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(56) References cited:
WO-A1-97/23466 **WO-A1-98/28270**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

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R. Kammerer

Renate Kammerer

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For the President of the European Patent Office.

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Description

Field of the invention

[0001] The present invention is directed to novel compounds, to a process for their preparation, their use and pharmaceutical compositions comprising the novel compounds. The novel compounds are useful in therapy, and in particular for the treatment of pain.

Background and prior art

[0002] 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 possess immunomodulatory activities.

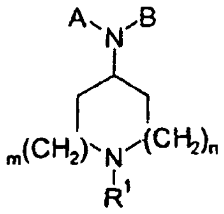
[0003] The identification of at least three different populations of opioid receptors (μ, δ and K) is now well established and all three are apparent in both central and peripheral nervous systems of many species including man. Analgesia has been observed in various animal models when one or more of these receptors has been activated.

[0004] With few exceptions, currently available selective opioid δ ligands are peptidic in nature and are unsuitable for administration by systemic routes. One example of a non-peptidic δ-agonist is SNC80 (*Bilsky E.J. et al., Journal of Pharmacology and Experimental Therapeutics, 273(1), pp. 359-366 (1995))*. There is however still a need for selective δ-agonists having not only improved selectivity, but also an improved side-effect profile.

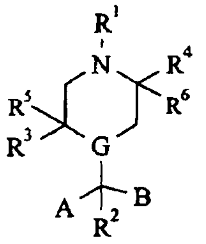
[0005] Thus, the problem underlying the present invention was to find new analgesics having improved analgesic effects, but also with an improved side-effect profile over current μ agonists, as well as having improved systemic efficacy.

[0006] 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 δ agonist compounds, described within the prior art, show significant convulsive effects when administered systemically.

[0007] We have now found that certain compounds not specifically disclosed by, but included within the scope of WO 98/28270 and WO97/23466 (their generic structures shown below), exhibit surprisingly improved δ-agonist properties and in vivo potency relative to compounds disclosed in WO98/28270 and WO97/23466, when administered systemically. The compounds of the present invention exhibit significant and unexpected increased levels of delta receptor agonism and metabolic stability.



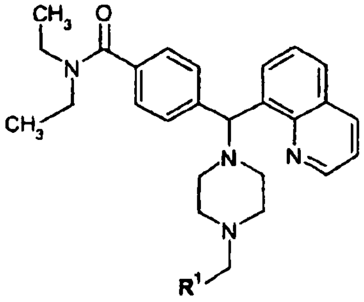
WO 98/28270 ;



WO/97/23466

Outline of the invention

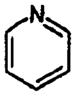
[0008] The novel compounds according to the present invention are defined by the formula I



I

wherein
R^1 is selected from

- **(i)** phenyl;

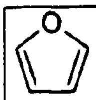


;

- **(ii)** pyridinyl

;

- **(iii)** thiophenyl
- **(iv)** furanyl



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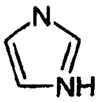
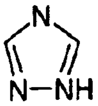


;

- **(v)** imidazolyl

 ;

(vi) triazolyl

where each R¹ phenyl ring and R¹ heteroaromatic ring may optionally and independently be further substituted by 1, 2 or 3 substituents selected from straight and branched C_1-C_6 alkyl, NO_2, CF_3, C_1-C_6 alkoxy, chloro, fluoro, bromo, and iodo. The substitutions on the phenyl ring and on the heteroaromatic ring may take place in any position on said ring systems.

[0009] Within the scope of the invention are also pharmaceutically acceptable salts of the compounds of the formula I, as well as isomers thereof.

[0010] In a preferred embodiment of the invention, the compounds of formula I are present as the (+)-enantiomer, or as the (-)-enantiomer.

[0011] 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.

[0012] The novel compounds of the present invention are useful in therapy, especially for the treatment of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive.

[0013] Compounds of the invention are 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.

[0014] Compounds of the invention are useful in disease states where degeneration or dysfunction of opioid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

[0015] Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety, urinary incontinence, various mental illnesses, cough, lung oedema, various gastrointestinal 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.Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (eg. amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotica, anxiolytics, neuromuscular blockers and opioids.

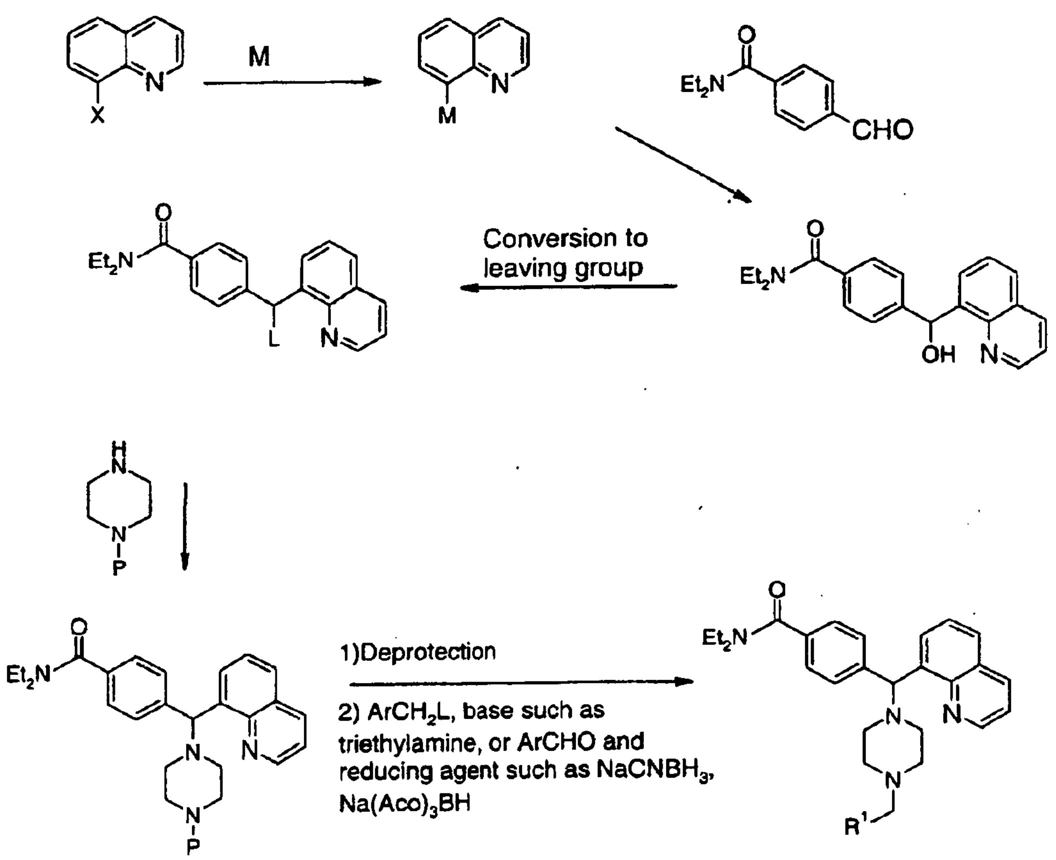
[0016] Also within the scope of the invention is the use of any of the compounds according to the formula I above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

[0017] A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I above, is administered to a patient in need of such treatment. Also included within the scope of the present invention, is any novel intermediate as described in Scheme I hereinafter useful in the synthesis of compounds of formula I above.

Methods of preparation

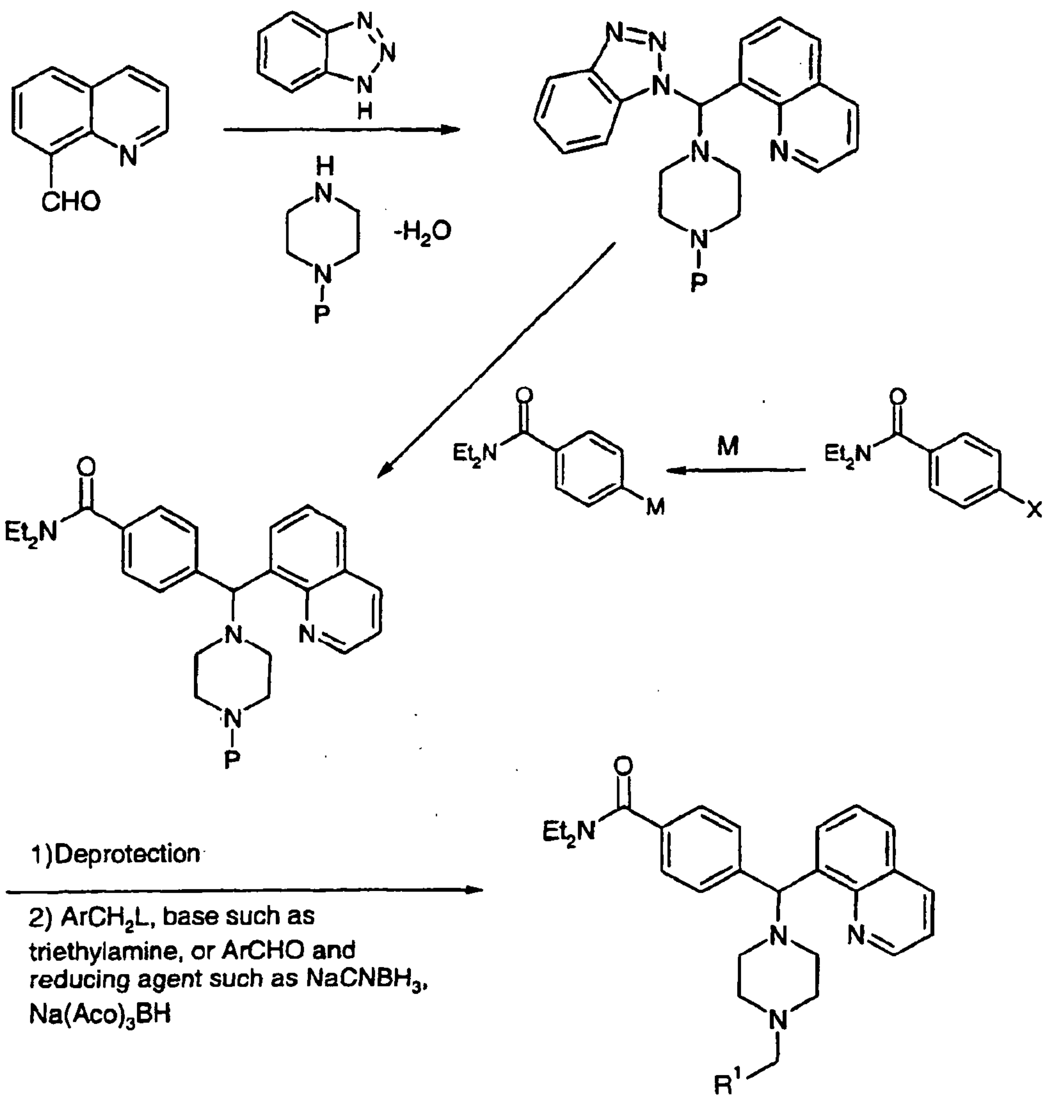
[0018] The compounds according to the present invention may be prepared by following any one of the procedures described in Schemes I, II, III, and IV. These known procedures are described in *J. March, Advanced Organic Chemistry, 4th Edition, John Wiley and sons (1992); Katritsky, A.R., Lan, X. Chem. Soc. Rev., pp. 363-373 (1994)*, which are hereby incorporated by reference.

