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(54) Title
1-aryl-4-substituted piperazine derivatives for use as CCR1 antagonists for the treatment of inflammation and immune disorders

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(71) Applicant(s)

Chemocentryx, Inc.

(72) Inventor(s)

McMaster, Brian E., Wright, J. J. Kim, Pennell, Andrew M. K., Dairaghi, Daniel

Joseph , Martichonok, Valeri V., Aggen, James B., Sen, Subhabrata

(74) Agent/Attorney

Spruon & Ferguson, Level 35 St Martins Tower 31 Market Street, Sydney, NSW, 2000

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(71) Applicant (for all designated States except US): CHEMOCENTRYX, INC. [US/US]; 1539 Industrial Road, San Carlos, CA 94070 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): PENNELL, Andrew, M., K. [GB/US]; 1481 Iancock Street, San Francisco, CA 94114 (US). AGGEN, James, B. [US/US]; 1311 California Drive, Burlingame, CA 94010 (US). WRIGHT, J., J., Kim [AU/US]; 720 Bair Island Road, Apt. 107, Redwood City, CA 94063 (US). SEN, Subrabra [IN/US]; 655 S. Fair Oaks Avenue, #P-204, Sunnyvale, CA 94086 (US). MCMASTER, Brian, E. [US/US]; 120 Walker Drive, Mountain View, CA 94043 (US). DAIRAGHI, Daniel, Joseph [US/US]; 178 El Dorado Avenue, Palo Alto, CA 94306 (US).

(74) Agents: KEZER, William, B. et al.; Townsend and Townsend and Crew I.P. Two Embarcadero Center, Eighth Floor, San Francisco, CA 94111-3834 (US).

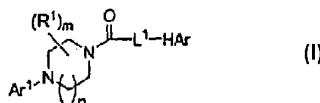
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(54) Title: 1-ARYL-4-SUBSTITUTED PIPERAZINES DERIVATIVES FOR USE AS CCR1 ANTAGONISTS FOR THE TREATMENT OF INFLAMMATION AND IMMUNE DISORDERS

WO 03/105853 A1



(57) Abstract: Compounds are provided that act as potent antagonists of the CCR1 receptor, and which have been further confirmed in animal testing for inflammation, one of the hallmark disease states for CCR1. The compounds are generally aryl piperazine derivatives and are useful in pharmaceutical compositions, methods for the treatment of CCR1-mediated diseases, and as controls in assays for the identification of competitive CCR1 antagonists.

1-ARYL-4-SUBSTITUTED PIPERAZINE DERIVATIVES FOR USE AS CCR1 ANTAGONISTS FOR
THE TREATMENT OF INFLAMMATION AND IMMUNE DISORDERS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of Provisional Application Serial No. 5 60/453,711, filed June 12, 2002, (originally USSN 10/171,398, filed June 12, 2002) the contents of which is incorporated herein by reference.

**STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER
FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT**

10 [0002] This application was supported in part by DARPA Grant No. N65236-99-1-5420. The government of the United States may have certain rights in this application.

**REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER
PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK.**

15 [0003] NOT APPLICABLE

BACKGROUND OF THE INVENTION

[0004] The present invention provides compounds, pharmaceutical compositions containing one or more of those compounds or their pharmaceutically acceptable salts, which 20 are effective in inhibiting the binding of various chemokines, such as MIP-1 α , leukotactin, MPIF-1 and RANTES, to the CCR1 receptor. As antagonists or modulators for the CCR1 receptor, the compounds and compositions have utility in treating inflammatory and immune disorder conditions and diseases.

[0005] Human health depends on the body's ability to detect and destroy foreign pathogens 25 that might otherwise take valuable resources from the individual and/or induce illness. The immune system, which comprises leukocytes (white blood cells (WBCs): T and B lymphocytes, monocytes, macrophages granulocytes, NK cell, mast cells, dendritic cell, and immune derived cells (for example, osteoclasts)), lymphoid tissues and lymphoid vessels, is the body's defense system. To combat infection, white blood cells circulate throughout the 30 body to detect pathogens. Once a pathogen is detected, innate immune cells and cytotoxic T

cells in particular are recruited to the infection site to destroy the pathogen. Chemokines act as molecular beacons for the recruitment and activation of immune cells, such as lymphocytes, monocytes and granulocytes, identifying sites where pathogens exist.

[0006] Despite the immune system's regulation of pathogens, certain inappropriate chemokine signaling can develop and has been attributed to triggering or sustaining inflammatory disorders, such as rheumatoid arthritis, multiple sclerosis and others. For example, in rheumatoid arthritis, unregulated chemokine accumulation in bone joints attracts and activates infiltrating macrophages and T-cells. The activities of these cells induce synovial cell proliferation that leads, at least in part, to inflammation and eventual bone and cartilage loss (see, DeVries, M.E., et al., *Semin Immunol* 11(2):95-104 (1999)). A hallmark of some demyelinating diseases such as multiple sclerosis is the chemokine-mediated monocyte/macrophage and T cell recruitment to the central nervous system (see, Kennedy, et al., *J. Clin. Immunol.* 19(5):273-279 (1999)). Chemokine recruitment of destructive WBCs to transplants has been implicated in their subsequent rejection. See, DeVries, M.E., et al., *ibid.* Because chemokines play pivotal roles in inflammation and lymphocyte development, the ability to specifically manipulate their activity has enormous impact on ameliorating and halting diseases that currently have no satisfactory treatment. In addition, transplant rejection may be minimized without the generalized and complicating effects of costly immunosuppressive pharmaceuticals.

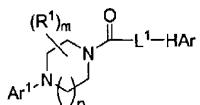
[0007] Chemokines, a group of greater than 40 small peptides (7-10 kD), ligate receptors expressed primarily on WBCs or immune derived cells, and signal through G-protein-coupled signaling cascades to mediate their chemoattractant and chemostimulant functions. Receptors may bind more than one ligand; for example, the receptor CCR1 ligates RANTES (regulated on activation normal T cell expressed), MIP-1 α (macrophage inflammatory protein), MIP-1 β /CK β 8, and Leukotactin chemokines (among others with lesser affinities). To date, 24 chemokine receptors are known. The sheer number of chemokines, multiple ligand binding receptors, and different receptor profiles on immune cells allow for tightly controlled and specific immune responses. See, Rossi, et al., *Ann. Rev. Immunol.* 18(1):217-242 (2000). Chemokine activity can be controlled through the modulation of their corresponding receptors, treating related inflammatory and immunological diseases and enabling organ and tissue transplants.

[0008] The receptor CCR1 and its chemokine ligands, including, for example MIP-1 α , MPIF-1/CK β 8, leukotactin and RANTES, represent significant therapeutic targets (see Saeki, et al., *Current Pharmaceutical Design* 9:1201-1208 (2003)) since they have been implicated in rheumatoid arthritis, transplant rejection (see, DeVries, M.E., et al., *ibid.*), and multiple sclerosis (see, Fischer, et al., *J Neuroimmunol.* 110(1-2):195-208 (2000); Izikson, et al., *J. Exp. Med.* 192(7):1075-1080 (2000); and Rottman, et al., *Eur. J. Immunol.* 30(8):2372-2377 (2000). In fact, function-blocking antibodies, modified chemokine receptor ligands and small organic compounds have been discovered, some of which have been successfully demonstrated to prevent or treat some chemokine-mediated diseases (reviewed in Rossi, et al., *ibid.*). Notably, in an experimental model of rheumatoid arthritis, disease development is diminished when a signaling-blocking, modified-RANTES ligand is administered (see Plater-Zyberk, et al., *Immunol. Lett.* 57(1-3):117-120 (1997)). While function-blocking antibody and small peptide therapies are promising, they suffer from the perils of degradation, extremely short half-lives once administered, and prohibitive expense to develop and manufacture, characteristic of most proteins. Small organic compounds are preferable since they often have longer half lives *in vivo*, require fewer doses to be effective, can often be administered orally, and are consequently less expensive. Some organic antagonists of CCR1 have been previously described (see, Hesselgesser, et al., *J. Biol. Chem.* 273(25):15687-15692 (1998); Ng, et al., *J. Med. Chem.* 42(22):4680-4694 (1999); Liang, et al., *J. Biol. Chem.* 275(25):19000-19008 (2000); and Liang, et al., *Eur. J. Pharmacol.* 389(1):41-49 (2000)). In view of the effectiveness demonstrated for treatment of disease in animal models (see, Liang, et al., *J. Biol. Chem.* 275(25):19000-19008 (2000)), the search has continued to identify additional compounds that can be used in the treatment of diseases mediated by CCR1 signaling.

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BRIEF SUMMARY OF THE INVENTION

[0009] The present invention provides compounds having the formula:



(I)

or a pharmaceutically acceptable salt thereof. In the formula above, the subscript n represents an integer of from 1 to 2, preferably 1. The subscript m represents an integer of from 0 to 10, limited by the number of available substituents positions on the piperazine or homopiperazine ring to which it is attached. For example, piperazine derivatives (n is 1) can have from 0 to 8 R¹ groups, preferably 0 to 4 R¹ groups, and more preferably 0, 1 or 2 R¹ groups. Each R¹ is a substituent independently selected from C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, -COR^a, -CO₂R^a, -CONR^aR^b, -NR^aCOR^b, -SO₂R^a, -X¹COR^a, -X¹CO₂R^a, -X¹CONR^aR^b, -X¹NR^aCOR^b, -X¹SO₂R^a, -X¹SO₂NR^aR^b, -X¹NR^aR^b, -X¹OR^a, wherein X¹ is a member selected from the group consisting of C₁₋₄ alkylene, C₂₋₄ alkenylene and C₂₋₄ alkynylene and each R^a and R^b is independently selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl and C₃₋₆ cycloalkyl, and wherein the aliphatic portions of each of said R¹ substituents is optionally substituted with from one to three members selected from the group consisting of OH, O(C₁₋₈ alkyl), SH, S(C₁₋₈ alkyl), CN, NO₂, NH₂, NH(C₁₋₈ alkyl) and N(C₁₋₈ alkyl)₂.

15 [0010] The symbol Ar¹ represents an optionally substituted aryl or heteroaryl group. Preferred aryl groups are phenyl and naphthyl. Preferred heteroaryl groups are those having from 5 to 10 ring vertices, at least one of which is a nitrogen atom (e.g., pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, quinolinyl, quinoxalinyl, purinyl and the like). Each of the Ar¹ rings is optionally substituted with from one to five R² substituents independently selected from halogen, -OR^c, -OC(O)R^c, -NR^cR^d, -SR^c, -R^c, -CN, -NO₂, -CO₂R^c, -CONR^cR^d, -C(O)R^c, -OC(O)NR^cR^d, -NR^dC(O)R^c, -NR^dC(O)₂R^c, -NR^cC(O)NR^cR^d, -NH-C(NH₂)=NH, -NR^cC(NH₂)=NH, -NH-C(NH₂)=NR^e, -NH-C(NHR^c)=NH, -S(O)R^c, -S(O)₂R^c, -NR^cS(O)₂R^c, -S(O)₂NR^cR^d, -N₃, -X²OR^c, -X²OC(O)R^c, -X²NR^cR^d, -X²SR^c, -X²CN, -X²NO₂, -X²CO₂R^c, -X²CONR^cR^d, -X²C(O)R^c, -X²OC(O)NR^cR^d, -X²NR^dC(O)R^c, -X²NR^dC(O)₂R^c, -X²NR^cC(O)NR^cR^d, -X²NH-C(NH₂)=NH, -X²NR^cC(NH₂)=NH, -X²NH-C(NH₂)=NR^e, -X²NH-C(NHR^c)=NH, -X²S(O)R^c, -X²S(O)₂R^c, -X²NR^cS(O)₂R^c, -X²S(O)₂NR^cR^d and -X²N₃, wherein X² is a member selected from the group consisting of C₁₋₄ alkylene, C₂₋₄ alkenylene and C₂₋₄ alkynylene and each R^c and R^d is independently selected from hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, heteroaryl, aryl-C₁₋₄ alkyl, and 30 aryloxy-C₁₋₄ alkyl, and each R^e is independently selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, heteroaryl, aryl-C₁₋₄ alkyl, and aryloxy-C₁₋₄ alkyl, and each of R^c, R^d and R^e is optionally further substituted with from one to three members selected from the group consisting of OH, O(C₁₋₈ alkyl), SH, S(C₁₋₈ alkyl), CN, NO₂, NH₂, NH(C₁₋₈ alkyl) and N(C₁₋₈ alkyl)₂.

[0011] The symbol HAr represents an optionally substituted heteroaryl group. The heteroaryl groups for HAr can be the same or different from any of the heteroaryl groups used for Ar¹. Generally, the HAr groups are monocyclic, but can also be fused bicyclic systems having from 5 to 10 ring atoms, at least one of which is a nitrogen atom. Certain 5 preferred heteroaryl groups are 5 or 6-membered rings having at least one nitrogen atom as a ring vertex and fused ring systems having a 5-membered ring fused to a benzene ring, for example pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxathiadiazolyl, pyrrolyl, thiazolyl, isothiazolyl, benzimidazolyl, benzopyrazolyl and benzotriazolyl, each of which is substituted with from one to five R³ substituents

10 independently selected from the group consisting of halogen, phenyl, thiienyl, furanyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, triazolyl, tetrazolyl, oxadiazolyl, -OR^f, -OC(O)R^f, -NR^fR^g, -SR^f, -R^h, -CN, -NO₂, -CO₂R^f, -CONR^fR^g, -C(O)R^f, -OC(O)NR^fR^g, -NR^gC(O)R^f, -NR^gC(O)R^h, -NR^fC(O)NR^fR^g, -NH-C(NH₂)=NH, -NR^hC(NH₂)=NH, -NH-C(NH₂)=NR^h, -NH-C(NHR^h)=NH, -15 S(O)R^h, -S(O)₂R^h, -NR^fS(O)₂R^h, -S(O)₂NR^fR^g, -NR^fS(O)₂NR^fR^g, -N₃, -X³OR^f, -X³OC(O)R^f, -X³NR^fR^g, -X³SR^f, -X³CN, -X³NO₂, -X³CO₂R^f, -X³CONR^fR^g, -X³C(O)R^f, -X³OC(O)NR^fR^g, -X³NR^gC(O)R^f, -X³NR^gC(O)R^h, -X³NR^fC(O)NR^fR^g, -X³NH-C(NH₂)=NH, -X³NR^hC(NH₂)=NH, -X³NH-C(NH₂)=NR^h, -X³NH-C(NHR^h)=NH, -X³S(O)R^h, -X³S(O)₂R^h, -X³NR^fS(O)₂R^h, -X³S(O)₂NR^fR^g and -X³N₃ wherein X³ is selected 20 from the group consisting of C₁₋₄ alkylene, C₂₋₄ alkenylene and C₂₋₄ alkynylene and each R^f and R^g is independently selected from hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, heteroaryl, aryl-C₁₋₄ alkyl, and aryloxy-C₁₋₄ alkyl, and each R^h is independently selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, heteroaryl, aryl-C₁₋₄ alkyl, and aryloxy-C₁₋₄ alkyl, and the 25 aliphatic portions of R^f, R^g and R^h are optionally further substituted with from one to three members selected from the group consisting of OH, O(C₁₋₈ alkyl), SH, S(C₁₋₈ alkyl), CN, NO₂, NH₂, NH(C₁₋₈ alkyl) and N(C₁₋₈ alkyl)₂ and wherein any phenyl, thiienyl, furanyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, triazolyl, tetrazolyl or oxadiazolyl R³ groups present are optionally 30 substituted with from one to three substituents selected from the group consisting of halogen, -OR^f, -NR^fR^g, -R^h, -CN, -NO₂, -CO₂R^f, -CONR^fR^g, -C(O)R^f, -X³OR^f, -X³NR^fR^g, -X³NR^fS(O)₂R^h and -X³S(O)₂NR^fR^g. Among the most preferred HAr groups are substituted or unsubstituted pyrazoles and substituted or unsubstituted benzopyrazoles. Preferably, substituted or unsubstituted pyrazoles are attached to the remainder of the molecule via a

nitrogen atom of the pyrazole ring. For those embodiments in which HAr is a benzopyrazole ring, attachment to the remainder of the molecule is preferably via a nitrogen on the pyrazole portion of the fused ring system.

[0012] The symbol L^1 represents a linking group having from one to three main chain atoms selected from the group consisting of C, N, O and S and being optionally substituted with from one to three substituents selected from the group consisting of halogen, phenyl, $-OR^i$, $-OC(O)R^i$, $-NR^iR^j$, $-SR^i$, $-R^k$, $-CN$, $-NO_2$, $-CO_2R^i$, $-CONR^iR^j$, $-C(O)R^i$, $-OC(O)NR^iR^j$, $-NR^iC(O)R^i$, $-NR^iC(O)_2R^k$, $-X^4OR^i$, $-X^4OC(O)R^i$, $-X^4NR^iR^j$, $-X^4SR^i$, $-X^4CN$, $-X^4NO_2$, $-X^4CO_2R^i$, $-X^4CONR^iR^j$, $-X^4C(O)R^i$, $-X^4OC(O)NR^iR^j$, $-X^4NR^iC(O)R^i$ and $-X^4NR^iC(O)_2R^k$, wherein X^4 is selected from the group consisting of C_{1-4} alkylene, C_{2-4} alkenylene and C_{2-4} alkynylene and each R^i and R^j is independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, aryl- C_{1-4} alkyl, and aryloxy- C_{1-4} alkyl, and each R^k is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, aryl- C_{1-4} alkyl, and aryloxy- C_{1-4} alkyl. In certain preferred embodiments, the linking groups are unsubstituted, while in other preferred embodiments, substituents are present that can increase partitioning into selected solvents or into selected tissues. For example, addition of a hydroxy group to a propylene linkage will generally provide compounds having more favorable solubility in water. Preferably, L^1 is selected from $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2O-$, $-CH_2NH-$, $-CH_2OCH_2-$ and $-CH_2NHCH_2-$.

[0013] In addition to the compounds provided herein, the present invention further provides pharmaceutical compositions containing one or more of these compounds, as well as methods for the use of these compounds in therapeutic methods, primarily to treat diseases associated with CCR1 signalling activity.

25

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Figure 1 provides selected and preferred Ar^1 groups for compounds of formulae I, II and III.

[0015] Figures 2 and 3 provide selected and preferred HAr groups for compounds of formulae I, II, III and IV.

[0016] Figures 4A-4C provide structures of selected commercially available starting materials.

[0017] Figures 5A-5N provide structures of selected and preferred compounds of formula I.

5

DETAILED DESCRIPTION OF THE INVENTION

I. Abbreviation and Definitions

[0018] The term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon radical, having the number of carbon atoms designated (*i.e.* C₁₋₈ means one to eight carbons). Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. The term "alkenyl" refers to an unsaturated alkyl group having one or more double bonds. Similarly, the term "alkynyl" refers to an unsaturated alkyl group having one or more triple bonds. Examples of such unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. The term "cycloalkyl" refers to hydrocarbon rings having the indicated number of ring atoms (e.g., C₃₋₆cycloalkyl) and being fully saturated or having no more than one double bond between ring vertices. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc.

[0019] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by -CH₂CH₂CH₂CH₂- . Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having four or fewer carbon atoms.

[0020] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively. Additionally, for dialkylamino groups, the alkyl portions can be the same or different and can also be combined to form a 3-7 membered ring with the nitrogen atom to which each is attached.

Accordingly, a group represented as -NR^aR^b is meant to include piperidinyl, pyrrolidinyl, morpholinyl, azetidinyl and the like.

[0021] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "C₁₋₄ haloalkyl" is meant to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0022] The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon group which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to five heteroatoms selected from N, O, and S, wherein the 10 nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl groups include phenyl, naphthyl and biphenyl, while non-limiting examples of heteroaryl groups include 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-pyrazolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, benzopyrazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable 20 substituents described below.

[0023] For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl and the like).

[0024] The above terms (e.g., "alkyl," "aryl" and "heteroaryl"), in some embodiments, will include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below. For brevity, the terms aryl and heteroaryl will refer to substituted or unsubstituted versions as provided below, while the term "alkyl" and related aliphatic radicals is meant to refer to unsubstituted version, unless 30 indicated to be substituted.

[0025] Substituents for the alkyl radicals (including those groups often referred to as alkylene, alkenyl, alkynyl and cycloalkyl) can be a variety of groups selected from: -halogen,

-OR', -NR'R'', -SR', -SiR'R'R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R', -OC(O)NR'R'', -NR'C(O)R', -NR'C(O)NR'R''', -NR'C(O)₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NR'S(O)₂R'', -CN and -NO₂ in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical.

5 R', R'' and R''' each independently refer to hydrogen, unsubstituted C₁₋₈ alkyl, unsubstituted heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted C₁₋₈ alkyl, C₁₋₈ alkoxy or C₁₋₈ thioalkoxy groups, or unsubstituted aryl-C₁₋₄ alkyl groups. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring. For example, -NR'R'' is meant to include 1-
10 pyrrolidinyl and 4-morpholinyl.

[0026] Similarly, substituents for the aryl and heteroaryl groups are varied and are generally selected from: -halogen, -OR', -OC(O)R', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R', -CONR'R', -C(O)R', -OC(O)NR'R'', -NR'C(O)R', -NR'C(O)₂R', -NR'C(O)NR'R''', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'',
15 -NR'S(O)₂R'', -N₃, perfluoro(C₁-C₄)alkoxy, and perfluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'' and R''' are independently selected from hydrogen, C₁₋₈ alkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-C₁₋₄ alkyl, and unsubstituted aryloxy-C₁₋₄ alkyl. Other suitable substituents include each of the above aryl
20 substituents attached to a ring atom by an alkylene tether of from 1-4 carbon atoms.

[0027] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CH₂)_q-U-, wherein T and U are independently -NH-, -O-, -CH₂- or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may
25 optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CH₂-, -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -(CH₂)_s-
30 X-(CH₂)_t-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'. The substituent R' in -NR'- and -S(O)₂NR' is selected from hydrogen or unsubstituted C₁₋₆ alkyl.

[0028] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

[0029] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the

- 5 particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperadine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by
- 10 contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al,
- 15 20 25 30 "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0030] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0031] In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0032] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0033] Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers, regioisomers and individual isomers (e.g., separate enantiomers) are all intended to be encompassed within the scope of the present invention. The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (³H), iodine-125 (¹²⁵I) or carbon-14 (¹⁴C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

II. General

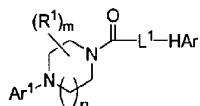
[0034] The present invention derives from the discovery that compounds of formula I (as well as the subgeneric formulae II, III and IV) act as potent antagonists of the CCR1 receptor.

This antagonist activity has been further confirmed in animal testing for inflammation, one of the hallmark disease states for CCR1. Accordingly, the compounds provided herein are useful in pharmaceutical compositions, methods for the treatment of CCR1-mediated diseases, and as controls in assays for the identification of competitive CCR1 antagonists.

5

III. Compounds

[0035] In one aspect, the present invention provides compounds having the formula:



(I)

10 or a pharmaceutically acceptable salt thereof.

[0036] In the formula above, the subscript n represents an integer of from 1 to 2, preferably 1. The subscript m represents an integer of from 0 to 10, limited by the number of available substituents positions on the piperazine or homopiperazine ring to which it is attached. For example, piperazine derivatives (n is 1) can have from 0 to 8 R¹ groups, preferably 0 to 4 R¹ groups, and more preferably 0, 1 or 2 R¹ groups.

