H, d, J=7.7Hz), 6.92 (1H, dd, J=2.6, 8.1Hz), 6.21 (1H, br. s), 5.13 (1H, dd, J=5.9, 8.8Hz), 4.26-4.14 (1H, m), 3.48-3.32 (2H, m), 3.18-3.00 (2H, m), 2.92 (1H, ddd, J=4.8, 8.4, 8.4Hz), 2.86-2.72 (1H, m), 2.78 (3H, s), 2.50 (1H, dd, J=4.8, 9.9Hz), 2.36-2.22 (1H, m), 2.20-2.02 (1H, m), 2.00-1.70 (2H,m), 1.63 (2H, ddd, J=7.3, 14.7, 14.7Hz), 0.98 (3H, t, J=7.3Hz)

HCl salt: brown powder.

mp: 105-114°C

IR(KBr) : 3350, 1635cm^{-1}.

MS m/z: 381(M^+).

Anal. Calcd for $C_{23}H_{31}N_3O_2 \cdot HCl \cdot 0.7H_2O \cdot 0.3C_6H_{14}O$: C,64.58 ; H, 8.22; N, 9.11

Found : C, 64.42 ; H, 8.54 ; N, 9.34.

Example 23

Preparation of 2-Chloro-4-{N-[1-(S)-phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)ethyl]-N-methylamino}-N'-propylbenzamide

(i) Methyl 2-chloro-4-{N-[1-(S)-phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)-ethyl]-N-methylamino}benzoate

This was prepared from 2-(R)-phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)ethanol and 1-(S)-phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)ethanol and methyl 2-chloro-4- methylaminobenzoate in 40% yield according to a procedure similar to that described in Example 1 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.86-7.80 (1H, m), 7.38-7.22 (5H, m), 6.83-6.78 (1H, m), 6.72-6.65 (1H, m), 5.10 (1H, dd, J=6.6, 7.7Hz), 4.60-4.55 (0.6H, m), 4.50-4.45 (0.4H, m), 4.38-4.22 (1H, m), 3.86 (3H, s), 3.85-3.75 (1H, m), 3.50-3.37 (1H, m), 3.13-2.90 (3H, m), 2.85 (1.8H, s), 2.84 (1.2H, s), 2.80-2.50 (3H, m), 2.20-1.95 (1H, m), 1.95-1.40 (7H, m).

(ii) 2-Chloro-4-{N-[1-(S)-phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)ethyl]-N-methylamino}benzoic acid

This was prepared from methyl 2-chloro-4-{N-[1-(S)-phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)ethyl]-N-methylamino}benzoate in 100% yield according to a procedure similar to that described in Example 1 (ii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.86-7.75 (1H, m), 7.38-7.22 (5H, m), 6.80-6.60 (2H, m), 5.20-5.10 (1H, m), 4.60-4.55 (0.6H, m), 4.50-4.45 (0.4H, m), 4.38-4.22 (1H, m), 3.85-3.37 (3H, m), 3.20-3.00 (2H, m), 2.80-2.50 (4H, m), 2.69 (3H, s), 2.20-1.95 (1H, m), 1.95-1.40 (7H, m).

(iii) 2-Chloro-4-{N-[1-(S)-phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 2-chloro-4-{N-[1-(S)-phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)ethyl]-N-methylamino}benzoic acid and n-propylamine in 68% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.78-7.72 (1H, m), 7.38-7.22 (5H, m), 6.79-6.70 (2H, m), 6.60-6.48 (1H, m), 5.07 (1H, dd, J=6.6, 7.3Hz), 4.60-4.55 (0.6H, m), 4.50-4.45 (0.4H, m), 4.38-4.22 (1H, m), 3.90-3.75 (1H, m), 3.50-3.37 (3H, m), 3.13-2.90 (2H, m), 2.82 (3H, s), 2.80-2.50 (4H, m), 2.20-1.95 (1H, m), 1.95-1.40 (9H, m), 0.99 (3H, t, J=7.3Hz).

Example 24

Preparation of 2-Chloro-4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 2-chloro-4-{N-[1-(S)-phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide in 89% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.76 (1H, d, J=8.8Hz), 7.40-7.20 (5H, m), 6.75 (1H, dd, J=2.6, 8.8Hz), 6.72 (1H, d, J=2.6Hz), 6.54 (1H, br. s), 5.07 (1H, dd, J=5.9, 9.2Hz), 4.30-4.20 (1H, m), 3.46-3.35 (2H, m), 3.12 (1H, dd, J=9.2, 12.8Hz), 3.01 (1H, dd, J=6.0, 13.0Hz), 2.95-2.78 (1H, m), 2.83 (3H, s), 2.72 (1H, d, J=9.9Hz), 2.58 (1H, dd, J=4.8, 9.5Hz), 2.35 (1H, ddd, J=6.0, 8.9, 9.0Hz), 2.18-2.00 (1H, m), 1.90-1.50 (4H, m), 0.99(3H, t, J=7.7Hz)

HCl salt: amorphous solid.

1R(KBr) : 3350, 1600cm^{-1}.

Anal. Calcd for $C_{23}H_{30}N_3O_2Cl \cdot HCl \cdot 0.2H_2O$: C, 60.58 ; H, 6.94; N, 9.21

Found : C, 60.29 ; H, 7.13 ; N, 9.13.

Example 25

Preparation of 2-Methoxy-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

(i) Methyl 2-methoxy-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoate

This was prepared from 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol and methyl 2-methoxy-4-methylaminobenzoate in 41% yield according to a procedure similar to that described in Example 1 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.79 (1H, d, J = 9.2Hz), 7.36-7.20 (5H, m), 6.40 (1H, dd, J = 2.4, 8.9Hz), 6.27 (1H, d, J=2.6Hz), 5.13 (1H, dd, J = 7.0, 8.1Hz), 4.60 (1H, d, J = 7.0Hz), 4.56 (1H, d, J = 6.6Hz), 4.25-4.15 (1H,m), 3.86 (3H, s), 3.82 (3H, s), 3.30 (3H, s), 3.14-2.96 (2H, m), 2.87 (3H, s), 2.90-2.80 (1H, m), 2.78-2.52 (3H, m), 2.14-1.96 (1H, m), 1.84-1.70 (1H, m)

(ii) 2-Methoxy-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid

This was prepared from methyl 2-methoxy-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoate in 100% yield according to a procedure similar to that described in Example 1 (ii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.98 (1H, d, J = 8.8Hz), 7.38-7.16 (5H, m), 6.54 (1H, dd, J = 2.4, 9.0Hz), 6.35-6.25 (1H,m), 5.20-5.05 (1H, m), 4.60 (1H, d, J = 7.0Hz), 4.56 (1H, d, J = 7.0Hz), 4.25-4.15 (1H,m), 3.99 (3H, s), 3.30 (3H, s), 3.14-3.05 (2H, m), 2.91 (3H, s), 2.90-2.52 (4H, m), 2.14-2.00 (1H, m), 1.90-1.70 (1H, m),

(iii) 2-Methoxy-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 2-methoxy-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and n-propylamine in 84% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 8.07 (1H, d, J = 8.8Hz), 7.78-7.68 (1H, m),7.36-7.20 (5H, m), 6.51 (1H, dd, J = 2.4, 9.0Hz), 6.27 (1H, d, J=2.2Hz), 5.11 (1H, dd, J = 6.6, 8.1Hz), 4.60 (1H, d, J = 7.0Hz), 4.56 (1H, d, J = 6.6Hz), 4.25-4.15 (1H,m), 3.89 (3H, s), 3.45-3.35 (2H, m), 3.30 (3H, s), 3.14-2.96 (2H, m), 2.86 (3H, s), 2.90-2.80 (1H, m), 2.78-2.52 (3H, m), 2.14-1.96 (1H, m), 1.84-1.70 (1H, m), 1.68-1.50 (2H, m), 0.97 (3H, t, J=7.3Hz)

Example 26

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-2-methoxy-N'-propylbenzamide

This was prepared from 2-methoxy-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide in 85% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 8.07 (1H, d, J = 8.8Hz), 7.78-7.68 (1H, m), 7.38-7.22 (5H, m), 6.53 (1H, dd, J = 2.2, 8.8Hz), 6.27 (1H, d, J=2.2Hz), 5.13 (1H, dd, J = 6.2, 8.4Hz), 4.30-4.20 (1H,m), 3.89 (3H, s), 3.45-3.35 (2H, m), 3.20-3.00 (2H, m), 2.95-2.80 (1H, m), 2.85 (3H, s), 2.74 (1H,d, J=9.5Hz), 2.58 (1H, dd, J=4.8, 9.5Hz), 2.40-2.27 (1H, m), 2.18-2.02 (1H, m), 1.95- 1.55 (4H, m), 0.97 (3H, t, J=7.3Hz)
HCl salt: amorphous solid.
1R(KBr) : 3400, 1600cm^{-1}.
Anal. Calcd for $C_{24}H_{33}N_3O_3 \cdot HCl \cdot 0.8CH_4O$: C, 62.89 ; H, 7.92; N, 8.87
Found : C, 63.16 ; H, 8.32 ; N, 9.20.

Example 27

Preparation of 3-Methoxy-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

(i) Methyl 3-methoxy-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoate

This was prepared from 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol and methyl 3-methoxy-4-methylaminobenzoate in 60% yield according to a procedure

similar to that described in Example 1 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.58-7.53 (2H, m), 7.31-7.20 (5H, m), 6.71 (1H, d, J=8.4Hz), 5.13 (1H, t, J = 7.3Hz), 4.59 (1H, d, J = 7.0Hz), 4.55 (1H, d, J = 7.0Hz), 4.15-4.05 (1H,m), 3.95 (3H, s), 3.89 (3H, s), 3.30 (3H, s), 3.09 (2H, d, J=7.3Hz), 2.87 (1H, dd, J=6.2, 9.9Hz), 2.60 (3H, s), 2.60-2.52 (2H, m), 2.47 (1H, dd, J=4.0, 9.9Hz), 2.08-1.92 (1H, m), 1.73-1.60 (1H, m)

(ii) 3-Methoxy-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid

This was prepared from methyl 3-methoxy-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoate in 100% yield according to a procedure similar to that described in Example 1 (ii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.52-7.45(2H, m), 7.32-7.12 (5H, m), 6.65 (1H, d, J=8.4Hz), 5.47 (1H, dd, J = 6.6, 7.0Hz), 4.64 (1H, d, J = 7.0Hz), 4.60 (1H, d, J = 6.6Hz), 4.45-4.35 (1H,m), 4.02 (3H, s), 3.85-3.70 (3H, m), 3.68-3.57 (1H, m), 3.32 (3H, s), 3.30-3.05 (2H, m), 2.64 (3H, s), 2.40-2.23 (1H, m), 2.15-2.00 (1H, m)

(iii) 3-Methoxy-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 3-methoxy-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and n-propylamine in 64% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.45 (1H, d, J = 1.8Hz), 7.32-7.18 (5H, m), 7.11 (1H, dd, J=1.8,8.4Hz), 6.66 (1H, d, J = 8.1Hz), 6.15-6.05 (1H,m), 5.03 (1H,t, J=7.7Hz), 4.59 (1H, d, J = 7.0Hz), 4.54 (1H, d, J = 7.0Hz), 4.15-4.05 (1H,m), 3.96 (3H, s), 3.45-3.35 (2H, m), 3.30 (3H, s), 3.08 (2H, d, J=7.7Hz), 2.95-2.85 (1H, m), 2.65-2.50 (2H, m), 2.57 (3H, s), 2.46 (1H, dd, J=4.4, 9.9Hz), 2.10-1.90 (1H, m), 1.75-1.55 (3H, m), 0.99 (3H, t, J=7.3Hz)

Example 28

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-3-methoxy-N'-propylbenzamide

This was prepared from 3-methoxy-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide in 77% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.48 (1H, d, J = 2.2Hz), 7.37-7.22 (5H, m), 7.12 (1H, dd, J=2.2, 8.4Hz), 6.72 (1H, d, J = 8.4Hz), 6.15-6.05 (1H,m), 5.16 (1H,dd, J=6.6, 8.8Hz), 4.15-4.05 (1H,m), 3.97 (3H, s), 3.45-3.35 (2H, m), 3.23 (2H, dd, J=8.8, 12.5Hz), 2.99 (1H, dd, J=6.4, 12.3Hz), 2.80-2.70 (1H, m), 2.59 (3H, s), 2.45 (1H, dd, J=4.4, 9.9Hz), 2.20-1.90 (2H, m), 1.75-1.40 (4H, m), 0.99 (3H, t, J=7.3Hz)
HCl salt: amorphous solid.
IR(KBr) : 3350, 1630cm^{-1}.

Example 29

Preparation of 3-chloro-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

(i) 3-chloro-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzonitrile

To a stirred solution of the mixture of 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol (251mg, 1.00mmol) and triethylamine (0.167ml, 1.20mmol) in CH_2Cl_2 (4ml) was added methanesulfonyl chloride (0.093ml, 1.20mmol) dropwise at 0°C (ice bath). After 15.5h stirring at room temperature, the reaction mixture was washed with saturated $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4), and concentrated to give 238mg of brown viscous oil-(i). To a suspension of NaH (48mg, 1.20mmol) in N,N-dimethylformamide (2ml) was added a solution of 3-chloro-4-methylaminobenzonitrile (200mg, 1.20mmol) at room temperature. After stirring for 45min, to this mixture was added a solution of the above brown viscous oil-(i) in N,N-dimethylformamide (2ml) at room temperature and the mixture was stirred at room temperature for 4.5h. H_2O was added to this mixture, basified with 25%-NH_4OH and extracted with CH_2Cl_2. The

extract was washed with water, brine, dried (Na_2SO_4), and concentrated to give brown oil, which was purified by column chromatography (silica gel 20g, CH_2Cl_2/MeOH: 100/1-50/1) to afford 244mg (61%) of brown oil.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.61 (1H, d, J=2.2Hz), 7.43-7.25 (6H, m), 6.98 (1H, d, J=8.4Hz), 5.03 (1H, dd, J = 7.3, 7.7Hz), 4.58 (1H, d, J = 6.6Hz), 4.54 (1H, d, J = 6.6Hz), 4.10-3.97 (1H,m), 3.31 (3H, s), 3.10 (2H, dd, J=1.5, 7.7Hz), 2.75-2.65 (1H, m), 2.69 (3H, s), 2.55-2.43 (3H, m), 2.03-1.85 (1H, m), 1.70-1.60 (1H, m)

(ii) 3-Chloro-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

To a suspension of *t*-BuOK (381mg, 3.05mmol) and H_2O (0.055ml, 3.05mmol) in *t*-BuOH (1.0ml) was added a solution of 3-chloro-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzonitrile (244mg, 0.611mmol) in *t*-BuOH (1.0ml) at room temperature. After refluxing for 0.5h, the mixture was allowed to cool to room temperature. *n*-Propyliodide (0.298ml, 3.05mmol) was added to the mixture, and the mixture was refluxed for 3h. After cooling down to room temperature, the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and washed with water and brine, dried (Na_2SO_4), and concentrated to give pale brown oil, which was purified by column chromatography (silice gel; 15g, CH_2Cl_2/MeOH: 80/1-50/1) to give 206 mg (73%) of ivory amorphous.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.77 (1H, d, J = 2.2Hz), 7.52 (1H,dd, J = 2.2, 8.4Hz), 7.36-7.20 (5H, m), 6.92 (1H, d, J=8.4Hz), 6.15-6.00 (1H,m), 4.91 (1H, dd, J=7.3, 7.7Hz), 4.57 (1H, d, J = 7.0Hz), 4.53 (1H, d, J = 7.0Hz), 4.10-3.98 (1H,m), 3.45-3.35 (2H, m), 3.29 (3H, s), 3.14 (1H, dd, J=7.7, 12.5Hz), 3.05 (1H, dd, J=7.3, 12.5Hz), 2.73 (1H, dd, J=6.2, 9.9Hz), 2.64 (3H, s), 2.55-2.43 (3H, m), 2.05-1.88 (1H, m), 1.75-1.55 (3H, m), 0.96 (3H, t, J=7.3Hz)

Example 30

Preparation of 3-Chloro-4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 3-chloro-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-

1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide in 96% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.81 (1H, d, J = 2.2Hz), 7.51 (1H,dd, J = 2.2, 8.4Hz), 7.42-7.22 (5H, m), 6.93 (1H, d, J=8.4Hz), 6.15-6.00 (1H,m), 4.99 (1H, dd, J=7.3, 7.9Hz), 4.20-4.05 (1H,m), 3.45-3.35 (2H, m), 3.16 (1H, dd, J=7.7, 12.5Hz), 3.08 (1H, dd, J=7.3, 12.5Hz), 2.75-2.60 (2H, m), 2.65 (3H, s), 2.41 (1H, dd, J=4.4, 9.5Hz), 2.25-2.15 (1H, m), 2.08-1.93 (1H, m), 1.90-1.40 (4H, m), 0.99 (3H, t, J=7.3Hz)

Fumaric acid salt: amorphous solid.

1R(KBr) : 3350, 1630cm^{-1}.

MS m/z: 416, 418 $(M+H)^+$.

Anal. Calcd for $C_{23}H_{30}N_3O_2Cl \cdot C_4H_4O_4 \cdot H_2O$: C, 58.96 ; H, 6.60; N, 7.64

Found : C, 59.35 ; H,6.64 ; N, 7.55.