SCHEME I



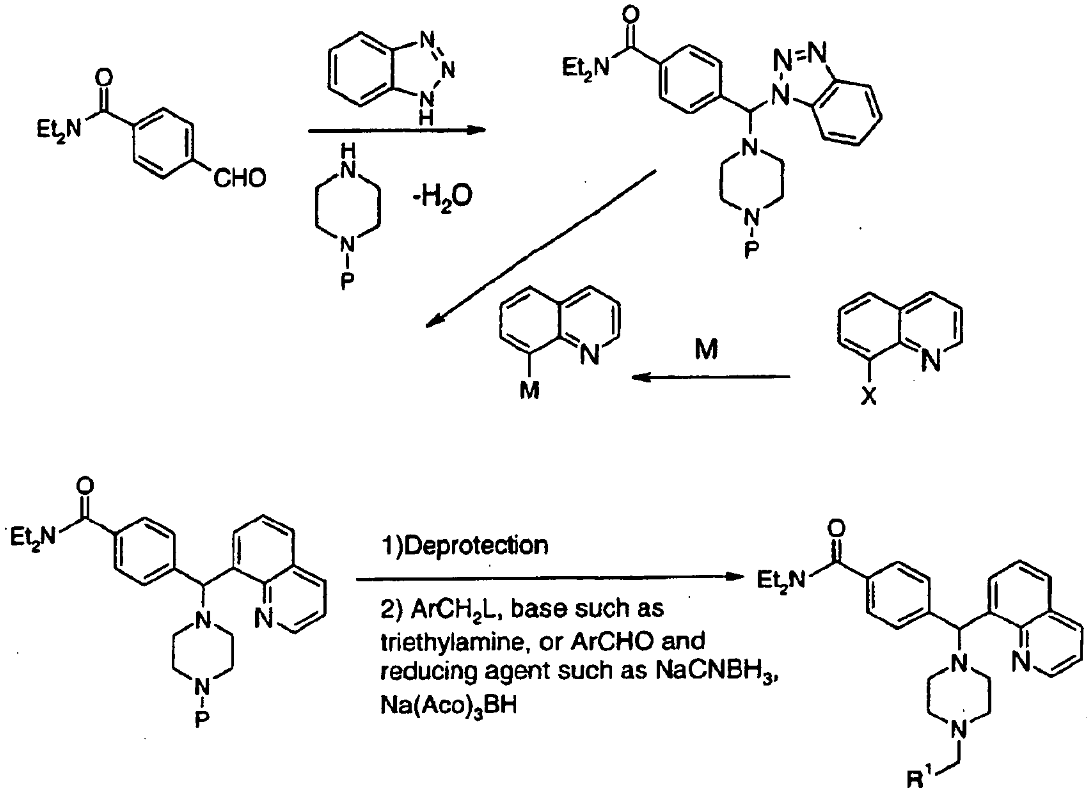
P=a protecting group such as Bn, Boc, CBz
M= Li, Mg, Zn
X=Br, I
L=Cl, Br, OMs, OTs, I
R^1= as defined in formula (I) above

SCHEME II



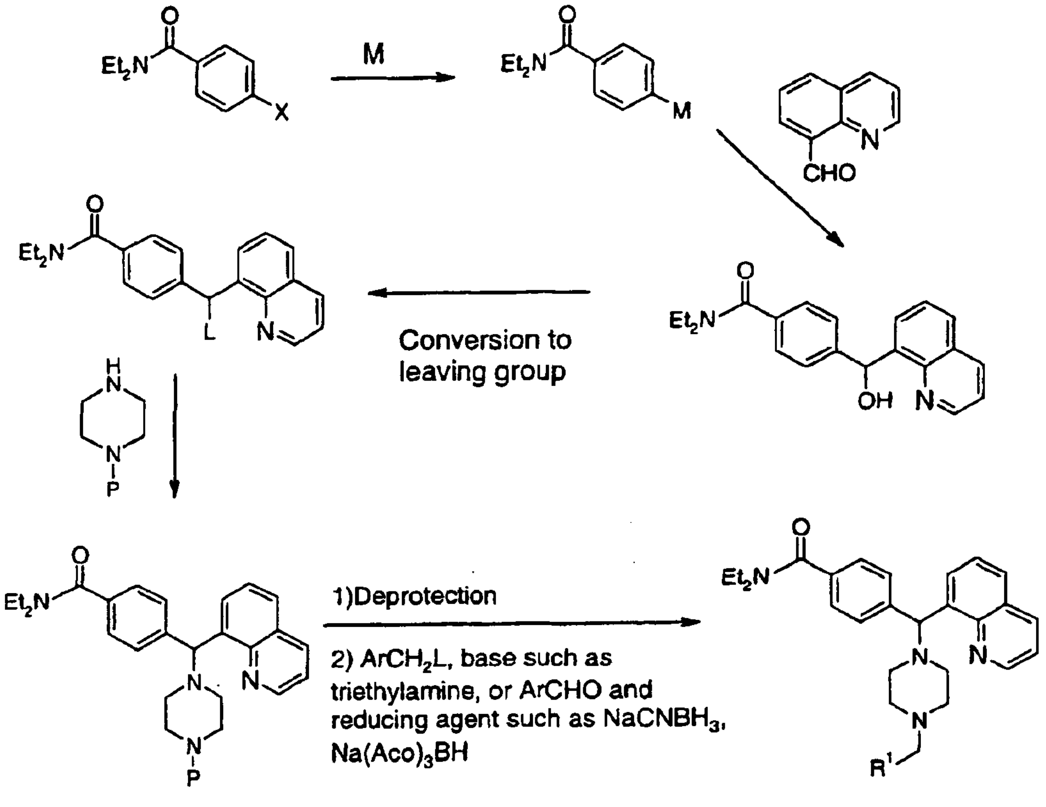
P=a protecting group such as Bn, Boc, CBz
M= Li, Mg, Zn
X=Br, I
L=Cl, Br, OMs, OTs, I
R^1=as defined in formula (I) above

SCHEME III



P=a protecting group such as Bn, Boc, CBz
M= Li, Mg, Zn
X=Br, I
L=Cl, Br, OMs, OTs, I
R^1=as defined in formula (I) above

SCHEME IV



P=a protecting group such as Bn, Boc, CBz
M= Li, Mg, Zn
X=Br, I
L=Cl, Br, OMs, OTs, I
R^1=as defined in formula (I) above

Examples

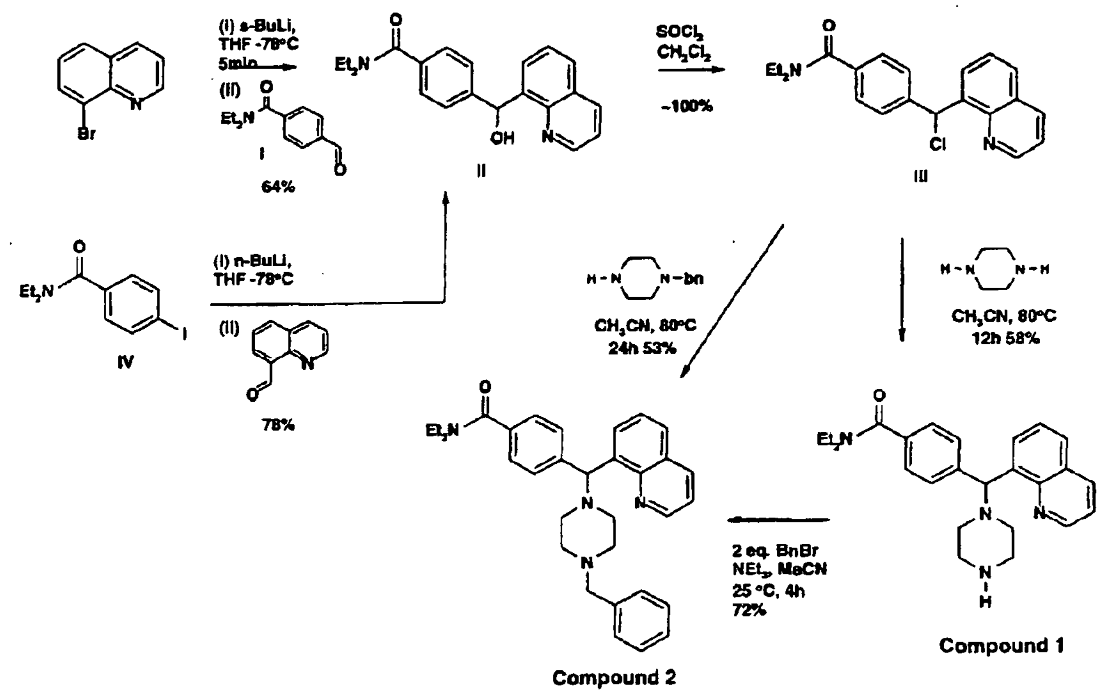
[0019] The invention will now be described in more detail by the following Examples, which are not to be construed as limiting the invention.

Example 1

Preparation of 4-[(4-benzyl-1-piperazinyl)(8-quinolinyl)methyl]-*N,N*-diethylbenzamide dihydrochloride (compound 2)

[0020] **The title compound** 2 was prepared by following the synthetic procedure of Scheme 1 below.

Scheme 1



(i) Preparation of *N,N*-diethyl-4-formylbenzamide (compound I).

[0021] 4-Formylbenzoic acid (11.2 g, 74.6 mmol) and triethylamine (10.4 mL, 75 mmol) was dissolved in THF (100 mL) and cooled to -10 °C. i-Butylchloroformate (10.3 mL, 78 mmol) was added and stirring was continued for 10 minutes at -10 °C before diethylamine (9.7 mL, 94 mmol) was added and solution was allowed to reach 25 °C. After concentration, aqueous workup and chromatography on silica (0-100 % EtOAc in heptane), a total of 7.4 g (50 %) compound I was obtained.

(ii) Preparation of *N,N*-diethyl-4-[hydroxy(quinolinyl)methyl]benzamide (compound II)

[0022] 8-Bromoquinoline (3.0 g, 14.4 mmol) was dissolved in dry THF (150 mL) and cooled to -78 °C under nitrogen. s-BuLi (11.1 mL, 1.3 M in pentane, 14.4 mmol) was added dropwise during 5 min *(Preparation and reactions with 8-lithioquinoline: Suggs, J. Org. Chem. 1980, 45, 1514.).* After further 5 min, N,N-diethyl-4-formylbenzamide (3.5 g, 17.0 mmol) was added dissolved in THF (5 mL). The solution was stirred 1 h, then NH_4Cl (aq.) was added. After concentration, aqueous workup and chromatography on silica (0-100 % EtOAc in heptane), a total of 3.5 g (70 %) **compound II** was obtained.
MS: 334, 262, 234, 215, 204, 178, 156, 129.

