(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 199712163 B2
(10) Patent No. 706436

(54) Title
Novel compounds with analgesic effect

(51)[6] International Patent Classification(s)
C07D 243/08 A61K 051/04
A61K 031/395

(21) Application No: 199712163 (22) Application Date: 1996 .12 .11

(87) WIPO No: W097/23467

(30) Priority Data

(31) Number	(32) Date	(33) Country
9504662	1995 .12 .22	SE

(43) Publication Date : 1997 .07 .17
(43) Publication Journal Date : 1997 .09 .11
(44) Accepted Journal Date : 1999 .06 .17

(71) Applicant(s)
Astra Pharma Inc.

(72) Inventor(s)
Edward Roberts; Claes Wahlestedt

(74) Agent/Attorney
E F WELLINGTON and CO,312 St Kilda Road,MELBOURNE VIC 3004

OPI DATE 17/07/97 APPLN. ID 12163/97
AOJP DATE 11/09/97 PCT NUMBER PCT/SE96/01636

AU9712163

(T)

(51) International Patent Classification ° :
C07D 243/08, A61K 31/395, 51/04

A1

(11) International Publication Number: WO 97/23467

(43) International Publication Date: 3 July 1997 (03.07.97)

(21) International Application Number: PCT/SE96/01636

(22) International Filing Date: 11 December 1996 (11.12.96)

(30) Priority Data:
9504662-9 22 December 1995 (22.12.95) SE

(71) Applicant *(for all designated States except MG US)*: ASTRA PHARMA INC. [CA/CA]; 1004 Middlegate Road, Mississauga, Ontario L4Y 1M4 (CA).

(71) Applicant *(for MG only)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ROBERTS, Edward [GB/CA]; 2541 Chestnut Circle, St. Lazare de Vaudreuil, Quebec J7T 2A1 (CA). WAHLESTEDT, Claes [SE/CA]; 6 Chelsea Place, Montreal, Quebec H3G 2J9 (CA).

(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).

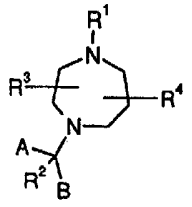
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NOVEL COMPOUNDS WITH ANALGESIC EFFECT

(57) Abstract

Compounds of formula (I) as well as their pharmaceutically acceptable salts, and pharmaceutical compositions comprising the novel compounds. The novel compounds of formula (I) are useful in the management of pain.



(I)

NOVEL COMPOUNDS WITH ANALGESIC EFFECT

Field of the invention

The present invention is related to novel compounds which are substituted 7-membered nitrogen rings, to a process for their preparation, their use and pharmaceutical compositions comprising the novel compounds. The novel compounds are used in therapy, and in particular for the treatment of pain.

Background and prior art

The δ receptor has been identified as having a role in many bodily functions such as circulatory and pain systems. Ligands for the δ receptor may therefore find potential use as analgesics, and/or as antihypertensive agents. Ligands for the δ receptor have also been shown to posess immunomodulatory activities.

The identification of at least three different populations of opioid receptors (μ, δ and κ) is now well established and all three are apparent in both central and peripheral nervous systems of many species including man. Analgesia has been observed in various animal models when one or more of these receptors has been activated.

With few exceptions, currently available selective opioid δ ligands are peptidic in nature and are unsuitable for administration by systemic routes. Some non-peptidic δ antagonists have been available for some time (see Takemori and Portoghese, 1992, Ann. Rev. Pharmacol. Tox., 32: 239-269. for review). These compounds, *e.g.* naltrindole, suffer from rather poor (*i.e.*, < 10-fold) selectivity for the δ receptor vs μ receptor binding and exhibit no analgesic activity, a fact which underscores the need for the development of highly selective non-peptidic δ ligands.

Recently, a non-peptidic δ agonist, BW 373U86, was described by Chang *et al.*, 1993, J. Pharmacol. Exp. Ther., 267: 852-857., as the first δ-selective non-peptide with analgesic activity, however, it shows significant affinity for the μ receptor.

Thus, the problem underlying the present invention was to find new analgesics having excellent analgesic effects, but also with an improved side-effect profile over current μ agonists and potential oral efficacy.

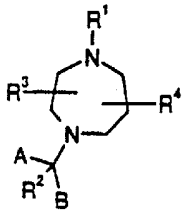
Analgesics that have been identified and are existing in the prior art have many disadvantages in that they suffer from poor pharmacokinetics and are not analgesic when administered by systemic routes. Also, it has been documented that preferred compounds, described within the prior art, show significant convulsive effects when administered systemically.

In WO 93/15062 and WO 95/045051, some diarylmethylpiperazine and diarylmethyl-piperidine compounds, including BW 373U86. are disclosed, but these prior art compounds are structurally distinct from the compounds acccording to the present invention.

The problem mentioned above has been solved by developing novel compounds which are 7-membered nitrogen rings, as will be described below.

Outline of the invention

The novel compounds according to the present invention are defined by the general formula (I)



wherein

A is a substituted or unsubstituted aromatic; an optionally substituted C_5-C_{10} hydroaromatic; a heteroaromatic or a heterohydroaromatic moiety having from 5 to 10 atoms selected from any of C, S, N and O, each optionally and independently substituted by 1 or 2 substituents independently selected from hydrogen, CH_3, $(CH_2)_oCF_3$, halogen, $CONR^5R^6$, CO_2R^5, COR^5, $(CH_2)_oNR^5R^6$, $(CH_2)_oCH_3$, $(CH_2)_oSOR^5R^6$, $(CH_2)_oSOR^5$, $(CH_2)_oSO_2R^5$, $(CH_2)_oSO_2NR^5$, $(CH_2)_oNR^5COR^6$ and $-NR^5(CH_2)_oCOR^1$; wherein o is 0, 1, or 2, and R^1, R^5 and R^6 are as defined below respectively;

R^1 is selected from hydrogen, a branched or straight C_1-C_6 alkyl, $CH_2CH{=}CH_2$, C_3-C_8 cycloalkyl, C_4-C_8 (alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl; C_6-C_{10} aryl; and heteroaryl having from 5 to 10 atoms selected from any of C, S, N and O;

R^5 and R^6 is each and independently as defined for R^1 above; or R^5 and R^6 taken together is $-(CH_2)r-$ wherein r is 4 or 5;

R^2 is selected from hydrogen, CH_3, OR^1, CO_2R^1, and $CH_2CO_2R^1$ wherein R^1 is as defined above;

B is a substituted or unsubstituted aromatic; an optionally substituted C_5-C_{10} hydroaromatic; a heteroaromatic or a heterohydroaromatic moiety having from 5 to 10 atoms selected from any of C, S, N and O, optionally substituted by 1-2 substituents each and independently selected from hydrogen, CH_3, CF_3, halogen, $(CH_2)_pCONR^5R^6$, $(CH_2)_pNR^5R^6$, $(CH_2)_pCOR^5$, $(CH_2)_pCO_2R^5$, OR^5, $(CH_2)_pSOR^5$, $(CH_2)_pSO_2R^5$, and $(CH_2)_pSO_2NR^5R^6$;
wherein p is 0, 1, 2 or 3 and wherein R^5 and R^6 are as defined above;

R^3 and R^4 is each and independently selected from R^5, $(CH_2)_pCONR^5R^6$, $(CH_2)_pNR^5R^6$, $(CH_2)_pCO_2R^5$, $(CH_2)_pPh$, $(CH_2)_p$(p-OH Ph), $(CH_2)_p$-3-indolyl, $(CH_2)_pSR^5$ or $(CH_2)_pOR^5$;
wherein p is 0, 1, 2, 3, or 4, and wherein R^5 and R^6 are as defined above.

Within the scope of the invention are also pharmaceutically acceptable salts of the compounds of the formula (I), as well as isomers, hydrates, isoforms and prodrugs thereof.