[0037] The symbol Ar¹ represents an optionally substituted aryl or heteroaryl group. Preferred aryl groups are phenyl and naphthyl. Preferred heteroaryl groups are those having from 5 to 10 ring vertices, at least one of which is a nitrogen atom (e.g., pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, quinolinyl, quinoxalinyl, purinyl and the like). Each of the 20 Ar¹ rings is optionally substituted with from one to five R² substituents independently selected from halogen, -OR^c, -OC(O)R^c, -NR^cR^d, -SR^c, -R^c, -CN, -NO₂, -CO₂R^c, -CONR^cR^d, -C(O)R^c, -OC(O)NR^cR^d, -NR^dC(O)R^c, -NR^dC(O)₂R^c, -NR^c-C(O)NR^cR^d, -NH-C(NH₂)=NH, -NR^cC(NH₂)=NH, -NH-C(NH₂)=NR^c, -NH-C(NHR^c)=NH, -S(O)R^c, -S(O)₂R^c, -NR^cS(O)₂R^c, -S(O)₂NR^cR^d, -N₃, -X²OR^c, -X²OC(O)R^c, -X²NR^cR^d, -X²SR^c, -X²CN, -X²NO₂, -X²CO₂R^c, 25 -X²CONR^cR^d, -X²C(O)R^c, -X²OC(O)NR^cR^d, -X²NR^dC(O)R^c, -X²NR^dC(O)₂R^c, -X²NR^cC(O)NR^cR^d, -X²NH-C(NH₂)=NH, -X²NR^cC(NH₂)=NH, -X²NH-C(NH₂)=NR^c, -X²NH-C(NHR^c)=NH, -X²S(O)R^c, -X²S(O)₂R^c, -X²NR^cS(O)₂R^c, -X²S(O)₂NR^cR^d and -X²N₃, wherein X² is a member selected from the group consisting of C₁₋₄ alkylene, C₂₋₄ alkenylene and C₂₋₄ alkynylene and each R^c and R^d is independently selected from hydrogen, C₁₋₈ alkyl,

C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, aryl- C_{1-4} alkyl, and aryloxy- C_{1-4} alkyl, and each R^e is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, aryl- C_{1-4} alkyl, and aryloxy- C_{1-4} alkyl, and each of R^c , R^d and R^e is optionally further substituted with

5 from one to three members selected from the group consisting of OH, O(C_{1-8} alkyl), SH, S(C_{1-8} alkyl), CN, NO₂, NH₂, NH(C_{1-8} alkyl) and N(C_{1-8} alkyl)₂.

[0038] HAr is an optionally substituted heteroaryl group. The heteroaryl groups for HAr can be the same or different from any of the heteroaryl groups used for Ar¹. Generally, the HAr groups are monocyclic, but can also be fused bicyclic systems having from 5 to 10 ring

10 atoms, at least one of which is a nitrogen atom. Certain preferred heteroaryl groups are 5 or 6-membered rings having at least one nitrogen atom as a ring vertex and fused ring systems having a 5-membered ring fused to a benzene ring, for example pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxathiadiazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, benzimidazolyl, benzopyrazolyl and benzotriazolyl. Preferably, the fused

15 bicyclic HAr moiety, when present, is attached to the remainder of the molecule through the 5-member ring. Additionally, each of the HAr groups is substituted with from one to five R^3 substituents independently selected from the group consisting of halogen, phenyl, thienyl, furanyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, thiadiazolyl, oxazolyl, isoxazolyl, isothiazolyl, triazolyl, tetrazolyl, oxadiazolyl, -OR^f, -OC(O)R^f, -NR^fR^g, 20 -SR^f, -R^h, -CN, -NO₂, -CO₂R^f, -CONR^fR^g, -C(O)R^f, -OC(O)NR^fR^g, -NR^gC(O)R^f, -NR^gC(O)₂R^h, -NR^fC(O)NR^fR^g, -NH-C(NH₂)=NH, -NR^hC(NH₂)=NH, -NH-C(NH₂)=NR^h, -NH-C(NHR^h)=NH, -S(O)R^h, -S(O)₂R^h, -NR^fS(O)R^h, -S(O)₂NR^fR^g, -NR^fS(O)R^h, -NR^fS(O)₂NR^fR^g, -N₃, -X³OR^f, -X³OC(O)R^f, -X³NR^fR^g, -X³SR^f, -X³CN, -X³NO₂, -X³CO₂R^f, -X³CONR^fR^g, -X³C(O)R^f, -X³OC(O)NR^fR^g, -X³NR^gC(O)R^f, -X³NR^gC(O)₂R^h, -X³NR^fR^g, 25 C(O)NR^fR^g, -X³NH-C(NH₂)=NH, -X³NR^hC(NH₂)=NH, -X³NH-C(NH₂)=NR^h, -X³NH-C(NHR^h)=NH, -X³S(O)R^h, -X³S(O)₂R^h, -X³NR^fS(O)₂R^h, -X³S(O)₂NR^fR^g and -X³N₃ wherein X³ is selected from the group consisting of C_{1-4} alkylene, C_{2-4} alkenylene and C_{2-4} alkynylene and each R^f and R^g is independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, aryl- C_{1-4} alkyl, and aryloxy- C_{1-4} alkyl, 30 and each R^h is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, aryl- C_{1-4} alkyl, and aryloxy- C_{1-4} alkyl, and the aliphatic portions of R^f, R^g and R^h are optionally further substituted with from one to three members selected from the group consisting of OH, O(C_{1-8} alkyl), SH, S(C_{1-8}

alkyl), CN, NO₂, NH₂, NH(C₁₋₈ alkyl) and N(C₁₋₈ alkyl)₂ and wherein any phenyl, thieryl, furanyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, triazolyl, tetrazolyl, or oxadiazolyl R³ groups present are optionally substituted with from one to three substituents selected from the group consisting of halogen, -OR^f, -NR^fR^g, -R^h, -CN, -NO₂, -CO₂R^f, -CONR^fR^g, -C(O)R^f, -X³OR^f, -X³NR^fR^g, -X³NR^fS(O)₂R^h and -X³S(O)₂NR^fR^g. Among the most preferred HAr groups are substituted or unsubstituted pyrazoles and substituted or unsubstituted benzopyrazoles. Preferably, substituted or unsubstituted pyrazoles are attached to the remainder of the molecule via a nitrogen atom of the pyrazole ring. For those embodiments in which HAr is a benzopyrazole ring, attachment to the remainder of the molecule is preferably via a nitrogen on the pyrazole portion of the fused ring system.

[0039] The symbol L¹ represents a linking group having from one to three main chain atoms selected from the group consisting of C, N, O and S and being optionally substituted with from one to three substituents selected from the group consisting of halogen, phenyl, -ORⁱ, -OC(O)Rⁱ, -NRⁱR^j, -SRⁱ, -R^k, -CN, -NO₂, -CO₂Rⁱ, -CONRⁱR^j, -C(O)Rⁱ, -OC(O)NRⁱR^j, -NRⁱC(O)Rⁱ, -NRⁱC(O)₂R^k, -X⁴ORⁱ, -X⁴OC(O)Rⁱ, -X⁴NRⁱR^j, -X⁴SRⁱ, -X⁴CN, -X⁴NO₂, -X⁴CO₂Rⁱ, -X⁴CONRⁱR^j, -X⁴C(O)Rⁱ, -X⁴OC(O)NRⁱR^j, -X⁴NRⁱC(O)Rⁱ and -X⁴NRⁱC(O)₂R^k, wherein X⁴ is selected from the group consisting of C₁₋₄ alkylene, C₂₋₄ alkenylene and C₂₋₄ alkynylene and each Rⁱ and R^j is independently selected from hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, heteroaryl, aryl-C₁₋₄ alkyl, and aryloxy-C₁₋₄ alkyl, and each R^k is independently selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, heteroaryl, aryl-C₁₋₄ alkyl, and aryloxy-C₁₋₄ alkyl. In certain preferred embodiments, the linking groups are unsubstituted, while in other preferred embodiments, substituents are present that can increase partitioning into selected solvents or into selected tissues. For example, addition of a hydroxy group to a propylene linkage will generally provide compounds having more favorable solubility in water. Preferably, L¹ is selected from -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂O-, -CH₂NH-, -CH₂OCH₂- and -CH₂NHCH₂-.

[0040] Returning to the piperazine or homopiperazine portion of the compounds, each R¹ is a substituent independently selected from C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, -COR^a, -CO₂R^a, -CONR^aR^b, -NR^aCOR^b, -SO₂R^a, -X¹COR^a, -X¹CO₂R^a, -X¹CONR^aR^b, -X¹NR^aCOR^b, -X¹SO₂R^a, -X¹SO₂NR^aR^b, -X¹NR^aR^b, -X¹OR^a, wherein X¹ is a member selected from the group consisting of C₁₋₄ alkylene, C₂₋₄

alkenylene and C₂₋₄ alkynylene and each R^a and R^b is independently selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl and C₃₋₆ cycloalkyl, and wherein the aliphatic portions of each of said R¹ substituents is optionally substituted with from one to three members selected from the group consisting of OH, O(C₁₋₈ alkyl), SH, S(C₁₋₈ alkyl), 5 CN, NO₂, NH₂, NH(C₁₋₈ alkyl) and N(C₁₋₈ alkyl)₂.

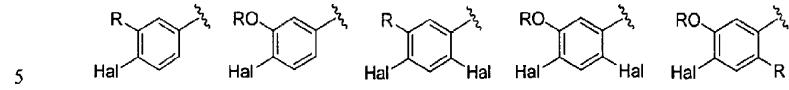
[0041] Excluded from the above generic formula, as well as each of the formulae below, are those compounds that are either commercially available or known in the literature, including: CAS Reg. No. 492422-98-7, 1-[[4-bromo-5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl]-4-(5-chloro-2-methylphenyl)-piperazine; CAS Reg. No. 351986-92-0, 1-10 [[4-chloro-5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl]-4-(4-fluorophenyl)-piperazine; CAS Reg. No. 356039-23-1, 1-[(3,5-dimethyl-4-nitro-1H-pyrazol-1-yl)acetyl]-4-(4-fluorophenyl)-piperazine; 1-(2-{4-nitro-3,5-dimethyl-1H-pyrazol-1-yl}propanoyl)-4-phenylpiperazine; 2-(2,4-Dinitro-imidazol-1-yl)-1-[4-(4-fluorophenyl)-piperazin-1-yl]-ethanone; 2-(2,4-Dinitro-imidazol-1-yl)-1-(4-phenyl-piperazin-1-yl)-ethanone; 2-(4-Nitro-15 imidazol-1-yl)-1-(4-phenyl-piperazin-1-yl)-ethanone; and CAS Reg. No. 492992-15-1, 3-[3-Fluoro-4-[4-[(1-pyrazolyl)acetyl]piperazine-1-yl]phenyl]-5-[(isoxazol-3-yl)amino]methyl]isoxazole.

[0042] A number of preferred groups of embodiments can be outlined as follows.

[0043] In a first group of preferred embodiments, the compounds are represented by 20 formula I in which Ar¹ is selected from

(i) phenyl, substituted with from 1 to 5 R² groups;
 (ii) pyridinyl, substituted with from 1 to 4 R² groups; and
 (iii) pyrimidinyl, substituted with from 1 to 3 R² groups;
 (iv) pyrazinyl, substituted with from 1 to 3 R² groups; and
 25 (v) pyridazinyl, substituted with from 1 to 3 R² groups;
 wherein each R² is a member independently selected from the group consisting of halogen, -OR^c, -OC(O)R^c, -NR^cR^d, -SR^c, -R^e, -CN, -NO₂, -CO₂R^c, -CONR^cR^d, -C(O)R^c, -OC(O)NR^cR^d, -NR^dC(O)R^c, -NR^dC(O)₂R^e, -NR^c-C(O)NR^cR^d, -S(O)R^e, -S(O)₂R^e, -NR^cS(O)₂R^e, -S(O)₂NR^cR^d and -N₃, wherein each R^c and R^d is independently selected from 30 hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, and each R^e is independently selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, wherein the aliphatic portions of R^c, R^d and R^e are

optionally further substituted with from one to three members selected from the group consisting of OH, O(C₁₋₈ alkyl), SH, S(C₁₋₈ alkyl), CN, NO₂, NH₂, NH(C₁₋₈ alkyl) and N(C₁₋₈ alkyl)₂. More preferably, Ar¹ is phenyl substituted with from 1 to 3 R² groups. Among the most preferred Ar¹ groups are those represented by:



wherein Hal is F, Cl or Br and each R is independently C₁₋₆ alkyl or C₁₋₆ cycloalkyl.

[0044] Further preferred are those embodiments in which L¹ is -CH₂- and is optionally

substituted with phenyl, -R^k, -X⁴ORⁱ, -X⁴OC(O)R^j, -X⁴NR^fR^j, -X⁴SRⁱ, -X⁴CN or -X⁴NO₂. In

still further preferred embodiments, HAr is selected from pyrazolyl, triazolyl and tetrazolyl,

10 each of which is optionally substituted with from one to three R³ groups independently selected from halogen, phenyl, thienyl, -OR^f, -OC(O)R^f, -NR^fR^g, -SR^f, -R^h, -CN, -NO₂, -CO₂R^f, -CONR^fR^g, -C(O)NR^fR^g, -NR^gC(O)R^f, -NR^gC(O)₂R^h, -NR^f-C(O)NR^fR^g, -S(O)R^h, -S(O)₂R^h, -S(O)₂NR^fR^g, -NR^fS(O)₂R^h, -NR^fS(O)₂NR^fR^g, -N₃, -X³OR^f, -X³OC(O)R^f, -X³NR^fR^g, -X³SR^f, -X³CN, -X³NO₂, -X³CO₂R^f, -X³CONR^fR^g, -X³C(O)R^f, -X³OC(O)NR^fR^g, -X³NR^gC(O)R^f, -X³NR^gC(O)₂R^h, -X³NR^f-C(O)NR^fR^g, -X³S(O)R^h, -X³S(O)₂R^h, -X³N₃ wherein R^f and R^g are each independently selected from the group consisting of H, C₁₋₈ alkyl and C₁₋₈ haloalkyl, and each R^h is independently selected from the group consisting of C₁₋₈ alkyl and C₁₋₈ haloalkyl. In still further preferred embodiments, the subscript n is 1, m is 0, 1 or 2, Ar¹ is phenyl substituted

15 with from one to three R² groups, HAr is pyrazolyl which is substituted with three R³ groups and L¹ is -CH₂-.

20 In the most preferred embodiments in this group, Ar¹ is selected from those substituted phenyl moieties provided in Figure 1.

[0045] In a second group of preferred embodiments, the compounds are represented by formula I in which Ar¹ is selected from

25 (i) phenyl, substituted with from 1 to 5 R² groups;

(ii) pyridinyl, substituted with from 1 to 4 R² groups; and

(iii) pyrimidinyl, substituted with from 1 to 3 R² groups;

(iv) pyrazinyl, substituted with from 1 to 3 R² groups; and

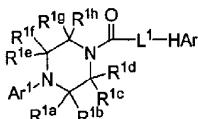
(v) pyridazinyl, substituted with from 1 to 3 R² groups;

30 wherein each R² is a member independently selected from the group consisting of halogen, -X²OR^c, -X²OC(O)R^c, -X²NR^cR^d, -X²SR^c, -X²CN, -X²NO₂, -X²CO₂R^c, -X²CONR^cR^d,

-X²C(O)R^c, -X²OC(O)NR^cR^d, -X²NR^dC(O)R^c, -X²NR^dC(O)₂R^e, -X²NR^cC(O)NR^cR^d, -X²S(O)R^e, -X²S(O)₂R^e, -X²NR^cS(O)₂R^e, -X²S(O)₂NR^cR^d and -X²N₃, wherein each R^c and R^d is independently selected from hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, and each R^e is independently selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl.

[0046] In a third group of preferred embodiments, the compounds are represented by formula I in which HAr is selected from pyrazolyl, triazolyl, tetrazolyl, benzimidazolyl, benzopyrazolyl and benzotriazolyl, each of which is optionally substituted with from one to five R³ groups independently selected from the group consisting of halogen, phenyl, thiienyl, -OR^f, -COR^f, -CO₂R^f, -CONR^fR^g, -NO₂, -R^h, -CN, -SR^f, -S(O)R^h, -S(O)₂R^h and -NR^fR^g, 10 wherein R^f and R^g are each independently selected from the group consisting of H, C₁₋₈ alkyl, C₃₋₆ cycloalkyl and C₁₋₈ haloalkyl, and each R^h is independently selected from the group consisting of C₁₋₈ alkyl, C₃₋₆ cycloalkyl and C₁₋₈ haloalkyl.

[0047] In another group of preferred embodiments, the compounds are represented by formula II:



III

or a pharmaceutically acceptable salt thereof, wherein each of R^{1a} , R^{1b} , R^{1c} , R^{1d} , R^{1e} , R^{1f} , R^{1g} and R^{1h} represents a member independently selected from the group consisting of H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl and C_{2-8} alkynyl. The remaining groups have the meanings provided above with reference to formula I in their most complete interpretation. Preferably, Ar^1 is selected from phenyl and naphthyl, each of which is optionally substituted with from one to five R^2 substituents independently selected from halogen, $-OR^c$, $-OC(O)R^c$, $-NR^dR^d$, $-SR^e$, $-R^e$, $-CN$, $-NO_2$, $-CO_2R^c$, $-CONR^dR^d$, $-C(O)R^c$, $-OC(O)NR^cR^d$, $-NR^dC(O)R^c$, $-NR^dC(O)_2R^e$, $-NR^c-C(O)NR^cR^d$, $-S(O)R^e$, $-S(O)_2R^e$, $-NR^cS(O)_2R^e$, $-S(O)_2NR^cR^d$ and $-N_3$, wherein each R^c and R^d is independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl and C_{2-8} alkynyl, and each R^e is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl and C_{2-8} alkynyl. In related preferred embodiments, Ar^1 is selected from phenyl and naphthyl, each of which is optionally substituted with from one to five R^2

substituents independently selected from halogen, $-X^2OR^e$, $-X^2OC(O)R^e$, $-X^2NR^eR^d$, $-X^2SR^e$, $-X^2CN$, $-X^2NO_2$, $-X^2CO_2R^e$, $-X^2CONR^eR^d$, $-X^2C(O)R^e$, $-X^2OC(O)NR^eR^d$, $-X^2NR^dC(O)R^e$, $-X^2NR^dC(O)_2R^e$, $-X^2NR^eC(O)NR^eR^d$, $-X^2S(O)R^e$, $-X^2S(O)_2R^e$, $-X^2NR^eS(O)_2R^e$, $-X^2S(O)_2NR^eR^d$ and $-X^2N_3$, wherein each R^e and R^d is independently selected from hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, and each R^e is independently selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl. Still more preferably, L¹ is a member selected from the group consisting of -CH₂-, -CH₂CH₂-, -CH₂O- and -CH₂NH-, each of which is optionally substituted with one or more substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl and phenyl. In still further preferred embodiments, HAr is selected from pyrazolyl, triazolyl, tetrazolyl and benzopyrazolyl, each of which is optionally substituted with from one to five R³ groups independently selected from halogen, phenyl, thienyl, -OR^f, -OC(O)R^f, -NR^fR^g, -SR^f, -R^h, -CN, -NO₂, -CO₂R^f, -CONR^fR^g, -C(O)R^f, -OC(O)NR^fR^g, -NR^gC(O)R^f, -NR^gC(O)₂R^h, -NR^fC(O)NR^fR^g, -S(O)R^h, -S(O)₂R^h, -NR^fS(O)₂R^h, -S(O)NR^fR^g, -NR^fS(O)₂NR^fR^g, -X³OR^f, -X³OC(O)R^f, -X³NR^fR^g, -X³SR^f, -X³CN, -X³NO₂, -X³CO₂R^f, -X³CONR^fR^g, -X³C(O)R^f, -X³OC(O)NR^fR^g, -X³NR^gC(O)R^f, -X³NR^gC(O)₂R^h, -X³NR^fC(O)NR^fR^g, -X³S(O)R^h, -X³S(O)₂R^h, -X³NR^fS(O)₂R^h and -X³S(O)₂NR^fR^g wherein X³ is selected from the group consisting of C₁₋₄ alkylene, C₂₋₄ alkenylene and C₂₋₄ alkynylene and each R^f and R^g is independently selected from hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, and each R^h is independently selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, and wherein any phenyl or thienyl group present is optionally substituted with from one to three substituents selected from the group consisting of halogen, -OR^f, -NR^fR^g, -R^h, -CN, -NO₂, -CO₂R^f, -CONR^fR^g, -C(O)R^f, -X³OR^f, -X³NR^fR^g, -X³NR^fS(O)₂R^h and -X³S(O)₂NR^fR^g. Still more preferably, HAr is pyrazolyl or benzopyrazolyl, each of which is optionally substituted with from one to three R³ groups independently selected from halogen, phenyl, thienyl, -OR^f, -CO₂R^f, -COR^f, -CONR^fR^g, -NO₂, -R^h, -CN, -SR^f, -S(O)R^h, -S(O)₂R^h and -NR^fR^g, wherein each R^f and R^g is independently selected from H, C₁₋₈ alkyl and C₁₋₈ haloalkyl, and each R^h is independently selected from C₁₋₈ alkyl and C₁₋₈ haloalkyl. Most preferably, HAr is selected from the substituted pyrazolyl moieties provided in Figures 2 and 3.

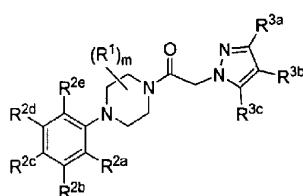
[0048] In a related group of preferred embodiments, the compound is represent by formula II, above, wherein Ar¹ is phenyl, optionally substituted with from one to five R² substituents independently selected from the group consisting of halogen, -OR^e, -OC(O)R^e, -NR^eR^d, -SR^e,

-R^e, -CN, -NO₂, -CO₂R^c, -CONR^cR^d, -C(O)R^c, -OC(O)NR^cR^d, -NR^dC(O)R^c, -NR^dC(O)₂R^c, -NR^c-C(O)NR^cR^d, -S(O)R^e, -S(O)₂R^c, -S(O)₂NR^cR^d and -N₃, wherein each R^c and R^d is independently selected from hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl, and C₂₋₈ alkynyl, and each R^c is independently selected from the group consisting of C₁₋₈

5 alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, wherein the alkyl portions of the substituents are optionally substituted with one or two hydroxy or amino groups; L¹ is -CH₂-; HAr is pyrazolyl or benzopyrazolyl, each of which is optionally substituted with from one to three R³ groups independently selected from the group consisting of halogen, phenyl, thienyl, OR^f, CO₂R^f, CONR^fR^g, NO₂, R^h, CN, SR^f, S(O)R^h, S(O)₂R^h and NR^fR^g, wherein each

10 R^f and R^g is independently selected from the group consisting of H, C₁₋₈ alkyl and C₁₋₈ haloalkyl, and each R^h is independently selected from the group consisting of C₁₋₈ alkyl and C₁₋₈ haloalkyl; and each of R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f}, R^{1g} and R^{1h} are members independently selected from the group consisting of H, C₁₋₄ alkyl and C₁₋₄ haloalkyl, wherein at least six of R^{1a} through R^{1h} are H.