Alternative route to prepare compound II from N,N-diethyl-4-iodobenzamide (compound IV)

[0023] **Compound IV** (0.67 g, 2.2 mmol) was dissolved in dry THF (25 mL) and cooled to -78 °C under nitrogen. n-BuLi (1.3 mL, 1.6 M in hexane, 2.2 mmol) was added dropwise during 5 min. After further 10 min, 8-formylquinoline (0.17 g, 1.1 mmol) (8-formylquinoline was made from 8-methylquinoline by oxidation with selenium dioxide at 150-155 °C for 12 h (*Kingsbury, J. Med. Chem. 1993, 3308.*) was added dissolved in THF (1 mL). The solution was stirred 1 h, then NH_4Cl (aq.) was added. After concentration, aqueous workup and chromatography on silica (0-100 % EtOAc in heptane), a total of 0.29 g (78 %) **compound II** was obtained.

(iii) Preparation of 4-[chloro(8-quinolinyl)methyl]-*N,N*-diethylbenzamide (compound III).

[0024] **Compound II** (2.0 g, 6.6 mmol) was dissolved in dry CH_2Cl_2 (25 mL) and $SOCl_2$ (0.53 mL, 7.3 mmol) was added. The solution was stirred at 25 °C for 30 min and the solvent was evaporated *in vacuo*. **Compound III** was obtained as an oil (~100%) and used in the next reaction without further purification.
MS: 348, 333, 233, 215, 204, 156.

(iv) Preparation of *N,N*-diethyl-4-[1-piperazinyl(8-quinolinyl)methyl]benzamide (compound 1).

[0025] The crude product **compound III** (~6.6 mmol) and piperazine (2.3 g, 26 mmol) was dissolved in dry MeCN (50 mL) and heated at reflux 12 h. The solvent was removed *in vacuo*, the residue dissolved in CH_2Cl_2 and washed with water and the organic phase dried (K_2CO_3) and evaporated *in vacuo*. After chromatography on silica (0-20 % MeOH in CH_2Cl_2, 1% NH_4OH), a total of 1.8 g (68 %, 2 steps) **compound 1** was obtained. Further purification could be achieved by reverse phase chromatograpy (LiChroprep RP-18, 10-50 % MeCN in water, 0.1 % TFA) to give 1.2 g colorless product. The dihydrochloride salt was made by treatment with 2 eq. HCl in ether.
Mp: 180-90 °C.
IR (KBr, ν_{max}) 3297, 2982, 2716, 2474, 1611, 1434, 1380, 1288, 1098 cm^{-1}.
MS (amine): 402, 318, 246, 217, 109.
^{1}H NMR (amine, $CDCl_3$): δ 1.2, 1.1 (2s, 6H), 2.94, 2.51 (2m, 8H), 3.5-3.1 (m, 5H), 6.05 (s, 1H), 8.94-7.20 (m, 10H).
Anal. ($C_{25}H_{30}N_4O$ x 3.2 CF_3CO_2H) C, N; H: calcd, 4.36; found, 3.90.

(v) Preparation of 4-[(4-benzyl-1-piperazinyl)(8-quinolinyl)methyl]-*N,N*-diethylbenzamide dihydrochloride (the title compound 2)

[0026] **Compound 1** (1.3 g, 3.2 mmol) and triethylamine (0.90 mL, 6.4 mmol) was dissolved in MeCN (10 mL). Benzyl bromide (0.77 mL, 6.4 mmol) was added with stirring at 25 °C. After 4 h the solution was concentrated and purified by chromatography on silica (0-5% MeOH in CH_2Cl_2, or by reverse phase chromatograpy (LiChroprep RP-18, 20-80 % MeCN in water, 0.1 % TFA). A total of 2.2 g (72 %) of the **title compound 2** was obtained. Treatment with 2 eq. HCl (aq.) and freeze drying gave the dihydrochloride salt (3.6g).
IR (2X HCl, KBr) : 2388, 1606, 1434, 1356, 1287 (cm-1).
^{1}H NMR (free amine, $CDCl_3$) δ = 1.05 (m, 6H), 2.5 (m, 8H), 3.1-3.6 (m, 6H), 6.04 (s, 1H), 7.18-8.98 (m, 15H).
Anal. ($C_{32}H_{38}Cl_2N_4O$) C, H, N.

Alternative procedure to prepare the title compound 2 from compound III

[0027] The crude product **compound III** (~13.2 mmol), triethylamine (2.0 mL, 14.5 mmol) and N-benzyl-piperazine (2.6 g, 14.5 mmol) was dissolved in dry MeCN (50 mL) and heated at reflux 12 h. More N-benzyl-piperazine (0.5 g, 2.8 mmol) was added and heating continued for 12 h. The solvent was removed *in vacuo*, the residue dissolved in CH_2Cl_2 and washed with water and the organic phase dried (K_2CO_3) and evaporated *in vacuo*. After chromatography on silica (0-10 % MeOH in CH_2Cl_2), a total of 3.5 g (53 %) of the **title compound 2** was obtained.

Examples 2 & 3

Separation of the enantiomers of compound 2 (compounds 3 and 4)

[0028] The preparative separation of this compound was done on a Chiralcel OD column (50mm X 50 cm) using Hexane / EtOH / Diethylamine 85:15:0.1 as the mobile phase. On the Chiralcel OD column, the (+)-isomer was found to elute first.

Example 2

(-)4-[(4-benzyl-1-piperazinyl)(8-quinolinyl)methyl]-*N,N*-diethylbenzamide (compound 3)

[0029] $[\alpha]_D^{25}$: -130° (c 0.78, MeOH)
^{1}H NMR: (CD_3OD): δ= 1.05 (m, 6H), 3.0-3.6 (m, 14H), 5.90 (s, 1H), 7.22 -8.20 (m, 13H), 8.78 (m, 1H), 9.50 (m, 1H).
ANALYSIS:Calc.w.3.1 H_2O, C: 61.85, H: 7.17, N: 9.02..Found C: 61.84, H: 6.60, N: 8.89

Example 3

(+)4-[(4-benzyl-1-piperazinyl)(8-quinolinyl)methyl]-*N,N*-diethylbenzamide (compound 4)

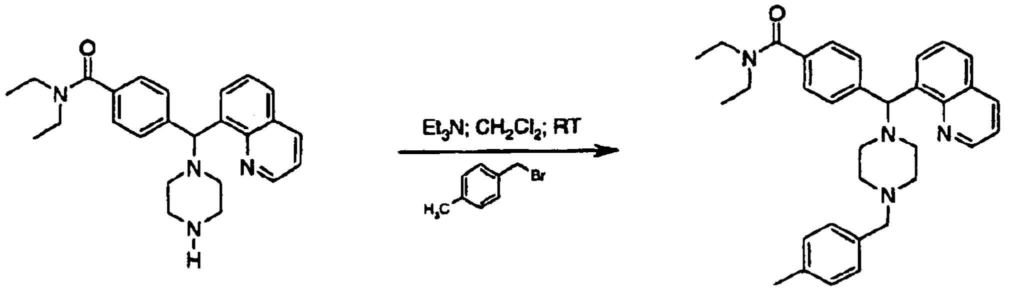
[0030] $[\alpha]_D^{25}$: +130° (c 0.69, MeOH)
^{1}H **NMR:** (CD_3OD): δ= 1.05 (m, 6H), 3.0-3.6 (m, 14H), 5.90 (s, 1H), 7.22 -8.20 (m, 13H), 8.78 (m, 1H), 9.50 (m, 1H).
ANALYSIS: Calc.w.3.2 H_2O, C: 61.67, H: 7.18, N: 8.99.. Found C: 61.70, H: 6.46, N: 8.84

Example 4

Preparation of *N,N*-diethyl-4-[[4-(4-methylbenzyl)-1-piperazinyl-1-(8-quinolinyl)methyl]benzamide(compound 5

[0031] The title **compound 5** was prepared by following the synthetic procedure of Scheme 2 below.

Scheme 2



Compound 1

Compound 5

[0032] To a solution of **compound 1** (0.80g; 1.99 mmol) in CH_2Cl_2 (20ml) was added Et_3N (0.83ml; 5.97mmol) followed by *p-methyl* benzyl bromide (773mg; 4.18mmol). The reaction mixture was stirred overnight and was then was concentrated under reduced pressure. Purification by reverse phase using 10%-30% CH_3CN/H_2O.
(M+1) calculated: 507.70, (M+1) observed: 507.20
IR (NaCl, free amine) 2969, 2807, 2360, 1628, 1455, 1425, 1286, 1134, 1095 (cm-1).
^{1}H **NMR** (CDCl3, **free** amine) δ = 1.0, 1.1 (2m, 6H, amide-Me), 2.31 (s, 3H, Ar-Me), 2.5 (m, 8H, piperazine-H), 3.2, 3.5 (2m, amide-CH2), 3.49 (s, 2H, ArCH2N), 6.03 (s, 1H, Ar2CH), 7.06-7.68 (m, 11H, Ar-H), 8.01-8.12 (m, 2H,Ar-H), 8.93 (m, 1H, Ar-H).
Anal. ($C_{32}H_{38}Cl_2N_4O$) C, H, N.

Examples 5 & 6

Separation of the Enantiomers of compound 5 to give compounds 6 and 7

[0033] The preparative separation of this compound was done on a semi preparative Chiralcel AD column (21 mm X 25 cm) using Hexane / EtOH / Diethylamine 80:20:0.1 as the mobile phase. On the Chiralcel AD column, the (-)-isomer was found to elute first.

Example 5

(-)4-[[4-(4-methylbenzyl)-1-piperazinyl](8-quinolinyl)methyl]-*N,N*-diethylbenzamide (compound 6)

[0034] $[\alpha]_D^{25}$::-131°(c1.0, MeOH)

Example 6

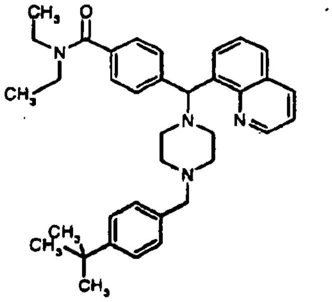
(+)4-[[4-(4-methylbenzyl)-1-piperazinyl](8-quinolinyl)methyl]-*N,N*-diethylbenzamide (compound 7)

[0035] $[\alpha]_D^{25}$: +124°(c 1.4,MeOH)

Example 7

Preparation of 4-[{4-[4-(tert-butyl)benzyl]-1-piperazinyl}(8-quinolinyl)methyl]-*N,N*-diethylbenzamide dihydrochloride (compound 8)

[0036]



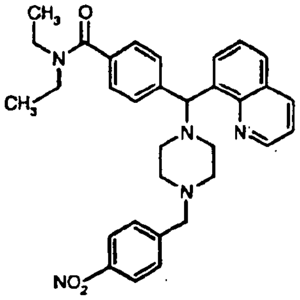
Compound 8

[0037] By procedure analogous to the preparation of compound 2, the title compound 8 was prepared. Alkylation was performed with 4-tert-butylbenzylbromide.
MS (ES) 549.53
(MH+).
IR (NaCl, free amine) 2963, 2807, 2360, 1631, 1456, 1425, 1285, 1135,1094, 1001 (cm^{-1}).
^1H NMR (CDCl3, free amine) δ = 1.0, 1.2 (2m, 6H), 1.29 (s, 9H), 2.50 (m, 8H), 3.2, 3.5 (2m), 3.50 (s, 2H), 6.04 (s, 1H), 7.16-7.68 (m, 11H). 7.98-8.10 (m, 2H), 8.92 (m, 1H). Anal. ($C_{36}H_{46}Cl_2N_4O$) C, H, N.

