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(54) PIPERAZINE DERIVATIVES USEFUL AS CCR5 ANTAGONISTS

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DERIVES DE PIPERAZINE FAISANT OFFICE D'ANTAGONISTES CCR5

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(56) References cited:
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Description

BACKGROUND

[0001] The present invention relates to piperazine derivatives useful as selective CCR5 antagonists, pharmaceutical compositions containing the compounds, and methods of treatment using the compounds. The invention also relates to the use of a combination of a CCR5 antagonist of this invention and one or more antiviral or other agents useful in the treatment of Human Immunodeficiency Virus (HIV). The invention further relates to the use of a CCR-5 antagonist of this invention, alone or in combination with another agent, in the treatment of solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis.

[0002] The global health crisis caused by HIV, the causative agent of Acquired Immunodeficiency Syndrome (AIDS), is unquestioned, and while recent advances in drug therapies have been successful in slowing the progression of AIDS, there is still a need to find a safer, more efficient, less expensive way to control the virus.

[0003] It has been reported that the CCR5 gene plays a role in resistance to HIV infection. HIV infection begins by attachment of the virus to a target cell membrane through interaction with the cellular receptor CD4 and a secondary chemokine co-receptor molecule, and proceeds by replication and dissemination of infected cells through the blood and other tissue. There are various chemokine receptors, but for macrophage-tropic HIV, believed to be the key pathogenic strain that replicates *in vivo* in the early stages of infection, the principal chemokine receptor required for the entry of HIV into the cell is CCR5. Therefore, interfering with the interaction between the viral receptor CCR5 and HIV can block HIV entry into the cell. The present invention relates to small molecules which are CCR5 antagonists.

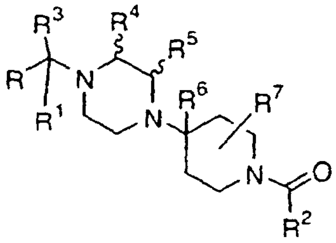
[0004] CCR-5 receptors have been reported to mediate cell transfer in inflammatory diseases such as arthritis, rheumatoid arthritis, atopic dermatitis, psoriasis, asthma and allergies, and inhibitors of such receptors are expected to be useful in the treatment of such diseases, and in the treatment of other inflammatory diseases or conditions such as inflammatory bowel disease, multiple sclerosis, solid organ transplant rejection and graft v. host disease.

[0005] Related piperazine derivatives which are muscarinic antagonists useful in the treatment of cognitive disorders such as Alzheimer's disease are disclosed in US patents 5,883,096; 6,037,352; 5,889,006.

[0006] A-M. Vandamme et al., Antiviral Chemistry & Chemotherapy, 9:187-203 (1998) disclose current clinical treatments of HIV-1 infections in man including at least triple drug combinations or so-called Highly Active Antiretroviral Therapy ("HAART"); HAART involves various combinations of nucleoside reverse transcriptase inhibitors ("NRTI"), non-nucleoside reverse transcriptase inhibitors ("NNRTI") and HIV protease inhibitors ("PI"). In compliant drug-naive patients, HAART is effective in reducing mortality and progression of HIV-1 to AIDS. However, these multidrug therapies do not eliminate HIV-1 and long-term treatment usually results in multidrug resistance. Development of new drug therapies to provide better HIV-1 treatment remains a priority.

SUMMARY OF THE INVENTION

[0007] The present invention relates to the treatment of HIV comprising administering to a mammal in need of such treatment an effective amount of a CCR5 antagonist represented by the structural formula I:



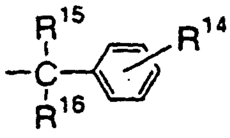
I

or a pharmaceutically acceptable salt thereof, wherein

R is R^8-phenyl, R^8-pyridyl, R^8-thiophenyl or R^8-naphthyl;

R^1 is hydrogen or C_1-C_6 alkyl;

R^2 is R^9, R^{10}, R^{11}-phenyl; R^9, R^{10}, R^{11}-substituted 6-membered heteroaryl; R^9, R^{10}, R^{11}-substituted 6-membered heteroaryl N-oxide; R^{12}, R^{13}-substituted 5-membered heteroaryl; naphthyl; fluorenyl; diphenylmethyl



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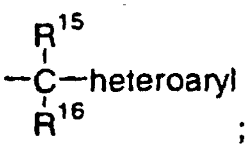


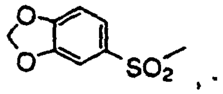
;

R^3 is hydrogen, C_1-C_6 alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkyl(C_1-C_6)alkyl, R^8-phenyl, R^8-phenyl(C_1-C_6)alkyl, R^8-naphthyl, R^8-naphthyl(C_1-C_6)alkyl, R^8-heteroaryl or R^8-heteroaryl(C_1-C_6)alkyl;

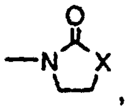
R^4, R^5, R^7 and R^{13} are independently selected from the group consisting of hydrogen and (C_1-C_6)-alkyl;

R^6 is hydrogen, C_1-C_6 alkyl or C_2-C_6 alkenyl;

R^8 is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-CF_3$, CF_3O-, $CH_3C(O)$-, -CN, CH_3SO_2-, CF_3SO_2-, R^{14}-phenyl, R^{14}-benzyl, $CH_3C(=NOCH_3)$, $CH_3C(=NOCH_2CH_3)$,



$-NH_2$, $-NHCOCF_3$, -NHCONH(C_1-C_6 alkyl), -NHCO(C_1-C_6 alkyl), $-NHSO_2$(C_1-C_6 alkyl), 5-membered heteroaryl and



wherein X is -0-, -NH- or $-N(CH_3)$-;

R^9 and R^{10} are independently selected from the group consisting of (C_1-C_6)alkyl, halogen, $-NR^{17}R^{18}$, -OH, $-CF_3$, $-OCH_3$, -O-acyl, $-OCF_3$ and $-Si(CH_3)_3$;

R^{11} is R^9, hydrogen, phenyl, $-NO_2$, -CN, $-CH_2F$, $-CHF_2$, -CHO, $-CH=NOR^{17}$, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl, $-N(R^{17})CONR^{18}R^{19}$, -NHCONH(chloro-($C_1$-$C_6$)alkyl), -NHCONH(($C_3$-$C_{10}$)cycloalkyl($C_1$-$C_6$)alkyl), -NHCO($C_1$-$C_6$)alkyl, $-NHCOCF_3$, $-NHSO_2N$((C_1-C_6)alkyl$)_2$, $-NHSO_2$(C_1-C_6)alkyl, $-N(SO_2CF_3)_2$, $-NHCO_2$(C_1-C_6)alkyl, C_3-C_{10} cycloalkyl, $-SR^{20}$, $-SOR^{20}$, $-SO_2R^{20}$, $-SO_2NH$(C_1-C_6 alkyl), $-OSO_2$(C_1-C_6)alkyl, $-OSO_2CF_3$, hydroxy(C_1-C_6)alkyl, $-CONR^{17}R^{18}$, $-CON(CH_2CH_2\text{-}O\text{-}CH_3)_2$, -OCONH($C_1$-$C_6$)alkyl, $-CO_2R^{17}$, $-Si(CH_3)_3$ or $-B(OC(CH_3)_2)_2$;

R^{12} is (C_1-C_6)alkyl, $-NH_2$ or R^{14}-phenyl;

R^{14} is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, $-CF_3$, $-CO_2R_{17}$, -CN, (C_1-C_6)alkoxy and halogen;

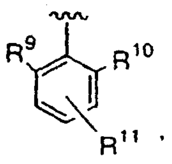
R^{15} and R^{16} are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl, or R^{15} and R^{16} together are a C_2-C_5 alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

R^{17}, R^{18} and R^{19} are independently selected from the group consisting of H and C_1-C_6 alkyl; and

R^{20} is C_1-C_6 alkyl or phenyl.

[0008] Preferred are compounds of formula I wherein R is R^8 -phenyl or R^8-naphthyl, especially wherein R^8 is a single substituent, and especially wherein the R^8 substituent is in the 4-position. For R^8-phenyl, preferred R^8 substituents are $-CF_3$, $-OCF_3$, CH_3SO_2-, CH_3CO-, $CH_3C(=NOCH_3)$-, Br and I. For R^8-naphthyl, R^8 is preferably C_1-C_6 alkoxy. Also preferred are compounds of formula I wherein R^3 is hydrogen, (C_1-C_6) alkyl, R^8-phenyl. R^8-benzyl or R^8-pyridyl; more preferred definitions for R^3 are methyl, ethyl, phenyl, benzyl and pyridyl. R^1 is preferably hydrogen. For compounds of formula I, R^6 is preferably hydrogen or methyl, especially methyl. R^4 is preferably methyl; R^5 and R^7 are each preferably hydrogen.

[0009] In compounds of formula I, R^2 is preferably R^9, R^{10}, R^{11}-phenyl, R^9, R^{10}, R^{11}-pyridyl or an N-oxide thereof, or R^9, R^{10}, R^{11}-pyrimidyl. When R^2 is pyridyl, it is preferably 3- or 4-pyridyl, and when pyrimidyl, it is preferably 5-pyrimidyl. The R^9 and R^{10} substituents are preferably attached to carbon ring members adjacent to the carbon joining the ring to the rest of the molecule and the R^{11} substituent can be attached to any of the remaining unsubstituted carbon ring members, for example as shown in the following structures:



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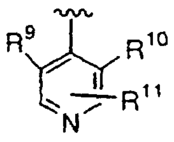

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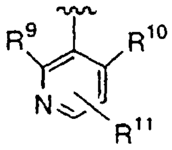

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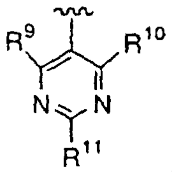

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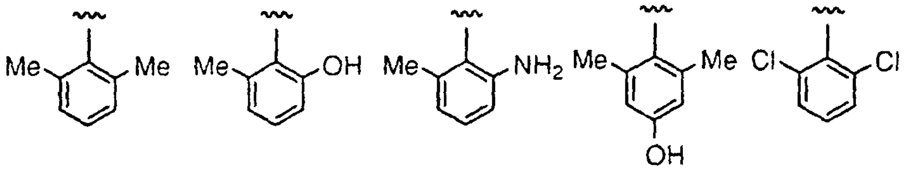
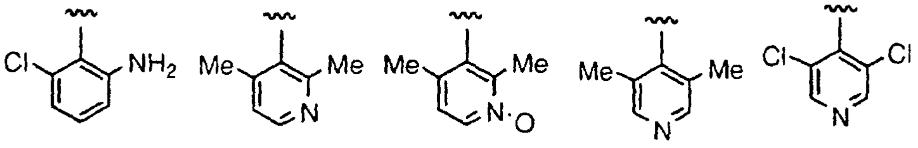
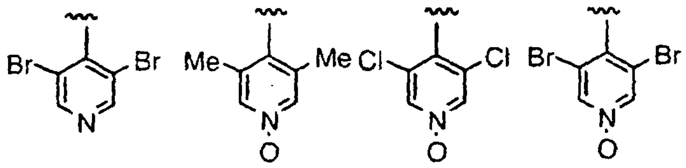
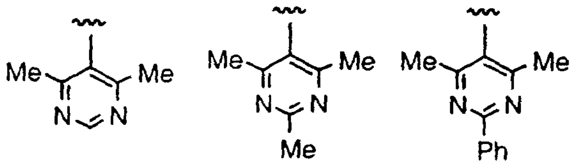
[0010] Preferred R^9 and R^{10} substituents are: (C_1-C_6)alkyl, especially methyl; halogen, especially chloro or bromo, -OH and $-NH_2$. When R^2 is phenyl, R^{11} is preferably hydrogen or -OH; when R^2 is pyridyl, R^{11} is preferably hydrogen; and when R^2 is pyrimidyl, R^{11} is preferably hydrogen, methyl or phenyl. Examples of particularly preferred R^2 groups are as follows:

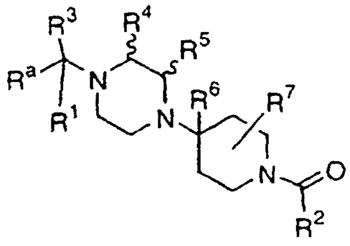








[0011] Also claimed are novel CCR5 antagonist compounds represented by the structural formula II



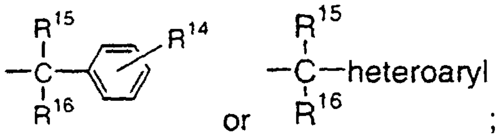
II

or a pharmaceutically acceptable salt thereof, wherein

(1) R^a is R^{8a}-phenyl, R^{8b}-pyridyl, R^{8b}-thiophenyl or R^8-naphthyl;

R^1 is hydrogen or C_1-C_6 alkyl;

R^2 is R^9, R^{10}, R^{11}-phenyl; R^9, R^{10}, R^{11}-substituted 6-membered heteroaryl; R^9, R^{10}, R^{11}-substituted 6-membered heteroaryl N-oxide; R^{12}, R^{13}-substituted 5-membered heteroaryl; naphthyl; fluorenyl; diphenylmethyl,

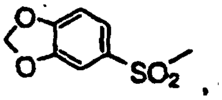


R^3 is hydrogen, C_1-C_6 alkyl, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkyl$(C_1$-$C_6)$alkyl, R^8-phenyl, R^8-phenyl$(C_1$-$C_6)$alkyl, R^8-naphthyl, R^8-naphthyl$(C_1$-$C_6)$alkyl, R^8-heteroaryl or R^8-heteroaryl$(C_1$-$C_6)$alkyl;

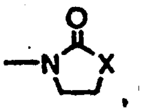
R^4, R^5, R^7 and R^{13} are independently selected from the group consisting of hydrogen and $(C_1$-$C_6)$-alkyl;

R^6 is hydrogen, C_1-C_6 alkyl or C_2-C_6 alkenyl;

R^8 is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy; $-CF_3$, CF_3O-, $CH_3C(O)$-, -CN, CH_3SO_2-, CF_3SO_2-, R^{14}-phenyl, R^{14}-benzyl, $CH_3C(=NOCH_3)$, $CH_3C(=NOCH_2CH_3)$,

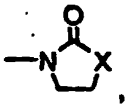


$-NH_2$, $-NHCOCF_3$, $-NHCONH(C_1$-C_6 alkyl), $-NHCO(C_1$-C_6 alkyl), $-NHSO_2(C_1$-C_6 alkyl), 5-membered heteroaryl and



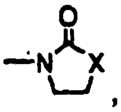
wherein X is -NH- or $-N(CH_3)$-;

R^{8a} is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, $-CF_3$, CF_3O-, -CN, CF_3SO_2-, R^{14}-phenyl, $-NHCOCF_3$, 5-membered heteroaryl and



wherein X is as defined above;

R^{8b} is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, $-CF_3$, CF_3O-, $CH_3C(O)$-, -CN, CF_3SO_2-, $CH_3C(=NOCH_3)$, $CH_3C(=NOCH_2CH_3)$, $-NHCOCF_3$, 5-membered heteroaryl and



wherein X is as defined above;

R^9 and R^{10} are independently selected from the group consisting of $(C_1$-$C_6)$alkyl, halogen, $-NR^{17}R^{18}$, -OH, $-CF_3$, $-OCH_3$, -O-acyl, $-OCF_3$ and $-Si(CH_3)_3$;

R^{11} is R^9, hydrogen, phenyl, $-NO_2$, -CN, $-CH_2F$, $-CHF_2$, -CHO, $-CH=NOR^{17}$, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl, $-N(R^{17})CONR^{18}R^{19}$, $-NHCONH$(chloro-$(C_1$-$C_6)$alkyl), $-NHCONH((C_3$-$C_{10})$cycloalkyl$(C_1$-$C_6)$alkyl), $-NHCO(C_1$-$C_6)$alkyl, $-NHCOCF_3$, $-NHSO_2N((C_1$-$C_6)$alkyl$)_2$, $-NHSO_2(C_1$-$C_6)$alkyl, $-N(SO_2CF_3)_2$, $-NHCO_2(C_1$-$C_6)$alkyl, C_3-C_{10} cycloalkyl, $-SR^{20}$, $-SOR^{20}$, $-SO_2R^{20}$, $-SO_2NH(C_1$-C_6 alkyl), $-OSO_2(C_1$-$C_6)$alkyl, $-OSO_2CF_3$, hydroxy$(C_1$-$C_6)$alkyl, $-CON\ R^{17}R^{18}$, $-CON(CH_2CH_2$-O-$CH_3)_2$, $-OCONH(C_1$-$C_6)$alkyl, $-CO_2R^{17}$, $-Si(CH_3)_3$ or $-B(OC(CH_3)_2)_2$;

R^{12} is $(C_1$-$C_6)$alkyl, $-NH_2$ or R^{14}-phenyl;

R^{14} is 1 to 3 substituents independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$ alkyl, $-CF_3$, $-CO_2R_{17}$, -CN, $(C_1$-$C_6)$alkoxy and halogen;

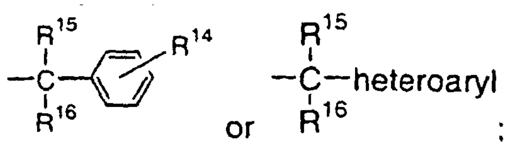
R^{15} and R^{16} are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl, or R^{15} and R^{16} together are a C_2-C_5 alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

R^{17}, R^{18} and R^{19} are independently selected from the group consisting of H and C_1-C_6 alkyl; and

R^{20} is C_1-C_6 alkyl or phenyl; or

(2) R^a is R^8-phenyl, R^8-pyridyl or R^8-thiophenyl;

R^2 is fluorenyl, diphenylmethyl,



and R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{20} are as defined in (1).

[0012] Preferred compounds of formula II are those defined in (1).

[0013] More preferred are those of formula II(1) wherein R^a is R^{8a}-phenyl or R^8-naphthyl, wherein R^{8a} is $-CF_3$, CF_3O- or halogen and R^8 is C_1-C_6 alkoxy. The R^{8a} or R^8 substituent is preferably a single substituent; it is especially preferred that the R^{8a} or R^8 substituent is in the 4-position. Also preferred are compounds of formula II(1) wherein R^3 is hydrogen, (C_1-C_6) alkyl, R^8-phenyl. R^8-benzyl or R^8-pyridyl; more preferred definitions for R3 are methyl, ethyl, phenyl, benzyl and pyridyl. R^1 is preferably hydrogen. For compounds of formula II(1), R^6 is preferably hydrogen or methyl, especially methyl. R^4 is preferably methyl; R^5 and R^7 are each preferably hydrogen.

[0014] R^2 in formula II(1) is preferably as defined for formula I, i.e., R^9, R^{10}, R^{11}-phenyl, R^9, R^{10}, R^{11}-pyridyl or an N-oxide thereof, or R^9, R^{10}, R^{11}-pyrimidyl, wherein the R^9, R^{10}, R^{11}-substitution is as defined above for preferred compounds of formula I.

[0015] Another aspect of the invention is a pharmaceutical composition for treatment of HIV comprising an effective amount of a CCR5 antagonist of formula II in combination with a pharmaceutically acceptable carrier. Another aspect of the invention is a pharmaceutical composition for treatment of solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis comprising an effective amount of a CCR5 antagonist of formula II in combination with a pharmaceutically acceptable carrier.

[0016] Yet another aspect of this invention is a method of treatment of HIV comprising administering to a human in need of such treatment an effective amount of a CCR5 antagonist compound of formula II. Another aspect of the invention is a method of treatment of solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis comprising administering to a human in need of such treatment an effective amount of a CCR5 antagonist compound of formula I or II.

[0017] Still another aspect of this invention is the use of a CCR5 antagonist of formula I or II of this invention in combination with one or more antiviral or other agents useful in the treatment of Human Immunodeficiency Virus for the treatment of AIDS. Still another aspect of this invention is the use of a CCR5 antagonist of formula I or II of this invention in combination with one or more other agents useful in the treatment of solid organ transplant rejection, graft v. host disease, inflammatory bowel disease, rheumatoid arthritis or multiple sclerosis. The CCR5 and antiviral or other agents which are components of the combination can be administered in a single dosage form or they can be administered separately; a kit comprising separate dosage forms of the actives is also contemplated.

DETAILED DESCRIPTION OF THE INVENTION

[0018] As used herein, the following terms are used as defined below unless otherwise indicated.

[0019] Alkyl represents straight and branched carbon chains and contains from one to six carbon atoms.

[0020] Alkenyl represents C_2-C_6 carbon chains having one or two unsaturated bonds, provided that two unsaturated bonds are not adjacent to each other.

[0021] Substituted phenyl means that the phenyl group can be substituted at any available position on the phenyl ring.

[0022] Acyl means a radical of a carboxylic acid having the formula alkyl-C(O)-, aryl-C(O)-, aralkyl-C(O)-, (C_3-C_7) cycloalkyl-C(O)-, (C_3-C_7)cycloalkyl-(C_1-C_6)alkyl-C(O)-, and heteroaryl-C(O)-, wherein alkyl and heteroaryl are as defined herein; aryl is R^{14}-phenyl or R^{14}-naphthyl; and aralkyl is aryl-(C_1-C_6)alkyl, wherein aryl is as defined above.

[0023] Heteroaryl represents cyclic aromatic groups of 5 or 6 atoms or bicyclic groups of 11 to 12 atoms having 1 or 2 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. For 6-membered heteroaryl rings, carbon atoms can be substituted by R^9, R^{10} or R^{11} groups. 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. For 5-membered heteroaryl rings, carbon atoms can be substituted by R^{12} or R^{13} groups. Typical 5-membered heteroaryl rings are furyl, thienyl, pyrrolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl and isoxazolyl. 5-Membered rings having one heteroatom can be joined through the 2- or 3- position; 5-membered rings having two heteroatoms are preferably joined through the 4-position. Bicyclic groups typically are benzo-fused ring systems derived from the heteroaryl groups named above, e.g. quinolyl, phthalazinyl, quinazolinyl, benzofuranyl, benzothienyl and indolyl.

[0024] Preferred points of substitution for 6-membered heteroaryl rings at R^2 are described above. When R^2 is a 5-membered heteroaryl group, the R^{12} and R^{13} substituents are preferably attached to carbon ring members adjacent to the carbon joining the ring to the rest of the molecule, and R^{12} is preferably alkyl; however, if a heteroatom is adjacent to the carbon joining the ring to the rest of the molecule (i.e., as in 2-pyrrolyl), R^{12} is preferably attached to a carbon ring member adjacent to the carbon joining the ring to the rest of the molecule.

[0025] Halogen represents fluoro, chloro, bromo and iodo.

[0026] One or more, preferaby one to four, antiviral agents useful in anti-HIV-1 therapy may be used in combination with a CCR5 antagonist of the present invention. The antiviral agent or agents may be combined with the CCR5 antagonist in a single dosage form, or the CCR5 antagonist and the antiviral agent or agents may be administered simultaneously or sequentially as separate dosage forms. The antiviral agents contemplated for use in combination with the compounds of the present invention comprise nucleoside and nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors and other antiviral drugs listed below not falling within these classifications. In particular, the combinations known as HAART (Highly Active Antiretroviral Therapy) are contemplated for use in combination with the CCR5 antagonists of this invention.

[0027] The term "nucleoside and nucleotide reverse transcriptase inhibitors" ("NRTI" s) as used herein means nucleosides and nucleotides and analogues thereof that inhibit the activity of HIV-1 reverse transcriptase, the enzyme which catalyzes the conversion of viral genomic HIV-1 RNA into proviral HIV-1 DNA.

[0028] Typical suitable NRTIs include zidovudine (AZT) available under the RETROVIR tradename from Glaxo-Wellcome Inc., Research Triangle, NC 27709; didanosine (ddI) available under the VIDEX tradename from Bristol-Myers Squibb Co., Princeton, NJ 08543; zalcitabine (ddC) available under the HIVID tradename from Roche Pharmaceuticals, Nutley, NJ 07110; stavudine (d4T) available under the ZERIT trademark from Bristol-Myers Squibb Co., Princeton, NJ 08543; lamivudine (3TC) available under the EPIVIR tradename from Glaxo-Wellcome Research Triangle, NC 27709; abacavir (1592U89) disclosed in WO96/30025 and available under the ZIAGEN trademark from Glaxo-Wellcome Research Triangle, NC 27709; adefovir dipivoxil [bis(POM)-PMEA] available under the PREVON tradename from Gilead Sciences, Foster City, CA 94404; lobucavir (BMS-180194), a nucleoside reverse transcriptase inhibitor disclosed in EP-0358154 and EP-0736533 and under development by Bristol-Myers Squibb, Princeton, NJ 08543; BCH-10652, a reverse transcriptase inhibitor (in the form of a racemic mixture of BCH-10618 and BCH-10619) under development by Biochem Pharma, Laval, Quebec H7V, 4A7, Canada; emitricitabine [(-)-FTC] licensed from Emory University under Emory Univ. U.S. Patent No. 5,814,639 and under development by Triangle Pharmaceuticals, Durham, NC 27707; beta-L-FD4 (also called beta-L-D4C and named beta-L-2', 3'-dideoxy-5-fluoro-cytidene) licensed by Yale University to Vion Pharmaceuticals, New Haven CT 06511; DAPD, the purine nucleoside, (-)-beta-D-2,6,-diamino-purine dioxolane disclosed in EP 0656778 and licensed by Emory University and the University of Georgia to Triangle Pharmaceuticals, Durham, NC 27707; and lodenosine (FddA), 9-(2,3-dideoxy-2-fluoro-b-D-threo-pentofuranosyl)adenine, a acid stable purine-based reverse transcriptase inhibitor discovered by the NIH and under development by U.S. Bioscience Inc., West Conshohoken, PA 19428.

[0029] The term "non-nucleoside reverse transcriptase inhibitors" ("NNRTI"s) as used herein means non-nucleosides that inhibit the activity of HIV-1 reverse transcriptase.

[0030] Typical suitable NNRTIs include nevirapine (BI-RG-587) available under the VIRAMUNE tradename from Boehringer Ingelheim, the manufacturer for Roxane Laboratories, Columbus, OH 43216; delaviradine (BHAP, U-90152) available under the RESCRIPTOR tradename from Pharmacia & Upjohn Co., Bridgewater NJ 08807; efavirenz (DMP-266) a benzoxazin-2-one disclosed in WO94/03440 and available under the SUSTIVA tradename from DuPont Pharmaceutical Co., Wilmington, DE 19880-0723; PNU-142721, a furopyridine-thio-pyrimide under development by Pharmacia and Upjohn, Bridgewater NJ 08807; AG-1549 (formerly Shionogi # S-1153); 5-(3,5-dichlorophenyl)- thio-4-isopropyl-1-(4-pyridyl)methyl-IH-imidazol-2-ylmethyl carbonate disclosed in WO 96 /10019 and under clinical development by Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020; MKC-442 (1-(ethoxy-methyl)-5-(1-methylethyl)-6-(phenylmethyl)-(2,4(1H,3H)-pyrimidinedione) discovered by Mitsubishi Chemical Co. and under development by Triangle Pharmaceuticals, Durham, NC 27707; and (+)-calanolide A (NSC-675451) and B, coumarin derivatives disclosed in NIH U.S. Patent No. 5,489,697, licensed to Med Chem Research, which is co-developing (+) calanolide A with Vita-Invest as an orally administrable product.

[0031] The term "protease inhibitor" ("PI") as used herein means inhibitors of the HIV-1 protease, an enzyme required for the proteolytic cleavage of viral polyprotein precursors (e.g., viral GAG and GAG Pol polyproteins), into the individual functional proteins found in infectious HIV-1. HIV protease inhibitors include compounds having a peptidomimetic structure, high molecular weight (7600 daltons) and substantial peptide character, e.g. CRIXIVAN(available from Merck) as well as nonpeptide protease inhibitors e.g., VIRACEPT (available from Agouron).

[0032] Typical suitable PIs include saquinavir (Ro 31-8959) available in hard gel capsules under the INVIRASE tradename and as soft gel capsules under the FORTOUASE tradename from Roche Pharmaceuticals, Nutley, NJ 07110-1199; ritonavir (ABT-538) available under the NORVIR tradename from Abbott Laboratories, Abbott Park, IL 60064; indinavir (MK-639) available under the CRIXIVAN tradename from Merck & Co., Inc., West Point, PA 19486-0004; nelfnavir (AG-1343) available under the VIRACEPT tradename from Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020; amprenavir (141W94), tradename AGENERASE, a nonpeptide protease inhibitor under development by Vertex Pharmaceuticals, Inc., Cambridge, MA 02139-4211 and available from Glaxo-Wellcome, Research Triangle, NC under an expanded access program; lasinavir (BMS-234475) available from Bristol-Myers Squibb, Princeton, NJ 08543 (originally discovered by Novartis, Basel, Switzerland (CGP-61755); DMP-450, a cyclic urea discovered by Dupont and under development by Triangle Pharmaceuticals; BMS-2322623, an azapeptide under development by Bristol-Myers Squibb, Princeton, NJ 08543, as a 2nd-generation HIV-1 PI; ABT-378 under development by Abbott , Abbott Park, IL 60064; and AG-1549 an orally active imidazole carbamate discovered by Shionogi (Shionogi #S-1153) and under development by Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020.

[0033] Other antiviral agents include hydroxyurea, ribavirin, IL-2, IL-12, pentafuside and Yissum Project No. 11607. Hydroxyurea (Droxia), a ribonucleoside triphosphate reductase inhibitor, the enzyme involved in the activation of T-cells, was discovered at the NCI is under development by Bristol-Myers Squibb; in preclinical studies, it was shown to have a synergistic effect on the activity of didanosine and has been studied with stavudine. IL-2 is disclosed in Ajinomoto EP-0142268 , Takeda EP-0176299, and Chiron U.S. Patent Nos. RE 33653, 4530787, 4569790, 4604377, 4748234, 4752585, and 4949314 is available under the PROLEUKIN (aldesleukin) tradename from Chiron Corp., Emeryville, CA 94608-2997 as a lyophilized powder for IV infusion or sc administration upon reconstitution and dilution with water; a dose of about 1 to about 20 million IU/day, sc is preferred; a dose of about 15 million IU/day, sc is more preferred. IL-12 is disclosed in WO6/25171 and is available from Roche Pharmaceuticals, Nutley, NJ 07110-1199 and American Home Products, Madison, NJ 07940; a dose of about 0.5 microgram/kg/day to about 10 microgram/kg/day, sc is preferred. Pentafuside (DP-178, T-20) a 36-amino acid synthetic peptide, disclosed in U.S. Patent No.5,464,933 licensed from Duke University to Trimeris which is developing pentafuside in collaboration with Duke University; pentafuside acts by inhibiting fusion of HIV-1 to target membranes. Pentafuside (3-100 mg /day) is given as a continuous sc infusion or injection together with efavirenz and 2 PI's to HIV-1 positive patients refractory to a triple combination therapy; use of 100 mg/day is preferred. Yissum Project No. 11607, a synthetic protein based on the HIV -1 Vif protein, is under preclinical development by Yissum Research Development Co., Jerusalem 91042 , Israel. Ribavirin, 1-β-D-ribofuranosyl-1 H-1,2,4-triazole-3-carboxamide, is available from ICN Pharmaceuticals, Inc., Costa Mesa, CA; its manufacture and formulation are described in U.S. Patent No. 4,211,771.

[0034] The term "anti-HIV-1 therapy" as used herein means any anti-HIV-1 drug found useful for treating HIV-1 infections in man alone, or as part of multidrug combination therapies, especially the HAART triple and quadruple combination therapies. Typical suitable known anti-HIV-1 therapies include, but are not limited to multidrug combination therapies such as (i) at least three anti-HIV-1 drugs selected from two NRTIs, one PI, a second PI, and one NNRTI; and (ii) at least two anti-HIV-1 drugs selected from , NNRTIs and Pis. Typical suitable HAART - multidrug combination therapies include:

> (a) triple combination therapies such as two NRTIs and one PI ; or (b) two NRTIs and one NNRTI ; and (c) quadruple combination therapies such as two NRTIs , one PI and a second PI or one NNRTI. In treatment of naive patients, it is preferred to start anti-HIV-1 treatment with the triple combination therapy; the use of two NRTIs and one PI is preferred unless there is intolerance to PIs. Drug compliance is essential. The CD4$^+$ and HIV-1-RNA plasma levels should be monitored every 3-6 months. Should viral load plateau, a fourth drug,e.g., one PI or one NNRTI could be added. See the table below wherein typical therapies are further described:

ANTI-HIV-1 MULTI DRUG COMBINATION THERAPIES

A. Triple Combination Therapies

[0035]

1. Two NRTIs[1] + one PI[2]
2. Two NRTIs[1] + one NNRTI[3]

B. Quadruple Combination Therapies[4]

[0036] Two NRTIs + one PI + a second PI or one NNRTI

C. ALTERNATIVES:[5]

[0037] Two NRTI[1]
[0038] One NRTI[5] + one PI[2]
[0039] Two PIs[6] ± one NRTI[7] or NNRTI[3]
[0040] One PI[2] + one NRTI[7] + one NNRTI[3]

FOOTNOTES TO TABLE

[0041]

1. One of the following: zidovudine + lamivudine; zidovudine + didanosine; stavudine + lamivudine; stavudine + didanosine; zidovudine + zalcitabine
2. Indinavir, nelfinavir, ritonavir or saquinavir soft gel capsules.
3. Nevirapine or delavirdine.
4. See A-M. Vandamne et al Antiviral Chemistry & Chemotherapy 9:187 at p 193-197 and Figures 1 + 2.
5. Alternative regimens are for patients unable to take a recommended regimen because of compliance problems or toxicity, and for those who fail or relapse on a recommended regimen. Double nucleoside combinations may lead to HIV- resistance and clinical failure in many patients.
6. Most data obtained with saquinavir and ritonavir (each 400 mg bid).
7. Zidovudine, stavudine or didanosine.

[0042] Agents known in the treatment of rheumatoid arthritis, transplant and graft v. host disease, inflammatory bowel disease and multiple sclerosis which can be administered in combination with the CCR5 antagonists of the present invention are as follows:

solid organ transplant rejection and graft v. host disease: immune suppressants such as cyclosporine and Interleukin-10 (IL-10), tacrolimus, antilymphocyte globulin, OKT-3 antibody, and steroids;
inflammatory bowel disease: IL-10 (see US 5,368,854), steroids and azulfidine;
rheumatoid arthritis: methotrexate, azathioprine, cyclophosphamide, steroids and mycophenolate mofetil;
multiple sclerosis: interferon-beta, interferon-alpha, and steroids.

[0043] Certain compounds of the invention may exist in different isomeric forms (e.g., enantiomers, diastereoisomers, atropisomers and rotamers). The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures.

[0044] Certain compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

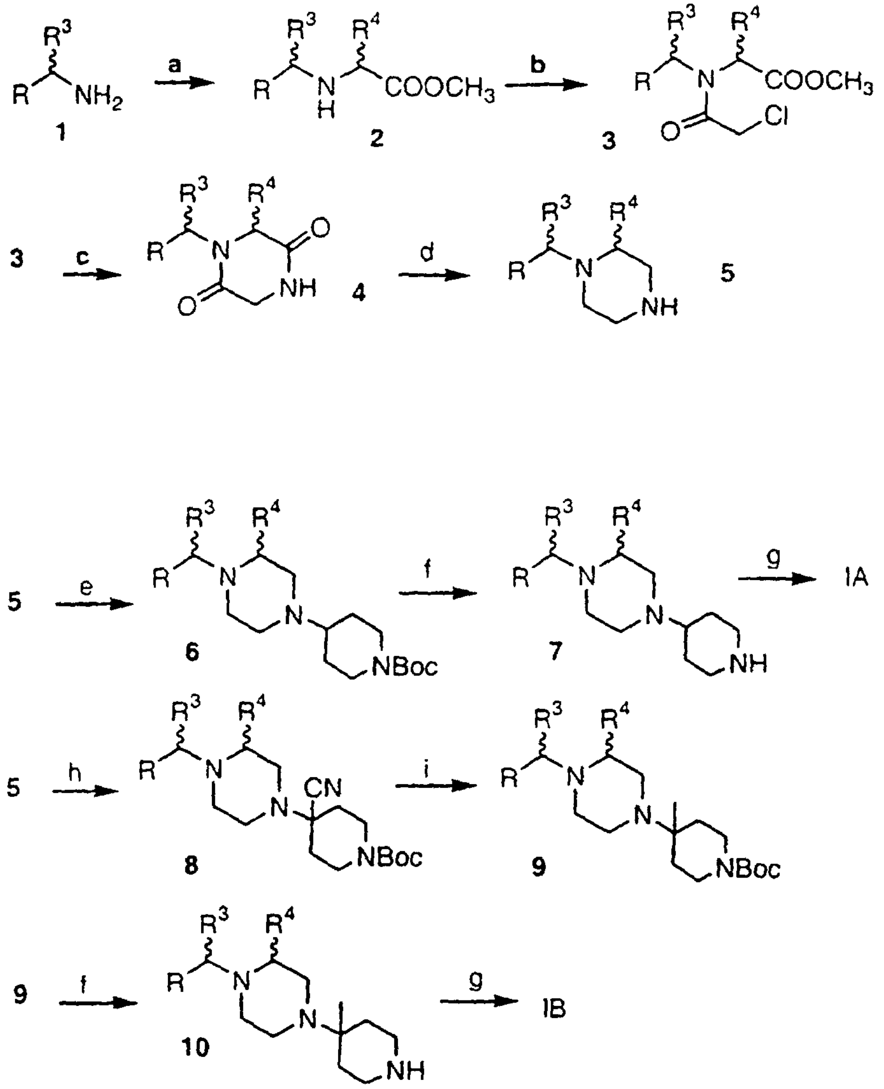
[0045] Certain basic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

[0046] All such acid 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.

[0047] Compounds of the invention can be made by the procedures known in the art, for example by the procedures described in the following reaction schemes, by the methods described in the examples below, and by using the methods described in WO96/26196 and WO98/05292.

[0048] The following solvents and reagents may be referred to herein by the abbreviations indicated: tetrahydrofuran (THF); ethanol (EtOH); methanol (MeOH); acetic acid (HOAc or AcOH); ethyl acetate (EtOAc); N,N-dimethylformamide (DMF); trifluoroacetic acid (TFA); 1-hydroxybenzotriazole (HOBT); m-chloroperbenzoic acid (MCPBA); triethylamine (Et_3N); diethyl ether (Et_2O); dimethylsulfoxide (DMSO); and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (DEC). RT is room temperature, and TLC is thin-layer chromatography. Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl, Ph is phenyl, and Ac is acetyl.

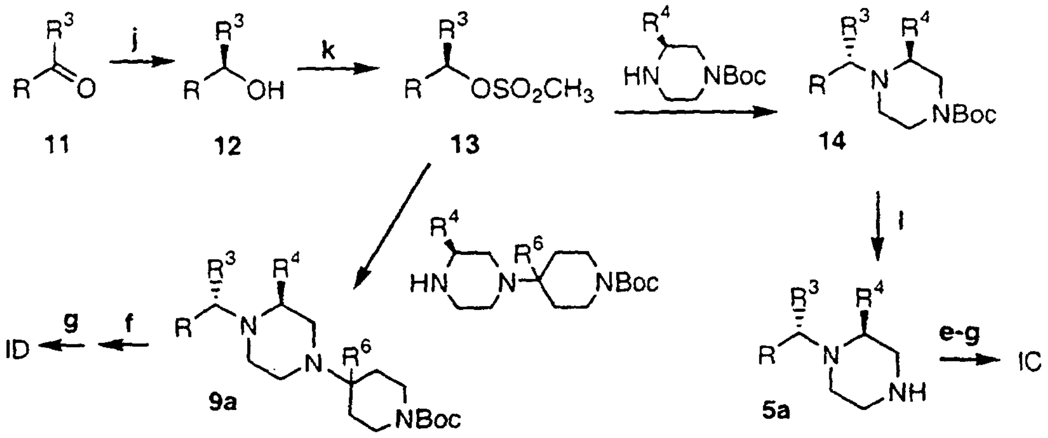
Scheme 1



Reagents and conditions: a: $R^4CH(OSO_2CF_3)CO_2CH_3$, base (e.g., K_2CO_3); b: $ClCH_2COCl$; c: NH_3; d: $NaBH_4$-BF_3; e: N-Boc-4-piperidone, $NaBH(OAc)_3$; f: CF_3CO_2H; g: acylation; h: N-Boc-4-piperidone, $Ti(OPr\text{-}i)_4$, Et_2AlCN; i: CH_3MgBr.

[0049] In **Scheme 1**, a benzylamine (**1**), wherein R and R^3 are as defined above and R^1 is hydrogen, is converted via (**2**) and (**3**) to the diketopiperazine (**4**), wherein R^4 is as defined above, which is reduced to the piperazine (**5**). Depending upon the desired R^6 substituent, this is processed in two ways. Reductive amination gives (**6**), which can be deprotected to (**7**) and finally acylated to the compounds of formula IA wherein R^5 and R^6 are H; alternatively, a modified Strecker reaction on (**5**) gives the aminonitrile (**8**), which, after treatment with methyl Grignard to give (**9**), deprotection to (**10**) and final N-acylation affords the compounds of formula IB wherein R^5 is H and R^6 is methyl. Acylation of (**7**) and (**10**) is carried out under standard conditions, e.g., with a compound R^2COOH and reagents such as DEC and HOBT. Use of a chiral compound of formula **1**, e.g., (S)-methyl 4-substituted benzylamine, and a chiral lactate in step **a**, e.g., methyl (R)-lactate triflate, will result in chiral compounds of formulas IA and IB.

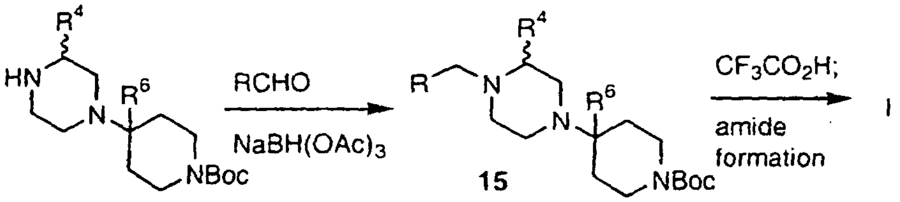
Scheme 2



Reagents: j: oxaborazolidine, BH_3; k: CH_3SO_2Cl, base; l: CF_3CO_2H.