Example 31

Preparation of 6-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylnicotinamide

(i) Methyl 6-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}nicotinate

This was prepared from 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol and methyl 6-methylaminonicotinate in 60% yield according to a procedure similar to that described in Example 29 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 8.83 (1H, d, J=2.2Hz), 8.01 (1H, dd, J=2.2, 9.2Hz), 7.35-7.20 (5H, m), 6.48 (1H, d, J=9.2Hz), 6.44-6.32 (1H, m), 4.59 (1H, d, J = 7.0Hz), 4.56 (1H, d, J = 6.6Hz), 4.22-4.12 (1H, m), 3.86 (3H, s), 3.30 (3H, s), 3.17-2.92 (3H, m), 2.83 (3H, s), 2.80-2.70 (1H, m), 2.65-2.50 (2H, m), 2.12-1.95 (1H, m), 1.80-1.65 (1H, m).

(ii) 6-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}nicotinic acid

This was prepared from methyl 6-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-

yl)-1-(S)-phenylethyl]-N-methylamino}nicotinate in 100% yield according to a procedure similar to that described in Example 1 (ii).

^{1}H NMR (270MHz, $CDCl_3$) δ 8.80-8.75 (1H, m), 7.95-7.87 (1H, m), 7.35-7.15 (5H, m), 6.57 (1H, br.s), 6.42 (1H, d, J=9.2Hz), 4.62 (1H, d, J = 6.6Hz), 4.59 (1H, d, J = 7.0Hz), 4.35-4.00 (2H, m), 3.50-3.25 (2H, m), 3.32 (3H, s), 3.18-3.08 (1H, m), 3.02-2.70 (3H, m), 2.79 (3H, s), 2.20-2.05 (1H, m), 1.90-1.80 (1H, m).

(iii) 6-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylnicotinamide

This was prepared from 6-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}nicotinic acid and n-propylamine in 65% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 8.57 (1H, d, J=2.6Hz), 7.89 (1H, dd, J=2.6, 9.2Hz), 7.35-7.20 (5H, m), 6.50 (1H, d, J=9.2Hz), 6.40-6.35 (1H, m), 6.00-5.90 (1H, m), 4.59 (1H, d, J = 7.0Hz), 4.56 (1H, d, J = 7.0Hz), 4.20-4.10 (1H, m), 3.45-3.35 (2H, m), 3.30 (3H, s), 3.17-2.92 (3H, m), 2.82 (3H, s), 2.80-2.70 (1H, m), 2.65-2.50 (2H, m), 2.12-1.95 (1H, m), 1.80-1.55 (3H, m), 0.99 (3H, t, J=7.3Hz).

Example 32

Preparation of 6-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylnicotinamide

This was prepared from 6-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylnicotinamide in 73% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 8.58 (1H, d, J=2.6Hz), 7.89 (1H, dd, J=2.6, 8.8Hz), 7.35-7.20 (5H, m), 6.50 (1H, d, J=9.5Hz), 6.36 (1H, dd, J=5.9, 9.9Hz), 6.00-5.92 (1H, m), 4.25-4.15 (1H, m), 3.45-3.35 (2H, m), 3.17 (1H, dd, J=9.9, 12.5Hz), 3.05-2.95 (2H, m), 2.81 (3H, s), 2.72 (1H, d, J=9.5Hz), 2.62 (1H, dd, J=4.8, 9.9Hz), 2.40-2.25 (1H, m), 2.17-2.02 (1H, m), 1.95-1.75 (2H, m), 1.70-1.55 (2H, m), 0.98 (3H, t, J=7.3Hz).

Fumaric acid salt: amorphous solid.

IR(KBr) : 3350, 1630cm^{-1}.

MS m/z: 383(M+H)$^+$.

Anal. Calcd for $C_{22}H_{30}N_4O_2 \cdot C_4H_4O_4 \cdot 1.5H_2O$: C, 59.42 ; H, 7.10; N, 10.66

Found : C, 59.50 ; H, 7.43 ; N, 10.73.

Example 33

Preparation of 4-{N-[1-(S)-(3-Methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide

(i) Methyl 4-{N-[1-(S)-(3-methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}benzoate

This was prepared from the mixture of 2-(R)-(3-methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)ethanol and 1-(S)-(3-methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)ethanol and methyl 4-methylaminobenzoate in 60% yield according to a procedure similar to that described in Example 1 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.89 (2H, d, J = 9.2Hz), 7.27-7.19 (1H, m), 6.98-6.88 (3H, m), 6.77 (2H, d, J=9.2Hz), 5.14 (2H, s), 5.14-5.08 (1H, m), 4.59 (1H, d, J = 6.6Hz), 4.55 (1H, d, J = 7.0Hz), 4.22-4.12 (1H, m), 3.85 (3H, s), 3.46 (3H, s), 3.30 (3H, s), 3.04 (2H, d, J = 8.1Hz), 2.88 (3H, s), 2.85-2.53 (4H, m), 2.10-1.98 (1H, m), 1.83-1.70 (1H, m).

(ii) 4-{N-[1-(S)-(3-Methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}benzoic acid

This was prepared from methyl 4-{N-[1-(S)-(3-methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}benzoate in 100% yield according to a procedure similar to that described in Example 1 (ii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.88 (2H, d, J = 8.8Hz), 7.30-7.12 (1H, m), 6.98-6.84 (3H, m), 6.68 (2H, d, J=8.8Hz), 5.15-5.05 (1H, m), 5.10 (2H, s), 4.55 (1H, d, J = 6.6Hz), 4.51 (1H, d, J = 7.0Hz), 4.18-4.08 (1H, m), 3.42 (3H, s), 3.25 (3H, s), 3.10-2.92 (2H, m), 2.85 (1H, dd, J=6.4, 9.9Hz), 2.74 (3H, s), 2.70-2.53 (3H, m), 2.10-1.93 (1H, m), 1.80-1.65 (1H, m).

(iii) 4-{N-[1-(S)-(3-Methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 4-{N-[1-(S)-(3-methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}benzoic acid and n-propylamine in 80% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.65 (2H, d, J = 9.2Hz), 7.28-7.18 (1H, m), 6.98-6.88 (3H, m), 6.76 (2H, d, J=8.8Hz), 6.05-5.90 (1H, m), 5.14 (2H, s), 5.08 (1H, dd, J=7.0, 7.7Hz), 4.59 (1H, d, J = 6.6Hz), 4.55 (1H, d, J = 7.0Hz), 4.22-4.12 (1H, m), 3.46 (3H, s), 3.45-3.35 (2H, m), 3.30 (3H, s), 3.03 (2H, d, J=7.7Hz), 2.86 (3H, s), 2.85-2.80 (1H, m), 2.75-2.50 (3H, m), 2.12-1.95 (1H, m), 1.85-1.52 (3H, m), 0.97 (3H, t, J=7.3Hz).

Example 34

Preparation of 4-{N-[1-(S)-(3-Hydroxyphenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 4-{N-[1-(S)-(3-methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide in 97% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$-DMSO-d6) δ 8.85 (1H, br.s), 7.69 (2H, d, J = 9.2Hz), 7.11 (1H, t, J=7.7Hz), 6.98-6.90 (1H, m), 6.82-6.68 (5H, m), 5.06 (1H, dd, J=6.2, 8.4Hz), 4.30-4.18 (1H, m), 3.67 (1H, br.s), 3.40-3.30 (2H, m), 3.15-2.95 (2H, m), 2.86 (3H, s), 2.85-2.67 (2H, m), 2.63-2.56 (1H, m), 2.55-2.43 (1H, m), 2.15-1.98 (1H, m), 1.70-1.52 (3H, m), 0.96 (3H, t, J=7.3Hz).

HCl salt: amorphous solid.

1R(KBr) : 3350, 1610cm^{-1}.

MS m/z: 397(M^+).

Anal. Calcd for $C_{23}H_{31}N_3O_3 \cdot HCl \cdot 2.3H_2O$: C, 58.11 ; H, 7.76; N, 8.84

Found : C,57.82 ; H,8.06 ; N, 9.24.

Example 35

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-(3-methoxyphenyl)-ethyl]-N-methylamino}-N'-propylbenzamide

To a solution of 4-{N-[1-(S)-(3-hydroxyphenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide (100mg, 0.252mmol) in MeOH (0.1ml)-CH_3CN (0.9ml) was added N,N-diisopropylethylamine (0.0641ml, 0.353mmol) and 10%-trimethylsilyl-diazomethane in CH_2Cl_2 (0.6ml) at room temperature. After stirring for 22h at room temperature, 25%-NH_4OH was added to the mixture and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4) and concentrated to give brown oil, which was purified by column chromato-graphy (silica gel 5g, CH_2Cl_2/MeOH: 30/1-10/1) to afford 55.2mg (53%) of white amorphous.

^1H NMR (270MHz, free amine, $CDCl_3$) δ 7.65 (2H, d, J=8.8Hz), 7.24 (1H, t, J=7.7Hz), 6.90-6.77 (5H, m), 6.05-5.90 (1H, m), 5.10 (1H, dd, J=5.9, 8.8Hz), 4.25-4.18 (1H, m), 3.77 (3H, s), 3.45-3.35 (2H, m), 3.11 (1H, dd, J=9.2, 12.8Hz), 3.01 (1H, dd, J=5.9, 12.8Hz), 2.95-2.80 (1H, m), 2.84 (3H, s), 2.72 (1H, d, J=9.5Hz), 2.56 (1H, dd, J=4.8, 9.5Hz), 2.38-2.25 (1H, m), 2.16-2.00 (1H, m), 1.85-1.55 (4H, m), 0.97 (3H, t, J=7.7Hz).

HCl salt: amorphous solid.

1R(neat, free amine) : 3350, 1610cm^{-1}.

MS m/z: 412$(M+H)^+$.

Anal. Calcd for $C_{24}H_{33}N_3O_3 \cdot HCl \cdot 0.5H_2O$: C, 63.08 ; H, 7.72; N, 9.19

Found : C,62.89 ; H, 7.77 ; N, 9.25.

Example 36

Preparation of 4-{N-[1-(S)-(3-*t*-Butoxycarbonylmethoxyphenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide

A mixture of 4-{N-[1-(S)-(3-hydroxyphenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide (100mg, 0.252mmol), *t*-butyl bromoacetate (0.0409ml, 0.277mmol) and K_2CO_3 (38.3mg, 0.277mmol) in DMF (1.5ml) was stirred at room temperature for 2h. H_2O was added to the mixture and extracted with AcOEt/toluene=2/1. The extract was washed with water,brine, dried (Na_2SO_4) and concentrated to give pale brown amorphous, which was purified by column chromato-graphy (silica gel 6g, CH_2Cl_2/MeOH: 30/1-10/1) to afford 80.1mg

(62%) of white amorphous.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.65 (2H, d, J=9.2Hz), 7.23 (1H, t, J=7.7Hz), 6.94-6.86 (2H, m), 6.82-6.72 (3H, m), 6.05-5.90 (1H, m), 5.09 (1H, dd, J=6.2, 8.8Hz), 4.48 (2H, s), 4.25-4.18 (1H, m), 3.45-3.35 (2H, m), 3.09 (1H, dd, J=9.2, 12.8Hz), 3.00 (1H, dd, J=5.9, 12.8Hz), 2.95-2.80 (1H, m), 2.83 (3H, s), 2.71 (1H, d, J=9.5Hz), 2.54 (1H, dd, J=4.8, 9.5Hz), 2.38-2.25 (1H, m), 2.16-2.00 (1H, m), 1.85-1.50 (4H, m), 1.46 (9H, s), 0.98 (3H, t, J=7.3Hz).

Example 37

Preparation of 4-{N-[1-(S)-(3-Carboxymethoxyphenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide

A solution of 4-{N-[1-(S)-(3-*t*-butoxycarbonylmethoxyphenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide (80.1mg, 0.157mmol) in trifluoroacetic acid (1ml) and CH_2Cl_2 (0.5ml) was stirred at room temperature for 1.5h. The solvent was evaporated. The residue was dissolved in CH_2Cl_2 and 1.0M hydrogen chloride solution in diethyl ether (1ml) was added. The white powder was collected and washed with Et_2O and dried under reduced pressure for 6.5h at 45°C to afford 86.2mg (quant) of white powder.

HCl salt: white powder.

^{1}H NMR (270MHz, $CDCl_3$-DMSO-d6) δ 12.49 (1H, br. s), 7.79 (2H, d, J=8.4Hz), 7.42 (1H, br. s), 7.23 (1H, t, J=7.7Hz), 7.07 (2H, d, J=8.4Hz), 6.85-6.76 (3H, m), 5.95-5.80 (1H, m), 4.53 (2H, s), 4.50-4.40 (1H, m), 4.00-3.70 (4H, m), 3.50-2.50 (3H, m), 2.80 (3H, s), 2.50-2.00 (2H, m), 1.75-1.55 (4H, m), 0.96 (3H, t, J=7.3Hz).

1R(KBr) : 3400, 1730, 1610cm^{-1}.

MS m/z: 456$(M+H)^+$.

mp. 108-110°C

Anal. Calcd for $C_{25}H_{33}N_3O_5 \cdot HCl \cdot 3.5H_2O$: C, 54.10 ; H, 7.45; N, 7.57

Found : C, 54.07 ; H, 7.49 ; N, 7.39

Example 38

Preparation of 4-{N-[1-(S)-Phenyl-2-(pyrrolidin-1-yl)ethyl]-N-methylamino}-N'-

propylbenzamide

(i) Methyl 4-{N-[1-(S)-phenyl-2-(pyrrolidin-1-yl)ethyl]-N-methylamino}benzoate

This was prepared from the mixture of 2-(R)-phenyl-2-(pyrrolidin-1-yl)ethanol and 1-(S)-phenyl-2-(pyrrolidin-1-yl)ethanol and methyl 4-methylaminobenzoate in 52% yield according to a procedure similar to that described in Example 1 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.88 (2H, d, J=9.2Hz), 7.38-7.20 (5H, m), 6.78 (2H, d, J=9.2Hz), 5.17 (1H, t, J=7.3Hz), 3.84 (3H, s), 3.04 (2H, d, J=7.3Hz), 2.86 (3H, s), 2.65-2.45 (4H, m), 1.80-1.65 (4H, m)

(ii) 4-{N-[1-(S)-Phenyl-2-(pyrrolidin-1-yl)ethyl]-N-methylamino}benzoic acid

This was prepared from methyl 4-{N-[1-(S)-phenyl-2-(pyrrolidin-1-yl)ethyl]-N-methylamino}benzoate in 100% yield according to a procedure similar to that described in Example 1 (ii).

^{1}H NMR (270MHz, $CDCl_3$-DMSO-d6) δ 7.92 (2H, d, J=8.8Hz), 7.38-7.20 (5H, m), 7.02 (2H, d, J=8.8Hz), 5.80 (1H, br.s), 4.00-3.00 (7H, m), 2.85 (3H, s), 2.20-1.90 (4H, m)

(iii) 4-{N-[1-(S)-Phenyl-2-(pyrrolidin-1-yl)ethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 4-{N-[1-(S)-phenyl-2-(pyrrolidin-1-yl)ethyl]-N-methylamino}benzoic acid and n-propylamine in 56% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, free amine $CDCl_3$) δ 7.65 (2H, d, J=8.8Hz), 7.36-7.20 (5H, m), 6.79 (2H, d, J=8.8Hz), 6.05-5.90 (1H, m), 5.14 (1H, t, J=7.0Hz), 3.45-3.35 (2H, m), 3.04 (2H, d, J=7.0Hz), 2.84 (3H, s), 2.65-2.45 (4H, m), 1.75-1.50 (6H, m), 0.97 (3H, t, J=7.3Hz).

HCl salt: amorphous solid.

1R(KBr) : 1610cm^{-1}.

MS m/z: 366$(M+H)^+$.

Anal. Calcd for $C_{23}H_{31}N_3O \cdot HCl \cdot 0.5H_2O$: C, 67.22 ; H, 8.09; N,10.22

Found : C, 67.48 ; H, 8.37 ; N, 10.32.

Example 39

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylphthalimide

This was prepared from 2-(R)-phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)ethanol and 1-(S)-phenyl-2-(3-(S)-tetrahydropyran-2-yloxypyrrolidin-1-yl)ethanol and 4-methylamino-N'-propylphthalimide in 16% over all yield according to a procedure similar to that described in Example 1 (i) and 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.63 (1H, d, J=8.4Hz), 7.38-7.22 (6H, m), 6.94 (1H, dd, J=2.6, 8.4Hz), 5.19 (1H, dd, J=5.9, 9.5Hz), 4.30-4.20 (1H, m), 3.59 (2H, t, J=7.3Hz), 3.18 (1H, dd, J=9.5, 13.2Hz), 3.03 (1H, dd, J=5.5, 12.8Hz), 2.95 (3H, s), 2.95-2.85 (1H, m), 2.71 (1H, d, J=9.2Hz), 2.61 (1H, dd, J=4.8, 9.5Hz), 2.37 (1H, ddd, J=5.9, 8.8, 8.8Hz), 2.20-2.05 (1H, m), 1.75-1.60 (4H,m), 0.93 (3H, t, J=7.3Hz)
HCl salt: amorphous solid.
1R(KBr) : 3400, 1760, 1700, 1620cm^{-1}.
Anal. Calcd for $C_{24}H_{29}N_3O_3 \cdot HCl \cdot 0.5H_2O$: C, 63.64 ; H,6.90; N, 9.28
Found : C,63.99 ; H, 7.18 ; N, 9.00.