Preferred compounds according to the invention are compounds of the formula (I) wherein

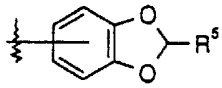
A is selected from phenyl, naphthyl, indolyl, benzofuranyl, benzothiophenyl, pyrryl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, and pyrrolidinyl; wherein

each A group being optionally substituted by 1 or 2 substituents independently selected from hydrogen, CH_3, $(CH_2)_oCF_3$, F, Cl, $CONR^5R^6$, CO_2R^5, COR^5, $(CH2)_oSOR^5$, $(CH2)_oSO_2R^5$, $(CH_2)_oSO_2NR^5$, $(CH_2)oNR^5COR^6$ and $NR^5(CH_2)_oCOR^6$; wherein R^5 and R^6 are as defined below, and o is 0 or 1;

R^1, R^5 and R^6 is each and independently selected from hydrogen, a branched or straight C_1-C_4 alkyl, C_3-C_5 cycloalkyl, C_4-C_8 (alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl, and phenyl;

R^2 is hydrogen, methyl, or OR^1 wherein R^1 is as defined above;

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, pyrryl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, pyrrolidinyl, indazolinyl, and



;

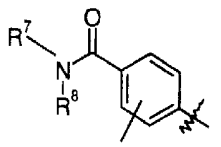
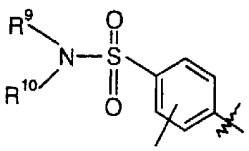
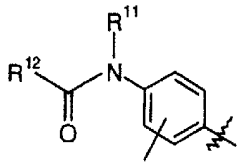
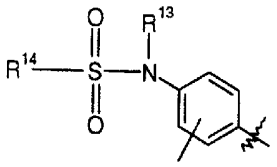
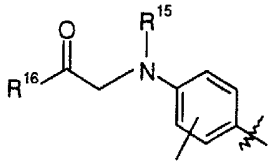
each B group being optionally substituted by 1-2 substituents independently selected from hydrogen, CH_3, CF_3, halogen, $(CH_2)_pCONR^5R^6$, $(CH_2)_pNR^5R^6$, $(CH_2)_pCOR^5$, $(CH_2)_pCO_2R^5$, and OR^5;

wherein p is 0 or 1, and wherein R^5 and R^6 are as defined above;

R^3 and R^4 are each and independently selected from hydrogen, CH_3, $CH(Me)_2$, $CH_2CH(Me)_2$, $CH(Me)CH_2CH_3$, $(CH_2)_pCON^5R^6$, $(CH_2)_pNR^5R^6$, $(CH_2)_pCONR^5R^6$, $(CH_2)_pCO_2R^5$, $(CH_2)_pPh$, $(CH_2)_p$(p-OH Ph), $(CH_2)_p$-3-indolyl, $(CH_2)_pSR^5$, and $(CH_2)_pOR^5$, wherein p is 0, 1, 2, or 3, and wherein R^5 and R^6 are as defined above.

Especially preferred compounds according to the invention are compounds of the formula (I) wherein

A is selected from





and


wherein the phenyl ring of each A substituent may be optionally and independently substituted by 1 or 2 substituents selected from H, CH_3, $(CH_2)_oCF_3$, F, Cl, $CONR^5R^6$, CO_2R^5, $(CH_2)_oSOR^5$, $(CH_2)oSO_2R^5$, $(CH_2)_oSO_2NR^5R^6$, $(CH_2)_oNR^5COR^6$, and $NR^5(CH_2)_oCOR^6$; wherein R^5 and R^6 are as defined below, and o is 0, 1 or 2;

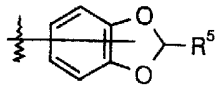
R^1 is selected from hydrogen, methyl, ethyl, $CH_2CH{=}CH_2$, or CH_2-cyclopropyl;

R^5 and R^6 is each and independently selected from phenyl, methyl and ethyl; or R^5 and R^6 taken together is -(CH_2)r- wherein r is 4 or 5;

R^2 is H, methyl, or OR^1;

R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, and R^{16}, is each and independently as defined for R^1 above;

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, indazolinyl, and



;

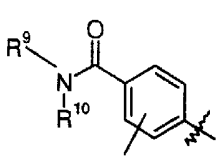
each B group being optionally substituted by 1-2 substituents independently selected from hydrogen, methyl, CF_3, halogen, $(CH_2)_pCONR^5R^6$, $(CH_2)_pNR^5R^6$, $(CH_2)_pCOR^5$, $(CH_2)_pCO_2R^5$, and OR^5,

wherein p is 0, 1, or 2, and wherein R^5 and R^6 are as defined above;

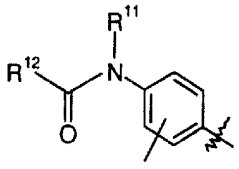
R^3 and R^4 are each and independently selected from H, CH_3, $CH(Me)_2$, $CH_2CH(Me)_2$, $CH(Me)CH_2CH_3$ $(CH_2)_pCONR^5R^6$, $(CH_2)_pNR^5R^6$, $(CH_2)_pCONR^5R^6$, $(CH_2)_pCO_2R^5$, $(CH_2)_pPh$, $(CH_2)_p$(p-OH Ph), $(CH_2)_p$-3-indolyl, $(CH_2)_pSR^5$, and $(CH_2)_pOR^5$;

wherein p is 0, 1, 2, or 3, and wherein R^5 and R^6 are as defined above.

Even more preferred is to use a compound where the A substituent is



or



and wherein R^9, R^{10}, R^{11} and R^{12}, are as defined above.

The substituents A and B respectively, may optionally be substituted at any position of the ring.

By "halogen" we mean chloro, fluoro, bromo and iodo.

By "aryl" we mean an aromatic ring having from 6 to 10 carbon atoms, such as phenyl and naphtyl.

By "heteroaryl" we mean an aromatic ring in which one or more of the from 5-10 atoms in the ring are elements other than carbon, such as N, S and O.

By "hydroaromatic" we mean a partly or fully saturated aromatic ring structure having 5-10 carbon atoms in the ring.

By "heterohydroaromatic" we mean a partly or fully saturated aromatic ring structure in which one or more of the 5-10 atoms in the ring are elements other than carbon, such as N, S and O.

By "isomers" we mean compounds of the formula (I), which differ by the position of their functional group and/or orientation. By "orientation" we mean stereoisomers, diastereoisomers, regioisomers and enantiomers.

By "isoforms" we mean compounds of the formula (I) which differ by their crystal lattice, such as crystalline compound and amorphous compounds.

By "prodrug" we mean pharmacologically acceptable derivatives, e.g. esters and amides, such that the resulting biotransformation product of the derivative is the active drug. The reference by Goodman and Gilmans, The Pharmacological basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs, p. 13-15, describing prodrugs generally, is hereby incorporated.

The novel compounds of the present invention are useful in therapy, especially for the treatment of pain.

A further aspect of the invention is the use of a compound of the formula (I) for the manufacture of a medicament for use in any of the diseases disclosed below.

The compounds are useful for modulating the analgesic effects acting at the μ opioid receptor subtype, including for modulating side effects seen with agents acting at the μ opioid receptor subtype such as morphine, especially respiratory depression, gut motility and abuse liability.

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

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

Compounds of the invention are useful for the treatment of diarrhea, depression, urinary incontinence, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Methods of preparation

Generalized Method A

An aldehyde or ketone is treated with a nucleophile such as a Grignard or organolithium species to produce the corresponding alcohol. This alcohol may then be converted into a suitable leaving group (X) such as an ester, sulphonate or halide which may in turn be displaced with a nucleophilic species such as a substituted or unsubstituted piperazine. N-(4)-unsubstituted piperazine derivatives may then be suitably substituted with a variety of groups via their organo halide or equivalent species, or acylated with a number of different acylating compounds. This sequence of events will give rise to compounds according to general formula I.

Generalized Method B

An N-protected amino acid, as its activated ester, may be reacted with a second amino acid ester. On treatment with an acid this species may then cyclize to form a piperazinedione. This dione may be reduced via a number of standard methods to the corresponding piperazine (*e.g.* a reducing agent such as lithium aluminium hydride, by conversion to the thioamide and subsequent desulphurization, hydrogenation in the presence of $POCl_3$ etc.) This piperazine may then be alkylated or acylated on one or more of the nitrogens and/or may be used subsequently in generalized method A.