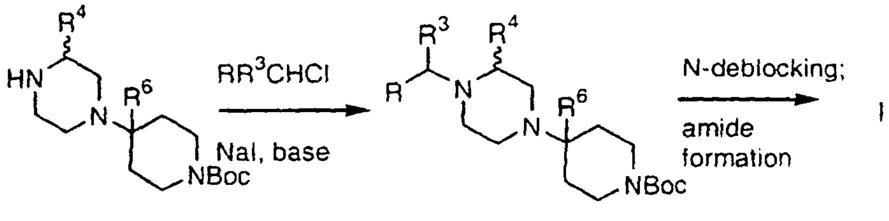
[0050] In **Scheme 2,** the compounds are prepared by an alkylation process on a pre-formed piperazine derivative. For example, preferred compounds with the S,S stereochemistry may be obtained in this way by chiral reduction of a ketone **(11)** to the alcohol **(12),** activation as the mesylate, and displacement with inversion by treatment with a suitable piperazine, which may either be mono-protected, in which case final elaboration requires deprotection followed by the steps described in **(e) - (g)** in Scheme 1 to obtain IC, or may be elaborated prior to the displacement step, in which case the final steps are **(f)** and **(g)** (deprotection and acylation) as in Scheme 1 to obtain ID.

Scheme 3



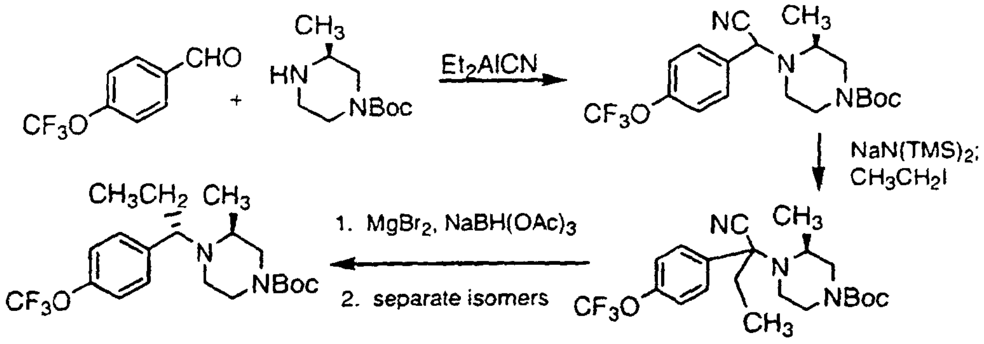
[0051] For compounds where R^3 and R^1 are each H, either the alkylation route of Scheme 2 or a reductive amination method as typified in Scheme 3 can be used.

Scheme 4

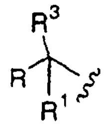


[0052] For diaryl compounds, wherein R and R^3 are each aryl, an alkylation method as typified in Scheme 4 is preferrred.

Scheme 5

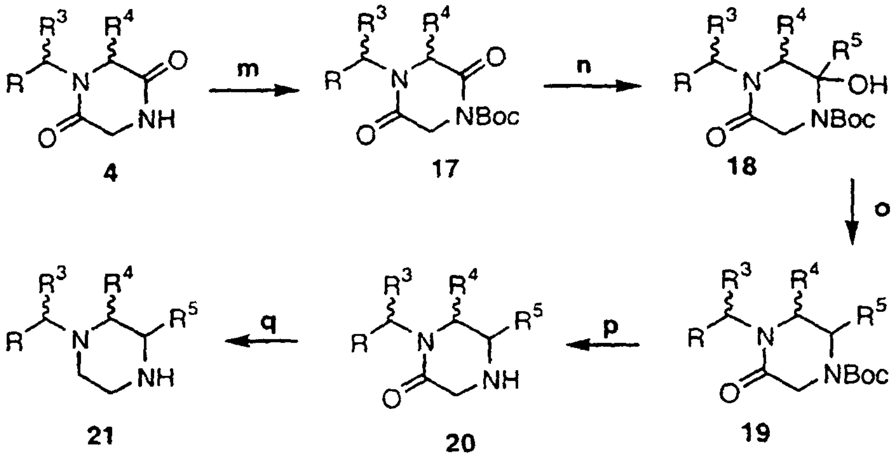


[0053] Piperazines of formula 14, especially those wherein R^3 is C_2-C_6 alkyl or benzyl, may also be obtained by a process wherein the



portion is introduced as shown above by an alkylation-decyanation sequence. The reaction is exemplified for compounds wherein R is CF_3O-phenyl, R^1 is hydrogen, R^3 is ethyl and R^4 is methyl, but using appropriate starting materials, other compounds of formula 14 can be similarly prepared.

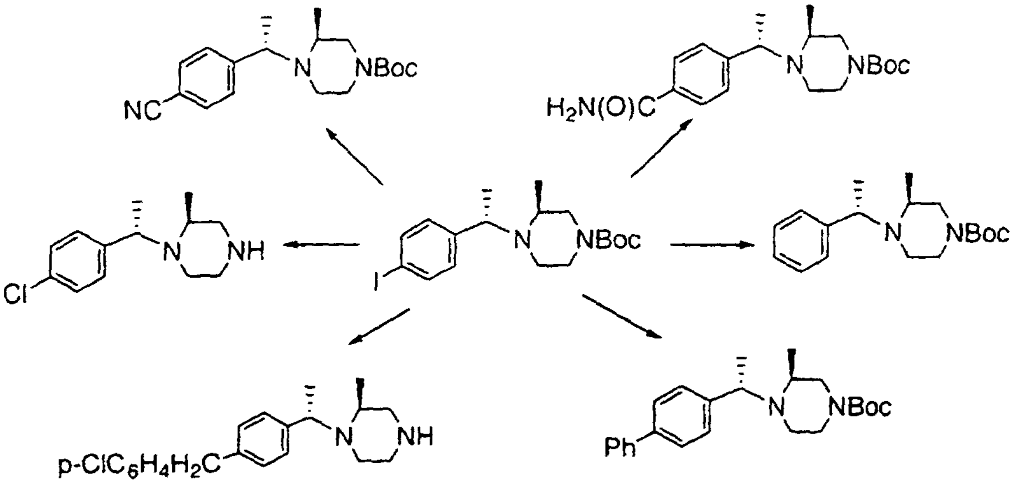
Scheme 6



Reagents: m: BOC_2O, base; n: R^6MgBr; o: CCl_3CO_2H, $NaBH_3CN$; p: CF_3CO_2H; q: $NaBH_4$, BF_3.

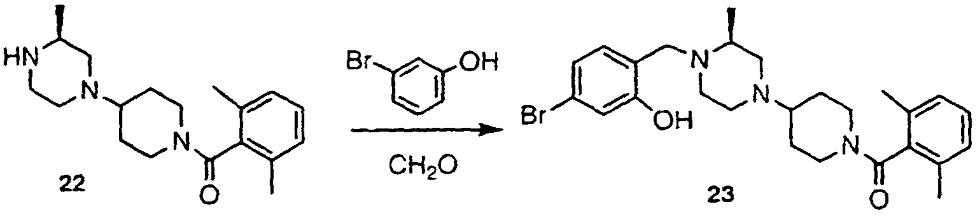
[0054] As shown in Scheme 6, compounds bearing an additional alkyl group at R^5 on the piperazine ring may be prepared from the diketopiperazine intermediates (**4**) of Scheme 1. (**4**) is activated by conversion to the N(t-butoxycarbonyl) compound (**17**); addition of a Grignard reagent and sequential reduction, deprotection and lactam reduction provides (**21**), which can be used to prepare compounds of formula I in the manner described for intermediate (**5**) in Scheme 1.

Scheme 7



[0055] Many piperazines wherein R is R^8-phenyl (or their Boc derivatives) shown in Scheme 1 can be obtained from a common intermediate, wherein R^8 is I. Several examples are shown in the above scheme, wherein R^8 is converted to Cl, CN, $-C(O)NH_2$, H, Ph and $p\text{-}ClC_6H_4CH_2\text{-}$. Detailed procedures for these conversions are provided in the examples below. The resultant piperazine or BOC-piperazine is then treated as shown in Scheme 1.

Scheme 8



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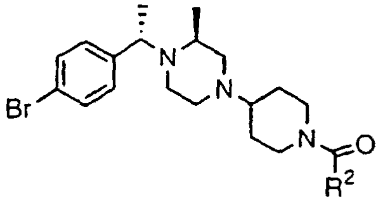
[0056] Some compounds of the invention may be obtained by a Mannich method, as shown in the specific example of Scheme 8.

[0057] Compounds useful in this invention are exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

Example 1

[0058]



A. $R^2 = 2,6\text{-}Me_2\text{-}C_6H_3$
B. $R^2 = 2\text{-}Me\text{-}6\text{-}NH_2\text{-}C_6H_3$
C. $R^2 = 2\text{-}NH_2\text{-}6\text{-}Cl\text{-}C_6H_3$

Step 1 : Stir methyl R-lactate (5.0 g) in CH_2Cl_2 (40 ml) at -70° C and add trfluoromethanesulfonic anhydride (7.6 ml), then 2,6-lutidine (7.8 ml).

Remove the cooling, stir 0.5h, wash with 2N HCl and add the organic solution to (S)-methyl 4-bromobenzylamine (9.0 g) and K_2CO_3 (11.2 g) in water (60 ml). Stir 20h at RT, dry the organic phase over K_2CO_3, evaporate and chromatograph on silica gel with $Et_2O\text{-}CH_2Cl_2$ to give the desired product (7.50 g) as a thick oil.

Step 2: Reflux the product of step 1 (7.5 g) in 1,2-dichloroethane (40 ml) and $ClCH_2COCl$ (5.0 ml) for 5h, then evaporate and use the resultant residue directly in the next step.

Step 3: Stir the product of step 2 in DMSO (80 ml), water (10 ml) and NaI (8 g), cool in ice, add conc. NH_4OH solution (15 ml) and stir to RT for 20h.

Add water (200 ml) dropwise, collect the solid, wash well with water and dry at 70° C/ 5 mm to give the diketopiperazine, suitable for the next step.

Step 4: Stir a mixture of the product of step 3 (6.8 g), 1,2-dimethoxyethane (60 ml) and $NaBH_4$ (3.4 g) under N_2, add $BF_3 \cdot OEt_2$ (6.8 ml) dropwise, then heat at 100° C for 10h. Cool and add CH_3OH (20 ml) dropwise, followed by conc. HCl (30 ml). Heat at 100° C for 1h., cool, basify with excess 2N NaOH and extract with EtOAc. Dry over K_2CO_3 and evaporate to obtain the piperazine (5.85 g), suitable for the next step.

Step 5: Stir for 20h. at RT a mixture of the product of step 4 (5.48 g), N-Boc-4-piperidinone (4.32 g), HOAc (1.15 ml), CH_2Cl_2 (80 ml) and sodium triacetoxy-borohydride ($NaBH(OAc)_3$) (8.3 g). Add excess aqueous Na_2CO_3 solution slowly, stir for 0.5h, separate and filter the organic phase through a pad of silca gel, washing with 10:1 CH_2Cl_2-Et_2O to elute all of the product. Evaporate and dissolve the residue in Et_2O (100 ml). Stir and add a 4M solution of HCl in 1,4-dioxane (10 ml) dropwise. Collect the solid, wash with Et_2O, and stir with CH_2Cl_2 and excess aqueous NaOH. Dry the organic phase over K_2CO_3 and evaporate to obtain the desired product (5.45 g).

Step 6: Stir at RT for 2h a mixture of the product of step 5 (1.5 g) and TFA (4 ml). Evaporate, dissolve in CH_2Cl_2 and wash with excess 1N NaOH solution. Dry over K_2CO_3 and evaporate to obtain the product (1.15 g).

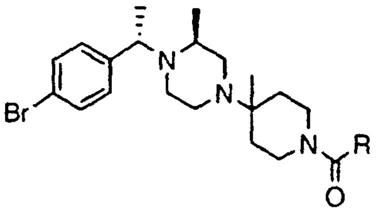
Compound 1A: Following the standard procedure, react the product of step 6 with 2,6-dimethylbenzoyl chloride in CH_2Cl_2 and aqueous NaOH, and convert the product to the hydrochloride. Mp 185-192° C (decomposition). HRMS found: 498.2130; MH^+ Calc: 498.2120.

Compound 1B: Following the standard procedure, couple the product of step 6 with 2-amino-6-methylbenzoic acid using HOBT and DEC with diisopropylethylamine in DMF, purify the amide by preparative TLC and convert to the hydrochloride. Mp 188-196° C (decomposition). HRMS found: 499.2069; MH^+ Calc: 499.2072.

Compound 1C: Following the above method, couple the product of step 6 with 2-amino-6-chlorobenzoic acid and convert after purification to the hydrochloride. Mp 192-200° C (decomposition). HRMS found: 519.1530; MH^+ Calc: 519.1526.

Example 2

[0059]



A. $R^2 = 2,6\text{-}Me_2C_6H_3$
B. $R^2 = 2\text{-}NH_2\text{-}6\text{-}Cl\text{-}C_6H_3$
C. $R^2 = 2\text{-}Me\text{-}6\text{-}OH\text{-}C_6H_3$
D. $R^2 = 2\text{-}Me\text{-}6\text{-}NH_2C_6H_3$

Step 1: Stir the product of Example 1, step 4 (1.00 g), N-t-butoxycarbonyl-4-piperidinone (0.77 g) and titanium (IV) isopropoxide ($Ti(OiPr)_4$) (1.00 g) for 20h at RT in CH_2Cl_2 (15 ml), reflux for 3h and cool to RT. Add diethylaluminum cyanide (Et_2AlCN) (4.2 ml of 1M toluene solution) and the stir for 5 days at RT under dry N_2. Workup in CH_2Cl_2-aq. NaOH, dry and evaporate the organic phase and chromatograph on silica gel with CH_2Cl_2-CH_3OH (100:1) to obtain the desired product (0.72 g).

Step 2: React the product of step 1 (0.70 g) in dry THF (15 ml) under N_2 with CH_3MgBr (4 ml of 3M Et_2O solution) at RT for 20h. Workup in EtOAc-water and filter the organic phase through silica gel, washing with EtOAc. Evaporate to obtain the desired product (0.65 g).

Step 3: Deprotect the product of step 2 with TFA according to the procedure described in Example 1, step 6.

Compound 2A: React the product of step 3 with dimethylbenzoyl chloride as described in Example 1 and convert to the HCl salt. Mp 180-187° C (decomposition). HRMS Found: 512.2272; MH^+ Calc: 512.2276.

Compound 2B: React the product of step 3 with 2-amino-6-chlorobenzoic acid as described in Example 1, purify the crude product by preparative TLC and convert to the HCl salt. Mp 195-200° C (decomposition). HRMS Found: 535.1662; MH^+ Calc: 535.1652.

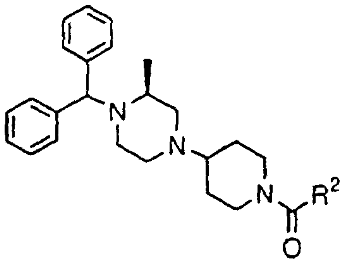
Compound 2C: React the product of step 3 with 2-hydroxy-6-methylbenzoic acid as described in Example 1, purify the crude product by preparative TLC and convert to the HCl salt. Mp 206-210° C (decomposition).

HRMS Found: 514.2067; MH^+ Calc: 514.2069.

Compound 2D: React the product of step 3 with 2-amino-6-methylbenzoic acid using a procedure similar to that described in Example 1, purify the crude product by preparative TLC and convert to the HCl salt. Mp 202-209° C (decomposition). HRMS Found: 513.2227; MH^+ Calc: 513.2229.

Example 3

[0060]



A. R^2 = 2,6-di-Me-C_6H_3
B. R^2 = 2-NH_2-6-Cl-C_6H_3
C. R^2 = 2,4-di-Me-3-pyridyl

Step 1: Reflux and stir a mixture of S-alanine methyl ester hydrochloride (14 g), anhydrous Na_2CO_3 (60 g), dry CH_3CN (125 ml), chlorodiphenylmethane (22.3 g) and NaI (5 g) for 6 hr. Cool, add ice-H_2O and extract with Et_2O (350 ml, then 50 ml). Combine the Et_2O extracts and wash with portions of 1N aq. HCl: 200 ml, 100 ml, then 4 x 10 ml. Combine the aqueous acid extracts, stir and add excess Na_2CO_3 in small poprtions until the mixture is basic. Extract with Et_2O, dry over $MgSO_4$ and evaporate to obtain the N-diphenylmethyl compound (23.2 g).

Step 2: Reflux all of the above compound with $ClCH_2COCl$ (10 ml) in dichloroethane (60 ml) for 4 h. Evaporate, and co-evaporate with toluene (20 ml). Dissolve the residue in CH_2Cl_2 (200 ml), stir for 0.5 h with activated carbon (10 g), filter and evaporate. Stir the residue with ice cooling in DMSO (200 ml) and gradually add concentrated aqueous NH_3 (100 ml), then NaI (10 g). Stir at RT for 20 hr. Add iced water (500 ml), collect the solid, wash well with water, then with several small portions of a 10:1 hexane-Et20 mixture, and dry at 50° C with high vacuum to obtain the solid diketopiperazine (15.5 g). Recrystallise a small sample from CH_2Cl_2-hexanes: mp 186-188° C; $[\alpha]_D^{20} = +272.6°$.

Step 3: Stir the product of step 2 (4.0 g) in dimethoxyethane (40 ml) and $NaBH_4$ (1.6 g) under N_2 and add $BF_3 \cdot OEt_2$ (3.2 ml) slowly. Reflux for 20 h. Cool and add CH_3OH (10 ml) dropwise, then conc. HCl (15 ml). Reflux for 2 h., and work up in excess 2N aq. NaOH and extract with CH_2Cl_2. Dry over K_2CO_3 and evaporate. Chromatograph on silica, eluting with CH_2Cl_2-CH_3OH mixtures, and finally with 5:1:0.1 v/v/v CH_2Cl_2:CH_3OH:NH_4OH. Combine and evaporate the product fractions to obtain the desired product (1.95 g) as a pale yellow gum.

Step 4: Stir a mixture of the product of step 3 (0.50 g), N-allyloxycarbonyl-4-piperidone (0.40 g), CH_2Cl_2 (5 ml) and $NaBH(OAc)_3$ (0. 70 g) at RT for 20 h. Work up in CH_2Cl_2 and excess aq. NaOH, dry over $MgSO_4$, evaporate and isolate the product by preparative TLC, eluting with 10% Et_2O in CH_2Cl_2, to obtain the desired compound (0.80 g) as an oil, contaminated with a small amount of starting ketone, but suitable for the next step.

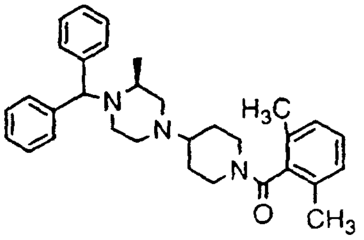
Step 5: Stir a mixture of the product of step 4 (0.80 g), CH_3CN (20 ml), water (5 ml) and piperidine (1.5 ml). Add tri(4-sulfophenyl)phosphine (0.072 g) and palladium (II) acetate (0.02 g) and stir at RT under N_2 for 2 h. Work up with aqueous NaOH, extract with 5:1 v/v toluene:CH_2Cl_2, dry over K_2CO_3 and evaporate to obtain a yellow oil, suitable for acylation.

Compound 3A: Stir and reflux a mixture of the product of step 5 (0.10 g), N-(2,6-dimethoxybenzoyl)-4-piperidinone (0.10 g), CH_2Cl_2 (2 ml) and $NaBH(OAc)_3$ (0.15 g) for 2.5 h., cool, and work up with CH_2Cl_2 and aqueous NaOH. Dry over $MgSO_4$, evaporate and isolate the major product by preparative TLC, eluting with 3:1 v/v Et_2O:CH_2Cl_2. Precipitate the hydrochoride to obtain the desired compound as the HCl salt (0.13 g). Mp 173-177° C (decomposition). HRMS Found: 482.3175; MH^+ Calc: 482.3171.

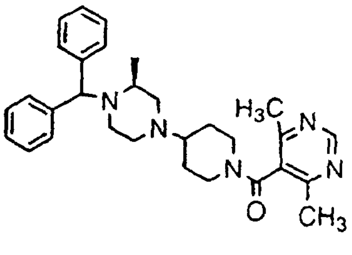
Compound 3B: Couple the product of step 5 with 2-amino-6-chlorobenzoic acid using DEC-HOBT as described in Example 1, isolate the product by PTLC and precipitate the hydrochloride to give compound 3B. Mp 188-195° C (decomposition). HRMS Found: 503.2567; MH^+ Calc: 503.2578.

Compound 3C: Couple the product of step 5 with 2,4-dimethylnicotinic acid using DEC-HOBt as described above, isolate the product by PTLC and precipitate the hydrochloride to give compound 3C. Mp 180-188° C (decomposition). HRMS Found: 483.3114; MH^+ Calc: 483.3124.

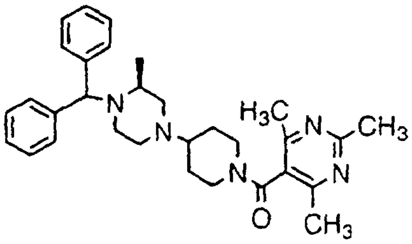
[0061] Using procedures similar to those described above, the following compounds were prepared:



3D: Mp. 85-89°C; HRMS (MH^+) found: 496.3343



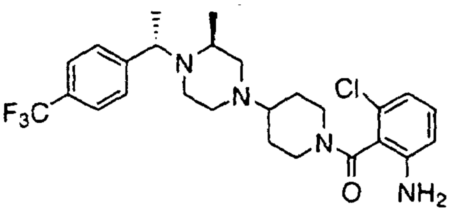
3E; Mp. 170-175°C



3F; Mp. 180-185°C

Example 4

[0062]



Step 1: A solution of 4-trifluoromethyl acetophenone (1.88 g; 10 mmol) in dry THF (10 ml) was cooled in an ice bath and treated with freshly prepared solid (S)-2-methyl oxaborolidine (0.54g; 2 mmol). After 10 min., a solution of 2M borane-methyl sulfide complex (3 ml; 6 mmol) in THF was added dropwise over 5 min. TLC at the end of 30 min. showed that the starting material had been converted to a more polar product. The reaction was quenched with about 5 ml of CH_3OH carefully until effervescence stopped; volatiles were removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed with 1N HCl, water, 10% $NaHCO_3$ solution and brine. Concentration in vacuo gave 2g of a yellow gum. Flash silica gel chromatography (FSGC) using 10-20% EtOAc in hexanes furnished the desired chiral alcohol (1.6 g; 84%) as a colorless oil. TLC
R_f = 0.6 in 25% EtOAc:hexanes.

Step 2: To a solution of the product of step 1 (1.55g; 8.16 mmol) in 10 ml of CH_2Cl_2 cooled in an ice bath were added Et_3N (2.3 ml; 16.32 mmol) and CH_3SO_2Cl (0.87 ml; 10.6 mmol) to form a turbid white solution. The reaction was quenched with water and the organic product was extracted with CH_2Cl_2, washing with water, 1N HCl, 10% $NaHCO_3$ solution and brine. Concentration in vacuo gave the chiral mesylate (2.1 g; 96%) as a pale yellow oil. TLC R_f = 0.6 in 25% EtOAc:hexanes.

Step 3: A solution of the product of step 2 (2.1 g; 7.8 mmol), the N-BOC protected 2(S)-methyl piperazine (1.56g;

7.8 mmol - prepared from the reaction of commercial 2(S)-methyl piperazine with N-(tert-butoxy-carbonyloxy) phthalimide) and 2,2,6,6-tetramethyl piperidine (1.34 ml; 8 mmol) in 14 ml of dry CN_3CN were heated at reflux until TLC indicated complete disappearance of the mesylate (16 h). The reaction mixture was cooled to RT, diluted with CH_2Cl_2 (50 ml) and washed with water (3 x 100 ml) and brine. The organic extract was dried over solid $MgSO_4$ and then concentrated to obtain 2.8 g of a yellow gum. FSGC (20% EtOAc in hexanes) served to isolate the desired (S,S)-diastereomer (1.5g; 52%) and its benzylic epimer, the (R,S)-diastereomer (0.5g; 17%) for a combined 69% yield. TLC R_f = 0.75 (S,S) and 0.56 (R,S) in 25% EtOAc:hexanes.

<u>Step 4:</u> TFA (6 ml) was added to a solution of the product of step 3 in 12 ml of CH_2Cl_2 and the resulting yellow-orange solution was stirred at RT for 8 h. The reaction was quenched by adding 1 N NaOH solution to adjust the pH to 10. Extractive work up in CH_2Cl_2 gave 1.1g of a yellow syrup. FSGC using 10% CH_3OH in CH_2Cl_2 removed the less polar impurity and gradient elution with 1 % Et_3N in 10% $CH_3OH:CH_2Cl_2$ was needed to elute the desired free amine of the (S,S) diastereomer. Yield = 0.9g (75%). TLC R_f = 0.5 in 10% $CH_3OH:CH_2Cl_2$.

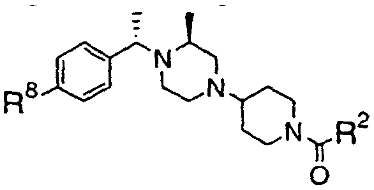
<u>Step 5:</u> A colorless solution of the product of step 4 (0.9g; 3.3 mmol), 4-piperidinone (0.86g; 4.3 mmol), $NaB(OAc)_3H$ (1.05g; 4.95 mmol) and glacial AcOH (80 µl) in 8 ml of CH_2Cl_2 was stirred at ambient temperature for a day. TLC indicated absence of starting material. The reaction mixture was diluted with 50 ml of CH_2Cl_2, washed with 1 N NaOH solution, water (2 x) and brine. The CH_2Cl_2 extract was dried over anhydrous $MgSO_4$ and concentrated to obtain 1.7g of yellow oil. FSGC (25% acetone in hexanes) was used to isolate the pure product (1.3g; 86%) as a white foam. TLC R_f = 0.6 in 25% acetone/hexanes.

<u>Step 6:</u> TFA (5 ml) was added to a solution of the product of step 5 (1.3g; 2.87 mmol) in CH_2Cl_2 (10 ml) and the resulting yellow orange solution was stirrred at RT for 7 h. The reaction was quenched with 1N NaOH solution and the pH was adjusted to 10. The organic product was extracted into 50 ml of CH_2Cl_2 and washed with water, then brine and dried over $MgSO_4$. Concentration gave the free amine (0.98g; 98%) as a yellow syrup. TLC R_f = 0.1 in 25% acetone/hexanes.

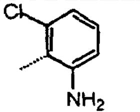
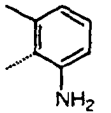
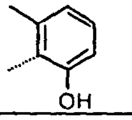
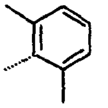
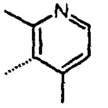
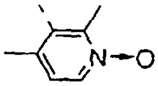
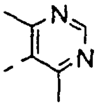
<u>Step 7:</u> The product of step 6 (0.78g; 2.21 mmol), DEC (0.65g; 3.4 mmol), HOBT (0.46g; 3.4 mmol) and 2-amino-6-chloro benzoic acid (0.51g; 2.9 mmol) were dissolved in 8 ml of CH_2Cl_2 to which was added diisopropylethyl amine (0.7 ml) and the mixture was stirred at ambient temperature for 16h. TLC analysis showed absence of starting material and formation of two over-lapping spots of medium polarity (rotomers of the hindered amide) as the major product. The crude product (1.3g) was isolated by extractive work up and purified through FSGC using 25% acetone in CH_2Cl_2 as eluant to give the title compound (0.88g; 80%) as a pale yellow foam. TLC R_f = 0.45 and 0.5 in 25% acetone:CH_2Cl_2.

[0063] A solution of hydrogen chloride in Et_2O (1 M; 3 ml) was added to a solution of the title compound free base (0.76g; 1.54 mmol) in CH_2Cl_2 (5ml) to obtain an instantaneous white precipitate. After stirring at RT for 2 h, the volatiles were removed on a rotary evaporator and the white residue was suspended in dry toluene (3 x 10 ml) and azeotroped. The white solid thus obtained was suspended in dry Et_2O containing 10% EtOAc, stirred for 30 min, filtered and washed with Et_2O (100 ml). The HCl salt of the title compound was dried under high vacuum to yield an off-white solid (0.88g; 95%). Mp: 205-210° C.

[0064] The product of step 6 was converted to other amides (4A-4E) as described in step 7 using the appropriate carboxylic acids. Physical data for compounds 4-4E having the following structures is as follows:

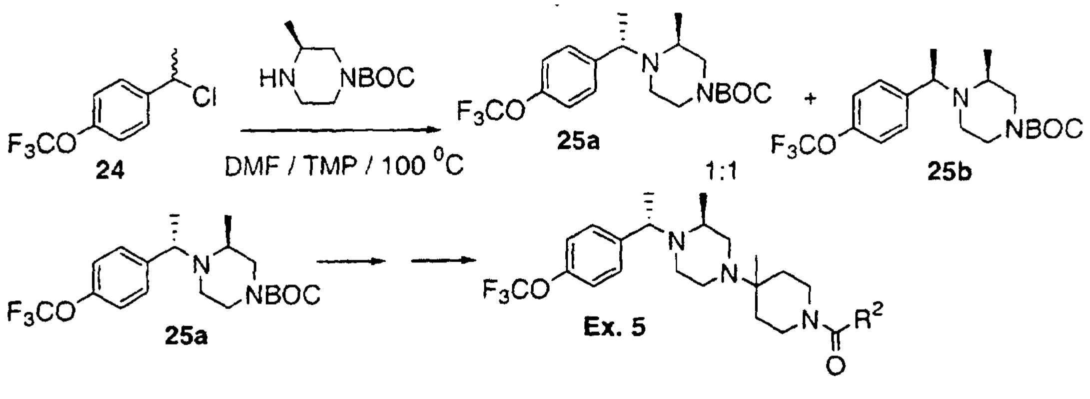


wherein R^8 and R^2 are as defined in the table:

Ex.	R^8	R^2	Mp (^{0} C)	HRMS (MH^+)
4	CF_3		205-210	509.2295
4A	CF_3		192-195	489.2841
4B	CF_3		203-206	490.2681
4C	CF_3		186-190	488.2902
4D	CF_3		207-210	489.2851
4E	CF_3		152	505
4F	CF_3		--	490.2796

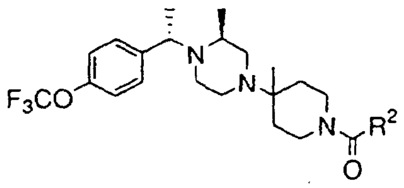
Example 5

[0065]

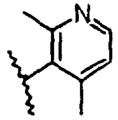
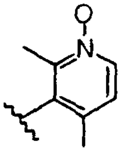
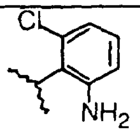
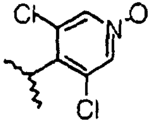
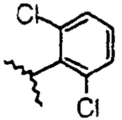
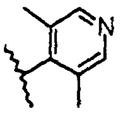
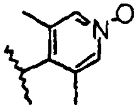
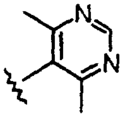
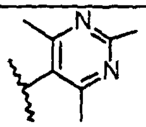


[0066] A solution of the racemic benzyl chloride **24** (1.26g, 5.62 mmol) which was prepared freshly from the corresponding carbinol, the 2(S)-methyl piperazine (1.12g, 5.62 mmol) and 2,2,6,6-tetramethyl piperidine (TMP) (1.9 ml, 11.2 mmol) were dissolved in dry DMF (2 ml) and heated to 100-110°C (internal temp.) for 10 h. TLC analysis showed absence of **24** and formation of two well-separated products. The mixture was diluted with water and the organics were extracted into Et_2O. The organic extract was washed with saturated NH_4Cl and brine and concentrated in vacuo to obtain 2 g of crude product. Flash chromatography on silica gel and elution first with 25% Et_2O-hexane followed by 25% EtOAc-hexane gave -0.5 grams of **25a** and -0.5 grams of **25b** respectively (-45% combined yield). TLC $R_f = 0.6$ (for **25a**) and 0.4 (for **25b**) in 25% EtOAc-hexanes.

Purified **25a** was treated as described previously to obtain the final products 5 to 5F having the formula

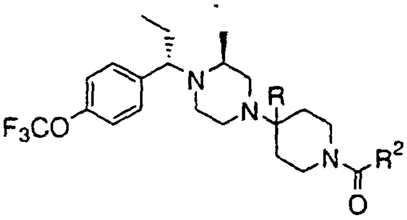


wherein R^2 is as defined in the table:

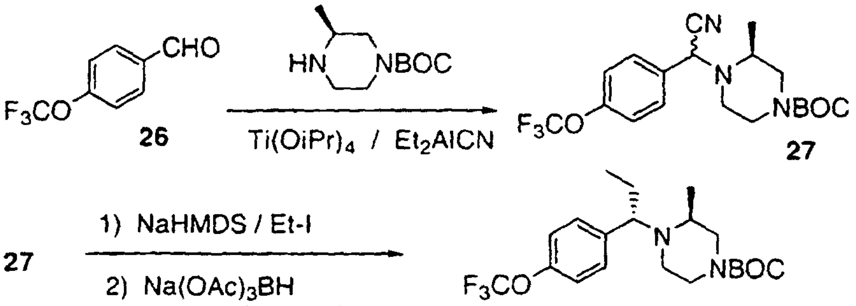
Ex.	R^2	mp (^{0}C)	HRMS
5		208-212	519.2958
5A		198-203	535.2913
5B		233 (sharp)	539.2390
5C		190	575.1800
5D		253	558.1887
5E		202	519.2964
5F		190	535.2901
5G		198-203	--
5H		205-210	--

Example 6

[0067]



Step 1:



26

27

27

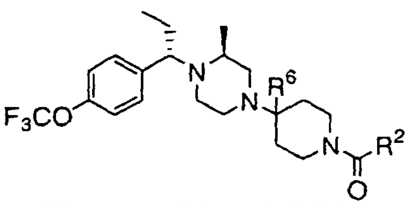
28a. (S,S)-Diastereomer
28b. (R,S)-Diastereomer

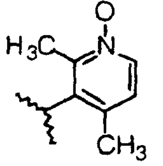
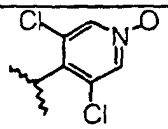
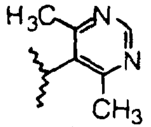
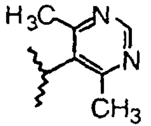
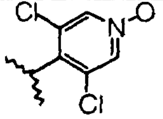
A mixture of the aldehyde **26** (3.9g, 20.5 mmol), the 2(S)-methyl-N-BOC-piperazine (4.1 g, 20.5 mmol) and Ti(OiPr)$_4$ (6.1 mL; 20.5 mmol) in 40 ml of CH_2Cl_2 was stirred at RT for 24 h. Et_2AlCN was introduced and stirred for an additonal day. The reaction mixture was processed as described before to obtain 4.71 grams (58%) of the cyano amine **27** after FSGC (TLC R_f = 0.45/0.5 for diastereomers seen with 25% Et_2O-hexanes as solvent).

Step 2: Sodium hexamethyldisilazide (1M; 3.1 ml) was added to a solution of **27** (1g; 2.5 mmol) in dry THF cooled in a dry ice/acetone bath. The resulting bright yellow solution was treated with CH_3CH_2I (7.5 mmol; 0.6 ml). The dry ice bath was removed and the reaction was stirred at ambient temperature for 15 min. followed by gentle warming in a warm water bath (40°C) for 30 min. TLC indicated two well-separated spots. Standard extractive work up and purification by FSGC gave two alkylated compounds (combined yield: 0.7g; 70%). TLC R_f = 0.6 and 0.4 (25% EtOAc/hexanes).

Step 3: The product of step 2 was stirred with $NaBH(OAc)_3$ (2x) and $MgBr_2$:OEt_2 (1x) in CH_3CN for a day. The reaction mixture was quenched with water, the organics were extracted into EtOAc and processed to obtain 0.8 grams of crude product. FSGC (25% EtOAc-hexanes) gave -0.4 grams of each diastereomer (combined yield -100%). TLC R_f = 0.55 (**28a**) and 0.45 (**28b**) in 25% EtOAc-hexanes.

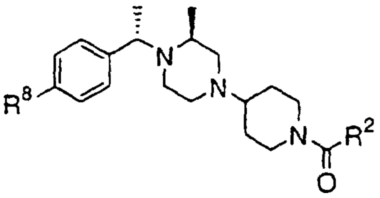
Step 4: Compound **28a** (S,S-diastereomer) was processed through the usual 5 step sequence to complete the synthesis of compounds of Example 6, 6A and 6B with an ipso-methyl group as well as compounds 6C and 6D which lack the ipso-methyl group:



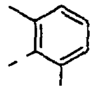
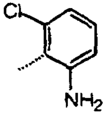
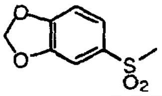
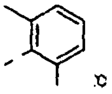
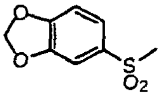
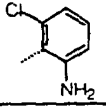
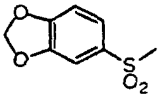
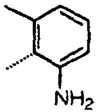
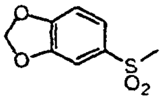
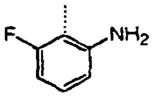
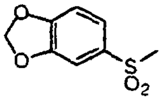
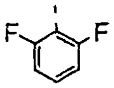
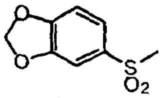
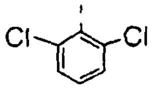
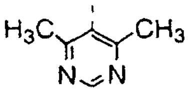
Ex.	R^6	R^2	mp (°C)	MS (MH^+)
6	CH_3		204	549.5
6A	CH_3		253	589.4
6B	CH_3		260	534.4
6C	H		225	520.4
6D	H		215	575.4

Example 7

[0068] The synthesis of compounds with an alkyl or arylsulfonyl R^8 group at the para position started with the corresponding para-substituted acetophenone which was treated as in Example 4, steps 1-6 to obtain the sulfone containing compounds of Example 7 havng the formula:

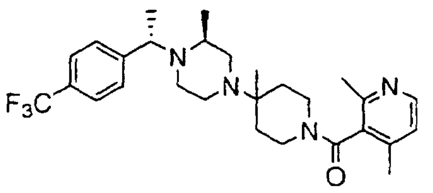


wherein R^8 and R^2 are as defined in the table:

Ex.	R^8	R^2	Mp (^{0} C)	HRMS (MH$^+$)
7	H_3CSO_2-		220-225	498.2790
7A	H_3CSO_2-		212-215	519.2197
7B			190 (dec.)	604.2861
7C			178 (dec.)	625.2246
7D			170 (dec.)	605.2799
7E			170 (dec.)	609.2540
7F			200 (dec.)	612.2336
7G			158 (dec.)	644.1735
7H	H_3CSO_2-		197 (dec.)	514.2847

Example 8

[0069]



Step 1: A solution of the product of Example 4, step 4 (1.25g; 4.6 mmol), N-BOC-4-piperidinone (0.91g; 4.6 mmol) and (Ti(OiPr)$_4$) (1.4 ml; 4.6 mmol) in 10 ml of CH_2Cl_2 was stirred at ambient temperature for 24 h. The reaction mixture was then treated with Et_2AlCN (5.5 ml; 1 M solution in toluene) and stirring continued for 20 h. The reaction mixture was diluted with EtOAc and stirred with saturated $NaHCO_3$ solution (10 min.) and the layers were separated as much as possible. The turbid (from inseparable aqueous layer) organic layer was treated with excess celite and filtered, washing the filtercake with EtOAc. The filtrate layers were separated and the organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated to obtain 2.16g (98%) of an amber gum.

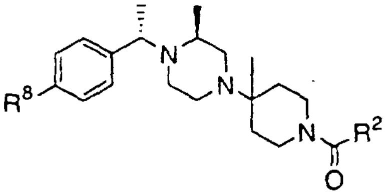
Step 2: The Strecker amine from step 1 (2.16g) was dissolved in dry THF, cooled in an ice bath and treated with CH_3MgBr (7.5 ml of a 3M solution in Et_2O). After 1 h, the ice bath was removed and the yellow, heterogeneous reaction mixture was stirred at RT for 18h. The reaction was quenched with saturated NH_4Cl solution, diluted with water and extracted with CH_2Cl_2. Concentration gave 2.2 g of a yellow gum which was purified by FSGC, eluting the major product away from more polar impurities using a 1:1 mixture of CH_2Cl_2:EtOAc. The ipso-methyl compound was isolated as a yellow gum (1.85g; 88%). TLC R_f = 0.5 in 1:1 Et_2O:hexanes.

Step 3: TFA (6 ml) was added to a solution of the product of step 2 (1.5g; 3.2 mmol) in 10 ml of CH_2Cl_2 and stirred at 25° C for 2 h. The reaction was quenched with 1 N NaOH solution to a pH of 9-10 and processed by extraction into CH_2Cl_2 to obtain 1.2 g of crude product. FSGC using 1:1 CH_2Cl_2:EtOAc removed all the less polar impurities and gradient elution with 10% CH_3OH in CH_2Cl_2 and finally with 10% (ca. 7N-NH_3) CH_3OH in CH_2Cl_2 led to the isolation of the free piperidine as a yellow gum (1.07g; 90%). TLC R_f = 0.2 in 10% CH_3OH:CH_2Cl_2.