Example 40

Preparation of 5-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propyl-2-thiophenecarboxamide

This was prepared from 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol and 5-methylamino-N'-propyl-2-thiophenecarboxamide in 49% yield according to a procedure similar to that described in Example 1 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.35-7.25 (5H, m), 7.18 (1H, d, J=4.4Hz), 5.83 (1H, d, J=4.0Hz), 5.68-5.60 (1H, m), 4.86 (1H, dd, J=7.0, 7.7Hz), 4.62 (1H, d, J=7.0Hz), 4.58 (1H, d, J=7.0Hz), 4.25-4.15 (1H, m), 3.40-3.30 (2H, m), 3.32 (3H, s), 3.13-3.00 (2H, m), 2.94 (1H, dd, J=6.2, 9.9Hz), 2.83 (3H, s), 2.80-2.70 (1H, m), 2.67-2.55 (2H, m), 2.15-2.00 (1H, m), 1.87-1.73 (1H, m), 1.70-1.50 (2H, m), 0.95 (3H, t, J=7.7Hz)

Example 41

Preparation of 5-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propyl-2-thiophenecarboxamide

This was prepared from 5-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propyl-2-thiophenecarboxamide in 78% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.38-7.24 (5H, m), 7.18 (1H, d, J=4.0Hz), 5.84 (1H, d, J=4.4Hz), 5.70-5.60 (1H, m), 4.88 (1H, dd, J=6.0, 9.0Hz), 4.30-4.22 (1H, m), 3.40-3.30 (2H, m), 3.15 (1H, dd, J=9.2, 12.8Hz), 3.07-2.95 (2H, m), 2.81 (3H, s), 2.75 (1H, d, J=9.5Hz), 2.63 (1H, dd, J=4.8, 9.5Hz), 2.42-2.30 (1H, m), 2.22-2.05 (1H,m), 1.80-1.50 (4H, m), 0.96 (3H, t, J=7.7Hz).

Fumaric acid salt: amorphous solid.

1R(KBr) : 3300, 1610cm^{-1}.

MS m/z=388$(M+H)^+$

Anal. Calcd for $C_{21}H_{29}N_3O_2S \cdot C_4H_4O_4 \cdot 0.5H_2O \cdot CH_4O$: C, 57.34 ; H, 7.03; N, 7.71

Found : C,57.37; H,7.31 ; N, 7.79.

Example 42

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]amino}-N'-propylbenzamide

(i) Methyl 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]amino}benzoate

This was prepared from 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol and methyl 4-aminobenzoate in 69% yield according to a procedure similar to that described in Example 1 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.75 (2H, d, J=8.8Hz), 7.37-7.27 (5H, m), 6.47 (2H, d, J=8.8Hz), 5.56 (1H, br. s), 4.65 (1H, d, J = 6.6Hz), 4.61 (1H, d, J = 7.0Hz), 4.35-4.28 (1H,m), 4.26-4.23 (1H, m), 3.80 (3H, s), 3.36 (3H, s), 2.90-2.76 (3H, m), 2.62-2.51

(2H, m), 2.48-2.42 (1H, m), 2.18-2.10 (1H, m), 1.84-1.82 (1H, m).

(ii) 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]amino}benzoic acid

This was prepared from methyl 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]amino}benzoate in 100% yield according to a procedure similar to that described in Example 1 (ii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.72 (2H, d, J=8.4Hz), 7.36-7.23 (5H, m), 6.42 (2H, d, J=8.4Hz), 5.80 (1H, br. s), 4.69-4.65 (1H, m), 4.63 (1H, d, J = 7.0Hz), 4.60 (1H, d, J =7.0Hz), 4.39-4.37 (1H, m), 4.32-4.22 (1H,m), 3.34 (3H, s), 3.00-2.82 (3H, m), 2.66-2.48 (3H, m), 2.17-2.10 (1H, m), 1.95-1.78 (1H, m)

(iii) 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]amino}-N'-propylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]amino}benzoic acid and n-propylamine in 62% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.49 (2H, d, J=8.5Hz), 7.38-7.24 (5H, m), 6.48 (2H, d, J=8.8Hz), 5.95-5.80 (1H, m), 5.46 (1H, br. s), 4.65 (1H, d, J = 7.0Hz), 4.61 (1H, d, J =7.0Hz), 4.32-4.23 (2H,m), 3.36 (3H, s), 3.38-3.31 (2H, m), 2.90-2.76 (3H, m), 2.59 (1H, dd, J=3.9, 10.8Hz), 2.53-2.42 (2H, m), 2.18-2.11 (1H, m), 1.83-1.82 (1H, m), 1.60-1.50 (2H, m), 0.93 (3H, t, J=7.3Hz).

Example 43

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]amino}-N'-propylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]amino}-N'-propylbenzamide in 67% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.50 (2H, d, J=8.8Hz), 7.38-7.22 (5H, m),

6.48 (2H, d, J=8.8Hz), 5.95-5.80 (1H, m), 5.39 (1H, br. s), 4.39-4.29 (2H,m), 3.40-3.28 (2H, m), 2.99-2.84 (2H, m), 2.73-2.53 (3H,m), 2.40-2.31 (1H, m), 2.26-2.13 (1H, m), 1.90-1.67 (2H, m), 1.65-1.50 (2H, m), 0.94 (3H, t, J=7.3Hz).

HCl salt: amorphous solid.

IR(KBr) : 3350, 1610cm-1.

Anal. Calcd for $C_{22}H_{29}N_3O_2 \cdot HCl \cdot 1.1H_2O$: C, 62.44 ; H, 8.05; N, 9.72

Found : C,62.36 ; H,7.66 ; N, 9.92.

Example 44

Preparation of 4-{N-[1-(S)-(3-Chlorophenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide

(i) Methyl 4-{N-[1-(S)-(3-chlorophenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}benzoate

This was prepared from the mixture of 2-(R)-(3-chlorophenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)ethanol and 1-(S)-(3-chlorophenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)ethanol and methyl 4-methylaminobenzoate in 66% yield according to a procedure similar to that described in Example 1 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.90 (2H, d, J = 8.8Hz), 7.30-7.14 (4H, m), 6.77 (2H, d, J=9.2Hz), 5.11 (1H, dd, J=7.0, 7.7Hz), 4.60 (1H, d, J =7.0Hz), 4.55 (1H, d, J = 7.0Hz), 4.22-4.13 (1H, m), 3.86 (3H, s), 3.30 (3H, s), 3.12-2.94 (2H, m), 2.90-2.78 (1H, m), 2.87 (3H, s), 2.76-2.52 (3H, m), 2.15-1.98 (1H, m), 1.85-1.70 (1H, m).

(ii) 4-{N-[1-(S)-(3-Chlorophenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}benzoic acid

This was prepared from methyl 4-{N-[1-(S)-(3-chlorophenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}benzoate in 96% yield according to a procedure similar to that described in Example 1 (ii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.93 (2H, d, J = 9.2Hz), 7.32-7.10 (4H, m), 6.82 (2H, d, J=9.2Hz), 5.40-5.25 (1H,m), 4.62 (1H, d, J =7.0Hz), 4.58 (1H, d, J = 7.0Hz), 4.30-4.18 (1H, m), 3.40-3.00 (3H, m), 3.31 (3H, s), 2.95-2.65(3H, m), 2.88 (3H, s), 2.20-2.00 (1H, m), 1.95-1.80 (1H, m).

(iii) 4-{N-[1-(S)-(3-Chlorophenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 4-{N-[1-(S)-(3-chlorophenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}benzoic acid and n-propylamine in 77% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.66(2H, d, J = 9.2Hz), 7.30-7.13 (4H, m), 6.78 (2H, d, J=9.2Hz), 6.02-5.92 (1H, m), 5.07 (1H, dd, J=6.6, 7.7Hz), 4.60 (1H, d, J = 7.0Hz), 4.55 (1H, d, J = 7.0Hz), 4.25-4.12 (1H, m), 3.45-3.35 (2H, m), 3.30 (3H, s), 3.12-2.93 (2H, m), 2.90-2.78 (1H, m), 2.85 (3H, s), 2.75-2.52 (3H, m), 2.13-1.97 (1H, m), 1.85-1.70 (1H, m), 1.69-1.54 (2H, m), 0.98(3H, t, J=7.3Hz).

Example 45

Preparation of 4-{N-[1-(S)-(3-Chlorophenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 4-{N-[1-(S)-(3-chlorophenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide in 83% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.67 (2H, d, J = 9.2Hz), 7.30-7.14 (4H, m), 6.79 (2H, d, J=8.8Hz), 6.03-5.94 (1H, m), 5.09 (1H, dd, J=6.2, 8.8Hz), 4.27-4.18 (1H, m), 3.45-3.35 (2H, m), 3.09 (1H, dd, J=8.8, 12.8Hz), 3.01 (1H, dd, J=6.2, 12.8Hz), 2.93-2.80 (1H, m), 2.84 (3H, s), 2.72 (1H, d, J=9.9Hz), 2.57 (1H, dd, J=5.0, 9.7Hz), 2.38-2.27 (1H, m), 2.17-2.02 (1H, m), 1.80-1.55 (4H, m), 0.98 (3H, t, J=7.3Hz).
Fumaric acid salt: amorphous solid.
1R(KBr) : 3350, 1610cm^{-1}.
MS m/z: 416$(M+H)^+$

Example 46

Preparation of 4-{N-[2-(3-(S)-Fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

(i) Methyl 4-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoate

This was prepared from 2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-fluoropyrrolidin-1-yl)-2-(R)-phenylethanol and methyl 4-methylaminobenzoate in 54% yield according to a procedure similar to that described in Example 1 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.89 (2H, d, J = 9.2Hz), 7.38-7.22 (5H, m), 6.78 (2H, d, J=9.2Hz), 5.25-4.95 (1H, m), 5.14 (1H, dd, J=6.6, 8.8Hz), 3.84 (3H, s), 3.18-3.00 (2H, m), 2.95-2.75 (3H, m), 2.89 (3H, s), 2.60-2.50 (1H, m), 2.15-1.85 (2H, m).

(ii) 4-{N-[2-(3-(S)-Fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid

This was prepared from methyl 4-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoate in 100% yield according to a procedure similar to that described in Example 1 (ii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.92 (2H, d, J = 8.8Hz), 7.40-7.10 (5H, m), 6.83 (2H, d, J=8.8Hz), 5.40-5.00 (2H, m), 3.40-3.15 (2H, m), 3.10-2.70 (4H, m), 2.90 (3H, s), 2.30-1.90 (2H, m).

(iii) 4-{N-[2-(3-(S)-Fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 4-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and n-propylamine in 73% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.65 (2H, d, J = 8.8Hz), 7.37-7.22 (5H, m), 6.79 (2H, d, J = 8.8Hz), 6.03-5.92 (1H, m), 5.25-4.95 (1H, m), 5.11 (1H, dd, J=6.2, 8.4Hz), 3.45-3.35 (2H, m), 3.18-3.02 (2H, m), 2.95-2.72 (3H, m), 2.87 (3H, s), 2.63-2.50 (1H, m), 2.18-1.85 (2H, m), 1.72-1.54 (2H, m), 0.97 (3H, t, J=7.3Hz)
HCl salt: amorphous solid.
1R(KBr) : 1605cm^{-1}.

MS m/z 384$(M+H)^+$

Anal. Calcd for $C_{23}H_{30}N_3OF \cdot HCl \cdot 0.3H_2O \cdot CH_4O$: C, 63.02 ; H, 7.84; N, 9.19.

Found : C, 62.69 ; H, 8.17 ; N, 9.57 .

Example 47

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(R)-phenylethyl]-N-methylamino}-N'-propylbenzamide

(i) Methyl 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(R)-phenylethyl]-N-methylamino}benzoate

This was prepared from 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(R)-phenylethanol and 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-2-(S)-phenylethanol and methyl 4-methylaminobenzoate in 49% yield according to a procedure similar to that described in Example 1 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.88 (2H, d, J = 8.8Hz), 7.34-7.23 (5H, m), 6.78 (2H, d, J=9.2Hz), 5.17 (1H, dd, J = 7.0, 7.7Hz), 4.58 (1H, d, J = 7.0Hz), 4.53 (1H, d, J = 6.6Hz), 4.22-4.15 (1H, m), 3.85 (3H, s), 3.68-3.52 (1H, m), 3.28 (3H, s), 3.08-3.04 (2H, m), 2.86 (3H, s), 2.76-2.67 (1H, m), 2.62-2.51 (2H, m), 2.08-1.97 (1H, m), 1.83-1.72 (1H, m).

(ii) 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(R)-phenylethyl]-N-methylamino}benzoic acid

This was prepared from methyl 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(R)-phenylethyl]-N-methylamino}benzoate in 100% yield according to a procedure similar to that described in Example 1 (ii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.89 (2H, d, J = 9.2Hz), 7.33-7.18 (5H, m), 6.75 (2H, d, J = 9.2Hz), 5.15 (1H, dd, J = 7.0, 7.3Hz), 4.57 (1H, d, J = 7.0Hz), 4.52 (1H, d, J = 7.0Hz), 4.25-4.15 (1H, m), 3.33 (3H, s), 3.05 (1H, d, J=6.6Hz), 2.88-2.84 (1H, m), 2.85(3H, s), 2.76-2.62 (1H, m), 2.50-2.61 (3H, m), 2.07-2.02 (1H, m), 1.78-1.73 (1H, m).

(iii) 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(R)-phenylethyl]-N-

methylamino}-N'-propylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(R)-phenylethyl]-N-methylamino}benzoic acid and n-propylamine in 60% yield according to a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.63 (2H, d, J = 9.2Hz), 7.34-7.24 (5H, m), 6.79 (2H, d, J = 9.2Hz), 5.98-5.82 (1H, m), 5.13 (1H, t, J = 7.3Hz), 4.58 (1H, d, J = 6.6Hz), 4.54 (1H, d, J = 7.0Hz), 4.26-4.13 (1H,m), 3.43-3.34 (2H, m), 3.29 (3H, s), 3.06 (2H, d, J=7.3Hz), 2.91-2.88 (1H, m), 2.85 (3H, s), 2.73-2.67 (1H, m), 2.61-2.54 (2H, m), 2.11-1.98 (1H, m), 1.84-1.72 (1H, m), 1.65-1.57 (2H, m), 0.97 (3H, t, J=7.3Hz).

Example 48

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(R)-phenylethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(R)-phenylethyl]-N-methylamino}-N'-propylbenzamide in 15% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.59 (2H, d, J=9.2Hz), 7.28-7.16 (5H, m), 6.75 (2H, d, J=8.8Hz), 6.07-5.94 (1H, m), 5.12 (1H, t, J=7.3Hz), 4.18-4.13 (1H, m), 3.35-3.27 (2H, m), 3.03 (2H, d, J=7.8Hz), 2.92-2.86 (1H, m), 2.73 (3H, s), 2.66 (1H, d, J=9.9Hz), 2.50 (1H, dd, J=4.8, 9.7Hz), 2.38-2.33 (1H, m), 2.09-1.96 (2H, m), 1.67-1.46 (3H, m), 0.90 (3H, t, J=7.3Hz)

1R(neat) : 3350, 1610cm^{-1}.

HCl salt: amorphous solid.

Anal. Calcd for $C_{23}H_{31}N_3O_2 \cdot HCl \cdot 1.9H_2O$: C, 61.52 ; H, 8.37; N, 9.20.

Found : C, 61.33 ; H, 7.97 ; N, 9.33 .

Example 49

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-pyrrolidinebenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and pyrrolidine in 77% yield according to

a procedure similar to that described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.47 (2H, d, J=8.8Hz), 7.33-7.21 (5H, m), 6.77 (2H, d, J=8.8Hz), 5.11 (1H, dd, J=6.6, 7.3Hz), 4.60 (1H, d, J=7.0Hz), 4.56 (1H, dd, J=7.0Hz), 4.21-4.15 (1H, m), 3.62-3.52 (4H, m), 3.30 (3H, s), 3.12-2.97 (2H, m), 2.82 (3H, s), 2.75-2.54 (4H, m), 2.09-1.74 (6H, m)

Example 50

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-pyrrolidinebenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-pyrrolidinebenzamide in 51% yield according to a procedure similar to that described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.49 (2H, d, J=9.2Hz), 7.46-7.23 (5H, m), 6.79 (2H, d, J=8.8Hz), 5.14 (1H, dd, J=6.2, 8.8Hz), 4.24-4.20 (1H, m), 3.68-3.52 (4H, m), 3.12 (1H, dd, J=8.8, 12.6Hz), 3.03 (1H, dd, J=6.2, 12.8Hz), 2.95-2.87 (1H, m), 2.81 (3H, s), 2.75 (1H, d, J=10.3Hz), 2.55 (1H, dd, J=4.8, 9.5Hz), 2.35-2.27 (1H, m), 2.17-2.03 (1H, m), 1.98-1.82 (6H, m)

1R(neat) : 3400, 1610cm^{-1}.