Deprotection of functional groups or further modifications may then be necessary, these are described for each individual case. Specific examples for the above transformations are given in the experimental.

All transformations contemplated use reagents (including salts) and solvents known to the art of chemistry and to biotransformations carried out in a suitable biological medium to bring about these transformations and includes all reaction enhancing agents (*e.g.* HMPA), and chiral resolutions using chiral salt formation and chiral biological resolutions.

The best mode of carrying out the invention known at present is to use the compounds 1, 2, 3, 4, 9 and 10.

Detailed description of the invention

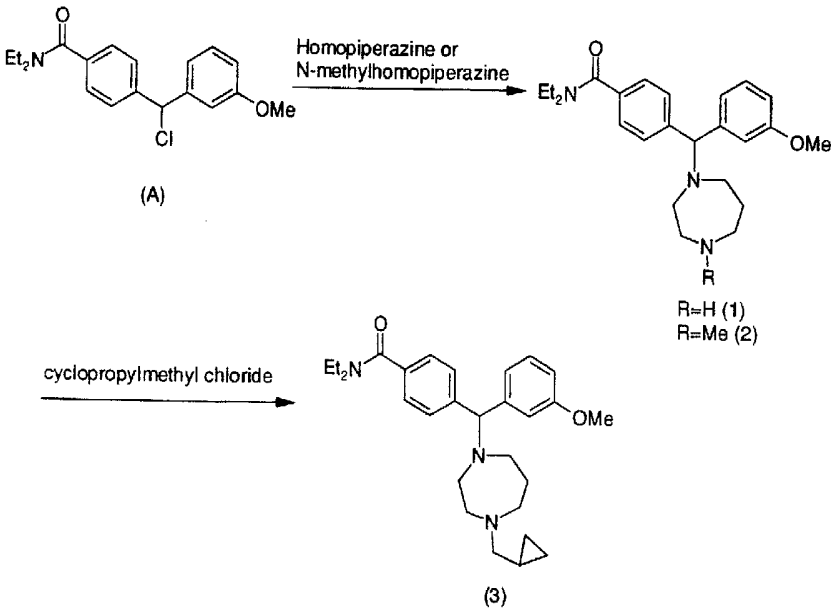
The invention will now be described in more detail by the following examples, which are not to be construed as limiting the invention.

EXAMPLES

The compounds according to Examples 1-3 were synthesized as shown in Scheme 1 below.

Scheme 1

4-(α-(1-Homopiperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide (1, 2 and 3).



A)

I. **Preparation of 4-(α-Hydroxyl-3-methoxybenzyl)-N,N-diethylbenzamide**

To a solution of 3-bromoanisole (5.61 g, 30.0 mmol) in dry THF (100 mL) was added dropwise a solution of n-butyllithium in hexane (1.6 M, 20 mL, 32 mmol) under nitrogen at -78°C. The mixture was stirred for 1 hr at the same temperature prior to the addition of 4-formyl-N,N-diethyl-benzamide (6.15 g, 30.0 mmol) in dry THF (20mL). The reaction

mixture was allowed to warm up to r.t (4 h), and then quenched with ammonium chloride (aq.). The solvent was removed *in vacuo*, the residue dissolved in ethyl acetate/heptane, 1:1, washed with brine and dried ($MgSO_4$). Evaporation of solvent *in vacuo* gave a crude product, which was purified by column chromatography on silica gel to afford 4-(α-hydroxyl-3-methoxybenzyl)-N,N-diethylbenzamide (6.15 g, 66%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.10 (3 H, br, $C\underline{H}_3CH_2N$-), 1.22 (3 H, br, $C\underline{H}_3CH_2N$-), 2.60 (1H, br, O<u>H</u>), 3.24 (2 H, br, $CH_3C\underline{H}_2N$-), 3.52 (2 H, br, $CH_3C\underline{H}_2N$-), 3.79 (3H, s, $OC\underline{H}_3$), 5.80 (1H, s, C<u>H</u>N), 6.81 (1 H, m, Ar<u>H</u>), 6.93 (1 H, m, Ar<u>H</u>), 6.94 (1H, m, Ar<u>H</u>), 7.25 (1 H, m, Ar<u>H</u>), 7.31 (2H, m, Ar<u>H</u>), 7.39 (2 H, m, Ar<u>H</u>).

II. <u>Preparation of 4-(α-Chloro-3-methoxybenzyl)-N,N-diethylbenzamide (compound A in Scheme 1)</u>

To a solution of 4-(α-hydroxyl-3-methoxybenzyl)-N,N-diethylbenzamide (3.13 g. 10.0 mmol), in AcOEt (20mL) was added 35% hydrochloric acid (20 mL) at 0° C. The reaction mixture was stirred for 12 hr at r.t. and extracted with AcOEt. The organic layers was washed with saturated ammonium chloride solution and brine, dried over $MgSO_4$ and evaporated to give a crude product, which was purified by column chromatography on silica gel to afford 4-(α-chloro-3-methoxybenzyl)-N,N-diethylbenzamide (**compound A**) (1.82 g, 55%): GC-MS: 331, 330, 296, 259, 224, 196, 165, 152, 112.

<u>Example 1</u>

<u>Preparation of 4-(α-(1-Homopiperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide (compound 1)</u>

A mixture of homopiperazine (200 mg, 2.0 mmol), 4-(α-chloro-3-methoxybenzyl)-N,N-diethylbenzamide (331 mg, 1.0 mmol) and K_2CO_3 (276 mg, 2.0 mmol) in dry acetonitrile (50 mL) was refluxed for 2 hr under nitrogen. after cooling down to r.t., the reaction

mixture was quenched with 1N aqueous NH_4OH solution and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$. Removal of solvents gave 4-(α-(1-homopiperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide (**compound 1**), which was purified by silica gel column eluting with MeOH-CH_2Cl_2 (2 : 98 → 10 : 90) to provide the title compound (254 mg, 64%).

GC-MS (R_t = 17.35 min) 396.30 (M^++1, 0.4%), 395.30 (M^+, 1.2), 380.25 (0.9), 337.20 (6.5), 325.25 (27.2), 297.15 (25.8), 251.10 (1.1), 224.10 (3.7), 196.10 (26.4), 165.15 (12.8), 152.10 (16.6), 112.15 (4.8), 99.20 (100); δ_H (400 MHz, $CDCl_3$) 1.10 (brs, 3H), 1.20 (brs, 3H), 1.82 (m, 2H), 2.66 (t, J=6.0 Hz, 2H), 2.72 (m, 2H), 2.97 (t, J=5.2 Hz, 2H), 3.12 (t, J=6.0 Hz, 2H), 3.23 (brs, 2H), 3.51 (brs, 2H), 3.77 (s, 3H), 4.60 (s, 1H), 5.26 (brs, 1H), 6.72 (m, 1H), 6.99 (m, 2H), 7.18 (t, J=8.0 Hz, 1H), 7.28 (d, J=8.0 Hz, 2H), 7.46 (d, J=8.0 Hz, 2H); δ_{C-13} (100 MHz, $CDCl_3$) 12.8, 14.2, 29.0, 39.2, 43.3, 46.0, 48.6, 53.0, 53.6, 55.2, 74.9, 112.3, 113.5, 120.2, 126.7, 127.8, 129.5, 135.9, 144.3, 144.4, 159.7, 171.0.

Its HBr salt: m.p. 137-140.5^{0}C (AcOEt-Ether); ν_{max} (KBr) cm^{-1} 3500, 1600, 1288; *Anal.*Calcd.for $C_{24}H_{33}N_3O_2$ .1.5HBr.0.8H_2O: C, 54.25; H, 6.85; N, 7.91. Found: C, 54.36; H, 6.89; N, 7.78.