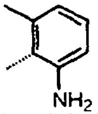
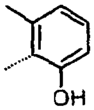
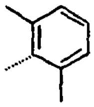
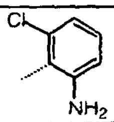
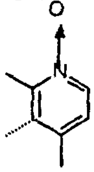
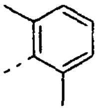
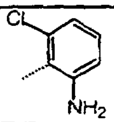
Step 4: A solution of the product of step 3 (1.03g; 2.8 mmol), 2,4-dimethyl nicotinic acid (0.42g; 2.8 mmol), DEC (0.8g; 4.2 mmol), HOBT (0.57g; 4.2 mmol) and diisopropyl ethyl amine (1ml; 5.6 mmol) in CH_2Cl_2 (15 ml) was stirred at 25° C for 24 h. The reaction mixture was diluted with CH_2Cl_2 (25 ml), washed with water, 10% $NaHCO_3$ solution and brine, then concentrated to obtain 1.6g of crude oil. FSGC of this material using gradient elution with 10% acetone-CH_2Cl_2 followed by 2-5% CH_3OH in CH_2Cl_2 gave the title compound (1.1 g; 80%) as a white foam. TLC R_f = 0.45 in 5% CH_3OH-CH_2Cl_2.

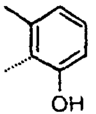
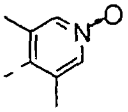
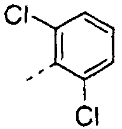
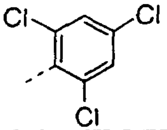
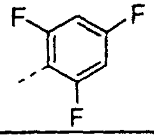
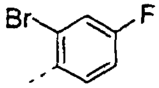
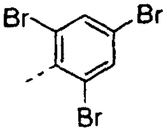
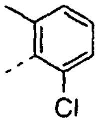
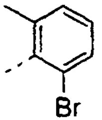
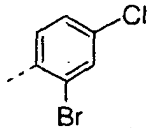
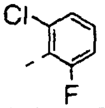
[0070] The free base of the title compound (1g; 2 mmol) isolated above was dissolved in a 1:1 mixture of EtOAc:Et_2O (8 ml) and a fresh solution of hydrogen chloride in Et_2O (6.1 ml of a 1 M solution) was added, instantly forming a white precipitate. After stirring at 25° C for 1 h, the volatiles were removed in vacuo. The product was suspended in Et_2O and filtered, washing the filtrate with Et_2O. The HCl salt of the title compound thus obtained was dried in vacuo (1.1g; mp. 213-215° C). HRMS (MH^+) 503.2997.

[0071] The following amides 8A-8E were prepared in a similar manner from the product of step 3 using appropriate acids, and compounds 8F-8H, wherein the R^8-substituent is a *p*-methyl sulfonyl group were similarly prepared.

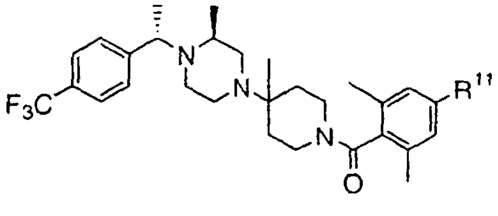


wherein R^8 and R^2 are as defined in the table:

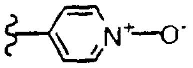
Ex.	R^8	R^2	Mp (^{0} C)	HRMS (MH^+)
8A	CF_3		216	503.3021
8B	CF_3		222-224	504.2850
8C	CF_3		262-263	502.3039
8D	CF_3		216-218	523.2466
8E	CF_3		210-212	519.2970
8F	$-SO_2CH_3$		201-205	512.2955
8G	$-SO_2CH_3$		217-221	533.2355

8H	-SO_2CH_3		216-219	514.2736
8I	-CF_3		195-198	--
8J	-CF_3		250-255	528.1791
8K	-CF_3		223-226	576.1562
8L	-CF_3		>245	528.2439
8M	-CF_3		176-181	570.1739
8N	-CF_3		218-223	708.0040
8O	-CF_3		215-220	522.2507
8P	-CF_3		208-212	566.1987
8Q	-CF_3		190-194	586.1442
8R	-CF_3		255-257	526.2243

[0072] Using procedures described following the table, compounds 8S-8EE of the structure



were prepared, wherein R^{11} is defined in the table:

Ex.	R^{11}	Mp (° C)	HRMS (MH^+)
8S	-OH	210-220 (2xHCl salt)	518.2997
8T	$-OC(O)NHCH_2CH_3$	205-210 (2xHCl salt)	589.3374
8U	$-OSO_2CH_3$	165-171 (2xHCl salt)	596.2757
8V		199-204 (2xHCl salt)	595.3254
8W	-CHO	88-92	530.2985
8X	$-CH{=}NH-OCH_3$	202-205 (2xHCl salt)	559.3260
8Y	$-CHF_2$	>245 (dec) (2xHCl salt)	552.3020
8Z	$-NH-C(O)-NH-CH_2CH_3$	214-219 (2xHCl salt)	588.3521
8AA	$-NH_2$	92-98	517.3154
8BB	$-NHSO_2CH_2CH_3$	205-211 (2xHCl salt)	609.3078
8CC	-F	212-217 (2xHCl salt)	520.2949
8DD	-Cl	235-238 (2xHCl salt)	536.2663
8EE	-Br	237-240 (2xHCl salt)	580.2141

8S: The tri-hydrochloride salt of the product of Example 8, step 3 (75 mg, 0.16 mmol), EDC (61 mg, 0.32 mmol), HOBT (49 mg, 0.32 mmol), iPr_2NEt (0.16 ml, 0.96 mmol), and 2,6-dimethyl-4-hydroxy-benzoic acid (53 mg, 0.32 mmol) were taken up in CH_2Cl_2 and stirred at 25 °C for 20 h. The solution was concentrated. Purification via preparative TLC (EtOAc, SiO_2) gave the title compound as a yellow oil. m.p. (2xHCl salt) 210-220 °C. HRMS (MH^+) calcd. for $C_{29}H_{39}O_2N_3F_3$, 518.2994; Found, 518.2997.

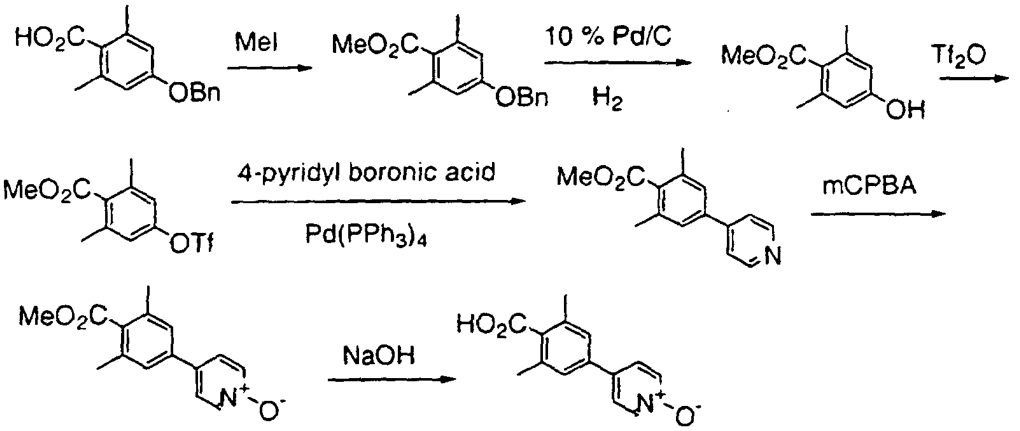
8T: 8S (100 mg, 0.19 mmol), ethyl isocyanate (0.05 ml, 0.58 mmol), and Et_3N (0.13 ml, 0.95 mmol) were taken up in CH_2Cl_2 and stirred at 25 °C for 16 h. The solution was diluted with CH_2Cl_2 and washed with 1 N NaOH. The organic layer was dried (Na_2SO_4), filtered, and concentrated. Purification via preparative TLC (2/1 EtOAc/hexanes, SiO_2) gave the title compound as a yellow oil.

8U: 8S (250 mg, 0.48 mmol), methane sulfonyl anhydride (250 mg, 1.44 mmol), and NaH (38 mg, 60 wt% in oil) were taken up in THF and stirred at 25 °C for 20 h. The solution was diluted with EtOAc and washed with sat'd $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated. Purification via preparative TLC (1/1 EtOAc/hexanes, SiO_2) gave the title compound as a yellow oil (280 mg, 98%).

8V: The tri-hydrochloride salt of the product of Example 8, step 3 (50 mg, 0.1 mmol), EDC (38 mg, 0.2 mmol), HOBT (27 mg, 0.2 mmol), iPr_2NEt (0.07 ml, 0.4 mmol), and 2,6-dimethyl-4-(4-pyridyl-N-oxide)-benzoic acid (73 mg, 0.3 mmol) (see preparation below) were taken up in CH_2Cl_2 and stirred at 25 °C for 19 h. The solution was concentrated. Purification via preparative TLC (2/1 acetone/hexanes, SiO_2) gave **8V** as a yellow oil (23 mg, 39%).

Preparation of 2,6-dimethyl-4-(4-pyridyl-N-oxide) benzoic acid

[0073]



Step A: 4-Benzyloxy-2,6-dimethyl benzoic acid (8.7 g, 34 mmol; Thea, S. et al *Journal of the American Chemical Society* **1985,** *50, 1867),* MeI (3.2 ml, 51 mmol), and Cs_2CO_3 (17 g, 51 mmol) were allowed to stir in DMF at 25 °C for 17 h. The solution was filtered and partitioned between Et_2O and water. The aqueous layer was extracted with Et_2O. The combined Et_2O layers were washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification via flash chromatography (10/1 hexanes/Et_2O, SiO_2) gave 8.6 g (94 %) of the methyl ester as a colorless oil.

Step B: The benzyl protected phenol (8.5 g, 32 mmol) and Pd/C (750 mg, 10 wt % Pd) were taken up in CH_3OH. The solution was charged with 50 psi H_2 and shaken in a Parr apparatus at 25 °C for 17h. The solution was filtered (Celite). Concentration gave 5.6 g (98 %) of the phenol as a white solid.

Step C: The phenol (3.5 g, 19.4 mmol) and iPr_2NEt (3.76 g, 29.1 mmol) were dissolved in CH_2Cl_2 at 0 °C. Triflic anhydride (Tf_2O) (4.2 ml, 25.2 mmol) was added dropwise to the solution at 0 °C. The solution was warmed to 25 °C and stirred at that temperature for 4.5 h. The solution was diluted with CH_2Cl_2 and washed with sat $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. Filtration and concentration gave the crude aryl triflate.

Purification via flash chromatography (10/1, hexanes/Et_2O, SIO_2) gave 5.7 g (94 %) of the triflate as a yellow oil.

Step D: The triflate (1 g, 3.2 mmol), 4-pyridyl boronic acid (1.2 g, 9.6 mmol), $Pd(PPh_3)_4$ (370 mg, 0.32 mmol), and Na_2CO_3 (1 g, 9.6 mmol) were taken up in DME/H_20 (4/1, 25 ml). The solution was heated to 90 °C (oil bath) under N_2 for18 h. The solution was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc. The combined EtOAc layers were dried (Na_2SO_4). Filtration and concentration gave a dark brown oil. Purification via flash chromatography (3/1 hexanes/EtOAc, SiO_2) gave 770 mg (100 %) of the pyridyl derivative as an orange oil.

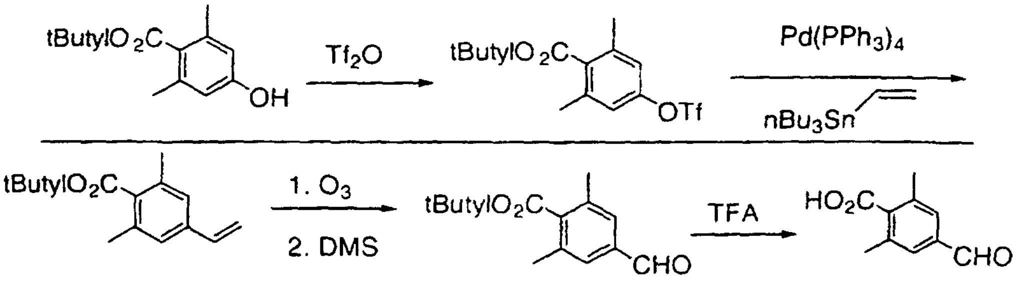
Step E: The pyridyl derivative (390 mg, 1.6 mmol) and mCPBA (550 mg, 3.2 mmol) were dissolved in CH_2Cl_2. The solution was stirred at 25 °C for 18 h. The solution was diluted with CH_2Cl_2 and washed with 1 N NaOH. The organic layer was dried (Na_2SO_4). Filtration and concentration gave 400 mg (97 %) of the N-oxide as an orange oil. HRMS (MH^+) calcd. for $C_{15}H_{16}O_3N$, 258.1130; Found, 258.1131.

Step F: The methyl ester (400 mg, 1.6 mmol) was taken up in 5 ml of 3 N NaOH and 2 ml of EtOH. The solution was heated at reflux for 20 h. The solution was concentrated. The residue was treated with conc. HCl. The resulting solid was filtered and washed with water and brine. After drying under high vacuum, the free acid (377 mg, 100 %) was obtained as a tan solid. m.p. >225 °C (decomp). HRMS (MH^+) calcd. for $C_{14}H_{14}O_3N$, 244.0974; Found, 244.0981.

8W: The tri-hydrochloride salt of the product of Example 8, step 3 (1.34 g, 2.8 mmol), 2,6-dimethyl-4-formyl benzoic acid (500 mg, 2.8 mmol) (see preparation below), EDC (1.1 g, 5.6 mmol), HOBT (760 mg, 5.6 mmol) and iPrNEt (2 ml, 11 mmol) were subjected to the standard coupling conditions. Purification via flash chromatography (2/1 hexanes/ EtOAc, SiO_2) gave 898 mg (61 %) of **8W** as a yellow foam.

Preparation of 2,6-dimethyl-4-formyl benzoic acid

[0074]



Step A: 4-Hydroxy-2,6-dimethyl-benzoic acid, tert-butyl ester (6.4 g, 29 mmol) and iPr_2NEt (5.6 g, 43 mmol) were taken up in CH_2Cl_2 and cooled to 0 °C. Tf_2O (5.8 ml, 34 mmol) was added slowly to the solution at 0 °C. The solution was stirred at 0 °C for 3 h. The solution was partitioned between sat. $NaHCO_3$ and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4). Filtration and concentration gave a brown oil. Purification via flash chromatography (20/1 hexanes/Et_2O, SiO_2) gave 7.99 g (82 %) of the triflate as a yellow solid.

Step B: The triflate (5 g, 15 mmol), LiCl (1.25 g, 30 mmol), $Pd(PPh_3)_4$ (340 mg, 0.3 mmol), and vinyl tributyl tin (4.5 ml, 16 mmol) were taken up in THF under N_2. The solution was heated at 70 °C for 16 h. The solution was partitioned between EtOAc and sat. KF. The mixture was filtered. The organic layer was separated, and the aqueous layers were extracted with EtOAc. The combined organic layers were dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via flash chromatography (20/1 hexanes/Et_2O, SiO_2) gave 1.96 g (57 %) of the olefin as a yellow oil.

Step C: The olefin (0.6 g, 2.6 mmol) was taken up in CH_2Cl_2/MeOH (1/1). The solution was cooled to -78 °C. Ozone was bubbled through the solution until a dark blue color persisted. The reaction was quenched with dimethyl sulfide. The reaction was concentrated to furnish the aldehyde as an oil.

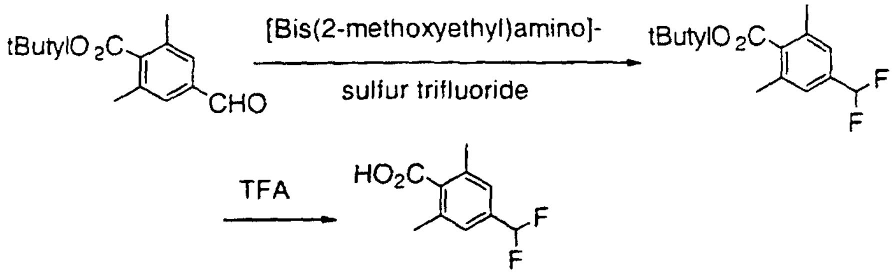
Step D: The tert-butyl ester (650 mg, 2.8 mmol) and TFA (3 ml) were taken up in CH_2Cl_2 and stirred at 25 °C for 19 h. Concentration of the solution gave the acid as a beige solid.

8X: 8W (100 mg, 0.19 mmol), H_2NOMe-HCl (28 mg, 0.34 mmol), NaOAc (32 mg, 0.46 mmol) were taken up in MeOH. The solution was stirred at 25 °C for 17h. The solution was concentrated. The residue was partitioned between CH_2Cl_2 and 1 N NaOH. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4). Filtration and concentration gave the crude product. Purification via preparative TLC (1/1 hexanes/EtOAc, SiO_2) gave 85 mg (84 %) of **8X.**

8Y: The tri-hydrochloride salt of the product of Example 8, step 3 (75 mg, 0.16 mmol) and 4-difluoromethyl-2,6-dimethyl benzoic acid (32 mg, 0.16 mmol) were subjected to the standard coupling conditions (EDC/HOBT/iPr_2NEt). Purification via preparative TLC (2/1 hexanes/EtOAc, SiO_2) gave 64 mg (73 %) of **8Y.**

Prepartion of 4-difluoromethyl-2,6-dimethyl benzoic acid

[0075]



Step A: The aldehyde (400 mg, 1.7 mmol), [bis(2-methoxyethyl)amino]-sulfur trifluoride (640 mg, 2.9 mmol), and EtOH (0.02 ml, 0.34 mmol) were taken up 1,2-dichloroethane and stirred at 65 °C for 6 h and at 25 °C for 19 h.

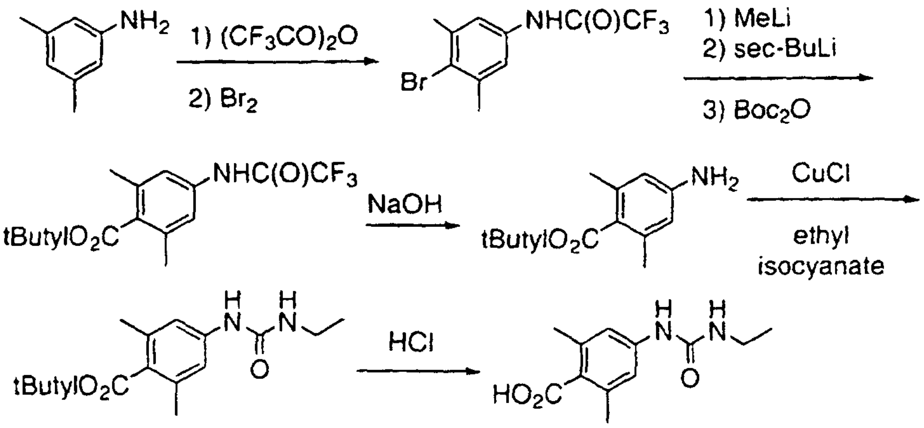
The solution was quenched with sat. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($NaSO_2$). Filtration and concentration gave the crude product. Purification via preparative TLC (10/1 hexanes/Et_2O, SiO_2) gave 210 mg (50 %) of the difluoro derivative.

Step B: The tert-butyl ester (210 mg, 0.82 mmol) and HCl (2.1 ml of 4 M in dioxane, 8.2 mmol) were taken up in MeOH. The solution was stirred at 45 °C for 20 h. The solution was concentrated to obtain the acid as a white solid.

8Z: The tri-hydrochloride salt of the product of Example 8, step 3 (811 mg, 1.7 mmol) and 4-[(ethylamino)carbonylamino]-2,6-dimethyl benzoic acid (400 mg, 1.7 mmol) (see preparation below) were subjected to the standard coupling conditions (EDC/HOBT/iPr_2NEt). Purification via flash chromatography (1/1 hexanes/acetone, SiO_2) gave 803 mg (81 %) of 8Z as a foam.

Preparation of 4-[(ethylamino)carbonylamino]-2,6-dimethyl benzoic acid

[0076]



Step A: 3,5-Dimethyl aniline (18.5 ml, 149 mmol) was taken up in CH_2Cl_2. The solution was cooled in a water bath. Trifluoroacetic anhydride (29.5 ml, 209 mmol) was added slowly to the solution. After the addition, the solution was stirred at 25 °C for 15 minutes. Bromine (7.3 ml, 142 mmol) was added slowly to the solution while maintaining the RT water bath. The solution was stirred at 25 °C for 3.5 h. The solution was quenched with 10% $Na_2S_2O_3$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), treated with activated carbon and filtered. Concentration gave an orange solid. Purification via recrystallization (hexanes/Et_2O) gave two crops (34 g total, 77%) of the brominated derivative as a white solid.

Step B: The aryl bromide (17 g, 57 mmol) was taken up in THF and cooled to -78 °C under N_2. Methyllithium/LiBr (54 ml of a 1.5 M solution in Et_2O, 80 mmol) was added slowly to the solution at -78 °C. After 5 min of stirring, sec-BuLi (62 ml of a 1.3 M in cyclohexane, 80 mmol) was added slowly to the reaction solution at -78 °C. After 5 min, di-t-butyl dicarbonate (22.5g, 103 mmol) in THF was added to the solution at -78 °C. The solution was warmed to 25 °C. After 30 min, the reaction mixture was partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$). Filtration and concentration gave a yellow solid. Purification via flash chromatography (1/1 to 1/4 hexanes/CH_2Cl_2, SiO_2) gave 13.1 g (72 %) of the tert-butyl ester as an off-white solid.

Step C: The trifluoro-acetamide (10 g, 31 mmol) and NaOH (2.5 g, 62 mmol) were taken up in MeOH/H_2O (3/1) and heated at 60 °C for 3 h. The solution was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water and dried (Na_2SO_4). Filtration and concentration gave 6.4 g (93 %) of the aniline as an orange solid.

Step D: The aniline (1 g, 4.5 mmol), ethyl isocyanate (0.4 ml, 5 mmol), and CuCl (90 mg, 0.9 mmol) were taken up in DMF at 0 °C. The solution was warmed to 25 °C and stirred at that temperature for 2h. The solution was partitioned between EtOAc and 10 % NH_4OH. The aqueous layer was extracted with EtOAc. The combined layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow solid.

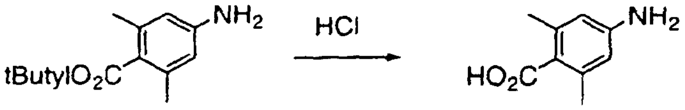
Purification via flash chromatography (3/1 to 1/1 hexanes/EtOAc, SiO_2) gave 904 mg (69 %) of the urea as a yellow solid.

Step E: The tert-butyl ester (900 mg, 3.1 mmol) and 4 M HCl in dioxane (3 ml) were taken up in iPrOH and heated at 45 °C for 3.5 h and at 25 °C for 16.5 h. The solution was concentrated under reduced pressure. The residue was partitioned between Et_2O and 1 N NaOH. The aqueous, basic layer was extracted with Et_2O. The aqueous layer was cooled to 0 °C and acidified with conc. HCl (pH = 1-2). The aqueous layer was extracted with EtOAc. The combined EtOAc layers were dried (Na_2SO_4). Filtration and concentration gave the 400 mg (55 %) of the acid as a white solid.

8AA: The tri-hydrochloride salt of the product of Example 8, step 3 (2 g, 4.3 mmol) and 4-amino-2,6-dimethyl benzoic acid (710 mg, 4.3 mmol) (see preparation below) were subjected to the standard coupling conditions (EDC/HOBT/ iPr_2NEt). Purification via flash chromatography (2/1 hexanes/acetone, SiO_2) gave 1.16 g (52 %) of **8AA** as a yellow foam.

Preparation of 4-amino-2,6-dimethyl benzoic acid

[0077]



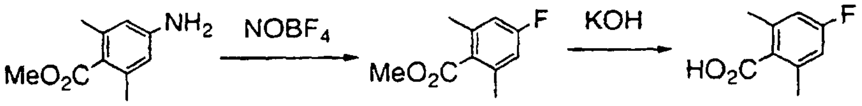
[0078] The tert-butyl ester (950 mg, 4.3 mmol) and HCl (11 ml, 4 M in dioxane) were taken up in MeOH at heated at 45 °C for 20 h. The solution was concentrated to obtain the acid (710 mg) in quantitative yield.

8BB: 8AA (100 mg, 0.19 mmol) and ethane sulfonyl chloride (0.02 ml, 0.21 mmol) were taken up in pyridine and stirred at 25 °C for 19 h. The solution was concentrated. The residue was partitioned between 1 N NaOH and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4). Filtration and concentration gave a brown oil. Purification via preparative TLC (2/1 hexanes/acetone, SIO_2) gave 100 mg (86 %) of **8BB** as a colorless oil.

8CC: The trihydrochloride salt of the product of Example 8, step 3 (127 mg, 0.27 mmol) and 4-fluoro-2,6-dimethyl benzoic acid (58 mg, 0.35 mmol) (see preparation below) were coupled according to the general procedure (EDC/ HOBT/iPr_2NEt). Purification via preparative TLC (2/1 hexanes/EtOAc, SiO_2) gave **8CC** as a colorless oil (87 mg bis-HCl salt, 54 %).

Preparation of 4-fluoro-2,6-dimethyl benzoic acid

[0079]

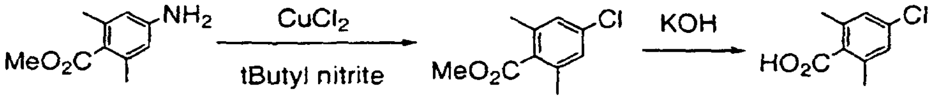


[0080] 4-Amino-2,6-dimethyl benzoic acid (200 mg, 1.1 mmol) and $NOBF_4$ (196 mg, 1.7 mmol) were heated in 1,2-dichlorobenzene at 100 °C for 30 min. The solution was cooled and diluted with MeOH and water. A few pellets (2-3) of KOH were added, and the solution was heated at reflux for 16 h. The solution was concentrated. The residue was partitioned between Et_2O and 1 N NaOH. The aqueous layer was extracted with Et_2O. The aqueous layer was cooled to 0 °C and acidified with conc. HCl (pH = 1-2). The aqueous layer was extracted with CH_2Cl_2. The organic layers were dried (Na_2SO_4). Filtration and concentration gave 58 mg (31 %) of the acid as a tan solid.

8DD: The trihydrochloride salt of the product of Example 8, step 3 (150 mg, 0.31 mmol) and 4-chloro-2,6-dimethyl benzoic acid (76 mg, 0.41 mmol) (see preparation below) were coupled according to the general procedure (EDG/ HOBT/iPr_2NEt). Purification via preparative TLC (4/1 hexanes/acetone, SiO_2) gave **8DD** as a colorless oil.

Preparation of 4-chloro-2,6-dimethyl benzoic acid

[0081]

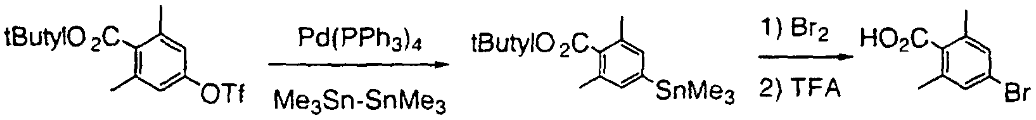


[0082] 4-Amino-2,6-dimethyl benzoic acid (172 mg, 0.96 mmol) and $CuCl_2$ (155 mg, 1.15 mmol) were taken up in CH_3CN at 0 °C. Tert-butyl nitrite (0.17 ml, 1.4 mmol) was added to the solution at 0 °C. The solution was warmed to 25 °C and then at 65 °C for 45 min. The solution was partitioned between Et_2O and water. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave the methyl ester. The methyl ester was hydrolyzed as described above for the fluoro derivative (KOH). After extractive workup, 4-chloro-2,6-dimethyl benzoic acid (158 mg, 89 %) was obtained as a yellow solid.

8EE: The trihydrochloride salt of the product of Example 8, step 3 (180 mg, 0.38 mmol) and 4-bromo-2,6-dimethyl benzoic acid (95 mg, 0.41 mmol) (see preparation below) were coupled according to the general procedure (EDC/HOBT/iPr_2NEt). Purification via preparative TLC (4/1 hexanes/acetone, SiO_2) gave **8EE** as a colorless oil (140 mg bis-HCl salt, 56 %).

Preparation of 4-bromo-2,6-dimethyl benzoic acid

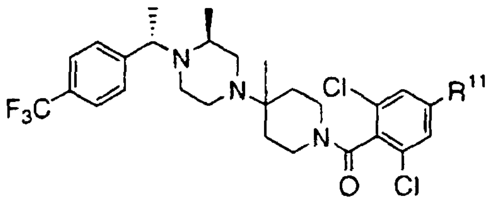
[0083]



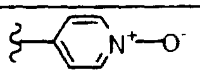
Step A: The triflate (500 mg, 1.48 mmol), hexamethylditin (0.31 mmol, 1.48 mmol), LiCl (377 mg, 8.9 mmol), and $Pd(PPh_3)_4$ (171 mg, 0.15 mmol) were heated in THF (70 °C) under N_2 for 21 h. The solution was partitioned between Et_2O and pH = 7 buffer (NH_4OAc). The aqueous layer was extracted with Et_2O. The combined Et_2O layers were washed with brine and dried (Na_2SO_4). Filtration and concentration gave the crude aryl stannane as a yellow semisolid.

Step B: The aryl stannane (0.74 mmol) was taken up in CH_2Cl_2 at 0 °C. Bromine (0.7 ml of 1 M Br_2 in CH_2Cl_2) was added to the solution. The solution was stirred at 0 °C for 30 min. The solution was diluted with CH_2Cl_2 and washed with 10 % $Na_2S_2O_3$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4). The solution was filtered. TFA (2 ml) was added to the solution, and the solution was stirred at 25 °C for 17 h. The solution was concentrated. The residue was partitioned between Et_2O and 1 N NaOH. The aqueous layer was extracted with Et_2O. The aqueous layer was cooled to 0 °C and acidified with conc. HCl (pH = 1-2). The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4). Filtration and concentration gave 100 mg (59 %) of the acid as a white solid.

[0084] Using procedures described following the table, compounds 8FF-8HH of the structure



were prepared, wherein R^{11} is defined in the table:

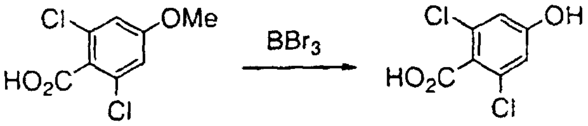
Ex.	R^{11}	Mp (^{0} C)	HRMS (MH^+)
8FF	$-OCH_3$	217-220 (2xHCl salt)	572.2048
8GG	-OH	198-204 (2xHCl salt)	558.1898
8HH		200-205 (2xHCl salt)	635.2172

8FF: The trihydrochloride salt of the product of Example 8, step 3 (100 mg, 0.21 mmol) and 2,6-dichloro-4-methoxy-benzoic acid (140 mg, 0.63 mmol) were coupled according to the general procedure (EDC/HOBT/iPr$_2$NEt). Purification via preparative TLC (3/1 hexanes/EtOAc, SiO$_2$) gave **8FF** as a colorless oil (27 mg, 23 %).

8GG: The trihydrochloride salt of the product of Example 8, step 3 (330mg, 0.7 mmol) and 2,6-dichloro-4-hydroxy-benzoic acid (290 mg, 1.4 mmol) (see preparation below) were coupled according to the general procedure (EDC/HOBT/iPr$_2$NEt). Purification via preparative TLC (1/1 hexanes/EtOAc, SiO$_2$) gave **8GG** as a colorless oil (75 mg, 19 %).

Preparation of 2,6-dichloro-4-hydroxy-benzoic acid

[0085]

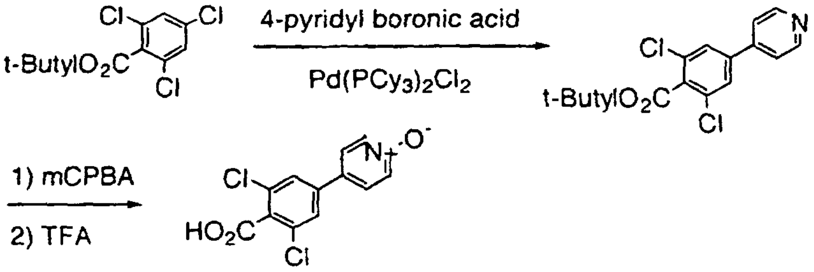


[0086] 2,6-Dichloro-4-methoxy-benzoic acid (500 mg, 2.3 mmol) was taken up in CH$_2$Cl$_2$ and cooled to -78 °C. BBr$_3$ (6.9 ml of a 1 M solution in CH$_2$Cl$_2$) was added to the solution at -78 °C. The solution was warmed to 25 °C and stirred at that temperature for 16 h. The solution was quenched with 3 N NaOH. The aqueous layer was extracted with CH$_2$Cl$_2$. The aqueous layer was cooled (0 °C) and acidified with conc. HCl (pH = 1-2). The aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were dried (Na$_2$SO$_4$). Filtration and concentration gave the crude phenol which was used without further purification.

8HH: The trihydrochloride salt of the product of Example 8, step 3 (96 mg, 0.2 mmol) and 2,6-dichloro-4-(4-pyridyl-N-oxide)-benzoic acid (55 mg, 0.2 mmol) (see preparation below) were coupled according to the general procedure (EDC/HOBT/iPr$_2$NEt). Purification via preparative TLC (1/5 hexanes/acetone, SiO$_2$) gave **8HH** as a colorless oil (54 mg, 43 %).

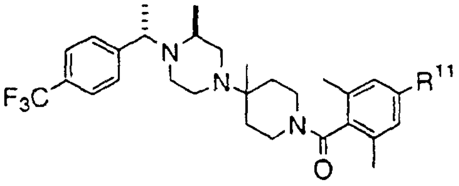
Preparation of 2,6-dichloro-4-(4-pyridyl-N-oxide) benzoic acid

[0087]

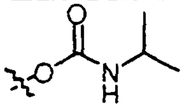
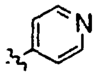
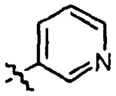
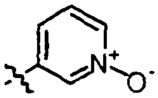
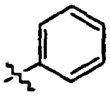
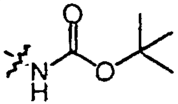
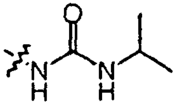
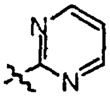
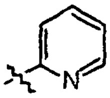
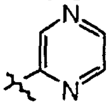
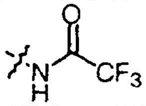
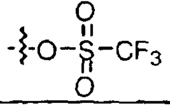


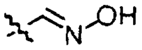
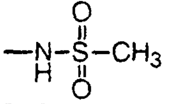
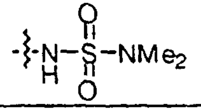
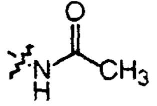
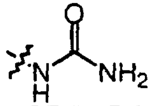
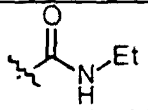
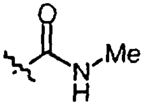
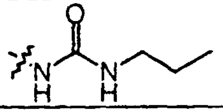
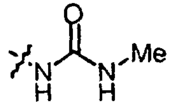
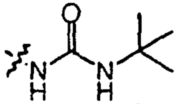
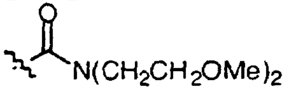
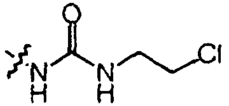
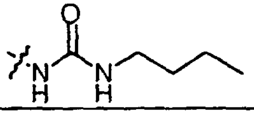
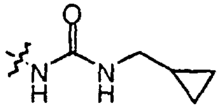
[0088] 2,4,6-Trichloro benzoic acid, tert-butyl ester (500 mg, 1.8 mmol), 4-pyridyl boronic acid (270 mg, 2.16 mmol), Pd(PCy$_3$)$_2$Cl$_2$ (130 mg, 0.18 mmol), and CsF (540 mg, 3.6 mmol) were taken up in NMP and heated at 100 °C under N$_2$ (16 h). The solution was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine and dried (Na$_2$SO$_4$). Filtration and concentration gave the crude product. Purification via preparative TLC (1/1 hexanes/EtOAc, SiO$_2$) gave 68 mg (12 %) of the pyridyl ester. The tert-butyl ester was converted into the acid as done previously for the dimethyl derivative (a. mCPBA /b. TFA).

[0089] Using suitable starting materials and the procedures described for examples 8S to 8HH, the compounds of the following structure were prepared:



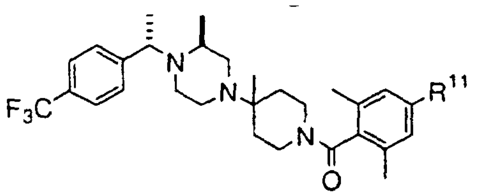
wherein R^{11} is defined in the table

Ex.	R^{11}	m.p. (°C)	HRMS (MH^+) calc.	HRMS (MH^+) found
8II	$-OCH_3$	236-240	532.3151	532.3166
8JJ	$-CH_3$	> 260	516.3202	516.3213
8KK		186-190	603.3522	603.3513
8LL		202-208	579.3311	579.3303
8MM		210-216	579.3311	579.3311
8NN		196-203	595.3260	595.3256
8OO		> 230 (dec)	578.3358	578.3368
8PP		135-140	617.3679	617.3671
8QQ		205-215	602.3682	602.3722
8RR	CH_2OH	> 235 (dec)	532.3151	532.3124
8SS		206-212	580.3263	580.3258
8TT		198-204	579.3311	579.3315
8UU		231-236	580.3263	580.3252
8VV		201-207	613.2977	613.2981
8WW	 $-O-\overset{O}{\underset{O}{S}}-CF_3$	215-220	650.2487	650.2497

8XX		198-201	545.3103	545.3098
8YY	 $-N(H)-S(=O)_2-CH_3$	210-214	595.2930	595..2921
8ZZ	CH_2F	> 245	534.3108	534.3117
8AB	 $-N(H)-S(=O)_2-NMe_2$	202-205	624.3195	624.3204
8AC		208-213	559.3260	559.3263
8AD		215-220	560.3212	560.3220
8AE		215-220	573.3416	573.3424
8AF		215-220	559.3260	559.3257
8AG		205-209	602.3682	602.3672
8AH		186-192	574.3369	574.3378
8AI		200-206	616.3838	616.3844
8AJ		165-173	661.3941	661.3949
8AK	CN	240-250	527.2998	527.2991
8AL		211-215	622.3136	622.3129
8AM		170-174	616.3838	616.3836
8AN		192-196	614.3682	614.3690

[0090] All melting points were done on the bis hydrochloride salts (2xHCl) except 8PP was performed on the free base

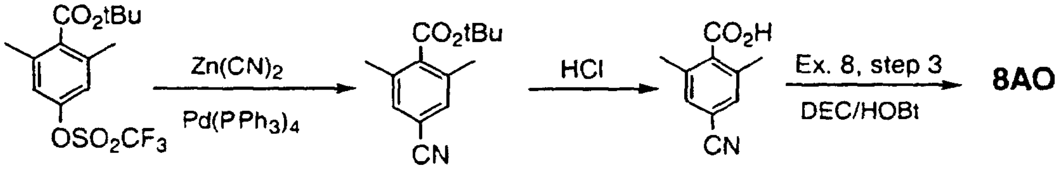
[0091] Using derivatives of the triflate intermediate described in **8Z** in procedures similar to those described above and following the table for **8AO-8AQ**, the compounds of the following structure were prepared:



wherein R^{11} is defined in the table

Ex.	R^{11}	m.p. (°C)
8AO	-CN	240-250
8AP	-CONHEt	215-220
8AQ	$-N(CH_3)CONHEt$	186-203
8AR	$-CONH_2$	200-208
8AS	$-CONHCH_3$	215-220
8AT	$-CON(CH_2CH_2OCH_3)_2$	165-173
8AU	$-CON(Et)_2$	170-180
8AV	$-N(CH_3)CONHCH_3$	198-210
8AW	$-NHCH_3$	190-200
8AX	$-N(CH_3)CONH_2$	190-220

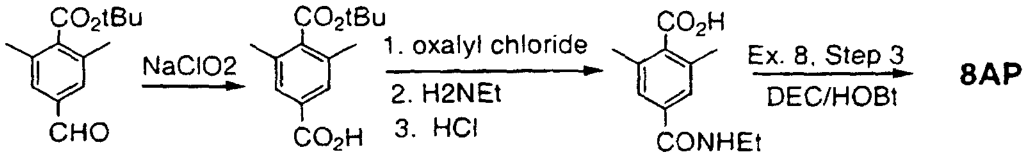
8AO:



Step 1: The triflate intermediate (see 8W) (0.4 g), $Zn(CN)_2$ (0.2 g), $Pd(PPh_3)_4$ (0.3 g) and DMF (1.5 ml) were heated at 80 °C for 17 h. The reaction was cooled to RT, diluted with EtOAc and saturated aqueous $NaHCO_3$. The EtOAc layer was removed, washed with water, dried with brine and evaporated to give a crude oil which was purified by preparative plate chromatography (2000 μM silica plates; 8:1 hexanes: EtOAc eluant), to give, after isolation of the appropriate band, the cyano intermediate (0.2 g) in 77% yield.

Step 2: The product of Step 1 (0.2 g) was dissolved in MeOH (1.5 ml) and HCl (4M solution in 1,4-dioxane; 2 ml) was added. The resulting solution was stirred at 50 °C for 3 h and evaporated. This crude intermediate (0.038 g) and the product of Example 8, Step 3 (65 mg; trihydrochloride form) were treated in the same fashion as Example 8, Step 4, using DMF (2 ml), HOBt (45 mg), DEC (60 mg) and diisopropyl ethyl amine (0.1 ml) to give, after isolation and purification, the free base form of **8AO**, which was converted to its HCl salt (45 mg) in 95% yield.