HCl salt: amorphous solid.

Anal. Calcd for $C_{24}H_{31}N_3O_2 \cdot HCl \cdot 2H_2O$: C, 61.65 ; H, 8.08; N, 8.83

Found : C,61.86 ; H, 7.79 ; N,9.02.

Example 51

Preparation of 4-{N-[2-(3-(S)-tert-Butyldimethylsilyloxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-ethoxybenzamide

(i) Methyl 4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoate

This was prepared from methyl 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoate in 100% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.90(2H, d, J=9.2Hz), 7.36-7.23(5H, m), 6.80(2H, d, J=9.2Hz), 5.18(1H, dd, J=5.9, 9.0Hz), 4.24-4.20(1H, m), 3.85(3H, s), 3.13(1H, dd, J=5.9, 12.8Hz), 2.94-2.88(2H, m), 2.85(3H, s), 2.73(1H, d, J=9.9Hz), 2.56(1H, dd, J=4.8, 9.5Hz), 2.36-2.30(1H, m), 2.27-2.05(1H, m), 1.80-1.50(2H,m).

(ii) Methyl 4-{N-[2-(3-(S)-tert-butyldimethylsilyloxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoate

To a stirred solution of methyl 4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-(S)-phenylethyl]-N-methylamino}benzoate (865mg, 2.44mmol) in DMF(10ml) was added imidazole(1.54g, 24.4mmol) and tert-butyldimethylsilylchloride(1.83g, 12.2mmol) at 0°C. After 3hr stirring, saturated $NaHCO_3$ aqueous solution was added to the reaction mixture and extracted with CH_2Cl_2. The extract was washed with water and brine, dried(Na_2SO_4), and concentrated to give brown oil, which was purified by column chromatography (silica gel; 40g, CH_2Cl_2/MeOH: 100/1-50/1) to give 760mg(66%) of title compound.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.79(2H, d, J=9.2Hz), 7.24-7.14(5H, m), 6.68(2H, d, J=9.2Hz), 5.05(1H, dd, J=6.2, 7.3Hz), 4.21-4.12(1H, m), 3.75(3H, s), 2.97-2.92(2H, m), 2.82-2.76(1H, m), 2.75(3H, s), 2.58-2.53(2H, m), 2.27(1H, dd, J=4.4, 9.2Hz), 1.93-1.86(1H, m), 1.58-1.47(1H,m), 0.74(9H, s), 0.01(6H, s).

(iii) 4-{N-[2-(3-(S)-tert-Butyldimethylsilyloxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid

This was prepared from methyl 4-{N-[2-(3-(S)-tert-butyldimethylsilyloxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoate in 32% yield according to the procedures similar to those described in Example 1-(ii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.90(2H, d, J=9.2Hz), 7.32-7.23(5H, m), 6.80(2H, d, J=9.2Hz), 5.29-5.26(1H,m), 4.32-4.25(1H, m), 3.26-3.12(2H, m), 3.12-3.06(1H, m), 2.85(3H, s), 2.73-2.65(2H, m), 2.46-2.41(1H, m), 2.07-2.00(1H, m), 1.71-1.62(1H, m), 0.84(9H, s), 0.01(6H, s).

(iv) 4-{N-[2-(3-(S)-tert-Butyldimethylsilyloxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-

methylamino}-N'-ethoxybenzamide

This was prepared from 4-{N-[2-(3-(S)-tert-butyldimethylsilyloxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and O-ethylhydroxylamine in 41% yield according to the procedures similar to those described in Example 1-(iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 8.39(1H, br.s), 7.62(2H, d, J=8.8Hz), 7.34-7.24(5H, m), 6.78(2H, d, J=9.2Hz), 5.11-5.09(1H,m), 4.32-4.23(1H, m), 4.07(2H, q, J=7.0Hz), 3.06-3.02(1H, m), 2.92-2.86(1H, m), 2.84(3H, s), 2.68-2.63(2H, m), 2.38(1H, dd, J=4.4, 9.2Hz), 2.03-1.96(1H, m), 1.68-1.62(2H, m), 1.32(3H, t, J=7.0Hz), 0.84(9H, s), 0.01(6H, s).

Example 52

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-ethoxybenzamide

To a stirred solution of 4-{N-[2-(3-(S)-tert-butyldimethylsilyloxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-ethoxybenzamide (44.7mg, 0.0901mmol) in THF(1ml) was added 1.0M solution of tetrabutylammonium fluoride in THF(0.273ml, 0.273mmol) at room temperature. After 18hr stirring, saturated $NaHCO_3$ aqueous solution was added to the reaction mixture and extracted with CH_2Cl_2. The extract was washed with water and brine, dried(Na_2SO_4), and concentrated to give brown oil, which was purified by column chromatography (silica gel; 20g, CH_2Cl_2/MeOH: 25/1-10/1) to give 28.4mg(82%) of title compound.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 8.60(1H, br.s), 7.64(2H, d, J=9.2Hz), 7.36-7.24(5H, m), 6.80(2H, d, J=9.2Hz), 5.16(1H,dd, J=5.9, 9.2Hz), 4.24-4.20(1H, m), 4.06(2H, q, J=7.0Hz), 3.14(1H, dd, J=9.2, 13.2Hz), 3.04(1H, dd, J=5.9, 12.0Hz), 2.89-2.83(1H, m), 2.83(3H, s), 2.76(1H, d, J=9.5Hz), 2.57(1H, dd, J=4.8, 9.9Hz), 2.38-2.29(1H, m), 2.16-2.03(1H, m), 1.90-1.56(2H, m), 1.32(3H, t, J=7.0Hz).

HCl salt: amorphous solid.

Anal. Calcd for $C_{22}H_{29}N_3O_3 \cdot HCl \cdot 0.7H_2O$: C, 58.04 ; H, 8.00 ; N,8.46

Found : C,58.26 ; H, 8.40 ; N,8.58.

Example 53

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-morpholinebenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and morpholine in 54% yield according to the procedures similar to those described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.32(2H, d, J=8.8Hz), 7.29-7.28(5H, m), 6.78(2H, d, J=8.8Hz), 5.10(1H, dd, J=7.0, 7.7Hz), 4.60(1H, d, J=7.0Hz), 4.55(1H, d, J=6.6Hz), 4.22-4.13(1H, m), 3.68-3.67(8H, m), 3.30(3H, s), 3.07-3.02(2H, m), 2.90-2.80(1H, m), 2.84(3H, s), 2.75-2.57(3H, m), 2.07-2.02(1H, m), 1.81-1.72(1H, m)

Example 54

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-morpholinebenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-morpholinebenzamide in 76% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.34(2H, d, J=9.2Hz), 7.30-7.24(5H, m), 6.80(2H, d, J=8.8Hz), 5.13(1H, dd, J=6.6, 8.8Hz), 4.27-4.21(1H, m), 3.81-3.58(8H, m), 3.16-2.96(2H, m), 2.92-2.87(1H, m), 2.82(3H, s), 2.75(1H, d, J=9.2Hz), 2.55(1H, dd, J=4.4, 9.5Hz), 2.36-2.27(1H, m), 2.12-2.09(1H, m), 1.75-1.60(2H, m)

IR(neat) : 3400, 1610cm^{-1}.

HCl salt: amorphous solid.
MS m/z:410$(M+H)^+$

Example 55

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(3-hydroxypropyl)benzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-

(S)-phenylethyl]-N-methylamino}benzoic acid and 3-amino-1-propanol in 48% yield according to the procedures similar to those described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.66(2H, d, J=9.2Hz), 7.40-7.20(5H, m), 6.80(2H, d, J=8.8Hz), 6.40-6.30(1H, m), 5.14(1H, dd, J=7.0, 7.7Hz), 4.60(1H, d, J=6.6Hz), 4.55(1H, d, J=6.6Hz), 4.25-4.13(1H, m), 3.73-3.55(4H, m), 3.30(3H, s), 3.13-3.00(2H, m), 2.90-2.80(1H, m), 2.86(3H, s), 2.78-2.52(3H, m), 2.13-1.98(1H, m), 1.81-1.45(4H, m)

Example 56

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}- N'-(3-hydroxypropyl)benzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(3-hydroxypropyl)benzamide in 82% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.66(2H, d, J=9.2Hz), 7.35-7.26(5H, m), 6.81(2H, d, J=9.2Hz), 6.42-6.33(1H, m), 5.15(1H, dd, J=5.9, 8.8Hz), 4.27-4.17(1H, m), 3.66(2H, t, J=5.5Hz), 3.59(2H, t, J=5.9Hz), 3.13(1H, dd, J=9.2, 12.8Hz), 3.03(1H, dd, J=5.9, 12.8Hz), 2.94-2.86(1H, m), 2.84(3H, s), 2.72(1H, d, J=9.5Hz), 2.56(1H, dd, J=4.8, 9.9Hz), 2.36-2.28(1H, m), 2.13-2.03(1H, m), 1.79-1.61(5H, m)

1R(neat) : 3350, 1610cm^{-1}.

HCl salt: amorphous solid.
MS m/z:398$(M+H)^+$

Example 57

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(R)-hydroxypropyl)benzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and (R)-(-)-1-amino-2-propanol in 83% yield according to the procedures similar to those described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.67(2H, d, J=8.8Hz), 7.40-7.20(5H, m), 6.80(2H, d, J=8.8Hz), 6.50-6.40(1H, m), 5.14(1H, dd, J=7.0, 7.7Hz), 4.59(1H, d, J=7.0Hz), 4.55(1H, d, J=7.0Hz), 4.23-4.13(1H, m), 4.07-3.95(1H, m), 3.66-3.55(1H, m), 3.40-3.20(1H, m), 3.30(3H, s), 3.13-3.00(2H, m), 2.90-2.80(1H, m), 2.85(3H, s), 2.76-2.52(3H, m), 2.13-1.98(1H, m), 1.85-1.45(2H, m), 1.23(3H, d, J=6.2Hz).

Example 58

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(R)-hydroxypropyl)benzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(R)-hydroxypropyl)benzamide in 84% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.68(2H, d, J=8.8Hz), 7.40-7.20(5H, m), 6.82(2H, d, J=8.8Hz), 6.50-6.38(1H, m), 5.16(1H, dd, J=5.9, 8.8Hz), 4.28-4.18(1H, m), 4.10-3.95(1H, m), 3.66-3.55(1H, m), 3.40-3.35(1H, m), 3.16-3.00(2H, m), 2.95-2.80(1H, m), 2.84(3H, s), 2.74(1H, d, J=9.2Hz), 2.56(1H, dd, J=4.4, 9.5Hz), 2.40-2.25(1H, m), 2.17-2.00(1H, m), 1.90-1.40(3H, m), 1.24(3H, d, J=6.6Hz).

IR(neat) : 3350, 1610cm^{-1}.

HCl salt: amorphous solid.
MS m/z:398$(M+H)^+$

Anal. Calcd for $C_{23}H_{31}N_3O_3 \cdot HCl \cdot 0.85CH_4O$: C, 62.11 ; H, 7.74 ; N, 9.11
Found : C,62.50 ; H, 8.13 ; N,9.37.

Example 59

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-isobutylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and isobutylamine in 72% yield according

to the procedures similar to those described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.65(2H, d, J=8.8Hz), 7.34-7.24(5H, m), 6.80(2H, d, J=8.8Hz), 6.04-5.92(1H, m), 5.18-5.08(1H, m), 4.59(1H, d, J=7.0Hz), 4.55(1H, d, J=6.6Hz), 4.22-4.13(1H, m), 3.29(3H, s), 3.28-3.23(2H, m), 3.10-3.02(2H, m), 2.84-2.80(1H, m), 2.84(3H, s), 2.72-2.57(3H, m), 2.12-1.98(1H, m), 1.89-1.79(1H, m), 1.78-1.69(1H, m), 0.96(6H, d, J=6.6Hz).

Example 60

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}- N'-isobutylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-isobutylbenzamide in 86% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.66(2H, d, J=8.8Hz), 7.35-7.26(5H, m), 6.81(2H, d, J=8.8Hz), 6.06-5.96(1H, m), 5.15(1H, dd, J=5.9, 8.8Hz), 4.26-4.18(1H, m), 3.26(2H, t, J=6.2Hz), 3.13(1H, dd, J=8.8, 12.8Hz), 3.03(1H, dd, J=5.9, 12.8Hz), 2.92-2.85(1H, m), 2.84(3H, s), 2.73(1H, d, J=9.5Hz), 2.56(1H, dd, J=4.6, 9.7Hz), 2.36-2.28(1H, m), 2.16-2.04(1H, m), 1.96-1.58(3H, m), 0.97(6H, d, J=7.0Hz).

1R(neat) : 3350, 1610cm^{-1}.

HCl salt: amorphous solid.

MS m/z:396$(M+H)^+$

Anal. Calcd for $C_{24}H_{33}N_3O_2 \cdot HCl \cdot 0.5H_2O$: C, 65.36 ; H, 8.00 ; N, 9.53
Found : C,65.58 ; H, 8.17 ; N,9.48.

Example 61

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-allylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-

(S)-phenylethyl]-N-methylamino}benzoic acid and allylamine in 33% yield according to the procedures similar to those described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.67(2H, d, J=8.8Hz), 7.31-7.26(5H, m), 6.79(2H, d, J=9.2Hz), 6.01-5.88(2H, m), 5.28-5.27(1H, m), 5.21-5.11(2H, m), 4.59(1H, d, J=7.0Hz), 4.55(1H, d, J=6.6Hz), 4.25-4.13(1H, m), 4.09-4.04(2H, m), 3.29(3H, s), 3.07-3.03(2H, m), 2.85-2.80(1H, m), 2.85(3H, s), 2.75-2.67(1H, m), 2.64-2.56(1H,m), 2.06-2.01(1H, m), 1.76-1.60(1H, m), 1.60-1.52(1H, m).

Example 62

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-allylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-allylbenzamide in 52% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.68(2H, d, J=8.8Hz), 7.35-7.26(5H, m), 6.81(2H, d, J=8.8Hz), 6.01-5.89(2H, m), 5.28-5.12(3H, m), 4.27-4.19(1H, m), 4.09-4.05(2H, m), 3.13(1H, dd, J=9.2, 12.8Hz), 3.03(1H, dd, J=5.9, 12.8Hz), 2.92-2.86(1H, m), 2.84(3H, s), 2.73(1H, d, J=9.2Hz), 2.56(1H, dd, J=4.8, 9.5Hz), 2.33-2.30(1H,m), 2.27-2.08(1H, m), 1.67-1.48(2H, m).

1R(neat) : 3350, 1610cm^{-1}.

HCl salt: amorphous solid.
MS m/z:380$(M+H)^+$

Anal. Calcd for $C_{23}H_{29}N_3O_2 \cdot HCl \cdot 0.1H_2O \cdot CH_4O$: C, 64.09 ; H, 7.66 ; N, 9.34
Found : C,63.86 ; H, 7.85 ; N,9.32.

Example 63

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-cyclopropylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and cyclopropylamine in 48% yield according to the procedures similar to those described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.61(2H, d, J=8.8Hz), 7.33-7.22(5H, m), 6.78(2H, d, J=8.8Hz), 6.11-6.02(1H, m), 5.15-5.11(1H, m), 4.59(1H, d, J=6.6Hz), 4.55(1H, d, J=6.6Hz), 4.19-4.14(1H, m), 3.29(3H, s), 3.07-3.03(2H, m), 2.90-2.80(1H, m), 2.84(3H, s), 2.72-2.66(1H, m), 2.64-2.56(2H,m), 2.08-2.01(1H, m), 1.79-1.73(1H, m), 1.37-1.25(1H, m), 0.94-0.80(2H, m), 0.60-0.54(2H, m).

Example 64

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}- N'-cyclopropylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-cyclopropylbenzamide in 76% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.63(2H, d, J=9.2Hz), 7.35-7.23(5H, m), 6.79(2H, d, J=8.8Hz), 6.12-6.04(1H, m), 5.15(1H, dd, J=5.9, 8.8Hz), 4.24-4.19(1H, m), 3.13(1H, dd, J=9.2, 12.8Hz),. 3.03(1H, dd, J=5.9, 10.3Hz), 2.94-2.84(2H, m), 2.83(3H, s), 2.78(1H, d, J=9.5Hz), 2.58-2.53(1H,m), 2.33-2.31(1H, m), 2.11-2.08 (1H, m), 1.68-1.61(2H, m), 0.87-0.80(2H, m), 0.60-0.54(2H, m).

IR(neat) : 3350, 1610cm^{-1}.

HCl salt: amorphous solid.

MS m/z:380$(M+H)^+$

Anal. Calcd for $C_{23}H_{29}N_3O_2 \cdot HCl \cdot 0.8H_2O$: C, 64.19 ; H, 7.40 ; N, 9.76

Found : C,64.04 ; H, 7.50 ; N,9.83.

Example 65

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(S)-sec-butylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and (S)-sec-butylamine in 18% yield according to the procedures similar to those described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.65(2H, d, J=8.8Hz), 7.40-7.20(5H, m), 6.79(2H, d, J=8.8Hz), 5.74(1H, d, J=8.4Hz), 5.13(1H, dd, J=6.6, 8.1Hz), 4.59(1H, d, J=7.0Hz), 4.55(1H, d, J=7.0Hz), 4.25-4.05(2H, m), 3.30(3H, s), 3.15-2.95(2H, m), 2.90-2.80(1H, m), 2.85(3H, s), 2.76-2.55(3H, m), 2.13-1.98(1H, m), 1.85-1.70(1H, m), 1.65-1.50(2H, m), 1.20(3H, d, J=6.6Hz), 0.95(3H, t, J=7.7Hz).