Example 2

Preparation of 4-(α-(4-Methyl-1-homopiperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide (compound 2)

A mixture of homopiperazine (114 mg, 1.14 mmol), 4-(α-chloro-3-methoxybenzyl)-N,N-diethylbenzamide (**compound A**)(100 mg, 0.3 mmol) and K_2CO_3 (138 mg, 1.0 mmol) in dry acetonitrile (10 mL) was refluxed for 5 hr under nitrogen. after cooling down to r.t., the reaction mixture was quenched with 1N aqueous NH_4OH solution and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous

NH_4Cl and brine, dried over $MgSO_4$. Removal of solvents gave 4-(α-(4-methyl-1-homopiperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide, which was purified by silica gel column eluting with MeOH-CH_2Cl_2 (5 : 95 → 10 : 90) to provide the title compound (82 mg, 67%).

GC-MS (R_t = 16.19 min) 410.10 (M^++1, 0.3%), 409.20 (M^+, 0.9), 351.15 (1.7), 324.15 (3.4), 296.15 (5.3), 264.10 (0.2), 237.00 (0.6), 224.05 (3.0), 196.05 (6.2), 152.00 (5.6), 113.15 (100); δ_H (400 MHz, $CDCl_3$) 1.10 (brs, 3H), 1.20 (brs, 3H), 1.79 (m, 2H), 2.38 (s, 3H), 2.59 (m, 2H), 2.65 (m, 4H), 2.72 (t, J=6.0 Hz, 2H), 3.24 (brs, 2H), 3.54 (brs, 2H), 3.78 (s, 3H), 4.54 (s, 1H), 6.72 (dt, J=8.0, 1.2 Hz, 1H), 6.99 (m, 2H), 7.18 (dt, J=8.0, 1.2 Hz, 1H), 7.27 (dd, J=8.4, 1.6 Hz, 2H), 7.44 (dd, J=8.4, 1.6 Hz, 2H); δ_{C-13} (100 MHz, $CDCl_3$) 12.9, 14.2, 27.7, 39.1, 43.2, 46.9, 52.7, 52.8, 55.2, 56.3, 59.1, 75.3, 112.0, 113.7, 120.4, 126.6, 127.9, 129.4, 135.7, 144.7, 144.8, 159.7, 171.1.

Its HBr salt: m.p. 165-178^{0}C (AcOEt-Ether); ν_{max} (KBr) cm^{-1} 3400, 1603, 1286; *Anal.*Calcd.for $C_{25}H_{35}N_3O_2.2.0HBr.0.6H_2O$: C, 51.57; H, 6.61; N, 7.22. Found: C, 51.88; H, 6.56; N, 6.92.

Example 3

Preparation of 4-(α-(4-Cyclopropylmethyl-1-homopiperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide (compound 3)

A mixture of 4-(α-(1-homopiperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide (**compound 1**) (119 mg, 0.3 mmol), (chloromethyl)cyclopropane (45 mg, 0.5 mmol), sodium iodide (75 mg, 0.5 mmol) and K_2CO_3 (138 mg, 1.0 mmol) in MeCN (10 mL) was refluxed for 2 hr. after cooling down to r.t., the reaction mixture was quenched with 1N aqueous NH_4OH solution and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$. Removal of solvents gave 4-(α-(4-cyclopropylmethyl-1-homopiperazinyl)-3-

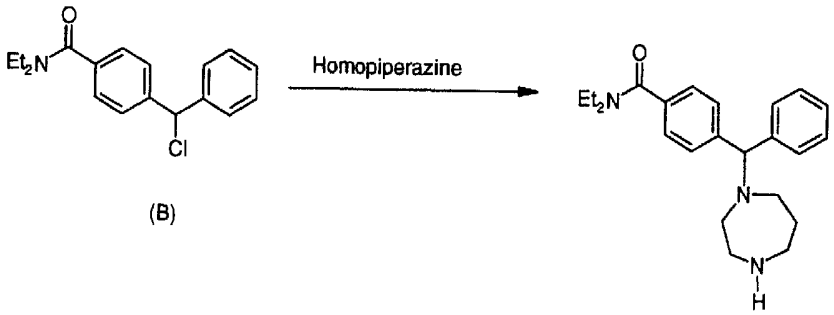
methoxybenzyl)-N,N-diethylbenzamide (**compound 3**), which was purified by silica gel column eluting with MeOH-CH_2Cl_2 (1 : 99 → 10 : 90) to provide the title compound (125 mg, 93%).

GC-MS (R_t = 25.44 min) 377.15 (0.2%), 365.10 (0.3), 352.25 (0.3), 337.20 (1.9), 323.15 (3.2), 296.15 (6.3), 259.10 (0.3), 237.05 (0.3), 224.00 (2.6), 196.10 (7.3), 153.20 (100), 110.10 (4.6); δ_H (400 MHz, $CDCl_3$) 0.33 (m, 2H), 0.69 (m, 2H), 1.11 (m, 3H), 1.20 (m, 4H), 2.11 (m, 2H), 2.69 (t, J=6.4 Hz, 2H), 2.81 (d, J=6.6 Hz, 2H), 2.90 (m, 2H), 3.13 (brs, 2H), 3.25 (brs, 2H), 3.30 (m, 2H), 3.51 (brs, 2H), 3.79 (s. 3H), 4.59 (s, 1H), 6.75 (ddd, J=8.4, 2.4, 1.2 Hz, 1H), 6.98 (m, 2H), 7.21 (t, J=8.0 Hz, 1H), 7.30 (d, J=8.0 Hz, 2H), 7.44 (d, J=8.0 Hz, 2H); δ_{C-13} (100 MHz, $CDCl_3$) 4.6, 6.5, 12.8, 14.1, 24.9, 39.1, 43.3, 48.8, 52.4, 52.5, 55.2, 55.5, 62.3, 74.9, 112.2, 113.8, 120.2, 126.7, 127.8, 129.6, 136.1, 143.6, 143.7, 159.8, 170.9.

Its HBr salt: m.p. 138-147^{0}C (AcOEt-Ether); ν_{max} (KBr) cm^{-1} 3435, 1606, 1287; *Anal.*Calcd.for $C_{28}H_{39}N_3O_2$.1.20HBr . 1.40H_2O: C, 58.80; H, 7.58; N, 7.35. Found: C, 58.82; H, 7.58; N, 7.24.

Scheme 2

4-(α-(1-Homopiperazinyl)benzyl)-N,N-diethylbenzamide hydrochloride (compound 4).



(B) (4)

The compound according to Example 4 was synthesized as shown in Scheme 2 above.

B)

I. Preparation of 4-(Phenyl-hydroxymethyl)-N,N-diethylbenzamide

4-Formyl-N,N-diethyl-benzamide (19.5 g, 95 mmol) was dissolved in dry THF, cooled to -78° C under nitrogen. Phenyl magnesium bromide (104 mL, 1.0M in THF) was added dropwise at -78° C. The temperature was allowed to rise slowly until reaction complete (1 h). The reaction was quenched with ammonium chloride (aq.). The solvent was removed *in vacuo*, the residue dissolved in ethyl acetate/heptane, 1:1, washed with brine and dried ($MgSO_4$). Evaporation of solvent *in vacuo* gave 26.5 g (98%) of 4-(phenyl-hydroxymethyl)-N,N-diethylbenzamide. MS: 282, 211, 165, 105, ^1H NMR: ($CDCl_3$): δ = 7.38-7.20 (m, 9H), 5.80 (d, J=3.5Hz, 1 H), 3.5, 3.2 (2br.s, 4H), 1.2, 1.05 (2br. s, 6H).

