

3-MONOSUBSTITUTED TROPANE DERIVATIVES
AS NOCICEPTIN RECEPTOR LIGANDS

5 **FIELD OF THE INVENTION**

The present invention relates to nociceptin receptor agonist 3-monosubstituted tropane derivatives useful in treating cough, pain, anxiety, asthma, alcohol abuse, depression, urinary incontinence or overactive bladder. Pharmaceutical compositions comprising the compounds and combinations of the claimed compounds with other
10 agents for treating cough, allergy or asthma symptoms are also disclosed.

BACKGROUND

Nociceptin is a seventeen amino acid neuropeptide that has been recently identified as a potent endogenous agonist of the opioid-like receptor NOP (previously
15 termed ORL-1). The NOP receptor is a G-protein coupled receptor with 47% overall homology to the opioid receptors and 64% identical in transmembrane domains. In spite of this homology, classical opioid ligands have very low affinity for this receptor. Activation of the NOP receptor leads to inhibition of adenylyl cyclase activity and modulation of neuronal K^+ and Ca^{+2} conductance. It is structurally related to the
20 opioid peptides but does not activate opioid receptors.

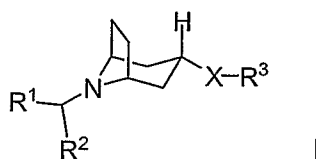
Nociceptin and its receptor are widely expressed throughout the central nervous system. Thus, nociceptin is likely to participate in a broad range of physiological and behavioral functions. Reports in literature have implicated its role in cough (see, for example, McLeod et al, *Pulmonary Pharmacology & Therapeutics*
25 (2002), **15**, 213-216) as well as in pain, feeding, locomotor activity, alcohol abuse, urinary incontinence, anxiety, stress, cardiovascular functions, sleep disturbance, Parkinson's Disease and Alzheimer's Disease.

3-Substituted 8-azabicyclo-[3.2.1]octanes were disclosed in US 6,262,066 B1, WO 95/04742, WO 97/48397, and WO 98/25924; 3-substituted 8-azabicyclo-
30 [3.2.1]octan-3-ols were disclosed in US 6,727,254 B2.

SUMMARY OF THE INVENTION

Compounds of the present invention are represented by formula I

-2-



or a pharmaceutically acceptable salt thereof, wherein

R^1 is R^4 -aryl, R^4 -arylalkyl, R^4 -heteroaryl, R^4 -heteroarylalkyl, R^4 -cycloalkyl, R^4 -cycloalkylalkyl, R^4 -heterocycloalkyl or R^4 -heterocycloalkylalkyl;

5 R^2 is R^5 -aryl, R^5 -arylalkyl, R^5 -heteroaryl, R^5 -heteroarylalkyl, R^5 -cycloalkyl, R^5 -cycloalkylalkyl, R^5 -heterocycloalkyl or R^5 -heterocycloalkylalkyl;

R^3 is R^6 -alkyl, R^6 -aryl, R^6 -heteroaryl, R^6 -cycloalkyl or R^6 -heterocycloalkyl;

X is a bond, (C_1-C_3) alkylene, $-(CH_2)_m-N(R^7)-(CH_2)_n-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-S-(CH_2)_n-$, $-C(O)-$, $-CH(OH)-$, $-C(O)N(R^7)-$, $-C(O)N(R^7)$ -alkylene or
10 $-N(R^7)C(O)-$;

n is 0, 1, 2, 3; 4, 5 or 6; m is 0, 1, 2, 3; 4, 5 or 6; provided that the sum of m and n is 0, 1, 2, 3; 4, 5 or 6;

each R^4 and R^5 is 1 to 3 substituents independently selected from the group consisting of H, halo, alkyl, cycloalkyl, $-CN$, $-CF_3$, $-(CH_2)_p-OR^8$, $-N(R^{10})_2$ and
15 $-(CH_2)_n-N(R^{10})_2$;

R^6 is 1 to 3 substituents independently selected from the group consisting of H, halo, alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, $-CN$, cyanoalkyl, $-CF_3$, $-C(O)alkyl$, $-(CH_2)_p-OR^8$, $-COOR^8$, $-N(R^{10})_2$, $-(CH_2)_n-N(R^{10})_2$ and $-C(O)N(R^{10})_2$;

p is 0, 1, 2, 3; 4, 5 or 6;

20 R^7 is H or alkyl;

R^8 and R^9 are independently selected from the group consisting of H, alkyl, cycloalkyl, haloalkyl, hydroxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkyl- $C(O)-$ and alkyl- $C(O)-N(R^7)-C(O)-$; and

R^{10} is independently selected from the group consisting of H and alkyl.

25 In another aspect, the invention relates to a pharmaceutical composition comprising at least one compound of formula I and a pharmaceutically acceptable carrier.

30 The compounds of the present invention are agonists of the NOP receptor, and therefore, in another aspect, the invention relates to a method of treating pain, anxiety, cough, asthma, alcohol abuse, depression, urinary incontinence or

overactive bladder, comprising administering to a mammal in need of such treatment an effective amount of at least one compound of formula I.

In another aspect, the invention relates to a method of treating cough, comprising administering to a mammal in need of such treatment an effective amount of a combination of: (a) at least one compound of formula I; and (b) one or more additional agents for treating cough, allergy or asthma symptoms selected from the group consisting of: antihistamines, 5-lipoxygenase inhibitors, leukotriene inhibitors, H₃ inhibitors, β -adrenergic receptor agonists, xanthine derivatives, α -adrenergic receptor agonists, mast cell stabilizers, anti-tussives, expectorants, NK₁, NK₂ and NK₃ tachykinin receptor antagonists, and GABA_B agonists.

In still another aspect, the invention relates to a pharmaceutical composition comprising at least one compound of formula I and one or more additional agents selected from the group consisting of: antihistamines, 5-lipoxygenase inhibitors, leukotriene inhibitors, H₃ inhibitors, β -adrenergic receptor agonists, xanthine derivatives, α -adrenergic receptor agonists, mast cell stabilizers, anti-tussives, expectorants, NK₁, NK₂ and NK₃ tachykinin receptor antagonists, and GABA_B agonists.

In another aspect, the invention relates to a method of treating urinary incontinence (UI) or overactive bladder comprising administering to a mammal in need of such treatment an effective amount of a combination of: (a) at least one compound of formula I; and (b) one or more agents useful for treating UI or overactive bladder.

In still another aspect, the invention relates to a pharmaceutical composition comprising at least one compound of formula I and one or more agents useful for treating UI or overactive bladder.

DETAILED DESCRIPTION OF THE INVENTION

Referring to formula I, above, preferred compounds of the invention are those wherein R¹ is R⁴-phenyl and R² is R⁵-phenyl, wherein R⁴ and R⁵ are independently selected from the group consisting of H, halo and alkyl. More preferably, R¹ is R⁴-phenyl wherein R⁴ is one halo atom, and R² is R⁵-phenyl wherein R⁵ is H or one halo atom. The preferred halo atom for R⁴ and R⁵ is chlorine. The R⁴ and R⁵ substituents are preferably in the 2-position in the phenyl ring.

-4-

X is preferably a bond, $-(CH_2)_m-N(R^7)-(CH_2)_n-$ wherein R^7 is H, m is 0 and n is 0 or 1, or $-C(O)N(R^7)-$ wherein R^7 is H. More preferably, X is a bond.

R^3 is preferably R^6 -aryl, R^6 -heteroaryl or R^6 -heterocycloalkyl, wherein aryl is preferably phenyl, heteroaryl is preferably pyridyl, pyrimidyl, imidazolyl or

5 benzimidazolyl, and heterocycloalkyl is preferably piperidinyll or morpholinyl.

Preferred R^6 substituents are H, halo, alkyl, OH, $-OCH_3$ (i.e., $-(CH_2)_n-OR^8$ wherein n is 0 or 1 and R^8 is H), hydroxyalkyl (i.e., $-(CH_2)_n-OR^8$ wherein n is 1 to 6 and R^8 is H), cycloalkyl and heterocycloalkylalkyl (e.g., piperidinylmethyl). More preferably, R^6 is one substituent selected from H, halo, alkyl, OH and $-OCH_3$.

10 Preferred compounds of the invention are those described below in Examples 1, 2, 8, 12, 13, 14, 16, 19, 20, 21, 23, 28, 29 and 62.

A preferred indication for compounds of formula I is the treatment of cough.

As used herein, the following terms are used as defined below unless otherwise indicated:

15 halo represents fluoro, chloro, bromo and iodo;

alkyl (including, for example, the alkyl portions of arylalkyl) represents straight and branched carbon chains and contains from one to six carbon atoms;

alkylene represents a divalent straight or branched alkyl chain, e.g., ethylene $-(CH_2)_2-$ or propylene $-(CH_2CH_2CH_2)-$;

20 cycloalkyl represents a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 3 to about 7 ring atoms. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like;

25 aryl (including the aryl portion of arylalkyl) represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is a phenyl or naphthyl ring), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of attachment;

30 heteroaryl represents cyclic aromatic groups of 5 or 6 atoms or bicyclic groups of 9 to 10 atoms having 1, 2 or 3 heteroatoms independently selected from O, S or N, said heteroatom(s) interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, provided

that the rings do not contain adjacent oxygen and/or sulfur atoms. Nitrogen atoms can form an N-oxide. All regioisomers are contemplated, e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl. Typical 6-membered heteroaryl groups are pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and the N-oxides thereof. Typical 5-membered heteroaryl rings are furyl, thienyl, pyrrolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl and isoxazolyl.

Bicyclic groups typically are benzo-fused ring systems derived from the heteroaryl groups named above, e.g. benzimidazolyl, quinolyl, phthalazinyl, quinazolinyl, benzofuranyl, benzothienyl and indolyl. The heteroaryl ring can be substituted with 1-3 R^4 , R^5 or R^6 groups, wherein any of the available substitutable carbon or nitrogen atoms in said heteroaryl group may be optionally and independently substituted;

heterocycloalkyl represents a saturated carbocyclic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 hetero atoms selected from —O-, -S-, -SO-, -SO₂ or —NH-; examples include but are not limited to 2- or 3-tetrahydrofuranyl, 2- or 3-tetrahydrothienyl, 2-, 3- or 4-piperidinyl, 2- or 3-pyrrolidinyl, 2- or 3-piperizinyl, 2- or 4-dioxanyl, 1,3-dioxolanyl, 1,3,5-trithianyl, pentamethylene sulfide, perhydroisoquinolinyl, decahydroquinolinyl, trimethylene oxide, azetidiny, 1-azacycloheptanyl, 1,3-dithianyl, 1,3,5-trioxanyl, morpholinyl, thiomorpholinyl, 1,4-thioxanyl, and 1,3,5-hexahydrotriazinyl, thiazolidinyl, tetrahydropyranyl. The heterocycloalkyl ring can be substituted with 1-3 R^4 , R^5 or R^6 groups, wherein any of the available substitutable carbon or nitrogen atoms in said heterocycloalkyl group may be optionally and independently substituted

Claim 1 does not include compounds known by the skilled artisan to be unstable.

The compounds of the invention can be in purified or isolated form. The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan, in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., R^4 , etc.) occurs more than one time in any constituent or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (e.g, a drug precursor) that is transformed *in vivo* to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of formula I or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C_1-C_8) alkyl, (C_2-C_{12}) alkanoyl-

oxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, 5 N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁-C₂)alkylamino(C₂-C₃)alkyl (such as β -dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di (C₁-C₂)alkylcarbamoyl-(C₁-C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂-C₃)alkyl, and the like.

10 Similarly, if a compound of formula I contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C₁-C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)-ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl, (C₁-C₆)alkoxycarbonyloxymethyl, N-(C₁-C₆)alkoxycarbonylaminomethyl, succinoyl, (C₁-C₆)alkanoyl, α -amino(C₁-C₄)alkanyl, 15 arylacyl and α -aminoacyl, or α -aminoacyl- α -aminoacyl, where each α -aminoacyl group is independently selected from the naturally occurring L-amino acids, P(O)(OH)₂, -P(O)(O(C₁-C₆)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of formula I incorporates an amine functional group, a prodrug 20 can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R"-carbonyl, R"O-carbonyl, NR"R"'-carbonyl where R" and R"' are each independently (C₁-C₁₀)alkyl, (C₃-C₇) cycloalkyl, benzyl, or R"-carbonyl is a natural α -aminoacyl or natural α -aminoacyl, —C(OH)C(O)OY¹ wherein Y¹ is H, (C₁-C₆)alkyl or benzyl, —C(OY²)Y³ wherein Y² is (C₁-C₄) alkyl and Y³ is (C₁-C₆)alkyl, carboxy (C₁-C₆)alkyl, amino(C₁-C₄)alkyl or mono-N— or di-N,N-(C₁-C₆)alkylaminoalkyl, —C(Y⁴)Y⁵ wherein Y⁴ is H or methyl and Y⁵ is mono-N— or di-N,N-(C₁-C₆)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like. 25

The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include 30 reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula I contains both a basic moiety, such as, but not limited to a pyridine or

imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula I may be formed, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are

considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C₁₋₄alkyl, or C₁₋₄alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C₁₋₂₀ alcohol or reactive derivative thereof, or by a 2,3-di (C₆₋₂₄)acyl glycerol.

One or more compounds of the invention may also exist as, or optionally converted to, a solvate. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanولات, methanولات, and the like. "Hydrate" is a solvate wherein the solvent molecule is H₂O.

Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard

methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

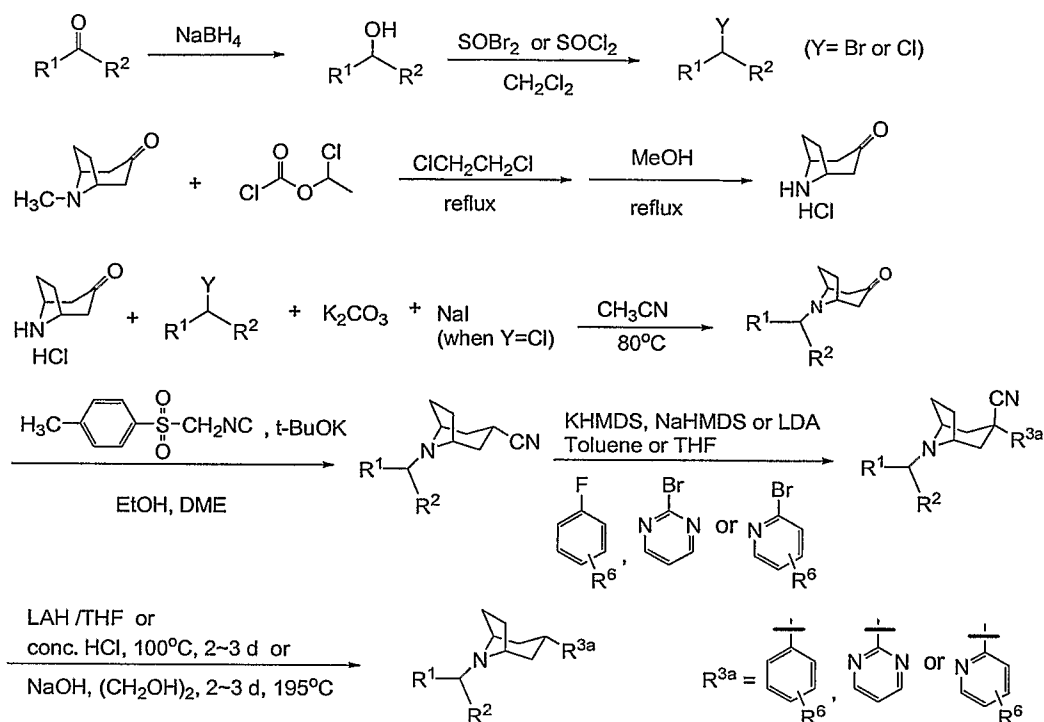
Compounds of Formula I, and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such
5 tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents,
10 including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for
15 example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers,
20 racemates or prodrugs of the inventive compounds.

Polymorphic forms of the compounds of Formula I, and of the salts, solvates, esters and prodrugs of the compounds of Formula I, are intended to be included in the present invention.

Compounds of the invention can be prepared by known methods from starting
25 materials either known in the art or prepared by methods known in the art. Scheme 1 shows a typical reaction scheme for preparing compounds of formula I wherein R^1 and R^2 are as defined above, X is a bond and R^{3a} is R^6 -phenyl or R^6 -heteroaryl joined to the tropane ring through a ring carbon (e.g., R^6 -(2-pyrimidyl) or R^6 -pyridyl).

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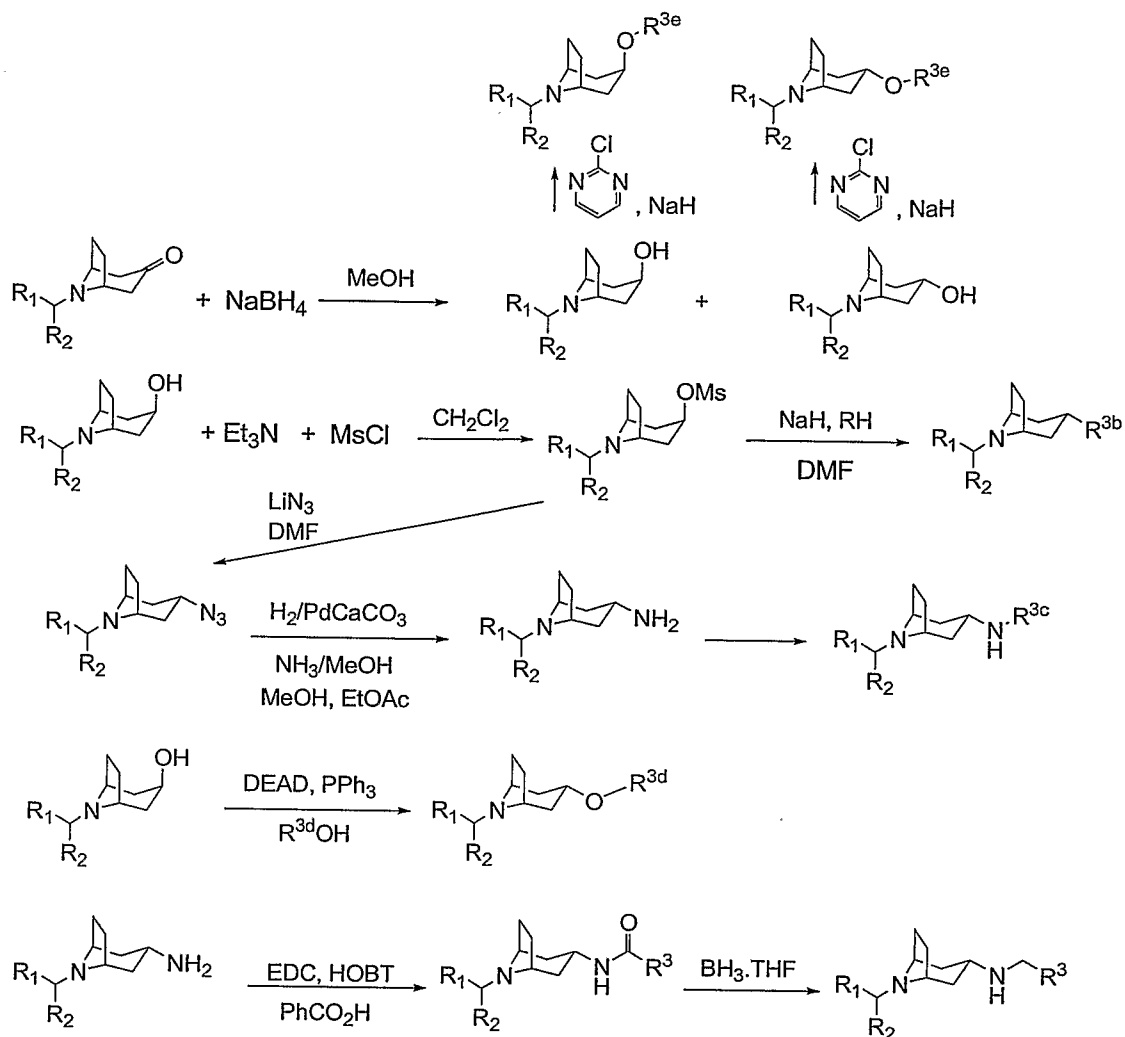
Scheme 1

Compounds of formula I in Scheme 1 wherein R^{3a} is pyridinyl can be converted to the corresponding piperidinyl compounds by hydrogenation with an agent such as PtO_2 .

Scheme 2 shows a typical reaction scheme for preparing compounds of formula I wherein R^1 and R^2 are as defined above, X is a bond and R^{3b} is R^6 -heteroaryl or R^6 -heterocycloalkyl joined to the tropane ring through a ring nitrogen (e.g., R^6 -(pyrazol-1-yl) or R^6 -piperidinyl). The mesylate intermediate is also used to prepare compounds of formula I wherein R^1 and R^2 are as defined above, X is $-N(R^7)-(CH_2)_n-$ wherein R^7 is H and n is 0, and R^{3c} is, for example, R^6 -pyridyl or R^6 -pyrimidyl, where the pyridyl or pyrimidyl ring is joined through a ring carbon atom. Also, the tropane alcohol intermediate can be converted to the compound wherein X is $-O-$ and R^{3d} is R^6 -phenyl or R^{3e} is R^6 -pyrimidyl; the amino-tropane intermediate can be converted to a compound wherein $-X-R^3$ is $-NHC(O)-R^3$, which can be reduced to obtain the corresponding $-NH-CH_2-R^3$ compound.

Scheme 2

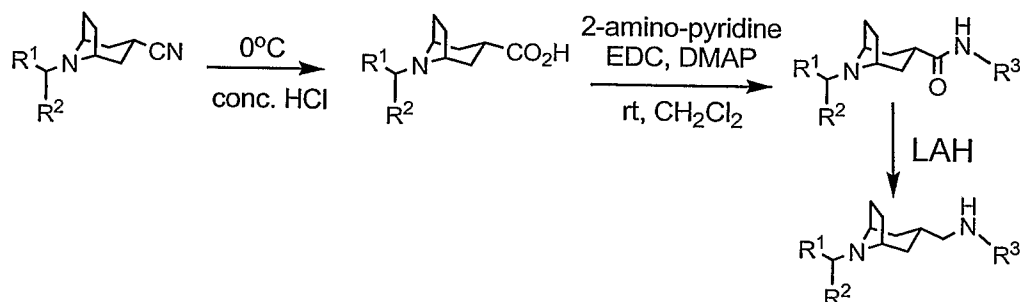
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Scheme 3 shows a typical reaction scheme for preparing compounds of formula I wherein R^1 , R^2 and R^3 are as defined above and X is $-\text{C}(\text{O})\text{N}(\text{R}^7)-$, which can be reduced to compounds wherein X is $-\text{CH}_2-\text{N}(\text{R}^7)-$.

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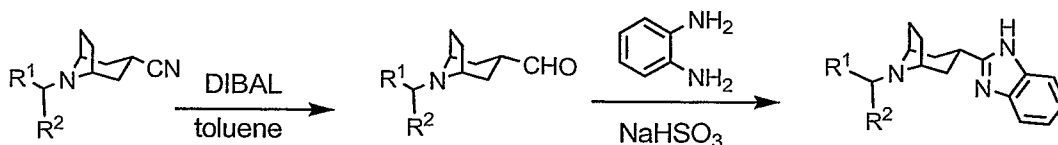
Scheme 3



Scheme 4 shows a reaction scheme for preparing compounds of formula I wherein R^1 and R^2 are as defined above, X is a bond, and R^3 is benzimidazolyl.

Scheme 4

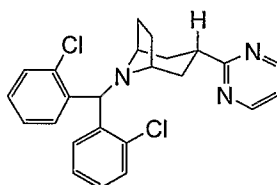
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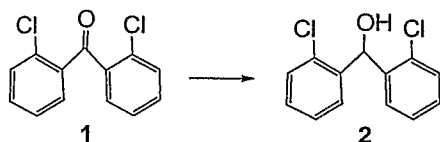
The starting materials used in the above procedures are commercially available or procedures for making them are known in the art.

The following solvents and reagents are referred to herein by the abbreviations indicated: tetrahydrofuran (THF); ethanol (EtOH); methanol (MeOH); N,N-dicyclohexylcarbodiimide (DCC); dichloroethane (DCE); ethyl acetate (EtOAc); lithium diisopropyl amide (LDA); triethylamine (Et₃N) and N,N-dimethylformamide (DMF); diisobutylaluminum hydride (DIBAL); hydroxybenzotriazole (HOBT); 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDCI); 4-dimethylaminopyridine (DMAP); diisopropylethylamine (DIPEA); methanesulfonyl (mesyl, Ms); sodium bis(trimethylsilyl)amide (NaHMDS); thin layer chromatography (TLC). Room temperature is abbreviated as rt.

Example 1

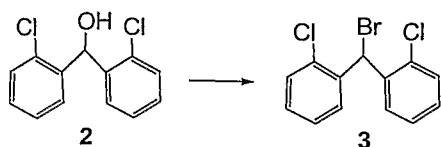


Step 1:



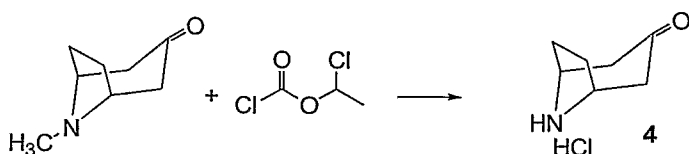
NaBH₄ (1.5 g, 39.82 mmol) was added to a solution of 2,2'-dichlorobenzophenone **1** (5 g, 19.9 mmol) in MeOH (40 ml) at rt. After stirring at rt for 2 h, the mixture was quenched with H₂O, neutralized with 1N HCl followed by evaporation of MeOH. The residue was extracted with EtOAc, washed with brine, dried (MgSO₄) and concentrated to give the desired compound **2** (5 g) as white solid which was used for next step reaction without purification. ¹H NMR (CDCl₃) δ 7.45 (m, 4H), 7.35 (m, 4H), 6.60 (d, 1H), 2.58 (d, 1H, OH).

Step 2:

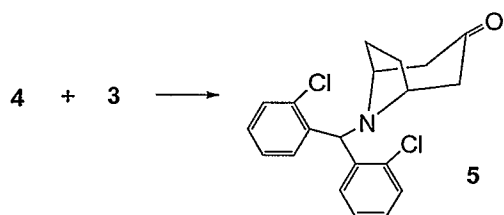


-14-

The product of Step 1 (20.36 g, 80.47 mmol) in CH_2Cl_2 was treated with SOBr_2 (30.11 g, 144.85 mmol) at 0 °C. After stirring at rt overnight, the mixture was quenched with ice and NaHCO_3 (aq.), extracted with CH_2Cl_2 , dried, filtered and concentrated to produce the desired compound **3** (23.6 g). ^1H NMR (CDCl_3) δ 7.6 (d, 2H), 7.4 (d, 2H), 7.13 (m, 4H), 7.0 (s, 1H).

Step 3:

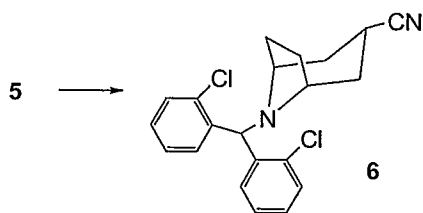
A solution of tropinone (10 g, 71.84 mmol) in DCE (200 ml) was added α -chloroethyl chloroformate (15.4 g, 108 mmol) dropwise at 0 °C. The mixture was then heated at reflux for 2h. Solvent was evaporated to give a brown residue. The residue was dissolved in MeOH (200 ml) and heated at reflux for 2 h. The MeOH was evaporated to give a solid which was stirred in EtOAc, filtered and washed with ether to give the desired compound **4** (7 g). Crude product was used for the next step without further purification. ^1H NMR (CDCl_3) δ 4.45 (s, br, 2H), 3.35 (dd, 2H), 2.58 (d, 2H), 2.49 (dd, 2H), 2.0 (m, 2H).

Step 4:

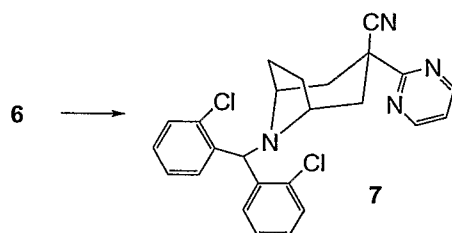
A mixture of **4** (26 g, 161 mmol), **3** (53 g, 168 mmol) and K_2CO_3 (110 g, 796 mmol) in anhydrous CH_3CN (410 ml) was heated at 80 °C. Reaction progress was monitored by ^1H NMR analysis. ~79% conversion was observed after 87 h. The reaction mixture was cooled to rt, diluted with CH_2Cl_2 , filtered and concentrated. Purification of the residue by SiO_2 chromatography (4-7% EtOAc/hexane) gave the desired compound **5**. ^1H NMR (CDCl_3) δ 7.9 (d, 2H), 7.3 (m, 4H), 7.2 (m, 2H), 5.7 (s, 1H), 3.35 (s, br, 2H), 2.7 (dd, 2H), 2.3 (m, 2H), 2.2 (d, 2H), 1.65 (dd, 2H).