15 [0049] In yet another group of preferred embodiments, compounds are provided having formula III:



III

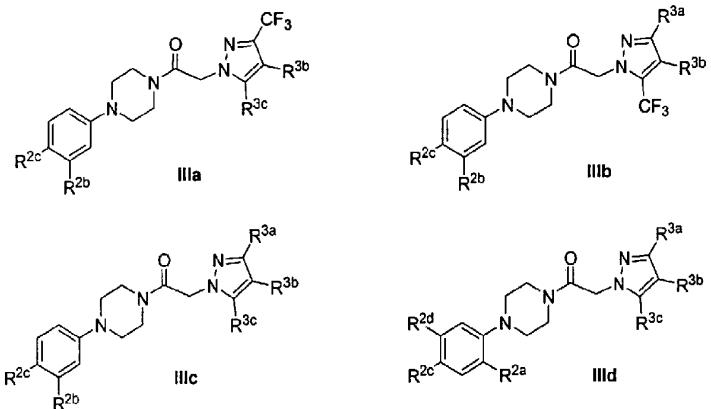
or a pharmaceutically acceptable salt thereof, wherein the subscript m is an integer of from 0 to 2; each R¹ is selected from C₁₋₄ alkyl and C₁₋₄ haloalkyl; R^{2a}, R^{2b}, R^{2c}, R^{2d} and R^{2e} are each members independently selected from hydrogen, halogen, -OR^c, -OC(O)R^c, -NR^cR^d, -SR^c, -R^e, -CN, -NO₂, -CO₂R^c, -CONR^cR^d, -C(O)R^c, -OC(O)NR^cR^d, -NR^dC(O)R^c, -NR^dC(O)₂R^c, -NR^c-C(O)NR^cR^d, -S(O)R^e, -S(O)₂R^c, -NR^cS(O)R^e, -S(O)₂NR^cR^d, -N₃, -X²OR^c, -X²OC(O)R^c, -X²NR^cR^d, -X²SR^c, -X²CN, -X²NO₂, -X²CO₂R^c, -X²CONR^cR^d, -X²C(O)R^c, -X²OC(O)NR^cR^d, -X²NR^dC(O)R^c, -X²NR^dC(O)₂R^c, -X²NR^cC(O)NR^cR^d, -X²S(O)R^e, -X²S(O)R^c, -X²NR^cS(O)R^e, -X²S(O)₂NR^cR^d and -X²N₃, wherein X² is C₁₋₄ alkylene, and each R^c and R^d is independently selected from hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, and each R^e is independently selected from the

group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, and each of R^c, R^d and R^e is optionally further substituted with from one to three members selected from the group consisting of OH, O(C₁₋₈ alkyl), SH, S(C₁₋₈ alkyl), CN, NO₂, NH₂, NH(C₁₋₈ alkyl) and N(C₁₋₈ alkyl)₂; R^{3a}, R^{3b} and R^{3c} are each members independently selected from hydrogen, halogen, phenyl, thiienyl, furanyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, triazolyl, tetrazolyl, oxadiazolyl, -OR^f, -OC(O)R^f, -NR^fR^g, -SR^f, -R^h, -CN, -NO₂, -CO₂R^f, -CONR^fR^g, -C(O)R^f, -OC(O)NR^fR^g, -NR^fC(O)R^f, -NR^fC(O)R^h, -NR^fC(O)NR^fR^g, -S(O)R^h, -S(O)₂R^h, -NR^fS(O)₂R^h, -S(O)₂NR^fR^g, -NR^fS(O)₂NR^fR^h, -NR^fS(O)₂NR^fR^g, -X³OR^f, -X³OC(O)R^f, -X³NR^fR^g, -X³SR^f, -X³CN, -X³NO₂, -X³CO₂R^f, -X³CONR^fR^g, -X³C(O)R^f, -X³OC(O)NR^fR^g, -X³NR^fC(O)R^f, -X³NR^fC(O)R^h, -X³NR^fC(O)NR^fR^g, -X³S(O)R^h, -X³S(O)₂R^h and -X³S(O)₂NR^fR^g wherein X³ is C₁₋₄ alkylene, each R^f and R^g is independently selected from hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, and each R^h is independently selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, and wherein any phenyl, thiienyl, furanyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, triazolyl, tetrazolyl, or oxadiazolyl group present is optionally substituted with from one to three substituents selected from the group consisting of halogen, -OR^f, -NR^fR^g, -R^h, -CN, -NO₂, -CO₂R^f, -CONR^fR^g, -C(O)R^f, -X³OR^f, -X³NR^fR^g, -X³NR^fS(O)₂R^h and -X³S(O)₂NR^fR^g.

[0050] Within the preferred group of formula III above, certain groups of embodiments are particularly preferred. In one group of particularly preferred embodiments, the subscript m is 0 or 1 and at least one of R^{2a} or R^{2e} is hydrogen. More preferably, at least one of R^{3a}, R^{3b} and R^{3c} is selected from halogen and C₁₋₄ haloalkyl. Still more preferably, R^{2d} is hydrogen and at least two of R^{2a}, R^{2b} and R^{2c} are selected from halogen and C₁₋₄ haloalkyl with the remaining member being other than hydrogen. In related, and preferred embodiments, m is 0 or 1 and at least one of R^{2a} or R^{2e} is hydrogen, R^{2d} is hydrogen, R^{2c} is selected from F, Cl, Br, CN, NO₂, CO₂CH₃, C(O)CH₃ and S(O)₂CH₃, and at least two of R^{3a}, R^{3b} and R^{3c} are selected from halogen and C₁₋₄ haloalkyl with the remaining member being other than hydrogen. In another group of particularly preferred embodiments, the subscript m is 0 or 1; and R^{2a} and R^{2e} are both hydrogen. More preferably, at least one of R^{3a}, R^{3b} and R^{3c} is selected from halogen and C₁₋₄ haloalkyl. Still more preferably, at least one of R^{3a}, R^{3b} and R^{3c} is selected from halogen and C₁₋₄ haloalkyl, and the remaining members of R^{3a}, R^{3b} and R^{3c} are other than hydrogen. In yet another group of particularly preferred embodiments, the subscript m is 0 or 1; and R^{2b}

and R^{2c} are both hydrogen. More preferably, at least one of R^{3a} , R^{3b} and R^{3c} is selected from halogen and C_{1-4} haloalkyl. Still more preferably, at least one of R^{3a} , R^{3b} and R^{3c} is selected from halogen and C_{1-4} haloalkyl, and the remaining members of R^{3a} , R^{3b} and R^{3c} are other than hydrogen.

5 [0051] Still other preferred groups of formula III above, are:



[0052] Turning first to the compounds of formula IIIa, R^{3b} is preferably halogen, nitro or cyano, more preferably halogen and most preferably chloro or bromo; R^{3c} is preferably C_{1-6} alkyl, C_{1-6} haloalkyl or C_{3-6} cycloalkyl; R^{2c} is halogen and R^{2b} is $-OR^c$ or R^e wherein R^c is

10 selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl and C_{2-8} alkynyl, and R^e is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl and C_{2-8} alkynyl, and each of R^c and R^e is optionally further substituted with from one to three members selected from the group consisting of OH, $O(C_{1-8}$ alkyl), SH, $S(C_{1-8}$ alkyl), CN, NO_2 , NH_2 , $NH(C_{1-8}$ alkyl) and $N(C_{1-8}$ alkyl) $_2$.

15 [0053] For the compounds of formula IIIb, R^{3b} is preferably halogen, nitro or cyano, more preferably halogen and most preferably chloro or bromo; R^{3a} is preferably C_{1-6} alkyl, C_{1-6} haloalkyl or C_{3-6} cycloalkyl; R^{2c} is preferably halogen and R^{2b} is preferably $-OR^c$ or R^e wherein R^c is selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl and C_{2-8} alkynyl, and R^e is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl and C_{2-8} alkynyl, and each of R^c and R^e is optionally further substituted with from one to three members selected from the group consisting of OH, $O(C_{1-8}$ alkyl), SH, $S(C_{1-8}$ alkyl), CN, NO_2 , NH_2 , $NH(C_{1-8}$ alkyl) and $N(C_{1-8}$ alkyl) $_2$.

[0054] For the compounds of formula IIIc, R^{3a} is selected from NH_2 , CF_3 , SCH_3 , Ph and thiienyl; R^{3b} is chloro or bromo; R^{3c} is preferably C_{1-6} alkyl, C_{1-6} haloalkyl or C_{3-6} cycloalkyl; R^{2c} is hydrogen, halogen, cyano or nitro; and R^{2b} is selected from hydrogen, halogen, $-OR^c$, $-OC(O)R^c$, $-NR^cR^d$, $-SR^c$, $-R^e$, $-CO_2R^c$, $-CONR^cR^d$, $-C(O)R^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-X^2OR^c$, $-X^2OC(O)R^c$, $-X^2NR^cR^d$, $-X^2SR^c$, $-X^2CO_2R^c$, $-X^2CONR^cR^d$, $-X^2C(O)R^c$, $-X^2OC(O)NR^cR^d$, $-X^2NR^dC(O)R^c$, $-X^2NR^dC(O)_2R^c$, $-X^2NR^cC(O)NR^cR^d$, $-X^2S(O)R^c$, $-X^2S(O)_2R^c$, $-X^2NR^cS(O)_2R^c$, $-X^2S(O)_2NR^cR^d$ and $-X^2N_3$, wherein X^2 is C_{1-4} alkylene, and each R^c and R^d is independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl and C_{2-8} alkynyl, and each R^e is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl and C_{2-8} alkynyl, and each of R^c , R^d and R^e is optionally further substituted with from one to three members selected from the group consisting of OH , $O(C_{1-8}$ alkyl), SH , $S(C_{1-8}$ alkyl), CN , NO_2 , NH_2 , $NH(C_{1-8}$ alkyl) and $N(C_{1-8}$ alkyl)₂. In the most preferred embodiments, R^{2c} is halogen, cyano or nitro; R^{2b} is R^e or $-OR^c$; R^{3a} is selected from the group consisting of NH_2 , CF_3 , SCH_3 , Ph and thiienyl; R^{3b} is chloro or bromo; and R^{3c} is selected from the group consisting of C_{1-6} alkyl and C_{3-6} cycloalkyl.

[0055] In related, and preferred embodiments, compounds of formula IIIc are provided wherein R^{3c} is selected from NH_2 , CF_3 , SCH_3 , Ph and thiienyl; R^{3b} is chloro or bromo; R^{3a} is preferably C_{1-6} alkyl, C_{1-6} haloalkyl or C_{3-6} cycloalkyl; R^{2c} is hydrogen, halogen, cyano or nitro, preferably halogen; and R^{2b} is selected from hydrogen, halogen, $-OR^c$, $-OC(O)R^c$, $-NR^cR^d$, $-SR^c$, $-R^e$, $-CO_2R^c$, $-CONR^cR^d$, $-C(O)R^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-X^2OR^c$, $-X^2OC(O)R^c$, $-X^2NR^cR^d$, $-X^2SR^c$, $-X^2CO_2R^c$, $-X^2CONR^cR^d$, $-X^2C(O)R^c$, $-X^2OC(O)NR^cR^d$, $-X^2NR^dC(O)R^c$, $-X^2NR^dC(O)_2R^c$, $-X^2NR^cC(O)NR^cR^d$, $-X^2S(O)R^c$, $-X^2S(O)_2R^c$, $-X^2NR^cS(O)_2R^c$, $-X^2S(O)_2NR^cR^d$ and $-X^2N_3$, wherein X^2 is C_{1-4} alkylene, and each R^c and R^d is independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl and C_{2-8} alkynyl, and each R^e is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl and C_{2-8} alkynyl, and each of R^c , R^d and R^e is optionally further substituted with from one to three members selected from the group consisting of OH , $O(C_{1-8}$ alkyl), SH , $S(C_{1-8}$ alkyl), CN , NO_2 , NH_2 , $NH(C_{1-8}$ alkyl) and $N(C_{1-8}$ alkyl)₂. In the most preferred embodiments, R^{2c} is halogen, cyano or nitro; R^{2b} is R^e or $-OR^c$; R^{3a} is selected from the group consisting of C_{1-6} alkyl and C_{3-6} cycloalkyl; R^{3c} is selected from the group consisting of NH_2 , CF_3 , SCH_3 , Ph and thiienyl; and R^{3b} is chloro or bromo.

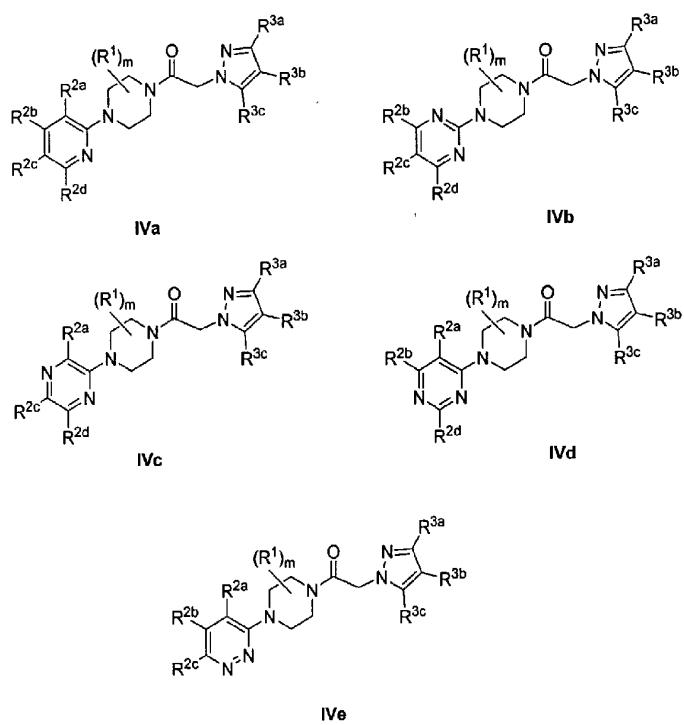
[0056] For the compounds of formula IIId, R^{3a} is selected from NH_2 , CF_3 , SCH_3 , Ph and thiienyl; R^{3b} is chloro or bromo; R^{3c} is preferably C_{1-6} alkyl, C_{1-6} haloalkyl or C_{3-6} cycloalkyl;

R^{2a} is preferably other than hydrogen, and is selected from halogen, $-OR^c$, $-OC(O)R^c$, $-NR^cR^d$, $-SR^c$, $-R^e$, $-CO_2R^c$, $-CONR^cR^d$, $-C(O)R^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-X^2OR^c$, $-X^2OC(O)R^c$, $-X^2NR^cR^d$, $-X^2SR^c$, $-X^2CO_2R^c$, $-X^2CONR^cR^d$, $-X^2C(O)R^c$, $-X^2OC(O)NR^cR^d$, $-X^2NR^dC(O)R^c$, $-X^2NR^dC(O)_2R^c$, $-X^2NR^cC(O)NR^cR^d$, $-X^2S(O)R^e$, $-X^2S(O)_2R^e$, $-X^2NR^cS(O)_2R^e$, $-X^2S(O)NR^cR^d$ and $-X^2N_3$; R^{2c} is hydrogen, halogen, cyano or nitro, preferably halogen; and R^{2d} is selected from hydrogen, halogen, $-OR^c$, $-OC(O)R^c$, $-NR^cR^d$, $-SR^c$, $-R^e$, $-CO_2R^c$, $-CONR^cR^d$, $-C(O)R^c$, $-S(O)R^e$, $-S(O)_2R^c$, $-X^2OR^c$, $-X^2OC(O)R^c$, $-X^2NR^cR^d$, $-X^2SR^c$, $-X^2CO_2R^c$, $-X^2CONR^cR^d$, $-X^2C(O)R^c$, $-X^2OC(O)NR^cR^d$, $-X^2NR^dC(O)R^c$, $-X^2NR^dC(O)_2R^c$, $-X^2NR^cC(O)NR^cR^d$, $-X^2S(O)R^e$, $-X^2S(O)_2R^e$, $-X^2NR^cS(O)_2R^e$, $-X^2S(O)_2NR^cR^d$ and $-X^2N_3$, wherein each X^2 is C_{1-4} alkylene, and each R^c and R^d is independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl and C_{2-8} alkynyl, and each R^e is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl and C_{2-8} alkynyl, and each of R^c , R^d and R^e is optionally further substituted with from one to three members selected from the group consisting of OH , $O(C_{1-8}$ alkyl), SH , $S(C_{1-8}$ alkyl), CN , NO_2 , NH_2 , $NH(C_{1-8}$ alkyl) and $N(C_{1-8}$ alkyl) $_2$; and no more than one of R^{2a} and R^{2d} is hydrogen. Preferably, each of R^{2a} and R^{2d} is other than hydrogen. In the most preferred embodiments, R^{2a} is other than hydrogen; R^{2c} is halogen, cyano or nitro; R^{2d} is R^e or $-OR^c$; R^{3a} is selected from the group consisting of C_{1-6} alkyl and C_{3-6} cycloalkyl; R^{3b} is chloro or bromo; and R^{3c} is selected from the group consisting of NH_2 , CF_3 , SCH_3 , Ph and thiienyl.

[0057] In related and preferred embodiments, compounds of formula IIId are provided wherein R^{3c} is selected from NH_2 , CF_3 , SCH_3 , Ph and thiienyl; R^{3b} is chloro or bromo; R^{3a} is preferably C_{1-6} alkyl, C_{1-6} haloalkyl or C_{3-6} cycloalkyl; R^{2a} is hydrogen, halogen, $-OR^c$, $-OC(O)R^c$, $-NR^cR^d$, $-SR^c$, $-R^e$, $-CO_2R^c$, $-CONR^cR^d$, $-C(O)R^c$, $-S(O)R^e$, $-S(O)_2R^c$, $-X^2OR^c$, $-X^2OC(O)R^c$, $-X^2NR^cR^d$, $-X^2SR^c$, $-X^2CO_2R^c$, $-X^2CONR^cR^d$, $-X^2C(O)R^c$, $-X^2OC(O)NR^cR^d$, $-X^2NR^dC(O)R^c$, $-X^2NR^dC(O)_2R^c$, $-X^2NR^cC(O)NR^cR^d$, $-X^2S(O)R^e$, $-X^2S(O)_2R^e$, $-X^2NR^cS(O)_2R^e$, $-X^2S(O)NR^cR^d$ and $-X^2N_3$; R^{2c} is hydrogen, halogen, cyano or nitro; and R^{2d} is selected from hydrogen, halogen, $-OR^c$, $-OC(O)R^c$, $-NR^cR^d$, $-SR^c$, $-R^e$, $-CO_2R^c$, $-CONR^cR^d$, $-C(O)R^c$, $-S(O)R^e$, $-S(O)_2R^c$, $-X^2OR^c$, $-X^2OC(O)R^c$, $-X^2NR^cR^d$, $-X^2SR^c$, $-X^2CO_2R^c$, $-X^2CONR^cR^d$, $-X^2C(O)R^c$, $-X^2OC(O)NR^cR^d$, $-X^2NR^dC(O)R^c$, $-X^2NR^dC(O)_2R^c$, $-X^2NR^cC(O)NR^cR^d$, $-X^2S(O)R^e$, $-X^2S(O)_2R^e$, $-X^2NR^cS(O)_2R^e$, $-X^2S(O)NR^cR^d$ and $-X^2N_3$, wherein each X^2 is C_{1-4} alkylene, and each R^c and R^d is independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl and C_{2-8} alkynyl, and each R^e

is independently selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, and each of R^c, R^d and R^e is optionally further substituted with from one to three members selected from the group consisting of OH, O(C₁₋₈ alkyl), SH, S(C₁₋₈ alkyl), CN, NO₂, NH₂, NH(C₁₋₈ alkyl) and N(C₁₋₈ alkyl)₂; and no more than 5 one of R^{2a} and R^{2d} is hydrogen. Preferably, each of R^{2a} and R^{2d} is other than hydrogen. In the most preferred embodiments, R^{2a} is other than hydrogen; R^{2c} is halogen, cyano or nitro; R^{2d} is R^e or -OR^c; R^{3a} is selected from the group consisting of NH₂, CF₃, SCH₃, Ph and thiienyl; R^{3b} is chloro or bromo; and R^{3c} is selected from the group consisting of C₁₋₆ alkyl and C₃₋₆ cycloalkyl.

10 [0058] In yet another group of preferred embodiments, the compounds are selected from formulae IVa-IVe:



wherein R¹ and the subscript m have the meaning provided above for formula III, and each of R^{2a}, R^{2b}, R^{2c} and R^{2d} are substituents independently selected from hydrogen, halogen, -OR^c,

-OC(O)R^c, -NR^cR^d, -SR^c, -R^e, -CN, -NO₂, -CO₂R^c, -CONR^cR^d, -C(O)R^c, -OC(O)NR^cR^d, -NR^dC(O)R^c, -NR^dC(O)₂R^c, -NR^c-C(O)NR^cR^d, -NH-C(NH₂)=NH, -NR^cC(NH₂)=NH, -NH-C(NH₂)=NR^c, -NH-C(NHR^c)=NH, -S(O)R^c, -S(O)₂R^c, -S(O)₂NR^cR^d, -NR^cS(O)₂R^e, -NR^cS(O)₂NR^d, -N₃, -X²OR^c, -X²OC(O)R^c, -X²NR^cR^d, -X²SR^c, -X²CN, -X²NO₂,

5 -X²CO₂R^c, -X²CONR^cR^d, -X²C(O)R^c, -X²OC(O)NR^cR^d, -X²NR^dC(O)R^c, -X²NR^dC(O)R^e, -X²NR^cC(O)NR^cR^d, -X²NH-C(NH₂)=NH, -X²NR^cC(NH₂)=NH, -X²NH-C(NH₂)=NR^c, -X²NH-C(NHR^c)=NH, -X²S(O)R^c, -X²S(O)₂R^c, -X²S(O)₂NR^cR^d, -X²NR^cS(O)₂R^e, -X¹N₃, aryl and heteroaryl, wherein X², R^c, R^d and R^e have the meanings provided above with respect to the compounds of formula I. Similarly, each of R^{3a}, R^{3b} and R^{3c} represents a substituent

10 independently selected from hydrogen, halogen, phenyl, thiienyl, furanyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, triazolyl, tetrazolyl, oxadiazolyl, -OR^f, -OC(O)R^f, -NR^fR^g, -SR^f, -R^h, -CN, -NO₂, -CO₂R^f, -CONR^fR^g, -C(O)R^f, -OC(O)NR^fR^g, -NR^gC(O)R^f, -NR^gC(O)₂R^h, -NR^f-C(O)NR^fR^g, -NH-C(NH₂)=NH, -NR^hC(NH₂)=NH, -NH-C(NH₂)=NR^h, -NH-C(NHR^h)=NH, -S(O)R^h, -

15 S(O)₂R^h, -S(O)₂NR^fR^g, -NR^fS(O)₂NR^fR^g, -N₃, -X³OR^f, -X³OC(O)R^f, -X³NR^fR^g, -X³SR^f, -X³CN, -X³NO₂, -X³CO₂R^f, -X³CONR^fR^g, -X³C(O)R^f, -X³OC(O)NR^fR^g, -X³NR^gC(O)R^f, -X³NR^gC(O)₂R^h, -X³NR^f-C(O)NR^fR^g, -X³NH-C(NH₂)=NH, -X³NR^hC(NH₂)=NH, -X³NH-C(NH₂)=NR^h, -X³NH-C(NHR^h)=NH, -X³S(O)R^h, -X³S(O)₂R^h, -X³S(O)₂NR^fR^g, -X³NR^fS(O)₂R^h and -X³N₃ wherein X³, R^f, R^g and R^h have the meaning

20 provided above with respect to the compounds of formula I, and wherein no more than two of R^{3a}, R^{3b} and R^{3c} are hydrogen, preferably, no more than one of R^{3a}, R^{3b} and R^{3c} is hydrogen, and still more preferably, each of R^{3a}, R^{3b} and R^{3c} is other than hydrogen.