Example 8

Preparation of *N,N*-diethyl-4-[[4-(4-nitrobenzyl)-1-piperazinyl(8-quinolinyl)methyl]benzamide dihydrochloride (compound 9)

[0038]



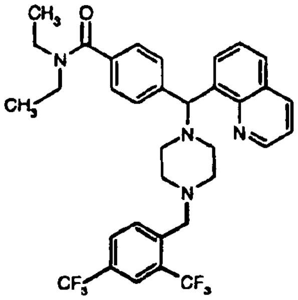
Compound 9

[0039] By procedure analogous to the preparation of compound 2 above, the **title compound 9** was prepared. Alkylation was performed with 4-nitrobenzylbromide.
MS (ES) 538.04 (MH+).
IR (NaCl, free amine) 2969, 2809, 2360, 1626, 1518, 1456, 1426, 1343, 1286, 1134, 1095, 1001 (cm-1).
^{1}**H NMR (CDCl3, free amine)** δ = 1.0, 1.2 (2m, 6H), 2.50 (m, 8H), 3.2, 3.5 (2m), 3.60 (s, 2H), 6.05 (s, 1H), 7.18-8.16 (m, 13H), 8.94 (m, 1H).
Anal. ($C_{32}H_{37}Cl_2N_5O_3$) C, H, N.

Example 9

Preparation of 4-[{4-(2,4-bis(trifluoromethyl-benzyl]-1-piperazinyl}(8-quinolinyl)methyl]-*N,N*-diethylbenzamide dihydrochloride (compound 10)

[0040]



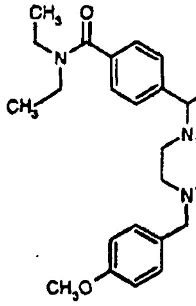
Compound 10

[0041] By following the procedure analogous to the preparation of compound 2 above, **the title compound 10** was prepared. Alkylation was performed with 2,4-bis(trifluoromethyl)benzylbromide.
MS (ES) 629.08 (MH+).
IR (NaCl, free amine) 2970, 2811, 2360, 1628, 1456, 1426, 1346, 1275, 1170, 1128 (cm^{-1}).
^{1}H **NMR (CDCl3, free** amine) δ = 1.0, 1.2 (2m, 6H), 2.48 (m, 8H), 3.2, 3.5 (2m), 3.71 (s, 2H), 6.06 (s, 1H), 7.20-8.14 (m, 12H), 8.95 (m, 1H). Anal. ($C_{34}H_{36}Cl_2F_6N_4O$) C, H, N

Example 10

Preparation of *N,N*-diethyl-4-[[4-(4-methoxybenzyl)-1-piperazinyl](8-Quinolinyl)methyl]benzamide dihydrochloride (compound 11)

[0042]



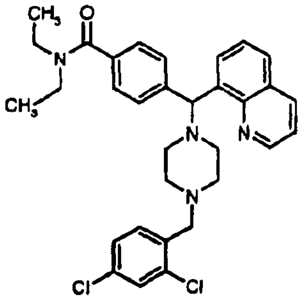
Compound 11

[0043] By procedure analogous to the preparation of compound 2 above, the **title compound 11** was prepared. Alkylation was performed with 4-methoxybenzylchloride.
MS (ES) 523.45 (MH+).
IR (NaCl, free amine) 2966, 2806, 2360, 1627, 1510, 1456, 1426, 1286, 1246, 1134, 1095 (cm-1).
^{1}**H NMR (CDCl3, free amine)** δ = 1.0, 1.2 (2m, 6H), 2.48 (m, 8H), 3.2, 3.5 (2m), 3.47 (s, 2H), 3.78 (s, 3H), 6.03 (s, 1H), 6.80-7.68 (m, 11H), 8.01-8.12 (m, 2H), 8.93 (m, 1H). Anal. ($C_{33}H_{40}Cl_2N_4O_2$) C, H, N.

Example 11

Preparation 4-[[4-(2,4-dichlorobenzyl)-1-piperazinyl](8-quinolinyl)methyl-*N,N*-diethylbenzamide dihydrochloride (compound 12)

[0044]



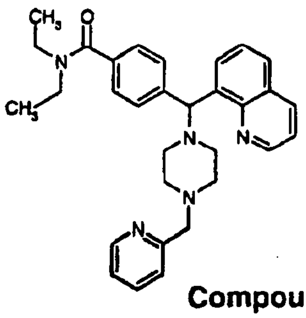
Compound 12

[0045] By following the procedure analogous to the preparation of compound 2 above, the **title compound 12** was prepared. Alkylation was performed with 2,4-dichlorobenzylchloride.
MS (ES) 562.45 (MH+).
IR (NaCl, free amine) 2968, 2810, 2360, 2341, 1627, 1470, 1426, 1285, 1134, 1095 (cm^{-1}).
^{1}**H NMR (CDCl3, free amine)** δ = 1.0, 1.1 (2m, 6H), 2.5 (m, 8H), 3.2, 3.5 (2m), 3.58 (s, 2H), 6.05 (s, 1H), 7.14-7.70 (m, 10H), 8.06 (m, 2H), 8.94 (m, 1H). Anal. ($C_{32}H_{36}Cl_4N_4O$) C, H, N.

Example 12

Preparation of *N,N*-diethyl-4-[[4-(2-pyridinylmethyl)-1-piperazinyl](8-quinolinyl)methyl]benzamide dihydrochloride (compound 13)

[0046]



Compound 13

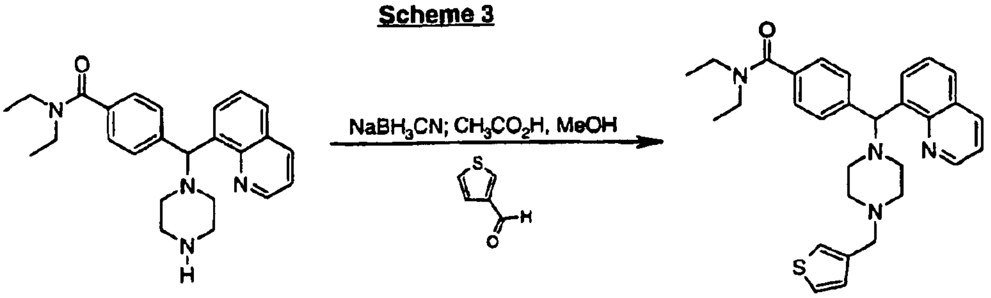
[0047] **Compound** 1 (80 mg, 0.20 mmol) was dissolved in MeOH (2 mL) with 2-pyridylcarboxaldehyde (39 µL, 0.40 mmol) and HOAc (1 µL, 0.02 mmol). Sodium cyanoborohydride (26 mg, 0.40 mmol) was added and stirring continued for 48 h. Solvent was evaporated and residue purified by chromatography on silica (0-10 % MeOH in CH_2Cl_2). 38 mg (39 %) product was obtained.
MS (ES) 494.19 (MH+).
IR (NaCl, free amine) 2968, 2809, 2360, 1626, 1455, 1428, 1286, 1134, 1094, 1001 (cm-1). **^{1}H NMR (CDCl3, free amine)** δ = 1.0, 1.2 (2m, 6H), 2.50 (m, 8H), 3.2, 3.5 (2m), 3.69 (s, 2H), 6.05 (s, 1H), 7.12-7.70 (m, 10H), 8.08 (m, 2H), 8.54 (m, 1H), 8.94 (m, 1H). Anal. ($C_{31}H_{37}Cl_2N_5O$) C, H, N.

Example 13

Preparation of *N,N*-diethyl-4-[[4-(3-thienylmethyl)-1-piperazinyl](8-quinolinyl)methyl]benzamide(compound 14)

[0048] The **title compound** 14 was prepared by following the synthetic procedure of Scheme 3 below.

Scheme 3



Compound 1 **Compound 14**

[0049] To a solution of compound 1 (500mg; 0.99 mmol) in methanol (10ml) was added thiophene 3-carboxaldehyde (104ul; 1.19mmol) followed by acetic acid (0.1ml; 1%) and sodium cyano borohydride (186.6mg; 2.97mmol). The reaction mixture was stirred overnight, then sodium hydroxide 2N was added and the mixture extracted with methylene chloride (3X). The combined methylene chloride extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by reverse phase using 10%-30% CH_3CN/H_2O (TFA as the buffer) gave 258mg of desired product (TFA salt).

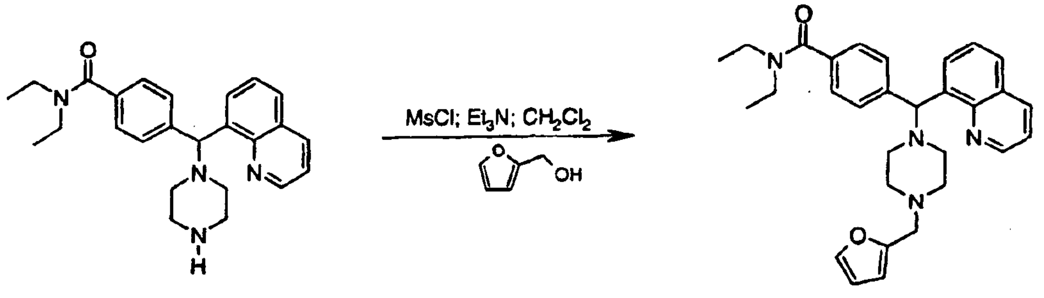
HPLC purity: >99% (215nm); >95% (254nm)
(M+1) calculated: 499.25, (M+1) observed: 499.46
Anal.: calculated for ($C_{30}H_{34}N_4OS$ X 2.80 $C_2HO_2F_3$ X 1.80 H_2O): C:50.28%; H:4.79%; N:6.59%; O:15.80%; S:3.77%; F:18.77% found: C:50.28%; H:4.83%; N:6.53%
^{1}HNMR: 8.95(dd, 1H, J=4.4, 2.0Hz), 8.38(dd, 1H, J=8.0, 2.0Hz), 8.00(dd, 1H, J=7.2, 1.6Hz), 7.84(dd, 1H, J=8.0, 1.6Hz), 7.52-7.62(m, 5H), 7.45(dd, 1H, J=4.8, 2.8Hz), 7.20(dd, 2H, J=8.8, 2.2Hz), 7.11(dd, 1H, J=4.8, 1.6Hz), 5.96(s, 1H), 4.27 (s, 2H), 3.34-3.44(m, 2H), 3.22-3.28(m, 4H), 3.04-3.14(m, 2H), 2.66-2.88(m, 4H), 1.04-1.14(m, 3H), 0.88-0.98(m, 3H)

Example 14

Preparation of *N,N*-diethyl-4-[(4-(2-furanylmethyl)-1-piperazinyl](8-Quinolinyl)methyl]benzamide (compound 15)

[0050] The **title compound 15** was prepared by following the synthetic procedure of Scheme 4 below.