Step 5:

-15-



Potassium tert-butoxide (232 g) was added slowly to a stirred solution of **5** (300 g) and tosylmethyl isocyanide (211 g) in anhydrous 1,2-dimethoxyethane (3.5 l) and absolute EtOH (240 ml) under N₂ at -40 °C. The mixture was slowly warmed to rt and stirred at rt overnight. The mixture was filtered and washed with EtOAc. Most of the solvent in the filtrate was evaporated *in vacuo* (bath temperature < 40 °C) to give a suspension which was filtered and washed with ether to give **6** (158 g). LC/ESI-MS *m/z*=371 (C₂₁H₂₀Cl₂N₂.H⁺).

Step 6:

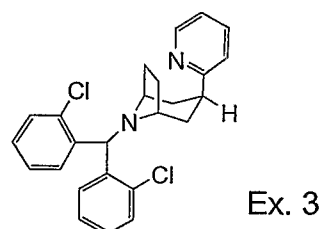
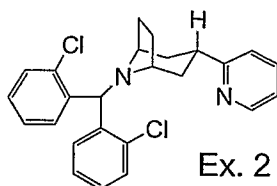
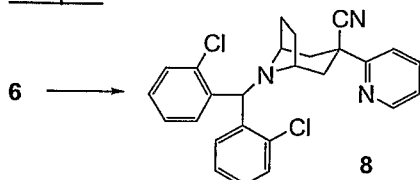
LDA was freshly generated from diisopropyl amine (2.27 ml, 16.15 mmol) and n-BuLi (2.5 M, 6.46 ml, 16.15 mmol) in THF (25 ml). The LDA solution was treated with a solution of **6** in THF (25 ml) dropwise at -40 °C, stirred for 2 h and 2-chloropyrimidine (1.85g, 16.15 mmol) was added. The mixture was slowly warmed to rt, stirred at rt overnight, quenched with water, extracted with EtOAc, dried (MgSO₄) and concentrated. Purification of the residue by SiO₂ chromatography (1:4 EtOAc/hexane) gave **7** (3 g). LC/ESI-MS *m/z*=449 (C₂₅H₂₂Cl₂N₄.H⁺).

Step 7:

A mixture of **7** (200 mg) and conc. HCl (2 ml) was heated at 100 °C in a sealed tube for 3 days, cooled to 0 °C, neutralized with aqueous NaOH solution, extracted with EtOAc, dried (MgSO₄) and concentrated. Purification of the residue by SiO₂ chromatography (0-50% EtOAc/hexane) gave the title compound (110 mg). LC/ESI-MS *m/z*=424 (C₂₄H₂₃Cl₂N₃.H⁺).

Examples 2 and 3

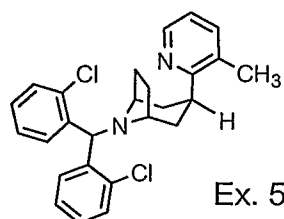
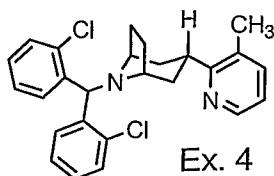
-16-

Step 1:

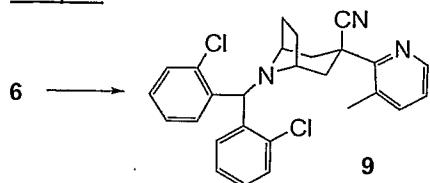
To a stirred solution of **6** (20 g, 53.9 mmol) in THF (100 ml) was added NaHMDS/THF (40.4 ml, 2M) dropwise at -78 °C under N₂. The solution was stirred at -78 °C for ~1 hr, then 2-bromopyridine (17 g, 154 mmol) in THF was added dropwise. After stirring for another hour at this temperature, the reaction flask was moved to a CH₃CN/dry ice bath. The reaction mixture was slowly warmed to rt, stirred at rt overnight, quenched with sat. aq. NH₄Cl at -78 °C, warmed to rt, and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and evaporated to dryness. The residue was washed with ether several times to give the desired compound **8** (19.1 g) which was used in the next reaction without further purification. LC/ESI-MS: *m/z* 448 (C₂₆H₂₃Cl₂N₃.H⁺).

Step 2:

A mixture of **8** (5 g), NaOH (20 g), and ethylene glycol (40 ml) was stirred and heated to 200 °C under N₂ atmosphere for two to three days. After the reaction was complete, the mixture was cooled to rt and dissolved in 1N HCl solution. The suspension was partitioned with CH₂Cl₂ under basic conditions. The organic layer was dried over Na₂SO₄, filtered, and evaporated to dryness. Purification of the residue by SiO₂ chromatography (EtOAc/hexane) gave Example 2 (~4.3 g), LC/ESI-MS: *m/z* 423 (C₂₅H₂₄Cl₂N₂.H⁺) and Example 3, LC/ESI-MS: *m/z* 423 (C₂₅H₂₄Cl₂N₂.H⁺).

Examples 4 and 5

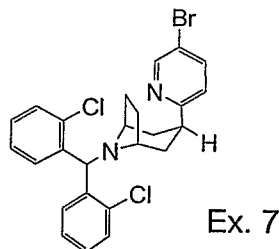
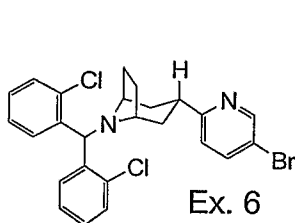
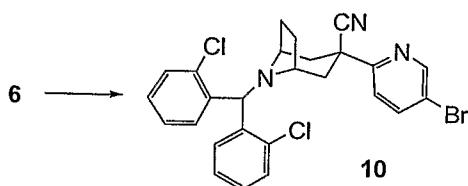
-17-

Step 1:

Compound **9** was prepared according to the procedure described in Example 2, Step 1, using **6**, NaHMDS and 2-bromo-3-methylpyridine. LC/ESI-MS: m/z 462 ($C_{27}H_{25}Cl_2N_3.H^+$).

Step 2:

To a stirred solution of **9** (1.92 g, 4.156 mmol) in THF was added 1 M LiAlH₄/THF solution (4.57 ml, 4.57 mmol) dropwise at rt under N₂. The mixture was stirred at 50 °C for 1 h. After cooling to rt, the following solutions were added sequentially: 190 μ l water, 570 μ l 15% NaOH, and 190 μ l water. The mixture was stirred, filtered, and evaporated to dryness. Purification of the residue by SiO₂ chromatography (EtOAc/hexane) gave Example 4 (~370 mg), LC/ESI-MS: m/z 437 ($C_{26}H_{26}Cl_2N_2.H^+$) and Example 5, LC/ESI-MS: m/z 437 ($C_{26}H_{26}Cl_2N_2.H^+$).

Examples 6 and 7Step 1:

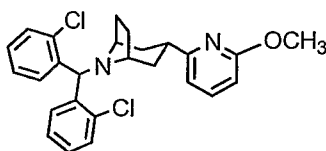
Compound **10** was prepared according to the procedure described in Example 2, Step 1, using **6**, NaHMDS and 2,5-dibromopyridine. LC/ESI-MS m/z =528 ($C_{26}H_{22}BrCl_2N_3.H^+$).

Step 2:

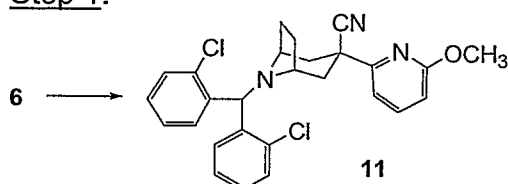
A mixture of **10** (210 mg) and conc. HCl (1.5 ml) was heated at 100 °C in a sealed tube for 3 days, cooled to rt, neutralized with aqueous NaOH solution, extracted with EtOAc, dried (MgSO₄) and concentrated. Purification of the residue by

SiO₂ chromatography (0-50% EtOAc/hexane) gave Example 6, LC/ESI-MS $m/z=503$ (C₂₅H₂₃BrCl₂N₂.H⁺) and Example 7, LC/ESI-MS: m/z 503 (C₂₅H₂₃BrCl₂N₂.H⁺).

Example 8



5 Step 1:

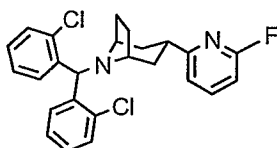


Compound **11** was prepared according to the procedure described in Example 2, Step 1, using **6**, NaHMDS and 2-bromo-6-methoxypyridine. LC/ESI-MS: m/z 478 (C₂₇H₂₅Cl₂N₃O.H⁺).

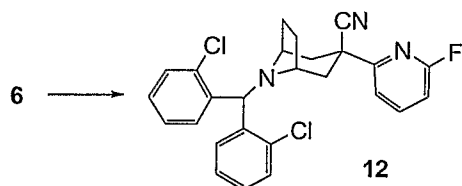
10 Step 2:

To a stirred solution of **11** (21 mg, 0.044 mmol) in THF, was added 1 M LiAlH₄/THF solution (132 μ l, 0.132 mmol) dropwise at 0 °C under N₂. The mixture was stirred at 60 °C overnight. After cooling to rt, the following solutions were added sequentially: 2 μ l water, 6 μ l 15% NaOH, and 2 μ l water. The mixture was stirred, filtered, and evaporated to dryness. Purification of the residue by SiO₂ chromatography (0-40% EtOAc/hexane) gave the title compound (5 mg). ESI-MS: m/z 453 (C₂₆H₂₆Cl₂N₂O.H⁺).

Example 9



20 Step 1:



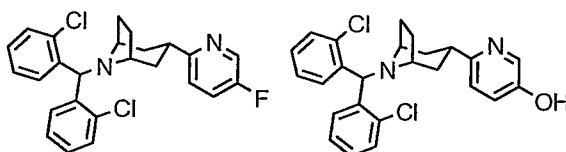
To a stirred solution of **6** (371 mg, 1 mmol) in THF was added NaHMD/THF (750 μ l, 2M) dropwise at -78 °C under N₂. The solution was stirred at -78 °C for ~0.5 hr, and then 2,6-difluoropyridine in THF was added dropwise. After stirring for at least

-19-

6 h at this temperature, the reaction mixture was slowly warmed to rt, and stirred over the weekend. The mixture was cooled to -78 °C, quenched with sat. aq. NH₄Cl, warmed to rt and partitioned between aq. NH₄Cl solution and EtOAc-hexane (1:1). The combined organic layers were dried over Na₂SO₄, filtered, and evaporated to dryness. Purification of the residue by SiO₂ chromatography gave **12** (194 mg). LC/ESI-MS: *m/z* 466 (C₂₆H₂₂Cl₂FN₃.H⁺).

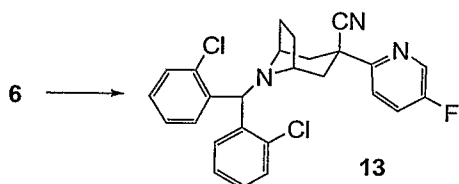
Step 2:

To a stirred solution of **12** (69.5 mg, 0.149 mmol) in THF was added 1 M LiAlH₄/THF solution (149 µl, 0.149 mmol) dropwise at rt under N₂. The mixture was stirred at rt overnight. The following solutions were added sequentially: 5 µl water, 15 µl 15% NaOH, and 5 µl water. The mixture was stirred, filtered, and evaporated to dryness. Purification of the residue by SiO₂ chromatography (0-100% EtOAc/hexane) gave the title compound (14 mg). LC/ESI-MS: *m/z* 441 (C₂₅H₂₃Cl₂FN₂.H⁺).

Examples 10 and 11

Ex. 10

Ex. 11

Step 1:

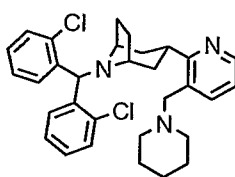
To a stirred solution of **6** (3336 mg, 9 mmol) in THF was added NaHMDS/THF (6750 µl, 2M, 13.5 mmol) dropwise at -78 °C under N₂. The solution was stirred at -78 °C for ~0.5 h, and then 2-bromo-5-fluoropyridine (5000 mg, 28.4 mmol) in THF was added dropwise. After stirring for at least 8 h at this temperature, the reaction mixture was slowly warmed to rt and stirred overnight. The mixture was cooled to -78 °C, quenched with sat. aq. NH₄Cl, warmed to rt and partitioned between aq. NH₄Cl solution and EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and evaporated to dryness. Purification of the residue by SiO₂ chromatography (EtOAc/hexane) gave **13** (1650 mg). ESI-MS: *m/z* 466 (C₂₆H₂₂Cl₂FN₃.H⁺).

Step 2:

-20-

A mixture of **13** (67 mg), NaOH (400 mg), and ethylene glycol (4 ml) in a sealed tube was stirred and heated to 150°C overnight. After cooling to rt, the mixture was added to H₂O and EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered, and evaporated to dryness. Purification of the residue by SiO₂ chromatography (0-100% EtOAc/hexane) gave Example 10 (~2 mg), ESI-MS: *m/z* 441 (C₂₅H₂₃Cl₂FN₂.H⁺) and Example 11 (5 mg), LC/ESI-MS: *m/z* 439 (C₂₅H₂₄Cl₂N₂O.H⁺).