[0059] Turning first to the compounds of formula IVa, in one group of particularly preferred embodiments, at least one of R^{3a}, R^{3b} and R^{3c} is selected from halogen and C₁₋₄ haloalkyl. Still more preferably, at least one of R^{2b} and R^{2d} is hydrogen and at least two of R^{3a}, R^{3b} and R^{3c} are selected from halogen and C₁₋₄ haloalkyl. In related, and preferred embodiments, R^{2c} is selected from F, Cl, Br, CN, NO₂, CO₂CH₃, C(O)CH₃ and S(O)₂CH₃, and at least two of R^{3a}, R^{3b} and R^{3c} are selected from halogen and C₁₋₄ haloalkyl with the remaining member being other than hydrogen.

25 [0060] Similarly, certain compounds of formula IVb are preferred. Particularly preferred are those compounds of formula IVb in which at least one of R^{3a}, R^{3b} and R^{3c} is selected from halogen and C₁₋₄ haloalkyl. Still more preferably, at least one of R^{2b} and R^{2d} is hydrogen and at least two of R^{3a}, R^{3b} and R^{3c} are selected from halogen and C₁₋₄ haloalkyl. In related, and

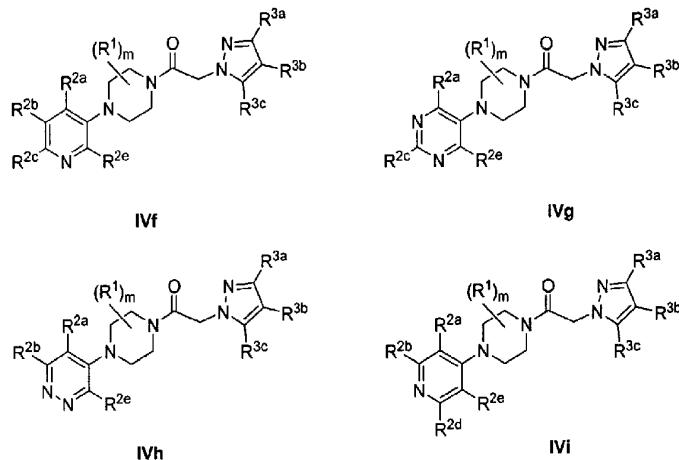
preferred embodiments, R^{2c} is selected from F, Cl, Br, CN, NO₂, CO₂CH₃, C(O)CH₃ and S(O)₂CH₃, and at least two of R^{3a} , R^{3b} and R^{3c} are selected from halogen and C₁₋₄haloalkyl with the remaining member being other than hydrogen.

[0061] Turning next to the compounds of formula IVc, preferred embodiments are those in which at least one of R^{2a} , R^{2c} and R^{2d} , preferably R^{2c} is selected from F, Cl, Br, CN, NO₂, CO₂CH₃, C(O)CH₃ and S(O)₂CH₃; and at least two of R^{3a} , R^{3b} and R^{3c} are selected from halogen and C₁₋₄haloalkyl with the remaining member being other than hydrogen. In other preferred embodiments, one of R^{2c} and R^{2d} is selected from F, Cl, Br, CN, NO₂, CO₂CH₃, C(O)CH₃ and S(O)₂CH₃, and the other is an aryl or heteroaryl group, for example, phenyl, 10 thienyl, furanyl, oxazolyl, isoxazolyl, thiazolyl and isothiazolyl, and at least two of R^{3a} , R^{3b} and R^{3c} are selected from halogen and C₁₋₄haloalkyl with the remaining member being other than hydrogen.

[0062] For the compounds of formula IVd, preferred embodiments are those in which at least one of R^{2a} , R^{2b} and R^{2d} is selected from F, Cl, Br, CN, NO₂, CO₂CH₃, C(O)CH₃ and S(O)₂CH₃, and at least two of R^{3a} , R^{3b} and R^{3c} are selected from halogen and C₁₋₄haloalkyl with the remaining member being other than hydrogen. In other preferred embodiments, one of R^{2b} and R^{2d} is selected from F, Cl, Br, CN, NO₂, CO₂CH₃, C(O)CH₃ and S(O)₂CH₃, and the other is an aryl or heteroaryl group, for example, phenyl, thienyl, furanyl, oxazolyl, isoxazolyl, thiazolyl and isothiazolyl, and at least two of R^{3a} , R^{3b} and R^{3c} are selected from 15 halogen and C₁₋₄haloalkyl with the remaining member being other than hydrogen.

[0063] For the compounds of formula IVe, preferred embodiments are those in which at least one of R^{2a} , R^{2b} and R^{2c} is selected from F, Cl, Br, CN, NO₂, CO₂CH₃, C(O)CH₃ and S(O)₂CH₃, and at least two of R^{3a} , R^{3b} and R^{3c} are selected from halogen and C₁₋₄haloalkyl with the remaining member being other than hydrogen. In other preferred embodiments, one of R^{2b} and R^{2c} is selected from F, Cl, Br, CN, NO₂, CO₂CH₃, C(O)CH₃ and S(O)₂CH₃, and the other is an aryl or heteroaryl group, for example, phenyl, thienyl, furanyl, oxazolyl, isoxazolyl, thiazolyl and isothiazolyl, and at least two of R^{3a} , R^{3b} and R^{3c} are selected from 20 halogen and C₁₋₄haloalkyl with the remaining member being other than hydrogen.

[0064] In yet another group of preferred embodiments, the compounds are selected from formulae IVf-IVi:

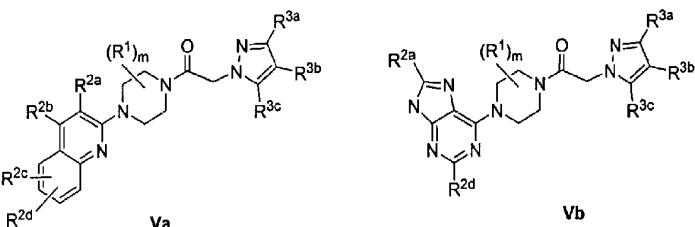


wherein R¹ and the subscript m have the meaning provided above for formula III, and each of

5 R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{3a}, R^{3b} and R^{3c} have the meaning provided above for formulae IVa-IVe.

Additionally, R^{2e} represents a substituent selected from the groups provided for R^{2a} in formulae IVa-IVe above.

[0065] In still other embodiments, compounds are provided having formulae Va and Vb:



10 wherein each of R¹, the subscript m, R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{3a}, R^{3b} and R^{3c} have the meaning provided above for formulae IVa-IVe.

IV. Pharmaceutical Compositions

[0066] In addition to the compounds provided above, compositions for modulating CCR1 activity in humans and animals will typically contain a pharmaceutical carrier or diluent.

[0067] The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must

5 be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0068] The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy and drug delivery. All methods include the
10 step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is

15 included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

[0069] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions and self emulsifications as described in U.S.

20 Patent Application 20020012680, hard or soft capsules, syrups, elixirs, solutions, buccal patch, oral gel, chewing gum, chewable tablets, effervescent powder and effervescent tablets. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, 25 coloring agents, antioxidants and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as cellulose, silicon dioxide, aluminum oxide, calcium carbonate, sodium carbonate, glucose, mannitol, sorbitol, 30 lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example PVP, cellulose, PEG, starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated, enterically or otherwise, by

known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874

5 to form osmotic therapeutic tablets for control release.

[0070] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

10 Additionally, emulsions can be prepared with a non-water miscible ingredient such as oils and stabilized with surfactants such as mono-diglycerides, PEG esters and the like.

[0071] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-

15 propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxyacetanol, or condensation products of ethylene

20 oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and

25 one or more sweetening agents, such as sucrose or saccharin.

[0072] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and

30 flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0073] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

5 Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0074] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents

10 may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

15 [0075] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. Oral solutions can be prepared in combination with, for example, cyclodextrin, PEG and surfactants.

[0076] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0077] The compounds of the present invention may also be administered in the form of 30 suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to

release the drug. Such materials include cocoa butter and polyethylene glycols.

Additionally, the compounds can be administered via ocular delivery by means of solutions or ointments. Still further, transdermal delivery of the subject compounds can be accomplished by means of iontophoretic patches and the like. For topical use, creams, 5 ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. As used herein, topical application is also meant to include the use of mouth washes and gargles.

V. Methods of Treating Diseases Modulated by CCR1

10 [0078] In yet another aspect, the present invention provides methods of treating CCR1-mediated conditions or diseases by administering to a subject having such a disease or condition, a therapeutically effective amount of a compound of formula I above. The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the 15 like.

[0079] CCR1 provides a target for interfering with or promoting specific aspects of immune cell functions, or more generally, with functions associated with CCR1 expression on a wide range of cell types in a mammal, such as a human. Compounds that inhibit CCR1, are particularly useful for modulating monocyte, macrophage, lymphocyte, granulocyte, NK 20 cell, mast cells, dendritic cell, and certain immune derived cell (for example, osteoclasts) function for therapeutic purposes. Accordingly, the present invention is directed to compounds which are useful in the prevention and/or treatment of a wide variety of inflammatory and immunoregulatory disorders and diseases (see Saeki, et al., *Current Pharmaceutical Design* 9:1201-1208 (2003)).

25 [0080] For example, an instant compound that inhibits one or more functions of CCR1 may be administered to inhibit (i.e., reduce or prevent) inflammation or cellular infiltration associated with an immune disorder. As a result, one or more inflammatory processes, such as leukocyte emigration or infiltration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, can be inhibited. For example, monocyte infiltration to an 30 inflammatory site (e.g., an affected joint in arthritis, or into the CNS in MS) can be inhibited according to the present method.

[0081] Similarly, an instant compound that promotes one or more functions of CCR1 is administered to stimulate (induce or enhance) an inflammatory response, such as leukocyte emigration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, resulting in the beneficial stimulation of inflammatory processes. For example,

5 monocytes can be recruited to combat bacterial infections.

[0082] Diseases and conditions associated with inflammation, immune disorders and infection can be treated using the method of the present invention. In a preferred embodiment, the disease or condition is one in which the actions of immune cells such monocyte, macrophage, lymphocyte, granulocyte, NK cell, mast cell, dendritic cell, or certain 10 immune derived cell (for example, osteoclasts) are to be inhibited or promoted, in order to modulate the inflammatory or autoimmune response.

[0083] In one group of embodiments, diseases or conditions, including chronic diseases, of humans or other species can treated with modulators of CCR1 function. These diseases or conditions include: (1) allergic diseases such as systemic anaphylaxis or hypersensitivity

15 responses, drug allergies, insect sting allergies and food allergies, (2) inflammatory bowel diseases, such as Crohn's disease, ulcerative colitis, ileitis and enteritis, (3) vaginitis, (4) psoriasis and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria and pruritus, (5) vasculitis, (6) spondyloarthropathies, (7) scleroderma, (8) asthma and respiratory allergic diseases such as allergic asthma, allergic 20 rhinitis, hypersensitivity lung diseases and the like, (9) autoimmune diseases, such as fibromyalgia, scleroderma, ankylosing spondylitis, juvenile RA, Still's disease, polyarticular juvenile RA, pauciarticular juvenile RA, polymyalgia rheumatica, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, polyarticular arthritis, multiple sclerosis, systemic lupus erythematosus, type I diabetes, type II diabetes, glomerulonephritis, and the like, (10) graft 25 rejection (including allograft rejection and graft-v-host disease), and (11) other diseases in which undesired inflammatory responses or immune disorders are to be inhibited, such as cardiovascular disease including atherosclerosis, myositis, neurodegenerative diseases (e.g., Alzheimer's disease), encephalitis, meningitis, hepatitis, nephritis, sepsis, sarcoidosis, allergic conjunctivitis, otitis, chronic obstructive pulmonary discase, sinusitis, Behcet's syndrome and 30 gout and (12) immune mediated food allergies such as Celiac disease.

[0084] In another group of embodiments, diseases or conditions can be treated with modulators of CCR1 function. Examples of diseases to be treated with modulators of CCR1

function include cancers, cardiovascular diseases, diseases in which angiogenesis or neovascularization play a role (neoplastic diseases, retinopathy and macular degeneration), infectious diseases (viral infections, *e.g.*, HIV infection, and bacterial infections) and immunosuppressive diseases such as organ transplant conditions and skin transplant

5 conditions. The term "organ transplant conditions" is meant to include bone marrow transplant conditions and solid organ (*e.g.*, kidney, liver, lung, heart, pancreas or combination thereof) transplant conditions.

[0085] The compounds of the present invention are accordingly useful in the prevention and treatment of a wide variety of inflammatory and immunoregulatory disorders and

10 diseases.

[0086] Depending on the disease to be treated and the subject's condition, the compounds of the present invention may be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of

15 administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

[0087] In the treatment or prevention of conditions which require chcmokine receptor modulation an appropriate dosage level will generally be about 0.001 to 100 mg per kg

20 patient body weight per day which can be administered in single or multiple doses.

Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. A suitable dosage level may be about 0.01 to 25 mg/kg per day, about 0.05 to 10 mg/kg per day, or about 0.1 to 5 mg/kg per day. Within this range the dosage may be 0.005 to 0.05, 0.05 to 0.5 or 0.5 to 5.0 mg/kg per day. For oral

25 administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per

30 day, preferably once or twice per day.

[0088] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including

the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, hereditary characteristics, general health, sex and diet of the subject, as well as the mode and time of administration, rate of excretion, drug combination, and the severity of the particular condition for the subject undergoing therapy.

5 [0089] Diseases and conditions associated with inflammation, immune disorder, infection and cancer can be treated or prevented with the present compounds, compositions, and methods.

[0090] The compounds and compositions of the present invention can be combined with other compounds and compositions having related utilities to prevent and treat the condition 10 or disease of interest, such as inflammatory or autoimmune disorders, conditions and diseases, including inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, psoriatic arthritis, polyarticular arthritis, multiple sclerosis, allergic diseases, psoriasis, atopic dermatitis and asthma, and those pathologies noted above.

[0091] For example, in the treatment or prevention of inflammation or autimmunity or for 15 example arthritis associated bone loss, the present compounds and compositions may be used in conjunction with an anti-inflammatory or analgesic agent such as an opiate agonist, a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of 20 nitric oxide, a non steroidal anti-inflammatory agent, or a cytokine-suppressing anti-inflammatory agent, for example with a compound such as acetaminophen, aspirin, codeine, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanil, sunlindac, tenidap, and the like. Similarly, the instant 25 compounds and compositions may be administered with an analgesic listed above; a potentiator such as caffeine, an H2 antagonist (e.g., ranitidine), simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo desoxy ephedrine; an antitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextromethorphan; a diuretic; and a sedating or non sedating 30 antihistamine.

[0092] Likewise, compounds and compositions of the present invention may be used in combination with other drugs that are used in the treatment, prevention, suppression or

amelioration of the diseases or conditions for which compounds and compositions of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound or composition of the present invention. When a compound or composition of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound or composition of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients or therapeutic agents, in addition to a compound or composition of the present invention. Examples of other therapeutic agents that may be combined with a compound or composition of the present invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) VLA-4 antagonists, (b) corticosteroids, such as beclomethasone, methylprednisolone, betamethasone, prednisone, prednisolone, dexamethasone, fluticasone, hydrocortisone, budesonide, triamcinolone, salmeterol, 15 salmeterol, salbutamol, formoterol; (c) immunosuppressants such as cyclosporine (cyclosporine A, Sandimmune®, Neoral®), tacrolimus (FK-506, Prograf®), rapamycin (sirolimus, Rapamune®) and other FK-506 type immunosuppressants, and mycophenolate, e.g., mycophenolate mofetil (CellCept®); (d) antihistamines (H1-histamine antagonists) such as brompheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, 20 diphenhydramine, diphenylpyraline, tripeptenamine, hydroxyzine, methdilazine, promethazine, trimethazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, desloratadine, and the like; (e) non steroid anti asthmatics (e.g., terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol and pirbuterol), theophylline, cromolyn sodium, atropine, 25 ipratropium bromide, leukotriene antagonists (e.g., zafirlukast, montelukast, pranlukast, iralukast, pobilukast and SKB-106,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); (f) non steroid anti-inflammatory agents (NSAIDs) such as propionic acid derivatives (e.g., alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, 30 oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid and tioxaprofen), acetic acid derivatives (e.g., indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fencloxic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpainac, sulindac, tiopinac, tolmetin, zidometacin and zomepirac), fenamic acid derivatives (e.g., flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives

(e.g., diflunisal and flufenisal), oxicams (e.g., isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (e.g., acetyl salicylic acid and sulfasalazine) and the pyrazolones (e.g., apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone and phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Celebrex®) and rofecoxib (Vioxx®); (h) inhibitors of phosphodiesterase type IV (PDE IV); (i) gold compounds such as auranofin and aurothioglucose, (j) etanercept (Enbrel®), (k) antibody therapies such as orthoclone (OKT3), daclizumab (Zenapax®), basiliximab (Simulect®) and infliximab (Remicade®), (l) other antagonists of the chemokine receptors, especially CCR5, CXCR2, CXCR3, CCR2, CCR3, CCR4, CCR7, CX₃CR1 and CXCR6; (m) lubricants or emollients such as petrolatum and lanolin, (n) keratolytic agents (e.g., tazarotene), (o) vitamin D₃ derivatives, e.g., calcipotriene or calcipotriol (Dovonex®), (p) PUVA, (q) anthralin (Dithrocreme®), (r) etretinate (Tegison®) and isotretinoin and (s) multiple sclerosis therapeutic agents such as interferon β -1 β (Betaseron®), interferon β -1 α (Avonex®), azathioprine (Imurek®, Imuran®), glatiramer acetate (Copaxone®), a glucocorticoid (e.g., prednisolone) and cyclophosphamide (t) DMARDs such as methotrexate (u) other compounds such as 5-aminosalicylic acid and prodrugs thereof; hydroxychloroquine; D-penicillamine; antimetabolites such as azathioprine, 6-mercaptopurine and methotrexate; DNA synthesis inhibitors such as hydroxyurea and microtubule disrupters such as colchicine. The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with an NSAID the weight ratio of the compound of the present invention to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

VI. EXAMPLES

[0093] The following examples are offered to illustrate, but not to limit the claimed invention.

[0094] Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). ¹H-NMR were recorded on a Varian

Mercury 400 MHz NMR spectrometer. Significant peaks are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet) and number of protons. Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative abundance of each ion (in parenthesis). In tables, a single m/e value is reported for the M+H (or, as noted, M-H) ion containing the most common atomic isotopes. Isotope patterns correspond to the expected formula in all cases. Electrospray ionization (ESI) mass spectrometry analysis was conducted on a Hewlett-Packard MSD electrospray mass spectrometer using the HP1100 HPLC for sample delivery. Normally the analyte was dissolved in methanol at 0.1 mg/mL and 1 microlitre was infused with the delivery solvent into the mass spectrometer, which scanned from 100 to 1500 daltons. All compounds could be analyzed in the positive ESI mode, using acetonitrile / water with 1% formic acid as the delivery solvent. The compounds provided below could also be analyzed in the negative ESI mode, using 2mM NH₄OAc in acetonitrile / water as delivery system.

[0095] Compounds within the scope of this invention can be synthesized as described below, using a variety of reactions known to the skilled artisan. A sample of useful routes to both the arylpiperazine subunits and to the heteroaromatic subunit are provided below. In the descriptions of the syntheses that follow, some of the arylpiperazine and pyrazole precursors were obtained from commercial sources. These commercial sources include Aldrich Chemical Co., Acros Organics, Ryan Scientific Incorporated, Oakwood Products Incorporated, Lancaster Chemicals, Sigma Chemical Co., Lancaster Chemical Co., TCI-America, Alfa Aesar, Davos Chemicals, and GFS Chemicals. Some examples of these commercially available compounds are shown in the Figures 4A-4C. Also, standard chemistries have been employed to link the arylpiperazine and heteroaromatic subunits (whether commercially obtained or prepared by the methods below) using a suitably optimized linker, such as the acetyl unit described in the body of this invention.

[0096] One skilled in the art will also recognize that alternative methods may be employed to synthesize the target compounds of this invention, and that the approaches described within the body of this document are not exhaustive, but do provide broadly applicable and practical routes to compounds of interest.

[0097] Certain molecules claimed in this patent can exist in different enantiomeric and diastereomeric forms and all such variants of these compounds are claimed.

[0098] Regioisomerism is a common property in organic chemistry, and is especially common with regards to certain structural types provided herein. Those skilled in the art will recognize, with respect to the compounds described herein, that the coupling reactions with the heteroaromatic ring systems can lead to either one of or a mixture of detectable

5 regioisomers.

[0099] The detailed description of the experimental procedures used to synthesize key compounds in this text lead to molecules that are described by the physical data identifying them as well as by the structural depictions associated with them.

[0100] Two regioisomers can sometimes exist for certain compounds of the invention. For

10 example, compounds such as those of formula III can be prepared wherein the pyrazole moiety is linked to the remainder of the molecule via either of the nitrogen atoms in the pyrazole ring. In these cases, both regioisomeric types have demonstrated biological properties and are meant to be within the scope of all the appended claims, whether explicitly drawn or not.

15 [0101] Those skilled in the art will also recognize that during standard work up procedures in organic chemistry, acids and bases are frequently used. Salts of the parent compounds are sometimes produced, if they possess the necessary intrinsic acidity or basicity, during the experimental procedures described within this patent.

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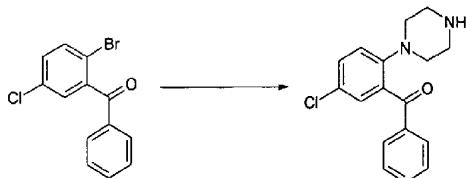
EXAMPLE 1

[0102] The piperazine ring can be formally attached to the terminal aryl unit in a number of ways: by aromatic nucleophilic displacement reactions, metal catalyzed coupling reactions (arylation reactions of secondary amines), ring expansion, rearrangement and cyclization reactions and the like. Also, different protection / deprotection strategies can be utilized.

25 Hence, either all or only part of the final molecular architecture can be present during the key aryl coupling step. Examples for a variety of such aryl coupling strategies are listed below.