8AP:



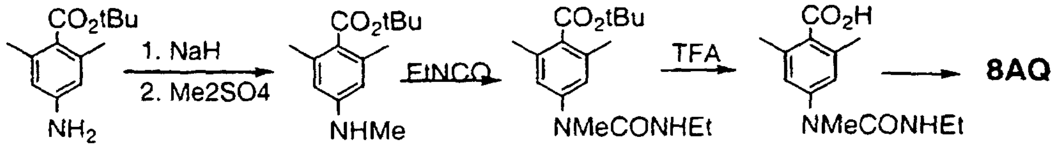
Step 1: 2,6-Dimethyl-4-formyl benzoic acid (1.96 g) (see 8W) was dissolved in t-butanol (94 ml) and 2-methyl-2-butene (24 ml). A solution of $NaClO_2$ (6.89 g), NaH_2PO_4 monohydrate (8.17 g) and water (45 ml) was added dropwise to the first solution. After complete addition, the pH was adjusted to 3 and two layers resulted. The organic

layer was removed and evaporated to give intermediate acid (1.80 g) as a white crystalline solid, which was used without purification.

Step 2: To a solution of the product of Step 1 (0.62 g), CH_2Cl_2 (5 ml) and DMF (1 drop) was added oxalyl chloride (0.31 ml) and the resulting solution was stirred for 10 min, at which time a second portion of oxalyl chloride (0.30 ml) was added. The reaction was stirred for 10 min, toluene was added and the mixture was evaporated to dryness. CH_2Cl_2 (10 ml) and $EtNH_2$ (1 ml) were added and the reaction was stirred for 2 days, then partitioned between brine and CH_2Cl_2. The CH_2Cl_2 layer was evaporated and HCl (4 ml of a 4 M solution in 1,4-dioxane) was added. The resulting solution was stirred for 3 h and evaporated to give a solid which was washed with Et_2O and collected to give the amide intermediate (0.13 g) in 24 % yield.

Step 3: The product of Example 8, Step 3 (60 mg; trihydrochloride form) and the product of step 2 (35 mg) were treated in the same fashion as Example 8, Step 4 to give, after work up and purification, **8AP** as the free base form, which was converted to the HCl salt (50 mg) in 62% yield.

8AQ:



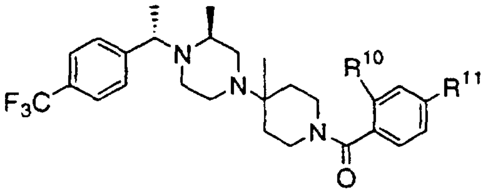
Step 1: To a solution of the amine intermediate (2 g) (see 8Z) was added NaH (0.4 g of a 60% oil dispersion). The resulting suspension was stirred for 15 min and Me_2SO_4 was added. After heating at reflux for 1.5 h, the reaction was cooled to RT, poured into saturated NH_4Cl aqueous solution and extracted with Et_2O. After evaporation, the crude reaction mixture was chromatographed on silica gel, eluting with 4:1 hexanes:EtOAc, to give, after evaporation of the appropriate fractions, the methylamine intermediate (0.8 g) in 38% yield.

Step 2: The product of Step 1 (0.12 g), THF (5 ml) and EtNCO (54 mg) were heated at reflux for 17 h. EtNCO (54 mg) and 1,4-dioxane (2 ml) were added and the resulting solution was heated in a sealed tube at 65 °C for 17 h. The solution was cooled, evaporated and purified by preparative plate chromatography (silica gel; 25% EtOAc: CH_2Cl_2), to give the desired product (0.1 g) as a crystalline solid in 64% yield.

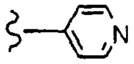
Step 3: The product of Step 2 (0.1 g) was treated in the same fashion as Example 8, Step 3 (p 28) to give the desired intermediate (0.08 g) which was used directly in the next step.

Step 4: The product of Example 8, Step 3(75 mg; trihydrochloride form) and the product of Step 3 (0.04 g) were treated in the same fashion as Example 8, Step 4, to give, after work up and purification, **8AQ** as the free base form, which was converted to the HCl salt (65 mg) in 62% yield.

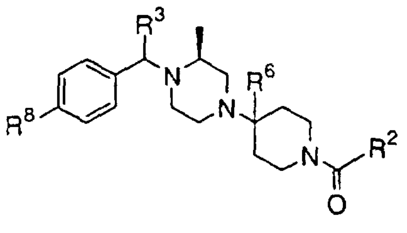
[0092] Using procedures described above and employing commercially available acids, compounds 8AY-8BT of the structure



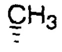
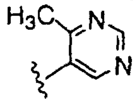
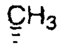
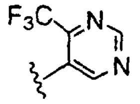
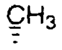
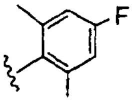
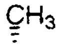
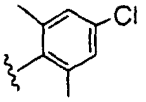
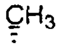
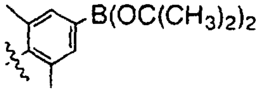
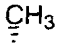
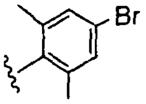
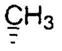
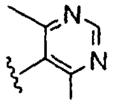
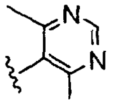
were prepared, wherein R^{10} and R^{11} are defined in the table:

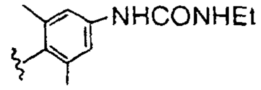
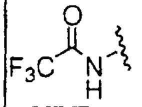
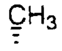
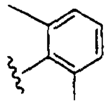
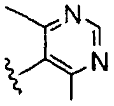
Ex.	R^{10}	R^{11}	Mp (° C)
8AY	$-CH_3$	H	205-208
8AZ	F	H	250-255
8BA	Cl	H	215-217
8BC	$-CH_3$	Br	228-231
8BD	$-CH_3$		194-198
8BE	Cl	Cl	240-241
8BF	Cl	F	268-270
8BG	Br	H	210-213
8BH	Cl	Br	213-217
8BI	Br	F	176-181
8BJ	I	H	184-190
8BK	$-CF_3$	F	204-209
8BL	F	F	268-270
8BM	Cl	NH_2	215-220
8BN	H	F	258-260
8BO	H	Br	238-240
8BP	H	Cl	235-240
8BQ	Br	Cl	190-194
8BR	CH_3CH_2-	H	211-214
8BS	$-Si(CH_3)_3$	H	230-240
8BT	Cl	NO_2	275-280

[0093] Using procedures similar to those described above, the following compounds were prepared:



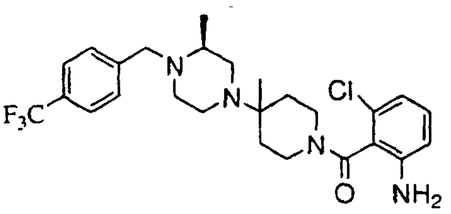
wherein R^8, R^3, R^6 and R^2 are as defined in the table:

Ex.	R^8	R^3	R^6	R^2	Mp (° C)
8BU	$-CF_3$		$-CH_3$		195-220
8BV	$-CF_3$		$-CH_3$		80-85
8BW	$-CF_3$		$-CH_3$		212-217
8BX	$-CF_3$		$-CH_3$		235-238
8BY	$-CF_3$		$-CH_3$		195-200
8BZ	$-CF_3$		$-CH_3$		237-240
8CA	$-CF_3$		$-CH_2CH_3$		179-181
8CB	$-CF_3$		$-CH_2CH_3$		200-202

8CD	$-CF_3$		$-CH_2CH_3$		199-205
8CE			$-CH_3$		206-210
8CF	$-CF_3$		$-CH_3$		235-239

Example 9

[0094]



<u>Step 1:</u> A solution of 4-N-BOC-2(S)-methyl piperazine (1.5g; 7.5 mmol), 4-methoxy-benzyl chloride (1.1 ml; 8.1

mmol) and diisopropyl ethyl amine (1.5 ml) in dry CH_3CN were heated at reflux for 5 h. The reaction mixture was cooled to RT and volatiles were removed in vacuo. The residue was dissolved in CH_2Cl_2 (30 ml) and washed with water and brine. Concentration gave the crude product, which was purified by FSGC (10% EtOAc-hexanes) to obtain 2.1 g (88%) of product as a pale yellow liquid.

TFA (6 ml) was added to a solution of the above compound (2.1 g; 6.56 mmol) in 12 ml of CH_2Cl_2 and the mixture stirred at 25° C for 1.5 h. The reaction was quenched with 1 N NaOH and adjusted to pH 10. Extractive work-up in CH_2Cl_2 furnished the desired product (1.4g; 97%) as a colorless gum.

Step 2: A mixture of the product of step 1 (1.4g; 6.36 mmol), N-BOC-4-piperidinone (1.27g; 6.4 mmol) and $Ti(OiPr)_4$ (1.9 ml; 6.4 mmol) was stirred at 25° C for 24h. A 1 M solution of Et_2AlCN in toluene (7.6 ml) was added to the reaction mixture and the mixture stirred at ambient temperature for another day. The Strecker amine thus formed was worked-up and isolated (2.7g; 100%) as described in Example 8, step 2. TLC R_f = 0.3 in 25% EtOAc-CH_2Cl_2.

The Strecker amine (2.7g; 6.3 mmol) was dissolved in 15 ml of dry THF at 0° C and CH_3MgBr (3M in Et_2O; 10.5 ml) was added to it. After 1 h, the ice bath was removed and the reaction allowed to proceed at RT for 15 h. TLC analysis of the heterogeneous reaction mixture showed no change from the starting material; the mixture was warmed at 60° C for 5 h with no observed change in TLC behavior. The reaction mixture was quenched with saturated NH_4Cl and organic products extracted into CH_2Cl_2. FSGC of the crude product (2.7g) using 15% acetone-hexanes as the eluant provided the desired ipso-methyl compound as a colorless gum (2.3g; 87%).

Step 3: The product of step 2 (1.7g; 4.08 mmol), ammonium formate (1.4g; 22 mmol) and 10% palladium on carbon (0.4g) were mixed in 20 ml of CH_3OH and heated at reflux for 5 h. The reaction mixture was filtered through celite and volatiles were removed. The residue was dissolved in CH_2Cl_2 and washed with 10% NaOH solution, water and brine. Concentration in vacuo gave 1.1 g (92%) of pale yellow gum.

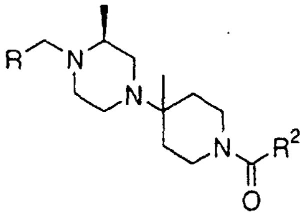
Step 4: A solution of the product of step 3 (0.12g; 0.4 mmol), p-trifluoromethyl benzyl bromide (0.1 g; 0.4 mmol) and diisopropyl ethyl amine (0.1 ml) in dry CH_3CN was gently warmed (60-70° C) for 16 h. The mixture was cooled and organic product isolated via extractive work-up in CH_2Cl_2. FSGC (10-30% Et_2O-CH_2Cl_2; R_f = 0.4) yielded the major product as a colorless film (0.12g; 68%).

Treatment of the above product (in CH_2Cl_2) with TFA (1 ml) for 1 h followed by basification and standard work-up provided the desired compound (0.09g; 96%) as a colorless film.

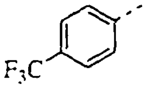
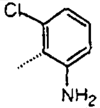
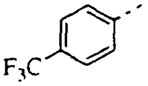
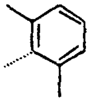
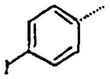
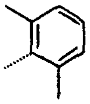
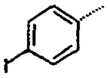
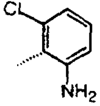
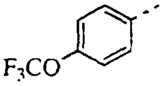
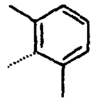
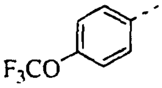
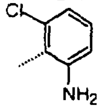
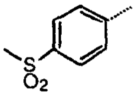
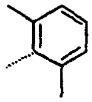
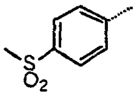
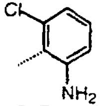
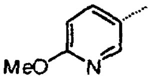
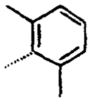
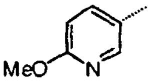
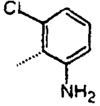
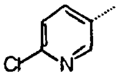
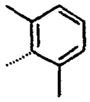
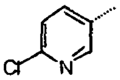
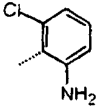
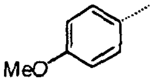
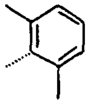
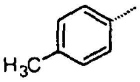
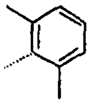
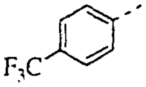
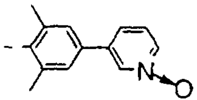
Step 5: The product of step 4 (0.045g; 0.13 mmol) and 6-chloro anthranilic acid (0.022g; 0.13 mmol) were coupled as described in Example 1 and after work-up and FSGC (5% CH_3OH in CH_2Cl_2) the title compound was isolated as a colorless film (0.058g; 90%).

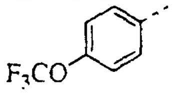
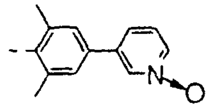
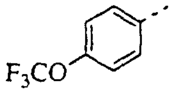
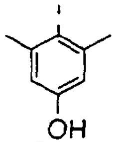
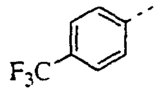
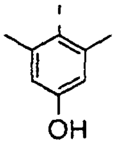
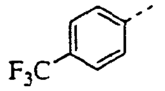
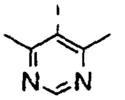
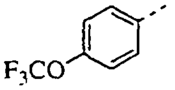
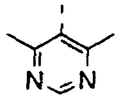
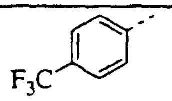
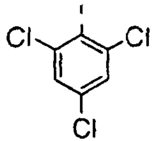
[0095] The HCl salt of the title compound was prepared in the usual manner by the reaction of the free base with 1 M HCl-Et_2O and processing the precipitate to obtain a beige solid (0.066g).

[0096] Using a similar procedure, the product of step 3 was converted to other compounds, first by alkylation of the piperazine nitrogen with the appropriate halide, followed by deprotection and coupling of the piperidinyl portion with the appropriate acid to form the amides of general structure:



wherein R and R^2 are as defined in the table:

Ex.	R	R^2	Mp (° C)	HRMS (MH$^+$)
9A			246-249	509.2293
9B			204-208	488.2895
9C			247-249	546.1978
9D			249-251	567.1407
9E			206-209	504.2848
9F			244-247	525.2242
9G			201-204	484.2630
9H			222-226	505.2039
9I			226-229	451.3060
9J			229-232	472.2474
9K			268-271	455.2577
9L			212-216	476.1975
9M			229-232	450.3126
9N			246-251	434.3168
9O			192-205	--

9P			185-196	--
9Q			202-210	--
9R			203-206	--
9S			190-205	--
9T			180-205	--
9U			258-262	--

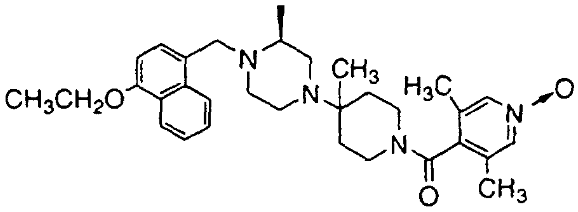
[0097] Using a similar procedure described below, compounds wherein R is 4-ethoxynaphthyl were also prepared:

Steps 1-3: See Example 9.

Step 4A: 4-Hydroxynaphthaldehyde (0.86g) and K_2CO_3 (1.38g, 2 equiv.) in CH_3CN (35 ml) were treated with CH_3CH_2I (0.80 ml, 2 equiv.), and the resulting mixture was stirred at RT for 20 h. The reaction mixture was concentrated in vacuo, the residue treated with EtOAc, and the mixture filtered. The filtrate was partitioned with H_2O. The dried ($MgSO_4$) EtOAc was concentrated in vacuo to give an orange-brown residue (0.89g). This residue was placed on preparative thin layer plates (10, 1000µ), and eluted with CH_2Cl_2 to give the title compound (0.82g).

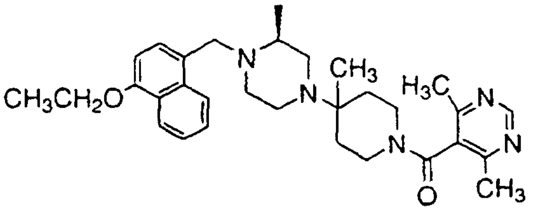
Step 4: Under argon, the products of step 3 (0.270g; 0.95 mmol) and step 4A (0.571 g; 2.9 mmol) in CH_2Cl_2 (25 ml) were stirred at RT for 30 min. $Na(OAc)_3BH$ (0.506g; 3.4 mmol) was added. After 19 h, the reaction mixture was quenched with dilute NaOH. The aqueous layer was washed with CH_2Cl_2 (3X). The combined CH_2Cl_2 solution was washed with H_2O (3X) and then brine. The dried ($MgSO_4$) CH_2Cl_2 solution was concentrated to -50 ml. Amberlyst 15 (4.5 meq/g: 2.4g; 11.025 mmeq) was added. After 19 h, additional Amberlyst 15 (2.3g) was added. After 7 h, the resin was washed with CH_2Cl_2 (5X), THF (5X), THF:H_2O (5X), H_2O (5X), CH_3OH (5X) and CH_2Cl_2 (5X). The resin was eluted with 2M NH_3 in CH_3OH (300 ml) (3X), followed by concentration in vacuo to give an amber oil (0.215g). The crude material was placed on preparative thin layer plates (4, 1000µ), and eluted with CH_2Cl_2: 2M NH_3 in CH_3OH (9:1) to give an amber oil (0.125g, 36%).

Step 5: Using the appropriate carboxylic acid in the procedure of Example 9, step 5, the following compounds were prepared:



9V

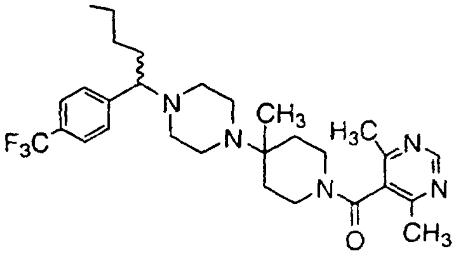
LCMS found M^+H = 531; HPLC* Retention time 5.52 min.



9W

LCMS found $M^+H = 516$; HPLC* Retention time 5.66 min.
*HPLC: VYDAC 218TP5405 column; gradient 5-95% B over 10 min hold 2 min; Soln A 0.1% TFA/H_2O, Soln B 0.1% TFA/CH_3CN at 245 nm.

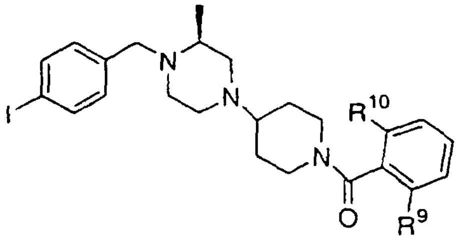
[0098] Using a similar procedure wherein the starting piperazine does not have the methyl substituent, the following compound was prepared:



(±) **9X**: M.p. 250 ºC

Example 10

[0099]



A. $R^9 = NH_2$; $R^{10} = Cl$
B. $R^9 = NH_2$; $R^{10} = CH_3$
C. $R^9, R^{10} = CH_3, CH_3$

Step 1: A solution of 4-N-BOC-2(S)-methyl piperazine (0.4g; 2 mmol), p-iodobenzaldehyde (0.46g; 2 mmol) and $NaBH(OAc)_3$ (0.65g; 3 mmol) in 6 ml of CH_2Cl_2 was heated at gentle reflux for 14 h. The contents were cooled, diluted with 30 ml of CH_2Cl_2 and washed with 1 N NaOH solution, water and brine to isolate an yellow oil (0.8g). FSGC (25% EtOAc-hexane) afforded the desired product (0.66g; 79%) as a colorless film. TLC $R_f = 0.6$ in 25% EtOAc-hexane

The BOC protecting group was removed from the product (0.66g; 1.58 mmol) by treatment with TFA (1 ml) in CH_2Cl_2 (2 ml). Following standard work up, the mono-alkylated piperazine (0.5g; 100%) was obtained as a colorless gum.

Step 2: $NaBH(OAc)_3$ (0.63g; 3 mmol) and two drops of AcOH were added to a solution of the product of step 1 (0.5g; 1.58 mmol) and N-BOC-piperidinone (0.6g; 3 mmol) in 5 ml of CH_2Cl_2 and the resulting solution was stirred at ambient temperature for 16 h. After the usual work up and FSGC, the desired product (0.6g; 76%) was obtained as a colorless oil. TLC $R_f = 0.4$ in 25% acetone-CH_2Cl_2.

The free piperidine (0.38g; 79%) was prepared from the N-BOC protected compound (0.6g; 1.2 mmol) by treatment with TFA (2 ml) in CH_2Cl_2 (5 ml).

Compound 10A: The coupling of 6-chloro anthranilic acid (0.065g; 0.38 mmol) with the product of step 2 (0.127g; 0.32 mmol) in the presence of DEC (0.092g; 0.48 mmol), HOBT (0.065g; 0.48 mmol) and diisopropylethyl amine (0.1 ml), followed by product isolation, were carried out as described previously. This procedure furnished the compound 10A (0.13g; 73%) as a colorless film. TLC R_f = 0.5 / 0.45 for a pair of rotomers in 2% CH_3OH-CH_2Cl_2.

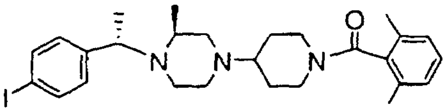
The HCl salt of the title compound was prepared in the usual manner. Mp: 198-202° C; HRMS (MH^+) = 553.1231.

Compound 10B: Coupling the product of step 2 with 6-methyl anthranilic acid gave compound 10B (HCl salt) in 73% yield. Mp: 197-200° C; HRMS (MH^+) = 533.1774.

Compound 10C: 2,6-Dimethyl benzoic acid was coupled to the product of step 2 to obtain the amide 10C (HCl salt) in 50% yield. Mp: 202-205° C; HRMS (MH^+) = 532.1826.

Example 11

[0100]



Step 1: (*S*)-Methylbenzylamine (27 ml, 0.2 mol) in CH_2Cl_2 (50 ml) was dropped into ice-cold trifluoroacetic anhydride (40 ml) in CH_2Cl_2 (200 ml) within 15 min. The mixture was stirred at RT for 1 h, then cooled in an ice water bath, iodine was added (27 g, 0.106 mol) and then [bis(trifluoroacetoxy)iodo]-benzene (25 g, 0.058 mol). After being stirred at RT overnight in the dark, more [bis(trifluoroacetoxy)iodo]benzene (24 g, 0.056 mol) was added and the mixture was stirred at RT for one more day. The mixture was diluted with CH_2Cl_2 (500 ml) and ice-cold Na_2SO_3 (10% aqueous, 500 ml) and stirred for 0.5 h. The organic layer was separated and washed with $NaHCO_3$, filtered through a short silica gel column and washed with CH_2Cl_2 (500 ml). After CH_2Cl_2 was evaporated, Et_2O (125 ml) was added and the mixture stirred for 10 min. Hexanes (600 ml) was added gradually to the Et_2O solution and the mixture was stirred for 0.5 h. The precipitate was collected and washed with hexanes. The white solid was dried at RT and iodo compound (36.5 g, 53% yield, R_f = 0.7, EtOAc/hexanes, 1:3) was obtained.

Step 2: The product of step 1 (11.2 g, 0.033 mol) was dissolved in CH_3OH (200 ml) and NaOH (15 g, 0.375 mol) in water (100 ml) was added dropwise. The mixture was stirred at RT for 2.5 h. After the CH_3OH was evaporated, the aqueous layer was extracted with Et_2O (3x100 ml) and the combined organic portion was washed with brine, dried over Na_2SO_4, filtered and concentrated to give a free amine.

Methyl-*R*-lactate (4.08 g, 0.039 mol) was dissolved in CH_2Cl_2 (40 ml) and the mixture was stirred and cooled in acetone-CO_2 to -78° C under N_2 atmosphere. Trifluoromethane sulfonic anhydride (10.2 g, 0.036 mmol) and then 2,6-lutidine (6.27 g, 0.059 mol) were added and the mixture was stirred for 5 min at -78° C. The mixture was warmed to RT and stirred for 30 min. More CH_2Cl_2 was added to the mixture and the solution was washed with 2N HCl. The freshly prepared amine from above was added to the triflate solution followed by K_2CO_3 (18 g, 0.132 mol) in water (20 ml). The mixture was stirred at RT overnight. Extractive work-up with CH_2Cl_2 followed by silica gel column chromatography gave a secondary amine (8.27 g, 75% yield, R_f = 0.65, hexanes/EtOAc, 3:1) as a yellow syrup.

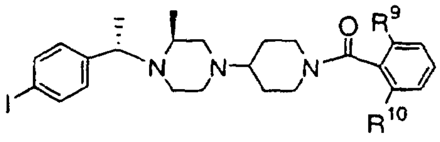
Step 3: The amine of step 2 (17.3 g, 0.052 mol) was dissolved in dichloroethane (100 ml) and $ClCH_2COCl$ (117.2 g, 82 ml, 1.04 mol). The mixture was stirred under reflux condition for 3 h. Both the solvent and $ClCH_2COCl$ were removed under vacuum. The remaining yellow syrup was dissolved in DMSO (40 ml) at 0° C and NaI (5.2 g, 0.035 mol) and NH_4OH (56 ml, 1.04 mol) were added. The reaction mixture was stirred 0° C for 30 min., warmed up to RT and stirred overnight. Water (100 ml) was added to the mixture and the precipitate was filtered and washed with water. The white solid obtained was dried in air to give the diketopiperazine (14.3 g, 77% yield, R_f = 0.56, hexanes/ EtOAc, 3:1).

Step 4: The diketopiperazine of step 3 (14.3 g, 0.04 mol) was dissolved in dimethoxy ethane (200 ml) and $NaBH_4$ (15.1 g, 0.4 mol) and $BF_3\cdot OEt_2$ (34 g, 29.5 ml, 0.24 mol) were added to the solution. The mixture was stirred under reflux conditions for 3 h and then cooled to about 0° C on a ice bath. CH_3OH (500 ml) and then concentrated HCl (300 ml) were added slowly to the mixture. The solution was stirred for 20 min. at RT and then under reflux conditions for 45 min. The mixture was concentrated and NaOH was added until the pH was more than 10. Extractive work up with EtOAc gave the desired piperazine as a yellow syrup (12.9 g, 98% yield).

Step 5: The product of step 4 (1.9 g, 5.79 mmol), N-BOC-4-piperidone (5.73 g, 28.8 mmol), $NaBH(OAc)_3$ (6.1 g, 28.8 mmol) and 2M AcOH (5.76 ml, 11.52 mmol) were combined in CH_2Cl_2 (150 ml) and the mixture was stirred overnight. After the solvent was removed, NaOH (3N) was added and extractive work up with EtOAc followed by silica gel chromatography afforded pure piperazino-piperidine (2.21 g, 75% yield, R_f = 0.18, hexanes/EtOAc, 1:1) as a syrup.

Step 6: The product of step 5 (1.9 g, 3.7 mmol) was dissolved in CH_2Cl_2 (10 ml) and TFA (10 ml) was added. The mixture was stirred at RT for 2 h. After the removal of the solvent and TFA under reduced pressure, NaOH solution (3N) was added to the remaining syrup and extractive work up with EtOAc gave the free piperazino-piperidine (1.3 g, 85% yield) as a yellow syrup. To a solution of the free piperazino-piperidine (200 mg, 0.484 mmol) in CH_2Cl_2 (2 ml) were added 2,6-dimethylbenzoic acid (150 mg, 0.99 mmol), DEC (191 mg, 0.99 mmol) and HOBT (135 mg, 0.99 mmol). The mixture was stirred at RT overnight and then the solvent was removed under reduced pressure. NaOH solution (3N) was added to the remaining syrup and extractive work up with EtOAc followed by column chromatography afforded the title compound (210 mg, 80% yield, $R_f = 0.37$, CH_2Cl_2/CH_3OH, 20:1). HRMS (as the HCl) calcd for $C_{27}H_{37}N_3OI$ $(M+H^+)$ 546.1981, found 546.1965. Mp: 190° C (dec.).

[0101] Using a similar procedure, compounds of the formula

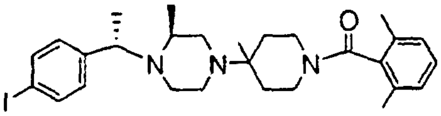


were prepared, wherein R^9 and R^{10} are as defined in the table:

Ex	R^9	R^{10}	Mp (°C)	HRMS
11A	$-CH_3$	$-NH_2$	198 (dec.)	547.1928
11B	-Cl	$-NH_2$	203 (dec.)	567.1395
11C	-OH	-OH	200 (dec.)	550.1555
11D	$-OCH_3$	$-OCH_3$	200 (dec.)	578.1860

Example 12

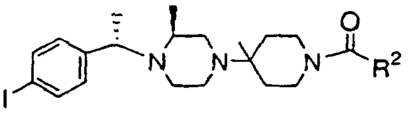
[0102]



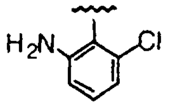
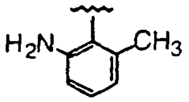
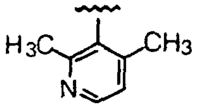
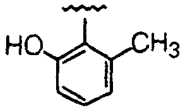
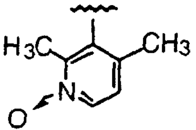
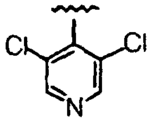
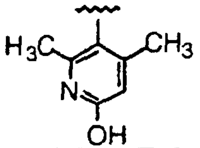
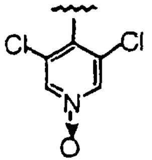
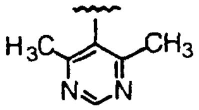
Step 1: To the solution of the product of Example 11, step 4 (1.4 g, 4.2 mmol) and 1-*tert*-butoxycarbonyl-4-piperidone (0.93 g, 4.67 mmol) in CH_2Cl_2 was added $Ti(OiPr)_4$ (1.19 g, 4.2 mmol) and the mixture was stirred at RT overnight. 1 M Et_2AlCN (5.04 ml, 5.04 mmol) was added, the mixture was stirred overnight at RT and the solvent was evaporated. Saturated $NaHCO_3$ was added to the residue and extractive work up with EtOAc gave the Strecker amine as a yellow syrup. The syrup was dissolved in THF (40 ml) and 3M CH_3MgBr (7 ml, 21 mmol) was added to the solution. The mixture was stirred at RT overnight, then cooled to 0° C and saturated NH_4Cl and water was added. Extractive work up with EtOAc followed by silica gel chromatography gave the piperazino-piperidine product (1.78 g, 81% yield, $R_f = 0.52$, hexanes/EtOAc, 2:1).

Step 2: Treat the product of step 1 in the manner described in Example 11, Step 6, to obtain the title compound. Mp. 190° C (dec.); HRMS (as the HCl salt): found 560.2145.

[0103] Using a similar procedure, compounds of the formula

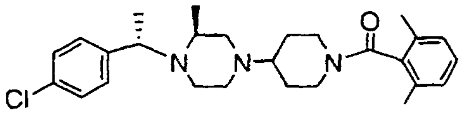


were prepared, wherein R^2 is as defined in the table:

Ex	R^2	mp (°C)	HRMS
12A		145 (dec.)	581.1537
12B		150 (dec.)	561.2083
12C		208 (dec.)	561.2096
12D		206 (dec.)	562.1944
12E		190 (dec.)	577.2029
12F		245 (dec.)	601.1006
12G		218 (dec.)	577.2029
12H		195 (dec.)	617.0945
12I		116 (dec.)	562.2048

Example 13

[0104]

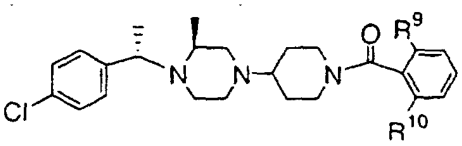


Step 1: To a solution of the N-BOC protected product of Example 11, step 4 (250 mg, 0.581 mmol) in DMF (2.5 ml), CuCl (1 g, 10.1 mmol) was added. The suspension was stirred under N_2 at 110° C for 24 h. After the mixture was cooled to RT, NH_4OH was added and the solution gradually turned bright blue. Extractive work up with EtOAc

gave a mixture of the chloro-substituted piperazine and its BOC derivative. After treating the mixture with TFA (5 ml) in CH_2Cl_2 (2 ml) for 2 h, the solvent was evaporated and NaOH (3N) was added. Extractive work up with EtOAc afforded the pure piperazine (110 mg, 79%) as a yellow syrup.

Step 2: The product of step 1 was treated in a manner similar to Example 11, steps 5 and 6, to obtain the title compound. Mp. 180° C (dec.); HRMS (as the HCl salt): found 454.2617.

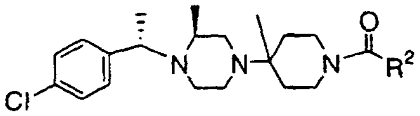
[0105] Using a similar procedure, compounds of the formula



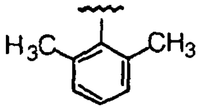
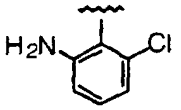
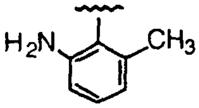
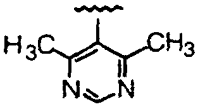
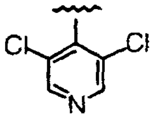
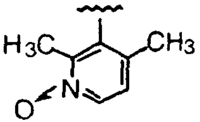
were prepared, wherein R^9 and R^{10} are as defined in the table:

Ex	R^9	R^{10}	Mp (°C)	HRMS
13A	$-CH_3$	$-NH_2$	200 (dec.)	455.2577
13B	-Cl	$-NH_2$	200 (dec.)	475.2023
13C	-Cl	-Cl	187 (dec.)	494.1536

[0106] Using the product of step 1 in the procedure of Example 12, compounds of the formula

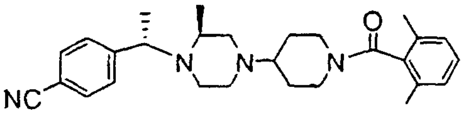


were prepared, wherein R^2 is as defined in the table:

Ex	R^2	Mp (° C)	HRMS
13D		197 (dec.)	468.2779
13E		205 (dec.)	489.2184
13F		210 (dec.)	469.2734
13G		195 (dec.)	470.2689
13H		260 (dec.)	509.1634
13I		200 (dec.)	485.2688

Example 14

[0107]

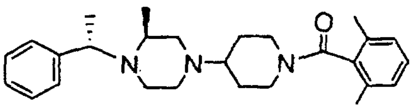


Step 1: To a solution of the N-BOC protected product of Example 11, step 4 (5 g, 0.012 mol) in DMF (20 ml), CuCN (20.8 g, 0.23 mol) was added. The suspension was stirred under N_2 at 110° C for 22 h. After the mixture was cooled to RT, NH_4OH was added and the solution gradually turned bright blue. Extractive work up with EtOAc followed by silica gel column chromatography gave the cyano derivative (2.29 g, 60% yield, R_f = 0.5, hexanes/EtOAc, 4:1), the carboxamide derivative (0.95 g, 23.6% yield, R_f = 0.2, CH_2Cl_2/CH_3OH, 10:1) and the unsubstituted derivative (85 mg, 2.4% yield, R_f = 0.75, hexanes/EtOAc, 2:1).

Step 2: The BOC group on the cyano compound of step 1 was first removed under acidic conditions and the resultant amine was converted to the title compound following the procedure of Example 11, steps 5 and 6. HRMS (as the HCl salt): found 445.4970.

Example 15

[0108]



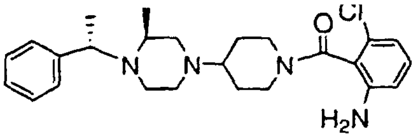
Step 1: To a solution of the N-BOC protected product of Example 11, step 4 (1.4 g, 3.26 mmol) and CuCl (1.61 g, 16.3 mmol) in CH_3OH at 0° C was added $NaBH_4$ (3.69 g, 97.6 mmol) slowly. A black precipitate was formed. The

mixture was warmed to RT and stirred overnight. The precipitate was removed by celite filtration and CH_3OH was removed under vacuum. Extractive work up with EtOAc afforded the desired compound (1g, 100% yield, $R_f = 0.55$, hexanes/EtOAc, 5:1) as a syrup.

Step 2: The BOC group on the product of step 1 was removed under acidic conditions and the resultant amine was converted to the title compound following the procedure of Example 11, steps 5 and 6.

Mp. 195° C; HRMS (as the HCl salt): found 420.3016.

[0109] Using a similar procedure, the following compound is prepared:

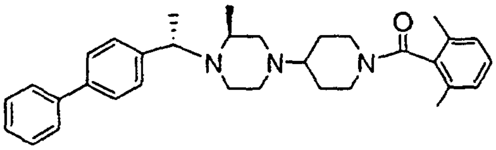


15A

HRMS (as the HCl salt): found 441.2426

Example 16

[0110]

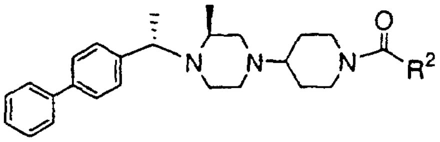


Step 1: To a solution of the N-BOC protected product of Example 11, step 4 (2.5 g, 5.8 mmol) in benzene were added phenyl boric acid (1.68 g, 13.8 mmol), 2M Na_2CO_3 (14 ml) and tetrakis(tri-phenyl phosphine) palladium (0.67 g, 0.58 mmol). The mixture was stirred under reflux overnight. Extractive work up with EtOAc followed by silica gel column chromatography gave the phenyl derivative (1.37g, 62% yield, $R_f = 0.5$, hexane/EtOAc, 5:1) as a syrup.

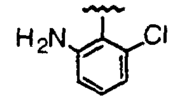
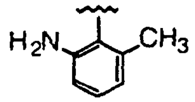
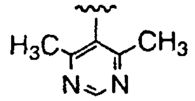
Step 2: The BOC group on the product of step 1 was removed under acidic conditions and the resultant amine was converted to the title compound following the procedure of Example 11, steps 5 and 6.

Mp. 190° C; HRMS (as the HCl salt): found 496.3319.

[0111] Using a similar procedure, compounds of the formula



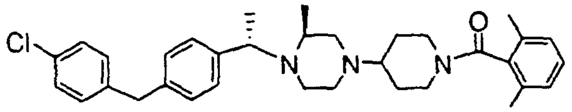
were prepared, wherein R^2 is as defined in the table:

Sch	Ex	R^2	Mp (° C)	HRMS
223254	16A		190 (dec.)	517.2754
223255	16B		65-70*	497.3287
2?5666	16C		190 (dec.)	498.3225

* free base

Example 17

[0112]



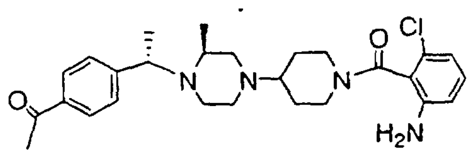
Step 1: The N-BOC protected product of Example 11, step 4 (800 mg, 1.88 mmol) was dissolved in dry THF and the temperature was brought to -78° C under N_2. Butyl lithium (2.5 M solution, 0.832 ml, 2 mmol) was added and the mixture was stirred at -78° C for 10 min. The solution then was dropped into p-chlorobenzyl aldehyde (234 mg, 2.07 mmol) in THF at -78° C. The mixture was stirred for 30 min. at -78° C, then gradually warmed up to RT. Saturated NH_4Cl was added to the mixture and extractive work up with EtOAc followed by silica gel column chromatography gave the desired alcohol (30 mg, 3.6% yield, R_f = 0.5, hexanes/EtOAc, 2: 1) as a yellow syrup.

Step 2: A solution of alcohol of step 1 (40 mg, 0.090 mmol), triethylsilane (52 mg, 0.45 mmol) and TFA (5 ml) in CH_2Cl_2 (5 ml) was stirred under reflux conditions for 2 h. After CH_2Cl_2, triethylsilane and TFA were removed under reduced pressure, NaOH solution (3N) was added to the remaining syrup. Extractive work up with EtOAc afforded the chlorobenzyl derivative (20 mg, 68% yield) as a yellow syrup..

Step 3: The product of step 2 was converted to the title compound following the procedure of Example 11, steps 5 and 6. Mp. 170° C (dec.); HRMS (as the HCl salt): found 544.3101.

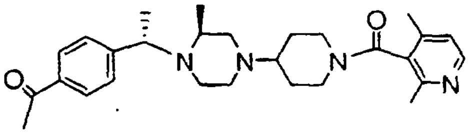
Example 18

[0113]



Step 1: To a solution of the N-BOC protected 4-piperidinyl derivative of the cyano compound of Example 14, step 1 (510 mg, 1.24 mmol) in Et_2O (4 ml) was added 3M CH_3MgBr (4 ml) in a dropwise manner. The mixture was stirred under reflux overnight. After the solution was cooled on ice-bath, 12N HCl (4 ml) was added and the mixture was stirred on a steam bath for 2 h. The solution was cooled to RT and solid NaOH pellets were added until the pH was more than 10. Extractive work up with EtOAc/CH_3OH (3:1) afforded the desired methyl ketone (249 mg, 61 % yield) as a syrup. Step 2: The product of step 1 was treated according to the standard DEC peptide coupling procedures of Example 11, step 6, to obtain the title compound. Mp. 210° C; HRMS (as the HCl salt): found 483.2522.