II. Preparation of 4-(Chloro-phenyl-methyl)-N,N-diethylbenzamide (compound B in Scheme 2)

4-(Phenyl-hydroxymethyl)-N,N-diethylbenzamide (24.5 g, 93 mmol) was dissolved in dichloromethane (300mL), dried with 4A molecular sieves, and transferred to a dry flask under nitrogen. Thionyl chloride (7.5 mL, 103 mmol) was added at 0° C. Solution stirred at 25° C for 1 h. Solvent evaporated *in vacuo*. Residue dissolved in toluene and solvent evaporated again. 4-(Chloro-phenyl-methyl)-N,N-diethylbenzamide (**compound B**) was obtained as an oil (~100%) which crystallized in the freezer. GC-MS (2 peaks): 296, 225, 165, 121 and 300, 266, 229, 195, 165. ^{1}H NMR: ($CDCl_3$): δ = 7.45-7.20 (m, 9H), 6.09 (s, 1H), 3.4 (br. m, 4H), 1.1 (br. m, 6H).

Example 4

Preparation of 4-(α-(1-Homopiperazinyl)benzyl)-N,N-diethylbenzamide (compound 4)

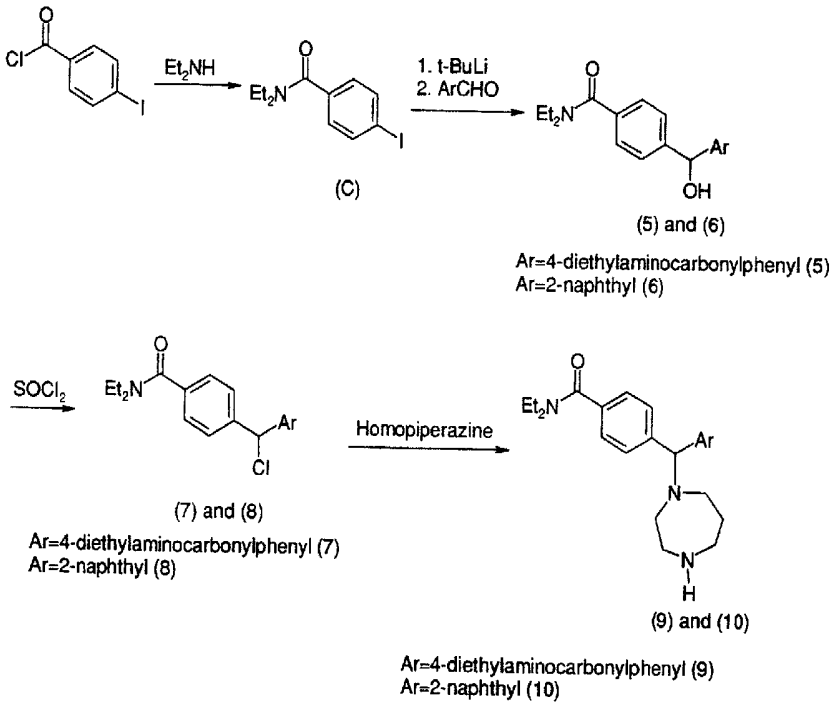
This compound was prepared as described for Example 1 (compound 1), but substituting compound A for compound B.

4-(α-(1-homopiperazinyl)benzyl)-N,N-diethylbenzamide (**compound 4**) as an oil. GC-MS: 365.30 (M^+, 2.6%), 322.25 (5.7), 295.15 (42.5), 281.20 (22.4), 267.15 (45.4), 236.10 (0.9), 194.15 (28.8), 165.15 (62.7), 99.20 (100); δ_H (400 MHz, $CDCl_3$) 1.08 (brs, 3H), 1.18 (brs, 3H), 1.69 (m, 2H), 2.56 (s, 1H), 2.62 (m, 4H), 2.85 (m, 2H), 2.97 (m, 2H), 3.23 (brs, 2H), 3.50 (brs, 2H), 4.63 (s, 1H), 7.16 (m, 1H), 7.26 (m, 4H), 7.40 (d, J=8.0 Hz, 2H), 7.44 (d, J=8.0 Hz, 2H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 12.6, 14.0, 30.7, 39.0, 43.1, 46.9, 49.6, 52.9, 56.1, 74.9, 126.4, 126.7, 127.6, 127.7, 128.3, 135.5, 142.9, 144.8, 171.0.

Its HCl salt (**compound 4**): m.p. 155-165 ^{0}C (AcOEt-Ether); ν_{max} (KBr) cm^{-1} 3418, 1628, 1591, 1074; *Anal.*Calcd.for $C_{23}H_{31}N_3O.2.50HCl.0.90H_2O$: C, 58.42; H, 7.52; N, 8.89. Found: C, 58.35; H, 7.52; N, 8.62.

Scheme 3

4-(α-(1-Homopiperazinyl)aryl)-N,N-diethylbenzamide hydrochloride (compounds 9 and 10).



The compounds according to Examples 5-10 were synthesized as shown in Scheme 3 above.

C)

I. **Preparation of 4-Iodo-N,N-diethylbenzamide (compound C in Scheme 3)**

To a solution 4-iodobenzoyl chloride (13.3 g, 50 mmol) in dry dichloromethane (50 mL) was slowly added diethylamine (30 mL) at 0 °C. After addition, the reaction mixture was warmed to r.t. and stirred for one hour at r.t., and then quenched with aqueous K_2CO_3 solution, extracted with diethyl ether (2 × 200 mL). The organic phases were washed with brine, dried over $MgSO_4$. Evaporation of solvents gave the crude product, which were puried by silica gel column eluting with MeOH-CH_2Cl_2 (1 : 99) to provide 4-iodo-N,N-diethylbenzamide (14.5 g, 95 %). GC-MS: 303.00 (M^+, 20.2%), 302.00 (52.1), 231.85 (7.6), 230.85 (100), 203.85 (1.1).

II. **Preparation of Di-(4-N,N-diethylaminocarbonylphenyl)methanol (compound 5)**

To a solution of 4-iodo-N,N-diethylbenzamide (1.51 g, 5.0 mmol) in dry THF (10 mL) was slowly added t-butyllithium (5 mL, 1.7 M, 8.5 mmol) at -78 °C. After 10 min, 4-formyl-N,N-diethylbenzamide (1.03 g, 5.0 mmol) in THF (5 mL) was dropwise added. the reaction mixture was warmed to r.t. and then quenched with aqueous NH_4Cl solution and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by silica gel column eluting with MeOH-CH_2Cl_2 (1 : 99 → 5 : 95) to provide Di-(4-N,N-diethylaminocarbonylphenyl)methanol (725 mg, 38 %). GC-MS: 382.20 (M^+, 2.9%), 364.15 (4.4), 310.05 (34.2), 283.15 (40.2), 204.05 (15.6), 154.55 (13.9), 119.05 (100); δ_H (400 MHz, $CDCl_3$) 1.06 (brs, 6H), 1.19 (brs, 6H), 3.20 (brs, 4H), 3.48 (brs, 4H), 5.26 (s, 1H), 5.66 (s, 1H), 7.21 (d, J=8.0 Hz, 4H), 7.31 (d, J=8.0 Hz, 4H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 12.5, 13.9, 39.0, 43.0, 74.5, 125.9, 126.2, 135.3, 145.3, 171.0.

III. **Preparation of 4-(α-chloro-4-N,N-diethylaminocarbonylbenzyl)-N,N-diethylbenzamide (compound 7)**

To a solution of di-(4-N,N-diethylaminocarbonylphenyl)methanol (400 mg, 1.05 mmol) in dry dichloromethane (10 mL) was dropwise added thionyl chloride (1.0 mL, 13.7 mmol) at r.t. The reaction mixture was stirred for one hour at r.t. Evaporation of solvents gave 4-(α-chloro-4-N,N-diethylaminocarbonylbenzyl)-N,N-diethylbenzamide, which was used directly in the next step: δ_H (400 MHz, $CDCl_3$) 1.16 (brs, 12 H), 3.38 (brs, 8H), 6.15 (s, 1H), 7.35 (d, J=8.0 Hz, 4H), 7.44 (d, J=8.0 Hz, 4H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 13.1, 39.1, 42.5, 62.7, 126.3, 127.5, 136.2, 141.3, 170.3.

Example 5

Preparation of 4-(α-(1-Homopiperazinyl)-4-N,N-diethylaminocarbonylbenzyl)-N,N-diethylbenzamide hydrochloride (compound 9)

This compound was prepared as described for compounds 1 and 4.