PROTOCOL A: Metal catalysed arylation reactions of secondary amines

Synthesis of (5-Chloro-2-piperazin-1-yl-phenyl)-phenyl-methanone



[0103] Piperazine (3.6 g, 42.5mmol), Pd(II)acetate (0.007g, 0.043mmol), sodium t-butoxide (0.22g, 2.4mmol) and BINAP (0.042g, 0.068mmol) were stirred at room

5 temperature in 10 mL dry toluene for 15 min. (2-Bromo-5-chloro-phenyl)-phenyl-methanone (0.5g, 1.7mmol) in 10 mL dry toluene was then added into the reaction mixture. The reaction mixture was refluxed at 110°C for 20 hrs, filtered through a celite bed, washed with toluene, concentrated, taken in ethyl acetate and extracted with 1.5 (N) HCl solution three times. The combined aqueous layers were washed with diethyl ether. The aqueous layer was neutralized
10 with 10% aqueous sodium hydroxide solution and then extracted with ethyl acetate three times. The combined ethyl acetate layers were washed with water and saturated brine solution, dried over anhydrous sodium sulfate and concentrated. Purification by flash chromatography (eluted with CHCl₃-MeOH) afforded the title compound as product.

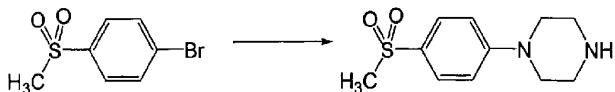
15 **Synthesis of 1-(4-Trifluoromethoxy-phenyl)-piperazine**



[0104] Piperazine (0.588g, 6.84mmol), Pd(II)acetate (0.027g, 0.123mmol), sodium t-butoxide (0.837g, 10.06mmol) and BINAP (0.154g, 0.286mmol) were stirred at room temperature in 10 mL dry toluene for 15 min. 4-trifluoromethoxybromo benzene (1.5 g,

20 6.22mmol) in 10 mL dry toluene was added into the reaction mixture. Then the reaction mixture was refluxed at 110°C for 20 hrs. The reaction mixture was filtered through a celite bed, washed with toluene, concentrated, ethyl acetate added and then extracted with 1.5 (N) aqueous HCl solution three times. The combined aqueous layers were washed with diethyl ether. The aqueous layer was neutralized with 10% aqueous sodium hydroxide solution and
25 then extracted with ethyl acetate three times. The combined ethyl acetate layers were washed with water and saturated brine solution, dried over anhydrous sodium sulfate and concentrated to afford the product.

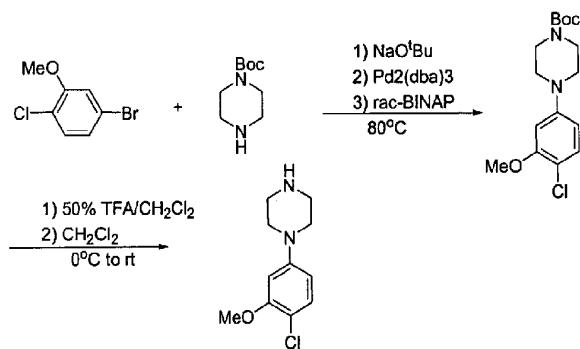
Synthesis of 1-(4-Methanesulfonyl-phenyl)-piperazine



[0105] Piperazine (0.98g, 11.5mmol), Pd(II)acetate (0.017g), sodium t-butoxide (0.37g, 5.2mmol) and BINAP (0.049g) were stirred at room temperature in 10 mL dry toluene for 15 min. 1-Bromo-4-methanesulfonyl-benzene (0.9 g, 3.8mmol) in 10 mL dry toluene was added into the reaction mixture. Then the reaction mixture was refluxed at 110°C for 20 hrs. The reaction mixture was filtered through a celite bed and washed with toluene. The toluene was concentrated and the reaction mixture was taken in ethyl acetate and extracted with 1.5 (N) HCl solution three times. The combined aqueous layers were washed with diethyl ether. The aqueous layer was neutralized with 10% aqueous sodium hydroxide solution and then extracted with ethyl acetate three times. The combined ethyl acetate layers were washed with water and saturated brine solution, dried over anhydrous sodium sulfate, concentrated and chromatographed (9/1-CHCl₃/MeOH) to afford the product.

15

Synthesis of 1-(4-Chloro-3-methoxy-phenyl)-piperazine



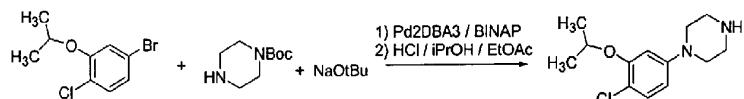
[0106] An oven dried glass vial was charged with 5-Bromo-2-chloroanisole (1.0 mmol), N-Bocpiperazine (1.2 mmol), NaOtBu (1.4 mmol), tris(dibenzylideneacetone)-dipalladium(0) {Pd₂dba₃} (0.0025 mmol, 0.5 mol %) and BINAP (0.0075 mmol), and the vial was then flushed with nitrogen and capped tightly. The mixture was heated to 80°C overnight and then cooled to room temperature, taken up in ether, filtered and concentrated. The crude product

was purified by flash column chromatography on silica gel with ethyl acetate to yield 4-(4-Chloro-3-methoxy-phenyl)-piperazine-1-carboxylic acid tert-butyl ester.

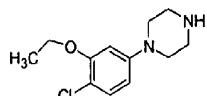
[0107] This product (*ca.* 1 mmol) was dissolved in a methylene chloride (10mL) and the reaction mixture was cooled to 0°C. To the reaction mixture was added TFA:CH₂Cl₂ (2:1)(50% overall) slowly and the reaction was allowed to warm to room temperature. When TLC (1:1 Ethyl acetate: hexane) suggested total consumption of starting material, solvent was removed and the oil residue was taken in ethyl acetate (2 x 25 mL) and washed with saturated aqueous NaHCO₃. The organic layer was dried by MgSO₄ and solvent was removed to yield the title compound as a yellow oil, which solidified on standing. ¹H NMR (400 MHz, CDCl₃): 7.18-7.22 (d, 1H), 6.44-6.48 (d, 1H), 6.36-6.42 (dd, 1H), 4.8 (s, 2H), 6.62-3.8 (m, 4H), 3.46-3.6 (m, 4H). ¹³C NMR (400 MHz, CDCl₃): 164, 158.2, 156.4, 148, 119.2, 117, 52.8, 52.2, 48.5, 46.2, 42, 40.4.

[0108] Similar approaches, using a key Buckwald coupling, were taken for the preparation of related phenylpiperazines, some examples of which are listed below.

Synthesis of 1-(4-Chloro-3-isopropoxy-phenyl)-piperazine

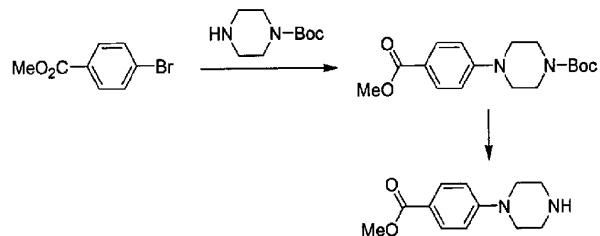


[0109] 1-Bromo-3-isopropoxy-4-chlorobenzene (preparation described elsewhere) was combined with 1.11g (6 mmol) of 1-Bocpiperazine, 672mg (7.0 mmol) of sodium tert-butoxide, 93mg (0.15 mmol) of *rac*-2,2'-Bis(diphenylphosphine)-1,1'-binaphthyl, and 45mg (0.05 mmol) Tris(dibenzylideneacetone)dipalladium (0) in a flask under an N₂ atmosphere, and the mixture was heated at 85°C for 3.5 hours. The resulting residue was partitioned between a 1/1 mixture of ether and ethyl acetate and water, and the phases were separated. The ether/ethyl acetate phase was diluted with one volume of hexanes, washed twice with 0.5M pH = 7 phosphate buffer, and once each with 1M NaOH and brine. The final organic phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to an oil. The oil was dissolved in ethyl acetate, 10mL each of 2M HCl in ether and methanol were added, and the product was isolated by filtration after crystallization. ¹H NMR (D₂O, 400MHz): 7.23 (d, 1H), 6.69 (s, 1H), 6.59 (d, 1H), 4.53 (m, 1H), 3.28 (m, 8H), 1.20 (d, 6H) ppm.

Synthesis of 1-(4-Chloro-3-ethoxy-phenyl)-piperazine

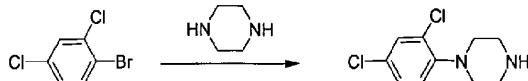
[0110] Title compound was obtained following the same procedure as that used to obtain 1-

5 (4-Chloro-3-isopropoxy-phenyl)-piperazine hydrochloride, with the single modification of adding ethanol in place of isopropanol during the ether-forming reaction. ^1H NMR (D_2O , 400MHz) 7.22 (d, 1H), 6.64 (s, 1H), 6.54 (d, 1H), 4.03 (q, 2H), 3.29 (m, 8H), 1.25 (t, 3H) ppm.

10 Synthesis of 4-Piperazin-1-yl-benzoic acid methyl ester

[0111] BINAP (230mg, 0.37mmol), Pd(II)acetate (417mg, 0.186mmol), tBuONa (1.25g, 13mmol), N-boc piperazine (1.9g, 10.2mmol) and THF (40mL) were mixed together and stirred at room temperature for 30min under a nitrogen atmosphere.

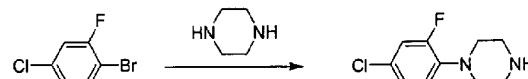
15 4-bromomethyl benzoate (2g, 9.3mmol) in THF (10mL) was added to the mixture drop wise and heated at 70°C for 14h. Excess THF was then evaporated and extracted with ethyl acetate. The crude product was obtained on concentration of the ethyl acetate layer after washing with brine and drying. Flash chromatography on silica gel done eluting with 8% ethyl acetate in petroleum ether yielded pure N-BOC protected product. This intermediate (650mg, 2.01mmol) was dissolved 20 in methanol (20mL) and then HCl saturated ether (7mL) was added. The mixture was stirred at room temperature for 14 hours and concentrated. The concentrate was washed with petroleum ether to obtain white solid compound, 4-Piperazin-1-yl-benzoic acid methyl ester.

Synthesis of 1-(2,4-Dichloro-phenyl)-piperazine

[0112] BINAP (219mg), Pd(II)acetate (397mg, 0.176mmol), tBuONa (1.19g, 12.3mmol), piperazine (837mg, 9.73mmol) and THF (40mL) were mixed together and stirred at room temperature for 30min under nitrogen atmosphere. 2,4-dichlorobromobenzene (2g, 8.84mmol) in THF (10mL) was added to the mixture drop wise and heated at 70°C for 14h. Excess THF was then evaporated and extracted with ethyl acetate. The crude product was obtained on concentration of the ethyl acetate layer after washing with brine and drying. Flash chromatography on silica gel eluting with 2% MeOH in CHCl₃ gave 1-(2,4-Dichloro-phenyl)-piperazine.

Synthesis of 1-(4-Chloro-phenyl)-3-(R)-methyl-piperazine

[0113] A single neck round bottom flask was charged with 1-chloro-4-iodo benzene (1.0 g, 0.0041 mol) and R(-)-2-methylpiperazine (0.5 g, 0.005 mol), potassium t-butoxide (0.705 g, 0.0062 mol), tris(benzylideneacetone)dipalladium(0) (0.095 g, 0.0002 mol) and 1,3 bis(2,6-diisopropylphenyl)imidazole-2-ylidene (0.073 g, 0.0001 mol). The flask was evacuated and filled with nitrogen. Dry dioxane (20 mL) was added and stirred at 70 °C overnight. The reaction mixture was diluted with dichloromethane and filtered. Crude compound was purified by column chromatography. The compound was dissolved in ether and purged with HCl gas to yield 1-(4-Chloro-phenyl)-3-methyl-piperazine.

Synthesis of 1-(4-Chloro-2-Fluorophenyl)-piperazine

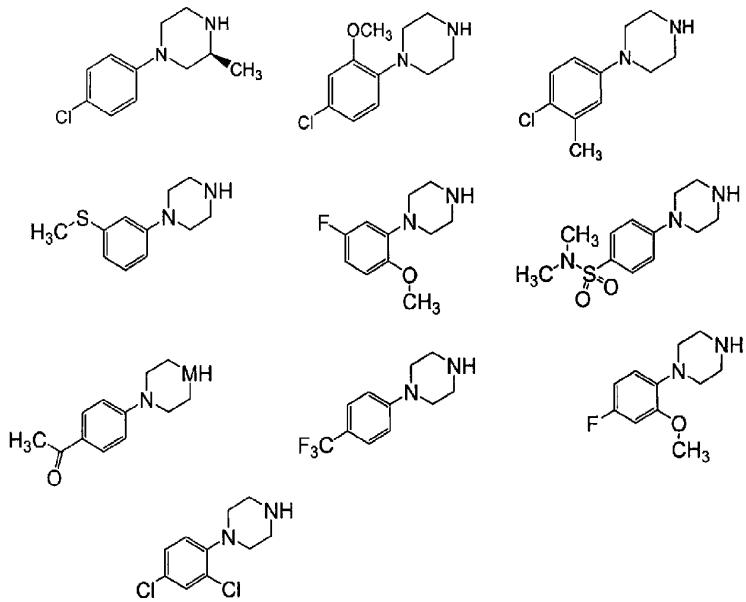
[0114] Piperazine (1.5 g, 17.8mmol), Pd(II)acetate (0.032g , 0.143mmol), sodium t-butoxide (0.688g, 10.06mmol) and BINAP (0.18g, 0.286mmol) were stirred at room temperature in 10 mL dry toluene for 15 min. 1-bromo-4-chloro-2-fluorobenzene (1.5g,

7.15mmol) in 10 mL dry toluene was added into the reaction mixture. Then the reaction mixture was refluxed at 110°C for 20 hrs. The reaction mixture was filtered through a celite bed and washed with toluene, then concentrated and the reaction mixture was taken into ethyl acetate and extracted with 1.5 (N) HCl solution three times. The combined aqueous layer was washed with diethyl ether. The aqueous layer was neutralized with 10% aqueous sodium hydroxide solution and then extracted with ethyl acetate three times. The combined ethyl acetate layers were washed with water and saturated brine solution, dried over anhydrous sodium sulfate, and concentrated to afford the product as a white solid.

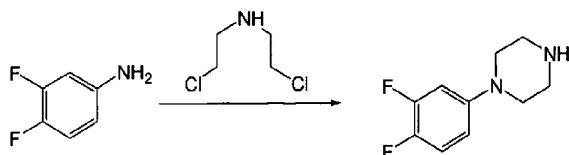
10 **Further examples of arylpiperazines synthesized by metal catalysed arylation methods (PROTOCOL A).**

[0115] Many other arylpiperazine derivatives were prepared in addition to the specific experimental examples listed above using similar Palladium mediated coupling methodologies. Examples are listed below.

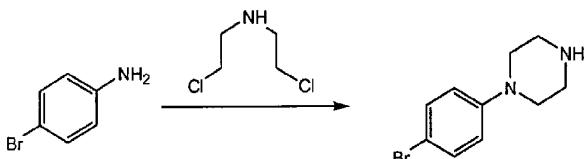
15



PROTOCOL B: Piperidine ring formation via cyclization reactions

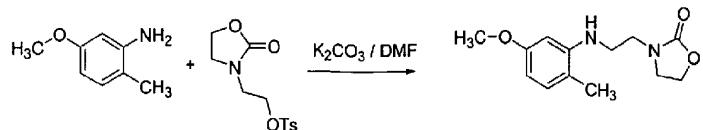
Synthesis of 1-(3,4-Difluoro-phenyl)-piperazine

[0116] 3,4-Difluoro-aniline (1g, 7.7mmol) was dissolved in dry n-butanol (10mL) and dry sodium carbonate (3.2g, 30mmol) was added to it and the reaction mixture stirred for 1 hour under nitrogen. Bis(2-chloroethyl) amine hydrochloride (1.38g, 7.7mmol) in nBuOH (10mL) were then added to the mixture *via* a syringe. The reaction was then heated at 120°C for 48h. The nBuOH was evaporated *in vacuo* and the residue was extracted with ethyl acetate. Drying of the organic layer with Na₂SO₄ followed by concentration afforded the crude product. Purification using flash column chromatography (chloroform/methanol) afforded 1-(3,4-Difluoro-phenyl)-piperazine as an off white solid.

Synthesis of 1-(4-bromo-phenyl)-piperazine

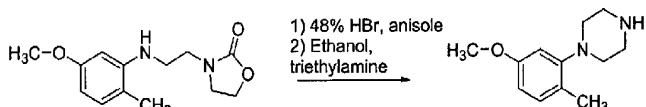
[0117] 4-Bromo-aniline (2g, 1.162mmol) was taken in dry nBuOH (25mL) and dry potassium carbonate (4.8g, 34.8mmol) was added to it and stirred at rt for 1h under nitrogen. Bis-(2-chloroethyl) amine hydrochloride 2 (2.49g, 13.9mmol) in nBuOH (10mL) was then added to the mixture through a syringe. The reaction mass was then heated at 100°C for 12h. nBuOH was evaporated in vacuo and the residue was extracted with ethyl acetate. Drying of the organic layer with Na₂SO₄ followed by concentration afforded the crude product that on 20 purification silica gel column (chloroform/methanol) afforded the title compound.

PROTOCOL C: Piperidine ring formation *via* a ring opening / ring cyclization strategy**Synthesis of 3-[2-(5-Methoxy-2-methyl-phenylamino)-ethyl]-oxazolidin-2-one:**



[0118] To a flask was added 2.95g (10.3 mmol) of Toluene-4-sulfonic acid, 2-(2-oxo-oxazolidin-3-yl)-ethyl ester, 1.56g (11.4 mmol) of 2-methyl-5-methoxyaniline, 2.58g (18.7 mmol) of potassium carbonate, and 22mL of anhydrous dimethylformamide, and the mixture was heated at 100 °C for seven hours. The reaction was allowed to cool to room temperature, and was partitioned between ethyl acetate and water. The phases were separated, and the ethyl acetate phase was washed with brine, dried over Na₂SO₄, filtered, and concentrated to an oil. The oil was purified by chromatography (120mL silica, 60 ethyl acetate / 40 hexanes) to give the corresponding product as a clear oil that solidified upon drying: ¹H NMR (DMSO-*d*6, 400MHz) 6.81 (d, 1H), 6.11 (s, 1H), 6.04 (d, 1H), 4.92 (t, 1H), 4.21 (t, 2H), 3.65 (s, 3H), 3.59 (m, 2H), 3.31 (m, 2H), 3.23 (m, 2H), 1.95 (s, 3H) ppm.

Synthesis of 1-(5-Methoxy-2-methyl-phenyl)-piperazine

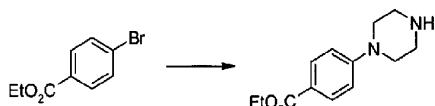


[0119] To 505mg (2.0 mmol) of 3-[2-(5-Methoxy-2-methyl-phenylamino)-ethyl]-oxazolidin-2-one in a flask was added 2mL of 48% HBr in acetic acid, 1mL of acetic acid, and 1 mL of anisole, and the mixture was heated at 90°C for six hours. The solution was allowed to cool to room temperature, and 5mL of CH₂Cl₂ was added. The product crystallized and was isolated by filtration. The solids were dissolved in 55mL of ethanol, 201 mg (2 mmol) of triethylamine were added, and the solution was heated at reflux for 3 hours. The solution was then concentrated *in vacuo* to give a residue that was partitioned between ether and water. The phases were separated, and the aqueous phase was basified with 1M NaOH. The aqueous phase was then extracted twice with ethyl acetate. The combined ethyl acetate phases were washed once with brine, dried over Na₂SO₄, filtered, and acidified with 2M HCl in ether. The product was isolated via filtration.

Addition of various piperazines to aryl halides and heteroaryl halides via aryl-halogen displacement methodologies

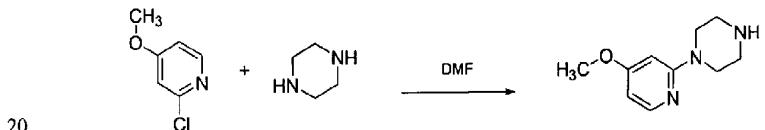
[0120] A direct halogen displacement strategy, with thermal assistance if necessary, can be complimentary to the metal mediated approaches, discussed above, for the construction of the ring systems provided herein.

5 **Synthesis of 4-Piperazin-1-yl-benzoic acid ethyl ester**



[0121] To 4-bromobenzoic acid (25g) and ethanol (1000mL) was added conc.sulfuric acid (20g) drop wise. The reaction mixture was heated at 85 °C overnight. The reaction was cooled and ethanol was removed by distillation and the reaction mixture quenched with water and extracted with ethyl acetate. The extract was washed with 10% sodium bicarbonate, water, brine and then concentrated to yield the crude ester. 4-bromoethyl benzoate (10.0 g, 0.0437 mol) was taken into 250 mL of dry DMF, pipcrazine (37g, 0.437 mol) was added, followed by 30g (0.2185 mol) of dry potassium carbonate, 1.0 g of TBAI and 1.5 g of potassium iodide. The reaction mixture was heated at 135 °C for over night. The reaction mixture was quenched with water and extracted with ethyl acetate. The extracts were washed with water, then brine and then concentrated to yield 4-Piperazin-1-yl-benzoic acid ethyl ester as an off-white solid.

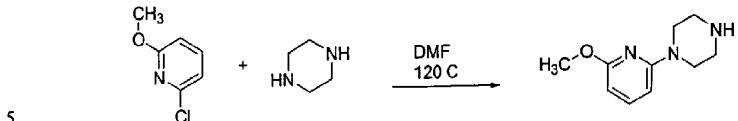
Synthesis of 1-(4-Methoxy-pyridin-2-yl)-piperazine:



[0122] To 756 mg (5.29 mmol) of 2-Chloro-4-methoxypyridine and 2.27g (26 mmol) of piperazine in a pressure flask was added 2.7mL dimethylformamide, and the mixture was heated at 115°C for 5 hours. The solution was allowed to cool before opening the flask, and the resulting slurry was partitioned between ethyl acetate and water. The phases were separated, and the aqueous phase was back-extracted once with ethyl acetate. The combined ethyl acetate phases were washed once with brine, dried over Na₂SO₄, filtered, and the filtrate was acidified with 2M HCl in ether. The product crystallized over night, and the

solids were isolated by filtration to yield product as a white solid: ^1H NMR (D_2O , 400MHz) 7.72 (d, 1H), 6.61 (d, 1H), 6.48 (s, 1H), 3.88 (s, 3H), 3.79 (m, 4H), 3.36 (m, 4H) ppm.

Synthesis of 1-(3-Methoxy-pyridin-2-yl)-piperazine:



[0123] To 966 mg (6.7 mmol) of 2-Chloro-6-methoxypyridine and 2.90 g (34 mmol) of piperazine in a pressure flask was added 3.3mL dimethylformamide, and the mixture was heated at 115°C for 5 hours. The solution was allowed to cool before opening the flask, and the resulting slurry was partitioned between ethyl acetate and water. The phases were

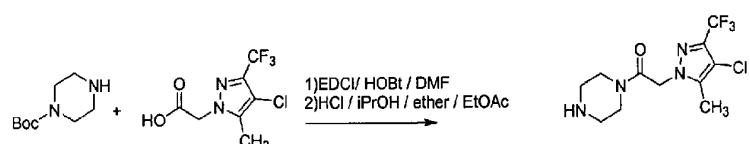
10 separated, and the aqueous phase was back-extracted once with ethyl acetate. The combined ethyl acetate phases were washed once with brine, dried over Na_2SO_4 , filtered, and the filtrate was acidified with 2M HCl in ether. The product crystallized overnight, and was isolated by filtration to give a white solid: ^1H NMR (D_2O , 400MHz) 7.73 (t, 1H), 6.52 (d, 1H), 6.31 (d, 1H), 3.81 (s, 3H), 3.68 (m, 4H), 3.26 (m, 4H) ppm.