Example 66

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}- N'-(S)-sec-butylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(S)-sec-butylbenzamide in 100% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.65(2H, d, J=9.2Hz), 7.40-7.20(5H, m), 6.80(2H, d, J=9.2Hz), 5.76(1H, d, J=8.4Hz), 5.14(1H, dd, J=6.2, 8.8Hz), 4.25-4.05(2H, m), 3.17-2.98(2H, m), 2.95-2.78(1H, m), 2.83(3H, s), 2.72(1H, d, J=9.5Hz), 2.57(1H, dd, J=4.8, 9.5Hz), 2.40-2.28(1H, m), 2.20-1.95(2H, m), 1.70-1.50(3H, m), 1.20(3H, d, J=6.6Hz), 0.95(3H, t, J=7.3Hz).

HCl salt: amorphous solid.
MS m/z:396$(M+H)^+$

Anal. Calcd for $C_{24}H_{33}N_3O_2 \cdot HCl \cdot 0.3H_2O \cdot CH_4O$: C, 63.96 ; H, 8.29 ; N, 8.95
Found : C,64.14 ; H, 8.01 ; N,8.70.

Example 67

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-

methylamino}-N'-(R)-sec-butylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and (R)-sec-butylamine in 18% yield according to the procedures similar to those described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.65(2H, d, J=8.8Hz), 7.33-7.23(5H, m), 6.79(2H, d, J=9.2Hz), 5.74(1H, d, J=8.1Hz), 5.13(1H, dd, J=6.6, 7.7Hz), 4.59(1H, d, J=6.6Hz), 4.55(1H, d, J=6.6Hz), 4.19-4.08(2H, m), 3.29(3H, s), 3.09-2.98(2H, m), 2.90-2.80(1H, m), 2.84(3H, s), 2.72-2.57(3H, m), 2.13-1.98(1H, m), 1.78-1.75(1H, m), 1.60-1.49(2H, m), 1.20(3H, d, J=6.6Hz), 0.94(3H, t, J=7.7Hz).

Example 68

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}- N'-(R)-sec-butylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(R)-sec-butylbenzamide in 95% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.65(2H, d, J=8.8Hz), 7.40-7.20(5H, m), 6.80(2H, d, J=8.8Hz), 5.78(1H, d, J=8.3Hz), 5.14(1H, dd, J=5.9, 8.8Hz), 4.25-4.03(2H, m), 3.17-2.98(2H, m), 2.95-2.78(1H, m), 2.83(3H, s), 2.71(1H, d, J=9.5Hz), 2.58(1H, dd, J=4.8, 9.5Hz), 2.42-2.30(1H, m), 2.23(1H, br.s), 2.15-2.00(1H, m), 1.70-1.50(3H, m), 1.20(3H, d, J=6.6Hz), 0.95(3H, t, J=7.3Hz).

HCl salt: amorphous solid.
MS m/z:396$(M+H)^+$

Anal. Calcd for $C_{24}H_{33}N_3O_2 \cdot HCl \cdot 0.4H_2O \cdot CH_4O$: C, 63.72 ; H, 8.30 ; N, 8.92
Found : C,63.96 ; H, 8.08 ; N,9.08.

Example 69

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propargylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and propargylamine in 18% yield according to the procedures similar to those described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.65(2H, d, J=8.8Hz), 7.34-7.24(5H, m), 6.80(2H, d, J=9.2Hz), 6.12-6.03(1H, m), 5.14(1H, dd, J=6.6, 7.3Hz), 4.59(1H, d, J=7.0Hz), 4.55(1H, d, J=7.0Hz), 4.23(2H, q, J=2.6Hz), 4.19-4.14(1H, m), 3.29(3H, s), 3.07-3.03(2H, m), 2.85-2.80(1H, m), 2.85(3H, s), 2.75-2.70(1H, m), 2.67-2.56(2H, m), 2.25(1H, t, J=2.6Hz), 2.08-2.01(1H, m), 1.87-1.70(1H, m).

Example 70

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propargylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propargylbenzamide in 77% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.67(2H, d, J=8.8Hz), 7.35-7.24(5H, m), 6.81(2H, d, J=8.8Hz), 6.13-6.03(1H, m), 5.16(1H, dd, J=5.9, 9.0Hz), 4.24-4.21(3H, m), 3.13(1H, dd, J=9.5, 12.8Hz), 3.03(1H, dd, J=5.9, 12.8Hz), 2.93-2.86(1H, m), 2.84(3H, s), 2.73(1H, d, J=8.3Hz), 2.58-2.53(1H, m), 2.32-2.24(2H, m), 2.11-2.05(1H, m), 1.76-1.58(2H, m).

IR(neat) : 3300, 1610cm^{-1}.

HCl salt: amorphous solid.
MS m/z:378$(M+H)^+$

Anal. Calcd for $C_{23}H_{27}N_3O_2 \cdot HCl \cdot 0.8H_2O \cdot CH_4O$: C, 62.61 ; H, 7.36 ; N, 9.13
Found : C,62.23 ; H, 7.26 ; N,9.50.

Example 71

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-

methylamino}-N'-(3,3,3,-trifluoropropyl)benzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and 3,3,3,-trifluoropropylamine in 39% yield according to the procedures similar to those described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.63(2H, d, J=8.8Hz), 7.31-7.24(5H, m), 6.80(2H, d, J=9.2Hz), 6.21-6.12 (1H, m), 5.14(1H, dd, J=7.0, 8.1Hz), 4.59(1H, d, J=7.0Hz), 4.55(1H, d, J=7.0Hz), 4.21-4.12(1H, m), 3.69(2H, q, J=6.2Hz), 3.29(3H, s), 3.07-3.03(2H, m), 2.85(3H, s), 2.84-2.80(1H, m), 2.72-2.67(1H, m), 2.64-2.56(2H, m), 2.50-2.38(2H, m), 2.08-2.01(1H, m), 1.77-1.76(1H, m).

Example 72

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(3,3,3,-trifluoropropyl)benzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(3,3,3,-trifluoropropyl)benzamide in 69% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.65(2H, d, J=8.8Hz), 7.36-7.26(5H, m), 6.81(2H, d, J=9.2Hz), 6.26-6.20 (1H, m), 5.16(1H, dd, J=5.9, 9.2Hz), 4.25-4.19(1H, m), 3.69(2H, q, J=6.2Hz), 3.17-3.02(2H, m), 2.99-2.88(1H, m), 2.84(3H, s), 2.80-2.72(1H, m), 2.59-2.53(1H, m), 2.52-2.38(2H, m), 2.37-2.28(1H, m), 2.16-2.05(1H, m), 1.80-1.75(2H, m).

1R(neat) : 3350, 1610cm^{-1}.

HCl salt: amorphous solid.
MS m/z:436$(M+H)^+$

Anal. Calcd for $C_{23}H_{28}N_3O_2F_3 \cdot HCl \cdot 0.4H_2O$: C, 57.65 ; H, 6.27 ; N, 8.77
Found : C,57.60 ; H, 6.26 ; N,8.50.

Example 73

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(S)-hydroxypropyl)benzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and (S)-(+)-1-amino-2-propanol in 55% yield according to the procedures similar to those described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.67(2H, d, J=9.2Hz), 7.40-7.20(5H, m), 6.80(2H, d, J=8.8Hz), 6.50-6.40(1H, m), 5.14(1H, dd, J=7.0, 7.7Hz), 4.60(1H, d, J=6.6Hz), 4.55(1H, d, J=7.0Hz), 4.23-4.13(1H, m), 4.07-3.95(1H, m), 3.66-3.55(1H, m), 3.40-3.25(1H, m), 3.30(3H, s), 3.13-3.00(2H, m), 2.90-2.80(1H, m), 2.86(3H, s), 2.76-2.52(3H, m), 2.13-1.98(1H, m), 1.85-1.45(2H, m), 1.23(3H, d, J=6.2Hz).

Example 74

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(S)-hydroxypropyl)benzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(S)-hydroxypropyl)benzamide in 81% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.68(2H, d, J=8.8Hz), 7.40-7.20(5H, m), 6.80(2H, d, J=8.8Hz), 6.60-6.50(1H, m), 5.15(1H, dd, J=5.9, 9.2Hz), 4.28-4.18(1H, m), 4.07-3.93(1H, m), 3.66-3.55(1H, m), 3.35-3.23(1H, m), 3.13(1H, dd, J=9.2, 12.8Hz), 3.03(1H, dd, J=5.9, 12.8Hz), 2.95-2.80(1H, m), 2.83(3H, s), 2.72(1H, d, J=9.5Hz), 2.56(1H, dd, J=4.8, 9.9Hz), 2.40-2.25(1H, m), 2.20-1.75(3H, m), 1.70-1.55(1H, m), 1.22(3H, d, J=6.2Hz).

IR(neat) : 3350, 1610cm^{-1}.

Maleic acid salt: amorphous solid.

MS m/z:396$(M-H)^-$

Anal. Calcd for $C_{23}H_{31}N_3O_3 \cdot C_4H_4O_4 \cdot 0.3H_2O$: C, 62.49 ; H, 6.91 ; N, 8.10
Found : C,62.65 ; H, 7.24 ; N,7.90.

Example 75

Preparation of 4-{N-[1-(R)-(3-Methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide

(i) Methyl 4-{N-[1-(R)-(3-methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}benzoate

2-(S)-(3-Methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)ethanol and 1-(R)-(3-methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)ethanol were prepared from (R)-1-(3-methoxymethoxyphenyl)-1,2-ethanediol-2-tosylate in 58% yield as a mixture according to the procedures similar to those described in Preparation 3. Title compound was prepared by reacting the mixture of 2-(S)-(3-methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)ethanol and 1-(R)-(3-methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)ethanol with methyl 4-methylaminobenzoate in 54% yield according to the procedures similar to those described in Example 1 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.88 (2H, d, J = 8.8Hz), 7.23-7.19 (1H, m), 6.95-6.90(3H, m), 6.77(2H, d, J=8.8Hz), 5.13(2H, s), 5.12-5.08(1H, m), 4.58 (1H, d, J = 6.6Hz), 4.53 (1H, d, J = 6.6Hz), 4.22-4.15 (1H, m), 3.84 (3H, s), 3.45(3H, s), 3.28 (3H, s), 3.13-2.92(2H, m), 2.88 (3H, s), 2.90-2.84(1H, m), 2.75-2.66(1H, m), 2.61-2.50(2H, m), 2.06-1.99(1H, m), 1.83-1.74(1H, m).

(ii) 4-{N-[1-(R)-(3-Methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}benzoic acid

This was prepared from methyl 4-{N-[1-(R)-(3-methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}benzoate in 91% yield according to the procedures similar to those described in Example 1 (ii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.91 (2H, d, J = 8.8Hz), 7.30-7.12(1H, m), 6.98-6.84(3H, m), 6.82(2H, d, J=9.2Hz), 5.35-5.25(1H, m), 5.14(2H, s), 4.60(1H, d, J = 7.0Hz), 4.55(1H, d, J = 7.0Hz), 4.30-4.20(1H, m), 3.45(3H, s), 3.30(3H, s), 3.25-3.05(2H, m), 2.90(3H, s), 2.90-2.60(4H, m), 2.20-2.00(1H, m), 1.90-1.80(1H, m).

(iii) 4-{N-[1-(R)-(3-Methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 4-{N-[1-(R)-(3-methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}benzoic acid and n-propylamine in 71% yield according to the procedures similar to those described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.64(2H, d, J= 8.8Hz), 7.28-7.18(1H, m), 6.98-6.88(3H, m), 6.78(2H, d, J=9.2Hz), 6.00-5.90(1H, m), 5.14(2H, s), 5.09(1H, t, J=7.7Hz), 4.58(1H, d, J = 7.0Hz), 4.54(1H, d, J = 7.0Hz), 4.25-4.12(1H, m), 3.46(3H, s), 3.45-3.35(2H, m), 3.29(3H, s), 3.08-2.96(2H, m), 2.92-2.80(1H, m), 2.86(3H, s), 2.75-2.50(3H, m), 2.12-1.95(1H, m), 1.85-1.52(3H, m), 0.97(3H, t, J=7.3Hz).

Example 76

Preparation of 4-{N-[1-(R)-(3-t-Butoxycarbonylmethoxyphenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 4-{N-[1-(R)-(3-methoxymethoxyphenyl)-2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide in 11% over all yield according to the procedures similar to those described in Example 2 and Example 36.

^{1}H NMR (270MHz, $CDCl_3$) δ 7.65(2H, d, J=8.8Hz), 7.26-7.20(1H, m), 6.92-6.89 (2H, m), 6.79(2H, d, J=9.2Hz), 6.79-6.75(1H, m), 6.01-5.92(1H, m), 5.11(1H, dd, J=7.0, 7.2Hz), 4.47(2H, s), 4.26-4.17(1H, m), 3.45-3.35(2H, m), 3.04(2H, d, J=7.3Hz), 2.98-2.91(1H, m), 2.81(3H, s), 2.69(1H, d, J=9.2Hz), 2.49(1H, dd, J=4.8, 9.9Hz), 2.40-2.25(1H, m), 2.17-2.06(1H, m), 1.75-1.52(4H, m), 1.45(9H, s), 0.98(3H, t, J=7.3Hz).

Example 77

Preparation of 4-{N-[1-(R)-(3-Carboxymethoxyphenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 4-{N-[1-(R)-(3-t-butoxycarbonylmethoxyphenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide in 86% yield according to the procedures similar to those described in Example 37.

HCl salt: ligt brown solid.

^{1}H NMR (270MHz, DMSO-d6) δ 10.55-10.15(1H, m), 8.32-8.24(1H, m), 7.91-7.80(2H, m), 7.34(1H, t, J=7.7Hz), 7.21-7.09(2H,m), 6.98-6.84(3H, m), 5.95-5.80(1H, m), 4.72(2H, s), 4.60-4.40(1H, m), 4.40-3.20(7H, m), 2.82(1.2H, s), 2.81(1.8H,s), 2.50-2.30(2H, m), 2.15-1.85(2H, m), 1.70-1.50(2H, m), 0.96(3H, t, J=7.3Hz).

1R(KBr) : 3400, 1730, 1610cm^{-1}.

MS m/z: 456(M+H)$^+$.

Anal. Calcd for $C_{25}H_{33}N_3O_5 \cdot HCl \cdot 3.5H_2O$: C, 54.10 ; H, 7.45; N, 7.57
Found : C, 54.49 ; H, 7.85 ; N, 7.76

Example 78

Preparation of 3-Fluoro-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

(i) Methyl 3-fluoro-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoate

This was prepared from 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol and methyl 3-fluoro-4-methylaminobenzoate in 52% yield according to the procedures similar to those described in Example 29 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.72-7.62(2H, m), 7.38-7.22 (5H, m), 6.81(1H, t, J=8.8Hz), 5.12-5.02(1H, m), 4.58 (1H, d, J = 7.0Hz), 4.55(1H, d, J = 7.0Hz), 4.15-4.03(1H,m), 3.88(3H, s), 3.30(3H, s), 3.18-2.95(2H, m), 2.88-2.78(1H, m), 2.71(3H, d, J=0.7Hz), 2.67-2.45(3H, m), 2.05-1.90(1H, m), 1.75-1.60(1H, m)

(ii) 3-Fluoro-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid

This was prepared from methyl 3-fluoro-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoate in 100%

yield according to the procedures similar to those described in Example 1 (ii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.63-7.54(2H, m), 7.38-7.22 (5H, m), 6.76(1H, t, J=8.4Hz), 5.27-5.17(1H,m), 4.61 (1H, d, J = 7.0Hz), 4.58(1H, d, J = 7.0Hz), 4.30-4.20(1H,m), 3.55-3.43(1H, m), 3.40-3.15(3H, m), 3.31(3H, s), 2.95-2.73(2H, m), 2.74(3H, s), 2.22-2.05(1H, m), 1.95-1.80(1H, m)

(iii) 3-Fluoro-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 3-fluoro-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and n-propylamine in 80% yield according to the procedures similar to those described in Example 1 (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.48 (1H, dd, J = 1.8, 14.3Hz), 7.41-7.20(6H, m), 6.80(1H, t, J = 8.8Hz), 6.08-6.00(1H,m), 5.03-4.92(1H,m), 4.58 (1H, d, J = 7.0Hz), 4.54(1H, d, J = 6.6Hz), 4.13-4.03(1H,m), 3.45-3.35(2H, m), 3.30(3H, s), 3.18-3.07(1H, m), 3.02(1H, dd, J=6.6, 12.8Hz), 2.83(1H, dd, J=6.2, 9.9Hz), 2.68(3H, s), 2.65-2.45((3H, m), 2.07-1.93 (1H, m), 1.75-1.55(3H, m), 0.99(3H, t, J=7.3Hz)

Example 79

Preparation of 3-Fluoro-4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 3-fluoro-4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide in 40% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.53 (1H, dd, J = 2.2, 14.3Hz), 7.41-7.24(6H, m), 6.83(1H, t, J = 8.8Hz), 6.11-6.02(1H,m), 5.12-5.02(1H,m), 4.22-4.13(1H,m), 3.45-3.35(2H, m), 3.35-3.23(1H, m), 3.00(1H, dd, J=5.5, 12.5Hz), 2.92-2.73(2H, m), 2.68(3H, s), 2.60-2.50(1H, m), 2.33-2.18(1H, m), 2.13-1.95(1H, m), 1.90 (1H, br. s), 1.70-1.48(3H, m), 0.99(3H, t, J=7.3Hz)

Maleic acid salt: amorphous solid.