Scheme 4



Compound 1

Compound 15

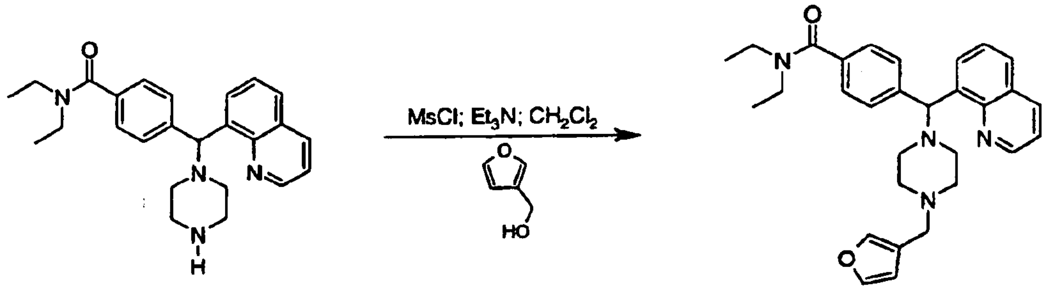
[0051] To a 0°C solution of furfurylalcohol (0.19ml; 2.24 mmol) and triethylamine (0.52ml; 3.73mmol) in methylene chloride (4ml) was added methanesulfonyl chloride (0.17ml; 2.24mmol). The mixture was stirred 1 hour at 0°C, then compound 1 (300mg; 0.75mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight, then heated to 45°C and stirred for 1 ½ hours. The reaction mixture was allowed to cool to room temperature and NaOH 2N was added untill pH was basic. The mixture was extracted with methylene chloride (3X). The combined methylene chloride extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by reverse phase using 10%-25% CH_3CN/H_2O (TFA as the buffer) gave 197mg of desired product (TFA salt).
HPLC purity: >99% (215nm, 254nm and 280nm)
(M+1) calculated: 483.63, (M+1) observed: 483.30
^{1}HNMR: 8.89(dd, 1H, J=4.4, 1.6Hz), 8.29(dd, 1H, J=8.0, 1.6Hz), 7.97(dd, 1H, J=7.2, 1.6Hz), 7.79(d, 1H, J=7.2Hz), 7.61(d, 2H, J=8.0Hz), 7.52-7.58(m, 2H), 7.48(dd, 1H, J=8.0, 4.4Hz), 7.19(d, 2H, J=8.0Hz), 6.56(d, 1H, J=3.2Hz), 6.40 (dd, 1H, J=3.2, 2.4Hz), 6.02(s, 1H), 4.26(s, 2H), 3.34-3.44(m, 2H), 3.16-3.26(m, 4H), 3.04-3.14(m, 2H), 2.68-2.86(m, 4H), 1.06-1.14(m, 3H), 0.90-0.98(m, 3H)

Example 15

Preparation of *N,N*-diethyl-4-[[4-(3-furanylmethyl)-1-piperazinyl](8-quinolinyl)methyl]benzamide(compound 16)

[0052] The **title compound 16** was prepared by following the synthetic procedure of Scheme 5 below.

Scheme 5



Compound 1 **Compound 16**

[0053] To a 0°C solution of 3-furanmethanol (220mg; 2.24 mmol) and triethylamine (0.52ml; 3.73mmol) in methylene chloride (4ml) was added methanesulfonyl chloride (0.17ml; 2.24mmol). The mixture was stirred 1 hour at 0°C, then compound 1 (300mg; 0.75mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight, then heated to 45°C and stirred for 3 ½ hours. The reaction mixture was allowed to cool to room temperature and NaOH 2N was added untill pH was basic. The mixture was extracted with methylene chloride (3X). The combined methylene chloride extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by reverse phase using 10%-25% CH_3CN/H_2O (TFA as the buffer) gave 293mg of desired product (TFA salt).

HPLC purity: >98% (215nm and 280nm); >99% (254nm)

(M+1) calculated: 483.63, (M+1) observed: 483.34

Anal.: calculated for ($C_{30}H_{34}N_4O_2$ X 3.10 $C_2HO_2F_3$ X 1.70 H_2O): C:50.17%; H:4.71%; N:6.46%; O:18.27% F:20.39% found: C:50.14%; H:4.76%; N:6.38%

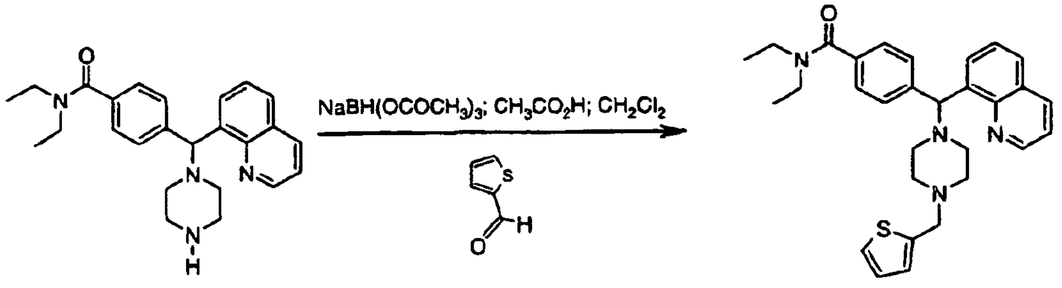
^{1}HNMR: 8.93(dd, 1H, J=4.4, 2.0Hz), 8.36(dd, 1H, J=8.6, 2.0Hz), 8.00(dd, 1H, J=7.4, 1.2Hz), 7.82(dd, 1H, J=7.6, 1.2Hz), 7.48-7.66(m, 6H), 7.19(d, 2H, J=8.0Hz), 6.46(s, 1H), 5.97(s, 1H), 4.13(s, 2H), 3.32-3.44(m, 2H), 3.20-3.28(m, 4H), 3.04-3.14(m, 2H), 2.66-2.86(m, 4H), 1.04-1.14(m, 3H), 0.88-0.98(m, 3H)

Example 16

Preparation of *N,N*-diethyl-4-[[4-(2-thiophenylmethyl)-1-piperazinyl](8-quinolinyl)methyl]benzamide dihydrochloride (compound 17)

[0054] The title compound 17 was prepared by following the synthetic procedure of Scheme 6 below.

Scheme 6



Compound 1 **Compound 17**

[0055] To a solution of compound 1 (0.99 mmol) in methylene chloride (10ml) was added 2-thiophenecarboxaldehyde

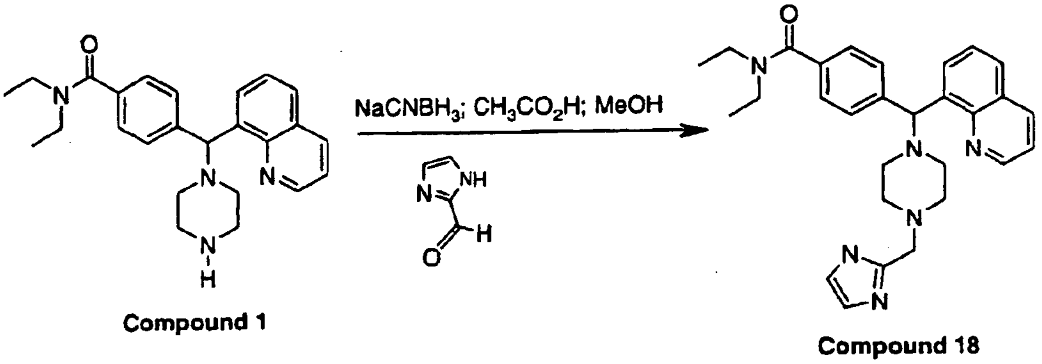
(190ul; 1.98mmol) followed by acetic acid (0.1ml; 1%). The mixture was stirred 30 minutes then sodium triacetoxyborohydride (0.63g; 2.97mmol) was added and the reaction mixture stirred overnight. The reaction mixture was neutralized with sodium hydroxide 2N and extracted with methylene chloride (3X). The combined methylene chloride extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by reverse phase using 10%-30% CH_3CN/H_2O (TFA as the buffer) gave 115mg of desired product (TFA salt).
HPLC purity: >99% (215nm); >96% (254nm)
(M+1) calculated: 499.25, (M+1) observed: 499.33
Anal.: calculated for ($C_{30}H_{34}N_4OS$ X 2.50 $C_2HO_2F_3$ X 0.10 H_2O): C:53.51%; H:4.71%; N:7.13%; O:12.42% S:4.08%; F:18.14% found: C:53.49%; H:4.63%; N:7.49%
^{1}HNMR: 8.91(dd, 1H, J=4.0, 1.6Hz), 8.30(dd, 1H, J=8.8, 1.6Hz), 7.96(dd, 1H, J=7.4, 1.4Hz), 7.81(d, 1H, J=7.2Hz), 7.62(d, 2H, J=8.0Hz), 7.46-7.58(m, 3H), 7.20(d, 2H, J=8.0Hz), 7.14-7.22(m, 1H), 7.00(dd, 1H, J=5.2, 3.6Hz), 6.03(s, 1H), 4.38(s, 2H), 3.34-3.44(m, 2H), 3.14-3.22(m, 4H), 3.06-3.12(m, 2H), 2.74-2.88(m, 4H), 1.04-1.14(m, 3H), 0.88-0.98 (m, 3H)

Example 17

Preparation of *N,N*-diethyl-4-[[4-(2-imidazolylmethyl)-1-pinerazinyl](8-Quinolinyl)methyl]benzamide dihydrochloride (compound 18)

[0056] The **title compound** 18 was prepared by following the synthetic procedure of Scheme 7 below.