15

PROTOCOL D: Synthesis and addition of elaborated piperazines to aryl and heteroaryl halides via aryl-halogen displacement methodologies

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-piperazin-1-yl-ethanone

20

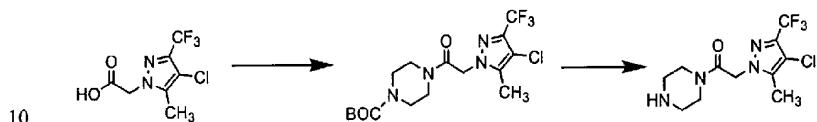


[0124] To a solution of 1.69g (9.1 mmol) Boc-piperazine, 2.0g (8.3 mmol) of (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid, and 1.12g (8.3 mmol) of 1-Hydroxybenzotriazole in 20mL of dimethylformamide at 0°C was added 1.73g (9.1 mmol) 25 of 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The reaction was allowed to stir and warm to room temperature over night, then was partitioned between ether and water. The phases were separated, and the ether phase was washed once each with 1M HCl,

water, 1M NaOH, and brine. The ether phase was then dried over Na₂SO₄, filtered, and concentrated to a residue.

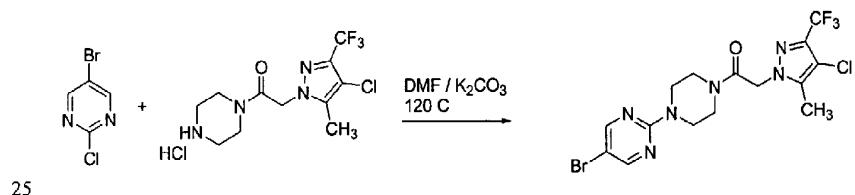
[0125] This crude residue was dissolved in 20mL ether and 8mL ethyl acetate, and 20mL of 5M HCl in isopropanol was added. After 1 hour the mixture was placed in the freezer over 5 night. The product was isolated by filtration to give a white solid. ¹H NMR (DMSO-*d*6, 400MHz) 9.21 (br s, 2H), 5.38 (s, 2H), 3.69 (m, 4H), 3.32 (m, 4H), 2.20 (s, 3H) ppm.

Alternative synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-piperazin-1-yl-ethanone



[0126] (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid (1.5g, 6.18mmol) was taken in dry DCM (20mL) and cooled to 0°C. To this cold mixture was added N-boc piperazine (1.15g, 6.18mmol) followed by addition of T3P (8g, 12.4mmol, 50% solution in EtOAc). The reaction was left overnight at rt. The mixture was diluted with CH₂Cl₂, washed with NaHCO₃ soln, brine, dried (Na₂SO₄) and concentrated to afford the crude product that was washed thoroughly with ether-pet ether to afford 4-[2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetyl]-piperazine-1-carboxylic acid tert-butyl ester (1.2g, 2.9mmol). This was dissolved in methanol (25mL) cooled to 0°C and HCl saturated ether (3mL) was added to it. The mixture was stirred at room temperature for 4h and concentrated. 20 Crystallization from MeOH / Petroleum ether yielded product.

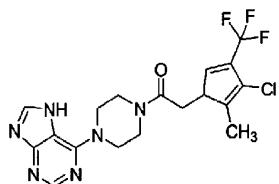
Synthesis of 1-[4-(5-Bromo-pyrimidin-2-yl)-piperazin-1-yl]-2-(4-chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone (PROTOCOL D)



[0127] To 86mg (0.25 mmol) of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-piperazin-1-yl-ethanone hydrochloride, 76mg (0.6 mmol) potassium carbonate, and 48mg (0.3 mmol) of 5-Bromo-2-chloropyrimidine in a vial was added 0.7mL anhydrous dimethylformamide, and the mixture was heated at 120°C for 12 hours. The reaction was 5 allowed to cool to room temperature, and was partitioned between ethyl acetate and water. The phases were separated, and the aqueous phase was back-extracted once with ethyl acetate. The combined ethyl acetate phases were washed once each with water, 0.5M pH = 7 phosphate buffer, water, 1M NaOH, and brine. The ethyl acetate phase was dried over Na₂SO₄, filtered, and acidified with 2M HCl in ether to precipitate the product as a powder: 10 ¹H NMR (DMSO-d₆, 400MHz) 8.48 (s, 2H), 5.37 (s, 2H), 3.81 (m, 2H), 3.72 (m, 2H), 3.57 (m, 4H), 2.18 (s, 3H) ppm; MS (ES) M+H expected = 467.0, found 466.9.

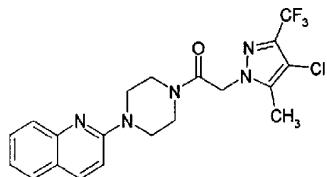
Additional compounds of the invention prepared by the aryl-halogen displacement method

15 **Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(7H-purin-6-yl)piperazin1-yl]-ethanone:**



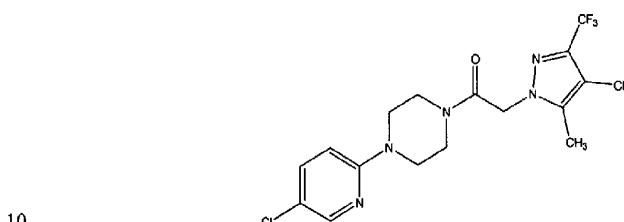
[0128] Title compound was prepared following protocol D, wherein 6-Chloropurine was 20 used as the heteroaryl halide component: ¹H NMR (DMSO-d₆, 400MHz) 8.23 (s, 1H), 8.14 (s, 1H), 5.39 (s, 2H), 4.32 (br, 2H), 4.22 (br, 2H), 3.60 (m, 4H), 2.19 (s, 3H) ppm; MS (ES) expect M+H = 429.1, found 429.0.

25 **Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-(4-quinolin-2-yl-piperazin-1-yl)ethanone:**



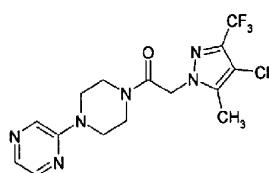
[0129] Title Compound was prepared following protocol D, wherein 2-Chloroquinoline was used as the heteroaryl halide component: ^1H NMR (DMSO-d6, 400MHz) 8.44 (d, 1H), 8.29 (br, 1H), 7.91 (d, 1H), 7.77 (t, 1H), 7.57 (d, 1H), 7.48 (t, 1H), 5.44 (s, 2H), 4.14 (br, 2H), 5 4.01 (br, 2H), 3.78 (br, 2H), 3.70 (br, 2H), 2.20 (s, 3H) ppm; MS (ES) expect M+H = 438.1, found 438.0.

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(5-chloropyridin-2-yl)piperazin-1-yl]ethanone:



[0130] Title compound was prepared following protocol D, wherein 2,5-Dichloropyridine was used as the heteroaryl halide component: MS (ES) expect M+H = 422.1, found = 422.0; HPLC retention time = 4.75 minutes (Agilent Zorbax SB-C18, 2.1X50mm, 5 μ , 35°C) using a 4.5 minute gradient of 20% to 95% B with a 1.1 minute wash at 95% B (A = 0.1% formic acid / 5% acetonitrile / 94.9% water, B = 0.08% formic acid / 99.9% acetonitrile).
15

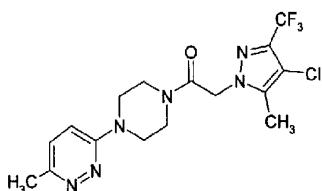
Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)ethanone:



[0131] Title compound was prepared following protocol D, wherein 2-Chloropyrazine was used as the heteroaryl halide component: ^1H NMR (DMSO-d6, 400MHz) 8.34 (s, 1H), 8.09 (d, 1H), 7.85 (d, 1H), 5.38 (s, 2H), 3.68 (m, 2H), 3.58 (m, 4H), 3.44 (m, 2H), 2.19 (s, 3H) ppm; MS (ES) expect $\text{M}+\text{H} = 389.1$, found 389.0.

5

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(6-methyl-pyridazin-3-yl)-piperazin-1-yl]-ethanone:

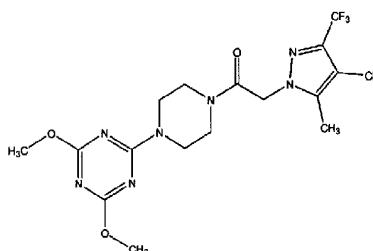


[0132] Title compound was prepared following protocol D, wherein 3-Chloro-6-

10 methylpyridazine was used as the heteroaryl halide component: MS (ES) expect $\text{M}+\text{H} = 403.1$, found = 403.0; HPLC retention time = 1.68 minutes (Agilent Zorbax SB-C18, 2.1X50mm, 5 μ , 35°C) using a 4.5 minute gradient of 20% to 95% B with a 1.1 minute wash at 95% B (A = 0.1% formic acid / 5% acetonitrile / 94.9% water, B = 0.08% formic acid / 99.9% acetonitrile).

15

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-piperazin-1-yl]-ethanone:



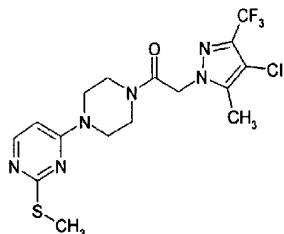
[0133] Title compound was prepared following protocol D, wherein 2-Chloro-4,6-

20 dimethoxytriazine was used as the heteroaryl halide component: MS (ES) expect $\text{M}+\text{H} = 450.1$, found = 450.0; HPLC retention time = 4.24 minutes (Agilent Zorbax SB-C18, 2.1X50mm, 5 μ , 35°C) using a 4.5 minute gradient of 20% to 95% B with a 1.1 minute wash

at 95% B (A = 0.1% formic acid / 5% acetonitrile / 94.9% water, B = 0.08% formic acid / 99.9% acetonitrile).

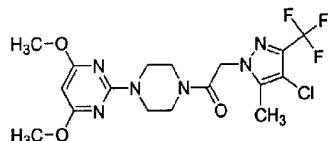
Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(2-

5 methylsulfanyl-pyrimidin-4-yl]-piperazin-1-yl]-ethanone:



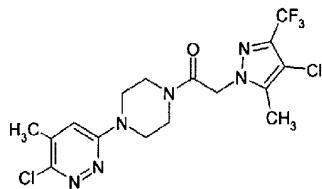
[0134] Title compound was prepared following protocol D, wherein 4-Chloro-2-methylthiopyrimidine was used as the heteroaryl halide component: ¹H NMR (DMSO-d6, 400MHz) 8.16 (d, 1H), 6.87 (d, 1H), 5.41 (s, 2H), 3.90 (br m, 4H), 3.62 (m, 4H), 2.57 (s, 10 3H), 2.19 (s, 3H) ppm; MS (ES) expect M+Na = 435.1, found 435.0.

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4,6-dimethoxy-pyrimidin-2-yl)-piperazin-1-yl]-ethanone:



15 [0135] Title compound was prepared following protocol D, wherein 2-Chloro-4,6-dimethoxypyrimidine was used as the heteroaryl halide component: MS (ES) expect M+H = 449.1, found = 449.0; HPLC retention time = 4.92 minutes (Agilent Zorbax SB-C18, 2.1X50mm, 5μ, 35°C) using a 4.5 minute gradient of 20% to 95% B with a 1.1 minute wash at 95% B (A = 0.1% formic acid / 5% acetonitrile / 94.9% water, B = 0.08% formic acid / 20 99.9% acetonitrile).

Synthesis of 1-[4-(6-Chloro-5-methyl-pyridazin-3-yl)-piperazin-1-yl]-2-(4-chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone:

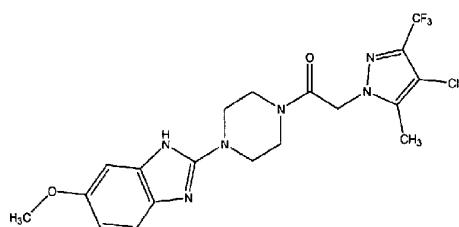


[0136] Title compound was prepared following protocol D, wherein 3,6-Dichloro-4-methylpyridazine was used as the heteroaryl halide component: MS (ES) expect M+H = 437.1, found = 437.0; HPLC retention time = 4.17 minutes (Agilent Zorbax SB-C18,

5 2.1X50mm, 5 μ , 35°C) using a 4.5 minute gradient of 20% to 95% B with a 1.1 minute wash at 95% B (A = 0.1% formic acid / 5% acetonitrile / 94.9% water, B = 0.08% formic acid / 99.9% acetonitrile).

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(5-methoxy-1-H-

10 **benzimidazol-2-yl)-piperazin-1-yl]-ethanone:**



[0137] Title compound was prepared following protocol D, wherein 2-Chloro-5-methoxybenzimidazole was used as the heteroaryl halide component: MS (ES) expect M+H = 457.1, found = 457.0; HPLC retention time = 2.85 minutes (Agilent Zorbax SB-C18,

15 2.1X50mm, 5 μ , 35°C) using a 4.5 minute gradient of 20% to 95% B with a 1.1 minute wash at 95% B (A = 0.1% formic acid / 5% acetonitrile / 94.9% water, B = 0.08% formic acid / 99.9% acetonitrile).

Further functionalization of arylpiperazine ring system after its formal construction

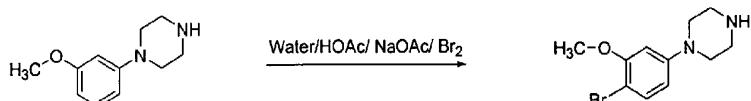
20

[0138] Key compounds of the current invention have, in addition to other selected substituents, a halogen atom at the 2- or 4-position. Approaches to install this are described in the following section.

[0139] Functionalization of the aryl ring within the arylpiperazine ring system can, in general, take place either before or after introduction of the piperazine ring, as illustrated in the examples below.

5 **PROTOCOL E: Selected examples of halogenation of aromatic systems after attachment of the piperazine ring system**

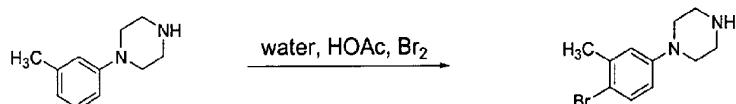
Synthesis of 1-(4-Bromo-3-methoxy-phenyl)-piperazine hydrochloride:



10 [0140] To a solution of 2.33g (8.8 mmol) of 1-(3-Methoxyphenyl)piperazine dihydrochloride and 756mg (9.7 mmol) sodium acetate in 70 mL of acetic acid and 15 mL of water at 0°C was added 1.55g (9.7 mmol) bromine. After 1 hour, the reaction was concentrated to an oil *in vacuo*, and the oil was partitioned between ethyl acetate and 1M NaOH. The phases were separated, and the ethyl acetate phase was washed once each with water and brine, dried over Na₂SO₄, filtered, and the filtrate was concentrated to an oil *in vacuo*. The oil was dissolved in a minimum volume of methanol, and the solution was acidified with 2M HCl in ether. The product was isolated by filtration. ¹H NMR (D₂O, 400MHz) 7.36 (d, 1H), 6.73 (s, 1H), 6.50 (d, 1H), 3.75 (s, 3H), 3.32 (m, 8H) ppm.

15

20 **Synthesis of 1-(4-Bromo-3-methyl-phenyl)-piperazine hydrochloride:**

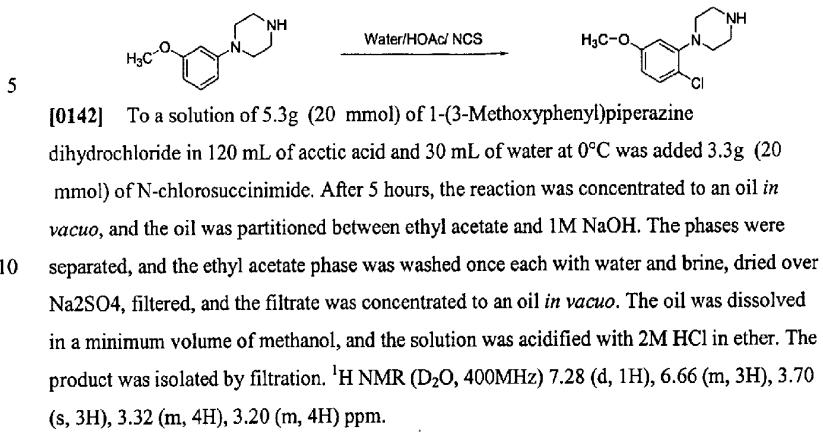


[0141] To a solution of 966 mg (4.0 mmol) of 1-(3-Methylphenyl)piperazine dihydrochloride in 9 mL of acetic acid and 1 mL of water at 0°C was added 640mg (4.0 mmol) of bromine. After 1 hour, the reaction was concentrated to an oil *in vacuo*, and the oil was partitioned between ethyl acetate and 1M NaOH. The phases were separated, and the ethyl acetate phase was washed once each with water and brine, dried over Na₂SO₄, filtered, and the filtrate was concentrated to an oil *in vacuo*. The oil was dissolved in a minimum volume of methanol, and the solution was acidified with 2M HCl in ether. The product was

25

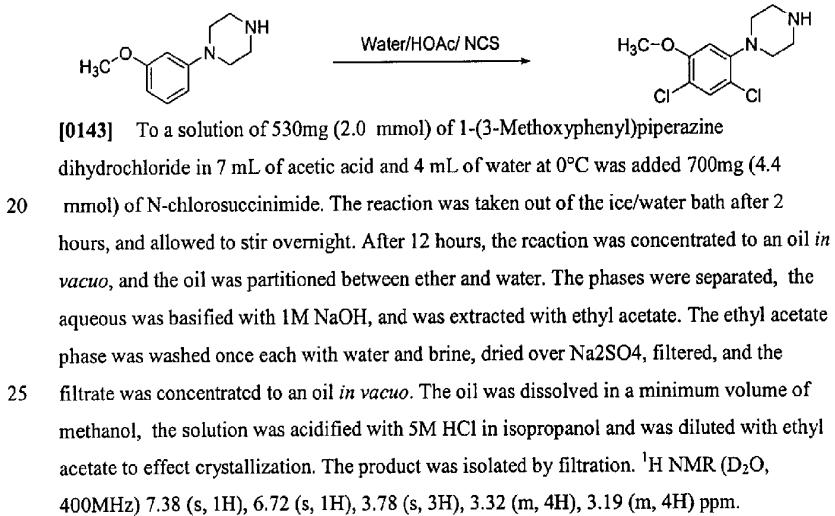
isolated by filtration. ^1H NMR (D_2O , 400MHz) 7.37 (d, 1H), 6.85 (s, 1H), 6.76 (d, 1H), 3.37 (m, 8H), 2.17 (s, 3H) ppm.

Synthesis of 1-(2-Chloro-5-methoxy-phenyl)-piperazine hydrochloride:



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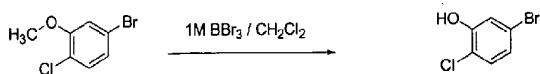
Synthesis of 1-(2,4-Dichloro-5-methoxy-phenyl)-piperazine hydrochloride:



PROTOCOL F: Selected examples of demethylation / etherification of aromatic precursors for attachment of the piperazine ring system to access key arylpiperazine moieties

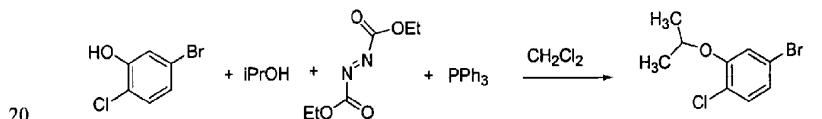
5

Synthesis of 3-Bromo-6-chlorophenol:



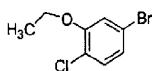
[0144] To 50 mL of a 1M solution of boron tribromide in CH₂Cl₂ at 0°C was added 5.71g (25.8 mmol) of 5-Bromo-2-chloroanisole. After 2 hours, the reaction was allowed to warm to room temperature. After 5 hours, the solution was cooled to 0°C, and quenched with methanol. The resulting solution was partitioned between water and ethyl acetate, and the phases were separated. The aqueous phase was back-extracted once with ethyl acetate. The combined ethyl acetate phases were diluted with one volume of ether, and were extracted twice with 1M NaOH. The combined basic aqueous phases were acidified with 12M HCl, and were extracted once with ethyl acetate. The final ethyl acetate phase was washed once with brine, dried over MgSO₄, filtered, and concentrated to give the phenol as a tan solid. ¹H NMR (DMSO-*d*6, 400MHz) 10.66 (s, 1H), 7.27 (d, 1H), 7.08 (s, 1H), 6.95 (d, 1H) ppm.

Synthesis of 1-Bromo-3-isopropoxy-4-chlorobenzene:



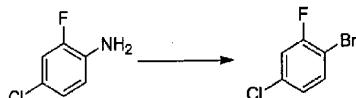
[0145] To 1.70g (6.5 mmol) of triphenylphosphine in 25mL of CH₂Cl₂ at 0°C was added 1.14g (6.5 mmol) of diethylazodicarboxylate. After 10 minutes, 390mg (6.5 mmol) of isopropanol was added, followed rapidly by 1.03g (5.0 mmol) of 3-Bromo-6-chlorophenol. The reaction was complete within three hours, and was partitioned between ether and water. The phases were separated, and the ether phase was diluted with hexanes and washed twice with 10% aqueous methanol and once with brine. The ether/hexanes phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield product as a clear oil.

PROTOCOL F: Additional examples of analogous ring systems constructed using similar demethylation / etherification strategies.



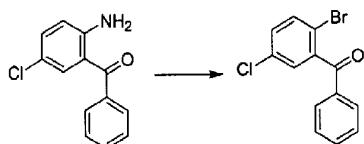
5 **PROTOCOL G: General procedure for the synthesis of elaborated aryl bromides from anilines**

Synthesis of 4-Chloro-2-fluoro-1-bromobenzene



10 [0146] Sodium nitrite (2.35 g, 34.13mmol) solution (40 mL) was added dropwise to 4-Chloro-2-fluoro aniline (4.5g, 31mmol) in 170 mL HBr at -10°C bath temperature, then the mixture was stirred for 30 min at -10°C bath temperature. In parallel, copper sulfate (10.22g, 24.29mmol) and sodium bromide (3.79 g, 36.8mmol) were mixed and the reaction mixture was heated at 60°C for 30 min. Then sodium sulfite (2.66g, 21.2mmol) was added into this 15 copper sulfate reaction mixture and heated for 95°C for 30 min. The reaction mixture was cooled to room temperature and solid formed was washed with water to afford white solid cuprous bromide. The diazonium salt was portion wise added into the freshly prepared cuprous bromide in 40 mL HBr at -10°C bath temperature and the reaction mixture was then warmed to room temperature. The reaction mixture was heated at 55°C for 20 min, cooled 20 and then extracted with ethyl acetate three times. The combined organic layer was washed with water and saturated brine solution, dried over sodium sulfate and concentrated. The crude material was purified by column chromatography (5:95 ethyl acetate: pet ether) to afford solid product.