Example 12

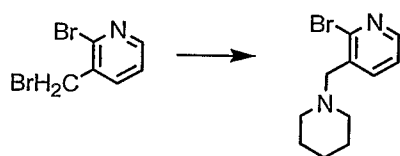


Step 1:



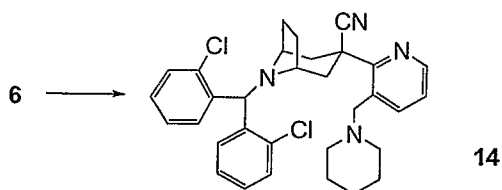
A mixture of 2-bromo-3-methylpyridine (1114 µl, 10 mmol), NBS (1780 mg, 10 mmol), and benzoyl peroxide (45 mg) in CCl₄ was refluxed for 3 h. After cooling to rt, the suspension was filtered. Purification of the residue by SiO₂ chromatography (EtOAc/hexane) gave the desired compound (600 mg). ESI-MS: *m/z* 250, 252, and 254 (C₆H₅Br₂N.H⁺)

Step 2:



To a solution of the product of Step 1 (595 mg, 2.36 mmol) in DMF was added piperidine (205 mg, 2.4 mmol) and K₂CO₃ (979 mg, 7.08 mmol), sequentially. The mixture was stirred at rt overnight, quenched with ice-water and then partitioned with ether. The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by SiO₂ chromatography (0-50% EtOAc/hexane) gave the desired compound (~450 mg). C₁₁H₁₅BrN₂, LC/ESI-MS: *m/z* 255 and 257 (C₁₁H₁₅BrN₂.H⁺)

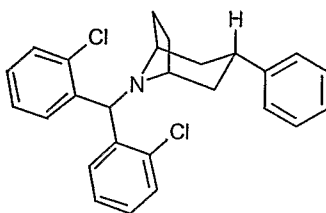
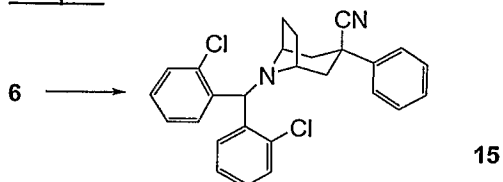
-21-

Step 3:

Compound **14** was prepared according to the procedure described in Example 2, Step 1, using **6**, NaHMDS and the product of Step 2. LC/ESI-MS: m/z 545 ($C_{32}H_{34}Cl_2N_4.H^+$).

Step 4:

14 and $LiAlH_4$ were used according to the procedure described in Example 9, Step 2, to obtain the title compound. LC/ESI-MS: m/z 520 ($C_{31}H_{35}Cl_2N_3.H^+$).

Example 13Step 1:

To a mixture of **6** (580 mg) and fluorobenzene (~1.5 ml) was added potassium bis(trimethylsilyl)amide (580 mg) in fluorobenzene (~2.5 ml) under N_2 . The mixture was stirred for 10 min, then heated in a microwave at 100 °C for 18 min. After cooling to rt, the mixture was quenched with saturated aq. NH_4Cl and partitioned with EtOAc. The organic layer was dried over Na_2SO_4 , filtered, and concentrated. The residue was washed with ether to give **15** (~450 mg). LC/ESI-MS: m/z 447 ($C_{27}H_{24}Cl_2N_2$).

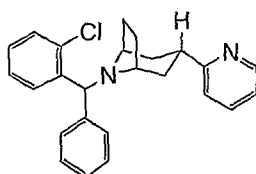
Step 2:

To a stirred solution of **15** (310 mg, 0.693 mmol) in THF was added 1 M $LiAlH_4$ /THF solution (693 μ l, 0.693 mmol) dropwise at rt under N_2 . The mixture was warmed to 60 °C and stirred overnight. The following solutions were added sequentially: 50 μ l water, 150 μ l 15% NaOH, and 50 μ l water. The mixture was stirred, filtered, and evaporated to dryness. Purification of the residue by SiO_2

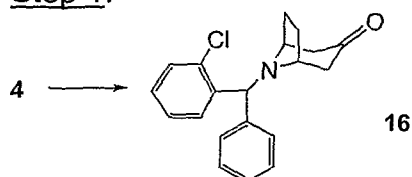
-22-

chromatography (0-50% EtOAc/hexane) gave the title compound (~80 mg). LC/ESI-MS: m/z 422 ($C_{26}H_{25}Cl_2N.H^+$).

Example 14

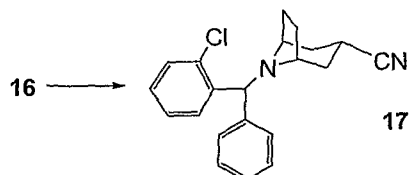


5 Step 1:



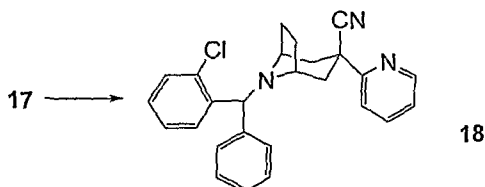
Compound **16** was prepared according to the procedure described in Example 1, Step 4, using **4**, 1-chloro-2-(chlorophenylmethyl)benzene and K_2CO_3 . 1H NMR ($CDCl_3$) δ 7.95 (d, 1H), 7.55 (d, 2H), 7.2 (m, 5H), 7.05 (t, 1H), 5.25 (s, 1H), 3.4 (s, b, 2H), 2.65 (d, b, 2H), 2.1 (d, b, 4H), 1.75 (m, 2H).

10 Step 2:



Compound **17** was prepared according to the procedure of Example 1, Step 5, using **16**, potassium tert-butoxide and tosylmethyl isocyanide. 1H NMR ($CDCl_3$) δ 7.9 (d, 1H), 7.45 (d, 2H), 7.25 (m, 5H), 7.05 (t, 1H), 5.0 (s, 1H), 3.15 (s, b, 2H), 2.7 (m, 1H), 2 (m, 4H), 1.65 (m, 2H), 1.25 (d, 2H).

15 Step 3:



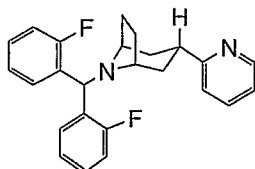
Compound **18** was prepared according to the procedure of Example 2, Step 1, using **17**, NaHMDS and 2-bromopyridine. LC/ESI-MS: m/z 414 ($C_{26}H_{24}ClN_3.H^+$).

20 Step 4:

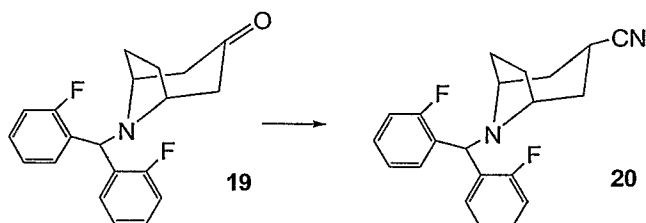
-23-

The procedure of Example 6, Step 2, was used with **18** and conc. HCl to give the title compound. LC/ESI-MS: m/z 389. ($C_{25}H_{25}ClN_2.H^+$).

Example 15

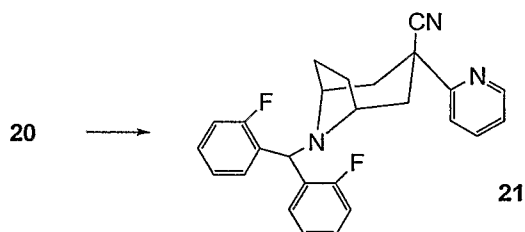


5 Step 1:



Compound **20** was prepared according to the procedure of Example 1, Step 5, using **19**, tosylmethyl isocyanide and potassium tert-butoxide in anhydrous 1,2-dimethoxyethane and absolute EtOH. ESI-MS: m/z 339 ($C_{21}H_{20}F_2N_2.H^+$).

10 Step 2:

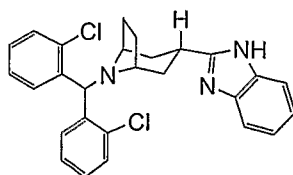


Compound **21** was prepared according to the procedure of Example 2, Step 1, using **20**, NaHMDS and 2-bromopyridine in THF. ESI-MS: m/z 416 ($C_{26}H_{23}F_2N_3.H^+$).

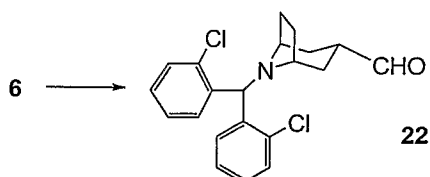
Step 3:

15 Using the procedure of Example 2, Step 2, with **21** and NaOH in ethylene glycol, the title compound was prepared. LC/ESI-MS $m/z=391$ ($C_{25}H_{24}F_2N_2.H^+$)

Example 16



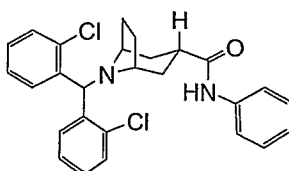
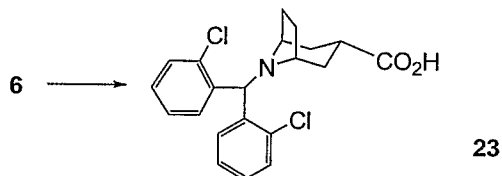
-24-

Step 1:

A solution of **6** (2 g) was added to DIBAL/toluene (7.5 ml, 1.5 M) at 0 °C. The mixture was slowly warmed to rt and then stirred at 50 °C for 3 h, quenched with MeOH and H₂O at 0°C, filtered, extracted with EtOAc, dried (MgSO₄), filtered and concentrated. Purification of the residue by SiO₂ chromatography (5% EtOAc/hexane) gave **22**. ¹H NMR (CDCl₃) δ 9.6 (s, 1H), 7.75, d, 2H), 7.2 (m, 4H), 7.1 (t, 2H), 5.4 (s, 1H), 3.1 (s, br, 1H), 2.5 (m, 1H), 2.2 (m, 2H), 1.75 (t, 2H), 1.5 (m, 4H). LC/ESI-MS *m/z*=374 (C₂₁H₂₁Cl₂NO.H⁺)

Step 2:

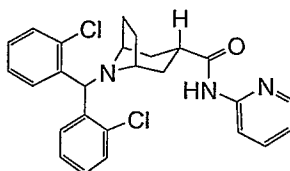
To a solution of **22** (410 mg) in EtOH was added 1,2-diaminobenzene (119 mg) and NaHSO₃ (2.3 ml, 40% in H₂O). The mixture was stirred at reflux for 3 h, concentrated, then partitioned between CH₂Cl₂ and water. The CH₂Cl₂ solution was dried (MgSO₄), filtered and concentrated. Purification of the residue by SiO₂ chromatography gave the title compound. LC/ESI-MS *m/z*=462 (C₂₇H₂₅Cl₂N₃.H⁺)

Example 17Step 1:

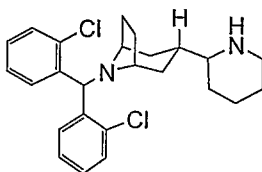
Compound **6** (1 g) was dissolved in conc. HCl and then kept at 0 °C for 3 days. The solution was then heated to 80 °C for 2 h, cooled to rt, and evaporated to dryness. Water was added and the solution was adjusted to pH 7 using 1 N NaOH solution. The aqueous solution was partitioned with EtOAc. The organic layer was dried over Na₂SO₄, filtered, and concentrated to give **23** (970 mg), which was directly used in the next step. ESI-MS: *m/z* 390 (C₂₁H₂₁Cl₂NO₂.H⁺).

Step 2:

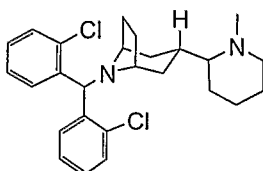
To a solution of **23** (21.5 mg, 0.055 mmol) in DMF at rt was added EDCI (15.9 mg, 0.0827 mmol) and HOBT (10.4 mg, 0.077 mmol) in DMF and aniline (5.6 mg, 0.06 mmol) in DMF. Et₃N (26 μ l, 0.187 mmol) was then added. The reaction mixture was stirred at rt overnight. Water and EtOAc were added to the reaction mixture. The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by SiO₂ chromatography gave the title compound (11.2 mg). LC/ESI-MS: *m/z* 465 (C₂₇H₂₆Cl₂N₂O.H⁺).

Example 18

To a mixture of **23** (118 mg, 0.303 mmol) and 2-aminopyridine (55 mg, 0.58 mmol) in anhydrous CH₂Cl₂ was added EDCI (118 mg, 0.76 mmol) and DMAP (15 mg, 0.123 mmol) at rt under N₂. The reaction mixture was stirred at rt overnight. The solvent was evaporated *in vacuo*, and ether and water were added to the residue. The organic layer was dried over Na₂SO₄, filtered and concentrated. Purification of the residue by SiO₂ chromatography gave the title compound (97 mg). LC/ESI-MS: *m/z* 466 (C₂₆H₂₅Cl₂N₃O.H⁺).

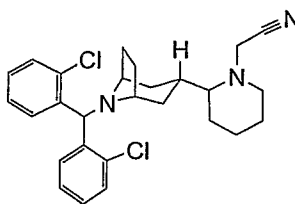
Example 19

PtO₂ (40 mg) was added to a solution of Example 2 (200 mg) in CH₂Cl₂. The mixture was stirred at rt under 1 atm H₂ environment through a balloon for ~24 h, filtered and concentrated. Purification of the residue by SiO₂ chromatography gave the title compound (~190 mg). LC/ESI-MS: *m/z* 429 (C₂₅H₃₀Cl₂N₂.H⁺).

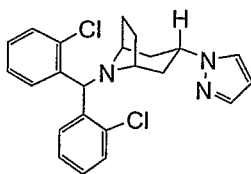
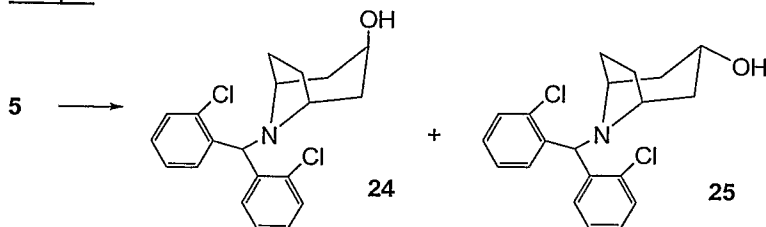
Example 20

-26-

A suspension of Example 19 (30 mg) in formic acid (100 μ l) and 37% aq. formaldehyde (200 μ l) was stirred and heated at 70 $^{\circ}$ C for $\sim$ 7 h. The mixture was evaporated to dryness, and then distributed to EtOAc and 1 N NaOH solution. The organic layer was dried over Na₂SO₄, filtered and concentrated. Purification of the residue by SiO₂ chromatography gave the title compound (17.8 mg). LC/ESI-MS: *m/z* 443 (C₂₆H₃₂Cl₂N₂.H⁺).