Using a similar procedure, the following compound is prepared:

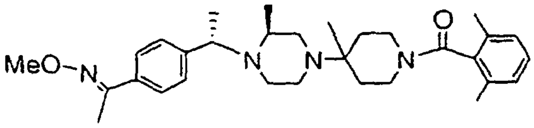


18A

Mp. 210° C (dec.); HRMS (as the HCl salt): found 463.3088

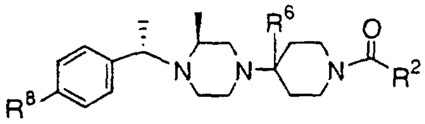
Example 19

[0114]

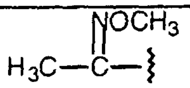
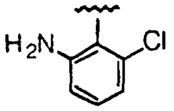
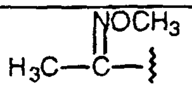
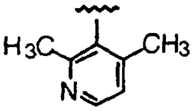
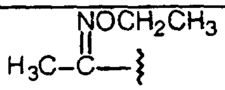
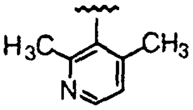
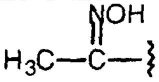
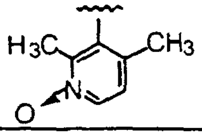
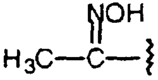
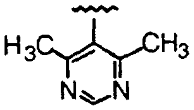


Step 1: To a solution of the product of Example 22 (140 mg, 0.29 mmol) in CH_3OH (10 ml) and EtOH (1 ml) were added $NH_2OCH_3 \cdot HCl$ (738 mg, 8.84 mmol) and NaOAc (725 mg, 8.84 mmol). The suspension was stirred at 40 °C overnight, the solvents were evaporated and water was added to the residue. Extractive work up with EtOAc followed by silica gel chromatography generated the title compound (99 mg, 68% yield, $R_f = 0.38$, CH_2Cl_2/CH_3OH, 20:1). HRMS (as the tartrate) calc'd. for $C_{31}H_{45}N_4O_2$ $(M+H^+)$ 505.3543; found 505.3542.

Using a similar procedure, compounds of the formula

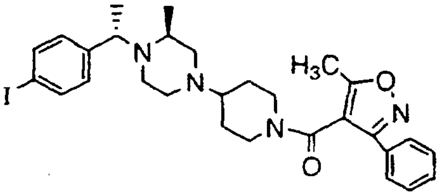


were prepared, wherein R^8, R^6 and R^2 are as defined in the table:

Ex	R^8	R^6	R^2	mp (° C)	HRMS
19A	 $H_3C-C(=NOCH_3)-$	H		194 (dec.)	512.2785
19B	 $H_3C-C(=NOCH_3)-$	H		150 (dec.)	492.3344
19C	 $H_3C-C(=NOCH_2CH_3)-$	H		--	506.3494
19D	 $H_3C-C(=NOH)-$	$-CH_3$		180 (dec.)	508.3296
19E	 $H_3C-C(=NOH)-$	$-CH_3$		195 (dec.)	493.3291

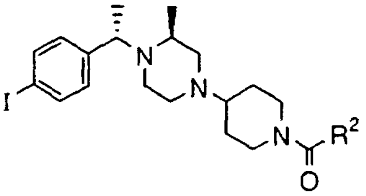
Example 20

[0115]

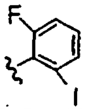
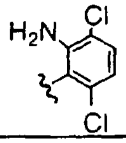
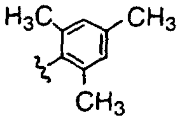
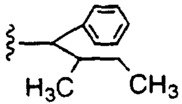
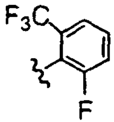
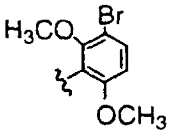
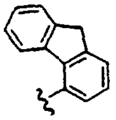
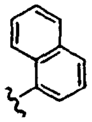
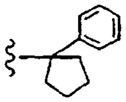
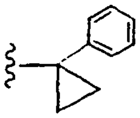
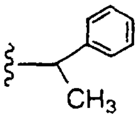


[0116] Dissolve the free piperazino-piperidine of Example 11, step 6 (1.7 g, 3.3 mmol) in $CHCl_3$ (30ml; = Stock solution A). Add 250 ul of stock solution A (0.027 mmol) to a slurry of 0.15 g (- 0.14 mmol) of resin bound cardodiimide (prepared by reacting Argopore-Cl resin with 1-(3-dimethylaminopropyl)3-ethyl carbodiimide in DMF at 100° C in DMF (1.5ml) in a polyethylene SPE cartridge. To this mixture add 75ul of a 1 M solution of 5-methyl-3-phenylisoxazole-4-carboxylic acid in DMF (0.075 mmol), and HOBT (24 ul of a 1 M solution in DMF). Shake this mixture for 14 h, filter and add 0.1 g of Amberlyst-15 resin (0.47 mmol) to the filtrate. Shake for 1 to 2 h, filter and wash the resin twice with each of the following solvents THF, CH_2Cl_2 and CH_3OH, then wash with THF and CH_2Cl_2. Treat the resin with 2M NH_3 in CH_3OH (1 time for 30 min, and 1 time for 5 min). Combine and concentrate the filtrates under reduced pressure to afford the title compound. LCMS found MH^+= 599.1 (calculated MW 598); TLC R_f = 0.74 ($CH_2Cl_2/CH_3OH/NH_4OH$ (95/5/0.5)).

[0117] Using the procedure above with the appropriate carboxylic acids gave the following compounds

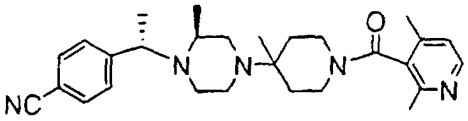


wherein R^2 is as defined in the table:

Ex.	R^2	LCMS results	TLC R_f values
20A		$MH^+ = 600.1$ $R_t = 6.56$ min.	0.92
20B		$MH^+ = 601.1$ $R_t = 5.69$ min.	0.63
20C		$MH^+ = 560.1$ $R_t = 5.77$ min.	0.60
20D		$MH^+ = 588.1$ $R_t = 6.61$ min.	0.66
20E		$MH^+ = 604.1$ $R_t = 5.60$ min.	0.87
20F		$MH^+ = 658.2$ $R_t = 5.69$ min.	0.86
20G		$MH^+ = 606.1$ $R_t = 6.17$ min.	0.43
20H		$MH^+ = 568.1$ $R_t = 5.67$ min.	0.57
20I		$MH^+ = 586.1$ $R_t = 6.02$ min.	0.63
20J		$MH^+ = 558.1$ $R_t = 5.35$ min.	0.33
20K		$MH^+ = 546.1$ $R_t = 5.37$ min.	0.52

Example 21

[0118]

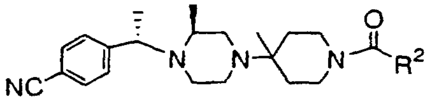


Step 1: The BOC group on the cyano compound of Example 14, step 1, was first removed under acidic conditions and the resulting amine (1.59 g, 6.96 mmol), 1-*tert*-butoxycarbonyl-4-piperidone (1.66g, 8.35 mmol) and $Ti(OiPr)_4$ (2.18 g, 7.66 mmol) in CH_2Cl_2 were stirred at RT overnight. 1 M Et_2AlCN (8.35 ml, 8.35 mmol) was added, the mixture was stirred overnight at RT and the solvent was evaporated. Saturated $NaHCO_3$ was added to the residue and extractive work up with EtOAc followed by column chromatography gave the Strecker amine as a yellow syrup (1.76 g, 58% yield, $R_f = 0.70$, Hexanes/EtOAc, 2:1).

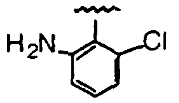
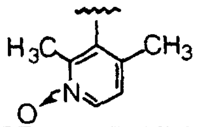
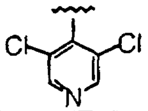
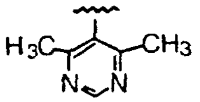
Step 2: The amine of Step 1 (200 mg, 0.46 mmol) was dissolved in anhydrous THF (2 ml) and 3M CH_3MgBr (0.76 ml, 2.29 mmol) was added dropwise. The mixture was stirred at RT overnight and then cooled to 0°C. Saturated NH_4Cl (10 ml) was added and a precipitate appeared. Water (40 ml) was addded and the precipitate disappeared. Extractive work up with EtOAc followed by column chromatography gave the desired ipso-methyl derivative (169 mg, 86% yield, $R_f = 0.53$, Hexanes/EtOAc, 2:1).

Step 3: The product of step 2 was treated in the manner described in Example 11, Step 6, to obtain the title compound. Dec. 198° C; HRMS (as the HCl salt): found 460.3079.

[0119] Using a similar procedure, compounds of the formula

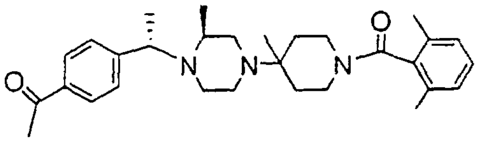


were prepared, wherein R^2 is as defined in the table:

Ex	R^2	Mp (°C)	HRMS
21A		205 (dec.)	480.2532
21B		65-75* * Mp for the free amine	476.3033
21C		250 (dec.)	500.1992
21D		195 (dec.)	461.3019

Example 22

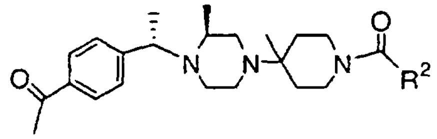
[0120]



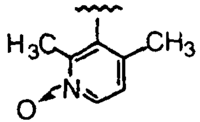
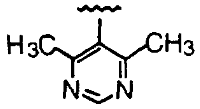
Step 1: The Strecker amine from Example 21, step 1 (380 mg, 0.87 mmol) was treated with CH_3MgBr (2.9 ml, 8.7 mmol) in Et_2O (5 ml) under reflux conditions overnight. The mixture was cooled on ice and water (5 ml) was added dropwise. 12N HCl (6 ml) was added and the mixture was stirred on a steam bath for 2 h. After the mixture was cooled on ice, NaOH was added until the pH of the solution was above 10. Extractive work up with EtOAc afforded a free amine as a syrup (307 mg, 100% yield).

Step 2: The product of step 1 was converted to the title compound following the peptide coupling procedure described in Example 11, step 6. Mp. 80-85° C; HRMS found 476.3271.

[0121] Using a similar procedure, compounds of the formula

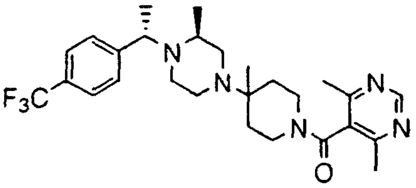


were prepared, wherein R^2 is as defined in the table:

Ex.	R^2	Mp (°C)	HRMS
22A		195 (dec.)	493.3172
22B		200 (dec.)	478.3178

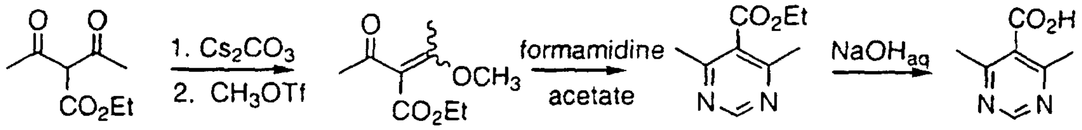
Example 23

[0122]



HCl salt

Steps 1-3:



Step 1: Ethyl diacetoacetate (93.4 g), Cs_2CO_3 (185 g) and CH_3CN (550 ml) were mixed together, using an overhead mechanical stirrer. CH_3CN (50 ml) was added and the resulting mixture was cooled to 0°C. Methyl trifluoromethane sulfonate (88.6 g) was added dropwise and after addition, the cooling bath was removed. The mixture was stirred for 1 h at RT, filtered, and the salts were washed with Et_2O (2 X 50 ml). The organic extracts were combined and Et_2O (300 ml) was added. The resulting mixture was filtered, the filter cake was washed with Et_2O (2 X 100 ml), the Et_2O extracts were combined and evaporated to half volume. The solution was cooled in an ice bath and washed once with cooled (0°C) 2 N NaOH (pH = 11). The Et_2O layer was dried over $MgSO_4$, filtered and evaporated to give the desired product as a yellow liquid (64.7 g) in 65% yield, which was used directly in the next step.

Step 2: The product of step 1 (64.2 g), sodium ethoxide in ethanol (commercial solution; 21 wt%; 113 g) ethanol (587 ml) and formamidine acetate (36.2 g) were mixed together at RT. After refluxing for 4 h, the mixture was cooled to RT, the resulting precipitate was filtered off and the ethanol was removed under vacuum. The resulting liquid was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 150 ml). The CH_2Cl_2 extracts were dried over $MgSO_4$, filtered and evaporated to give a dark crude liquid (50.7 g) which was purified by silica gel chromatography (980 g; 4:1 hexanes:EtOAc as eluant). After evaporation of the appropriate fractions, the desired product (28.5 g) was isolated in 46% yield and used directly in the next step.

Step 3: The product of step 2 (28.1 g), NaOH (6.72 g), water (65 ml) and EtOH (130 ml) were mixed together at RT and heated at reflux for 1 h. The resulting solution was cooled to RT and the volatile materials were removed in vacuo until a thick paste resulted. Water (20 ml) was added, the mixture was cooled to 0°C and conc. HCl (14.3 ml) was added dropwise with stirring. The resulting white precipitate was collected by filtration, washed with ice water (2 X 10 ml) and air dried with suction for 30 min. The resulting white solid was treated with toluene (2 x 20 ml), the solvent was removed in vacuo at 50°C and then dried under vacuum (1 mm Hg) for 18 h. The desired product (14.9 g) was isolated as a white solid in 63% yield, mp: 176-178°C. Elemental analysis of $C_7H_8N_2O_2$: calc'd C 55.26%, H 5.30%, N 18.41%; found: C 55.13%, H 5.44%, N 18.18%.

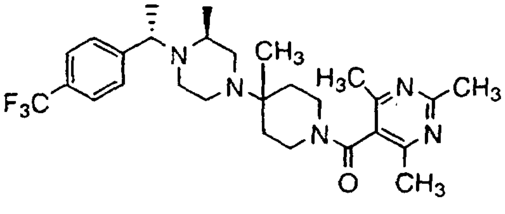
A second crop of product was isolated by evaporation of the aqueous filtrate (from above) to dryness and addition of water (20 ml). The resulting mixture was stirred at RT for 5 min, cooled in an ice bath and the precipitate formed was collected by filtration. The resulting solid was washed with ice water (2 X 5 ml) and dried as described above to give the product (4.68 g) as a cream colored solid to give a combined yield of 83%.

Step 4: The product of Example 4, step 6 (trihydrochloride form; 5.4 g), DMF (11.3 ml), HOBt (3.07 g), diisopropyl ethyl amine (12.3 ml) and the product of step 3 (3.45 g) were mixed together and DEC (4.35 g) was added in portions over 15 min. The resulting mixture was heated at 45°C for 18 h, cooled to RT, diluted with EtOAc (80 ml) and washed with 2 N NaOH (25 ml). The aqueous layer was extracted with EtOAc (3 x 25 ml), the organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered and evaporated. The resulting crude oil was purified by silica gel chromatography (170 g; 76:19:5 hexanes:EtOAc:Et_3N as eluant). After evaporation of the appropriate fractions, the free base form of the title compound (5.21 g) was isolated as a light colored foam in 91 % yield.

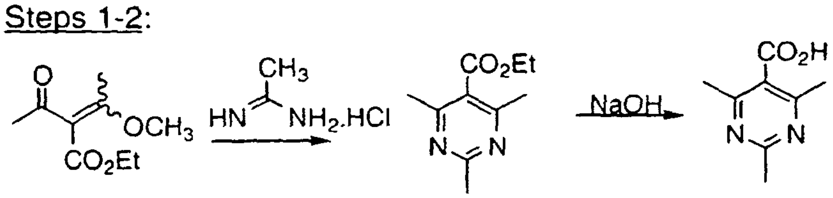
Step 5: To a cooled (0°C) solution of the free base of step 4 (2.00 g) and EtOAc (20 ml) was added HCl (3.0 ml of a 4.0 M solution in 1,4-dioxane). The resulting mixture was warmed to RT, diluted with Et_2O (20 ml), filtered, washed with Et_2O (2 X 20 ml), air dried with suction for 10 min and then under vacuum (1 mm Hg) at 90°C for 5 h to give the title compound (2.30 g) as a white solid in 97% yield. mp: 159-162°C.

Elemental analysis of $C_{27}H_{36}N_5OF_3$•2HCl•0.5H_2O: calc'd: C 55.38%, H 6.71%, N 11.96%, Cl 12.11%; found: C 55.19%, H 6.69%, N 11.75%, Cl 11.45%.

[0123] Additional pyrimidine derivative-compounds were made using similar procedures:



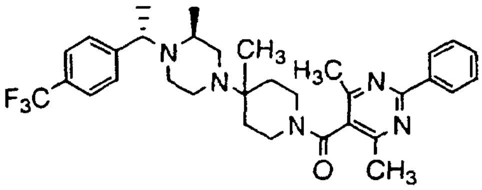
HCl salt **23A**



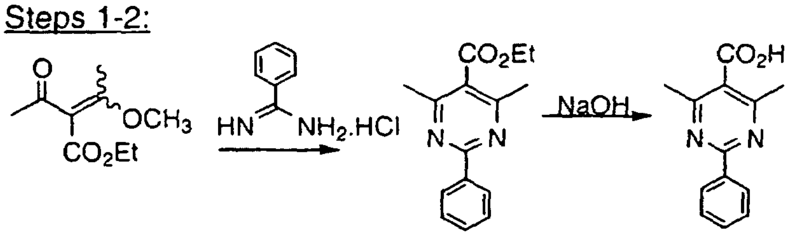
Step 1: The product of Example 23, step 1 was treated in the same manner as in Example 23, step 2, substituting acetamidine hydrochloride (2.03 g) for formamidine acetate. The amounts of the reagents were: product of Example 23, step 1 (4.0 g), ethanol (20 ml) and sodium ethoxide in ethanol (commercial solution; 21 wt%; 8.03 g). After extraction and purification as described above, the product was isolated (1.7 g) as a colorless liquid in 41 % yield, which was used directly in the next step.

Step 2: The product of step 1 (1.7 g) was treated in the same manner as Example 23, step 3, using ethanol (5 ml), water (5 ml) and NaOH (1.0 g). After extraction and purification as described above, the product was isolated (0.12 g) as a white solid in 8% yield, which was used directly in the next step.

Step 3: The product of Example 4, step 6 (0.05 g), and the product of step 2 (immediately above) (0.028 g) were subjected to the same reaction conditions as in Example 23, step 4, using HOBt (20 mg), DEC (45 mg), diisopropyl ethylamine (40 mg) and DMF (1.5 ml). After extraction and purification as described above, the product was converted to its HCl salt using the procedure outlined for Example 23, step 5 to give the title compound (77 mg) as a white solid in 97% yield over the two steps. mp: 185-190°C.



HCl salt **23B**

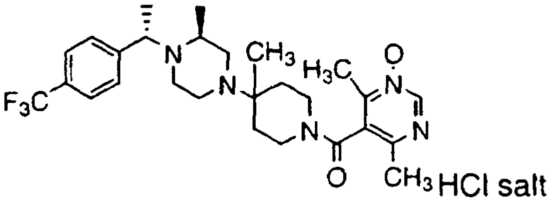


Step 1: The product of Example 23, step 1 was treated in the same as in Example 23, step 2, substituting benzamidine hydrochloride (3.35 g) for formamidine acetate. The amounts of the reagents were: product of Example 23, step 1 (4.0 g), ethanol (20 ml) and sodium ethoxide in ethanol (commercial solution; 21 wt%; 8.03 g). After extraction and purification as described above, the product was isolated (4.5 g) as a liquid in 82% yield which was used directly in the next step.

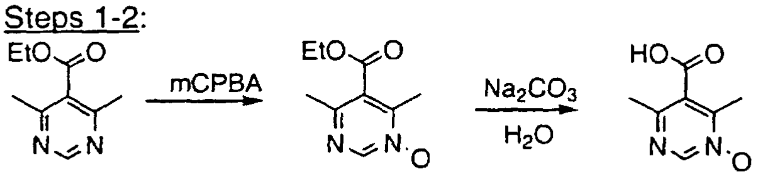
Step 2: The product of step 1 (4.5 g) was treated in the same manner as Example 23, step 3, using ethanol (10 ml), water (10 ml) and NaOH (2.0 g). After extraction and purification as described above, the product was isolated (3.0 g) as a white solid in 77% yield which was used directly in the next step.

Step 3: The product of Example 4, step 6 (75 mg), and the product of step 2 (immediately above) (39 mg) were subjected to the same reaction conditions as in Example 23, step 4, using HOBt (35 mg), DEC (53 mg), diisopropyl ethylamine (100 mg) and DMF (2 ml). After extraction and purification as described above, the product was converted to its HCl salt using the procedure outlined for Example 23, step 5 to give the title compound (98 mg) as a white solid in 96% yield over the two steps.

mp:250-253°C.



23C



Step 1: The product of Example 23, step 2 (528 mg) was dissolved in CH_2Cl_2 (5.0 ml) and meta-chloroperbenzoic acid (mCPBA) (600 mg) was added in three portions at RT. The resulting mixture was stirred at RT for 24 h and CH_2Cl_2 (2 ml) and mCPBA (200 mg) were added. After 3 h, the mixture was poured onto a silica gel column (40 g) and eluted with 1:1 hexanes:EtOAc and then 10:1 CH_2Cl_2:CH_3OH. After evaporation of the appropriate fractions, the product was isolated (512 mg) as a waxy white solid in 89% yield, which was used directly in the next step.

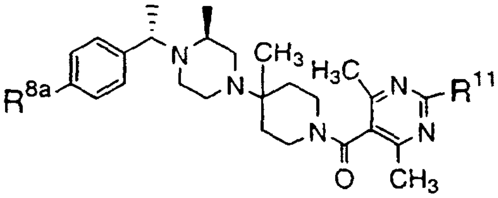
Step 2: The product of step 1 was dissolved in CH_3OH (1.8 ml) and a solution of 1.0 M Na_2CO_3 (1.5 ml) was added. After stirring at RT for 36 h, the resulting mixture was evaporated to dryness, toluene (2 ml) was added and the mixture was evaporated to dryness. The resulting crude solid (153 mg) was used directly in the next step without purification.

Step 3: The product of Example 4, step 6 (94 mg), and the product of step 2 (immediately above) (76 mg) were subjected to the same reaction conditions as in Example 23, step 4, using HOBt (92 mg), DEC (130 mg), diisopropyl ethylamine (0.14 ml) and DMF (0.25 ml). After extraction and purification by preparative thin layer chromatography (1000 μM silica plate; 95:5 EtOAc:Et_3N eluant), the free base form of the title compound was isolated (52 mg) as a foam in 40% yield. HRMS: calc'd: $M{\cdot}H^+$:

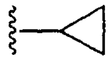
$C_{27}H_{37}N_5O_2F_3$: 520.2899; measured: 520.2908.

Step 4: The product of step 3 (52 mg) was subjected to the reaction conditions in Example 23, step 5, using EtOAc (1.0 ml) and HCl (4.0 M solution in 1,4-dioxane; 75 μl) to give, after work up, the title compound (44.5 mg) as a white solid in 76% yield. mp: decompostion above 161°C.

[0124] Using similar procedures, the compounds of the formula



were also prepared, wherein R^{8a} and R^{11} are as defined in the table:

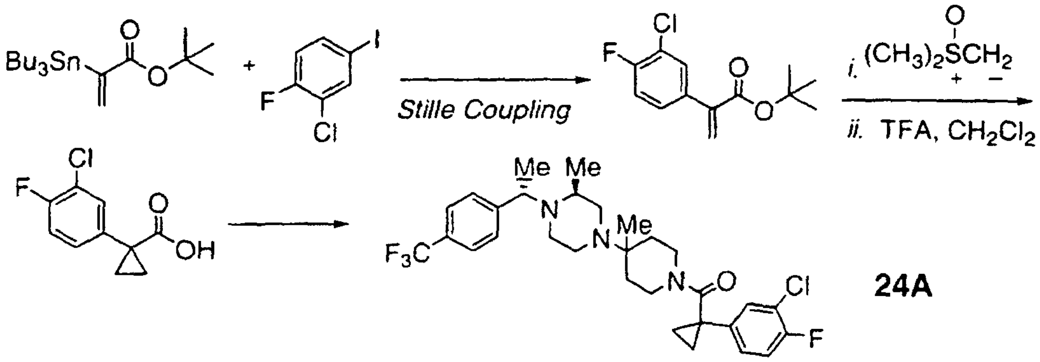
Ex.	R^{8a}	R^{11}	m.p. (°C)
23D	$-CF_3$	-OH	175-185
23E	$-CF_3$	$-OCH_3$	169-173
23F	$-CF_3$	$-NH_2$	200-210
23G	$-CF_3$	-NHCONHEt	184-190
23H	$-CF_3$	$-CF_3$	83-86
23I	$-CF_3$		154-159
23J	$-CF_3$	$-SCH_3$	>176 (dec)
23K	$-OCF_3$	$-CH_3$	205-210
23L	$-OCF_3$	Ph	239-242
23M	$-OCF_3$	$-OCH_3$	200-210
23N	$-OCF_3$	-OH	185-191

Example 24

Arylcyclopropylamides

[0125]

Method A:



24A

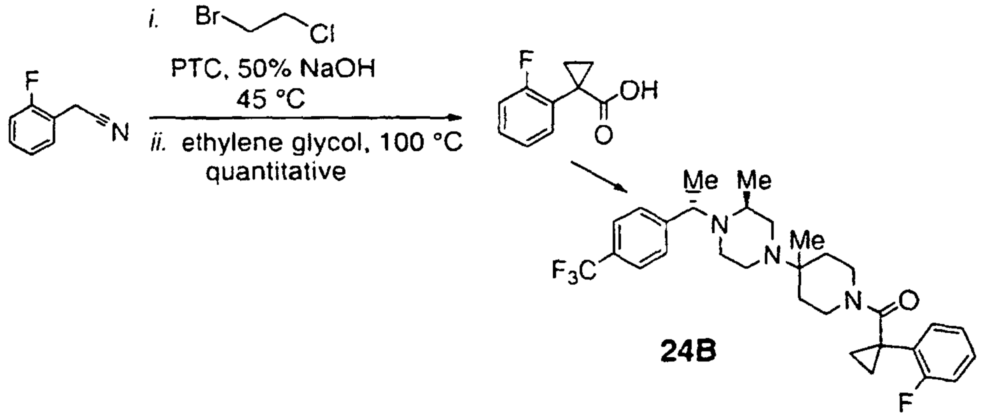
Step 1: To the stannane (0.39 g, 0.95 mmol) in DMF (10 ml) was added the 2-chloro-4-fluoroiodobenzene (0.73 g, 2.86 mmol), CuI (0.19 g, 1.05 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.11 g, 0.095 mmol).

The reaction was stirred at RT under N_2 for 21 h. The reaction mixture was added to Et_2O and the heterogeneous solution filtered through a bed of celite, washing with EtOAc. The filtrate was washed with water and brine and dried ($MgSO_4$). Filtration and evaporation of the solvent in vacuo afforded a residue that was preadsorbed on silica gel. Purification by silica gel chromatography (4% EtOAc/hexane) yielded the arylacrylate (0.19 g, 78%), which was used directly in the next step.

Step 2: To trimethylsulfoxonium iodide (0.18 g, 0.81 mmol) in DMSO (1.6 ml) was added potassium *tert*-butoxide (0.09 g, 0.81 mmol). The reaction mixture was stirred at RT for 1 h, at which time the arylacrylate (0.19 g, 0.74 mmol) in DMSO (1.6 ml) was added. The reaction mixture was stirred at RT for 5 h and water was added. The mixture was extracted with EtOAc. The combined organic layers were washed with water and brine and dried ($MgSO_4$). Filtration and evaporation of the solvent in vacuo afforded the arylcyclopropyl ester that was used directly by taking up into CH_2Cl_2 (3 ml) and adding TFA (0.5 ml). The reaction mixture was stirred at RT for 15 h and then concentrated in vacuo to afford the arylcyclopropylcarboxylic acid (0.14 g, 91%-2 steps). Without further purification, the carboxylic acid was coupled to the product of example 8, step 3, using the procedure of Example 8, step

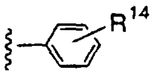
4 to obtain **24A** as the HCl salt. HRMS (M+H): found 566.2561.

Method B:

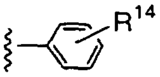
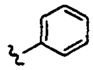
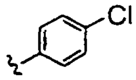
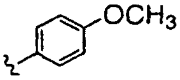
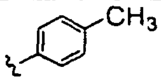
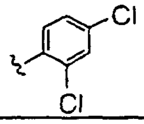
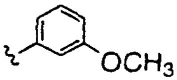
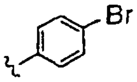
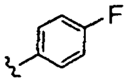
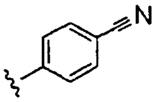
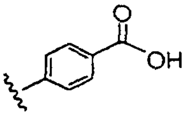
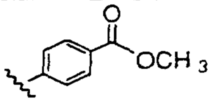
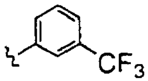
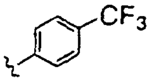
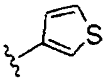
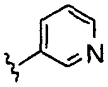


To the 2-fluorophenylacetonitrile (0.80 g, 5.92 mmol), benzyltriethylammonium chloride (0.03 g, 0.12 mmol), and 1-bromo-2-chloroethane (1.70 g, 11.9 mmol) was added 50% aqueous NaOH (3.5 ml). The reaction was stirred at 45 °C for 21 h and ethylene glycol was added (3 ml). The reaction was then warmed to 100 °C and stirred for 7 h. Upon cooling to RT, the reaction was diluted with water and washed with EtOAc. The aqueous layer was acidified to pH 2-3 with aqueous 6N HCl. The acidified solution was extracted with Et_2O. The combined Et_2O extracts were washed with water and brine and dried ($MgSO_4$). Filtration and evaporation of the solvent in vacuo afforded a pale yellow solid (1.06 g, 99%). The arylcyclopropyl acid was coupled to the product of example 8, step 3, using the procedure of Example 8, step 4 to obtain **24B** as the HCl salt. HRMS (M+H): found 532.2949.

[0126] Using similar procedures, the compounds of the formula were prepared, wherein

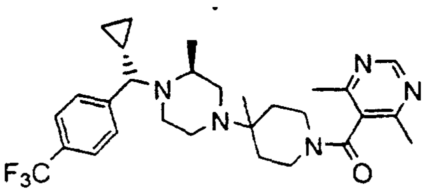


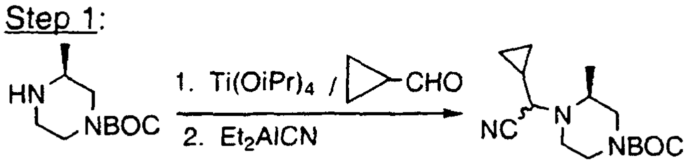
is as defined in the table:

Ex.		HRMS (M+H)	m.p. (°C)
24C		--	240-245
24D		--	>225
24E		--	172-176
24F		--	225-230
24G		--	>225
24H		544.3151	--
24I		592.2150	--
24J		532.2956	--
24K		539.3003	--
24L		558.2949	--
24M		572.3107	--
24N		582.2910	--
24O		582.2910	--
24P		520.2609	--
24Q		515.2991	

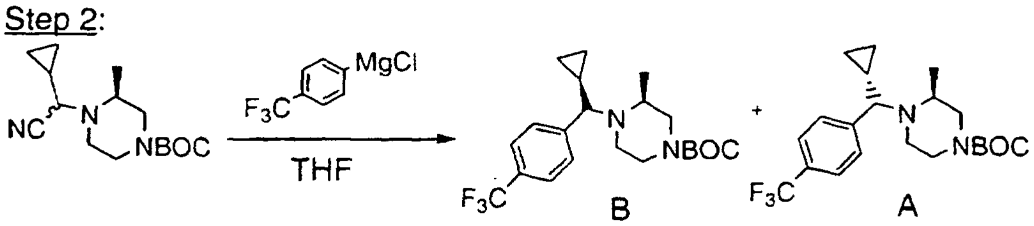
Example 25

[0127]

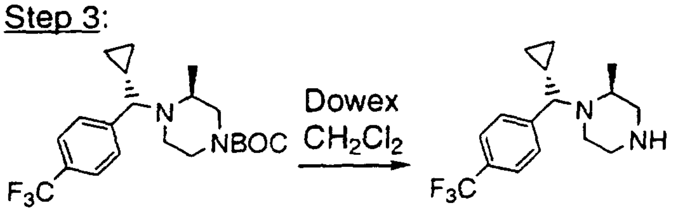




Cyclopropyl carboxaldehyde (3.4 ml), S-methyl N-BOC piperazine (8.28 g), CH_2Cl_2 (82 ml) and $Ti(OiPr)_4$ (15.80 ml) were mixed together and stirred at RT for 23 h, then the resulting solution was cooled to 0 °C and Et_2AlCN (1.0 M in toluene; 62.1 ml) was added. The solution was stirred for 5 h at RT. A mixture of KF (20 g) and Celite (10 g) was added, followed by cautious addition of EtOAc (120 ml) and water (120 ml). The resulting slurry was stirred for 15 min, filtered, washed with EtOAc (3 X 35 ml) and the EtOAc layer was removed, washed with brine, dried over Na_2SO_4, filtered and evaporated to give the desired intermediate (12.0 g) which was used directly in the next step.



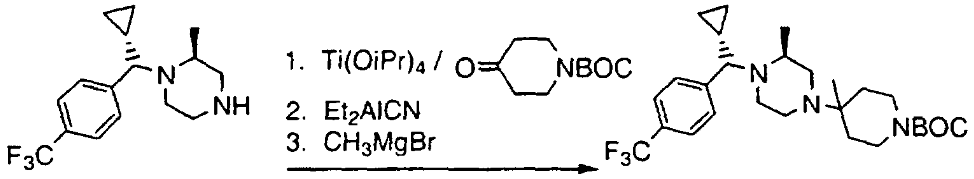
[0128] To a 0°C solution of 4-iodobenzotrifluoride (40 g) and THF (52 ml) was added isopropyl magnesium chloride (2.0 M in Et_2O; 74 ml). The resulting solution was stirred at RT for 1 h and then added to a 0 °C solution of the product of step 1 (10.0 g) and THF (26 ml) over 10 min. The reaction solution was warmed to RT, stirred overnight and EtOAc (50 ml) was added. After stirring for 10 min, 2 N NaOH (50 ml) was added and the resulting mixture was stirred for 30 min, filtered and the salts were washed with EtOAc (3 X 20 ml). The combined EtOAc extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated to give the crude product (28 g) as a gold oil which was chromatographed on silica gel (1 kg), eluting with hexanes:EtOAc (8:1). Two diastereomeric products were collected as a single fraction (15.9 g) and further purified by column chromatography as described above to give intermediate A (R_f=0.47 in 4:1 hexanes:EtOAc; 5.34 g), which was contaminated with an unidentified impurity. (The second diastereomer B (R_f=0.29 in 4:1 hexanes:EtOAc) was also collected.)



[0129] To a solution of A from Step 2 (3.96 g) and CH_2Cl_2 (120 ml) was added DOWEX 50X2-100 ion exchange resin (15 g) and the resulting mixture was shaken for 2.5 h at RT. The resin was filtered off and washed with CH_2Cl_2

(2 X 40 ml). The resin was treated with 7 N NH_3 in CH_3OH (30 ml), the resin was filtered off and this procedure was repeated two times. The CH_3OH extracts were combined and evaporated. The resulting oil was treated with toluene: CH_2Cl_2 (1:1; 15 ml) and evaporated to give the piperazine intermediate (0.80 g) as a clear oil. HRMS: calc'd: MH^+: $C_{16}H_{21}N_2F_3$:299.1735; measured:299.1748.

Step 4:

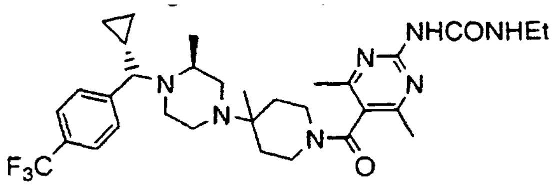


[0130] The product of Step 3 (0.57 g) was treated in the same fashion as Example 8, Step 1, using N-BOC 4-piperidone (0.42 g), CH_2Cl_2 (3.84 ml), $Ti(OiPr)_4$ (3.39 ml), Et_2AlCN (2.88 ml) and CH_3MgBr (3.0 M in Et_2O; 3.2 ml) to give the desired product (0.78 g) as a clear oil in 82 % yield.

Step 5: The product of Step 4 (0.12 g) was treated withAcOH:CH_2Cl_2 (3:1, v:v; 1.4 ml) followed by BF_3Et_2O (0.14 ml). After stirring for 1 h, the resulting solution was diluted with CH_2Cl_2 (10 ml), cooled to 0°C and the pH was adjusted to 10 with solid NaOH. Water (2 ml) was added and the CH_2Cl_2 layer was removed. After further extraction (2 X 10 ml) with CH_2Cl_2, the organic layer was washed with water, brine, dried over Na_2SO_4, filtered and evaporated to give the free piperidine (80 mg) in 81 % yield.

Step 6: The product of Step 5 (57 mg) was treated in the same fashion as in Example 8, Step 4, using DMF (0.30 ml), HOBt (41 mg), DEC (57 mg), diisopropyl ethyl amine (0.08 ml) and 4,6-dimethyl 5-pyrimidine carboxylic acid (43 mg); the reaction was stirred at 45°C for 5 h. Purification of the crude oil was carried out by preparative plate chromatography (silica adsorbent; 2000 μM; 76:19:5 EtOAc:hexanes:Et_3N as eluant) to give, after elution of the desired band (1:1 CH_2Cl_2:MeOH) and concentration of solvent, the title compound (70 mg) as a clear oil in 93% yield. The HCl salt was prepared as described for Example 8, Step 4 (78 mg) in 100% yield. mp:147-149°C.

[0131] Using a similar procedure, the following compound was prepared:

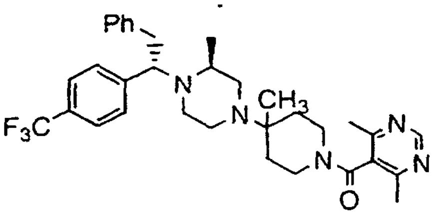


25A

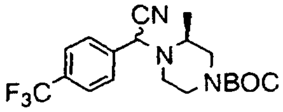
m.p. >188 (dec).

Example 26

[0132]

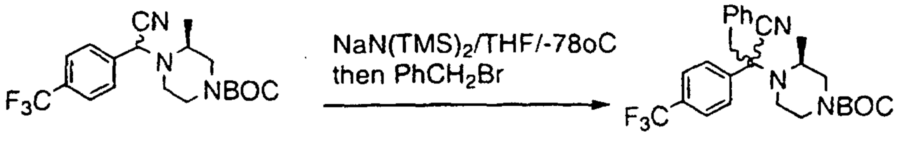


Step 1:



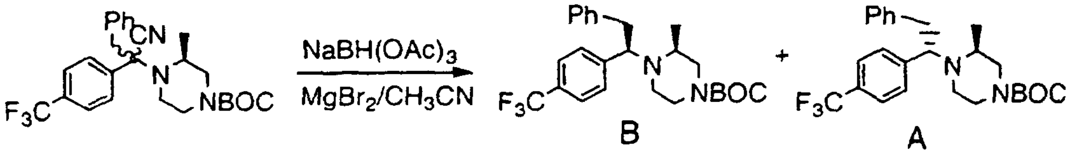
[0133] The desired compound was prepared in a manner similar to Example 25, Step 1, using p-trifluoromethyl benzaldehyde (20 g) instead of cyclopropyl carboxaldehyde, to give, after work up, a mixture of diastereomers (22.7 g) in 59% yield.

Step 2:



[0134] To a -70°C solution of the product of step 1 (1.9 g) and THF (15 ml) was added NaHMDS (1.0 M in THF; 7.5 ml) followed by benzyl bromide (2 ml). The cooling bath was removed and the resulting solution was stirred for 45 min. Concentrated NH_4OH (10 ml) was added and the reaction was stirred for 30 min. The resulting mixture was partitioned between water and CH_2Cl_2, the CH_2Cl_2 extracts were removed and evaporated and the crude oil was purified by column chromatography (silica gel; 2:1 hexanes:CH_2Cl_2; 10:1 to 7:1 hexanes:EtOAc as eluant) to give, after evaporation of the appropriate fractions, a mixture of intermediates (1.92 g) as a yellow foam.

Step 3:



[0135] The mixture of Step 2 (1.91 g), CH_3CN (35 ml), sodium triacetoxy borohydride (4.0 g) and magnesium bromide etherate (2.25 g) were mixed and stirred at RT for 70 h. Water (25 ml) was added and then, gradually, a solution of Na_2CO_3 (10 g) in water (50 ml). After extraction with EtOAc (2 X 50 ml), drying and evaporation of the organic layer, the resulting oil was purified by preparative plate chromatography (5 X 2000 mM silica plates; 6:1 hexanes:EtOAc as eluant). The less polar band was removed, treated with 1:1 methanol:CH_2Cl_2 , filtered and evaporated to give intermediate A (0.84 g) as a white foam. HRMS: calc'd: MH^+: $C_{25}H_{29}O_2N_2F_3$:449.2407; measured:4492416.

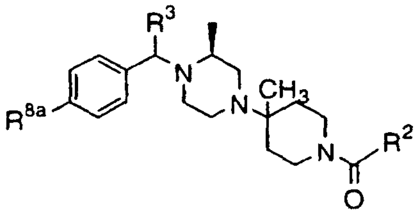
Step 4: The product of Step 3 (0.81 g) was treated in the same fashion as in Example 8, Step 3, using TFA (5 ml) and CH_2Cl_2 (10 ml), to give, after work up, the free piperazine (0.60 g) as a clear gum. HRMS: calc'd: MH^+: $C_{20}H_{23}N_2F_3$: 349.1892; measured:349.1894.