25 **Synthesis of (2-Bromo-5-chloro-phenyl)-phenyl-methanone**

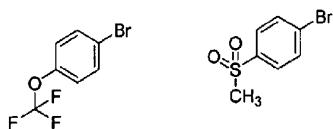


[0147] Sodium nitrite (2.5 g, 36.28mmol) solution (40 mL) was dropwise added to the aniline (7g, 30.2mmol) in 100 mL HBr at -10°C bath temperature, then the mixture was stirred for 30 min at -10°C bath temperature to make diazonium salt.

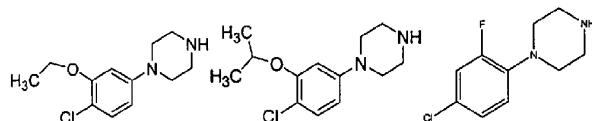
[0148] Copper sulfate (10.22g, 24.29mmol) and sodium bromide (3.79 g, 36.8mmol) was 5 heated at 60°C for 30 min. Then sodium sulfite (2.66g, 21.2mmol) was added into copper sulfate reaction mixture and heated for 95°C for 30 min. Then the reaction mixture was cooled to rt and solid formed was washed with water to afford white solid cuprous bromide.

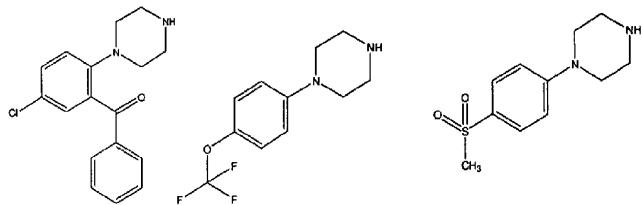
[0149] Diazonium salt was portion wise added into the freshly prepared cuprous bromide in 40 mL HBr at -10°C bath temperature and the reaction mixture warmed to room temperature. 10 Then the reaction mixture was heated at 55°C for 20 min, cooled to room temperature and extracted with ethyl acetate three times. The combined organic layer was washed with water and saturated brine solution, dried over sodium sulfate and concentrated. The product was purified by crystallization from DCM/Pet ether.

15 **PROTOCOL G: Additional examples of analogous ring systems constructed using similar Sandmeyer type strategies**



[0150] These preceding aryl bromides and similar substrates were used in a variety of 20 chemistries, already described, to access arylpiperazines such as those listed below.





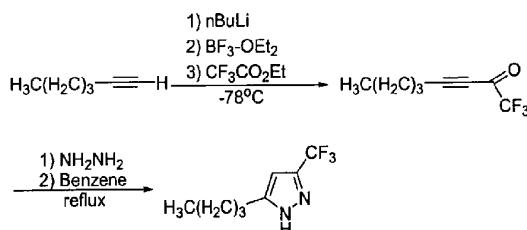
Synthesis of heteroaromatic ring systems: core ring structure formation

5 [0151] The types of chemistries which can be applied to synthesize the key heteroaryl ring structures are listed below. They are separated into examples of ring formation and ring functionalization reactions.

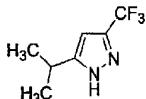
PROTOCOL H: Pyrazole synthesis via addition of hydrazines to α,β -acetylenic ketones

10

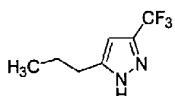
Synthesis of 5-Butyl-3-trifluoromethyl-1H-pyrazole



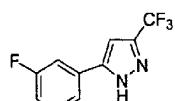
[0152] To a solution of 1-Hexyne (3.37 mL, 29.4 mmol) in THF (30 mL) was added n-BuLi (2.78 M, 10.2 mL, 29.4 mmol). The solution was stirred at -78°C for 30 minutes then 15 CF₃CO₂Et (3.5 mL, 29.35 mL) and BF₃-OEt₂ were added successively. The reaction was further stirred at -78°C for 2h and was quenched with satd. NH₄Cl. It was then warmed up to the room temperature. The THF was removed, the residue taken into ether, washed with saturated brine solution, dried over Na₂SO₄ and reduced. The crude product was then dissolved in benzene (25 mL) and hydrazine (29.4 mmol) was added. The reaction mixture 20 was refluxed overnight, then cooled, the solvent evaporated, and the residue taken into CH₂Cl₂ (30 mL), washed with brine, dried over Na₂SO₄ and concentrated to give the title compound as colorless oil.

Synthesis of 5-isopropyl-3-trifluoromethyl-1H-pyrazole.

[0153] Following protocol H, 3-methylbutyne was treated with n-BuLi, CF₃CO₂Et and BF₃-OEt₂ in THF. Reaction with hydrazine in benzene under similar reaction conditions 5 yielded title compound.

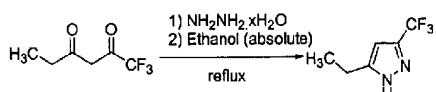
Synthesis of 5-propyl-3-trifluoromethyl-1H-pyrazole.

[0154] Following protocol H, 1-pentyne was treated with n-BuLi, CF₃CO₂Et and BF₃-OEt₂ 10 in THF. Reaction with hydrazine in benzene under similar reaction conditions yielded title compound.

Synthesis of 5-(3-Fluorophenyl)-3-trifluoromethyl-1H-pyrazole.

[0155] Following protocol H, 1-Ethynyl-3-fluoro-benzene was treated with n-BuLi, 15 CF₃CO₂Et and BF₃-OEt₂ in THF. Reaction with hydrazine in benzene under similar reaction conditions yielded title compound.

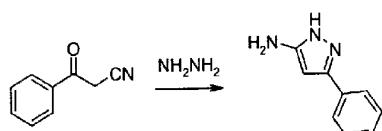
PROTOCOL I: General procedure for the synthesis of pyrazoles via condensation of 20 hydrazines with β -diketones:

Synthesis of 5-ethyl-3-trifluoromethyl-1H-pyrazole

[0156] To a solution of 1,1,1-Trifluoro-hexane-2,4-dione (1 g, 5.95 mmol) in absolute ethanol (10 mL) was added $\text{NH}_2\text{NH}_2 \cdot x\text{H}_2\text{O}$ drop-wise at 0°C. The reaction mixture warmed to the room temperature during 1 hour and refluxed overnight. Ethanol was then evaporated, residue dissolved in ethyl acetate (20 mL), washed consecutively with saturated brine solution and water, dried with Na_2SO_4 and concentrated to give the title compound as colorless oil.

PROTOCOL J: Pyrazole synthesis via condensation of hydrazines with β -Cyanoketones

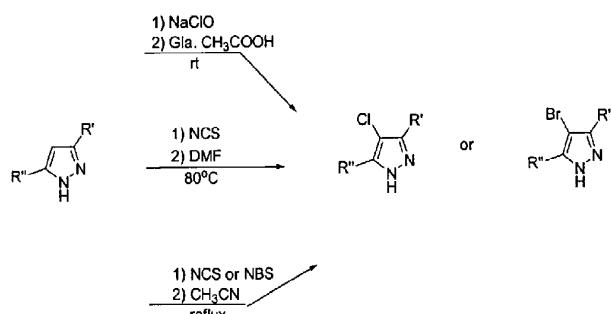
10 **Synthesis of 5-Phenyl-1-pyrazol-3-amine**

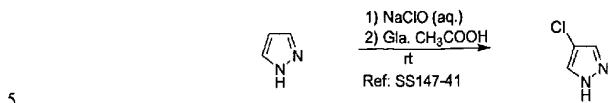


[0157] 2.0 g (0.0138 mol, 1eq) of benzoylacetonitrile in 40 mL of absolute ethanol was added 2.0 g (0.0399 mol, 3eq) of anhydrous hydrazine and the reaction mixture stirred at 85°C for 2 h. Ethanol was removed at 50 °C under vacuum. 5-Phenyl-1-pyrazol-3-amine, obtained as a yellow solid, was washed with pet ether (100 mL) and dried under vacuum.

Synthesis of functionalized heteroaryl ring systems

Chlorination or bromination of Pyrazoles



PROTOCOL K: chlorination of pyrazoles with NaOCl in glacial Acetic acid**Synthesis of 4-Chloro-1H-pyrazole.**

[0158] To a solution of pyrazole (0.5 g, 7.34 mmol) in glacial acetic acid (4 mL) was added NaOCl (0.55 g, 7.34 mmol). The reaction mixture was left at room temperature for 18h, then neutralized with saturated Na₂CO₃ solution, extracted with CH₂Cl₂ (2 x 25 mL), the combined organic layers evaporated, then diluted with NaOH, and further extracted with CH₂Cl₂ (3 X 20 mL). The organic extracts were combined, dried over Na₂SO₄ and evaporated to give the title compound as a white solid.

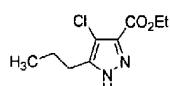
10

Synthesis of 4-Chloro-3-trifluoromethyl-1H-pyrazole

15 [0159] Following protocol K, 3-trifluoromethylpyrazole was treated with glacial acetic acid and NaOCl, yielding title compound.

Synthesis of 4-Chloro-3-methyl-1H-pyrazole.

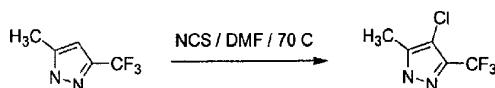
20 [0160] Following protocol K, 3-methylpyrazole was treated with glacial acetic acid and NaOCl, yielding title compound.

Synthesis of 4-Chloro-5-propyl-1H-pyrazole-3-carboxylic acid ethyl ester.

[0161] Following protocol K, 5-propyl-1H-pyrazole-3-carboxylic acid ethyl ester was treated with glacial acetic acid and NaOCl under similar reaction conditions, yielding the title compound.

5 **PROTOCOL L: chlorination or bromination of pyrazoles with N-chlorosuccinimide (NCS) or N-bromosuccinimide (NBS):**

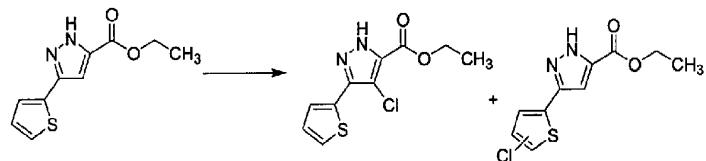
Synthesis of 4-Chloro-3-methyl-5-trifluoromethyl-1H-pyrazole



10 [0162] 3-methyl-5-trifluoromethylpyrazole was taken into dry DMF (20mL) and N-chloro succinimide (1.78g) was added in portions. The mixture was then heated at 70°C for 22h, cooled to room temperature, and then water (100mL) was added and the mixture extracted with ethyl acetate (4X25mL). The organic layer was washed with water and brine and dried with Na₂SO₄. Evaporation of the solvent afforded the title compound.

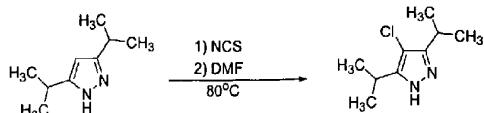
15

Syntheses of 4-Chloro-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester



[0163] Pyrazole(1eq) in DMF (0.14M Solution) was treated with NCS (1.5 eq.) in portions, and when all the NCS was dissolved in the reaction mixture, it was then heated at 70°C overnight. The reaction mixture was then cooled to rt and quenched with water, extracted with ethyl acetate and dried in MgSO₄. Two products were isolated, including the title compound

Synthesis of 4-Chloro-3, 5-diisopropyl-pyrazole



[0164] Following protocol L, a the solution of 3, 5-diisopropyl-pyrazole (0.5 g , 3.57 mmol) in DMF (10 mL) was added NCS (0.72 g , 5.3 mmol) in portions under vigorous stirring. The reaction mixture was then heated at 80°C for 14h and then the reaction was 5 quenched with water. It was then extracted with ethyl acetate (2 x 30 mL). The combined organics were washed with brine. The organic extracts were combined and dried with Na₂SO₄ and finally evaporated to give the title compound as colorless oil.

Synthesis of 4-Chloro-3-thiophen-2-yl-1H-pyrazole.



[0165] Following protocol L, 3-thiophen-2-yl-1H-pyrazole was treated with NCS in DMF., to yield title compound.

Synthesis of 5-tert-Butyl-4-chloro-3-trifluoromethyl-1H-pyrazole.



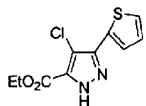
[0166] Following protocol L, 5-tert-butyl-3-trifluoromethyl-1H-pyrazole was treated with NCS in DMF to yield title compound.

Synthesis of 4-Chloro-3-methyl-1H-pyrazole-5-carboxylic acid ethyl ester.



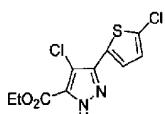
[0167] Following protocol L, 3-methyl-2H-pyrazole-5-carboxylic acid ethyl ester was treated with NCS in DMF to yield the title compound.

Synthesis of 4-Chloro-3-thiophen-2-yl-1H-pyrazole-5-carboxylic acid ethyl ester.



[0168] Following protocol L, 3-Thiophen-2-yl-1H-pyrazole-5-carboxylic acid ethyl ester was treated with NCS in DMF to yield the title compound.

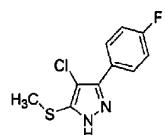
5 **Synthesis of 4-Chloro-5-(5-chloro-thiophen-2-yl)-2H-pyrazole-3-carboxylic acid ethyl ester.**



[0169] Following protocol L, 3-Thiophen-2-yl-1H-pyrazole-5-carboxylic acid ethyl ester was treated with NCS in DMF under to yield the title compound.

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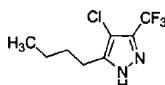
Synthesis of 4-Chloro-3-(4-fluoro-phenyl)-5-methylsulfanyl-1H-pyrazole.



[0170] Following protocol L, 3-(4-fluoro-phenyl)-5-methylsulfanyl-1H-pyrazole was treated with NCS in to yield the title compound.

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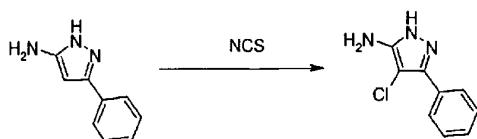
Synthesis of 5-Butyl-4-chloro-3-trifluoromethyl-1H-pyrazole.



[0171] Following protocol L, 5-butyl-3-trifluoromethyl-1H-pyrazole was treated with NCS in DMF to yield the title compound.

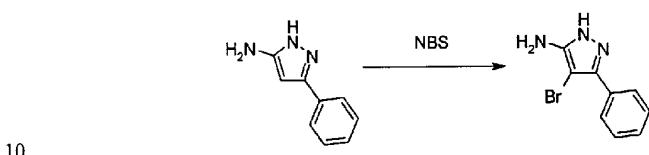
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Synthesis of 4-Chloro-5-phenyl-1-pyrazol-3-amine



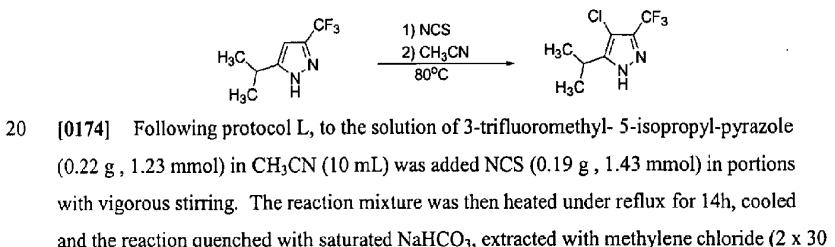
[0172] Following protocol L, to 0.5 g (0.0031 mol, 1eq) of 5-phenyl-1-pyrazol-3-amine in 25 mL of dry acetonitrile was added 0.4 g (0.0031 mol, 1eq) of N-chlorosuccinimide portion wise and the reaction mixture stirred at room temperature for 30 min. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water, brine and concentrated. The product was purified by 60-120 silica gel column (1% of methanol in chloroform).

Synthesis of 4-Bromo-5-phenyl-1-pyrazol-3-amine



[0173] Following protocol L, to 0.5 g (0.0031 mol, 1eq) of 5-phenyl-1-pyrazol-3-amine in 25 mL of dry acetonitrile was added 0.55 g (0.0031 mol, 1eq) of N-bromosuccinimide portion wise and the reaction mixture stirred at room temperature for 30 min. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water, brine and concentrated. The product was purified by 60-120 silica gel column (1% of methanol in chloroform).

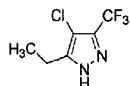
Synthesis of 4-Chloro-5-isopropyl-3-trifluoromethylpyrazole.



[0174] Following protocol L, to the solution of 3-trifluoromethyl- 5-isopropyl-pyrazole (0.22 g, 1.23 mmol) in CH₃CN (10 mL) was added NCS (0.19 g, 1.43 mmol) in portions with vigorous stirring. The reaction mixture was then heated under reflux for 14h, cooled and the reaction quenched with saturated NaHCO₃, extracted with methylene chloride (2 x 30

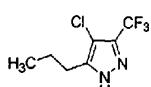
mL) and the combined organic extracts was washed with brine, dried with Na_2SO_4 and evaporated to give the title compound as a white solid.

Synthesis of 4-chloro-5-Ethyl-3-trifluoromethyl-1H-pyrazole.



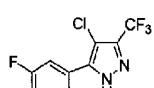
[0175] Following protocol L, 5-ethyl-3-trifluoromethyl-1H-pyrazole was treated with NCS in CH_3CN to yield title compound

Synthesis of 4-chloro-5-propyl-3-trifluoromethyl-1H-pyrazole.



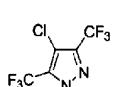
[0176] Following protocol L, 5-propyl-3-trifluoromethyl-1H-pyrazole was treated with NCS in CH_3CN to yield the title compound.

Synthesis of 4-chloro-5-(3-fluorophenyl)-3-trifluoromethyl-1H-pyrazole.



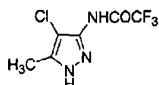
[0177] Following protocol L, 5-(3-fluorophenyl)-3-trifluoromethyl-1H-pyrazole was treated with NCS in CH_3CN to yield the title compound.

Synthesis of 4-chloro-3,5-bistrifluoromethyl-1H-pyrazole.



[0178] Following protocol L, 3,5-bistrifluoromethyl-1H-pyrazole was treated with NCS in CH_3CN to yield the title compound.

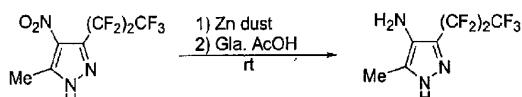
Synthesis of N-(4-Chloro-5-methyl-1H-pyrazol-3-yl)-2,2,2-trifluoro-acetamide.



[0179] Following protocol L, 2,2,2-Trifluoro-N-(5-methyl-1H-pyrazol-3-yl)-acetamide was treated with NCS in CH₃CN to yield the title compound.

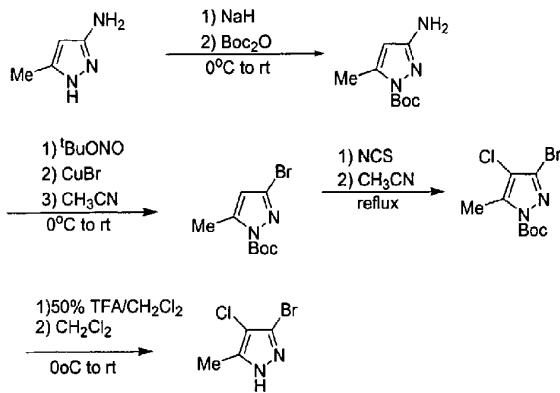
5 **PROTOCOL M: General procedure for reduction of Nitropyrazoles**

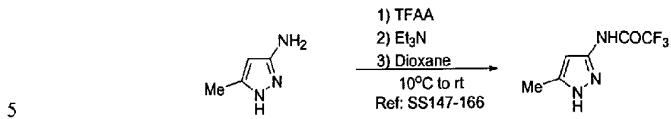
Synthesis of 3-Heptafluoropropyl-5-methyl-1H-pyrazol-4-ylamine.



[0180] To a suspension of zinc dust (1.5 g) in glacial acetic acid (10 mL) was added drop-wise, a solution of 3-Heptafluoropropyl-5-methyl-4-nitro-1H-pyrazole (0.295 g, 1.0 mmol) in glacial acetic acid (5 mL). The reaction mixture was then allowed to stir at room temperature for 14h. The zinc salts were then removed by filtration and the residue washed with ethyl acetate. The combined organic extract was concentrated in vaccum, re-dissolved in CHCl₃, washed with NaHCO₃, water and brine. Finally the organic layer was dried with Na₂SO₄ and solvent evaporated to give the title compound as white solid.

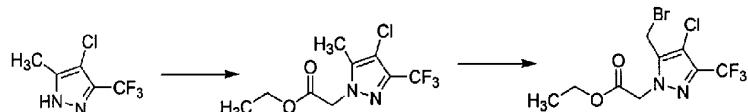
Synthesis of Bromo-pyrazoles for aryl-aryl cross coupling reactions and for metal mediated aminations



General procedure for trifluoroacetylation of aminopyrazoles:Synthesis of 2,2,2-Trifluoro-N-(5-methyl-1H-pyrazol-3-yl)-acetamide.

[0181] To a solution of 3-amino-5-methylpyrazole (0.97 g, 10 mmol) and Et₃N (1.39 mL, 10 mmol) in dioxane (25 mL) was added Trifluoroacetic anhydride (TFAA) (1.39 mL, 10 mmol) drop-wise at 10°C. The reaction mixture was stirred at that temperature for 1h then slowly warmed to room temperature through next 1h. Once the reaction is over dioxane was

10 evaporated, residue resolved in water (20 mL), washed with methylene chloride (30 mL). Organic layer was then dried with Na₂SO₄ and concentrated to give the title compound as white solid.

PROTOCOL N: Functionalization of alkyl substituted heteroaryl ring systems:15 aminomethylationSynthesis of (5-Bromomethyl-4-chloro-3-methyl-pyrazol-1-yl)-acetic acid ethyl ester

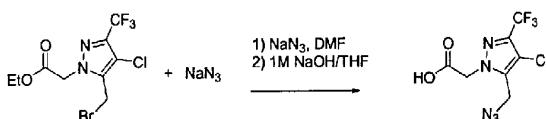
Reagents and Conditions: i) BrCH₂CO₂Et/K₂CO₃/CH₃CN; ii) NBS/AIBN/CCl₄

20 [0182] 4-Chloro-3-methyl-5-trifluoromethyl-1H-pyrazole, (10g, 54mmol) was dissolved in acetonitrile (100mL) and potassium carbonate (30g, 0.215mol) added. After stirring at room temperature for 1 hour, ethyl bromoacetate (11g, 65mmol) was added. After 14h at 70°C, the mixture was filtered and the filtrate was concentrated to obtain the crude product, which was re-crystallized from petroleum ether.

[0183] This intermediate ester (5g, 0.019mol) was taken in CCl₄ (100mL) and AIBN (0.053g, 0.33mmol) was added to it under nitrogen. The mixture was irradiated with a regular light bulb. The mixture was brought to reflux and then NBS (3.42g, 0.019mol), in four

portions in 15min intervals, was added to the mixture. After complete addition the mixture was left refluxing under the influence of light for 3h. The reaction mixture was then filtered and the filtrate was washed with water and brine. Drying the organic layer (Na_2SO_4) followed by evaporation of the solvent afforded (5-Bromomethyl-4-chloro-3-trifluoromethyl-pyrazol-1-yl)-acetic acid ethyl ester.