GC-MS: 407.20 (1.5%), 394.25 (9.3), 366.15 (12.4), 293.15 (4.1), 265.15 (11.6), 165.15 (19.1), 99.10 (100); δ_H (400 MHz, $CDCl_3$) 1.11 (brs, 6H), 1.21 (brs, 6H), 1.69 (m, 2H), 2.36 (brs, 1H), 2.63 (m, 4H), 2.97 (m, 2H), 3.00 (m, 2H), 3.25 (brs, 4H), 3.52 (brs, 4H), 4.63 (s, 1H), 7.27 (d, J=8.4 Hz, 4H), 7.43 (d, J=8.4 Hz, 4H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 12.8, 14.1, 30.9, 39.1, 43.2, 47.1, 49.7, 53.0, 56.4, 74.9, 126.5, 127.7, 135.8, 144.5, 171.1.

Its HCl salt: m.p. 158-164 ^{0}C (AcOEt-Ether); ν_{max} (KBr) cm^{-1} 3498, 1627, 1047; *Anal.*Calcd.for $C_{28}H_{40}N_4O_2$. 2.70HCl . 0.30H_2O: C, 59.16; H, 7.68; N, 9.86. Found: C, 59.25; H, 7.66; N, 9.63.

IV. Preparation of 4-(α-hydroxy-2-naphthylmethyl)-N,N-diethylbenzamide (compound 6)

This compound was prepared as described for compounds 1 and 4.

GC-MS: 333.20 (M^+, 58.2%), 332.20 (100), 316.15 (2.6), 261.10 (88.3), 215.05 (18.8), 155.05 (54.8), 127.10 (29.0); δ_H (400 MHz, $CDCl_3$) 0.93 (brs, 3H), 1.11 (brs, 3H), 3.08 (brs, 2H), 3.38 (brs, 2H), 4.80 (brs, 1H), 5.73 (s, 1H), 7.13 (d, J=8.0 Hz, 2H), 7.27 (d, J=8.0 Hz, 2H), 7.30 (dd, J=8.4, 1.6 Hz, 1H), 7.37 (m, 2H), 7.63 (d, J=8.4 Hz, 1H), 7.70 (m, 2H), 7.74 (s, 1H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 12.5, 13.8, 39.0, 43.0, 75.0, 124.7, 124.8, 125.5, 125.7, 126.0, 126.3, 127.3, 127.6, 127.7, 132.4, 132.7, 135.2, 141.3, 145.2, 171.1.

V. Preparation of 4-(α-chloro-2-naphthyl)-N,N-diethylbenzamide (compound 8)

This compound was prepared as described for compounds 1 and 4.

Used directly in the next step: δ_H (400 MHz, $CDCl_3$) 1.15 (brs, 6H), 3.38 (brs, 4H), 6.28 (s, 1H), 7.35 (m, 2H), 7.47 (m, 5H), 7.80 (m, 4H).

Example 6

Preparation of 4-(α-(1-Homopiperazinyl)-2-naphthylmethyl)-N,N-diethylbenzamide hydrochloride (compound 10)

This compound was prepared as described for compounds 1 and 4.

GC-MS: 415.15 (M^+, 1.0%), 400.20 (0.6), 356.20 (4.0), 345.25 (14.8), 317.15 (15.7), 244.00 (7.7), 215.15 (44.4), 99.15 (100); δ_H (400 MHz, $CDCl_3$) 1.07 (brs, 3H), 1.17 (brs, 3H), 1.69 (m, 2H), 2.63 (brs, 1H), 2.67 (m, 4H), 2.86 (m, 2H), 2.98 (m, 2H), 3.20 (brs, 2H), 3.48 (brs, 2H), 4.80 (s, 1H), 7.30 (d, J=8.0 Hz, 2H), 7.42 (m, 2H), 7.52 (d, J=8.0 Hz, 2H), 7.61 (m, 1H), 7.78 (m, 4H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 12.7, 14.0, 30.9, 39.0, 43.1,

47.0, 49.6, 53.0, 56.2, 75.0, 125.5, 125.7, 125.8, 126.4, 126.5, 127.4, 127.6, 127.7, 128.1, 132.5, 133.2, 135.5, 140.6, 144.7, 171.0.

Its HCl salt: m.p. 165-172 ^{0}C (AcOEt-Ether); ν_{max} (KBr) cm^{-1} 3462, 1612 , 1106; *Anal.*Calcd.for $C_{27}H_{33}N_3O$. 2.0HCl . 1.60H_2O: C, 62.69; H, 7.44; N, 8.12. Found: C, 62.80; H, 7.37; N, 8.03.

Pharmaceutical compositions

The novel compounds according to the present invention may be administered orally, intramuscularly, subcutaneously, intraperitoneally, intrathoracially, intravenously, intrathecally and intracerebroventricularly.

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

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

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

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the

necessary binding properties in suitable proportions and compacted in the shape and size desired.

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

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

Pharmaceutically acceptable salts are acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium acetate, camsylate, carbonate, chloride, cetrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glucaptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannata, tartrate, teoclate, triethiodide, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminium, calcium, lithium, magnesium, potassium, sodium, and zinc.

Preferred pharmaceutically acceptable salts are the hydrochlorides and citrates.

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

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

Liquid from compositions include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

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

Preferably the pharmaceutical compositions is in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

Biological evaluation

A) *IN VITRO* MODEL

Cell culture

Human 293S cells expressing cloned human μ, δ, and κ receptors and neomycin resistance were grown in suspension at 37°C and 5% CO_2 in shaker flasks containing calcium-free DMEM10% FBS, 5% BCS, 0.1% Pluronic F-68, and 600 μg/ml geneticin.

Membrane preparation

Cells were pelleted and resuspended in lysis buffer (50 mM Tris, pH 7.0, 2.5 mM EDTA, with PMSF added just prior to use to 0.1 mM from a 0.1 M stock in ethanol), incubated on ice for 15 min, then homogenized with a polytron for 30 sec. The suspension was spun at 1000g (max) for 10 min at 4°C. The supernatant was saved on ice and the pellets resuspended and spun as before. The supernatants from both spins were combined and spun at 46,000 g(max) for 30 min. The pellets were resuspended in cold Tris buffer (50 mM Tris/Cl, pH 7.0) and spun again. The final pellets were resuspended in membrane buffer (50 mM Tris, 0.32 M sucrose, pH 7.0). Aliquots (1 ml) in polypropylene tubes were frozen in dry ice/ethanol and stored at -70°C until use. The protein concentrations were determined by a modified Lowry assay with SDS.

Binding assays

Membranes were thawed at 37°C, cooled on ice, passed 3 times through a 25-gauge needle, and diluted into binding buffer (50 mM Tris, 3 mM $MgCl_2$, 1 mg/ml BSA (Sigma A-7888), pH 7.4, which was stored at 4°C after filtration through a 0.22 m filter, and to which had been freshly added 5 μg/ml aprotinin, 10 μM bestatin, 10 μM diprotin A, no DTT). Aliquots of 100 μl (for μg protein) were added to iced 12x75 mm polypropylene tubes containing 100 μl of the appropriate radioligand (see Table 1) and 100

µl of test peptides at various concentrations. Total (TB) and nonspecific (NS) binding were determined in the absence and presence of 10 µM naloxone respectively. The tubes were vortexed and incubated at 25°C for 60-75 min, after which time the contents are rapidly vacuum-filtered and washed with about 12 ml/tube iced wash buffer (50 mM Tris, pH 7.0, 3 mM $MgCl_2$) through GF/B filters (Whatman) presoaked for at least 2h in 0.1% polyethyleneimine. The radioactivity (dpm) retained on the filters was measured with a beta counter after soaking the filters for at least 12h in minivials containing 6-7 ml scintillation fluid. If the assay is set up in 96-place deep well plates, the filtration is over 96-place PEI-soaked unifilters, which were washed with 3 x 1 ml wash buffer, and dried in an oven at 55°C for 2h. The filter plates were counted in a TopCount (Packard) after adding 50 µl MS-20 scintillation fluid/well.