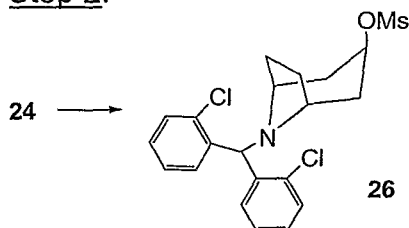
Example 21

A mixture of Example 19 (55 mg, 0.128 mmol) and K₂CO₃ (53 mg, 0.385 mmol) in DMF was stirred at rt for 20 min, and then bromoacetonitrile (17.8 μ l, 0.256 mmol) was added. The mixture was stirred at rt for 30 min and then heated at 60 $^{\circ}$ C overnight. The mixture was cooled to rt, quenched with water, extracted with ether, dried over MgSO₄, filtered and concentrated. Recrystallization of the residue gave the title compound (16 mg). LC/ESI-MS: *m/z* 468 (C₂₇H₃₁Cl₂N₃.H⁺).

Example 22Step1:

To a stirred solution of **5** (5 g) in MeOH (200 ml) was added NaBH₄ (0.7 g) at 0 $^{\circ}$ C. The mixture was stirred at 0 $^{\circ}$ C for 2 h. The MeOH was evaporated and the resultant residue was treated with aqueous NH₄Cl, extracted with EtOAc, dried (MgSO₄), filtered and concentrated. Purification of the residue by SiO₂ chromatography gave compound **24** (2.54 g), LC/ESI-MS: *m/z* 362 (C₂₀H₂₁Cl₂NO.H⁺) and compound **25** (1.71 g), LC/ESI-MS: *m/z* 362 (C₂₀H₂₁Cl₂NO.H⁺).

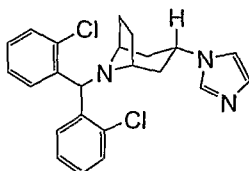
-27-

Step 2:

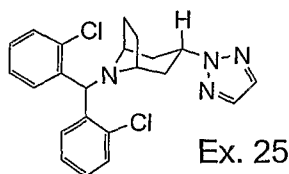
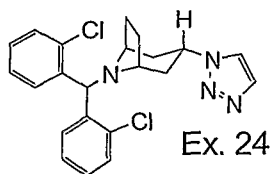
To a stirred solution of **24** (1.38g) in CH₂Cl₂ (35 ml) was added Et₃N (0.64 ml) and CH₃SO₂Cl (0.36 ml) at 0 °C. The mixture was stirred at 0 °C for 3.5 h, quenched with water, extracted with CH₂Cl₂, dried (Na₂SO₄), filtered and concentrated to give **26**. LC/ESI-MS: *m/z*=440 (C₂₁H₂₃Cl₂NO₃S.H⁺). The crude product was used in the next reaction without further purification.

Step 3:

To a solution of **26** (286 mg) in DMF (3 ml) was added NaH (60% in mineral oil, 39 mg) at 0 °C. The mixture was stirred at 0 °C for 10 min., warmed to rt, then pyrazole was added and the mixture stirred at 60 °C overnight. The reaction was quenched with aqueous NH₄Cl, and the mixture extracted with EtOAc, dried over Na₂SO₄, and purified by preparative TLC to give the title compound. LC/ESI-MS: *m/z*=412 (C₂₃H₂₃Cl₂N₃.H⁺).

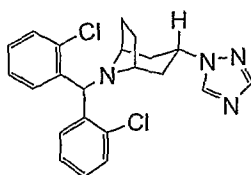
Example 23

The title compound was prepared according to the procedure of Example 22, Step 3, using **26** and imidazole. ESI-MS: *m/z*=412 (C₂₃H₂₃Cl₂N₃.H⁺).

Examples 24 and 25

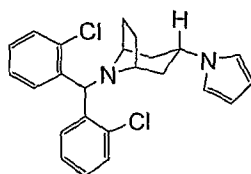
A mixture of the title compounds was prepared according to the procedure of Example 22, Step 3, using **26** and 1,2,3-triazole. Purification of the mixture by SiO₂ chromatography (EtOAc/hexane) gave Example 24, LC/ESI-MS: *m/z* 413 (C₂₂H₂₂Cl₂N₄.H⁺) and Example 25, LC/ESI-MS: *m/z* 413 (C₂₂H₂₂Cl₂N₄.H⁺).

-28-

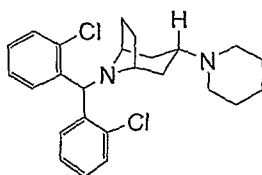
Example 26

The title compound was prepared according to the procedure of Example 22, Step 3, using **26** and 1,2,4-triazole. ESI-MS: $m/z=413$ ($C_{22}H_{22}Cl_2N_4.H^+$).

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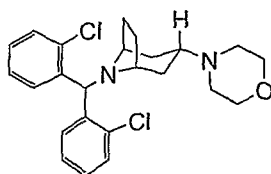
Example 27

The title compound was prepared according to the procedure of Example 22, Step 3, using **26** and pyrrole. ESI-MS: $m/z=411$ ($C_{24}H_{24}Cl_2N_2.H^+$).

Example 28

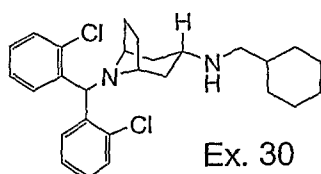
10

The title compound was prepared according to the procedure of Example 22, Step 3, using **26** and piperidine. ESI-MS: $m/z=429$ ($C_{25}H_{30}Cl_2N_2.H^+$).

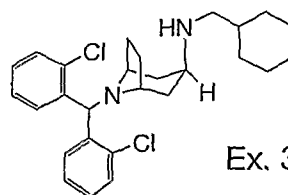
Example 29

15

The title compound was prepared according to the procedure of Example 22, Step 3, using **26** and morpholine. ESI-MS: $m/z=431$ ($C_{24}H_{28}Cl_2N_2O.H^+$).

Examples 30 and 31

Ex. 30



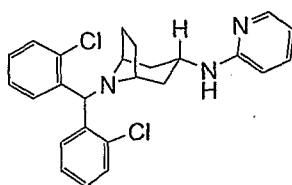
Ex. 31

To a solution of aminomethylcyclohexane (39 μ l, 0.3 mmol) and **5** (72 mg) in THF was added $NaBH_3CN$ (32 mg, 0.5 mmol). The mixture was stirred for ~2 h and

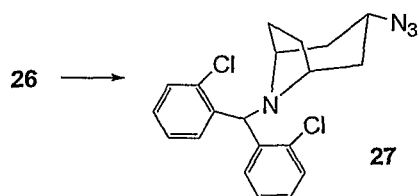
20

then HOAc (60 mg, 1 mmol) was added. The mixture was stirred overnight at rt, water and 1N NaOH were added, and the mixture was extracted with ether and concentrated. Purification of the residue by SiO₂ chromatography gave Example 30, LC/ESI-MS: *m/z* 457 (C₂₇H₃₄Cl₂N₂.H⁺) and Example 31, LC/ESI-MS: *m/z* 457 (C₂₇H₃₄Cl₂N₂.H⁺).

Example 32

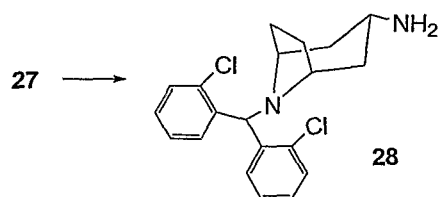


Step 1:



A mixture of **26** (1.68 g) and lithium azide (225 g) in DMF (5 ml) was stirred at rt for 24 h, quenched with NH₄Cl (aq.), extracted with EtOAc, dried over Na₂SO₄ and concentrated. Purification of the residue by SiO₂ chromatography gave **27**. LC/ESI-MS: *m/z*= 387 (C₂₀H₂₀Cl₂N₄.H⁺).

Step 2:

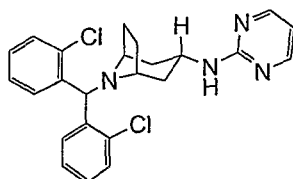


A mixture of **27** (895 mg) and Lindlar catalyst (90 mg) in 1:1 MeOH and EtOAc (20 ml) in the presence of NH₃ in MeOH (2M, 1 ml) was stirred under H₂ at 1 atm for 2 h. The mixture was filtered and concentrated to give **28**. LC/ESI-MS: *m/z*= 361 (C₂₀H₂₂Cl₂N₂.H⁺).

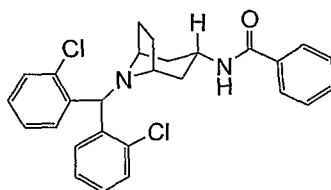
Step 3:

A mixture of **28** (223 mg) and DIPEA (80 mg) in 2-fluoropyridine was stirred at 130 °C for 36 h. The mixture was concentrated, treated with NH₄Cl (aq.), extracted with EtOAc, dried and concentrated. Purification of the residue by SiO₂ chromatography gave the title compound (163 mg). ESI-MS: *m/z*= 438 (C₂₅H₂₅Cl₂N₃.H⁺).

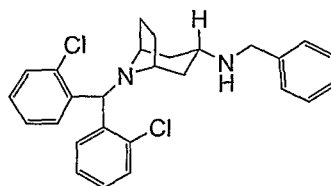
-30-

Example 33

NaH (14 mg, 60% in mineral oil) was added to a solution of **28** (103 mg) in DMF at 0 °C. The mixture was warmed to rt, 2-chloropyrimidine (65 mg) was added, and the mixture was heated to 60 °C for 0.5 h, then stirred at rt overnight. The mixture was quenched with NH₄Cl (aq.), extracted with CH₂Cl₂, dried over Na₂SO₄, filtered and concentrated. Purification of the residue by SiO₂ preparative thin layer chromatography (20% EtOAc/hexane) gave the title compound (16 mg). LC/ESI-MS: m/z=439 (C₂₄H₂₄Cl₂N₄.H⁺).

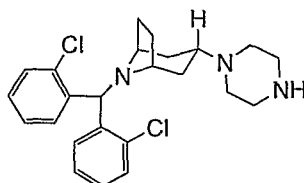
Example 34

A mixture of **28** (328 mg), benzoic acid (122 mg), EDC (175 mg), and HOBT (123 mg) in DMF (2 ml) was stirred at rt overnight. The mixture was quenched with water, extracted with EtOAc, dried over MgSO₄ and concentrated. Purification of the residue by SiO₂ chromatography (0 ~ 20% EtOAc/hexane) gave the title compound. LC/ESI-MS: m/z=465 (C₂₇H₂₆Cl₂N₂O.H⁺).

Example 35

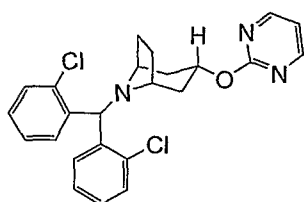
BH₃.THF (1.4 ml, 1M) was added to a solution of Example 34 (258 mg) in THF. The mixture was stirred at 60 °C overnight. The mixture was concentrated, treated with water, extracted with CH₂Cl₂ and concentrated. Purification of the residue by Gilson HPLC gave the title compound (25 mg). LC/ESI-MS: m/z=451 (C₂₇H₂₈Cl₂N₂.H⁺).

-31-

Example 36

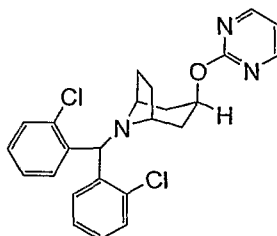
The title compound was prepared according to the procedure of Example 22, Step 3, using **26** and piperazine. ESI-MS: $m/z=430$ ($C_{24}H_{29}Cl_2N_3 \cdot H^+$).

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Example 37

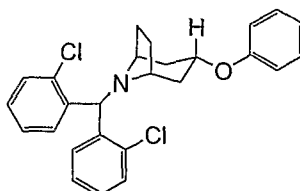
A mixture of **25** (56 mg), 2-chloropyrimidine (19 mg) and NaH (16 mg, 60% in mineral oil) in DMF (2 ml) was stirred at 0 °C for 2 h, then at rt for 3 days. The mixture was quenched with aqueous NH_4Cl , extracted with EtOAc, dried over Na_2SO_4 and concentrated. Purification of the residue by preparative TLC gave the title compound (36 mg). ESI-MS: $m/z=440$ ($C_{24}H_{23}Cl_2N_3O \cdot H^+$).

10

Example 38

The title compound was prepared according to the procedure of Example 37 using **24**, 2-chloropyrimidine and NaH. ESI-MS: $m/z=440$ ($C_{24}H_{23}Cl_2N_3O \cdot H^+$).

15

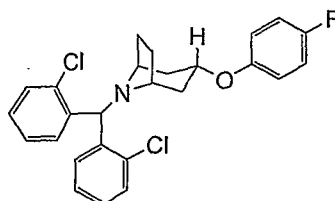
Example 39

Diethyl azodicarboxylate (111 mg) in THF was added to a mixture of **24** (210 mg), phenol (55 mg) and triphenylphosphine (152 mg) in THF. The mixture was stirred at rt overnight. The mixture was concentrated, treated with hexane, filtered and concentrated. Purification of the residue by SiO_2 chromatography (0 ~ 20%

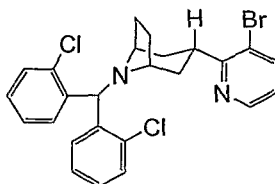
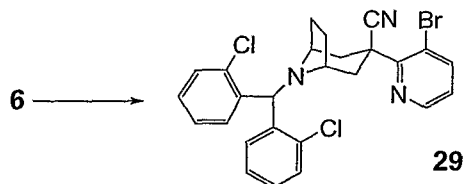
20

-32-

EtOAc/hexane) gave the title compound (30 mg). LC/ESI-MS; $m/z=438$ ($C_{26}H_{25}Cl_2NO.H^+$).

Example 40

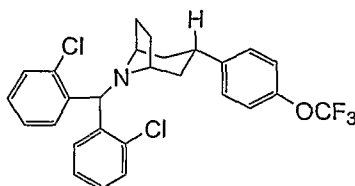
- 5 The title compound was prepared according to the procedure of Example 39 using **24**, *p*-fluorophenol, diethyl azodicarboxylate, and triphenylphosphine. LC/ESI-MS; $m/z=456$ ($C_{26}H_{24}Cl_2FNO.H^+$).

Example 4110 Step 1:

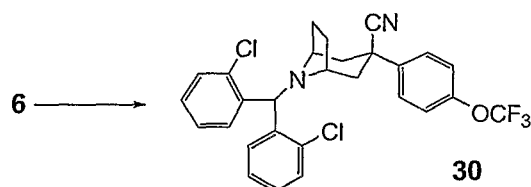
Compound **29** was prepared according to the procedure described in Example 2, Step 1, using **6**, NaHMDS and 2,3-dibromopyridine. LC/ESI-MS m/z 528 ($C_{26}H_{22}BrCl_2N_3.H^+$).