1R(KBr) : 3350, 1620cm^{-1}.

MS : 400(M+H)$^+$

Anal. Calcd for $C_{23}H_{30}N_3O_2F \cdot C_4H_4O_4 \cdot 0.5H_2O$: C, 61.82 ; H, 6.72; N, 8.01
Found : C, 61.52 ; H,6.70 ; N, 8.02.

Example 80

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2,2,3,3,3,-pentafluoropropyl)benzamide

This was prepared from 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol and 4-methylamino-N'-(2,2,3,3,3,-pentafluoropropyl)benzamide in 32% yield according to the procedures similar to those described in Example 1 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.67(2H, d, J=8.8Hz), 7.34-7.25 (5H, m), 6.81(2H, d, J=9.2Hz), 6.30-6.13(1H, m), 5.15(1H, t, J=7.7Hz), 4.59 (1H, d, J = 6.6Hz), 4.55(1H, d, J = 6.6Hz), 4.23-4.10(3H,m), 3.30(3H, s), 3.07-3.04(2H, m), 2.87(3H, s), 2.84-2.80(1H, m), 2.76-2.67(1H, m), 2.64-2.53(2H, m), 2.09-2.01(1H, m), 1.77-1.70(1H, m)

Example 81

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2,2,3,3,3,-pentafluoropropyl)benzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2,2,3,3,3,-pentafluoropropyl)benzamide in 97% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.69(2H, d, J=8.8Hz), 7.36-7.26 (5H, m), 6.82(2H, d, J=8.8Hz), 6.20-6.16(1H, m), 5.16(1H, dd, J=5.5, 8.8Hz), 4.25-4.21(1H, m), 4.14(2H, dd, J=6.2, 14.7Hz), 3.14(1H, dd, J=9.2, 12.8Hz), 3.04(1H, dd, J=5.9, 12.8Hz), 2.95-2.88(1H, m), 2.86(3H, s), 2.73(1H, d, J=9.5Hz), 2.57(1H, dd, J=4.8, 9.5Hz), 2.37-2.29(1H, m), 2.16-2.05(1H, m), 1.80-1.60(2H, m)

IR(neat) : 3350, 1610cm^{-1}.

HCl salt: amorphous solid.

MS m/z:470(M-H)$^-$

Anal. Calcd for $C_{23}H_{26}N_3O_2F_5 \cdot HCl \cdot 0.4CH_4O$: C, 53.63 ; H, 5.44 ; N, 8.16
Found : C,53.90 ; H, 5.33 ; N,7.79.

Example 82

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-tert-amylbenzamide

This was prepared from 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol and 4-methylamino-N'-tert-amylbenzamide in 36% yield according to the procedures similar to those described in Example 1 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.60(2H, d, J=8.8Hz), 7.34-7.23 (5H, m), 6.78(2H, d, J=8.8Hz), 5.73-5.62(1H, m), 5.13(1H, dd, J=6.2, 8.4Hz), 4.60 (1H, d, J = 7.0Hz), 4.55(1H, d, J =7.0Hz), 4.17-4.15(1H, m), 3.30(3H, s), 3.07-3.02(2H, m), 2.83(3H, s), 2.86-2.80(1H, m), 2.72-2.64(1H, m), 2.63-2.57(2H, m), 2.09-2.01(1H, m), 1.87-1.79(1H, m), 1.83(2H, q, J=7.3Hz), 1.39(6H, s), 0.88(3H, t, J=7.3Hz).

Example 83

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-tert-amylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-tert-amylbenzamide in 88% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.62(2H, d, J=8.8Hz), 7.35-7.22 (5H, m), 6.79(2H, d, J=8.8Hz), 5.73-5.63(1H, m), 5.14(1H, dd, J=5.9, 9.2Hz), 4.24-4.20(1H,m),

3.12(1H, dd, J=8.8, 12.8Hz), 3.03(1H, dd, J=5.9, 12.8Hz), 2.93-2.86(1H, m), 2.83(3H, s), 2.73(1H, d, J=9.9Hz), 2.56(1H, dd, J=4.8, 9.5Hz), 2.36-2.27(1H, m), 2.14-2.04(1H, m), 1.83(2H, q, J=7.3Hz), 1.80-1.60(2H,m), 1.40(6H, s), 0.88(3H, t, J=7.3Hz).

IR(neat) : 3350, 1610cm^{-1}.

HCl salt: amorphous solid.
MS m/z:410(M+H)$^+$

Anal. Calcd for $C_{25}H_{35}N_3O_2 \cdot HCl \cdot 0.2CH_4O$: C, 66.78 ; H, 8.16 ; N, 9.35
Found : C,66.67 ; H, 8.43 ; N,9.33.

Example 84

Preparation of 4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-tert-butylbenzamide

This was prepared from 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol and 4-methylamino-N'-tert-butylbenzamide in 66% yield according to the procedures similar to those described in Example 1 (i).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.61(2H, d, J=8.8Hz), 7.40-7.20 (5H, m), 6.78(2H, d, J=9.2Hz), 5.90-5.65(1H, m), 5.18-5.10(1H, m), 4.60 (1H, d, J = 6.6Hz), 4.56(1H, d, J =7.0Hz), 4.24-4.14(1H,m), 3.30(3H, s), 3.10-2.98(2H, m), 2.90-2.78(1H, m), 2.84(3H, s), 2.76-2.54(3H, m), 2.15-1.95(1H, m), 1.80-1.60(1H, m), 1.45(9H, s).

Example 85

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-tert-butylbenzamide

This was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-tert-butylbenzamide in 52% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.62(2H, d, J=8.8Hz), 7.35-7.24 (5H, m), 6.79(2H, d, J=9.2Hz), 5.83-5.77(1H, m), 5.14(1H, dd, J=5.5, 8.8Hz), 4.26-4.18(1H,m), 3.13(1H, dd, J=9.2, 12.8Hz), 3.03(1H, dd, J=5.9, 12.8Hz), 2.92-2.86(1H, m), 2.83(3H, s), 2.74(1H, d, J=9.9Hz), 2.55(1H, dd, J=4.8, 9.9Hz), 2.36-2.27(1H, m), 2.11-2.08(1H, m), 1.72-1.54(2H, m), 1.45(9H, s).

1R(neat) : 3350, 1610cm^{-1}.

HCl salt: amorphous solid.

MS m/z:396$(M+H)^+$

Anal. Calcd for $C_{24}H_{33}N_3O_2 \cdot HCl \cdot 1.2H_2O$: C, 63.55 ; H, 8.09 ; N, 9.26

Found : C,63.34 ; H,7.93 ; N,9.01.

Example 86

Preparation of 5-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylpicolinamide

This was prepared from 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol and 5-methylamino-N'-propylpicolinamide in 24% over all yield according to the procedures similar to those described in Example 1 (i) and Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 8.12(1H, d, J=3.3Hz), 8.02(1H, d, J=8.8Hz), 7.82-7.74(1H, m), 7.38-7.24 (5H, m), 7.13(1H, dd, J=3.3, 8.8Hz), 5.10(1H, dd, J=5.5, 9.5Hz), 4.30-4.20(1H, m), 3.45-3.35(2H, m), 3.17(1H, dd, J=9.5, 12.8Hz), 3.01(1H, dd, J=5.5, 12.8Hz), 2.95-2.84(1H, m), 2.91(3H, s), 2.70(1H, d, J=9.2Hz), 2.61(1H, dd, J=4.8, 9.5Hz), 2.42-2.30(1H, m), 2.18-2.02(1H, m), 1.80-1.55(4H,m), 0.98(3H, t, J=7.3Hz).

Fumaric acid salt: amorphous solid.

1R(KBr) : 3400, 1650cm^{-1}.

MS m/z:383$(M+H)^+$

Anal. Calcd for $C_{22}H_{30}N_4O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$: C, 61.52 ; H, 6.95 ; N, 11.04
Found : C, 61.75 ; H, 7.09 ; N, 10.95.

Example 87

Preparation of 4-{N-Hydroxy-N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]amino}-N'-propylbenzamide

This was prepared from 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol and methyl 4-hydroxyaminobenzoate in 33% over all yield according to the procedures similar to those described in Example 1 (i),(ii) and (iii).

^{1}H NMR (270MHz, $CDCl_3$) δ 7.55(2H, d, J=8.8Hz), 7.43-7.18 (5H, m), 6.90(2H, d, J=8.8Hz), 6.05-5.95(1H, m), 4.87(1H, dd, J=5.1, 10.3Hz), 4.63 (1H, d, J = 7.0Hz), 4.60(1H, d, J =7.0Hz), 4.30-4.20(1H, m), 3.58-3.46(2H, m), 3.43-3.25(2H, m), 3.35(3H, s), 2.95-2.50(4H, m), 2.20-1.80(2H, m), 1.70-1.50(2H, m), 0.96(3H, t, J=7.3Hz).

Example 88

Preparation of 4-{N-Hydroxy-N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]amino}-N'-propylbenzamide

This was prepared from 4-{N-hydroxy-N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]amino}-N'-propylbenzamide in 63% yield according to the procedures similar to those described in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 8.86(1H, s), 8.18-8.08(1H ,m), 7.64(2H, d, J=8.8Hz), 7.42(2H, d, J=6.6Hz). 7.27-7.12 (3H, m), 7.07(2H, d, J=8.8Hz), 4.96(1H, dd, J=6.6, 7.3Hz), 4.62 (1H, d, J = 4.8Hz), 4.15-4.05(1H,m), 3.20-3.10(2H, m), 3.07-2.92(2H, m), 2.74(1H, dd, J=6.2, 9.5Hz), 2.56(2H, t, J=7.3Hz), 2.36(1H, dd, J=4.0, 9.5Hz), 2.00-1.80(1H, m), 1.55-1.40(3H, m), 0.86(3H, t, J=7.3Hz).

Fumaric acid salt: amorphous solid.

IR(KBr) : 3300, 1630cm^{-1}.

MS m/z:384(M+H)$^+$

Anal. Calcd for $C_{22}H_{29}N_3O_3 \cdot C_4H_4O_4 \cdot 0.5H_2O$: C, 61.40 ; H, 6.74 ; N, 8.26
Found : C, 61.40 ; H,6.78 ; N, 8.08.

Example 89

Preparation of 4-{N-[2-(3-(S)-Fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(S)-hydroxypropyl)benzamide

This was prepared from 4-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}benzoic acid and (S)-(+)-1-amino-2-propanol in 38% yield according to the procedures similar to those described in Example 1 (iii).

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.67(2H, d, J = 8.8Hz), 7.35-7.23 (5H, m), 6.78(2H, d, J = 8.8Hz), 6.47-6.42 (1H, m), 5.21-4.94(1H, m), 5.11(1H, dd, J=6.2, 8.4Hz), 4.03-3.97(1H, m), 3.64-3.56(1H, m), 3.35-3.25(1H, m), 3.16-3.01(2H, m), 2.89-2.76(3H, m), 2.87(3H, s), 2.58-2.50(1H, m), 2.11-1.90(1H, m), 1.76-1.55(2H, m), 1.22(3H, d, J=6.6Hz)

Fumaric acid salt: amorphous solid.

MS m/z: 400(M+H)$^+$

Anal. Calcd for $C_{23}H_{30}N_3O_2F \cdot C_4H_4O_4 \cdot 0.8CH_4O$: C, 61.70 ; H, 6.93; N, 7.76.
Found : C, 61.52 ; H, 6.59 ; N,7.64 .

Example 90

Preparation of 2-Chloro-4-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-fluoropyrrolidin-1-yl)-2-(R)-phenylethanol and 2-chloro-4-methylamino-

N'-propylbenzamide in 13% yield according to the procedures similar to those described in Example 1 (i).

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.75(1H, d, J = 8.4Hz), 7.38-7.20 (5H, m), 6.78-6.70(2H, m), 6.58-6.50 (1H, m), 5.25-4.95(1H, m), 5.04(1H, dd, J=6.2, 8.4Hz), 3.50-3.37(2H, m), 3.12(1H, dd, J=9.2, 12.8Hz), 3.03(1H, dd, J=5.9, 12.8Hz), 2.90-2.75(2H, m), 2.85(3H, s), 2.60-2.50(1H, m), 2.17-1.85 (2H, m), 1.70-1.55(3H, m), 0.99(3H, t, J=7.3Hz).

Fumaric acid salt: amorphous solid.

MS m/z: 418$(M+H)^+$

Anal. Calcd for $C_{23}H_{29}N_3OFCl \cdot C_4H_4O_4 \cdot 0.1H_2O$: C, 60.52 ; H, 6.25; N, 7.84.
Found : C, 60.16 ; H, 6.61 ; N,7.64 .

Example 91

Preparation of 4-{N-[2-(3-(S)-Fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-hydroxyamino}-N'-propylbenzamide

This was prepared from 2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-fluoropyrrolidin-1-yl)-2-(R)-phenylethanol and 4-hydroxyamino-N'propylbenzamide in 56% yield according to the procedures similar to those described in Example 1 (i).

HCl salt:.
mp: 195-200°C

^{1}H NMR (270MHz, DMSO) δ 10.67(1H, br. s), 9.35-9.20(1H, m), 8.30-8.20(1H, m), 7.70(2H, d, J = 8.4Hz), 7.50-7.15 (7H, m), 5.70-5.35(2H, m), 4.25-3.30(6H, m), 3.25-3.10(2H, m), 2.70-2.10(2H, m), 1.60-1.40(2H, m), 0.86(3H, t, J=7.3Hz)

IR(KBr) : 1600 cm^{-1}

MS m/z: 384(M-H)$^-$

Anal. Calcd for $C_{22}H_{28}N_3O_2F \cdot HCl$: C, 62.63 ; H, 6.93; N, 9.96.
Found : C, 62.23 ; H, 7.10 ; N,9.79 .

Example 92

Preparation of 5-{N-[2-(3-(S)-Fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylpicolinamide

This was prepared from 2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-fluoropyrrolidin-1-yl)-2-(R)-phenylethanol and 5-methylamino-N'-propylpicolinamide in 26% yield according to the procedures similar to those described in Example 1 (i).

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 8.10(1H, d, J=2.9Hz), 8.01(1H, d, J=8.8Hz), 7.82-7.74(1H, m), 7.38-7.24 (5H, m), 7.11(1H, dd, J=2.9, 8.8Hz), 5.23-4.95(1H, m), 5.07(1H, dd, J=5.9, 9.5Hz), 3.45-3.35(2H, m), 3.18(1H, dd, J=9.5, 12.8Hz), 3.03(1H, dd, J=5.9, 12.8Hz), 2.95-2.75(2H, m), 2.93(3H, s), 2.60-2.50(1H, m), 2.18-1.90(2H, m), 1.70-1.55(3H, m), 0.98(3H, t, J=7.3Hz)..

Fumaric acid salt: amorphous solid.
1R(KBr) : 1650cm^{-1}.

MS m/z:385(M+H)$^+$

Anal. Calcd for $C_{22}H_{29}N_4OF \cdot C_4H_4O_4 \cdot 0.6H_2O$: C, 61.07 ; H, 6.74 ; N, 10.96
Found : C, 60.87 ; H, 6.35 ; N, 10.89.

Example 93

Preparation of 4-{N-Methylamino-N-[2-(3-pyrrolin-1-yl)-1-(S)-phenylethyl]}-N'-propylbenzamide

This was prepared from 2-(R)-phenyl-2-(3-pyrrolin-1-yl)ethanol and 4-methylamino-N'-propylbenzamide in 12% yield according to the procedures similar to

those described in Example 1 (i).

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.65(2H, d, J =9.2Hz), 7.35-7.24 (5H, m), 6.80(2H, d, J=9.2Hz), 5.97 (1H,br. s), 5.72(2H, s), 5.12(1H, dd, J=7.0, 7.7Hz), 3.58-3.49(4H, m), 3.38(2H, dd, J=5.9, 7.3Hz), 3.25-3.21(2H, m), 2.86(3H, s), 1.61(2H, dd, J=7.3, 14.7Hz), 0.97(3H, t, J=7.3Hz)

1R(neat) : 2950, 1650cm^{-1}.

HCl salt: amorphous solid.

MS m/z: 363(M^+)

Anal. Calcd for $C_{23}H_{29}N_3O \cdot HCl \cdot 0.1CH_4O \cdot 0.9H_2O$: C, 66.16 ; H, 7.74; N, 10.02.
Found : C, 66.56 ; H,7.64 ; N,9.65 .

Example 94

Preparation of 4-{N-[2-(3-(R)-fluoropyrrolidine1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 2-(3-(R)-fluoropyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(R)-fluoropyrrolidin-1-yl)-2-(R)-phenylethanol and 4-methylamino-N'-propylbenzamide in 47% yield according to the procedures similar to those described in Example 1 (i).