Step 5: The product of Step 4 (0.39 g) was treated in the same fashion as in Example 8, Step 1, using N-BOC 4-piperidone (0.25 g), CH_2Cl_2 (8 ml), $Ti(OiPr)_4$ (0.40 mg), Et_2AlCN (2 ml) and CH_3MgBr (3.0 M in Et_2O; 1.5 ml) to give the desired BOC-protected piperidinyl intermediate (0.44 g) as a clear oil in 72 % yield. HRMS: calc'd: MH^+: $C_{31}H_{42}O_2N_3F_3$:546.3307; measured:546.3315.

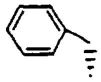
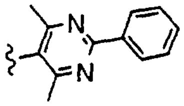
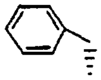
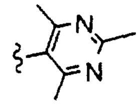
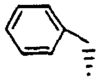
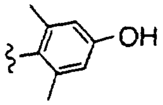
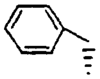
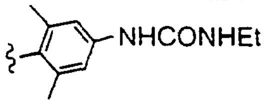
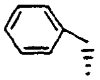
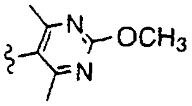
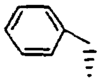
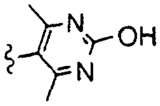
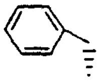
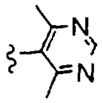
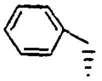
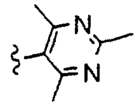
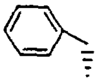
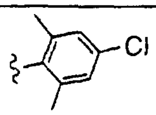
Step 6: The product of step 5 (0.43 g) was treated in the same fashion as in Example 8, Step 3, using TFA (3 ml), CH_2Cl_2 (2 ml) and water (0.2 ml) to give, after work up, the free piperidinyl intermediate (0.37 g) as a clear oil.

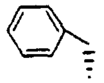
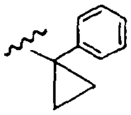
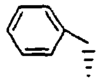
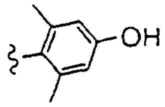
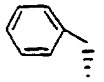
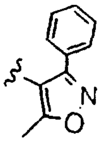
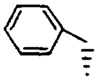
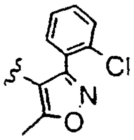
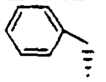
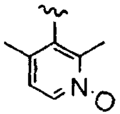
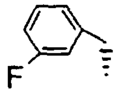
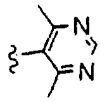
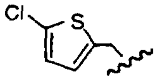
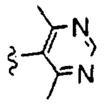
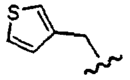
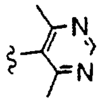
Step 7: The product of step 6 (50 mg) was treated in the same fashion as in Example 8, Step 4, using CH_2Cl_2 (3 ml), HOBt (28 mg), DEC (40 mg), diisopropyl ethyl amine (42 mg) and 4,6-dimethyl 5-pyrimidine carboxylic acid (24 mg); the reaction was stirred at RT for 2 days. Using the procedure described in Example 8, Step 4, the HCl salt of the title compound was prepared (59 mg) in 91 % yield (from the product of Step 5).
M.p:187-196°C. HRMS: calc'd: MH^+: $C_{33}H_{40}ON_5F_3$:580.3263;
measured:580.3263.

[0136] Using a similar procedure, compounds of the formula



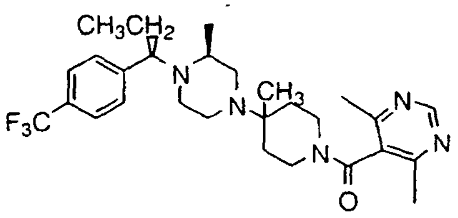
were prepared, wherein R^{8a}, R^3 and R^2 are as defined in the table:

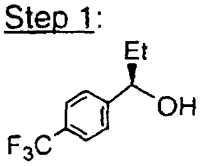
Ex.	R^{8a}	R^3	R^2	Mp (°C)
26B	-CF3			86-92
26C	-CF3			83-90
26D	-CF3			195-205
26E	-CF3			118-125
26F	-OCF3			175-185
26G	-OCF3			180-190
26H	-OCF3			220-230
26I	-OCF3			195-210
26J	-OCF3			190-200

26K	-OCF3			180-205
26L	-OCF3			230-240
26M	-OCF3			60-65
26N	-OCF3			65-68
26O	-OCF3			60-62
26P	-CF3			256-258
26Q	-CF3			254-256 (dec)
26R	-CF3			249-250 (dec)

Example 27

[0137]





[0138] 4'-Trifluoromethyl)propiophenone (2.02 g, 0.01 mol) and (S)-2-methyl-CBS-oxazaborolidine (1M in THF) (2.0 ml, 0.002 mol) in THF (10 ml) was cooled in an ice-bath and borane-methyl sulfide complex (2M in THF) (3 ml, 0.006 mol) was added dropwise to the mixture. The mixture was stirred for 30 min at 0° C and CH_3OH was added slowly until no bubbles appeared. The solvents were removed under reduced pressure and HCl solution (1N) was added to the mixture. EtOAc extractive work up followed by silica gel chromatography afforded the alcohol (1.47 g) in 72% yield.

Step 2: A solution of the product of Step 1 (4.32 g, 0.021 mol) and Et_3N (5.9 ml, 0.042 mol) in CH_2Cl_2 (20 ml) was cooled to 0° C in ice bath and CH_3SO_2Cl (2.13 ml, 0.028 mol) was added dropwise. The mixture was stirred at 0° C for 1 h and the ice bath was removed. Water was added to the mixture and CH_2Cl_2 extractive work up afforded the mesylate (5.99 g) in quantitative yield.

Step 3: The product of Step 2 (5.93 g, 0.021 mol) and 1-*tert*-butoxycarbonyl-3*S* -methyl piperazine (4.2 g, 0.021 mol) were dissolved in anhydrous CH_3CN (20 ml) and oven-dry K_2CO_3 (4.35 g, 0.032 mol) was added to the solution. The mixture was stirred under reflux for 2 days, then diluted with water. EtOAc extractive work up followed by silica gel chromatography gave the desired product (3.16 g) in 39% yield.

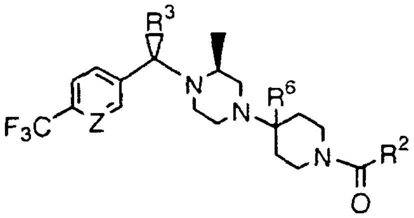
Step 4: TFA (10 ml) was added to a solution of the product of Step 3(1.15 g, 2.59 mmol) in CH_2Cl_2 (5 ml) and the mixture was stirred at RT for 2 h, then concentrated under reduced pressure. NaOH (3N) was added to the residue and extractive work up with EtOAc gave the desired amine in quantitative yield.

Step 5: The product of Step 4 and 1-*tert*-butoxycarbonyl-4-piperidone (0.94 g, 4.74 mmol) were treated with Ti $(OiPr)_4$, Et_2AlCN and CH_3MgBr in a manner similar to that described in Example 8, step 1, to obtain the desired product (1.09 g) in 87% yield (from the amine of Step 4).

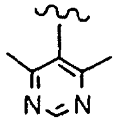
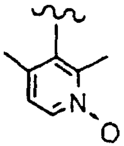
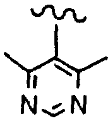
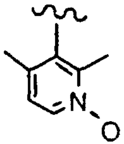
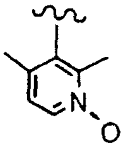
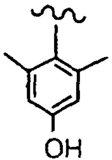
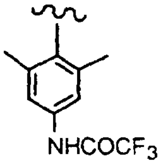
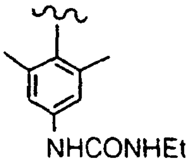
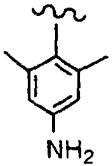
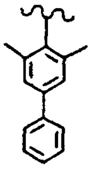
Step 6: TFA (4 ml) was added to a solution of the product of Step 5 (0.76 mg, 1.57 mmol) in CH_2Cl_2 (2 ml) and the mixture was stirred at RT for 2 h before it was concentrated under reduced pressure. NaOH (3N) was added to the residue and extractive work up with EtOAc gave the desired amine in quantitative yield.

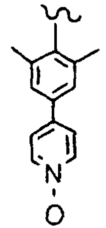
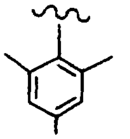
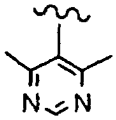
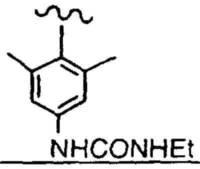
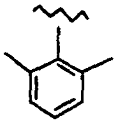
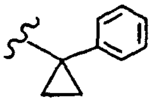
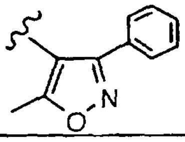
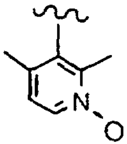
Step 7: The amine of Step 6 and 4,6-dimethylpyrimidine 5-carboxylic acid (0.36 g, 2.35 mmol), were coupled as described in Example 8, Step 4, to obtain the title compound (0.58 g) in 72% yield. M.p. 160; HRMS (MH^+) found: 518.3123.

[0139] Using a similar procedure, compounds of the formula

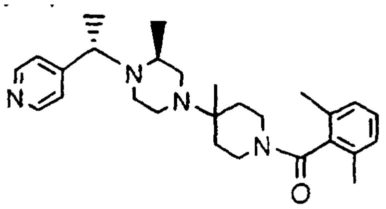


were prepared wherein Z, R^3, R^6 and R^2 are as defined in the table below:

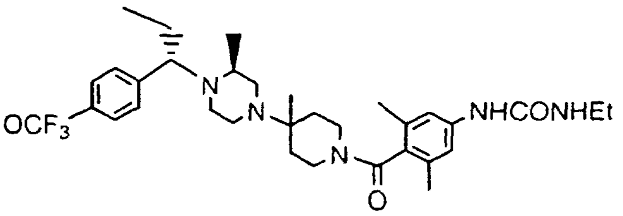
Ex.	Z	R^3	R^6	R^2	Dec.(0°C)	HRMS
27A	N	Me	H		185	491.2744
27B	N	Me	H		190	506.2729
27C	N	Me	Me		190	505.2898
27D	N	Me	Me		200	520.2902
27E	CH	Et	Me		197	533.3097
27F	CH	Et	Me		215	532.3147
27G	CH	Et	Me		230	627.3145
27H	CH	Et	Me		210	602.3678
27I	CH	Et	Me		215	531.3305
27J	CH	Et	Me		215	593.3470

27K	CH	Et	Me		195	609.3424
27L	CH	Et	Me		170	745.2308
27M	N	n-Pr	Me		204	533.3207
27N	N	n-Pr	Me		210	617.3798
27O	N	n-Pr	Me		202	531.3304
27P	N	n-Pr	Me		165	543.3311
27Q	N	n-Pr	Me		225	584.3205
27R	N	n-Pr	Me		195	548.3217

[0140] Using similar procedures, the following compounds were also prepared:



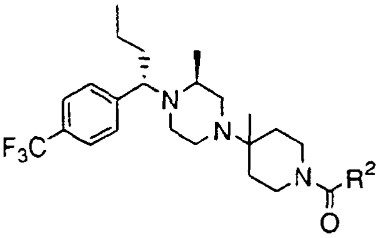
27S: M.p. 236 °C



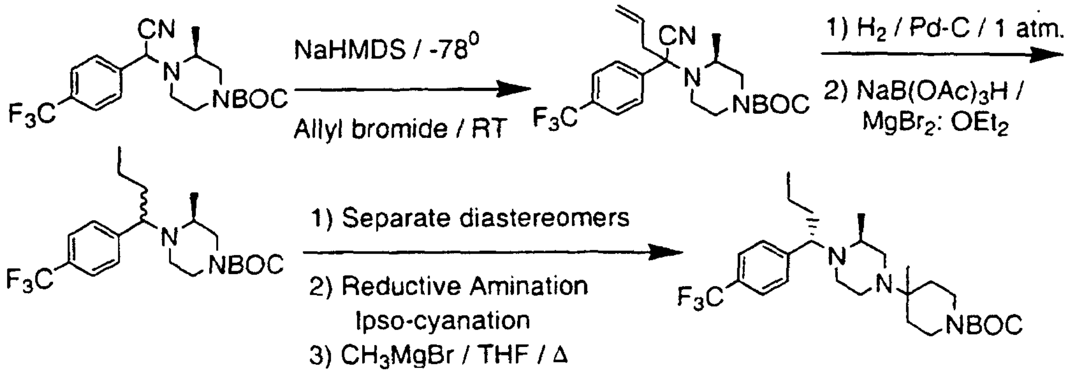
27T: M.p. 213 °C

Example 28

[0141]



Steps 1-4:



Step 1: The cyano amine was prepared from p-trifluoromethyl benzaldehyde and 2(S)-methyl-4-(tert-butoxycarbonyl) piperazine exactly as describedin Example 6, Step 1.

Step 2: A solution of the cyano amine 2 (2.5 g; 6.53 mmol) in 30 ml of dry THF was placed under a blanket of N_2 and cooled to -78° C. This solution was treated with a solution of sodium hexa-methyl disilazide in THF (1M; 26 ml) followed after 5 min with neat allyl bromide (6 ml). Upon removal of the bath and letting the reaction mixture warm to RT (-1h), it changed from a yellow solution to dark reddish brown solution. The reaction was quenched with saturated NH_4Cl solution and the product extracted with EtOAc, washed with water, brine and dried. Concentration in vacuo afforded a brown semi solid. FSGC of this material using 25% Et_2O in hexane as eluant gave 2.5 grams (92%) of the desired product as an amber gum (TLC R_f = 0.65, 0.6 for two overlapping spots).

Step 3: A solution of the product of Step 2 (2.4g) in CH_3OH was treated with 10% Pd/C (0.2g) and placed under a balloon of H_2 gas. After stirring at RT for 4 h, the catalyst was removed via filtration through celite. Concentration of the filtrate yielded an amber gum.

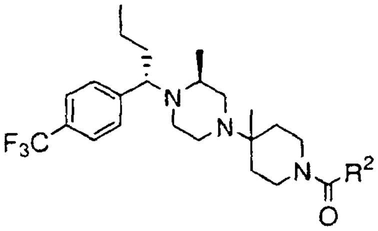
The α-propyl nitrile obtained above was dissolved in CH_3CN (12 ml). Magnesium bromide etherate (2.1 g; 8.14 mmol) and sodium triacetoxy borohydride (3.44 g; 16.2 mmol) were added and the reaction mixture was stirred at RT overnight. The reaction was quenched with water and rendered basic with saturated $NaHCO_3$. The organic products were extracted with EtOAc and processed to obtain - 2 g of crude material. FSGC (10-25% Et_2O in hexane) served to isolate two diasteromeric products (1.7g total; 79% for two steps):

(S, S)-Diastereomer (**A**): TLC R_f = 0.6 (25% Et_2O-Hexane). 0.9 g of a colorless gum.
(R, S)-Diastereomer (**B**): TLC R_f = 0.5 (25% Et_2O-Hexane). 0.8 g of a colorless gum.

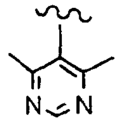
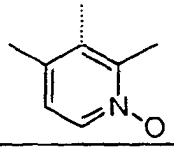
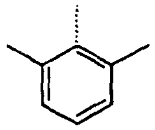
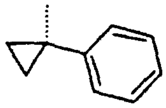
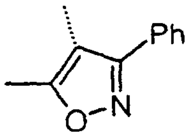
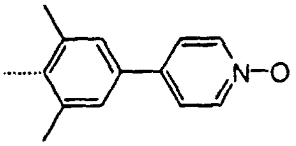
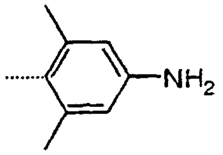
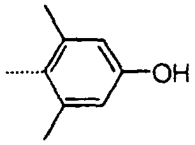
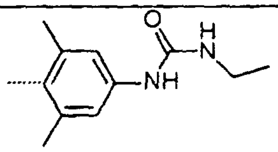
Step 4: Removal of the BOC-protecting group from the intermediate **A** was accomplished by treatment with TFA in CH_2Cl_2. The isolated free piperazine (0.68g; 2.3 mmol), N-(tert-butoxycarbonyl)-4-piperidinone (0.45g; 2.3 mmol) and $Ti(OiPr)_4$ (0.7 mL; 2.5 mmol) were dissolved in 10 ml of CH_2Cl_2 and stirred overnight. Et_2AlCN (1 M in toluene; 2.7 ml) was introduced into the reaction mixture and the resultant solution was stirred for a day. The reaction was diluted with EtOAc and quenched with water. Celite was added to aid in the filtration of titanium and aluminum salts. The biphasic filtrate was washed with water, brine and dried. Concentration in vacuo yielded 1.1 g of a yellow gum (TLC R_f = 0.55 in 25% EtOAc-hexane).

The resultant ipso-cyano compound was dissolved in dry THF (8 ml) and treated with a solution of CH_3MgBr (3M in Et_2O; 6 ml) and stirred overnight at RT. The reaction flask was placed in a cold water bath and carefully quenched with saturated NH_4Cl solution. The organic product was extracted with EtOAc and washed with water and brine. Concentration to a crude product which was purified by rapid FSGC (10-25% EtOAc in hexane) gave the BOC-piperidinyl compound as a pale yellow gum (1.1g; 100%). TLC R_f = 0.6 in 25% EtOAc-hexane.

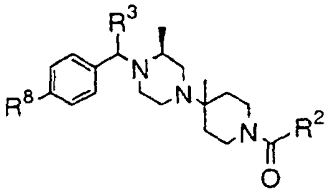
Step 5: The BOC-protecting group on the piperidine nitrogen in the product of Step 4 was removed by treatment with TFA in CH_2Cl_2. Basification with I M NaOH and processing in CH_2Cl_2 afforded the unprotected piperidine in 90% yield. This intermediate was coupled (EDCl, HOBt) to aryl and heteroaryl carboxylic acids to obtain the amides exemplified in the following table:



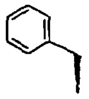
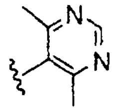
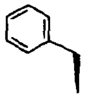
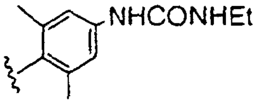
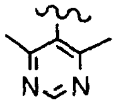
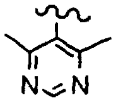
wherein R^2 is as defined in the table:

Ex.	R^2	Mp (° C)	HRMS (MH^+)
28A		249	Calculated: 532.3263 Found: 532.3268
28B		59	Calculated: 547.3260 Found: 547.3278
28C		246	Calculated: 530.3358 Found: 530.3372
28D		239	Calculated: 542.3358 Found: 542.3361
28E		258	Calculated: 583.3260 Found: 583.3272
28F		102	Calculated: 623.3573 Found: 623.3572
28G		216	Calculated: 545.3467 Found: 545.3459
28H		217	Calculated: 546.3307 Found: 546.3309
28I		223	Calculated: 616.3838 Found: 616.3848

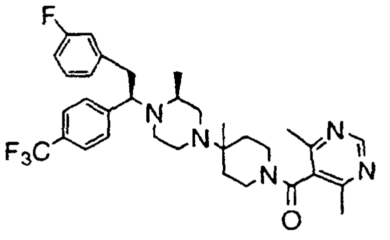
[0142] Using similar procedures, the following compounds were prepared:



wherein R^8, R^3 and R^2 are as defined in the table:

Ex.	R^8	R^3	R^2	Mp (° C)
28J	$-CF_3$			195-220
28K	$-CF_3$			105-115
28L	CH_3CONH-			177-180
28M	$-CF_3$			224-232

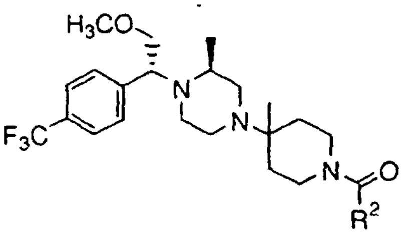
[0143] Using 3-fluoro benzyl bromide or chloride in place of benzyl bromide in the procedure of Example 28, steps 1-4 (processing isomer B in step 3), then using the process of Example 1, step 5, followed by the process of Example 26, steps 6-7, the following compound was prepared (HCl salt):



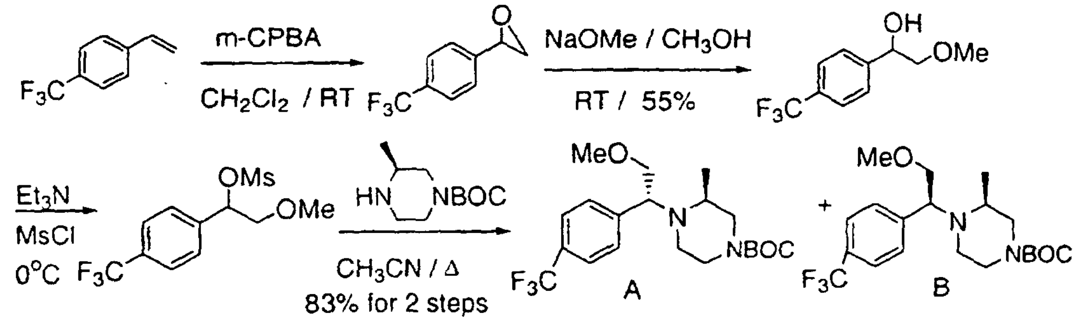
28N: m.p. 185-193 °C

Example 29

[0144]



Steps 1-3:



Step1: Solid m-CPBA was added to a solution of p-trifluoromethyl styrene (3g; 17.4 mmol) in 30 ml of CH_2Cl_2 and stirred at RT for 20 h. About 20 ml of a saturated solution of $NaHCO_3$ was added and stirred at RT for 2 h. The mixture was diluted with 20 ml of CH_2Cl_2 and the organic product extracted into the CH_2Cl_2 layer. The organic extract was processed to obtain the crude product. FSGC gave 3g (90%) of the desired epoxide as a colorless oil. TLC R_f = 0.8 (25% EtOAc in hexane).

Step 2: Freshly prepared $NaOCH_3$ (0.6g; 10.6 mmol) was added to a solution of the product of Step 1 (2g; 10.6 mmol) in 20 ml of anhydrous CH_3OH. After stirring at RT for a day, CH_3OH was removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed with water and brine. Concentration, followed by FSGC, furnished 1.3 g (55%) of the carbinol as a colorless oil (R_f = 0.3 50% Et_2O in hexane).

Step 3: The carbinol of Step 2 (1.3g; 5.9 mmol) was dissolved in CH_2Cl_2 and cooled in an ice bath. Sequential treatment with Et_3N (1.7 ml; 12 mmol) and CH_3SO_2Cl (0.6 ml; 7.7 mmol) and stirring for 30 min formed the mesylate. The product was extracted by standard work up (yield = 100%).

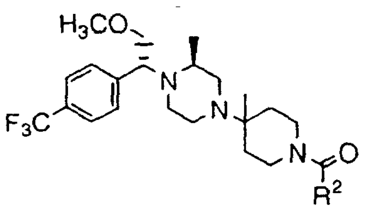
The mesylate (1.76g; 5.9 mmol) and 2(S)-methyl-4-(tert-butoxycarbonyl) piperazine (2.4 g; 12 mmol) were dissolved in 5 ml of CH_3CN and heated to reflux for 19 h. The reaction mixture was cooled to RT and directly subjected to flash chromatography on silica gel. Eluting with 25%, then 50% Et_2O in hexane served to isolate the diastereomeric products **A** and **B** (Total yield = 86%).

A: R_f = 0.5 (50% Et_2O in hexane). Light yellow gum (0.9g; 42%)

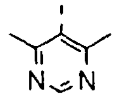
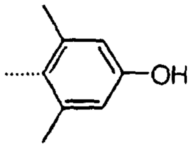
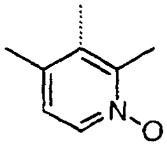
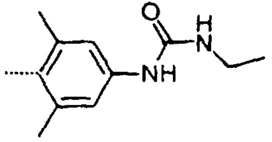
B: R_f = 0.4 (50% Et_2O in hexane). Amber gum (1.13g; 44%)

Step 4: Reductive amination of the free piperazine dervied from **A** (0.9g; 2.2 mmol) with N-BOC-piperidin-4-one with the installation of the ipso-methyl group was carried out as described in Example 1, step 4. to obtain the BOC-protected piperidinyl compound (0.87g; 92%). R_f = 0.3 (50% EtOAc in hexane).

Step 5: The BOC protecting group was removed from the piperidine nitrogen via TFA, and the resultant compound was coupled with acids using the EDCl / HOBt method as described in Example 8, step 4, to obtain the compounds shown in the following table:

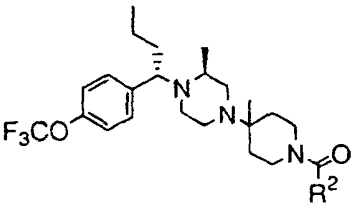


wherein R^2 is as shown in the table:

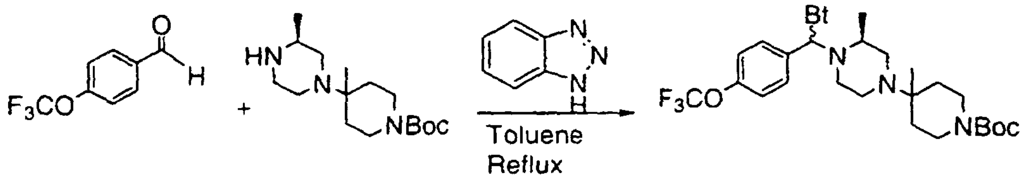
Ex.	R^2	Mp (° C)	HRMS (MH^+)
29A		163	Calculated: 534.3056 Found: 534.3050
29B		208	Calculated: 548.3100 Found: 548.3092
29C		101	Calculated: 549.3053 Found: 549.3057
29D		192	Calculated: 618.3631 Found: 618.3638

Example 30

[0145]

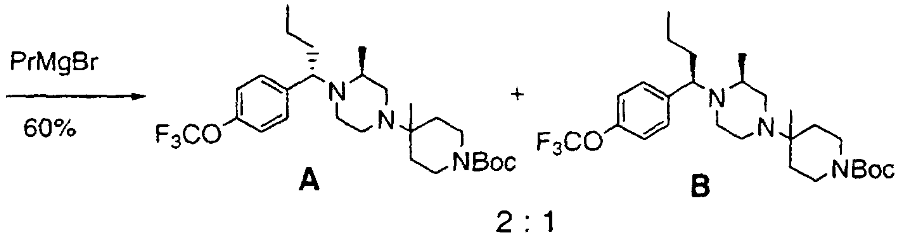


Step 1:



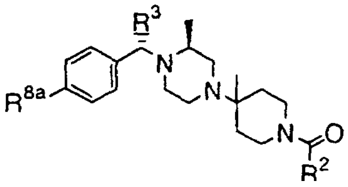
[0146] A solution of *p*-trifluoromethoxy benzaldehyde (0.48 ml, 3.36 mmol), the piperidino-pipiperazine (1.00g, 3.36 mmol) and benzotriazole (0.48g, 4.00 mmol) in dry toluene were heated at reflux for 6 h. The reaction mixture was cooled to RT and the solvent was removed *in vacuo.* Following NMR verification of the formation of the product, the product was used without further purification in the next step.

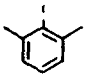
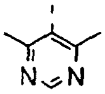
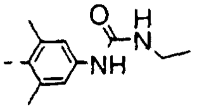
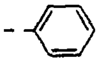
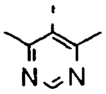
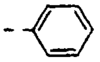
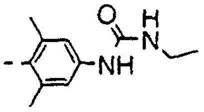
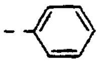
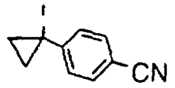
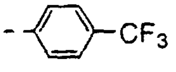
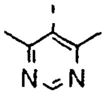
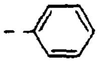
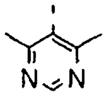
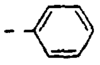
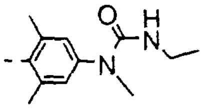
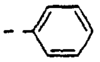
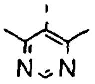
Step 2:



[0147] To a solution of the product of Step 1 (1.16g, 1.97 mmol) in 20 ml of toluene was added a solution of n-propyl magnesium bromide (2M in Et_2O, 1.1 ml) and the mixture stirred at RT for 15 h. The reaction mixture was quenched by pouring onto ice and saturated aqueous NH_4Cl solution. The aqueous layer was extracted with EtOAc, washed with 1M NaOH solution, water and brine. Concentration and purification by FSGC (20% EtOAc - hexane) provided the desired product **A**. Further elution with 30% EtOAc in hexane gave the (R, S) diastereomer **B**.

Step 3: The amine **A** was treated with TFA in CH_2Cl_2 to remove the BOC-protecting group. Coupling of the free piperidine with acids using EDCI /HOBt provided compounds 30-30B in the following table; similar methods were used to prepare compounds 30C-I.

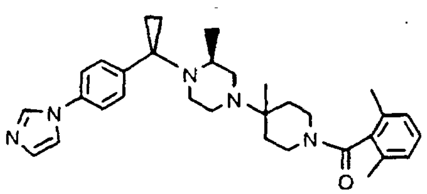


Ex.	R^{8a}	R^3	R^2	Mp (° C)	HRMS (MH^+) found
30	$-OCF_3$	n-Pr		237	546.3314
30A	$-OCF_3$	n-Pr		241	548.3217
30B	$-OCF_3$	n-Pr		219	632.3779
30C	H			175-178	--
30D	H			177-189	--
30E	H			84-90	--
30F	$-CF_3$			180-192	--
30G*	$-CF_3$			180-186	--
30H	H			178-188	--
30I*	$-OCF_3$			165-175	--

Mixture of diastereomers

Example 31

[0148]



[0149] A solution of the product of Example 12, step 2 (150 mg, 0.27 mmol), imidazole (27.4 mg, 0.403mmol), 1,10-phenanthroline (48 mg, 0.27 mmol), *trans,trans*-dibenzylideneacetone (6.28 mg, 0.027 mmol), copper (II) trifluoromethanesulfonate benzene complex (15 mg, 0.027 mmol) and Cs_2CO_3 (96.1 mg, 0.30 mmol) in xylene (2 ml) was stirred at 110° C for 5 days. The reaction mixture was cooled to RT and saturated $NaHCO_3$ was added. Extractive EtOAc work up followed by silica gel chromatography gave the title compound (70 mg, 52% yield). Dec. 215° C (HCl salt). HRMS calcd for $C_{29}H_{39}ClN_3OS$ (M+H+) 500.3389, found 500.3396.

[0150] The following assays can be used to determine the CCR5 antagonistic activity of the compounds of the invention.

CCR5 Membrane Binding Assay:

[0151] A high throughput screen utilizing a CCR5 membrane binding assay identifies inhibitors of RANTES binding. This assay utilizes membranes prepared from NIH 3T3 cells expressing the human CCR5 chemokine receptor which have the ability to bind to RANTES, a natural ligand for the receptor. Using a 96-well plate format, membrane preparations are incubated with ^{125}I-RANTES in the presence or absence of compound for one hour. Compounds are serially diluted over a wide range of 0.001ug/ml to 1 ug/ml and tested in triplicates. Reaction cocktails are harvested through glass fiber filters, and washed thoroughly. Total counts for replicates are averaged and data reported as the concentration required to inhibit 50 percent of total ^{125}I-RANTES binding. Compounds with potent activity in the membrane binding assay are further characterized in secondary cell-based HIV-1 entry and replication assays.

HIV-1 Entry Assay:

[0152] Replication defective HIV-1 reporter virions are generated by cotransfection of a plasmid encoding the NL4-3 strain of HIV-1 (which has been modified by mutation of the envelope gene and introduction of a luciferase reporter plasmid) along with a plasmid encoding one of several HIV-1 envelope genes as described by Connor et al , Virology, 206 (1995), p. 935-944. Following transfection of the two plasmids by calcium phosphate precipitation, the viral supernatants are harvested on day 3 and a functional viral titer determined. These stocks are then used to infect U87 cells stably expressing CD4 and the chemokine receptor CCR5 which have been preincubated with or without test compound. Infections are carried out for 2 hours at 37 °C, the cells washed and media replaced with fresh media containing compound. The cells are incubated for 3 days, lysed and luciferase activity determined. Results are reported as the concentration of compound required to inhibit 50% of the luciferase activity in the control cultures.

HIV-1 Replication Assay:

[0153] This assay uses primary peripheral blood mononuclear cells or the stable U87-CCR5 cell line to determine the effect of anti-CCR5 compounds to block infection of primary HIV-1 strains. The primary lymphocytes are purified from normal healthy donors and stimulated *in vitro* with PHA and IL-2 three days prior to infection. Using a 96-well plate format, cells are pretreated with drug for 1 hour at 37 °C and subsequently infected with an M-tropic HIV-1 isolates. Following infection, the cells are washed to remove residual inoculum and cultured in the presence of compound for 4 days. Culture supernatants are harvested and viral replication measured by determination of viral p24 antigen concentration.

Calcium Flux Assay:

[0154] Cells expressing the HIV coreceptor CCR5 are loaded with calcium sensitive dyes prior to addition of compound or the natural CCR5 ligand. Compounds with agonist properties will induce a calcium flux signal in the cell, while

CCR5 antagonists are identified as compounds which do not induce signaling by themselves but are capable of blocking signaling by the natural ligand RANTES.

GTPyS Binding Assay:

[0155] A GTPyS binding assay measures receptor activation by CCR5 ligands. This assay measures the binding of ^{35}S labeled-GTP to receptor coupled G-proteins that occurs as a result of receptor activation by an appropriate ligand. In this assay, the CCR5 ligand, RANTES, is incubated with membranes from CCR5 expressing cells and binding to the receptor activation (or binding) is determined by assaying for bound ^{35}S label. The assay quantitatively determines if compounds exhibit agonist characteristics by inducing activation of the receptor or alternatively antagonist properties by measuring inhibition of RANTES binding in a competitive or non-competitive fashion.

Chemotaxis Assay:

[0156] The chemotaxis assay is a functional assay which characterizes the agonist vs. antagonist properties of the test compounds. The assay measures the ability of a non-adherent murine cell line expressing human CCR5 (BaF-550) to migrate across a membrane in response to either test compounds or natural ligands (i.e., RANTES, MIP-1β). Cells migrate across the permeable membrane towards compounds with agonist activity. Compounds that are antagonists not only fail to induce chemotaxis, but are also capable of inhibiting cell migration in response to known CCR5 ligands.

[0157] The role of CC chemokine receptors such as CCR-5 receptors in inflammatory conditions has been reported in such publications as Immunology Letters. 57, (1997), 117-120 (arthritis); Clinical & Experimental Rheumatology, 17 (4) (1999), p. 419-425 (rheumatoid arthritis); Clinical & Experimental Immunology, 117 (2) (1999), p.237-243 (atopic dermatitis); International Journal of Immunopharmacology, 20 (11) (1998), p. 661-7 (psoriasis); Journal of Allergy & Clinical Immunology, 100 (6, Pt 2) (1997), p. S52-5 (asthma); and Journal of Immunology, 159 (6) (1997), p. 2962-72 (allergies).

[0158] In the assay to determine inhibition of RANTES binding, compounds of the invention range in activity from a Ki of about 0.5 to about 1500 nM, with preferred compounds having a range of activity from about 0.5 to about 750 nM, more preferably about 0.5 to 300 nM, and most preferably about 0.5 to 50 nM. The results for preferred and representative compounds of formulas I and II in the test to determine inhibition of RANTES binding are given in the table below. In the table, "Ex. No." stands for "Example Number" and "nM" stands for "nanomolar."

Ex. No.	Ki(nM) Inhibition of RANTES binding
3C	9.97
6C	30.0
11	10.5
16	60
20A	1300
23	2.95

[0159] For preparing pharmaceutical compositions of the CCR5 antagonist 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 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

[0160] Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

[0161] 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, e.g. nitrogen.

[0162] Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

[0163] The CCR5 antagonist 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.

[0164] Preferably the CCR5 antagonist compound is administered orally.

[0165] Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

[0166] The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 10 mg to about 500 mg, preferably from about 25 mg to about 300 mg, more preferably from about 50 mg to about 250 mg, and most preferably from about 55 mg to about 200 mg, according to the particular application.

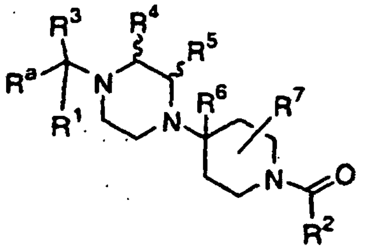
[0167] The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

[0168] The amount and frequency of administration of the CCR5 antagonist compounds of the invention and/or 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 recommended daily dosage regimen for oral administration can range from about 100 mg/day to about 300 mg/day, preferably 150 mg/day to 250 mg/day, more preferably about 200 mg/day, in two to four divided doses.

[0169] The doses and dosage regimen of the NRTIs, NNRTIs, PIs and other agents will be determined by attending clinician in view of the approved doses and dosage regimen in the package insert or as set forth in the protocol taking into consideration the age, sex and condition of the patient and the severity of the HIV-1 infection.

Claims

1. A compound represented by the structural formula II



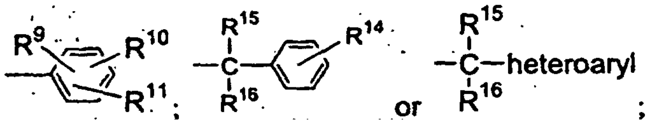
II

or a pharmaceutically acceptable salt thereof, wherein

(1) R^a is R^{8a}-phenyl, R^{8b}-pyridyl, R^{8b}-thiophenyl or R^8-naphthyl;

R^1 is hydrogen or C_1-C_6 alkyl;

R^2 is 6-membered heteroaryl substituted by R^9, R^{10} and R^{11}; 6-membered heteroaryl N-oxide substituted by R^9, R^{10} and R^{11}; 5-membered heteroaryl substituted by R^{12} and R^{13}; naphthyl; fluorenyl; diphenylmethyl;

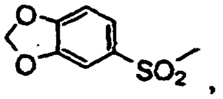


R^3 is hydrogen, C_1-C_6 alkyl, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkyl$(C_1$-$C_6)$alkyl, R^8-phenyl, R^8-phenyl$(C_1$-$C_6)$alkyl, R^8-naphthyl, R^8-naphthyl$(C_1$-$C_6)$alkyl, R^8-heteroaryl or R^8-heteroaryl $(C_1$-$C_6)$alkyl;

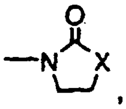
R^4, R^5, R^7 and R^{13} are independently selected from the group consisting of hydrogen and $(C_1$-$C_6)$-alkyl;

R^6 is hydrogen, C_1-C_6 alkyl or C_2-C_6 alkenyl;

R^8 is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-CF_3$, CF_3O-, $CH_3C(O)$-, -CN, CH_3SO_2-, CF_3SO_2-, R^{14}-phenyl, R^{14}-benzyl, $CH_3C(=NOCH_3)$, $CH_3C(=NOCH_2CH_3)$,

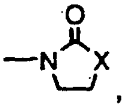


$-NH_2$, $-NHCOCF_3$, -NHCONH(C_1-C_6 alkyl), -NHCO(C_1-C_6 alkyl), $-NHSO_2$(C_1-C_6 alkyl), 5-membered heteroaryl and



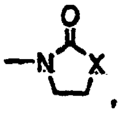
wherein X is -O-, -NH- or $-N(CH_3)$-;

R^{8a} is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, $-CF_3$, CF_3O-, -CN, CF_3SO_2-, R^{14}-phenyl, $-NHCOCF_3$, 5-membered heteroaryl and



wherein X is as defined above;

R^{8b} is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, $-CF_3$, CF_3O-, $CH_3C(O)$-, -CN, CF_3SO_2-, $CH_3C(=NOCH_3)$, $CH_3C(=NOCH_2CH_3)$, $-NHCOCF_3$, 5-membered heteroaryl and



wherein X is as defined above;

R^9 and R^{10} are independently selected from the group consisting of (C_1-C_6)alkyl, halogen, $-NR^{17}R^{18}$, -OH, $-CF_3$, $-OCH_3$, -O-acyl, $-OCF_3$ and $-Si(CH_3)_3$;

R^{11} is R^9, hydrogen, phenyl, $-NO_2$, -CN, $-CH_2F$, $-CHF_2$, -CHO, $-CH=NOR^{17}$, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl, $-N(R^{17})CONR^{18}R^{19}$, -NHCONH(chloro-($C_1$-$C_6$)alkyl), -NHCONH(($C_3$-$C_{10}$)cycloalkyl ($C_1$-$C_6$)alkyl), -NHCO($C_1$-$C_6$)alkyl, $-NHCOCF_3$, $-NHSO_2N((C_1$-$C_6)alkyl)_2$, $-NHSO_2(C_1$-$C_6)$alkyl, $-N(SO_2CF_3)_2$, $-NHCO_2(C_1$-$C_6)$alkyl, C_3-C_{10} cycloalkyl, $-SR^{20}$, $-SOR^{20}$, $-SO_2R^{20}$, $-SO_2NH(C_1$-C_6 alkyl), $-OSO_2(C_1$-$C_6)$alkyl, $-OSO_2CF_3$, hydroxy(C_1-C_6)alkyl, -CON $R^{17}R^{18}$, $-CON(CH_2CH_2$-O-$CH_3)_2$, -OCONH(C_1-C_6)alkyl, $-CO_2R^{17}$, $-Si(CH_3)_3$ or $-B(OC(CH_3)_2)_2$;

R^{12} is (C_1-C_6)alkyl, $-NH_2$ or R^{14}-phenyl;

R^{14} is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, $-CF_3$, $-CO_2R_{17}$, -CN, (C_1-C_6)alkoxy and halogen;

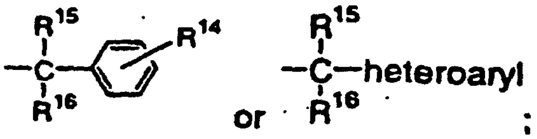
R^{15} and R^{16} are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl, or R^{15} and R^{16} together are a C_2-C_5 alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

R^{17}, R^{18} and R^{19} are independently selected from the group consisting of H and C_1-C_6 alkyl; and

R^{20} is C_1-C_6 alkyl or phenyl; or

(2) R^a is R^8-phenyl, R^8-pyridyl or R^8-thiophenyl;

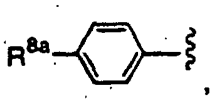
R^2 is fluorenyl, diphenylmethyl,



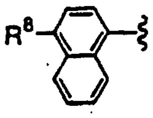
and R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{20} are as defined in (1).