15 Step 2:

The title compound was prepared according to the procedure described in Example 6, Step 2, using **29** and conc. HCl. LC/ESI-MS m/z 503 ($C_{25}H_{23}BrCl_2N_2.H^+$).

Example 4220 Step 1:

-33-

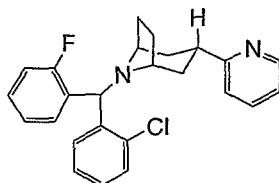


Compound **30** was prepared according to the procedure described in Example 13, Step 1, using **6** and 1-fluoro-4-trifluoromethoxybenzene. LC/ESI-MS m/z 531 ($C_{28}H_{23}Cl_2F_3N_2O.H^+$).

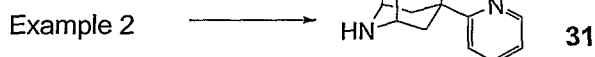
5 Step 2:

The title compound was prepared according to the procedure of Example 8, Step 2, using **30** and LAH. LC/ESI-MS m/z 506 ($C_{27}H_{24}Cl_2F_3NO.H^+$).

Example 43



10 Step 1:



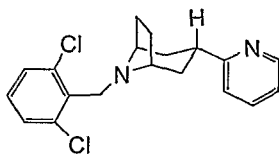
A mixture of Example 2 (4 g), $Pd(OH)_2/C$ (12 %, 1g) and ammonium formate (9 g) in MeOH (100 ml) was stirred at reflux for 3 days. The mixture was filtered, concentrated, treated with water, extracted with 15% MeOH/ CH_2Cl_2 , dried over $MgSO_4$ and concentrated. Purification of the residue by SiO_2 chromatography ($NH_3/MeOH/CH_2Cl_2$) gave the title compound (1.5 g). LC/ESI-MS; $m/z=189$ ($C_{16}H_{12}N_2.H^+$).

Step 2:

A mixture of **31** (129 mg), chloro-(2-chlorophenyl)-(2-fluorophenyl)methane (175 mg), K_2CO_3 (380 mg) and NaI (103 mg) in CH_3CN (2 ml) was stirred in a sealed tube at 75 °C overnight. The mixture was cooled to rt, treated with CH_2Cl_2 , filtered and concentrated. Purification of the residue by SiO_2 chromatography (0 ~ 10% EtOAc/hexane) gave the title compound (84 mg). LC/ESI-MS; $m/z=407$ ($C_{25}H_{24}ClFN_2.H^+$).

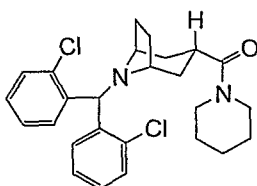
Example 44

-34-

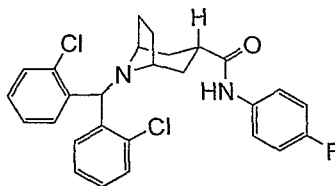


The title compound was prepared according to the procedure of Example 43, Step 2, using **31**, 2,6-dichlorobenzylbromide and K_2CO_3 (508 mg). LC/ESI-MS; $m/z=247(C_{19}H_{20}Cl_2N_2.H^+)$.

5

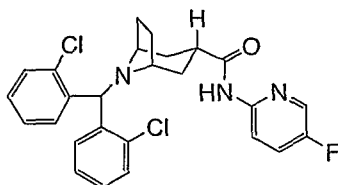
Example 45

The title compound was prepared according to the procedure of Example 17 using **23** and piperidine. LC/ESI-MS: m/z 457 ($C_{26}H_{30}Cl_2N_2O.H^+$).

Example 46

10

The title compound was prepared according to the procedure of Example 17 using **23** and 4-fluoroaniline. LC/ESI-MS: m/z 483 ($C_{27}H_{25}Cl_2FN_2O.H^+$).

Example 47

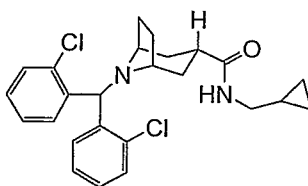
15

DMAP (4 mg) was added to a mixture of **23** (43 mg, 0.11 mmol), 2-amino-5-fluoropyridine (24.6 mg, 0.58 mmol) and DCC (34 mg, 0.166 mmol) in anhydrous CH_2Cl_2 at rt and stirred at rt for 3 days. The mixture was filtered, and the filtrate was washed with water and saturated aq. NH_4Cl . The organic solution was dried over Na_2SO_4 , filtered and concentrated. Purification of the residue by SiO_2 chromatography (EtOAc/hexane) gave the title compound (15.5 mg). LC/ESI-MS: m/z 484 ($C_{26}H_{24}Cl_2FN_3O.H^+$).

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Example 48

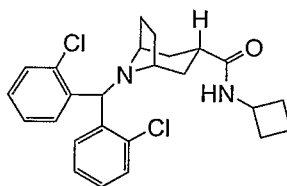
-35-



To PS-EDC resin (45 mg, 0.0615 mmol) in a cartridge was added **23** (8 mg, 0.0205 mmol) and HOBt (4.2 mg, 0.031 mmol) in 1 ml CH₃CN-THF (3:2). A solution of cyclopropanemethylamine in CH₃CN (1 M, 45 μ l, 0.045 mmol) was then added to the mixture. The cartridge was capped and shaken overnight. The mixture was treated with PS-isocyanate (40 mg, ~0.0615 mmol), PS-trisamine resins (30 mg, ~0.123 mmol) and 0.5 ml CH₃CN-THF (3:2). The cartridge was capped and shaken for 6 h. The mixture was filtered and rinsed twice with CH₃CN, and the filtrate was concentrated to give the title compound (6.4 mg). LC/ESI-MS: *m/z* 443

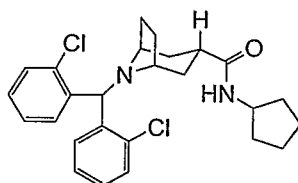
(C₂₅H₂₈Cl₂N₂O.H⁺).

Example 49



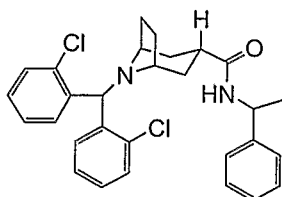
The title compound was prepared according to the procedure of Example 48 using **23** and cyclobutylamine/CH₃CN (1 M). LC/ESI-MS: *m/z* 443 (C₂₅H₂₈Cl₂N₂O.H⁺).

Example 50



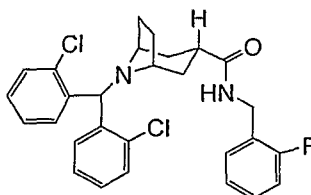
The title compound was prepared according to the procedure of Example 48 using **23** and cyclopentylamine/CH₃CN (1 M). LC/ESI-MS: *m/z* 457 (C₂₆H₃₀Cl₂N₂O.H⁺).

Example 51

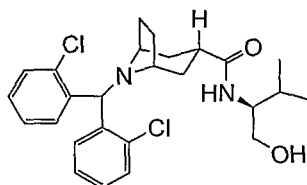


-36-

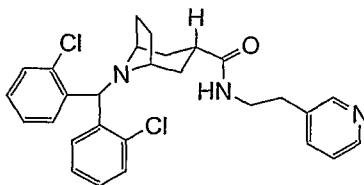
The title compound was prepared according to the procedure of Example 48 using **23** and α -methylbenzylamine/ CH_3CN (1 M). LC/ESI-MS: m/z 493 ($\text{C}_{29}\text{H}_{30}\text{Cl}_2\text{N}_2\text{O} \cdot \text{H}^+$).

Example 52

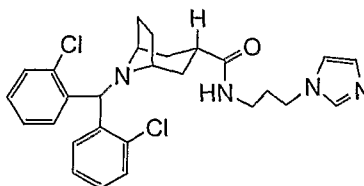
The title compound was prepared according to the procedure of Example 48 using **23** and 2-fluorobenzylamine/ CH_3CN (1 M). LC/ESI-MS: m/z 497 ($\text{C}_{28}\text{H}_{27}\text{Cl}_2\text{FN}_2\text{O} \cdot \text{H}^+$).

Example 53

The title compound was prepared according to the procedure of Example 48 using **23** and 2-S-amino-3-methyl-1-butanol/ CH_3CN (1 M). LC/ESI-MS: m/z 475 ($\text{C}_{26}\text{H}_{32}\text{Cl}_2\text{N}_2\text{O}_2 \cdot \text{H}^+$).

Example 54

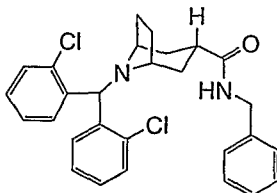
The title compound was prepared according to the procedure of Example 48 using **23** and 3-(2-aminoethyl)pyridine/ CH_3CN (1 M). LC/ESI-MS: m/z 494 ($\text{C}_{28}\text{H}_{29}\text{Cl}_2\text{N}_3\text{O} \cdot \text{H}^+$).

Example 55

-37-

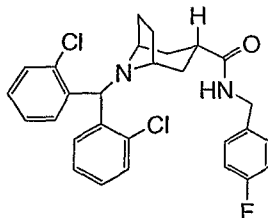
The title compound was prepared according to the procedure of Example 48 using **23** and *N*-(3-aminopropyl)imidazole/ CH_3CN (1 M). LC/ESI-MS: m/z 497 ($\text{C}_{27}\text{H}_{30}\text{Cl}_2\text{N}_4\text{O} \cdot \text{H}^+$).

Example 56



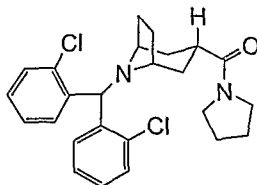
To PS-EDC resin (45 mg, 0.0615 mmol) in a cartridge was added **23** (8 mg, 0.0205 mmol) in 1 ml CH_3CN -THF (3:2) and HOBT (4.2 mg, 0.031 mmol) in THF (200 μl). The mixture was shaken at rt for 1 min, and then benzylamine/ CH_3CN (1 M, 41 μl , 0.041 mmol) was added. The cartridge was capped and shaken overnight. The mixture was treated with PS-isocyanate (45 mg, 0.0615 mmol), PS-trisamine (40 mg, 0.123 mmol) resins and 0.5 ml CH_3CN -THF (3:2). The cartridge was capped and shaken for 6 h. The mixture was filtered and rinsed twice with CH_3CN . The filtrate was concentrated to give the title compound (5.5 mg). LC/ESI-MS: m/z 479 ($\text{C}_{28}\text{H}_{28}\text{Cl}_2\text{N}_2\text{O} \cdot \text{H}^+$).

Example 57



The title compound was prepared according to the procedure of Example 56 using **23** and 4-fluorobenzylamine/ CH_3CN (1 M). LC/ESI-MS: m/z 497 ($\text{C}_{28}\text{H}_{27}\text{Cl}_2\text{FN}_2\text{O} \cdot \text{H}^+$).

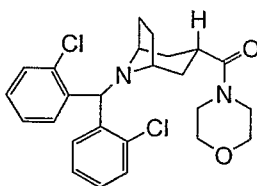
Example 58



The title compound was prepared according to the procedure of Example 56 using **23** and pyrrolidine/ CH_3CN (1 M). LC/ESI-MS: m/z 443 ($\text{C}_{25}\text{H}_{28}\text{Cl}_2\text{N}_2\text{O} \cdot \text{H}^+$).

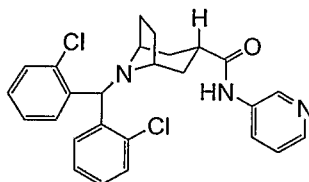
Example 59

-38-



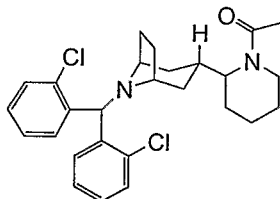
The title compound was prepared according to the procedure of Example 56 using **23** and morpholine/CH₃CN (1 M). LC/ESI-MS: *m/z* 459 (C₂₅H₂₈Cl₂N₂O₂.H⁺).

Example 60



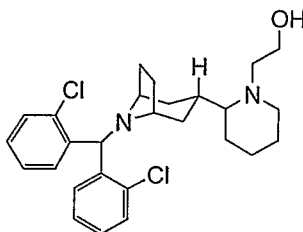
The title compound was prepared according to the procedure of Example 18 using **23** and 3-aminopyridine. LC/ESI-MS: *m/z* 466 (C₂₆H₂₅Cl₂N₃O.H⁺).

Example 61



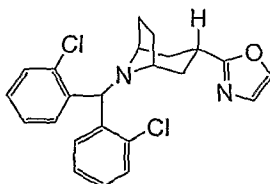
A mixture of Example 19 (34 mg) in pyridine/ acetic anhydride (1:1) was stirred at 0 °C overnight and then concentrated. Purification of the residue by SiO₂ chromatography gave the title compound (13 mg). LC/ESI-MS: *m/z* 471 (C₂₇H₃₂Cl₂N₂O.H⁺).

Example 62

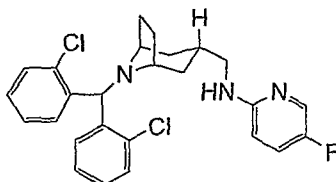


A mixture of Example 19 (40.3 mg, 0.094 mmol), K₂CO₃ (26 mg, 0.188 mmole), and 2-bromoethanol (13.3 μl, 0.188 mmol) in DMF was stirred at 50 °C for 3 days. The mixture was cooled to rt, quenched with water, and extracted with ether. The organic solution was dried over Na₂SO₄, filtered and concentrated. Purification of the residue by SiO₂ chromatography gave the title compound (9.4 mg). LC/ESI-MS: *m/z* 473 (C₂₇H₃₄Cl₂N₂O.H⁺).

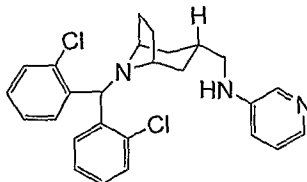
-39-

Example 63

To a solution of **22** in MeOH (75 mg, 0.2 mmol) was added K₂CO₃ (83 mg, 0.6 mmol) and tosylmethyl isocyanide (39.1 mg, 0.2 mmol). The mixture was refluxed under nitrogen for 2 h, cooled to rt and extracted with EtOAc. The organic solution was dried over Na₂SO₄ and concentrated. Purification of the residue by SiO₂ chromatography gave the title compound (11.5 mg). LC/ESI-MS: *m/z* 413 (C₂₃H₂₂Cl₂N₂O.H⁺).