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.67(2H, d, J = 8.8Hz), 7.34-7.24 (5H, m), 6.79(2H, d, J = 8.8Hz), 6.13 (1H, br. s), 5.25-4.95(1H, m), 5.13(1H, dd, J=6.2, 8.4Hz), 3.41-3.34(2H, m), 3.17-3.05(2H, m), 3.02-2.77(3H, m), 2.82(3H, s), 2.59-2.51(1H, m), 2.09-1.91(2H, m), 1.72-1.54(2H, m), 0.95(3H, t, J=7.3Hz)

HCl salt: amorphous solid.

MS m/z: 383(M^+)

Anal. Calcd for $C_{23}H_{30}N_3OF \cdot HCl \cdot 0.5H_2O$: C, 64.40 ; H, 7.52; N, 9.80.
Found : C, 64.51 ; H, 7.74 ; N, 9.46.

Example 95

Preparation of 4-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(R)-phenylethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 2-(3-(S)-fluoropyrrolidin-1-yl)-1-(R)-phenylethanol and 2-(3-(S)-fluoropyrrolidin-1-yl)-2-(S)-phenylethanol and 4-methylamino-N'-propylbenzamide in 28% yield according to the procedures similar to those described in Example 1 (i).

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.65(2H, d, J = 8.4Hz), 7.30-7.24 (5H, m), 6.80(2H, d, J = 8.4Hz), 6.00 (1H, br. s), 5.25-4.95(2H, m), 3.43-3.36(2H, m), 3.13-3.07(2H, m), 3.01-2.89(2H, m), 2.83(3H, s), 2.58-2.55(1H, m), 2.10-2.00(1H, m), 2.00-1.92(1H, m), 1.73-1.55(3H, m), 0.97(3H, t, J=7.3Hz)

HCl salt: amorphous solid.

MS m/z: 383(M^+)

Anal. Calcd for $C_{23}H_{30}N_3OF \cdot HCl \cdot 2H_2O$: C, 60.58 ; H, 7.74; N, 9.21.
Found : C, 60.59 ; H, 7.36 ; N, 9.23.

Example 96

Preparation of 4-{N-[2-(3-(S)-Chloropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

This was prepared from 2-(3-(S)-chloropyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-chloropyrrolidin-1-yl)-2-(R)-phenylethanol and 4-methylamino-N'-propylbenzamide in 40% yield according to the procedures similar to those described in Example 1 (i).

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.68(2H, d, J = 8.8Hz), 7.33-7.27 (5H, m), 6.78(2H, d, J = 8.8Hz), 6.23 (1H, br. s), 5.08(1H, dd, J=7.3, 7.7Hz), 4.30-4.25(1H,, m),

3.40-3.33(2H, m), 3.13-3.08(3H, m), 2.84(3H, s), 2.81-2.65(3H, m), 2.36-2.22(1H, m), 2.02-1.95(1H, m), 1.63-1.53(2H, m), 0.94(3H, t, J=7.3Hz).

HCl salt: amorphous solid.

MS m/z: 399(M^+)

Anal. Calcd for $C_{23}H_{30}N_3OCl \cdot HCl \cdot 2.5H_2O$: C, 57.38 ; H, 7.54; N,8.73.
Found : C,57.10 ; H, 7.42 ; N,8.48.

Example 97

Preparation of 4-{N-[2-(3-(S)-Chloropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(S)-hydroxypropyl)benzamide

This was prepared from 2-(3-(S)-chloropyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-chloropyrrolidin-1-yl)-2-(R)-phenylethanol and 4-methylamino-N'-(2-(S)-hydroxypropyl)benzamide in 45% yield according to the procedures similar to those described in Example 1 (i).

^1H NMR (270MHz, free amine, $CDCl_3$) δ 7.68(2H, d, J = 9.2Hz), 7.35-7.28 (5H, m), 6.79(2H, d, J = 8.8Hz), 6.52 (1H, br. s), 5.10(1H, t, J=7.3Hz), 4.32-4.27(1H, m), 4.02-3.97(1H, m), 3.64-3.56(1H, m), 3.35-3.24(1H, m), 3.14-3.10(3H, m), 2.86(3H, s), 2.82-2.76(2H, m), 2.74-2.69(1H, m), 2.38-2.27(1H, m), 2.05-1.80(2H, m), 1.22(3H, d, J=6.2Hz)

HCl salt: amorphous solid.

MS m/z: 415(M^+)

Example 98

Preparation of 4-{N-[2-(3-(S)-Chloropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(R)-hydroxypropyl)benzamide

This was prepared from 2-(3-(S)-chloropyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-chloropyrrolidin-1-yl)-2-(R)-phenylethanol and 4-methylamino-N'-(2-(R)-

hydroxypropyl)benzamide in 44% yield according to the procedures similar to those described in Example 1 (i).

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.68(2H, d, J = 9.2Hz), 7.35-7.23 (5H, m), 6.79(2H, d, J = 9.2Hz), 6.53 (1H, br. s), 5.11(1H, t, J=7.3Hz), 4.33-4.27(1H, m), 4.03-3.98(1H, m), 3.64-3.56(1H, m), 3.35-3.25(1H, m), 3.16-3.11(1H, m), 3.12(2H, d, J=7.3Hz), 2.85(3H, s), 2.83-2.71(3H, m), 2.36-2.27(1H, m), 2.04-1.98(1H, m), 1.22(3H, d, J=6.2Hz)

HCl salt: amorphous solid.

MS m/z: 416$(M+H)^+$

Anal. Calcd for $C_{23}H_{30}N_3O_2Cl \cdot HCl \cdot H_2O$: C, 58.72 ; H,7.07; N,8.93.
Found : C, 58.56 ; H, 7.00 ; N,8.76 .

Example 99

Preparation of 4-{N-[2-(3-Oxopyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

To a stirred solution of oxalylchloride(0.26ml, 3.0mmol) in CH_2Cl_2(15ml) was added a solution of DMSO(0.29ml, 4.0mmol) in CH_2Cl_2(1ml) at -78°C. The reaction mixture was stirred for 10min and a solution of 4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide(573mg, 1.5mmol) in CH_2Cl_2(5ml) was added and stirring was continued for an additional 15 min at -78°C, 60min at -45°C. Triethylamine(1.6ml, 11.0mmol) was added and then the reaction mixture was allowed to warm to room temperature. Saturated NH_4Cl aqueous solution was added and extracted with AcOEt. The extract was washed with water and brine, dried(Na_2SO_4), and concentrated to give brown oil, which was purified by column chromatography (silica gel; 70g, CH_2Cl_2/MeOH: 50/1-40/1) to give 195mg(34%) of pale yellow oil.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.66(2H, d, J = 9.2Hz), 7.36-7.25 (5H, m), 6.80(2H, d, J = 9.2Hz), 6.01 (1H, br. s), 5.17(1H, t, J=7.3Hz), 3.43-3.36(2H, m), 3.17-

3.13(2H, m), 3.07-2.92(4H, m), 2.85(3H, s), 2.35(2H, t, J=7.0Hz), 1.6-1.53(2H, m), 0.97(3H, t, J=7.7Hz).

HCl salt: amorphous solid.

MS m/z: 379(M^+)

Example 100

Preparation of 4-{N-[2-(3-(S)-Hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide

4-{N-[2-(3-(S)-Methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide was prepared from 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethanol and 2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-2-(R)-phenylethanol and 4-methylamino-N'-propylbenzamide according to the procedures similar to those described in Example 1 (i). Title compound was prepared from 4-{N-[2-(3-(S)-methoxymethoxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide in 65% over all yield according to the procedures similar to those described in Example 2. The title compound was the same as one obtained in Example 2.

^{1}H NMR (270MHz, free amine, $CDCl_3$) δ 7.66(2H, d, J=8.8Hz), 7.40-7.20(5H, m), 6.80(2H, d, J=9.2Hz), 6.05-5.90(1H, m), 5.14(1H, dd, J=5.9, 9.2Hz), 4.28-4.16(1H, m), 3.46-3.32(2H, m), 3.12(1H, dd, J=9.2, 12.8Hz), 3.03(1H, dd, J=5.9, 12.8Hz), 2.95-2.80(1H,m), 2.83(3H, s), 2.72(1H, d, J=9.5Hz), 2.56(1H, dd, J=4.8, 9.9Hz), 2.33(1H, ddd, J=6.2, 8.8, 8.8Hz), 2.18-2.00(1H, m), 1.89(1H, br. s), 1.70-1.50(3H, m), 0.97(3H, t, J=7.3Hz)

HCl salt: amorphous solid.

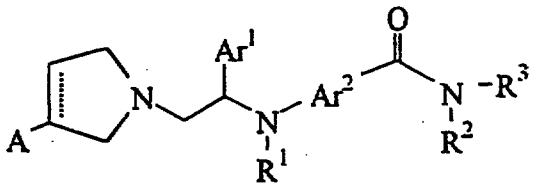
MS m/z:382($M+H)^+$

Anal. Calcd for $C_{23}H_{31}N_3O_2 \cdot HCl \cdot 1.5H_2O \cdot CH_4O$: C, 60.43 ; H, 8.24 ; N, 8.81

Found : C,60.23 ; H,8.62 ; N,9.03.

The chemical structures of the compounds prepared in Examples 1 to 100 are summarized in the following tables. In the tables, H- represents hydrogen; Me-, Et-, Pr-, Bu-, Pe- and Am- represent methyl, ethyl, propyl, butyl, pentyl and amyl respectively; F- and Cl- represent fluorine and chlorine respectively; All- and Prp- represent allyl and propargyl respectively; MeO-and EtO- represent methoxy and ethoxy respectively; HO- represents hydroxy; Car- represents carboxy; Ph-, Py-, Th- and Bn- represent phenyl, pyridyl, thienyl and benzyl respectively; MOM-, t-Boc-, 2-THP- and TBDMS- represent methoxymethyl, t-butoxycarbonyl, tetrahydropyran-2-yl and t-butyldimethylsilyl respectively; tri-F-Pr-, penta-F-Pr- and 2-HO-Pr-represent 3,3,3-trifluoropropyl, 2,2,3,3,3-pentafluoropropyl and 2-hydroxypropyl respectively; O= represents oxo; and cyc represents cyclic.

Table 1



(I)

Ex.-#	A	Ar^1	Ar^2	R^1	R^2	R^3
1	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	Pr-	H-
2	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	Pr-	H-
3	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	Me-	H-
4	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	Me-	H-
5	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	Et-	H-
6	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	Et-	H-
7	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	Bu-	H-
8	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	Bu-	H-
9	(S)-2-THP-O-	(S)-Ph-	1,4-Ph-	Me-	Pe-	H-
10	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	Pe-	H-
11	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	i-Pr-	H-
12	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	i-Pr-	H-
13	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	Ph-	H-
14	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	Ph-	H-
15	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	2-Cl-Bn-	H-
16	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	2-Cl-Bn-	H-
17	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	Me-	Me-
18	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	Me-	Me-
19	(S)-2-THP-O-	(S)-Ph-	1,4-Ph-	Me-	Pr-	Me-
20	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	Pr-	Me-
21	(S)-MOM-O-	(S)-Ph-	1,3-Ph-	Me-	Pr-	H-
22	(S)-HO-	(S)-Ph-	1,3-Ph-	Me-	Pr-	H-

Table 1 (continued)

Ex.-#	A	Ar^1	Ar^2	R^1	R^2	R^3
33	(S)-MOM-O-	(S)-3-MOM-O-Ph-	1,4-Ph-	Me-	Pr-	H-
34	(S)-HO-	(S)-3-HO-Ph-	1,4-Ph-	Me-	Pr-	H-
35	(S)-HO-	(S)-3-MeO-Ph-	1,4-Ph-	Me-	Pr-	H-
36	(S)-HO-	(S)-3-t-Boc-MeO-	1,4-Ph-	Me-	Pr-	H-
37	(S)-HO-	(S)-3-Car-MeO-Ph-	1,4-Ph-	Me-	Pr-	H-
38	H-	(S)-Ph-	1,4-Ph-	Me-	Pr-	H-
40	(S)-MOM-O-	(S)-Ph-	2,5-Th-	Me-	Pr-	H-
41	(S)-HO-	(S)-Ph-	2,5-Th-	Me-	Pr-	H-
42	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	H-	Pr-	H-
43	(S)-HO-	(S)-Ph-	1,4-Ph-	H-	Pr-	H-
44	(S)-MOM-O-	(S)-3-Cl-Ph-	1,4-Ph-	Me-	Pr-	H-
45	(S)-HO-	(S)-3-Cl-Ph-	1,4-Ph-	Me-	Pr-	H-
46	(S)-F-	(S)-Ph-	1,4-Ph-	Me-	Pr-	H-
47	(S)-MOM-O-	(R)-Ph-	1,4-Ph-	Me-	Pr-	H-
48	(S)-HO-	(R)-Ph-	1,4-Ph-	Me-	Pr-	H-
51	(S)-TBDMS-O-	(S)-Ph-	1,4-Ph-	Me-	EtO-	H-
52	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	EtO-	H-
55	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	3-HO-Pr-	H-
56	(S)-HO-	(S)-Ph	1,4-Ph-	Me-	3-HO-Pr-	H-
57	(S)-MOM-O-	(S)-Ph	1,4-Ph-	Me-	2-(R)-HO-Pr-	H-
58	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	2-(R)-HO-Pr-	H-

Table 1 (continued)

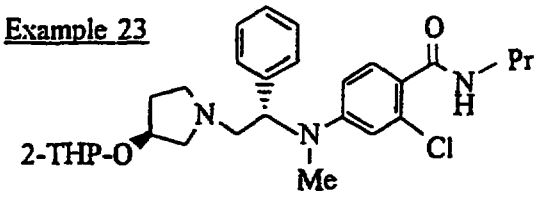
Ex.-#	A	Ar^1	Ar^2	R^1	R^2	R^3
59	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	i-Bu-	H-
60	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	i-Bu-	H-
61	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	All-	H-
62	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	All-	H-
63	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	cyc-Pr-	H-
64	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	cyc-Pr-	H-
65	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	(S)-sec-Bu-	H-
66	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	(S)-sec-Bu-	H-
67	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	(R)-sec-Bu-	H-
68	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	(R)-sec-Bu-	H-
69	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	Prp-	H-
70	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	Prp-	H-
71	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	tri-F-Pr-	H-
72	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	tri-F-Pr-	H-
73	(S)-MOM-O-	(S)-Ph	1,4-Ph	Me	2-(S)-HO-Pr	H
74	(S)-OH	(S)-Ph-	1,4-Ph-	Me-	2-(S)-HO-Pr-	H-
75	(S)-MOM-O-	(R)-3-MOM-O-Ph-	1,4-Ph-	Me-	Pr-	H-
76	(S)-HO-	(R)-3-t-Boc-MeO-Ph-	1,4-Ph-	Me-	Pr-	H-
77	(S)-HO-	(R)-3-Car-MeO-Ph-	1,4-Ph-	Me-	Pr-	H-

Table 1 (continued)

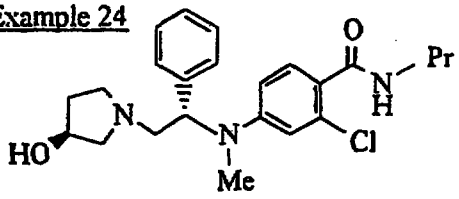
Ex.-#	A	Ar^1	Ar^2	R^1	R^2	R^3
80	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	penta-F-Pr-	H-
81	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	penta-F-Pr-	H-
82	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	t-Am-	H-
83	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	t-Am-	H-
84	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	Me-	t-Bu-	H-
85	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	t-Bu-	H-
87	(S)-MOM-O-	(S)-Ph-	1,4-Ph-	HO-	Pr-	H-
88	(S)-HO-	(S)-Ph-	1,4-Ph-	HO-	Pr-	H-
89	(S)-F-	(S)-Ph-	1,4-Ph-	Me-	2-(S)-HO-Pr-	H-
91	(S)-F-	(S)-Ph-	1,4-Ph-	HO-	Pr-	H-
94	(R)-F-	(S)-Ph-	1,4-Ph-	Me-	Pr-	H-
95	(S)-F-	(R)-Ph-	1,4-Ph-	Me-	Pr-	H-
96	(S)-Cl-	(S)-Ph-	1,4-Ph-	Me-	Pr-	H-
97	(S)-Cl-	(S)-Ph-	1,4-Ph-	Me-	2-(S)-HO-Pr-	H-
98	(S)-Cl-	(S)-Ph-	1,4-Ph-	Me-	2-(R)-HO-Pr-	H-
99	O=	(S)-Ph-	1,4-Ph-	Me-	Pr-	H-
100	(S)-HO-	(S)-Ph-	1,4-Ph-	Me-	Pr-	H-