Data analysis

The specific binding (SB) was calculated as TB-NS, and the SB in the presence of various test peptides was expressed as percentage of control SB. Values of IC_{50} and Hill coefficient (n_H) for ligands in displacing specifically bound radioligand were calculated from logit plots or curve fitting programs such as Ligand, GraphPad Prism, SigmaPlot, or ReceptorFit. Values of K_i were calculated from the Cheng-Prussoff equation. Mean ± S.E.M. values of IC_{50}, K_i and n_H were reported for ligands tested in at least three displacement curves.

Receptor saturation experiments

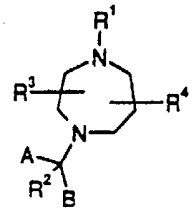
Radioligand K_δ values were determined by performing the binding assays on cell membranes with the appropriate radioligands at concentrations ranging from 0.2 to 5 times the estimated K_δ (up to 10 times if amounts of radioligand required are feasable). The specific radioligand binding was expressed as pmole/mg membrane protein. Values of K_δ and B_{max} from individual experiments were obtained from nonlinear fits of specifically bound (B) vs. nM free (F) radioligand from individual according to a one-site model.

B) BIOLOGICAL MODEL (*IN VIVO* MODEL)

The well characterized hot plate test (Jolicoeur et al., 1991, "Neurobehavioral evidence for kappa agonist activity of the morphinan derivation 14-b-methyl 8-oxacyclorphan [BC(3016)]": Pharmacol. Biochem. Behav. 38: 401-405.) and tail flick test (D'Amour, F.E. and Smith, D.L. (1941): "A method for determining loss of pain sensation", J. Pharmacol. Exp. Ther. 72: 74-79; Nance, P.A. and Sanyor, J. (1987): "Substance P-induced long-term blockade of spinal adrenergic analgesia: reversal by morphine and naloxone"; J. Pharm. Exp. Ther. 340: 972-977) were used to evaluate the effectiveness of compounds of the present invention as potent analgesics.

The claims defining the invention are as follows:

1. A compound of the general formula (I)



wherein

A is a substituted or unsubstituted aromatic; an optionally substituted C_5-C_{10} hydroaromatic; a heteroaromatic or a heterohydroaromatic moiety having from 5 to 10 atoms selected from any of C, S, N and O, each optionally and independently substituted by 1 or 2 substituents independently selected from hydrogen, CH_3, $(CH_2)_oCF_3$, halogen, $CONR^5R^6$, CO_2R^5, COR^5, $(CH_2)_oNR^5R^6$, $(CH_2)_oCH_3$, $(CH_2)_oSOR^5R^6$, $(CH_2)_oSOR^5$, $(CH_2)_oSO_2R^5$, $(CH_2)_oSO_2NR^5$, $(CH_2)_oNR^5COR^6$ and $-NR^5(CH_2)_oCOR^1$; wherein o is 0, 1, or 2, and R^1, R^5 and R^6 are as defined below respectively;

R^1 is selected from hydrogen, a branched or straight C_1-C_6 alkyl, $CH_2CH=CH_2$, C_3-C_8 cycloalkyl, C_4-C_8 (alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl; C_6-C_{10} aryl; and heteroaryl having from 5 to 10 atoms selected from any of C, S, N and O;

R^5 and R^6 is each and independently as defined for R^1 above; or R^5 and R^6 taken together is $-(CH_2)r-$ wherein r is 4 or 5;

R^2 is selected from hydrogen, CH_3, OR^1, CO_2R^1, and $CH_2CO_2R^1$ wherein R^1 is as defined above;

B is a substituted or unsubstituted aromatic; an optionally substituted C_5-C_{10} hydroaromatic; a heteroaromatic or a heterohydroaromatic moiety having from 5 to 10 atoms selected from any of C, S, N and O, optionally substituted by 1-2 substituents each and independently selected from hydrogen, CH_3, CF_3, halogen, $(CH_2)_pCONR^5R^6$, $(CH_2)_pNR^5R^6$, $(CH_2)_pCOR^5$, $(CH_2)_pCO_2R^5$, OR^5, $(CH_2)_pSOR^5$, $(CH_2)_pSO_2R^5$, and $(CH_2)_pSO_2NR^5R^6$;
wherein p is 0, 1, 2 or 3 and wherein R^5 and R^6 are as defined above;

R^3 and R^4 is each and independently selected from R^5, $(CH_2)_pCONR^5R^6$, $(CH_2)_pNR^5R^6$, $(CH_2)_pCONR^5R^6$, $(CH_2)_pCO_2R^5$, $(CH_2)_pPh$, $(CH_2)_p$(p-OH Ph), $(CH_2)_p$-3-indolyl, $(CH_2)_pSR^5$ or $(CH_2)_pOR^5$;
wherein p is 0, 1, 2, 3, or 4, and wherein R^5 and R^6 are as defined above;

as well as pharmaceutically acceptable salts of the compounds of the formula (I), isomers, hydrates, isoforms and prodrugs thereof.

2. A compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof of the formula I according to claim 1, wherein

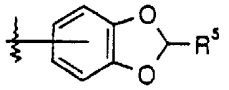
A is selected from phenyl, naphthyl, indolyl, benzofuranyl, benzothiophenyl, pyrryl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, and pyrrolidinyl; wherein

each A group being optionally substituted by 1-2 substituents independently selected from hydrogen, CH_3, $(CH_2)_oCF_3$, F, Cl, $CONR^5R^6$, CO_2R^5, COR^5, $(CH2)_oSOR^5$, $(CH2)_oSO_2R^5$, $(CH_2)_oSO_2NR^5$, $(CH_2)oNR^5COR^6$ and $NR^5(CH_2)_oCOR^6$; wherein R^5 and R^6 are as defined below, and o is 0 or 1;

R^1, R^5 and R^6 is each and independently selected from hydrogen, a branched or straight C_1-C_4 alkyl, C_3-C_5 cycloalkyl, C_4-C_8 (alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl, and phenyl;

R^2 is hydrogen, methyl, or OR^1 wherein R^1 is as defined above;

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, pyrryl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, pyrrolidinyl, indazolinyl, and



;

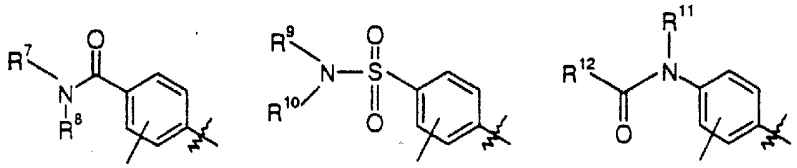
each B group being optionally substituted by 1-2 substituents independently selected from hydrogen, CH_3, CF_3, halogen, $(CH_2)_pCONR^5R^6$, $(CH_2)_pNR^5R^6$, $(CH_2)_pCOR^5$, $(CH_2)_pCO_2R^5$, and OR^5,

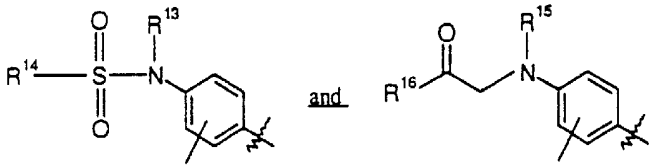
wherein p is 0 or 1, and wherein R^5 and R^6 are as defined above;

R^3 and R^4 are each and independently selected from hydrogen, CH_3, $CH(Me)_2$, $CH_2CH(Me)_2$, $CH(Me)CH_2CH_3$ $(CH_2)_pCON^5R^6$, $(CH_2)_pNR^5R^6$, $(CH_2)_pCONR^5R^6$, $(CH_2)_pCO_2R^5$, $(CH_2)_pPh$, $(CH_2)_p$(p-OH Ph), $(CH_2)_p$-3-indolyl, $(CH_2)_pSR^5$, and $(CH_2)_pOR^5$, wherein p is 0, 1, 2, or 3, and wherein R^5 and R^6 are as defined above.