Example 64

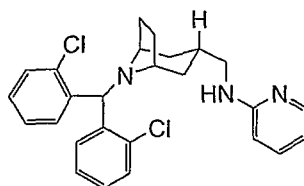
LAH/THF (1 M, 25 μl) was added to a stirred solution of Example 47 (8 mg, 0.0165 mmol) in THF at 0 °C under nitrogen. The mixture was warmed to rt, stirred overnight and H₂O (2 μl), 15% NaOH (6 μl), and H₂O (2 μl) were added sequentially. The mixture was stirred, filtered and concentrated. Purification of the residue by SiO₂ chromatography gave the title compound (2.5 mg). LC/ESI-MS: *m/z* 470 (C₂₆H₂₆Cl₂FN₃.H⁺).

Example 65

NaBH(OAc)₃ (32 mg, 0.15 mmol) was added to a solution of **22** (37.4 mg, 0.1 mmol) and 3-aminopyridine (9.6 mg, 0.1 mmol) in CH₂Cl₂ under nitrogen. The mixture was stirred at rt for 3 h, quenched with saturated NaHCO₃ solution, and extracted with EtOAc. The organic solution was dried over Na₂SO₄, filtered and concentrated. Purification of the residue by SiO₂ chromatography gave the title compound (19.5 mg). LC/ESI-MS: *m/z* 452 (C₂₆H₂₇Cl₂N₃.H⁺).

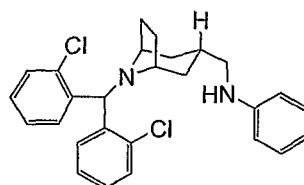
Example 66

-40-



The title compound was prepared according to the procedure of Example 65 using **22**, NaBH(OAc)₃ and 2-aminopyridine. LC/ESI-MS: *m/z* 452 (C₂₆H₂₇Cl₂N₃·H⁺).

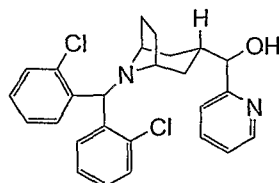
Example 67



5

The title compound was prepared according to the procedure of Example 65 using **22**, NaBH(OAc)₃ and aniline. LC/ESI-MS: *m/z* 451 (C₂₇H₂₈Cl₂N₂·H⁺).

Example 68

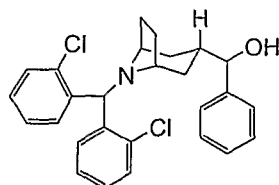


10

Isopropylmagnesium chloride (2M in THF, 500 μl, 1 mmol) was added to a solution of 2-bromopyridine (95.4 μl, 1 mmol) in THF dropwise at rt under nitrogen. The mixture was stirred at rt for 1.5 h, a solution of **22** in THF was added, and the mixture was stirred overnight. The reaction mixture was quenched with water, extracted with CH₂Cl₂, dried over MgSO₄, filtered and concentrated. Purification of the residue by SiO₂ chromatography (EtOAc/hexane) gave the title compound (26 mg). LC/ESI-MS: *m/z* 453 (C₂₆H₂₆Cl₂N₂O·H⁺).

15

Example 69

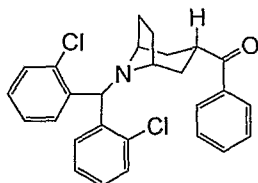


20

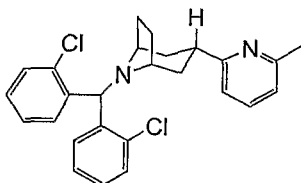
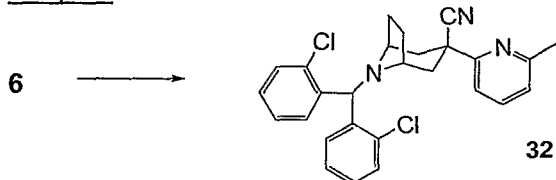
Phenylmagnesium bromide (1M in THF, 400 μl, 0.4 mmol) was added to a solution of **22** (75 mg, 0.2 mmol) in ether dropwise at -78 °C under nitrogen. The mixture was stirred at -78 °C for 5 h, quenched with saturated NH₄Cl solution, extracted with ether, dried over Na₂SO₄, filtered and concentrated. Purification of the

-41-

residue by SiO₂ chromatography (EtOAc/hexane) gave the title compound (33.5 mg).
LC/ESI-MS: *m/z* 452 (C₂₇H₂₇Cl₂NO.H⁺).

Example 70

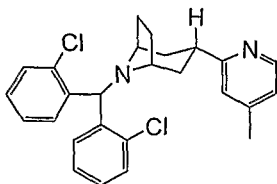
- 5 A mixture of Example 69 (22 mg, 0.049 mmol) and Dess-Martin periodinane (42 mg, 0.097 mmol) in CH₂Cl₂ was stirred at rt overnight. The mixture was diluted with ether (4 ml) and poured into a solution of saturated aqueous NaHCO₃ and sodium thiosulfate (126 mg, in 2 ml). The organic solution was washed with brine, dried over Na₂SO₄, and concentrated to give the title compound (18.5 mg). LC/ESI-MS: *m/z* 450 (C₂₇H₂₅Cl₂NO.H⁺).

Example 71Step 1:

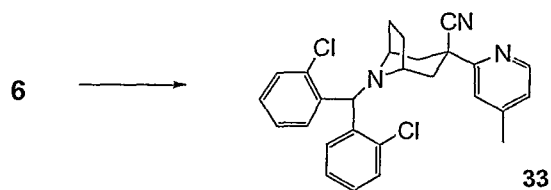
- 15 Compound **32** was prepared according to the procedure of Example 2, Step 1, using **6**, NaHMDS and 2-bromo-6-methylpyridine. LC/ESI-MS: *m/z* 462 (C₂₇H₂₅Cl₂N₃.H⁺).

Step 2:

- 20 The title compound was prepared according to the procedure of Example 2, Step 2, using **32** and NaOH. LC/ESI-MS: *m/z* 437 (C₂₆H₂₆Cl₂N₂.H⁺).

Example 72Step 1:

-42-

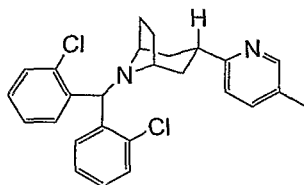


Compound **33** was prepared according to the procedure Example 2, Step 1, using **6**, NaHMDS and 2-bromo-4-methylpyridine. LC/ESI-MS: m/z 462 ($C_{27}H_{25}Cl_2N_3 \cdot H^+$).

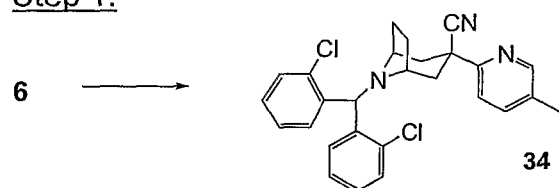
5 Step 2:

The title compound was prepared according to the procedure of Example 2, Step 2, using **33** and NaOH. LC/ESI-MS: m/z 437 ($C_{26}H_{26}Cl_2N_2 \cdot H^+$).

Example 73



10 Step 1:

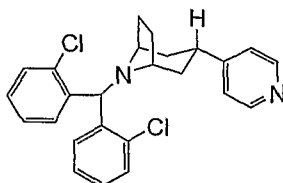


Compound **34** was prepared according to the procedure Example 2, Step 1, using **6**, NaHMDS and 2-bromo-5-methylpyridine. LC/ESI-MS: m/z 462 ($C_{27}H_{25}Cl_2N_3 \cdot H^+$).

15 Step 2:

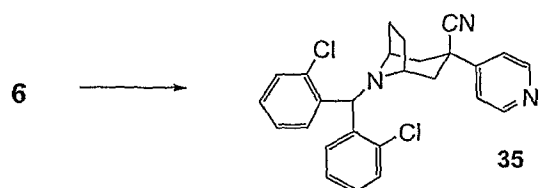
The title compound was prepared according to the procedure of Example 2, Step 2, using **34** and NaOH. LC/ESI-MS: m/z 437 ($C_{26}H_{26}Cl_2N_2 \cdot H^+$).

Example 74



20 Step 1:

-43-



Compound **35** was prepared according to the procedure Example 2, Step 1, using **6**, NaHMDS and 4-bromo-pyridine (derived from 4-bromo-pyridine hydrobromide). LC/ESI-MS: m/z 448 ($C_{26}H_{23}Cl_2N_3 \cdot H^+$).

5 Step 2:

The title compound was prepared according to the procedure of Example 2, Step 2, using **35** and NaOH. LC/ESI-MS: m/z 423 ($C_{25}H_{24}Cl_2N_2 \cdot H^+$).

The compounds of formula I exhibit greater than 50-fold selectivity over
 10 classical opioid receptors. The NOP receptor shares a high degree of homology with classical opioid receptors (i.e., μ , κ and δ), but the NOP receptor is not activated by endogenous opioids, and endogenous opioids do not activate the NOP receptor. Codeine and other opioids used as cough suppressants are known to activate the mu-opioid receptor, causing side effects such as respiratory depression, constipation,
 15 tolerance and physical dependency. NOP receptor agonists do not activate the mu-opioid receptor, and therefore are expected to result in a superior safety profile compared to opioids.

The NOP receptor agonist activity of compounds of formula I, and their effect on cough and respiration can be measured by the following tests.

20 Nociceptin binding assay

CHO cell membrane preparation expressing the NOP receptor (2 mg) was incubated with varying concentrations of [125 I][Tyr 14]nociceptin (3-500 pM) in a buffer containing 50 mM HEPES (pH7.4), 10 mM NaCl, 1mM MgCl $_2$, 2.5 mM CaCl $_2$, 1 mg/ml bovine serum albumin and 0.025% bacitracin. In a number of studies, assays were carried
 25 out in buffer 50 mM tris-HCl (pH 7.4), 1 mg/ml bovine serum albumin and 0.025% bacitracin. Samples were incubated for 1h at room temperature (22°C). Radiolabelled ligand bound to the membrane was harvested over GF/B filters presoaked in 0.1% polyethyleneimine using a Brandell cell harvester and washed five times with 5 ml cold distilled water. Nonspecific binding was determined in parallel by

similar assays performed in the presence of 1 μ M nociceptin. All assay points were performed in duplicates of total and non-specific binding.

Calculations of K_i were made using methods well known in the art.

For compounds of this invention, K_i values were determined to be in the range
5 of about 1 to about 500 nM, with compounds having a K_i value less than 10 nM being preferred.

Using the procedures described the European Journal of Pharmacology, 336 (1997), p. 233-242, the agonist activity of compounds of the invention is determined.
Cough Studies

10 The effects of a nociceptin agonist are evaluated in capsaicin-induced cough in the guinea pig according to the methods of Bolser et al. British Journal of Pharmacology (1995) 114, 735-738 (also see McLeod et al, British Journal of Pharmacology (2001) 132,1175-1178). This model is a widely used method to evaluate the activity of potential antitussive drugs. Overnight fasted male Hartley guinea pigs (350-450 g,
15 Charles River, Bloomington, MA, USA) are placed in a 12" x 14" transparent chamber. The animals are exposed to aerosolized capsaicin (300 μ M, for 4 min) produced by a jet nebulizer (Puritan Bennett, Lenexa, KS, USA) to elicit the cough reflex. Each guinea pig is exposed only once to capsaicin. The number of coughs are detected by a microphone placed in the chamber and verified by a trained observer. The signal
20 from the microphone is relayed to a polygraph which provides a record of the number of coughs. Either vehicle (methylcellulose 1 ml/kg, p.o.) or test compound is given 2 hours before aerosolized capsaicin. The antitussive activity of baclofen (3 mg/kg, p.o.) is also tested as a positive control.

Respiratory Measurements

25 Studies are performed on male Hartley guinea pigs ranging in weight from 450 to 550 g. The animals are fasted overnight but given water and libitum. The guinea pigs are placed in a whole-body, head-out plethysmograph and a rubber collar is placed over the animal's head to provide an airtight seal between the guinea pig and the plethysmograph. Airflow is measured as a differential pressure across a wire mesh
30 screen which covers a 1-in hole in the wall of the plethysmograph. The airflow signal is integrated to a signal proportional to volume using a preamplifier circuit and a pulmonary function computer (Buxco Electronics, Sharon, CT., model XA). A head chamber is attached to the plethysmograph and air from a compressed gas source

(21%O₂, balance N₂) is circulated through the head chamber for the duration of study. All respiratory measurements are made while the guinea pigs breathe this circulating air.

The volume signal from each animal is fed into a data acquisition/analysis system (Buxco Electronics, model XA) that calculates tidal volume and respiratory rate on a breath-by-breath basis. These signals are visually displayed on a monitor. Tidal volume and respiratory rate are recorded as an average value every minute.

The guinea pigs are allowed to equilibrate in the plethysmograph for 30 min. Baseline measurements are obtained at the end of this 30 min period. The guinea pigs are then removed from the plethysmograph and orally dosed with test compound (10 mg/kg, p.o.), baclofen (3 mg/kg, p.o.) or a methylcellulose vehicle placebo (2 ml/kg, p.o.). Immediately after dosing, the guinea pigs are placed into the plethysmograph, the head chamber and circulating air are reconnected and respiratory variables (tidal volume (V_T), respiratory rate (f) and minute volume ($MV = V_T \times f$)) are measured at 30, 60, 90 and 120 min post treatment. This study is performed under ACUC protocol #960103.

One to three compounds of formula I can be administered in the methods of this invention, preferably one.

Compounds of this invention exhibit anti-tussive activity, making them useful for suppressing coughing in mammals. For mammals treated for coughing, at least one nociceptin receptor NOP agonist of formula I may be administered along with one or more additional agents for treating cough, allergy or asthma symptoms selected from antihistamines, 5-lipoxygenase inhibitors, leukotriene inhibitors, H₃ inhibitors, β -adrenergic receptor agonists, xanthine derivatives, α -adrenergic receptor agonists, mast cell stabilizers, anti-tussives, expectorants, NK₁, NK₂ and NK₃ tachykinin receptor antagonists, and GABA_B agonists. Preferably a combination of this invention comprises one compound of formula I and 1-3 additional agents, preferably 1-2 additional agents, and more preferably 1 additional agent.