Scheme 7



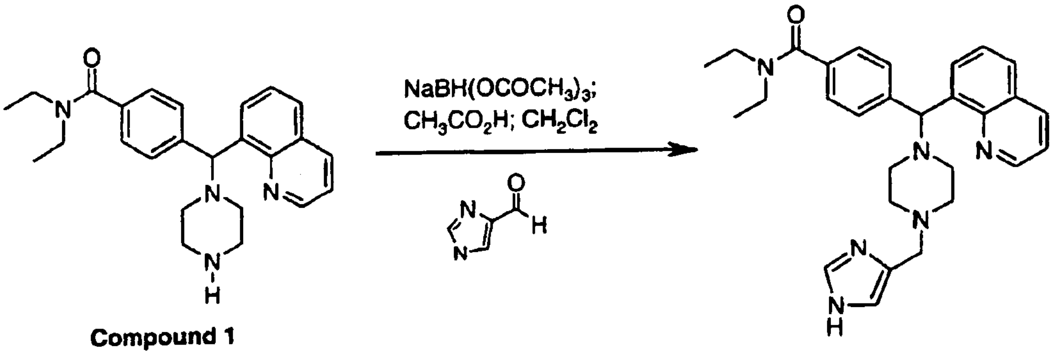
[0057] To a solution of compound 1 (0.99 mmol) in methanol (10ml) was added 2-imidazolecarboxaldehyde (114mg; 1.19mmol) followed by acetic acid (0.5ml; 5%). The mixture was stirred 3 hours then sodium cyanoborohydride (186.6mg; 2.97mmol) was added and the reaction mixture was stirred overnight. The reaction mixture was neutralized with sodium hydroxide 2N and extracted with methylene chloride (3X). The combined methylene chloride extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by reverse phase using 10%-30% CH_3CN/H_2O (TFA as the buffer) gave the TFA salt. The HCl salt was made using HCl/ether. Yield: 60.3mg of desired product (HCl salt).
HPLC purity: >95% (215nm); >93% (254nm)
(M+1 calculated: 483.29, (M+1) observed: 483.19
^{1}HNMR: 9.12-9.22(m, 1H), 8.54-8.62(m, 1H), 8.08-8.16(m, 1H), 7.98-8.04(m, 1H), 7.60-7.86(m, 4H), 7.38-7.46(m, 2H), 7.22-7.32(m, 2H), 6.32(s, 1H), 4.11(s, 2H), 2.94-3.40(m, 12H), 0.88-1.12(m, 6H).

Example 18

Preparation of N,N-diethyl-4-[[4-(4-imidazolylmethyl)-1-piperazinyl](8-quinolinyl)methyl]benzamide dihydrochloride (compound 19)

[0058] The **title compound 19** was prepared by following the synthetic procedure of Scheme 8 below.

Scheme 8



Compound 1

Compound 19

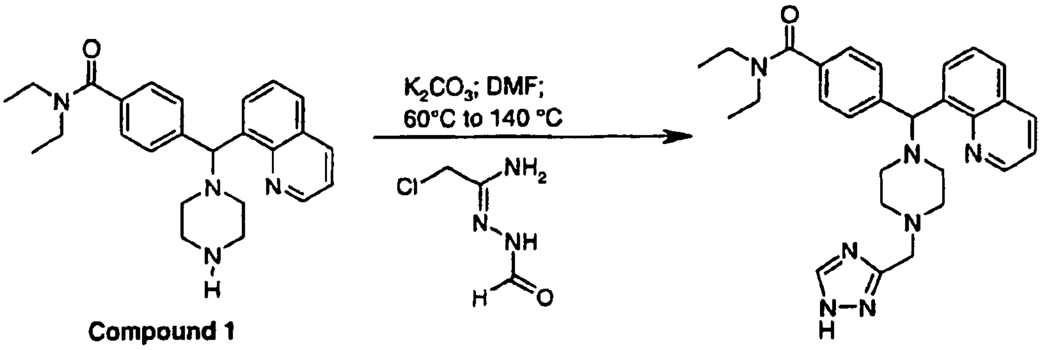
[0059] To a room temperature solution of 434 (400mg; 0.99 mmol) and 4-imidazole carboxaldehyde (95.5mg; 0.99mmol) in methylene chloride (10ml) was added acetic acid (0.1ml). The mixture was stirred for 5 hours then sodium triacetoxyborohydride (632mg; 2.98mmol) was added. The reaction mixture was stirred overnight and was neutralized with sodium hydroxide 2N. The mixture was extracted with methylene chloride (3X). The combined methylene chloride extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by reverse phase chromatography using 15% CH_3CN/H_2O (TFA as the buffer) gave 103mg of desired product (TFA salt).
HPLC purity: >99% (215nm, 254nm and 280nm)
(M+1) calculated: 483.28, (M+1) observed: 482.96
Anal.: calculated for ($C_{29}H_{34}N_6O$ X 3.80 $C_2HO_2F_3$ X 0.80 H_2O): C:47.25%; H:4.27%; N:9.03%; O:16.17%; F:23.28%
found: C:47.31%; H:4.40%; N:8.87
^{1}HNMR: 8.99(dd, 1H, J=4.4, 1.2Hz), 8.76(d, 1H, J=1.2Hz), 8.39(dd, 1H, J=8.8, 1.2Hz), 7.93(dd, 1H, J=7.2, 1.6Hz), 7.86(dd, 1H, J=8.0, 1.6Hz), 7.71(d, 2H, J=8.8Hz), 7.60(dd, 1H, J=8.8, 4.4Hz), 7.56(dd, 1H, J=8.0, 7.2Hz), 7.40(s, 1H), 7.27(d, 2H, J=8.8Hz), 6.12(s, 1H) 3.74(s, 2H), 3.38(q, 2H, J=6.4Hz), 3.10-3.25(m, 6H), 3.06(q, 2H, J=7.2Hz), 2.75-2.90 (m, 2H), 1.08(t, 3H, J=6.4Hz), 0.92(t, 3H, J=7.2Hz)

Example 19

Preparation of N,N-diethyl-4-[[4-(3-triazolylmethyl)-1-piperazinyl](8-quinolinyl)methylbenzamide dihydrochloride (compound 20)

[0060] The **title compound 20** was prepared by following the synthetic procedure of Scheme 9 below.

Scheme 9



Compound 1

Compound 20

[0061] To a room temperature solution 434 (200mg; 0.50 mmol) in dimethylformamide (10ml) was added potassium carbonate (275mg; 1.99mmol), followed by N-formamido-2-(chloromethyl)acetamidine (170mg; 1.24mmol). The reaction mixture was heated to 60°C and stirred for 2 days, then the temperature was raised to 140°C and stirred for 3 hours. The reaction mixture was allowed to cool to room temperature and water was added. The mixture was extracted with ethylacetate (3X). The combined ethylacetate extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by reverse phase chromatography using 20% CH_3CN/H_2O (TFA as the buffer) gave 21mg of desired product (TFA salt).
HPLC purity: >99% (215nm, 254nm and 280nm)
(M+1) calculated: 484.28, (M+1) observed: 483.92
Anal.: calculated for ($C_{28}H_{33}N_7O$ X 3.30 $C_2HO_2F_3$ X 3.30 H_2O): C:45.20%; H:4.70%; N:10.66%; 0:18.97%; F:20.46% found: C:45.12%; H:4.60%; N:10.84
^{1}HNMR: 8.94(dd, 1H, J=4.4, 1.6Hz), 8.38(s, 1H), 8.33(dd, 1H, J=8.0, 1.2Hz), 7.93(d, 1H, J=7.2Hz), 7.85(d, 1H, J=7.2Hz), 7.65(d, 2H, J=8.8Hz), 7.51-7.58(m, 2H), 7.23(d, 2H, J=8.8Hz), 6.15(s, 1H), 4.21(s, 2H), 3.40-3.50(m, 2H), 3.10-3.30(m, 8H), 2.90-3.10(m, 2H), 0.90-1.30(m, 6H)

Pharmaceutical compositions

[0062] The novel compounds according to the present invention may be administered orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

[0063] A preferred route of administration is orally, intravenously or intramuscularly.

[0064] 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 as the most appropriate for a particular patient.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] Pharmaceutically acceptable salts are acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium acetate, camsylate, carbonate, chloride, citrate, 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, tannate, 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 bitartrates. The hydrochloride salts are particularly preferred.

[0071] 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.

[0072] Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

[0073] 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.

[0074] 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.

[0075] 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

In vitro model

Cell culture

[0076] 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

[0077] 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

[0078] 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, see Table 1) 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 mini vials 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

[0079] 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. Biological data are reported below in Table 1.

Table 1.

Summary of biological data.

Example #	HDELTA	HDELTA		RAT BRAIN		MOUSE BRAIN		MLM		RLM	
		EC50	% EMAX	EC50	% EMAX	EC50	% EMAX	10000 % rem.	100000 % rem.	10000 % rem.	100000 % rem.
12	0.692	0.76	97.73	20.99	106.43	27.14	91.34	0	53.5	21.5	66
13	1.033	1.44	101.18	17.7	111.96	25.77	112.68	1.667	71.667	10	62.667
14	0.181	0.76	88.65	14.26	102.02	20.49	106.48	0	49	13.5	84.5
15	0.787	0.79	88.99	14.16	108.81	16.01	109.85	0	68	10	86
16	1.509	2.39	99.36	30.83	100.5	24.2	98.41	0.5	46.5	9.5	64.5
17	1.091	3.03	95.66	49.47	105.91	75.1	92.47	0	21.5	5.5	75
18	1.54	5.85	93.82	452.31	111.01	429.56	108.41				
19	18.751	85.24	97.88	2807.47	56.35	1365.82	48.68				

Receptor saturation experiments

[0080] Radioligand $K\delta$ 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 $K\delta$ (up to 10 times if amounts of radioligand required are feasable). The specific radioligand binding was expressed as pmole/mg membrane protein. Values of $K\delta$ 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.

DETERMINATION OF MECHANO-ALLODYNIA USING VON FREY TESTING

[0081] Testing was performed between 08:00 and 16 00h using the method described by Chaplan et al. (1994). Rats were placed in Plexiglas cages on top of a wire mesh bottom which allowed access to the paw, and were left to habituate for 10-15 min. The area tested was the mid-plantar left hind paw, avoiding the less sensitive foot pads. The paw was touched with a series of 8 Von Frey hairs with logarithmically incremental stiffness (0.41, 0.69, 1.20, 2.04, 3.63, 5.50, 8.51, and 15.14 grams; Stoelting, Ill, USA). The von Frey hair was applied from underneath the mesh floor perpendicular to the plantar surface with sufficient force to cause a slight buckling against the paw, and held for approximately 6-8 seconds. A positive response was noted if the paw was sharply withdrawn. Flinching immediately upon removal of the hair was also considered a positive response. Ambulation was considered an ambiguous response, and in such cases the stimulus was repeated.

TESTING PROTOCOL

[0082] The animals were tested on postoperative day 1 for the FCA-treated group. The 50% withdrawal threshold was determined using the up-down method of Dixon (1980). Testing was started with the 2.04 g hair, in the middle of the series. Stimuli were always presented in a consecutive way, whether ascending or descending. In the absence of a paw withdrawal response to the initially selected hair, a stronger stimulus was presented; in the event of paw withdrawal, the next weaker stimulus was chosen. Optimal threshold calculation by this method requires 6 responses in the immediate vicinity of the 50% threshold, and counting of these 6 responses began when the first change in response occurred, e.g. the threshold was first crossed. In cases where thresholds fell outside the range of stimuli, values of 15.14 (normal sensitivity) or 0.41 (maximally allodynic) were respectively assigned. The resulting pattern of positive and negative responses was tabulated using the convention, X = no withdrawal; O = withdrawal, and the 50% withdrawal threshold was interpolated using the formula:

$$50\%\ \text{g threshold} = 10^{(Xf + k\delta)} / 10{,}000$$

where Xf = value of the last von Frey hair used (log units); k = tabular value (from Chaplan et al. (1994)) for the pattern of positive / negative responses; and δ = mean difference between stimuli (log units). Here δ = 0.224.