2. A compound of claim 1 wherein R^a is R^{8a}-phenyl or R^8-naphthyl.

3. A compound of claim 2 wherein R^a is



wherein R^{8a} is - CF_3, CF_3O- or halogen; or R^a is

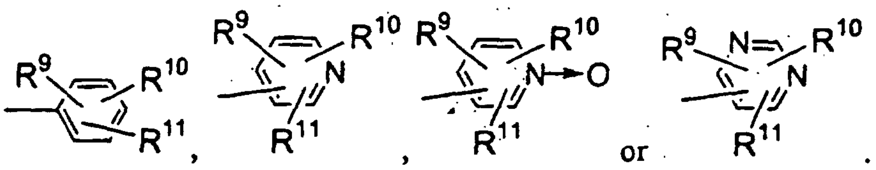


wherein R^8 is C_1-C_6 alkoxy.

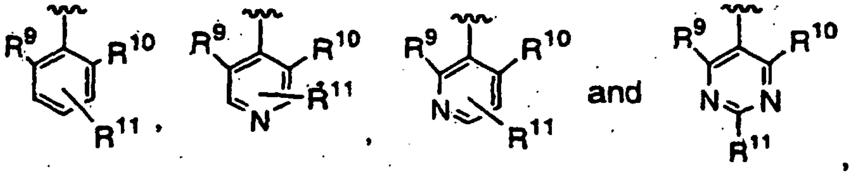
4. A compound of claim 1 wherein R^3 is hydrogen, (C_1-C_6) alkyl, R^8-phenyl, R^8-benzyl or R^8-pyridyl.

5. A compound of claim 1 wherein R^1 is hydrogen; R^6 is hydrogen or methyl; R^4 is methyl; and R^5 and R^7 are each hydrogen.

6. The compound of Claim 1 wherein R^2 is

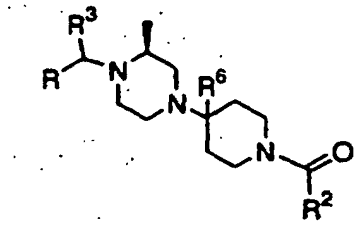


7. A compound of claim 6 wherein R^2 is selected from the group consisting of

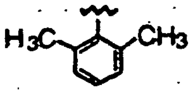


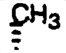
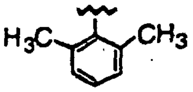
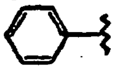
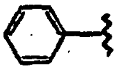
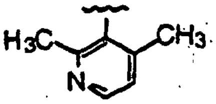
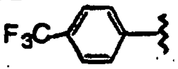
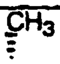
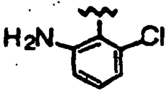
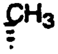
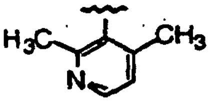
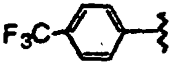
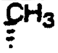
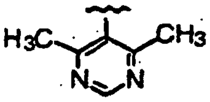
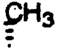
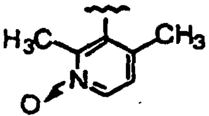
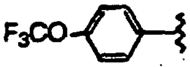
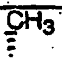
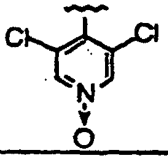
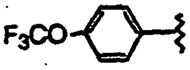
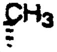
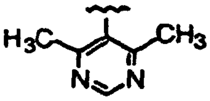
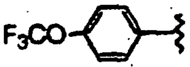
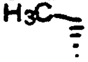
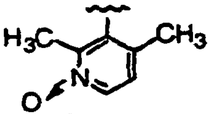
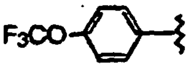
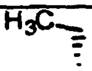
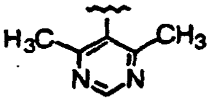
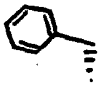
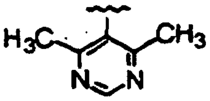
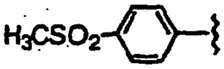
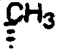
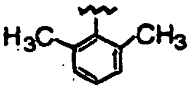
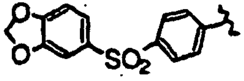
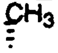
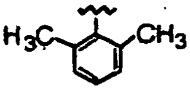
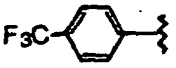
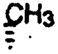
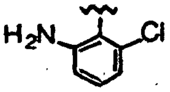
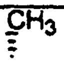
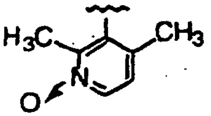
wherein R^9 and R^{10} are selected from the group consisting of (C_1-C_6)alkyl, halogen, -OH and -NH_2.

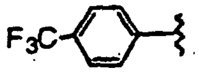
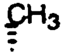
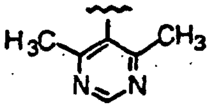
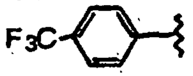
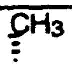
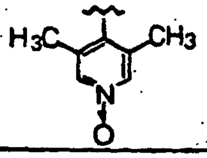
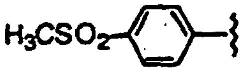
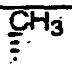
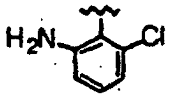
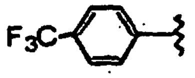
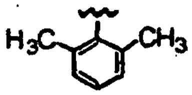
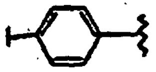
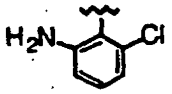
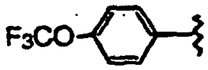
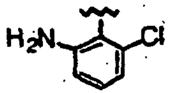
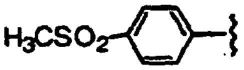
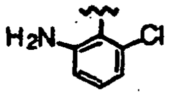
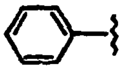
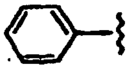
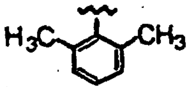
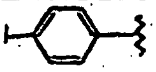
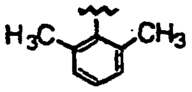
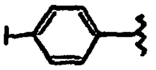
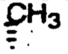
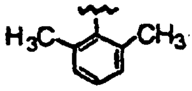
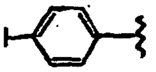
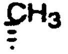
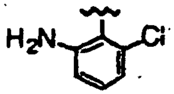
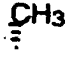
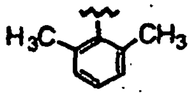
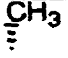
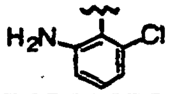
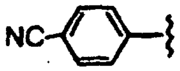
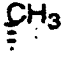
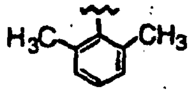
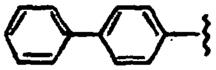
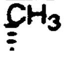
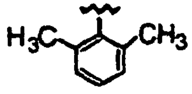
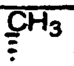
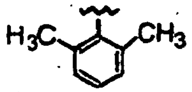
8. A compound selected from the group consisting of those represented by the structural formula

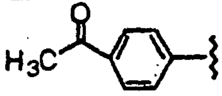
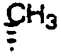
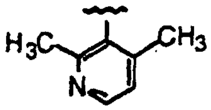
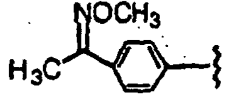
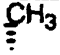
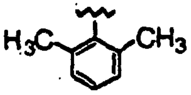
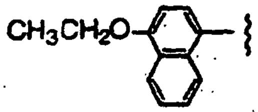
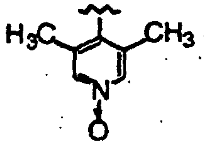
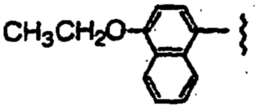
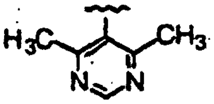
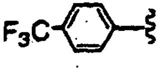
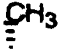
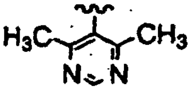
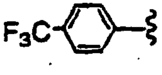
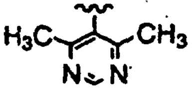
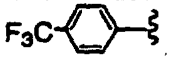
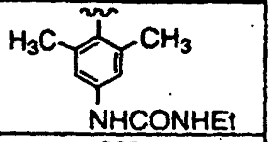
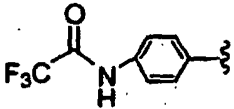
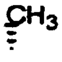
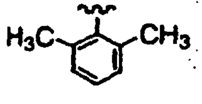
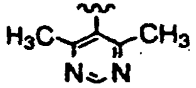
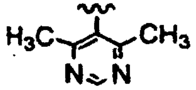
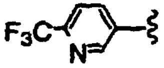
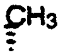
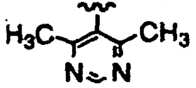
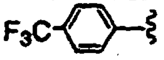
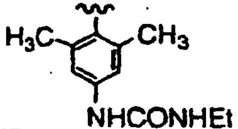
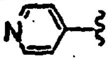
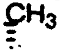
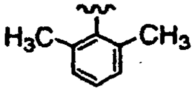
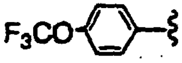
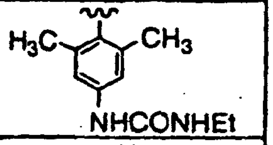
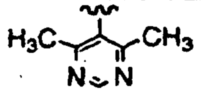


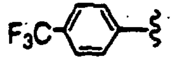
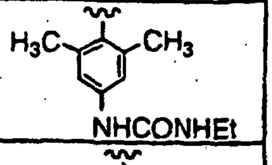
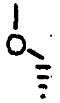
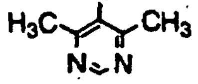
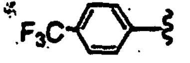
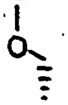
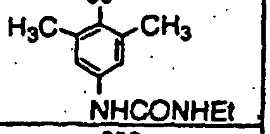
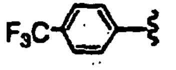
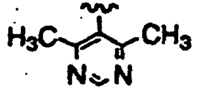
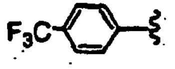
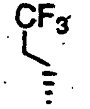
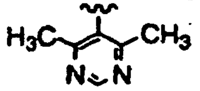
wherein R, R^3, R^6 and R^2 are as defined in the following table:

R	R^3	R^6	R^2
	CH_3	H	

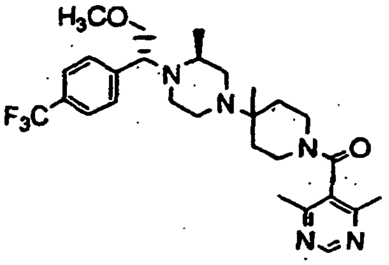
		-CH3	
		H	
		H	
		H	
		H	
		-CH3	
		-CH3	
		-CH3	
		-CH3	
		-CH3	
		-CH3	
		H	
		H	
		-CH3	
		-CH3	

		-CH3	
		-CH3	
		-CH3	
	H	-CH3	
	H	-CH3	
	H	-CH3	
	H	-CH3	
		-CH3	
	H	H	
		H	
		-CH3	
		H	
		-CH3	
		H	
		H	
		H	

		H	
		-CH3	
	H	-CH3	
	H	-CH3	
		-CH2CH3	
		-CH2CH3	
		-CH2CH3	
		-CH3	
		-CH3	
		-CH3	
		-CH3	
		-CH3	
		-CH3	
		-CH3	
		-CH3	

		-CH₃	
		-CH₃	
		-CH₃	
		-CH₃	
		-CH₃	

9. A compound having the formula



10. A pharmaceutical composition for the treatment of Human Immunodeficiency Virus, solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis, comprising an effective amount of a CCR5 antagonist of any preceding claim in combination with a pharmaceutically acceptable carrier.

11. The use of a compound of any of claims 1 to 9 for the preparation of a medicament for treating Human Immunodeficiency Virus, solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis.

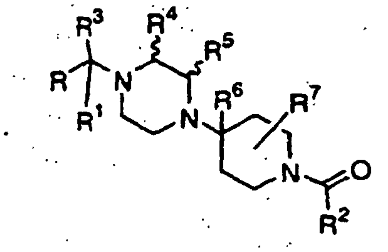
12. The use of a compound of any of claims 1 to 9 for the preparation of a medicament for combined use with one or more antiviral or other agents useful in the treatment of Human Immunodeficiency Virus,

13. The use of claim 12 wherein the antiviral agent is selected from the group consisting of nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

14. The use of a compound of any of claims 1 to 8 for the preparation of a medicament for combined use with one or more agents for treating solid organ transplant rejection, graft v. host disease, inflammatory bowel disease, rheumatoid arthritis or multiple sclerosis.

15. The use of a CCR5 antagonist of formula I for the preparation of a medicament for treating Human Immunodeficiency Virus, solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory

bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis, wherein the CCR5 antagonist is represented by the structural formula I:



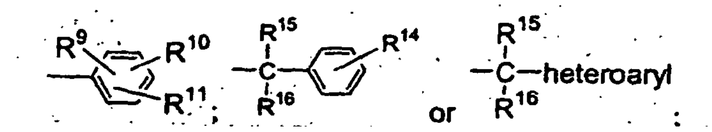
I

or a pharmaceutically acceptable salt thereof, wherein

R is R^8-phenyl, R^8-pyridyl, R^8-thiophenyl or R^8-naphthyl;

R^1 is hydrogen or C_1-C_6 alkyl;

R^2 is 6-membered heteroaryl substituted by R^9, R^{10} and R^{11}; 6-membered heteroaryl N-oxide substituted by R^9, R^{10} and R^{11}; 5-membered heteroaryl substituted by R^{12} and R^{13}; naphthyl; fluorenyl; diphenylmethyl;

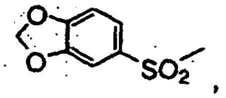


R^3 is hydrogen, C_1-C_6 alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkyl(C_1-C_6)alkyl, R^8-phenyl, R^8-phenyl(C_1-C_6)alkyl, R^8-naphthyl, R^8-naphthyl(C_1-C_6)alkyl, R^8-heteroaryl or R^8-heteroaryl(C_1-C_6)alkyl;

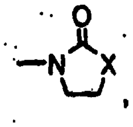
R^4, R^5, R^7 and R^{13} are independently selected from the group consisting of hydrogen and (C_1-C_6)-alkyl;

R^6 is hydrogen, C_1-C_6 alkyl or C_2-C_6 alkenyl;

R^8 is 1 to 3, substituents independently selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-CF_3$, CF_3O-, $CH_3C(O)$-, -CN, CH_3SO_2-, CF_3SO_2-, R^{14}-phenyl, R^{14}-benzyl, $CH_3C(=NOCH_3)$, $CH_3C(=NOCH_2CH_3)$,



$-NH_2$, $-NHCOCF_3$, -NHCONH(C_1-C_6 alkyl), -NHCO(C_1-C_6 alkyl), $-NHSO_2$(C_1-C_6 alkyl), 5-membered heteroaryl and



wherein X is -O-, -NH- or $-N(CH_3)$-;

R^9 and R^{10} are independently selected from the group consisting of (C_1-C_6)alkyl, halogen, $-NR^{17}R^{18}$, -OH, $-CF_3$, $-OCH_3$, -O-acyl, $-OCF_3$ and $-Si(CH_3)_3$;

R^{11} is R^9, hydrogen, phenyl, $-NO_2$, -CN, $-CH_2F$, $-CHF_2$, -CHO, $-CH=NOR^{17}$, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl, $-N(R^{17})CONR^{18}R^{19}$, -NHCONH(chloro-($C_1$-$C_6$)alkyl), -NHCONH(($C_3$-$C_{10}$)-cycloalkyl($C_1$-$C_6$)alkyl), -NHCO($C_1$-$C_6$)alkyl, $-NHCOCF_3$, $-NHSO_2N$((C_1-C_6)alkyl)$_2$, $-NHSO_2$(C_1-C_6)alkyl, $-N(SO_2CF_3)_2$, $-NHCO_2$(C_1-C_6)alkyl, C_3-C_{10} cycloalkyl, $-SR^{20}$, $-SOR^{20}$, $-SO_2R^{20}$, $-SO_2NH$(C_1-C_6 alkyl), $-OSO_2$(C_1-C_6)alkyl, $-OSO_2CF_3$, hydroxy(C_1-C_6)alkyl, -CON $R^{17}R^{18}$, $-CON(CH_2CH_2\text{-}O\text{-}CH_3)_2$, -OCONH($C_1$-$C_6$)alkyl, $-CO_2R^{17}$, $-Si(CH_3)_3$ or $-B(OC(CH_3)_2)_2$;

R^{12} is (C_1-C_6)alkyl, $-NH_2$ or R^{14}-phenyl;

R^{14} is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, -CF_3, -CO_2R_{17}, -CN, (C_1-C_6)alkoxy and halogen;

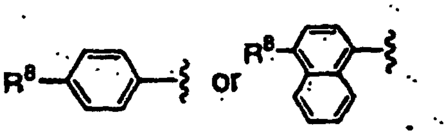
R^{15} and R^{16} are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl, or R^{15} and R^{16} together are a C_2-C_5 alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

R^{17}, R^{18} and R^{19} are independently selected from the group consisting of H and C_1-C_6 alkyl; and

R^{20} is C_1-C_6 alkyl or phenyl.

16. The use of claim 15 wherein R is R^8-phenyl or R^8-naphthyl.

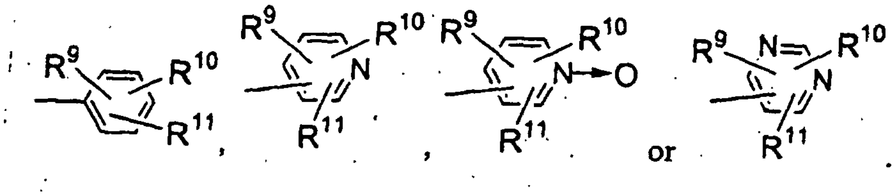
17. The use of claim 16 wherein R is



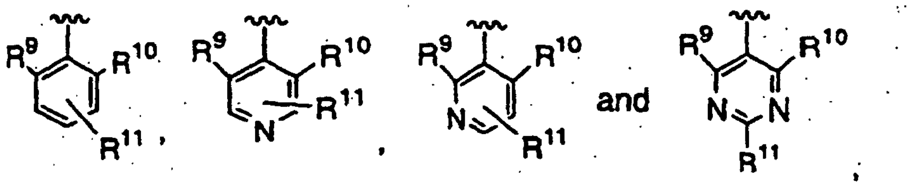
18. The use of claim 15 wherein R^3 is hydrogen, (C_1-C_6) alkyl, R^8-phenyl, R^8-benzyl or R^8-pyridyl.

19. The use of claim 15 wherein R^1 is hydrogen and R^6 is hydrogen or methyl.

20. The use of Claim 15 wherein R^2 is



21. The use of claim 20 wherein R^2 is selected from the group consisting of



wherein R^9 and R^{10} are selected from the group consisting of (C_1-C_6)alkyl, halogen, -OH and -NH_2.

22. The use of claim 21 wherein R^2 is phenyl or pyridyl and R^{11} is hydrogen, or wherein R^2 is pyrimidyl and R^{11} is hydrogen, methyl or phenyl.

23. The use of claim 15 for the treatment of Human Immunodeficiency Virus, further comprising one or more antiviral or other agents useful in the treatment of Human immunodeficiency Virus.

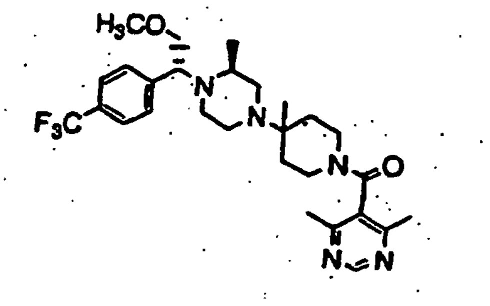
24. The use of claim 23 wherein the antiviral agent is selected from the group consisting of nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

25. The use of claim 15 for the treatment of solid organ transplant rejection, graft v. host disease, inflammatory bowel disease, rheumatoid arthritis or multiple sclerosis, further comprising one or more other agents useful in the treatment of said diseases.

26. A kit comprising in separate containers in a single package pharmaceutical compositions for use in combination to treat Human Immunodeficiency Virus which comprises in one container a pharmaceutical composition comprising an effective amount of a CCR5 antagonist of claim 15 in a pharmaceutically acceptable carrier, and in separate containers, one or more pharmaceutical composition comprising an effective amount of a antiviral or other agent useful in the treatment of Human Immunodeficiency Virus in a pharmaceutically acceptable carrier.

27. A pharmaceutical composition in the form of a cream for topical application comprising a compound of Formula II as defined in any of claims 1 to 9 and a pharmaceutically acceptable carrier

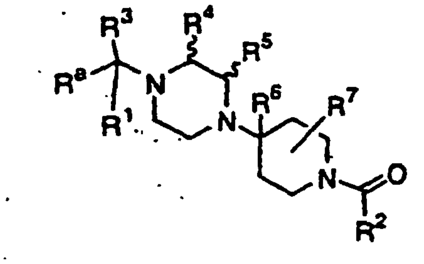
28. A pharmaceutical composition in the form of a cream for topical application comprising a compound of Formula



and a pharmaceutically acceptable carrier.

Patentansprüche

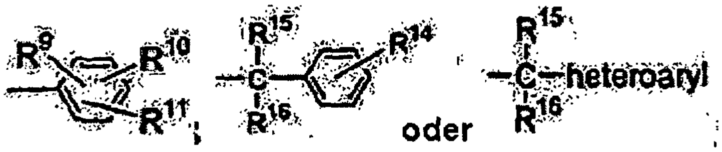
1. Verbindung mit der Strukturformel II



II

oder ein pharmazeutisch annehmbares Salz davon; worin

(1) R^a R^{8a}-Phenyl, R^{8b}-Pyridyl, R^{8b}-Thiophenyl oder R^8-Naphthyl ist;
R^1 Wasserstoff oder (C_1-C_6)-Alkyl ist;
R^2 6-gliederiges Heteroaryl, das mit R^9, R^{10} und R^{11} substituiert ist; 6-gliedriges Heteroaryl-N-oxid, das mit R^9, R^{10} und R^{11} substituiert ist; 5-gliedriges Heteroaryl, das mit R^{12} und R^{13} substituiert ist; Naphthyl; Fluorenyl; Diphenylmethyl;



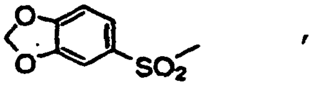
ist;
R^3 Wasserstoff, C_1-C_6-Alkyl, (C_1-C_6) -Alkoxy (C_1-C_6) alkyl, C_3-C_{10}-Cycloalkyl, C_3-C_{10}-Cycloalkyl(C_1-C_6)alkyl, R^8-Phenyl, R^8-Phenyl(C_1-C_6)alkyl, R^8-Naphthyl, R^8-Naphthyl(C_1-C_6)alkyl, R^8-Heteroaryl oder R^8-Heteroaryl

(C_1-C_6)alkyl ist;

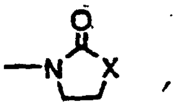
R^4, R^5, R^7 und R^{13} unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und (C_1-C_6)-Alkyl;

R^6 Wasserstoff, C_1-C_6-Alkyl oder C_2-C_6-Alkenyl ist;

R^8 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Halogen, C_1-C_6-Alkyl, C_1-C_6-Alkoxy, -CF_3, CF_3O-, $CH_3C(O)$-, -CN, CH_3SO_2-, CF_3SO_2-, R^{14}-Phenyl, R^{14}-Benzyl, $CH_3C(=NOCH_3)$, $CH_3C(=NOCH_2CH_3)$,



NH_2, -$NHCOCF_3$, -NHCONH(C_1-C_6-alkyl), -NHCO(C_1-C_6-alkyl), -$NHSO_2$(C_1-C_6-alkyl), 5-gliedrigem Heteroaryl und



wobei X -O-, -NH- oder -$N(CH_3)$- ist;

R^{8a} 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Halogen, -CF_3, CF_3O-, -CN, CF_3SO_2-, R^{14}-Phenyl, -$NHCOCF_3$, 5-gliedrigem Heteroaryl und

worin X wie oben definiert ist;

R^{8b} 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Halogen, -CF_3, CF_3O-, $CH_3C(O)$-, -CN, CF_3SO_2-, $CH_3C(=NOCH_3)$, $CH_3C(=NOCH_2CH_3)$, -$NHCOCF_3$, 5-gliedrigem Heteroaryl und

worin X wie oben definiert ist;

R^9 und R^{10} unabhängig ausgewählt sind aus der Gruppe bestehend aus (C_1-C_6)-Alkyl, Halogen, -$NR^{17}R^{18}$, -OH, -CF_3, -OCH_3, -O-Acyl, -OCF_3 und -$Si(CH_3)_3$;

R^{11} R^9, Wasserstoff, Phenyl, -NO_2, -CN, -CH_2F, -CHF_2, -CHO, -CH=NOR^{17}, Pyridyl, Pyridyl N-oxid, Pyrimidinyl, Pyrazinyl, -N(R^{17})$CONR^{18}R^{19}$, -NHCONH (chlor- (C_1-C_6)alkyl) , NHCONH ((C_3-C_{10})-cycloalkyl (C_1-C_6) alkyl) , -NHCO (C_1-C_6)alkyl, -$NHCOCF_3$, -$NHSO_2N$((C_1-C_6)alkyl)$_2$, -$NHSO_2$(C_1-C_6)alkyl, -N (SO_2CF_3)$_2$, -$NHCO_2$(C_1-C_6)alkyl, C_3-C_{10}-Cycloalkyl, -SR^{20}, -SOR^{20}, -SO_2R^{20}, -SO_2NH(C_1-C_6-alkyl), -OSO_2(C_1-C_6)alkyl, -OSO_2CF_3, Hydroxy(C_1-C_6)alkyl, -$CONR^{17}R^{18}$, -$CON(CH_2CH_2$-O-$CH_3)_2$, -OCONH(C_1-C_6)alkyl, -CO_2R^{17}, -Si $(CH_3)_3$ oder -$B(OC(CH_3)_2)_2$ ist;

R^{12} (C_1-C_6)-Alkyl, -NH_2 oder R^{14}-Phenyl ist;

R^{14} 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, (C_1-C_6)-Alkyl, -CF_3, -CO_2R^{17}, -CN, (C_1-C_6)-Alkoxy und Halogen;

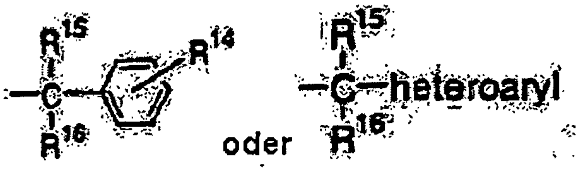
R^{15} und R^{16} unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und C_1-C_6-Alkyl, oder R^{15} und R^{16} zusammen eine C_2-C_5-Akylengruppe sind und mit dem Kohlenstoff, an den sie gebunden sind, einen Spiroring mit 3 bis 6 Kohlenstoffatomen bilden:

R^{17}, R^{18} und R^{19} unabhängig ausgewählt sind aus der Gruppe bestehend aus H und C_1-C_6-Alkyl; und

R^{20} C_1-C_6-Alkyl oder Phenyl ist; oder

(2) R^a R^8-Phenyl, R^8-Pyridyl oder R^8-Thiophenyl ist;

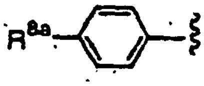
R^2 Fluorenyl, Diphenylmethyl,



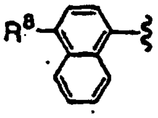
ist
und R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} und R^{20} wie in (1) definiert sind.

2. Verbindung nach Anspruch 1, bei der Ra R^{8a}-Phenyl oder R^8-Naphthyl ist.

3. Verbindung nach Anspruch 2, worin R^a



ist, worin R^{8a} -CF_3, CF_3O- oder Halogen ist; oder R^a



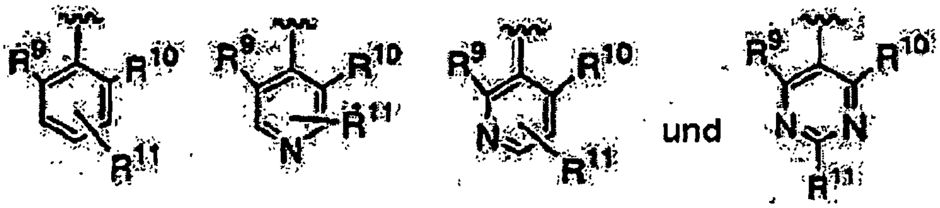
ist, wobei R^8 C_1-C_6-Alkoxy ist.

4. Verbindung nach Anspruch 1, worin R^3 Wasserstoff, (C_1-C_6)-Alkyl, R^8-Phenyl, R^8-Benzyl oder R^8-Pyridyl ist.

5. Verbindung nach Anspruch 1, bei der R^1 Wasserstoff ist; R^6 Wasserstoff oder Methyl ist; R^4 Methyl ist und R^5 und R^7 jeweils Wasserstoff sind.

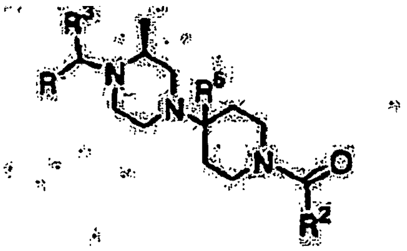
6. Verbindung nach Anspruch 1, bei der R^2 wie folgt ist:

7. Verbindung nach Anspruch 6, bei der R^2 ausgewählt ist aus der Gruppe bestehend aus:

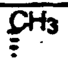
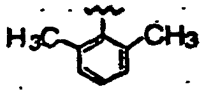


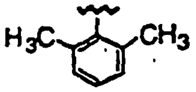
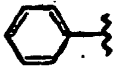
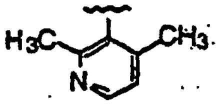
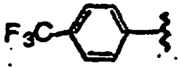
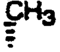
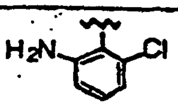
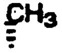
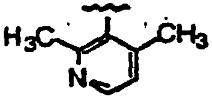
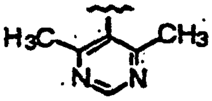
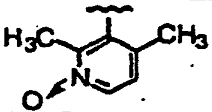
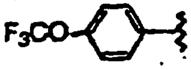
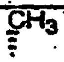
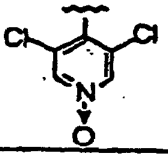
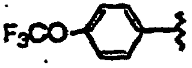
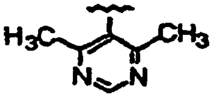
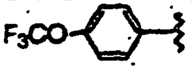
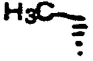
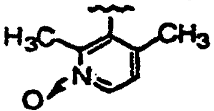
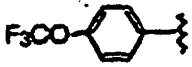
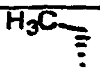
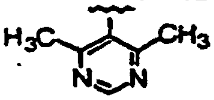
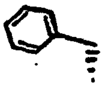
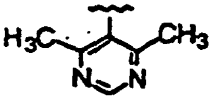
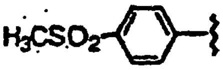
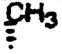
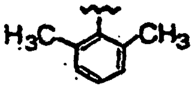
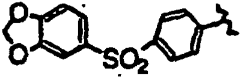
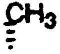
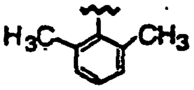
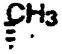
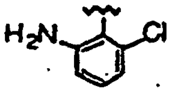
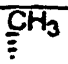
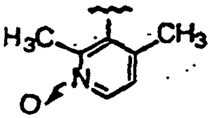
worin R^9 und R^{10} ausgewählt sind aus der Gruppe bestehend aus (C_1-C_6)-Alkyl, Halogen, -OH und -NH_2.

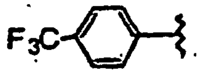
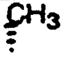
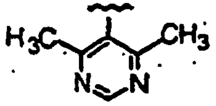
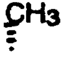
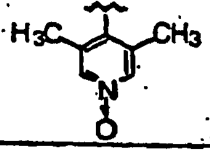
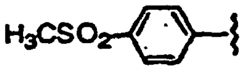
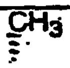
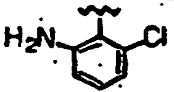
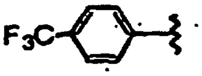
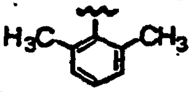
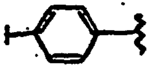
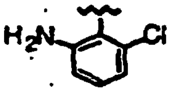
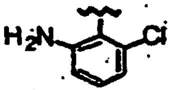
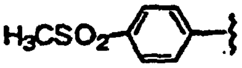
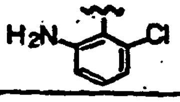
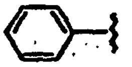
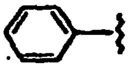
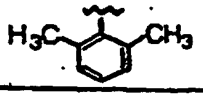
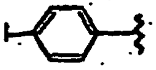
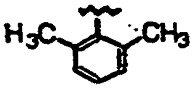
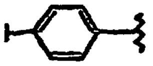
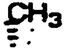
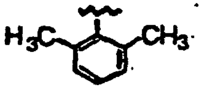
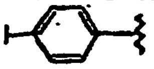
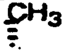
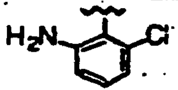
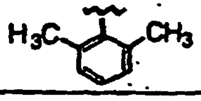
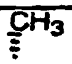
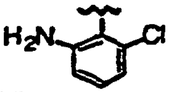
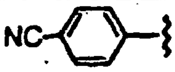
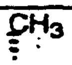
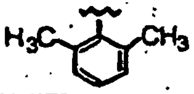
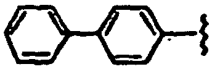
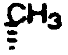
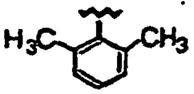
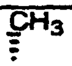
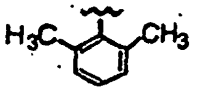
8. Verbindung ausgewählt aus der Gruppe bestehend aus jenen, die durch die folgende Strukturformel wiedergegeben werden:

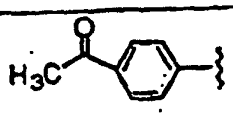
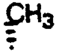
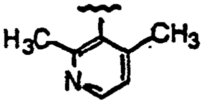
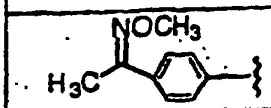
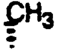
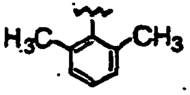
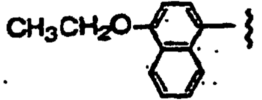
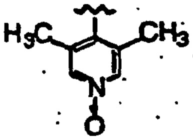
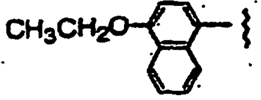
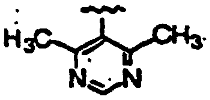
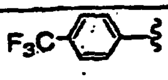
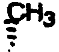
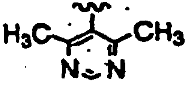
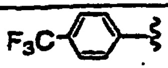
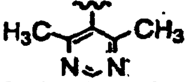
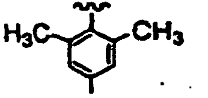
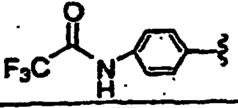
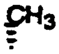
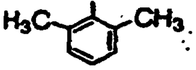
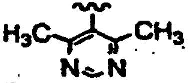
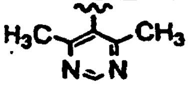
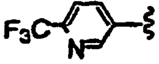
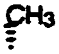
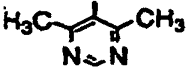
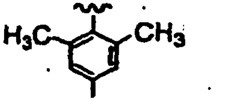
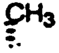
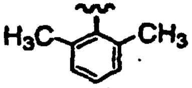
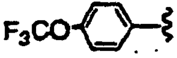
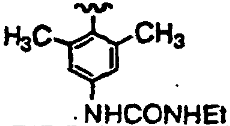
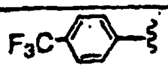
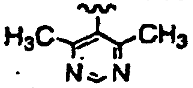


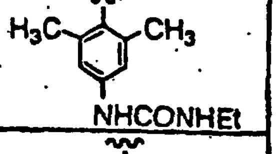
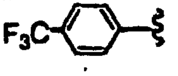
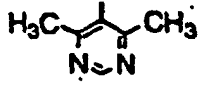
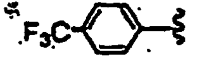
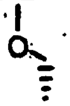
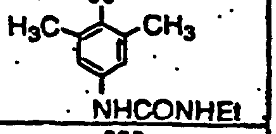
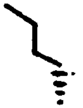
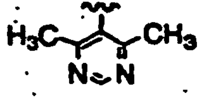
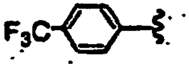
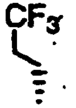
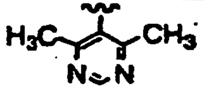
wobei R, R^3, R^6 und R^2 wie in der folgenden Tabelle definiert sind:

R	R^3	R^6	R^2
		H	

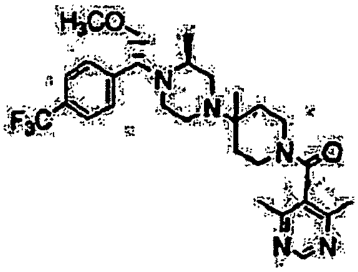
		$-CH_3$	
		H	
		H	
		H	
		H	
		$-CH_3$	
		$-CH_3$	
		$-CH_3$	
		$-CH_3$	
		$-CH_3$	
		$-CH_3$	
		H	
		H	
		$-CH_3$	
		$-CH_3$	

		-CH3	
		-CH3	
		-CH3	
	H	-CH3	
	H	-CH3	
	H	-CH3	
	H	-CH3	
		-CH3	
	H	H	
		H	
		-CH3	
		H	
		-CH3	
		H	
		H	
		H	

		H	
		$-CH_3$	
	H	$-CH_3$	
	H	$-CH_3$	
		$-CH_2CH_3$	
		$-CH_2CH_3$	
		$-CH_2CH_3$	
		$-CH_3$	
		$-CH_3$	
		$-CH_3$	
		$-CH_3$	
		$-CH_3$	
		$-CH_3$	
		$-CH_3$	
		$-CH_3$	

		-CH$_3$	
		-CH$_3$	
		-CH$_3$	
		-CH$_3$	
		-CH$_3$	

9. Verbindung mit der Formel:



10. Pharmazeutische Zusammensetzung zur Behandlung von HIV-Virus, Abstoßung von soliden Organtransplantaten, Graft-versus-Host-Erkrankung, Arthritis, rheumatoider Arthritis, entzündlicher Darmerkrankung, atopischer Dermatitis, Psoriasis, Asthma, Allergien oder multipler Sklerose, die eine wirksame Menge eines CCR5-Antagonisten gemäß einem der vorhergehenden Ansprüche in Kombination mit einem pharmazeutisch annehmbaren Träger enthält.

11. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 9 zur Herstellung eines Medikaments zur Behandlung von HIV-Virus, Abstoßung von soliden Organtransplantaten, Graft-versus-Host-Erkrankung, Arthritis, rheumatoider Arthritis, entzündlicher Darmerkrankung, atopischer Dermatitis, Psoriasis, Asthma, Allergien oder multipler Sklerose.

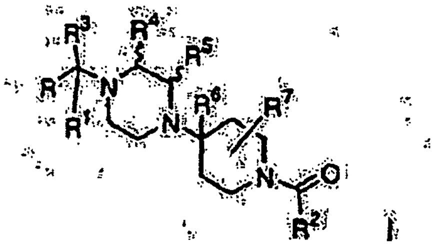
12. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 9 zur Herstellung eines Medikaments zur kombinierten Verwendung mit einem oder mehreren Antivirus- oder anderen Mitteln, die zur Behandlung von HIV brauchbar sind.

13. Verwendung nach Anspruch 12, bei der das Antivirusmittel ausgewählt ist aus der Gruppe bestehend aus Nukleosid-reverse-Transkriptase-Inhibitoren, Nicht-Nukleosid-reverse-Transkriptase-Inhibitoren und Protease-Inhibito-

ren.

14. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 8 zur Herstellung eines Medikaments zur kombinierten Verwendung mit einem oder mehreren Mitteln zur Behandlung von Abstoßung solider Organtransplantate, Graft-versus-Host-Erkrankung, entzündlicher Darmerkrankung, rheumatoider Arthritis oder multipler Sklerose.