3. A compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof according to claim 2, wherein

A is selected from





and

wherein the phenyl ring of each A substituent may be optionally and independently substituted by 1 or 2 substituents selected from H, CH_3, $(CH_2)_oCF_3$, F, Cl, $CONR^5R^6$, CO_2R^5, $(CH_2)_oSOR^5$, $(CH_2)oSO_2R^5$, $(CH_2)_oSO_2NR^5R^6$, $(CH_2)_oNR^5COR^6$, and $NR^5(CH_2)_oCOR^6$; wherein R^5 and R^6 are as defined below, and o is 0, 1 or 2;

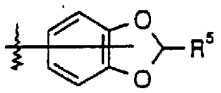
R^1 is selected from hydrogen, methyl, ethyl, $CH_2CH{=}CH_2$, or CH_2-cyclopropyl;

R^5 and R^6 is each and independently selected from phenyl, methyl and ethyl; or R^5 and R^6 taken together is $-(CH_2)r-$ wherein r is 4 or 5;

R^2 is H, methyl, or OR^1;

R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, and R^{16}, is each and independently as defined for R^1 above;

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, indazolinyl, and



each B group being optionally substituted by 1-2 substituents independently selected from hydrogen, methyl, CF_3, halogen, $(CH_2)_pCONR^5R^6$, $(CH_2)_pNR^5R^6$, $(CH_2)_pCOR^5$, $(CH_2)_pCO_2R^5$, and OR^5,

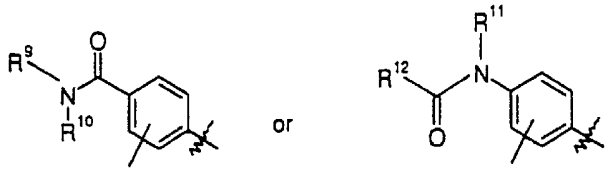
wherein p is 0, 1, or 2, and wherein R^5 and R^6 are as defined above;

R^3 and R^4 are each and independently selected from H, CH_3, $CH(Me)_2$, $CH_2CH(Me)_2$, $CH(Me)CH_2CH_3$ $(CH_2)_pCONR^5R^6$, $(CH_2)_pNR^5R^6$, $(CH_2)_pCONR^5R^6$, $(CH_2)_pCO_2R^5$, $(CH_2)_pPh$, $(CH_2)_p$(p-OH Ph), $(CH_2)_p$-3-indolyl, $(CH_2)_pSR^5$, and $(CH_2)_pOR^5$

wherein p is 0, 1, 2, or 3, and wherein R^5 and R^6 are as defined above.

4. A compound or pharmaceutically salts or isomers or hydrates or isoforms or prodrugs thereof according to claim 3, wherein

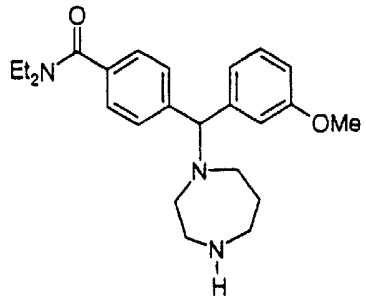
A is defined as



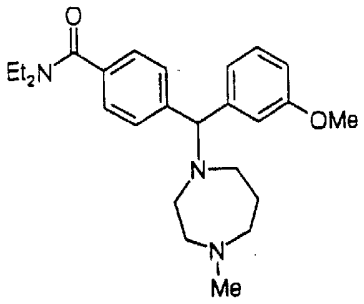
and wherein R^9, R^{10}, R^{11} and R^{12}, are as defined in claim 3.

5. A compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof according to any one of claims 1-4, in the form of its hydrochloride salt.

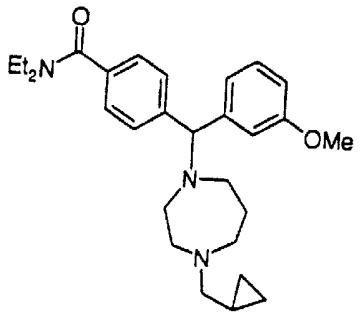
6. A compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof of the formula (I) of claim 1, which compound is



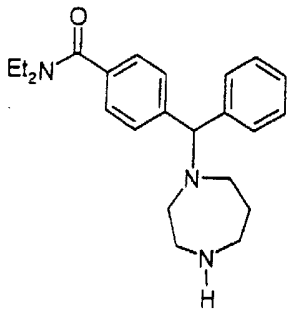
7. A compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof of the formula (I) of claim 1, which compound is



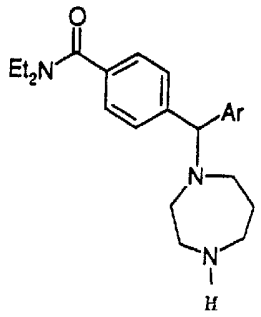
8. A compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof of the formula (I) of claim 1, which compound is



9. A compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof of the formula (I) of claim 1, which compound is

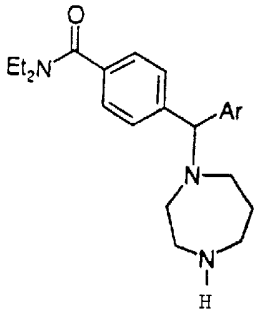


10. A compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof of the formula (I) of claim 1, which compound is



wherein Ar is 4-diethylaminocarbonylphenyl.

11. A compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof of the formula (I) of claim 1, which compound is



wherein Ar is 2-naphthyl.

12. A compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof according to any one of claims 1-11, which is in a form suitable for use in therapy.

13. A compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof according to claim 12, wherein the therapy is pain management.

14. A compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof according to claim 12, wherein the therapy is directed towards gastrointestinal disorders.

15. A compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof according to claim 12, wherein the therapy is directed towards spinal injuries.

16. A compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof according to claim 12, wherein the therapy is directed to disorders of the sympathetic nervous system.

17. A compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof according to any one of claims 1-11, further characterized in that it is isotopically labelled.

18. Use of a compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof according to any one of claims 1-11, in the form of a diagnostic agent.

19. Use of a compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof according to any one of claims 1-11, in the manufacture of a medicament, said medicament being formulated for use in the treatment of pain.

20. Use of a compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof according to any one of claims 1-11, in the manufacture of a medicament, said medicament being formulated for use in the treatment of gastrointestinal disorders.

21. Use of a compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof according to any one

of claims 1-11, in the manufacture of a medicament, said medicament being formulated for use in the treatment of spinal injuries.

22. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof of the formula I according to any one of claims 1-11 as an active ingredient, together with a pharmaceutically acceptable carrier.

23. A process for the preparation of a compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof according to the formula (I) of any one of claims 1-11, where applicable, wherein:

A)

(i) an aldehyde or ketone is treated with a nucleophile, giving the corresponding alcohol;

(ii) the alcohol is converted into a suitable leaving group, which in turn is displaced with a homopiperazine derivative; and

(iii) a N-(4)-unsubstituted homopiperazine derivative is substituted via its organo halide or equivalent species, or acylated; or

B)

(i) a N-protected amino acid ester is reacted with a second amino acid ester, and thereafter treated with an acid, giving a homopiperazinedione;

(ii) the dione is reduced to the corresponding homopiperazine; and

(iii) the homopiperazine is alkylated or acylated on one or more of the nitrogens.

24. A compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof according to the formula I of any one of claims 1-11, when obtained by the process of claim 23.

25. A method for the treatment of pain, wherein an effective amount of a compound or pharmaceutically acceptable salts or isomers or hydrates or isoforms or prodrugs thereof according to the formula I according to any one of claims 1-11 and 24, or a pharmaceutical composition according to claim 22, is administered to a subject in need of pain management.

DATED this 21st day of April 1999

ASTRA PHARMA INC.,
By its Patent Attorneys,
E. F. WELLINGTON & CO.,
By:

(Bruce Wellington)

A/KA/4700