[0083] Von Frey thresholds were converted to percent of maximum possible effect (% MPE), according to Chaplan et al. 1994. The following equation was used to compute % MPE:

$$\%\ \text{MPE} = \frac{\text{Drug treated threshold (g) - allodynia threshold (g)}}{\text{Control threshold (g) - allodynia threshold (g)}} \text{ X } 100$$

ADMINISTRATION OF TEST SUBSTANCE

[0084] Rats were injected (subcutaneously, intraperitoneally, intravenously or orally) with a test substance prior to von Frey testing, the time between administration of test compound and the von Frey test varied depending upon the nature of the test compound.

WRITHING TEST

[0085] Acetic acid will bring abdominal contractions when administered intraperitoneally in mice. These will then extend their body in a typical pattern. When analgesic drugs are administered, this described movement is less frequently observed and the drug selected as a potential good candidate.

[0086] A complete and typical Writhing reflexe is considered only when the following elements are present: the animal is not in movement; the lower back is slightly depressed; the plantar aspect of *both* paws is observable.

(i) Solutions preparation

[0087] Acetic acid (AcOH): 120 μL of Acetic Acid is added to 19.88 ml of distilled water in order to obtain a final volume of 20 ml with a final concentration of 0.6% AcOH. The solution is then mixed (vortex) and ready for injection.

[0088] Compound (drug): Each compound is prepared and dissolved in the most suitable vehicle according to standard procedures.

(ii) Solutions administration

[0089] The compound (drug) is administered orally, intraperitoneally (i.p.), subcutaneously (s.c.) or intravenously (i.v.)) at 10 ml/kg (considering the average mice body weight) 20, 30 or 40 minutes (according to the class of compound and its characteristics) prior to testing. When the compound is delivered centrally: Intraventricularly (i.c.v.) or intrathecally (i.t.) a volume of 5 μL is administered.

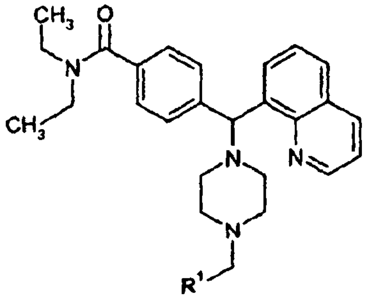
[0090] The AcOH is administered intraperitoneally (i.p.) in two sites at 10 ml/kg (considering the average mice body weight) immediately prior to testing.

(iii) Testing

[0091] The animal (mouse) is observed for a period of 20 minutes and the number of occasions (Writhing reflex) noted and compiled at the end of the experiment. Mice are kept in individual "shoe box" cages with contact bedding. A total of 4 mice are usually observed at the same time: one control and three doses of drug.

Claims

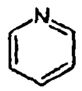
1. A compound according to formula I



I

wherein
R¹ is selected from

(i) phenyl;
(ii) pyridinyl



;

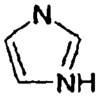
(iii) thiophenyl


;

(iv) furanyl


;

(v) imidazolyl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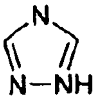
and
(vi) triazolyl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where each phenyl ring and heteroaromatic ring may optionally and independently be further substituted by 1, 2 or 3 substituents selected from straight and branched C_1-C_6 alkyl, NO_2, CF_3, C_1-C_6 alkoxy, chloro, fluoro, bromo, and iodo;
as well as pharmaceutically acceptable salts thereof and isomers thereof.

2. A compound according to claim 1, wherein the optional substituent(s) on the aromatic or the heteroaromatic ring (s) is selected from anyone of NO_2, iso-butyl, CF_3, methoxy, methyl, or chloro.

3. A compound according to claim 1 or 2, selected from any one of
4-[(4-benzyl-1-piperazinyl)(8-quinolinyl)methyl]-*N,N* diethylbenzamide dihydrochloride (compound 2);
N,N-diethyl-4-[[4-(4-methylbenzyl)-1-piperazinyl](8-quinolinyl)methyl]benzamide (compound 5);
4-[{4-[4-(tert-butyl)benzyl]-1-piperazinyl}(8-quinolinyl)methyl]-*N,N*-diethylbenzamide dihydrochloride (compound 8);
N,N-diethyl-4-[[4-(4-nitrobenzyl)-1-piperazinyl)(8-quinolinyl)methyl]benzamide dihydrochloride (compound 9);
4-[{4-[2,4-bis(trifluoromethyl)benzyl]-1-piperazinyl}(8-quinolinyl)methyl]-*N,N*-diethylbenzamide dihydrochloride (compound 10);
N,N-diethyl-4-[[4-(4-methoxybenzyl)-1-piperazinyl](8-quinolinyl)methyl]benzamide dihydrochloride (compound 11);
4-[[4-(2,4-dichlorobenzyl)-1-piperazinyl](8-quinolinyl)methyl]-*N,N*-diethylbenzamide dihydrochloride (compound 12);
N,N-diethyl-4-[[4-(2-pyridinylmethyl)-1-piperazinyl](8-quinolinyl)methyl]benzamide dihydrochloride (compound 13);
N,N-diethyl-4-[[4-(3-thienylmethyl)-1-piperazinyl](8-quinolinyl)methyl]benzamide (compound 14);
N,N-diethyl-4-[[4-(2-furanylmethyl)-1-piperazinyl](8-quinolinyl)methyl]benzamide (compound 15);

N,N-diethyl-4-[[4-(3-furanylmethyl)-1-piperazinyl](8-quinolinyl)methyl]benzamide(compound 16);

N,N-diethyl-4-[[4-(2-thiophenylmethyl)-1-piperazinyl](8-quinolinyl)methyl]benzamide dihydrochloride (compound 17);

N,N-diethyl-[[4-(2-imidazolylmethyl)-1-piperazinyl)(8-quinolinyl)methyl]benzamide dihydrochloride (compound 18);

N,N-diethyl-4-[[4-(4-imidazolylmethyl)-1-piperazinyl](8-quinolinyl)methyl]benzamide dihydrochloride (compound 19); and

N,N diethyl-4-[[4-(3-triazolylmethyl)-1-piperazinyl](8-quinolinyl)methyl)benzamide dihydrochloride (compound 20).

4. A compound according to any one of claims 1-3, which compound is present as the (+)-enantiomer.

5. A compound according to anyone of claims 1-3, which compound is present as the (-)-enantiomer.

6. A compound according to any of the preceding claims, in form of its hydrochloride, sulfate, tartrate or citrate salts.

7. A compound according to claim 4, selected from any one of
(+)4-[(4-benzyl-1-piperazinyl)(8-quinolinyl)methyl]-N,N-diethylbenzamide; and
(+)4-[[4-(4-methylbenzyl)-1-piperazinyl](8-quinolinyl)methyl]-N,N-diethylbenzamide

8. A compound according to claim 5, selected from any one of
(-)4-[(4-benzyl-1-piperazinyl)(8-quinolinyl)methyl]-N,N-diethylbenzamide; and
(-)4-[[4-(4-methylbenzyl)-1-piperazinyl](8-quinolinyl)methyl]-N,N-diethylbenzamide.

9. A compound according to any of claims 1-8 for use in therapy.

10. A compound according to claim 9, wherein the therapy is pain management.

11. A compound according to claim 9, wherein the therapy is directed towards gastrointestinal disorders.

12. A compound according to claim 9, wherein the therapy is directed towards spinal injuries.

13. A compound according to claim 9, wherein the therapy is directed to disorders of the sympathetic nervous system.

14. Use of a compound according to formula I of claim 1 for the manufacture of a medicament for use in the treatment of pain.

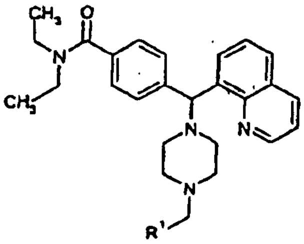
15. Use of a compound according to formula I of claim 1 for the manufacture of a medicament for use in the treatment of gastrointestinal disorders.

16. Use of a compound according to formula I of claim 1 for the manufacture of a medicament for use in the treatment of spinal injuries.

17. A pharmaceutical composition comprising a compound of the formula I according to claim 1 as an active ingredient, together with a pharmacologically and pharmaceutically acceptable carrier.

Patentansprüche

1. Verbindungen der Formel I



wobei
R^1 ausgewählt ist aus

(i) Phenyl;

;

(ii) Pyridinyl

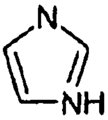
;

(iii) Thiophenyl

;

(iv) Furanyl

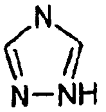
(v) Imidazolyl



;

und

(vi) Triazolyl



;

wobei der Phenylring und der heteroaromatische Ring jeweils gegebenenfalls unabhängig voneinander durch 1, 2 oder 3 Substituenten, ausgewählt aus geradkettigem und verzweigtem C_1-C_6-Alkyl, NO_2, CF_3, C_1-C_6-Alkoxy, Chlor, Fluor, Brom und Iod weiter substituiert sein können;
sowie deren pharmazeutisch unbedenkliche Salze und Isomere.

2. Verbindungen nach Anspruch 1, wobei der/die gegebenenfalls vorhandene(n) Substituent(en) am aromatischen bzw. heteroaromatischen Ring ausgewählt ist aus NO_2, Isobutyl, CF_3, Methoxy, Methyl und Chlor.