Table 2

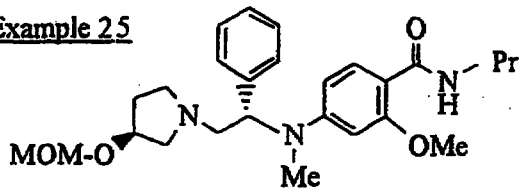
Example 23



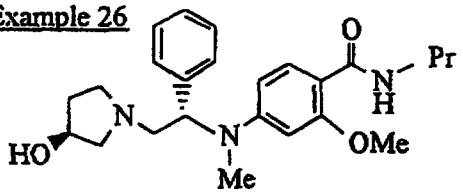
Example 24



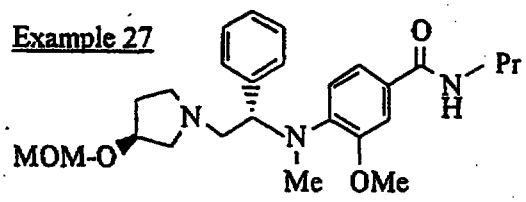
Example 25



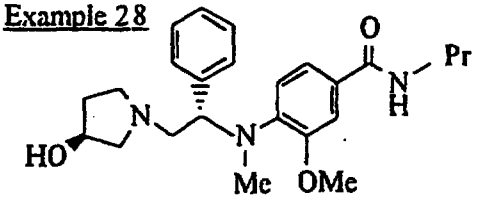
Example 26



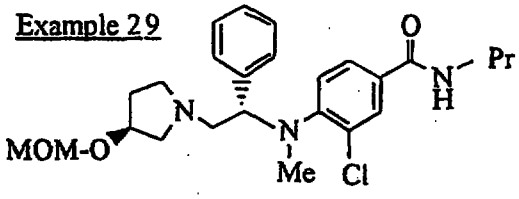
Example 27



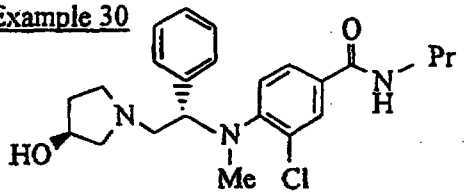
Example 28



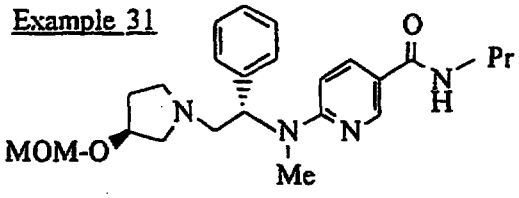
Example 29



Example 30



Example 31



Example 32

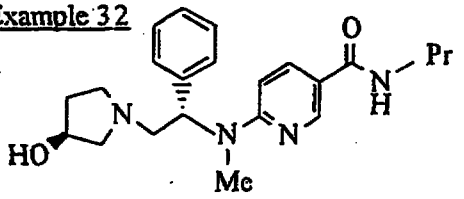
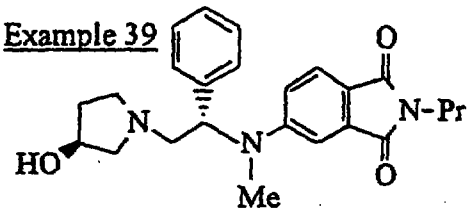
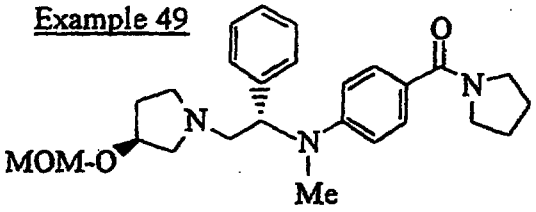


Table 2 (continued)

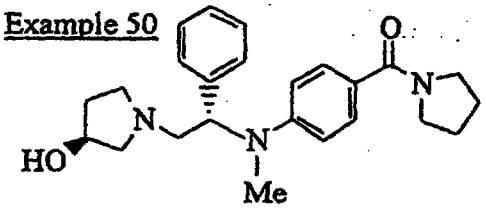
Example 39



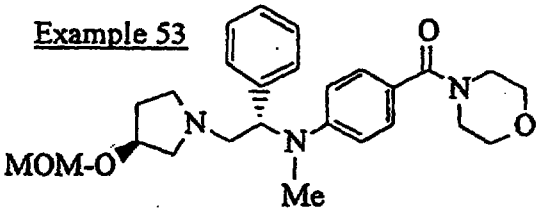
Example 49



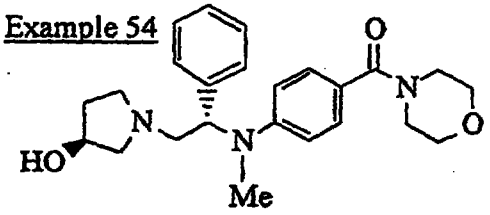
Example 50



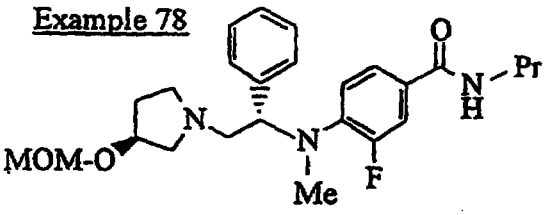
Example 53



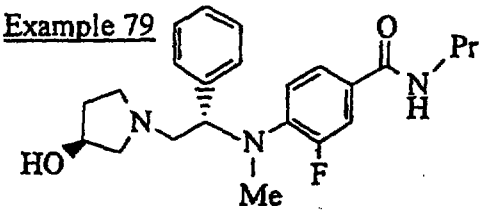
Example 54



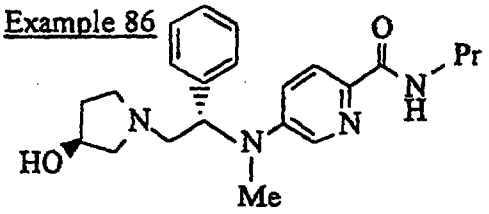
Example 78



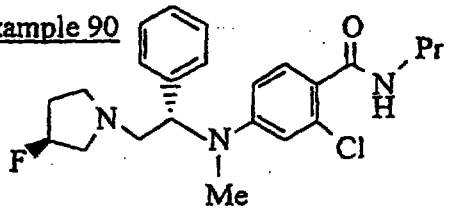
Example 79



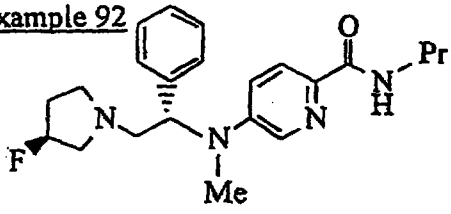
Example 86



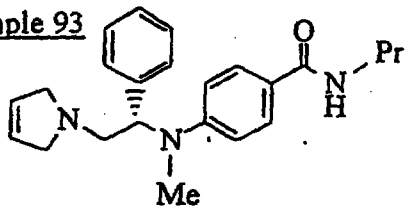
Example 90



Example 92

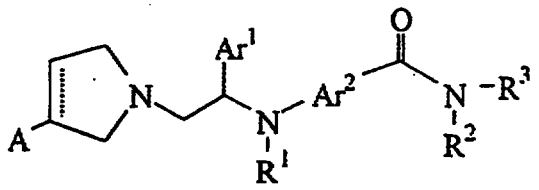


Example 93



CLAIMS

1. A compound of the following formula:



(I)

and the salts thereof, wherein

A is hydrogen, halo, hydroxy, C_1-C_6 alkyl, halo C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_6 alkoxy, oxo, OY wherein Y is a hydroxy protecting group, or absent;

the broken line represents an optional double bond with proviso that if the broken line is a double bond, then A is absent;

Ar^1 is phenyl optionally substituted by one or more substituents selected from halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy-C_1-C_4 alkoxy, CF_3, carboxy-C_1-C_4 alkoxy and C_1-C_4 alkoxy-carbonyl-C_1-C_4 alkoxy;

Ar^2 is aryl or heteroaryl selected from phenyl, naphthyl, pyridyl, thienyl, furyl, pyrrolyl and pyrimidyl, the aryl or heteroaryl being optionally substituted by one or more substituents selected from halo, hydroxy, amino, nitro, carboxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylamino, di C_1-C_4 alkylamino, halo C_1-C_4 alkyl, C_1-C_4 alkylthio and sulfonyl methyl;

R^1 is hydrogen, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy or OY wherein Y is a hydroxy protecting group; and

R^2 and R^3 are independently selected from hydrogen, hydroxy, C_1-C_7 alkyl optionally substituted by one or more hydroxy or halo, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_7 alkoxy, phenyl optionally substituted by halo, phenyl C_1-C_7 alkyl, halo substituted phenyl C_1-C_7 alkyl, and $(CH_2)nX$-R^4 wherein n is one or two; X is O, NH or S and R^4 is C_1-C_3 alkyl, or when Ar^2 is phenyl, -Ar^2-C(=O)-N(R^2)- is a phthalimide group and R^3 is C_1-C_7 alkyl, or

R^2 and R^3, together with the nitrogen atom to which they are attached, form a pyrrolidine, piperidine or morpholine ring, optionally substituted by C_1-C_3 alkyl or halo.

2. A compound according to Claim 1, wherein

A is hydrogen, halo, hydroxy, oxo or OY; or if the broken line is a double bond, then A is absent;

Ar^1 is phenyl optionally substituted by one to three substituents selected from halo, hydroxy, C_1-C_4 alkoxy, carboxy C_1-C_4 alkoxy and C_1-C_4 alkoxy-carbonyl-C_1-C_4 alkoxy;

Ar^2 is phenyl, pyridyl or thienyl, optionally substituted by one to two halo or C_1-C_4 alkoxy;

R^1 is hydrogen, hydroxy or C_1-C_4 alkyl; and

R^2 and R^3 are independently selected from hydrogen, C_1-C_7 alkyl optionally substituted by one or more hydroxy or halo, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_4 alkoxy phenyl and halo substituted phenyl C_1-C_7 alkyl, when Ar^2 is phenyl, -Ar^2-C(=O)-N(R^2)- is a phthalimide group and R^3 is C_1-C_7 alkyl, or

R^2 and R^3, together with the nitrogen atom to which they are attached, form a pyrrolidine or morpholine ring.

3. A compound according to Claim 2, wherein

A is hydrogen, fluorine, chlorine, hydroxy or OY wherein Y is methoxymethyl or tetrahydropyranyl; or if the broken line is a double bond, then A is absent;

Ar^1 is phenyl optionally substituted by chlorine, hydroxy, methoxy or carboxymethoxy;

Ar^2 is phenyl, pyridyl or thienyl, optionally substituted by chlorine, fluorine or methoxy;

R^1 is C_1-C_4 alkyl;

R^2 is C_1-C_7 alkyl optionally substituted by hydroxy or fluorine, C_2-C_6 alkenyl, halo substituted phenylmethyl or phenyl; and

R^3 is hydrogen or methyl; or

R^2 and R^3, together with the nitrogen atom to which they are attached, form a pyrrolidine or morpholine ring.

4. A compound accroding to Claim 3, wherein

A is hydroxy, fluorine or chlorine; or if the broken line is a double bond, then A is absent; Ar^1 is phenyl optionally substituted by carboxymethoxy; Ar^2 is phenyl optionally substituted by methoxy or pyridyl; R^1 is C_1-C_4 alkyl; R^2 is C_1-C_7 alkyl optionally substitute by hydroxy; and R^3 is hydrogen.

5. A compound according to Claim 4 selected from

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-2-methoxy-N'-propylbenzamide;

6-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylnicotinamide;

4-{N-[1-(S)-(3-carboxymethoxyphenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(S)-hydroxypropyl)benzamide;

5-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylpicolinamide;

4-{N-methylamino-N-[2-(3-pyrrolin-1-yl)-1-(S)-phenylethyl]}-N'-propylbenzamide; and

4-{N-[2-(3-(S)-chloropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(S)-hydroxypropyl)benzamide.

6. A compound according to Claim 3 selected from

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-isopropylbenzamide;

3-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

2-chloro-4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-3-methoxy-N'-propylbenzamide;

3-chloro-4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[1-(S)-(3-hydroxyphenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-(3-methoxyphenyl)-ethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[1-(S)-phenyl-2-(pyrrolidin-1-yl)ethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[1-(S)-(3-chlorophenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(R)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-pyrrolidinebenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-morpholinebenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(R)-hydroxypropyl)benzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-isobutylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-allylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(3,3,3,-trifluoropropyl)benzamide;

3-fluoro-4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2,2,3,3,3,-pentafluoropropyl)benzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-tert-amylbenzamide;

5-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylpicolinamide;

4-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(S)-hydroxypropyl)benzamide;

2-chloro-4-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide; and

4-{N-[2-(3-(S)-chloropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide.

7. A compound according to Claim 2 selected from

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-methylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-ethylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-butylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-pentylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-phenylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-chlorobenzyl)benzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N',N'-dimethylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-methyl-N'-propylbenzamide;

5-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propyl-2-thiophenecarboxamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]amino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylphthalimide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-ethoxybenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(3-hydroxypropyl)benzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-cyclopropylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(S)-sec-butylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(R)-sec-butylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propargylbenzamide;

4-{N-[1-(R)-(3-carboxymethoxyphenyl)-2-(3-(S)-hydroxypyrrolidin-1-yl)-ethyl]-N-

methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-tert-butylbenzamide;

4-{N-hydroxy-N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]amino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-hydroxyamino}-N'-propylbenzamide;

4-{N-[2-(3-(R)-fluoropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-fluoropyrrolidin-1-yl)-1-(R)-phenylethyl]-N-methylamino}-N'-propylbenzamide;

4-{N-[2-(3-(S)-chloropyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-(2-(R)-hydroxypropyl)benzamide; and

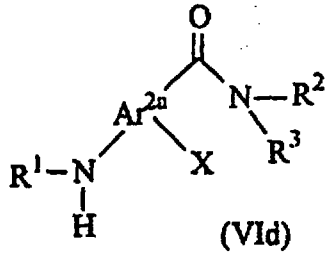
4-{N-[2-(3-oxopyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamino}-N'-propylbenzamide.

8. A pharmaceutical composition for the prevention or treatment of a medical condition for which agonist activity toward opioid kappa receptor is needed, in a mammalian subject, which comprises a therapeutically effective amount of a compound according to Claim 1, and a pharmaceutically inert carrier.

9. A pharmaceutical composition according to Claim 8, which is useful as an analgesic, anesthetic, anti-inflammatory or neuroprotective agent, or useful in the treatment of arthritis, stroke or functional bowel disease.

10. A method for the treatment of a medical condition for which agonist activity toward opioid kappa receptor is needed, in a mammalian subject, which comprises administering to said subject a therapeutically effective amount of a compound according to Claim 1.

11. A compound of the following formula:



(VId)

wherein

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Ar^{2a} is phenyl, pyridyl or thienyl;

X is hydrogen, halo or C_1-C_7 alkoxy;

R^1 is hydrogen, optionally protected hydroxy or C_1-C_4 alkyl; and

R^2 and R^3 are independently hydrogen or C_1-C_7 alkyl optionally substituted by hydroxy or halo.

12. A compound according to Claim 11 selected from

4-methylamino-N'-propylbenzamide;

5-N-methylamino-N'-propylpicolinamide;

2-chloro-4-methylamino-N'-propylbenzamide;

4-methylamino-N'-(2-(S)-hydroxypropyl)benzamide;

4-methylamino-N'-(2-(R)-hydroxypropyl)benzamide;

4-methylamino-N'-(2,2,3,3,3-pentafluoropropyl)benzamide; and

4-methylamino-N'-tert-amylbezamide.

13. A compound selected from

2-(3-(S)-fluoropyrrolidin-1-yl)-1-(S)-phenylethanol;

2-(3-(S)-fluoropyrrolidin-1-yl)-2-(R)-phenylethanol;

2-(R)-phenyl-2-(3-pyrroline-1-yl)ethanol;

2-(3-(R)-fluoropyrrolidin-1-yl)-1-(S)-phenylethanol;

2-(3-(R)-fluoropyrrolidin-1-yl)-2-(R)-phenylethanol;

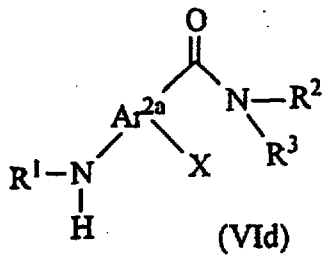
2-(3-(S)-fluoropyrrolidin-1-yl)-1-(R)-phenylethanol;

2-(3-(S)-fluoropyrrolidin-1-yl)-2-(S)-phenylethanol

2-(3-(S)-chloropyrrolidin-1-yl)-1-(S)-phenylethanol; and

2-(3-(S)-chloropyrrolidin-1-yl)-2-(R)-phenylethanol.

14. A process for producing a compound of formula (I), which comprises reacting an amide compound of the formula (VId):

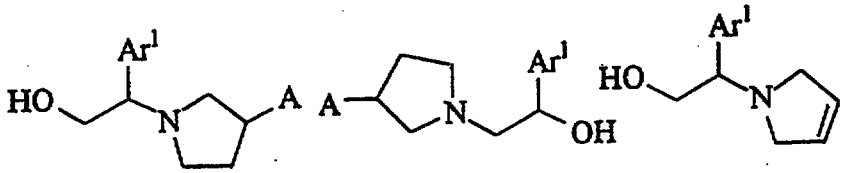


(VId)

with an ethanol compound selected from compounds (Va), (Vb) and (Vc), and a mixture of compounds (Va) and (Vb):

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(Va) (Vb) (Vc)

in the absence or presence of a base in a reaction inert solevent.

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