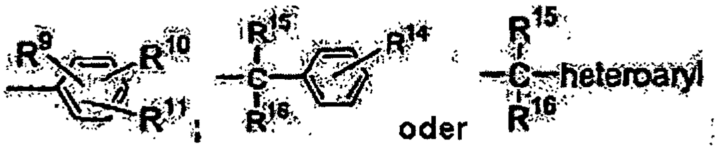
15. Verwendung eines CCR5-Antagonisten der Formel I zur Herstellung eines Medikaments zur Behandlung von HIV-Virus, Abstoßung von soliden Organtransplantaten, Graft-versus-Host-Erkrankung, Arthritis, rheumatoider Arthritis, entzündlicher Darmerkrankung, atopischer Dermatitis, Psoriasis, Asthma, Allergien oder multipler Sklerose, wobei der CCR5-Antagonist durch die Strukturformel I wiedergegeben wird:



oder ein pharmazeutisch annehmbares Salz davon; worin R R^8-Phenyl, R^8-Pyridyl, R^8-Thiophenyl oder R^8-Naphthyl ist;

R^1 Wasserstoff oder C_1-C_6-Alkyl ist;

R^2 6-gliedriges Heteroaryl, das durch R^9, R^{10} und R^{11} substituiert ist; 6-gliedriges Heteroaryl-N-oxid, das durch R^9, R^{10} und R^{11} substituiert ist; 5-gliedriges Heteroaryl, das durch R^{12} und R^{13} substituiert ist; Naphthyl; Fluorenyl; Diphenylmethyl;



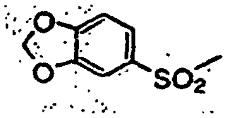
ist;

R^3 Wasserstoff, C_1-C_6-Alkyl, $(C_1$-$C_6)$-Alkoxy$(C_1$-$C_6)$alkyl, C_3-C_{10}-Cycloalkyl, C_3-C_{10}-Cycloalkyl$(C_1$-$C_6)$alkyl, R^8-Phenyl, R^8-Phenyl$(C_1$-$C_6)$alkyl, R^8-Naphthyl, R^8-Naphthyl$(C_1$-$C_6)$alkyl, R^8-Heteroaryl oder R^8-Heteroaryl$(C_1$-$C_6)$ alkyl ist;

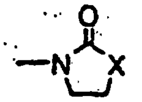
R^4, R^5, R^7 und R^{13} unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und $(C_1$-$C_6)$-Alkyl;

R^6 Wasserstoff, C_1-C_6-Alkyl oder C_2-C_6-Alkenyl ist;

R^8 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Halogen, C_1-C_6-Alkyl, C_1-C_6-Alkoxy, $-CF_3$, CF_3O-, $CH_3C(O)$-, -CN, CH_3SO_2-, CF_3SO_2-, R^{14}-Phenyl, R^{14}-Benzyl, $CH_3C(=NOCH_3)$, $CH_3C(=NOCH_2CH_3)$,



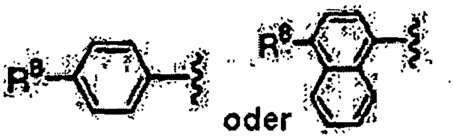
$-NH_2$, $-NHCOCF_3$, $-NHCONH(C_1$-C_6-alkyl), $-NHCO(C_1$-C_6-alkyl), $-NHSO_2(C_1$-C_6-alkyl), 5-gliedrigem Heteroaryl und

 ,

wobei X -O-, -NH- oder -N(CH_3)- ist;
R^9 und R^{10} unabhängig ausgewählt sind aus der Gruppe bestehend aus (C_1-C_6)-Alkyl, Halogen, -$NR^{17}R^{18}$, -OH, -CF_3, -OCH_3, -0-Acyl, -OCF_3 und -Si(CH_3)$_3$;
R^{11} R^9, Wasserstoff, Phenyl, -NO_2, -CN, -CH_2F, -CHF_2, -CHO, -CH=NOR^{17}, Pyridyl, Pyridyl N-oxid, Pyrimidinyl, Pyrazinyl, -N (R^{17})$CONR^{18}R^{19}$, -NHCONH (chlor- (C_1-C_6)alkyl), -NHCONH ((C_3-C_{10})-cycloalkyl (C_1-C_6)alkyl), -NHCO(C_1-C_6)alkyl, -$NHCOCF_3$, -$NHSO_2N$((C_1-C_6)alkyl)$_2$, -$NHSO_2$(C_1-C_6)alkyl, -N(SO_2CF_3)$_2$, -$NHCO_2$(C_1-C_6)alkyl, C_3-C_{10}-Cycloalkyl, -SR^{20}, -SOR^{20}, -SO_2R^{20}, -SO_2NH(C_1-C_6-alkyl), - OSO_2(C_1-C_6)alkyl, -OSO_2CF_3, Hydroxy (C_1-C_6)alkyl, -$CONR^{17}R^{18}$, -CON(CH_2CH_2-O-CH_3)$_2$, -OCONH (C_1-C_6)alkyl, -CO_2R^{17}, -Si(CH_3)$_3$ oder -B(OC(CH_3)$_2$)$_2$ ist;
R^{12} (C_1-C_6)-Alkyl, -NH_2 oder R^{14}-Phenyl ist;
R^{14} 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, (C_1-C_6)-Alkyl, -CF_3, -CO_2R^{17}, -CN, (C_1-C_6)-Alkoxy und Halogen;
R^{15} und R^{16} unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und C_1-C_6-Alkyl, oder R^{15} und R^{16} zusammen eine C_2-C_5-Akylengruppe sind und mit dem Kohlenstoff, an den sie gebunden sind, einen Spiroring mit 3 bis 6 Kohlenstoffatomen bilden;
R^{17}, R^{18} und R^{19} unabhängig ausgewählt sind aus der Gruppe bestehend aus H und C_1-C_6-Alkyl; und
R^{20} C_1-C_6-Alkyl oder Phenyl ist.

16. Verwendung nach Anspruch 15, bei der R R^8-Phenyl oder R^8-Naphthyl ist.

17. Verwendung nach Anspruch 16, bei der R



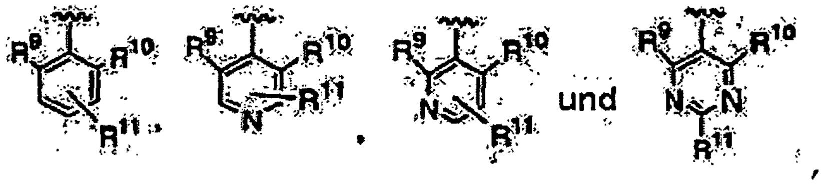
ist.

18. Verwendung nach Anspruch 15, bei der R^3 Wasserstoff, (C_1-C_6)-Alkyl, R^8-Phenyl, R^8-Benzyl oder R^8-Pyridyl ist.

19. Verwendung nach Anspruch 15, bei der R^1 Wasserstoff ist und R^6 Wasserstoff oder Methyl ist.

20. Verwendung nach Anspruch 15, bei der R^2 wie folgt ist:

21. Verwendung nach Anspruch 20, bei der R^2 ausgewählt ist aus der Gruppe bestehend aus:



worin R^9 und R^{10} ausgewählt sind aus der Gruppe bestehend aus (C_1-C_6)-Alkyl, Halogen, -OH und -NH_2.

22. Verwendung nach Anspruch 21, bei der R^2 Phenyl oder Pyridyl ist und R^{11} Wasserstoff ist, oder bei der R^2 Pyrimidyl ist und R^{11} Wasserstoff, Methyl oder Phenyl ist.

23. Verwendung nach Anspruch 15 zur Behandlung des HIV-Virus, wobei ferner ein oder mehrere Antivus- oder andere Mittel vorhanden sind, die zur Behandlung des HIV-Virus brauchbar sind.

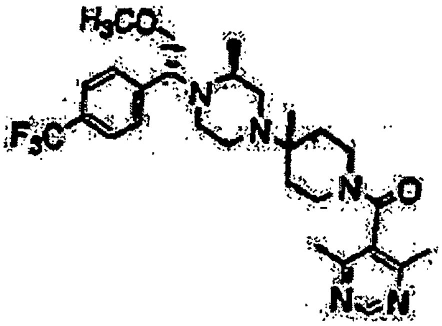
24. Verwendung nach Anspruch 23, bei der das Antivirusmittel ausgewählt ist aus der Gruppe bestehend aus Nukleosid-reverse-Transkriptase-Inhibitoren, Nicht-Nukleosid-reverse-Transkriptase-Inhibitoren und Protease-Inhibitoren.

25. Verwendung nach Anspruch 15 zur Behandlung von Abstoßung von soliden Organtransplantaten, Graft-versus-Host-Erkrankung, entzündlicher Darmerkrankung, rheumatoider Arthritis oder multipler Sklerose, wobei ferner ein oder mehrere andere Mittel vorhanden sind, die zur Behandlung dieser Erkrankungen brauchbar sind.

26. Kit, der in separaten Behältern in einer Einzelpackung pharmazeutische Zusammensetzungen zur kombinierten Verwendung zur Behandlung des HIV-Virus enthält und der in einem Behälter eine pharmazeutische Zusammensetzung aufweist, die eine wirksame Menge eines CCR5-Antagonisten gemäß Anspruch 15 in einem pharmazeutisch annehmbaren Träger enthält und in separaten Behältern eine oder mehrere pharmazeutische Zusammensetzung(en) aufweist, die eine wirksame Menge eines Antivirus- oder anderen Mittels, das zur Behandlung des HIV-Virus brauchbar ist, in einem pharmazeutisch annehmbaren Träger enthält.

27. Pharmazeutische Zusammensetzung in Form einer Creme zur topischen Aufbringung, die eine Verbindung der Formel II gemäß einem der Ansprüche 1 bis 9 und einen pharmazeutisch annehmbaren Träger enthält.

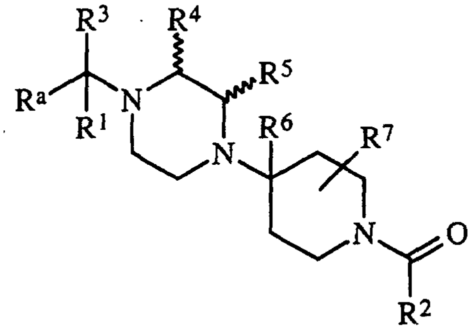
28. Pharmazeutische Zusammensetzung in Form einer Creme zur topischen Aufbringung, die eine Verbindung der Formel



und einen pharmazeutisch annehmbaren Träger enthält.

Revendications

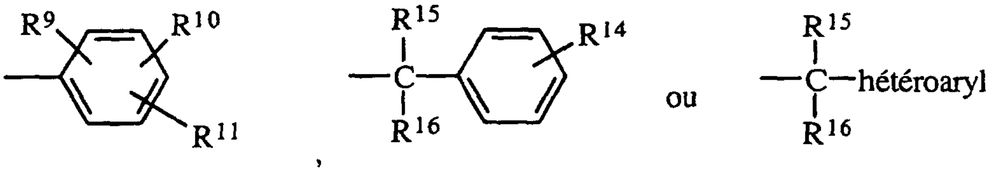
1. Composé de formule développée II



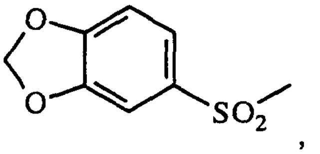
II

dans laquelle :

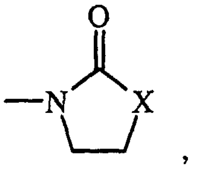
(1) R^a représente un groupe R^{8a}-phényle, R^{8b}-pyridyle, R^{8b}-thiophényle ou R^8-naphtyle,
R^1 représente un atome d'hydrogène ou un groupe alkyle en C_1 à C_6,
R^2 représente un groupe hétéroaryle à 6 chaînons, substitué par R^9, R^{10} et
R^{11}, un groupe hétéroaryle-N-oxyde à 6 chaînons, substitué par R^9, R^{10} et
R^{11}, un groupe hétéroaryle à 5 chaînons, substitué par R^{12} et R^{13}, un groupe naphtyle, un groupe fluorényle, un groupe diphénylméthyle, ou un groupe



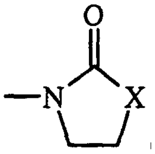
R^3 représente un atome d'hydrogène ou un groupe alkyle en C_1 à C_6, alcoxy(C_1 à C_6)alkyle(C_1 à C_6), cycloalkyle en C_3 à C_{10}, cycloalkyl(C_3 à C_{10})alkyle(C_1 à C_6), R^8-phényle, R^8-phénylalkyle(C_1 à C_6), R^8-naphtyle, R^8-naphtylalkyle(C_1 à C_6), R^8-hétéroaryle ou R^8-hétéroarylalkyle(C_1 à C_6),
R^4, R^5, R^7 et R^{13} représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C_1 à C_6,
R^6 représente un atome d'hydrogène, un groupe alkyle en C_1 à C_6 ou un groupe alcényle en C_2 à C_6,
R^8 représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes alkyle en C_1 à C_6, alcoxy en C_1 à C_6, $-CF_3$, CF_3O-, $CH_3C(O)-$, -CN, CH_3SO_2-, CF_3SO_2-, R^{14}-phényle, R^{14}-benzyle, $CH_3C(=NOCH_3)$, $CH_3C(=NOCH_2CH_3)$,



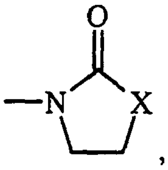
$-NH_2$, $-NHCOCF_3$, -NHCONH(alkyl en C_1-C_6), -NHCO(alkyl en C_1-C_6), $-NHSO_2$(alkyl en C_1-C_6), hétéroaryle à 5 chaînons et



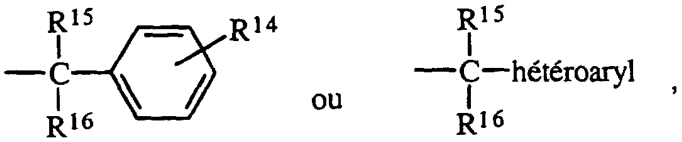
où X est -O-, -NH- ou -N(CH_3)-,
R^{8a} représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes -CF_3, CF_3O-, -CN, CF_3SO_2-, R^{14}-phényle, -$NHCOCF_3$, hétéroaryle à 5 chaînons et



où X est tel que défini précédemment,
R^{8b} représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes -CF_3, CF_3O-, $CH_3C(O)$-, -CN, CF_3SO_2-, $CH_3C(=NOCH_3)$, $CH_3C(=NOCH_2CH_3)$, - $NHCOCF_3$, hétéroaryle à 5 chaînons et



où X est tel que défini précédemment,
R^9 et R^{10} représentent chacun indépendamment un atome d'halogène ou un groupe alkyle en C_1 à C_6, -$NR^{17}R^{18}$, -OH, -CF_3, -OCH_3, -O-acyl, -OCF_3 ou -$Si(CH_3)_3$,
R^{11} représente R^9, un atome d'hydrogène, ou un groupe phényle, -NO_2, - CN, -CH_2F, -CHF_2, -CHO, -$CH=NOR^{17}$, pyridyle, pyridyle-N-oxyde, pyrimidinyle, pyrazinyle, -$N(R^{17})CONR^{18}R^{19}$, -NHCONH(chloroalkyl en C_1 à C_6), -NHCONH(cycloalkyl(C_3 à C_{10})alkyl(C_1 à C_6)), -NHCOalkyl(C_1 à C_6), -$NHCOCF_3$, -$NHSO_2N$(alkyl en C_1 à C_6)$_2$, -$NHSO_2$alkyl(C_1 à C_6), -$N(SO_2CF_3)_2$, -$NHCO_2$alkyl(C_1 à C_6), cycloalkyle en C_3 à C_{10}, -SR^{20}, -SOR^{20}, -SO_2R^{20}, -SO_2NHalkyl(C_1 à C_6), -OSO_2alkyl(C_1 à C_6), -OSO_2CF_3, hydroxyalkyle en C_1 à C_6, -$CONR^{17}R^{18}$, -$CON(CH_2CH_2\text{-}O\text{-}CH_3)_2$, -OCONHalkyl($C_1$ à C_6), -CO_2R^{17}, -$Si(CH_3)_3$ ou -$B(OC(CH_3)_3)_2$,
R^{12} représente un groupe alkyle en C_1 à C_6, -NH_2 ou R^{14}-phényle,
R^{14} représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes alkyle en C_1 à C_6, -CF_3, -CO_2R^{17}, -CN et alcoxy en C_1 à C_6,
R^{15} et R^{16} représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C_1 à C_6, ou bien R^{15} et R^{16} forment ensemble un groupe alkylène en C_2 à C_5 et forment avec l'atome de carbone auquel ils sont liés un cycle spiro ayant 3 à 6 atomes de carbone,
R^{17}, R^{18} et R^{19} représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C_1 à C_6, et
R^{20} représente un groupe alkyle en C_1 à C_6 ou un groupe phényle, ou bien
(2) R^a représente un groupe R^8-phényle, R^8-pyridyle ou R^8-thiophényle, R^2 représente un groupe fluorényle, diphénylméthyle,

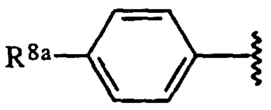


et R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} et R^{20} ont les définitions indiquées dans la partie (1),

ou un sel pharmaceutiquement acceptable d'un tel composé.

2. Composé selon la revendication 1, pour lequel R^a représente un groupe R^{8a}-phényle ou R^8-naphtyle.

3. Composé selon la revendication 2, pour lequel R^a représente



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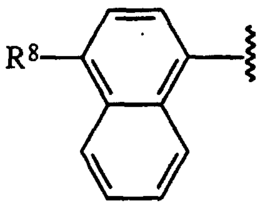
où R^{8a} représente un atome d'halogène ou un groupe $-CF_3$ ou CF_3O-, ou bien R^a représente

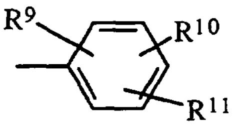


où R^8 représente un groupe alcoxy en C_1 à C_6.

4. Composé selon la revendication 1, pour lequel R^3 représente un atome d'hydrogène ou un groupe alkyle en C_1 à C_6, R^8-phényle, R^8-benzyle ou R^8-pyridyle.

5. Composé selon la revendication 1, pour lequel R^1 représente un atome d'hydrogène, R^6 représente un atome d'hydrogène ou un groupe méthyle, R^4 représente un groupe méthyle, et R^5 et R^7 représentent des atomes d'hydrogène.

6. Composé selon la revendication 1, pour lequel R^2 représente



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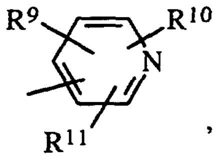

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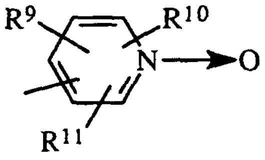

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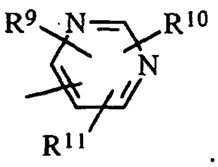

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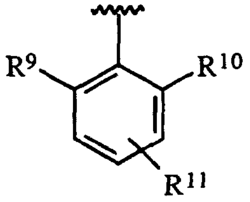
7. Composé selon la revendication 6, pour lequel R^2 représente un groupe choisi parmi les groupes



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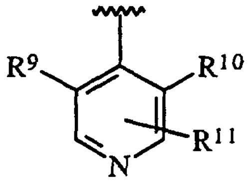

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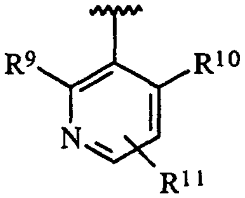

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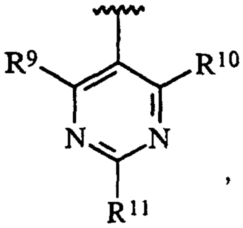

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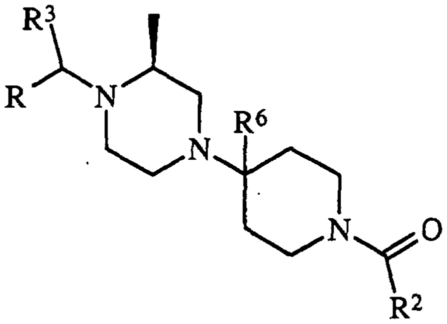
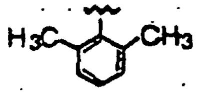
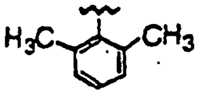
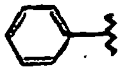
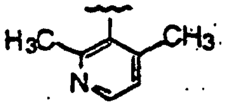
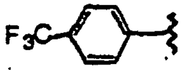
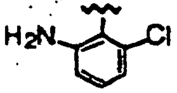
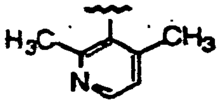
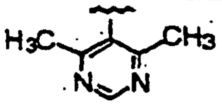
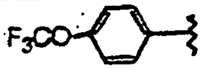
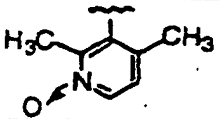
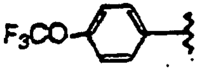
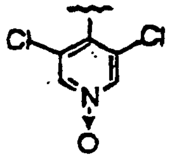
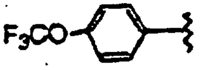
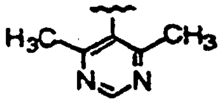
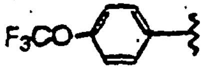
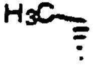
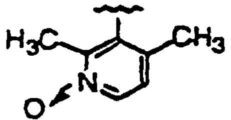
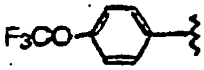
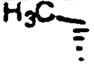
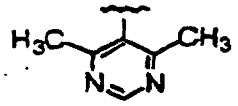
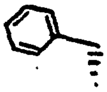
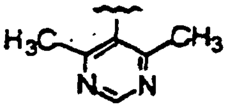
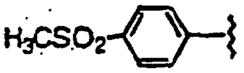
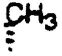
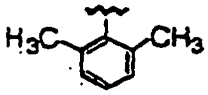
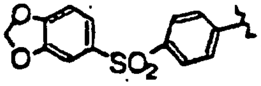
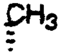
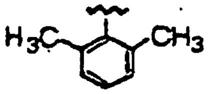
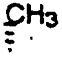
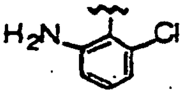
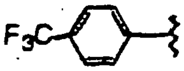
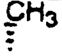
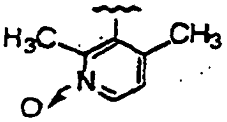
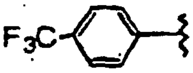
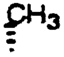
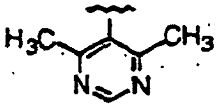
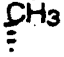
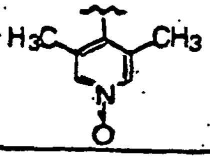
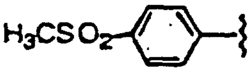
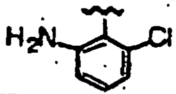
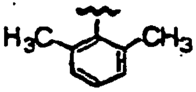
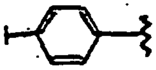
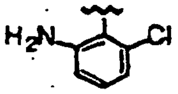
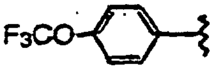
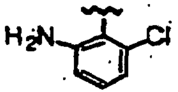
dans lesquels R^9 et R^{10} représentent chacun un atome d'halogène ou un groupe alkyle en C_1 à C_6, $-OH$ ou $-NH_2$.

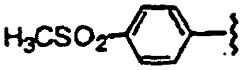
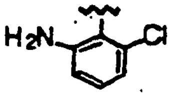
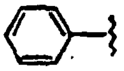
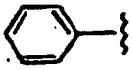
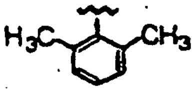
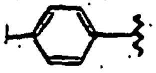
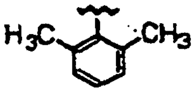
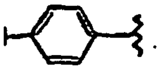
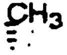
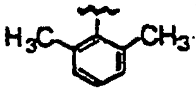
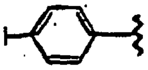
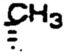
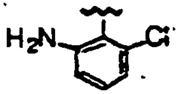
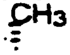
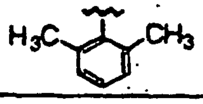
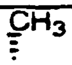
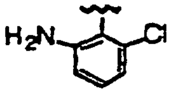
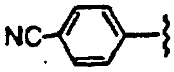
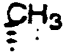
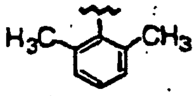
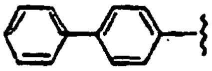
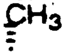
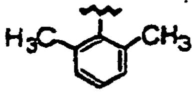
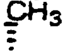
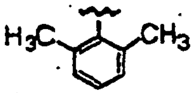
8. Composé choisi parmi les composés de formule développée

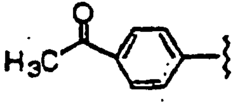
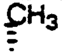
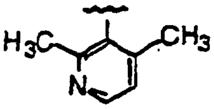
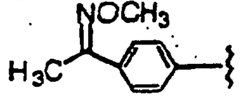
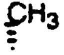
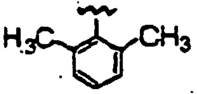
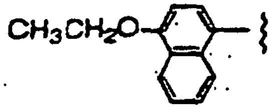
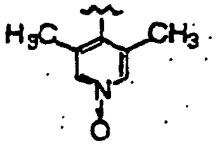
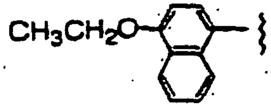
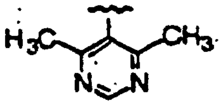
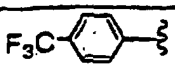
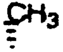
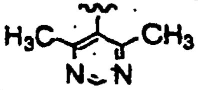


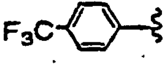
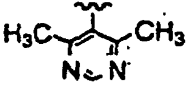
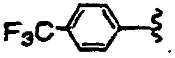
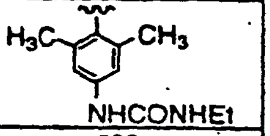
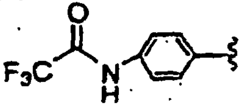
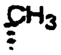
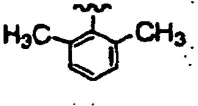
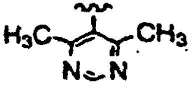
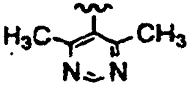
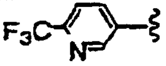
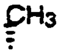
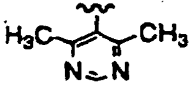
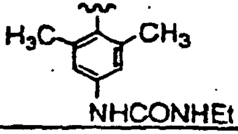
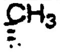
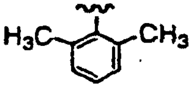
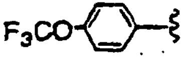
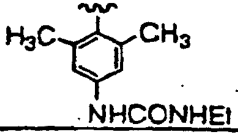
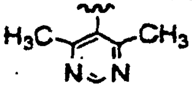
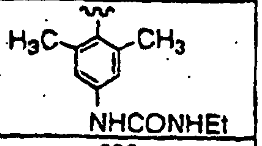
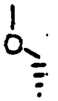
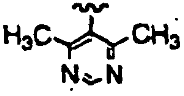
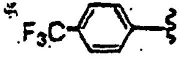
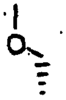
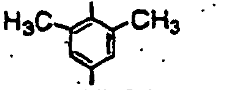
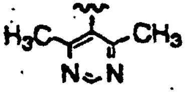
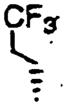
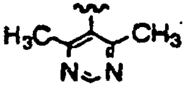
dans laquelle R, R^3, R^6 et R^2 ont les significations indiquées dans le tableau suivant :

R	R^3	R^6	R^2
	CH_3	H	
	CH_3	$-CH_3$	
		H	
	CH_3	H	
	CH_3	H	
	CH_3	H	
	CH_3	$-CH_3$	
	CH_3	$-CH_3$	
	CH_3	$-CH_3$	

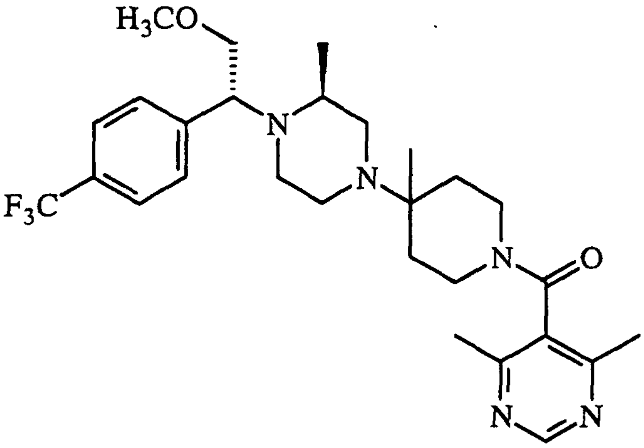
		$-CH_3$	
		$-CH_3$	
		$-CH_3$	
		H	
		H	
		$-CH_3$	
		$-CH_3$	
		$-CH_3$	
		$-CH_3$	
		$-CH_3$	
	H	$-CH_3$	
	H	$-CH_3$	
	H	$-CH_3$	

	H	$-CH_3$	
		$-CH_3$	
	H	H	
		H	
		$-CH_3$	
		H	
		$-CH_3$	
		H	
		H	
		H	

		H	
		$-CH_3$	
	H	$-CH_3$	
	H	$-CH_3$	
		$-CH_2CH_3$	

		-CH$_2$CH$_3$	
		-CH$_2$CH$_3$	
		-CH$_3$	
		-CH$_3$	
		-CH$_3$	
		-CH$_3$	
		-CH$_3$	
		-CH$_3$	
		-CH$_3$	
		-CH$_3$	
		-CH$_3$	
		-CH$_3$	
		-CH$_3$	
		-CH$_3$	
		-CH$_3$	

9. Composé de formule



10. Composition pharmaceutique pour le traitement du virus d'immunodéficience humaine, du rejet de greffe d'organe solide, des maladies dues à l'opposition entre le greffon et l'hôte, de l'arthrite, de l'arthrite rhumatoïde, des maladies inflammatoires de l'intestin, de la dermatite atopique, du psoriasis, de l'asthme, des allergies ou de la sclérose multiple, qui comprend une quantité efficace d'un antagoniste de CCR5 selon l'une quelconque des revendications précédentes, en combinaison avec un support pharmaceutiquement acceptable.

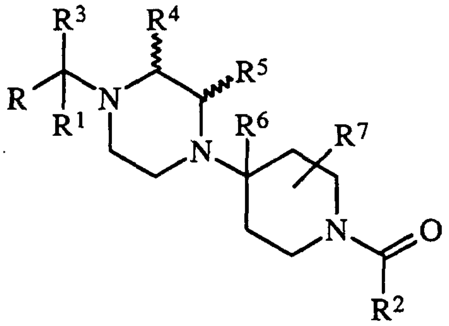
11. Utilisation d'un composé selon l'une quelconque des revendications 1 à 9, pour la préparation d'un médicament destiné au traitement du virus d'immunodéficience humaine, du rejet de greffe d'organe solide, des maladies dues à l'opposition entre le greffon et l'hôte, de l'arthrite, de l'arthrite rhumatoïde, des maladies inflammatoires de l'intestin, de la dermatite atopique, du psoriasis, de l'asthme, des allergies ou de la sclérose multiple.

12. Utilisation d'un composé selon l'une quelconque des revendications 1 à 9, pour la préparation d'un médicament destiné à une utilisation combinée avec un ou plusieurs agents antiviraux ou autres agents utiles dans le traitement du virus d'immunodéficience humaine.

13. Utilisation selon la revendication 12, dans laquelle l'agent antiviral est un agent choisi parmi les inhibiteurs de transcriptase inverse de type nucléoside, les inhibiteurs de transcriptase inverse de type non-nucléoside et les inhibiteurs de protéase.

14. Utilisation d'un composé selon l'une quelconque des revendications 1 à 9, pour la préparation d'un médicament destiné à une utilisation combinée avec un ou plusieurs agents pour le traitement du rejet de greffe d'organe solide, des maladies dues à l'opposition entre le greffon et l'hôte, des maladies inflammatoires de l'intestin, de l'arthrite rhumatoïde ou de la sclérose multiple.

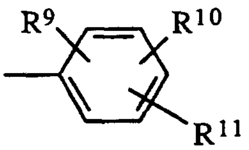
15. Utilisation pour la préparation d'un médicament destiné au traitement du virus d'immunodéficience humaine, du rejet de greffe d'organe solide, des maladies dues à l'opposition entre le greffon et l'hôte, de l'arthrite, de l'arthrite rhumatoïde, des maladies inflammatoires de l'intestin, de la dermatite atopique, du psoriasis, de l'asthme, des allergies ou de la sclérose multiple, d'un antagoniste de CCR5 représenté par la formule développée I :



I

dans laquelle :

R représente un groupe R^8-phényle, R^8-pyridyle, R^8-thiophényle ou R^8-naphtyle,
R^1 représente un atome d'hydrogène ou un groupe alkyle en C_1 à C_6,
R^2 représente un groupe hétéroaryle à 6 chaînons, substitué par R^9, R^{10} et R^{11}, un groupe hétéroaryle-N-oxyde à 6 chaînons, substitué par R^9, R^{10} et R^{11}, un groupe hétéroaryle à 5 chaînons, substitué par R^{12} et R^{13}, un groupe naphtyle, un groupe fluorényle, un groupe diphénylméthyle, ou un groupe



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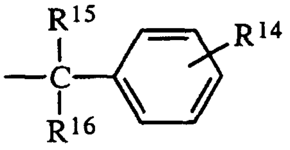

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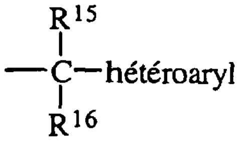
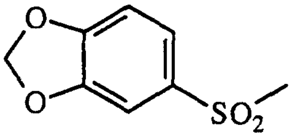


R^3 représente un atome d'hydrogène ou un groupe alkyle en C_1 à C_6, alcoxy(C_1 à C_6)alkyle(C_1 à C_6), cycloalkyle en C_3 à C_{10}, cycloalkyl(C_3 à C_{10})alkyle(C_1 à C_6), R^8-phényle, R^8-phénylalkyle(C_1 à C_6), R^8-naphtyle, R^8-naphtylalkyle(C_1 à C_6), R^8-hétéroaryle ou R^8-hétéroarylalkyle(C_1 à C_6),
R^4, R^5, R^7 et R^{13} représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C_1 à C_6,
R^6 représente un atome d'hydrogène, un groupe alkyle en C_1 à C_6 ou un groupe alcényle en C_2 à C_6,
R^8 représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes alkyle en C_1 à C_6, alcoxy en C_1 à C_6, $-CF_3$, CF_3O-, $CH_3C(O)-$, $-CN$, CH_3SO_2-, CF_3SO_2-, R^{14}-phényle, R^{14}-benzyle, $CH_3C(=NOCH_3)$, $CH_3C(=NOCH_2CH_3)$,



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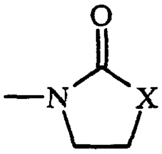
$-NH_2$, $-NHCOCF_3$, -NHCONH(alkyl en C_1-C_6), -NHCO(alkyl en C_1-C_6), $-NHSO_2$(alkyl en C_1-C_6), hétéroaryle à 5 chaînons et



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où X est -O-, -NH- ou $-N(CH_3)-$,
R^9 et R^{10} représentent chacun indépendamment un atome d'halogène ou un groupe alkyle en C_1 à C_6,

$-NR^{17}R^{18}$, -OH, $-CF_3$, $-OCH_3$, -O-acyl, $-OCF_3$ ou $-Si(CH_3)_3$,

R^{11} représente R^9, un atome d'hydrogène, ou un groupe phényle, $-NO_2$, - CN, $-CH_2F$, $-CHF_2$, -CHO, $-CH=NOR^{17}$, pyridyle, pyridyle-N-oxyde, pyrimidinyle, pyrazinyle, $-N(R^{17})CONR^{18}R^{19}$, -NHCONH(chloroalkyl en C_1 à C_6), -NHCONH(cycloalkyl(C_3 à C_{10})alkyl(C_1 à C_6)), -NHCOalkyl(C_1 à C_6), $-NHCOCF_3$, $-NHSO_2N$(alkyl en C_1 à $C_6)_2$, $-NHSO_2$alkyl(C_1 à C_6), $-N(SO_2CF_3)_2$, $-NHCO_2$alkyl(C_1 à C_6), cycloalkyle en C_3 à C_{10}, $-SR^{20}$, $-SOR^{20}$, $-SO_2R^{20}$, $-SO_2$NHalkyl(C_1 à C_6), $-OSO_2$alkyl(C_1 à C_6), $-OSO_2CF_3$, hydroxyalkyle en C_1 à C_6, $-CONR^{17}R^{18}$, $-CON(CH_2CH_2\text{-}O\text{-}CH_3)_2$, -OCONHalkyl($C_1$ à C_6), $-CO_2R^{17}$, $-Si(CH_3)_3$ ou $-B(OC(CH_3)_3)_2$,

R^{12} représente un groupe alkyle en C_1 à C_6, $-NH_2$ ou R^{14}-phényle,

R^{14} représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes alkyle en C_1 à C_6, $-CF_3$, $-CO_2R^{17}$, -CN et alcoxy en C_1 à C_6,

R^{15} et R^{16} représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C_1 à C_6, ou bien R^{15} et R^{16} forment ensemble un groupe alkylène en C_2 à C_5 et forment avec l'atome de carbone auquel ils sont liés un cycle spiro ayant 3 à 6 atomes de carbone,

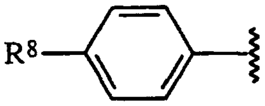
R^{17}, R^{18} et R^{19} représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C_1 à C_6, et

R^{20} représente un groupe alkyle en C_1 à C_6 ou un groupe phényle,

ou d'un sel pharmaceutiquement acceptable d'un tel composé.

16. Utilisation selon la revendication 15, dans laquelle R représente un groupe R^8-phényle ou R^8-naphtyle.

17. Utilisation selon la revendication 16, dans laquelle R représente



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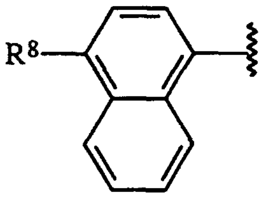
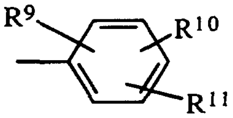


18. Utilisation selon la revendication 15, dans laquelle R^3 représente un atome d'hydrogène ou un groupe alkyle en C_1 à C_6, R^8-phényle, R^8-benzyle ou R^8-pyridyle.

19. Utilisation selon la revendication 15, dans laquelle R^1 représente un atome d'hydrogène et R^6 représente un atome d'hydrogène ou un groupe méthyle.

20. Utilisation selon la revendication 15, dans laquelle R^2 représente



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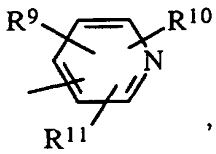

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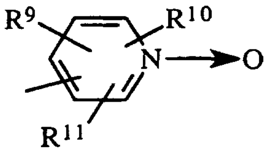

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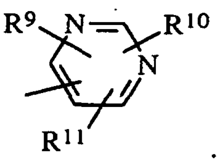

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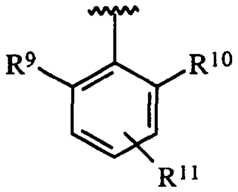
21. Utilisation selon la revendication 20, dans laquelle R^2 représente un groupe choisi parmi les groupes



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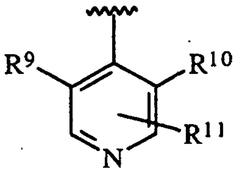

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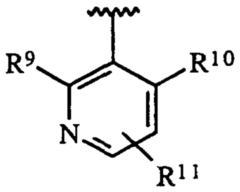

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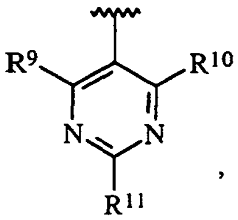

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dans lesquels R^9 et R^{10} représentent chacun un atome d'halogène ou un groupe alkyle en C_1 à C_6, -OH ou $-NH_2$.

22. Utilisation selon la revendication 21, dans laquelle R^2 est un cycle phényle ou pyridyle et R^{11} est un atome d'hydrogène, ou bien R^2 est un cycle pyrimidyle et R^{11} est un atome d'hydrogène ou un groupe méthyle ou phényle.

23. Utilisation selon la revendication 15, pour le traitement du virus d'immunodéficience humaine, qui comprend en outre l'utilisation d'un ou plusieurs agents antiviraux ou autres agents utiles dans le traitement du virus d'immunodéficience humaine.

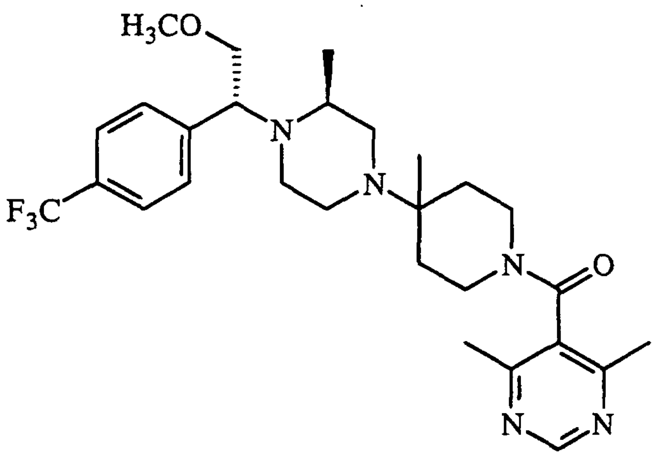
24. Utilisation selon la revendication 23, dans laquelle l'agent antiviral est un agent choisi parmi les inhibiteurs de transcriptase inverse de type nucléoside, les inhibiteurs de transcriptase inverse de type non-nucléoside et les inhibiteurs de protéase.

25. Utilisation selon la revendication 15, pour le traitement du rejet de greffe d'un organe solide, des maladies dues à l'opposition entre le greffon et l'hôte, des maladies inflammatoires de l'intestin, de l'arthrite rhumatoïde ou de la sclérose multiple, qui comprend en outre l'utilisation d'un ou plusieurs autres agents utiles dans le traitement de ces maladies.

26. Nécessaire comprenant dans des récipients séparés et dans un emballage unique, des compositions pharmaceutiques destinées à être utilisées en combinaison pour le traitement du virus d'immunodéficience humaine, qui comprend, dans un récipient, une composition pharmaceutique contenant une quantité efficace d'un antagoniste de CCR5 selon la revendication 15, dans un support pharmaceutiquement acceptable, et, dans des récipients séparés, une ou plusieurs compositions pharmaceutiques contenant une quantité efficace d'un agent antiviral ou d'un autre agent utile dans le traitement du virus d'immunodéficience humaine, dans un support pharmaceutiquement acceptable.

27. Composition pharmaceutique sous la forme d'une crème pour application topique, qui comprend un composé de formule II tel que défini dans l'une quelconque des revendications 1 à 9, et un support pharmaceutiquement acceptable.

28. Composition pharmaceutique sous la forme d'une crème pour application topique, qui comprend un composé de formule



et un support pharmaceutiquement acceptable.