3. Verbindungen nach Anspruch 1 oder 2, ausgewählt aus den folgenden Verbindungen:

   4-[(4-Benzyl-1-piperazinyl)(8-chinolinyl)methyl]-*N,N*-diethylbenzamiddihydrochlorid (Verbindung 2);

   N,N-Diethyl-4-[[4-(4-methylbenzyl)-1-piperazinyl](8-chinolinyl)methyl]benzamid (Verbindung 5);

   4-[{4-[4-(tert.-Butyl)benzyl]-1-piperazinyl}(8-chinolinyl)methyl]-*N,N*-diethylbenzamiddihydrochlorid (Verbindung, 8);

   N,N-Diethyl-4-[[4-(4-nitrobenzyl)-1-piperazinyl](8-chinolinyl)methyl]benzamiddihydrochlorid (Verbindung 9);

   4-[{4-[2,4-Bis(trifluormethyl)benzyl]-1-piperazinyl}(8-chinolinyl)methyl]-*N,N*-diethylbenzamiddihydrochlorid (Verbindung 10);

   N,N-Diethyl-4-[[4-(4-methoxybenzyl)-1-piperazinyl](8-chinolinyl)methyl]benzamiddihydrochlorid (Verbindung 11);

   4-[[4-(2,4-Dichlorbenzyl)-1-piperazinyl] (8-chinolinyl) methyl]-*N,N*-diethylbenzamiddihydrochlorid (Verbindung 12);

   N,N-Diethyl-4-[[4-(2-pyridinylmethyl)-1-piperazinyl](8-chinolinyl)methyl]benzamiddihydrochlorid (Verbindung 13);

   N,N-Diethyl-4-[[4- (3-thienylmethyl)-1-piperazinyl](8-chinolinyl)methyl]benzamid (Verbindung 14);

   N,N-Diethyl-4-[[4-(2-furanylmethyl)-1-piperazinyl](8-chinolinyl)methyl]benzamid (Verbindung 15);

   N,N-Diethyl-4-[[4-(3-furanylmethyl)-1-piperazinyl](8-chinolinyl)methyl]benzamid (Verbindung 16);

   N,N-Diethyl-4-[[4-(2-thiophenylmethyl)-1-piperazinyl](8-chinolinyl)methyl]benzamiddihydrochlorid (Verbindung 17);

   N,N-Diethyl-4-[[4-(2-imidazolylmethyl)-1-piperazinyl](8-chinolinyl)methyl]benzamiddihydrochlorid (Verbindung 18);

   N,N-Diethyl-4-[[4-(4-imidazolylmethyl)-1-piperazinyl](8-chinolinyl)methyl]benzamiddihydrochlorid (Verbindung 19) und

   N,N-Diethyl-4-[[4-(3-triazolylmethyl)-1-piperazinyl](8-chinolinyl)methyl]benzamiddihydrochlorid (Verbindung 20);

4. Verbindungen nach einem der Ansprüche 1 bis 3, wobei die Verbindung als (+)-Enantiomer vorliegt.

5. Verbindungen nach einem der Ansprüche 1 bis 3, wobei die Verbindung als (-)-Enantiomer vorliegt.

6. Verbindungen nach einem der vorhergehenden Ansprüche in Form ihrer Hydrochlorid-, Sulfat-, Tartrat- oder Citratsalze.

7. Verbindung nach Anspruch 4, ausgewählt aus

   (+)-4-[(4-Benzyl-1-piperazinyl)(8-chinolinyl)-methyl]-*N,N*-diethylbenzamid und

   (+)-4-[(4-Methylbenzyl)-1-piperazinyl](8-chinolinyl)methyl]-*N,N*-diethylbenzamid.

8. Verbindung nach Anspruch 5, ausgewählt aus

   (-)-4-[(4-Benzyl-1-piperazinyl)(8-chinolinyl)-methyl]-*N,N*-diethylbenzamid und

   (-)-4-[[4-Methylbenzyl)-1-piperazinyl](8-chinolinyl)methyl]-*N,N*-diethylbenzamid.

9. Verbindungen nach einem der Ansprüche 1-8 zur Verwendung in der Therapie.

10. Verbindungen nach Anspruch 9; wobei es sich bei der Therapie um die Behandlung von Schmerzen handelt.

11. Verbindungen nach Anspruch 9, wobei die Therapie auf gastrointestinale Erkrankungen abzielt.

12. Verbindungen nach Anspruch 9, wobei die Therapie auf Rückenmarksverletzungen abzielt.

13. Verbindungen nach Anspruch 9, wobei die Therapie auf Erkrankungen des sympathischen Nervensystems abzielt.

14. Verwendung einer Verbindung der Formel I nach Anspruch 1 zur Herstellung eines Medikaments zur Verwendung bei der Behandlung von Schmerzen.

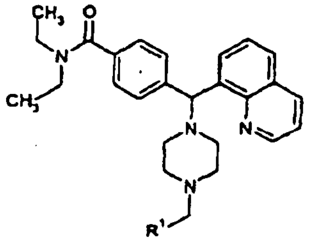
15. Verwendung einer Verbindung der Formel I nach Anspruch 1 zur Herstellung eines Medikaments zur Verwendung bei der Behandlung von gastrointestinalen Erkrankungen.

16. Verwendung einer Verbindung der Formel I nach Anspruch 1 zur Herstellung eines Medikaments zur Verwendung bei der Behandlung von Rückenmarksverletzungen.

17. Pharmazeutische Zusammensetzung, enthaltend eine Verbindung der Formel I nach Anspruch 1, als Wirkstoff, zusammen mit einem pharmakologisch und pharmazeutisch unbedenklichen Träger.

Revendications

1. Composé selon la formule I

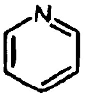


I

dans laquelle
R^1 est choisi parmi :

(i) un phényle ;

(ii) un pyridinyle



;

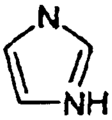
(iii) un thiophényle

;

(iv) un furanyle

;

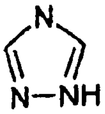
(v) un imidazolyle



;

et

(vi) un triazolyle



;

;

où chaque noyau phényle et chaque noyau hétéroaromatique peuvent éventuellement et indépendamment être davantage substitués par 1, 2 ou 3 substituants choisis parmi un alkyle en C_1-C_6 linéaire et ramifié, NO_2, CF_3, un alcoxy en C_1-C_6, un chloro, un fluoro, un bromo et un iodo ;
ainsi que des sels pharmaceutiquement acceptables de celui-ci et des isomères de celui-ci.

2. Composé selon la revendication 1, dans lequel le (les) substituant(s) éventuel(s) sur le (les) noyau(x) aromatique(s) ou hétéroaromatique(s) est (sont) choisi(s) de façon quelconque parmi NO_2, un isobutyle, CF_3, un méthoxy, un méthyle ou un chloro.

3. Composé selon la revendication 1 ou 2, choisi de façon quelconque parmi :

   le dichlorhydrate de 4-[(4-benzyl-1-pipérazinyl)(8-quinoléinyl)méthyl]-*N,N*-diéthylbenzamide (composé 2) ;

   le *N,N*-diéthyl-4-[[4-(4-méthylbenzyl)-1-pipérazinyl](8-quinoléinyl)méthyl]benzamide (composé 5) ;

   le dichlorhydrate de 4-[{4-[4-(tert-butyl)benzyl]-1-pipérazinyl} (8-quinoléinyl)méthyl]-*N,N*-diéthylbenzamide (composé 8) ;

   le dichlorhydrate de *N,N*-diéthyl-4-[[4-(4-nitrobenzyl)-1-pipérazinyl](8-quinoléinyl)-méthyl]benzamide (composé 9) ;

   le dichlorhydrate de 4-[{4-[2,4-bis(trifluorméthyl)benzyl]-1-pipérazinyl}(8-quinoléinyl)méthyl]-*N,N*-diéthylbenzamide (composé 10) ;

   le dichlorhydrate de *N,N*-diéthyl-4-[[4-(4-methoxybenzyl)-1-pipérazinyl](8-quinoléinyl)-méthyl]benzamide (composé 11) ;

   le dichlorhydrate de 4-[[4-[2,4-dichlorobenzyl)-1-pipérazinyl] (8-quinoléinyl)méthyl]-*N,N*-diéthylbenzamide (composé 12) ;

   le dichlorhydrate de *N,N*-diéthyl-4-[[4-(2-pyridinylméthyl)-1-pipérazinyl](8-quinoléinyl)-méthyl]benzamide (composé 13) ;

   le *N,N*-diéthyl-4-[[4-(3-thienylméthyl)-1-pipérazinyl](8-quinoléinyl)méthyl]benzamide (composé 14) ;

   le *N,N*-diéthyl-4-[[4-(2-furanylméthyl)-1-pipérazinyl](8-quinoléinyl)méthyl]benzamide (composé 15) ;

   le *N,N*-diéthyl-4-[[4-(3-furanylméthyl)-1-pipérazinyl](8-quinoléinyl)méthyl]benzamide (composé 16) ;

   le dichlorhydrate de *N,N*-diéthyl-4-[[4-(2-thiophénylméthyl)-1-pipérazinyl](8-quinoléinyl)-méthyl]benzamide (composé 17) ;

   le dichlorhydrate de *N,N*-diéthyl-4-[[4-(2-imidazolylméthyl)-1-pipérazinyl] (8-quinoléinyl)-méthyl]benzamide (composé 18) ;

   le dichlorhydrate de *N,N*-diéthyl-4-[[4-(4-imidazolylméthyl) -1-pipérazinyl] (8-quinoléinyl)-méthyl]benzamide (composé 19) ; et

   le dichlorhydrate de *N,N*-diéthyl-4-[[4-(3-triazolylméthyl)-1-pipérazinyl](8-quinoléinyl)-méthyl]benzamide (composé 20) ;

4. Composé selon l'une quelconque des revendications 1 à 3, lequel composé est présent sous forme de l'énantiomère (+).

5. Composé selon l'une quelconque des revendications 1 à 3, lequel composé est présent sous forme de l'énantiomère (-).

6. Composé selon l'une quelconque des revendications précédentes, sous forme de ses sels de chlorhydrate, de sulfate, de tartrate ou de citrate.

7. Composé selon la revendication 4, choisi de façon quelconque parmi

   le (+)-4-[(4-benzyl-1-pipérazinyl)(8-quinoléinyl)-méthyl]-*N,N*-diéthylbenzamide ; et

   le (+)-4-[[(4-méthylbenzyl)-1-pipérazinyl](8-quinoléinyl)méthyl]-*N,N*-diéthylbenzamide.

8. Composé selon la revendication 5, choisi de façon quelconque parmi

le (-)-4-[(4-benzyl-1-pipérazinyl)(8-quinoléinyl)-méthyl]-*N,N*-diéthylbenzamide ; et

le (-)-4-[[(4-méthylbenzyl)-1-pipérazinyl](8-quinoléinyl)méthyl]-*N,N*-diéthylbenzamide.

9. Composé selon l'une quelconque des revendications 1 à 8, destiné à être utilisé en thérapie.

10. Composé selon la revendication 9, la thérapie étant le soulagement de la douleur.

11. Composé selon la revendication 9, la thérapie visant des troubles gastro-intestinaux.

12. Composé selon la revendication 9, la thérapie visant des lésions de la colonne vertébrale.

13. Composé selon la revendication 9, la thérapie visant des troubles du système nerveux sympathique.

14. Utilisation d'un composé de formule I selon la revendication 1 pour la fabrication d'un médicament destiné à être utilisé pour le traitement de la douleur.

15. Utilisation d'un composé de formule I selon la revendication 1 pour la fabrication d'un médicament destiné à être utilisé pour le traitement de troubles gastro-intestinaux.

16. Utilisation d'un composé d formule I selon la revendication 1 pour la fabrication d'un médicament destiné à être utilisé pour le traitement de lésions spinales.

17. Composition pharmaceutique comprenant un composé de formule I selon la revendication 1 en tant qu'ingrédient actif, conjointement avec un support pharmacologiquement et pharmaceutiquement acceptable.