Non limitative examples of antihistamines include: astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine (also known as SCH-34117), doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine,

mizolastine, equitazine, mianserin, noberastine, meclizine, norastemizole, picumast, pyrillamine, promethazine, terfenadine, tripeleminamine, temelastine, trimeprazine and triprolidine.

Non-limitative examples of histamine H₃ receptor antagonists include:

- 5 thioperamide, impromidine, burimamide, clobenpropit, impentamine, mifetidine, S-sopromidine, R-sopromidine, SKF-91486, GR-175737, GT-2016, UCL-1199 and clozapine. Other compounds can readily be evaluated to determine activity at H₃ receptors by known methods, including the guinea pig brain membrane assay and the guinea pig neuronal ileum contraction assay, both of which are described in U.S. Patent 5,352,707. Another useful assay utilizes rat brain membranes and is described by West et al., "Identification of Two-H₃-Histamine Receptor Subtypes," *Molecular Pharmacology*, Vol. 38, pages 610-613 (1990).

- The term "leukotriene inhibitor" includes any agent or compound that inhibits, restrains, retards or otherwise interacts with the action or activity of leukotrienes. Non-limitative examples of leukotriene inhibitors include montelukast [R-(E)-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)-ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]-methyl]cyclo-propaneacetic acid and its sodium salt, described in EP 0 480 717; 1-(((R)-(3-(2-(6,7-difluoro-2-quinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)-phenyl)thio) methyl)cyclopropaneacetic acid, and its sodium salt, described in WO 97/28797 and U.S. Patent 5,270,324; 1-(((1(R)-3(3-(2-(2,3-dichlorothieno[3,2-b]-pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio) methyl)cyclopropaneacetic acid, and its sodium salt, described in WO 97/28797 and U.S. Patent 5,472,964; pranlukast, N-[4-oxo-2-(1H-tetrazol-5-yl)-4H-1-benzopyran-8-yl]-p-(4-phenylbutoxy) benzamide) described in WO 97/28797 and EP 173,516; 25 zafirlukast, (cyclopentyl-3-[2-methoxy-4-[(o-tolylsulfonyl) carbamoyl]benzyl]-1-methyl-indole-5-carbamate) described in WO 97/28797 and EP 199,543; and [2-[[2(4-tert-butyl-2-thiazolyl)-5-benzofuranyl] oxymethyl]phenyl]acetic acid, described in U.S. Patent 5,296,495 and Japanese patent JP08325265 A.

- The term "5-lipoxygenase inhibitor" or "5-LO inhibitor" includes any agent or compound that inhibits, restrains, retards or otherwise interacts with the enzymatic action of 5-lipoxygenase. Non-limitative examples of 5-lipoxygenase inhibitors include zileuton, docebenone, piri-post, ICI-D2318, and ABT 761.

Non-limitative examples of β -adrenergic receptor agonists include: albuterol, bitolterol, isoetharine, mataproterenol, perbuterol, salmeterol, terbutaline, isoproterenol, ephedrine and epinephrine.

A non-limitative example of a xanthine derivative is theophylline.

5 Non-limitative examples of α -adrenergic receptor agonists include arylalkylamines, (e.g., phenylpropanolamine and pseudoephedrine), imidazoles (e.g., naphazoline, oxymetazoline, tetrahydrozoline, and xylometazoline), and cycloalkylamines (e.g., propylhexedrine).

A non-limitative example of a mast cell stabilizer is nedocromil sodium.

10 Non-limitative examples of anti-tussive agents include codeine, dextromethorphan, benzonatate, chlophedianol, and noscapine.

A non-limitative example of an expectorant is guaifenesin.

Non-limitative examples of NK₁, NK₂ and NK₃ tachykinin receptor antagonists include CP-99,994 and SR 48968.

15 Non-limitative examples of GABA_B agonists include baclofen and 3-aminopropyl-phosphinic acid.

Compounds of this invention are useful in treating UI or overactive bladder in mammals. At least one compound of formula I may be administered along with one or more additional agents for treating UI or overactive bladder. Agents known to
20 treat UI or overactive bladder include muscarinic antagonists, for example darifenacin, tolterodine, solifenacin, trospium, duloxetine and temiverine, and antispasmodic and/or anticholinergic agents such as oxybutynin and hyoscyamine. Preferably a combination of this invention comprises one compound of formula I and 1 additional agent.

25 For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art,
30 e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

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

5 Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

10 Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral
15 administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

20 Preferably a compound of this invention is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

25 The quantity of active compound of formula I in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally,
30 treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

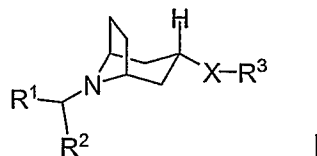
The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical
5 recommended dosage regimen is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to provide relief from pain, anxiety, depression, asthma or alcohol abuse. The compounds are non-toxic when administered within this dosage range.

When the NOP agonist of formula I is administered in combination with one or
10 more additional agents, the compound of formula I and the additional agent(s) are preferably administered in a combined dosage form (e.g., a single tablet), although they can be administered separately. The additional agents are administered in amounts effective to provide relief from cough, allergy or asthma symptoms, preferably from about 0.1 mg to 1000 mg, more preferably from about 1 mg to 300 mg
15 per unit dose. A typical recommended dosage regimen of the additional agent is from 1 mg to 2000 mg/day, preferably 1 to 1000 mg/day, in two to four divided doses. Typical dosage amounts of the other agents may be determined from the literature, for example in The Physicians's Desk Reference.

While the present invention has been described in conjunction with the specific
20 embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound represented by the formula



I

- 5 or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 is R^4 -aryl, R^4 -arylalkyl, R^4 -heteroaryl, R^4 -heteroarylalkyl, R^4 -cycloalkyl, R^4 -cycloalkylalkyl, R^4 -heterocycloalkyl or R^4 -heterocycloalkylalkyl;

R^2 is R^5 -aryl, R^5 -arylalkyl, R^5 -heteroaryl, R^5 -heteroarylalkyl, R^5 -cycloalkyl, R^5 -cycloalkylalkyl, R^5 -heterocycloalkyl or R^5 -heterocycloalkylalkyl;

- 10 R^3 is R^6 -alkyl, R^6 -aryl, R^6 -heteroaryl, R^6 -cycloalkyl or R^6 -heterocycloalkyl;

X is a bond, (C_1-C_3) alkylene, $-(CH_2)_m-N(R^7)-(CH_2)_n-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-S-(CH_2)_n-$, $-C(O)-$, $-CH(OH)-$, $-C(O)N(R^7)-$, $-C(O)N(R^7)$ -alkylene or $-N(R^7)C(O)-$;

- 15 n is 0, 1, 2, 3; 4, 5 or 6; m is 0, 1, 2, 3; 4, 5 or 6; provided that the sum of m and n is 0, 1, 2, 3; 4, 5 or 6;

each R^4 and R^5 is 1 to 3 substituents independently selected from the group consisting of H, halo, alkyl, cycloalkyl, $-CN$, $-CF_3$, $-(CH_2)_p-OR^8$, $-N(R^{10})_2$ and $-(CH_2)_n-N(R^{10})_2$;

- 20 R^6 is 1 to 3 substituents independently selected from the group consisting of H, halo, alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, $-CN$, cyanoalkyl, $-CF_3$, $-C(O)alkyl$, $-(CH_2)_p-OR^8$, $-COOR^8$, $-N(R^{10})_2$, $-(CH_2)_n-N(R^{10})_2$ and $-C(O)N(R^{10})_2$;

p is 0, 1, 2, 3; 4, 5 or 6;

R^7 is H or alkyl;

- 25 R^8 and R^9 are independently selected from the group consisting of H, alkyl, cycloalkyl, haloalkyl, hydroxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkyl- $C(O)-$ and alkyl- $C(O)-N(R^7)-C(O)-$; and

R^{10} is independently selected from the group consisting of H and alkyl.

- 30 2. A compound of claim 1 wherein R^1 is R^4 -phenyl and R^2 is R^5 -phenyl, wherein R^4 and R^5 are independently selected from the group consisting of H, halo and alkyl.

-51-

3. A compound of claim 2 wherein R^1 is R^4 -phenyl wherein R^4 is one halo atom, and R^2 is R^5 -phenyl wherein R^5 is one halo atom.

4. A compound of claim 3 wherein R^4 and R^5 are chlorine.

5

5. A compound of claim 1 wherein X is a bond, $-N(R^7)-(CH_2)_n-$ wherein R^7 is H and n is 0 or 1, or $-C(O)N(R^7)-$ wherein R^7 is H.

6. A compound of claim 5 wherein X is a bond.

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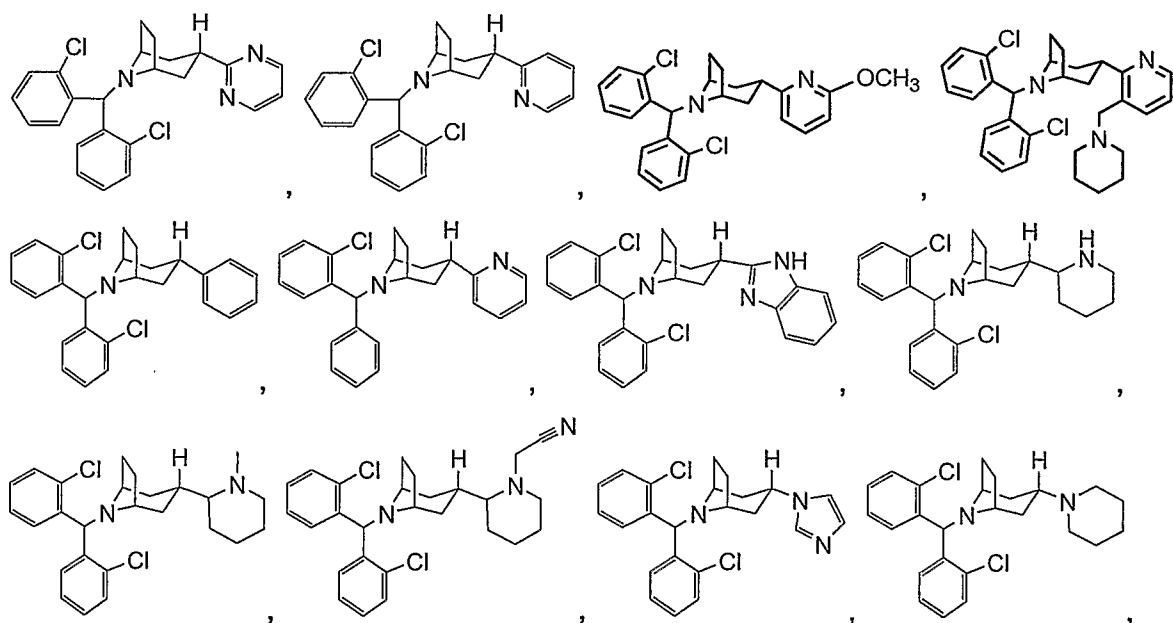
7. A compound of claim 1 wherein R^3 is R^6 -aryl, R^6 -heteroaryl or R^6 -heterocycloalkyl.

8. A compound of claim 7 wherein R^3 is R^6 -phenyl, R^6 -pyridyl, R^6 -pyrimidyl, R^6 -imidazolyl, R^6 -benzimidazolyl, R^6 -piperidyl or R^6 -morpholyl.

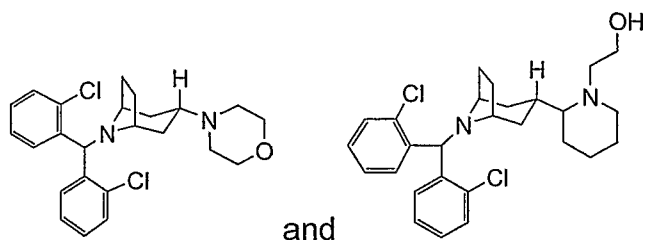
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9. A compound of claim 8 wherein R^6 is one substituent selected from the group consisting of H, halo, alkyl, OH and $-OCH_3$.

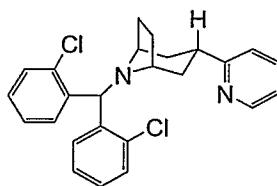
20 10. A compound of claim 1 selected from the group consisting of



-52-



11. The compound having the formula



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12. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

10 13. A pharmaceutical composition comprising: a therapeutically effective amount of a compound of claim 1; a therapeutically effective amount of one or more additional agents selected from the group consisting of: antihistamines, 5-lipoxygenase inhibitors, leukotriene inhibitors, H₃ inhibitors, β -adrenergic receptor agonists, xanthine derivatives, α -adrenergic receptor agonists, mast cell stabilizers, anti-

15 tussives, expectorants, NK₁, NK₂ and NK₃ tachykinin receptor antagonists; GABA_B agonists, muscarinic antagonists, anticholinergic agents and antispasmodic agents; and a pharmaceutically acceptable carrier.

20 14. A method of treating cough, pain, anxiety, asthma, depression, alcohol abuse, urinary incontinence or overactive bladder comprising administering an effective amount of a compound of claim 1 to a mammal in need of such treatment.

25 15. The method of claim 14 for treating cough comprising administering an effective amount of a compound of claim 1 to a mammal in need of such treatment.

16. The method of treating cough comprising administering to a mammal in need of such treatment an effective amount of a combination of a compound of claim 1 and

1-3 additional agents for treating cough, allergy or asthma symptoms selected from the group consisting of: antihistamines, 5-lipoxygenase inhibitors, leukotriene inhibitors, H₃ inhibitors, β -adrenergic receptor agonists, xanthine derivatives, α -adrenergic receptor agonists, mast cell stabilizers, anti-tussives, expectorants, NK₁,
5 NK₂ and NK₃ tachykinin receptor antagonists, and GABA_B agonists.

17. The method of claim 14 for treating urinary incontinence or overactive bladder comprising administering an effective amount of a compound of claim 1 to a mammal in need of such treatment.

10

18. The method of treating urinary incontinence or overactive bladder comprising administering to a mammal in need of such treatment an effective amount of a combination of a compound of claim 1 and an agent for treating urinary incontinence or overactive bladder selected from the group consisting of muscarinic antagonists, anticholinergic agents and antispasmodics.

15

19. The method of claim 18 wherein the compound of claim 1 is administered in combination with darifenacin, tolterodine, solifenacin, trospium, duloxetine, temiverine, oxybutynin or hyoscyamine.