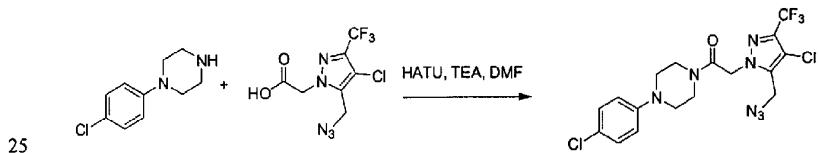
PROTOCOL O: Synthesis of (5-Azidomethyl-4-chloro-3-trifluoromethyl-pyrazol-1-yl)-acetic acid:



10 [0184] To 4.6g (13.2 mmol) of (5-Bromomethyl-4-chloro-3-trifluoromethyl-pyrazol-1-yl)-acetic acid ethyl ester dissolved in 40 mL of anhydrous dimethylformamide was added 1.03g (15.8 mmol) of sodium azide. After stirring for 12 hours, the solution was partitioned between ethyl acetate and water. The phases were separated, the aqueous phase was back-extracted with ethyl acetate and the combined ethyl acetate phases were washed with water and brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to yield an orange oil.

[0185] The oil was dissolved in 25mL of tetrahydrofuran, 25mL of 1M NaOH was added, and the mixture was stirred vigorously for three hours. The tetrahydrofuran was then removed *in vacuo*, and the aqueous solution was washed once with ether. The aqueous phase was then acidified with 1M HCl, and extracted twice with ethyl acetate. The combined ethyl acetate phases were washed with brine, dried over Na_2SO_4 , filtered, and concentrated to yield the title compounds as an orange solid.

PROTOCOL P (*vide infra*): Synthesis of 2-(5-Azidomethyl-4-chloro-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chlorophenyl)-piperazin-1-yl]-ethanone:

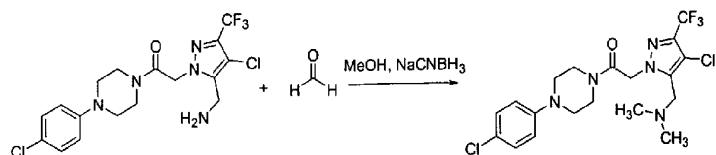


[0186] To 2.71g (13.7 mmol) of 1-(4-Chlorophenyl)piperazine and 3.58 g (12.5 mmol) of (5-Azidomethyl-4-chloro-3-trifluoromethyl-pyrazol-1-yl)-acetic acid in 40 mL of anhydrous dimethylformamide was added 4.36 mL (31.2 mmol) of triethylamine. The solution was cooled to 0°C, and 5.21g (13.7 mmol) of O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) was added. After 2 hours the reaction was diluted with two volumes of water, and the solvent was decanted away from the resulting oil. The oil was crystallized by dissolving in methanol and adding water in small portions. The product was isolated as a white solid by filtration: ¹H NMR (DMSO-*d*6, 400MHz) 7.23 (d, 2H), 6.97 (d, 2H), 5.48 (s, 2H), 4.62 (s, 2H), 3.60 (m, 4H), 3.24 (m, 2H), 3.12 (m, 2H) ppm; 10 MS (ES) M+H expected = 462.1, found = 462.0.

PROTOCOL Q: Synthesis of 2-(5-Aminomethyl-4-chloro-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chlorophenyl)-piperazin-1-yl]-ethanone

15 [0187] 2.85g (6.2 mmol) of 2-(5-Azidomethyl-4-chloro-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chlorophenyl)-piperazin-1-yl]-ethanone was dissolved in 80mL methanol, and 3.61g (16.0 mmol) of SnCl₂ hydrate was added. After two hours, the reaction was concentrated *in vacuo* to remove the methanol. The residue was partitioned between 0.5M NaOH and ethyl acetate, and the phases were separated. The aqueous phase was back-extracted once with 20 ethyl acetate. The combined ethyl acetate phases were extracted twice with 1M HCl. The acidic aqueous phase was basified with 1M NaOH, and was extracted once with ethyl acetate. The final ethyl acetate phase was washed once with brine, dried over Na₂SO₄, filtered, and concentrated to an oil. The oil was dissolved in methanol, acidified with 2M HCl in ether, and the product was isolated by filtration after precipitation: ¹H NMR (DMSO-*d*6, 400MHz) 8.58 (s, 3H), 7.27 (d, 2H), 7.03 (d, 2H), 5.71 (s, 2H), 4.10 (d, 2H), 3.64 (m, 4H), 3.32 (m, 2H), 3.19 (m, 2H) ppm; MS (ES) M+H expected = 436.1, found = 436.0.

Synthesis of 2-(5-N,N-Dimethylaminomethyl-4-chloro-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chlorophenyl)-piperazin-1-yl]-ethanone:



[0188] To a solution of 50mg (0.1 mmol) of 2-(5-Aminomethyl-4-chloro-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chlorophenyl)-piperazin-1-yl]-ethanone hydrochloride and 13mg (0.20 mmol) sodium cyanoborohydride in 0.7mL methanol was added 0.025mL (0.3 mmol) of 37% aqueous formaldehyde. After stirring for four hours, the reaction was quenched with 0.1mL 12M HCl. One hour later, the solution was concentrated *in vacuo*. The residue was partitioned between water and ether, and the phases were separated. The ether phase was back-extracted once with water. The combined aqueous phases were basified with 1M NaOH, and was extracted once with ethyl acetate. The ethyl acetate phase was washed once with brine, dried over Na₂SO₄, filtered, and concentrated to an oil. The oil was dissolved in methanol, acidified with 2M HCl in ether, and the product was isolated as a white solid by filtration: ¹H NMR (DMSO-*d*6, 400MHz) 11.07 (br, 1H), 7.26 (d, 2H), 7.02 (d, 2H), 5.76 (s, 2H), 4.43 (s, 2H), 3.62 (m, 4H), 3.31 (m, 2H), 3.18 (m, 2H), 2.81 (s, 6H) ppm; MS (ES) M+H expected = 464.1, found = 464.0.

PROTOCOL R: Urea derivatization of aminomethyl functionality on pyrazole ring system

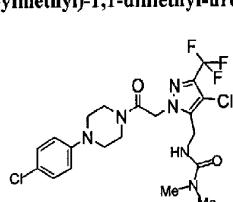
[0189] To a slurry of 12 mg (0.07 mmol) carbonyldiimidazole and 25 mg (0.05 mmol) of 2-(5-Aminomethyl-4-chloro-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chlorophenyl)-piperazin-1-yl]-2-oxo-ethyl]-5-trifluoromethyl-2H-pyrazol-3-ylmethyl)-urea:

[0189] To a slurry of 12 mg (0.07 mmol) carbonyldiimidazole and 25 mg (0.05 mmol) of 2-(5-Aminomethyl-4-chloro-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chlorophenyl)-piperazin-1-

yl]-ethanone hydrochloride in 1.0 mL CH₂Cl₂ at 0°C was added 23 mg (0.22 mmol) of triethylamine dissolved in 0.2 mL CH₂Cl₂ over five minutes. The mixture was allowed to warm to room temperature after one hour, and was stirred for an additional hour.

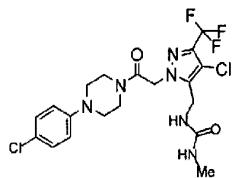
[0190] 1.0 mL (0.5 mmol) of 0.5M ammonia in dioxane was added, and the resulting solution was stirred for 12 hours. The solution was concentrated *in vacuo*, and the resulting residue was partitioned between ethyl acetate and water. The phases were separated, and the aqueous phase was back-extracted once with ethyl acetate. The combined ethyl acetate phases were washed once each with water, 1M NaOH, brine, dried over Na₂SO₄, filtered, and concentrated to a residue. The residue was triturated with ethyl acetate, and the product was isolated as a white solid by filtration: ¹H NMR (DMSO-*d*6, 400MHz) 7.23 (d, 2H), 6.96 (d, 2H), 6.48 (t, 1H), 5.62 (s, 2H), 5.48 (s, 2H), 4.16 (d, 2H), 3.57 (m, 4H), 3.25 (m, 2H), 3.14 (m, 2H) ppm; MS (ES) M+H expected = 479.1, found = 479.0.

Synthesis of 3-(4-Chloro-2-{2-[4-(4-chloro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-5-trifluoromethyl-2H-pyrazol-3-ylmethyl)-1,1-dimethyl-urea:



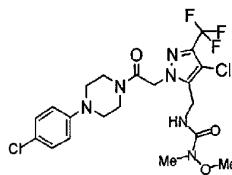
[0191] Title compound was prepared following protocol R, using 2M dimethylamine in tetrahydrofuran as the amine component in the second step, to give the desired product as a solid: ¹H NMR (DMSO-*d*6, 400MHz): 7.23 (d, 2H), 6.96 (d, 2H), 6.81 (t, 1H), 5.43 (s, 2H), 4.21 (d, 2H), 3.56 (m, 4H), 3.22 (m, 2H), 3.13 (m, 2H), 2.73 (s, 3H) ppm; MS (ES) M+H expected = 507.1, found = 507.1.

Synthesis of 1-(4-Chloro-2-{2-[4-(4-chloro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-5-trifluoromethyl-2H-pyrazol-3-ylmethyl)-3-methyl-urea:



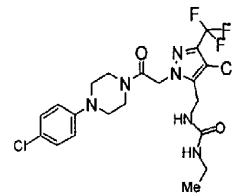
[0192] Title compound was prepared following the protocol R, using 2M methylamine in tetrahydrofuran as the amine component in the second step, to give the desired product as a solid: ¹H NMR (DMSO-*d*6, 400MHz) 7.23 (d, 2H), 6.96 (d, 2H), 6.45 (t, 1H), 5.86 (m, 1H), 5.48 (s, 2H), 4.18 (d, 2H), 3.58 (m, 4H), 3.31 (s, 3H), 3.25 (m, 2H), 3.13 (m, 2H) ppm; MS (ES) M+H expected = 493.1, found = 493.0.

Synthesis of 3-(4-Chloro-2-{2-[4-(4-chloro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-5-trifluoromethyl-2H-pyrazol-3-ylmethyl)-1-methoxy-1-methyl-urea:



10 [0193] Title compound was prepared following protocol R, using 1M N₂O-dimethylhydroxylamine in tetrahydrofuran as the amine component in the second step, to give the desired product as a solid: ¹H NMR (DMSO-*d*6, 400MHz) 7.63 (t, 1H), 7.23 (d, 2H), 6.96 (d, 2H), 5.42 (s, 2H), 4.25 (d, 2H), 3.57 (m, 4H), 3.52 (s, 3H), 3.25 (m, 2H), 3.13 (m, 2H), 2.89 (s, 3H) ppm; MS (ES) M+H expected = 523.1, found 523.0.

Synthesis of 1-(4-Chloro-2-{2-[4-(4-chloro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-5-trifluoromethyl-2H-pyrazol-3-ylmethyl)-3-ethyl-urea:



[0194] Title compound was prepared following protocol R, using 2M ethylamine in tetrahydrofuran as the amine component in the second step, to give the desired product as a solid: ¹H NMR (DMSO-*d*6, 400MHz) 7.26 (d, 2H), 7.03 (d, 2H), 6.95 (br, 1H), 6.47 (br, 1H), 5.49 (s, 2H), 4.17 (s, 1H), 3.61 (m, 4H), 3.28 (m, 2H), 3.17 (m, 2H), 2.95 (q, 2H), 0.93 (t, 3H) ppm; MS (ES) M+H expected = 507.1, found = 507.0

Coupling of pyrazolyl systems with carboxylic acid equivalents

[0195] The following synthesis is an example of this type of chemistry: additional 10 examples (procedure N) have been described elsewhere in this patent.

Synthesis of 4-Chloro-3-methyl-5-trifluoromethylpyrazol-1-yl)-acetic acid

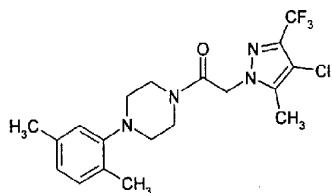


Reagents and conditions: BrCH₂CO₂Et/K₂CO₃/CH₃CN, then LiOH/THF

[0196] 4-Chloro-3-methyl-5-trifluoromethylpyrazole (10g, 0.0539 mol) was taken in acetonitrile (100mL) and K₂CO₃ (30g, 0.213 mol) was added to it. The mixture was stirred at rt for 1h and ethyl bromoacetate (11g, 0.065mol) was added slowly to it. The mixture was then stirred for 12h at 70°C. The mixture was filtered and the filtrate was concentrated to get 20 a crude mixture. This crude product was re-crystallized from pet ether to obtain the corresponding ester

[0197] The ester (14.8g, 0.0565 mol) was dissolved in THF (100mL) and a solution of LiOH (6.9g) in water (50mL) was added to it. The mixture was stirred for 10h at room temperature. Excess THF was evaporated under reduced pressure and the aqueous layer was 25 washed with ethyl acetate to remove any unhydrolysed material. The aqueous layer was then acidified with 1.5N HCl and extracted with ethyl acetate. The ethyl acetate layer was dried and concentrated to obtain the crude acid. On re-crystallization from ether/pet, product was obtained as white crystals.

30 **Couplings of arylpiperazines with pyrazolyl-acetic acid derivatives**

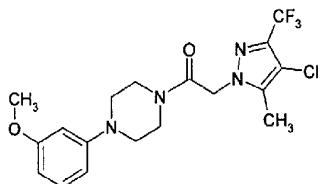
PROTOCOL P: Compounds prepared by HATU mediated coupling:**Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(2,5-dimethyl-phenyl)-piperazin-1-yl]-ethanone**

[0198] To 38mg (0.20 mmol) of 1-(2,5-Dimethylphenyl)piperazine and 53mg (0.22 mmol) of (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid in 1.6 mL of anhydrous dimethylformamide was added 62mg (0.6 mmol) of triethylamine, followed by 84mg

10 (0.22 mmol) of O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU). After 6 hours, the reaction was partitioned between ethyl acetate and water, and the phases were separated. The aqueous phase was back-extracted once with ethyl acetate, and the combined ethyl acetate phases were washed once each with 0.5M pH = 7 phosphate buffer, water, 1M NaOH, water, brine. The ethyl acetate phase was 15 then dried over Na₂SO₄, filtered, and concentrated to a residue *in vacuo*. The residue was dissolved in a minimum volume of 5M HCl in isopropanol, and was precipitated by diluting the solution with ethyl acetate. The product was isolated by filtration to give a white solid: ¹H NMR (DMSO-*d*6, 400MHz) 7.07 (d 1H), 6.90 (s, 1H), 6.82 (d, 1H), 5.39 (s, 2H), 3.66 (m, 4H), 2.98 (m, 2H), 2.89 (m, 2H), 2.26 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H) ppm; MS (ES) M+H 20 expected = 415.1, found 415.1.

Examples of additional compounds prepared by HATU mediated coupling:

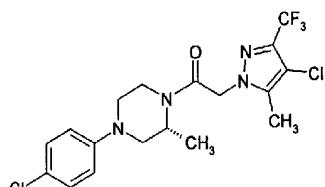
Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(3-methoxy-phenyl)-piperazin-1-yl]-ethanone:



[0199] Title compound was prepared following protocol P, wherein 1-(3-methoxyphenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a white solid: ¹H NMR (DMSO-*d*6, 400MHz) 7.15 (t, 1H), 6.65 (d, 1H), 6.60 (s, 1H), 6.47 (d, 1H), 5.38 (s, 2H), 3.72 (s, 3H), 3.65 (m, 4H), 3.28 (m, 2H), 3.19 (m, 2H), 2.18 (s, 3H) ppm; MS (ES) M+H expect = 417.1, found = 417.1.

10

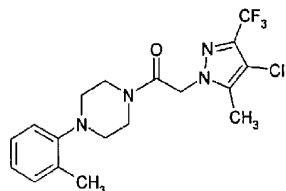
Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chloro-phenyl)-2-(R)-methyl-piperazin-1-yl]-ethanone:



[0200] Title compound was prepared following the HATU mediated coupling protocol P, wherein 1-(4-Chlorophenyl)-3-(R)-methylpiperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a white solid: ¹H NMR (CDCl₃, 300MHz) 7.25 (d 2H), 6.83 (d, 2H), 4.91 (m, 3H), 4.28 (m, 1H), 3.80-3.10 (m, 4H), 2.86 (m, 1H), 2.71 (m, 1H), 2.29 (s, 3H), 1.40 (m, 3H) ppm; MS (ES) expect M+H = 435.1, found 435.0.

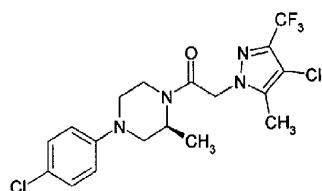
20

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-(4-o-tolyl-piperazin-1-yl)-ethanone:



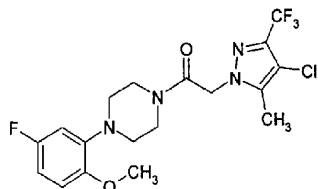
[0201] Title compound was prepared following the HATU mediated coupling protocol P, 5 wherein 1-(2-Methylphenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ¹H NMR (DMSO-*d*6, 400MHz) 7.14 (m, 2H), 6.98 (m, 2H), 5.37 (s, 2H), 3.60 (m, 4H), 2.89 (m, 2H), 2.81 (m, 2H), 2.27 (s, 3H), 2.20 (s, 3H) ppm; MS (ES) M+H expect = 401.1, found = 401.1.

10 **Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chlorophenyl)-2-(S)-methyl-piperazin-1-yl]-ethanone:**



[0202] Title compound was prepared following the HATU mediated coupling protocol P, 15 wherein 1-(4-Chlorophenyl)-3-(S)-methylpiperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ¹H NMR (CDCl₃, 300MHz) 7.25 (d 2H), 6.83 (d, 2H), 4.91 (m, 3H), 4.28 (m, 1H), 3.80-3.10 (m, 4H), 2.86 (m, 1H), 2.71 (m, 1H), 2.29 (s, 3H), 1.40 (m, 3H) ppm; MS (ES) M+H expected = 435.1, found = 435.0.

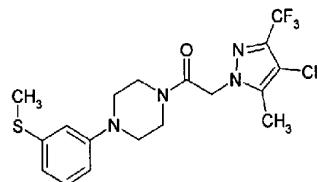
Synthesis of 2-(4-Chloro-3-trifluoromethyl-5-methyl-pyrazol-1-yl)-1-[4-(5-fluoro-2-methoxy-phenyl)-piperazin-1-yl]-ethanone



[0203] Title compound was prepared following the HATU mediated coupling protocol P,
 5 wherein 1-(2-Methoxy-5-fluorophenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 6.93 (m, 1H), 6.77 (m, 3H), 5.36 (s, 2H), 3.77 (s, 3H), 3.59 (m, 4H), 3.07 (m, 2H), 2.98 (m, 2H), 2.19 (s, 3H) ppm; MS (ES) M+H expect 435.1, found 435.0.

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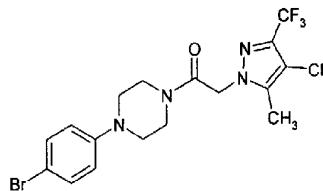
Synthesis of 2-{4-chloro-3-methyl-5-trifluoromethyl-pyrazol-1-yl}-1-[4-(3-Methylsulfonyl-phenyl)-piperazin-1-yl]-ethanone



[0204] Title compound was prepared following the HATU mediated coupling protocol P,
 15 wherein 1-(3-Methylthiophenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.21 (t, 1H), 6.98 (s, 1H), 6.91 (d, 1H), 6.81 (d, 1H), 5.39 (s, 2H), 3.68 (m, 4H), 3.34 (m, 2H), 3.24 (m, 2H), 2.44 (s, 3H), 2.19 (s, 3H) ppm; MS (ES) M+H expect 433.1, found 433.0.

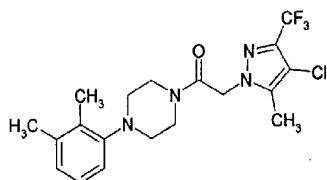
20

Synthesis of 1-[4-(4-Bromo-phenyl)-piperazin-1-yl]-2-(4-chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone:



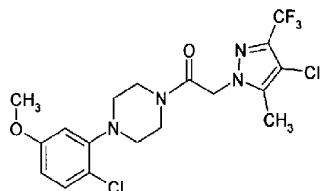
[0205] Title compound was prepared following the HATU mediated coupling protocol P, 5 wherein 1-(4-Bromophenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ¹H NMR (DMSO-*d*6, 400MHz) 7.36 (d, 2H), 6.92 (d, 2H), 5.37 (s, 2H), 3.60 (m, 4H), 3.24 (m, 2H), 3.14 (m, 2H), 2.18 (s, 3H) ppm; MS (ES) M+H expect = 465.0, found = 465.0.

10 **Synthesis of 2-(4-Chloro-3-trifluoromethyl-5-methyl-pyrazol-1-yl)-1-[4-(2,3-dimethyl-phenyl)piperazin-1-yl]-ethanone**



[0206] Title compound was prepared following the HATU mediated coupling protocol P, 15 wherein 1-(2,3-Dimethylphenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ¹H NMR (DMSO-*d*6, 400MHz) 7.04 (t, 1H), 6.99 (m, 2H), 5.38 (s, 2H), 3.64 (m, 4H), 2.89 (m, 2H), 2.81 (m, 2H), 2.21 (m, 9H) ppm; MS (ES) M+H expect 415.1, found 415.1.

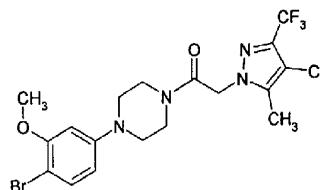
Synthesis of 2-(4-Chloro-3-trifluoromethyl-5-methyl-pyrazol-1-yl)-1-[4-(2-chloro-5-methoxy-phenyl)-piperazin-1-yl]-ethanone



[0207] Title compound was prepared following the HATU mediated coupling protocol P,
 5 wherein 1-(2-Chloro-5-methoxyphenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.31 (d, 1H), 6.65 (m, 2H), 5.37 (s, 2H), 3.73 (s, 3H), 3.62 (m, 4H), 3.02 (m, 2H), 2.96 (m, 2H), 2.19 (s, 3H) ppm; MS (ES) M+H expected = 451.1, found = 451.0.

10

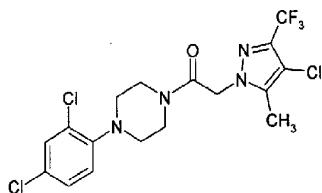
Synthesis of 1-[4-(4-Bromo-3-methoxy-phenyl)-piperazin-1-yl]-2-(4-chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone:



[0208] Title compound was prepared following the HATU mediated coupling protocol P,
 15 wherein 1-(4-Bromo-3-methoxyphenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.34 (d, 1H), 6.71 (s, 1H), 6.52 (d, 1H), 5.39 (s, 2H), 3.82 (s, 3H), 3.62 (m, 4H), 3.30 (m, 2H), 3.20 (m, 2H), 2.19 (s, 3H) ppm; MS (ES) M+H expected = 495.0, found = 495.0.

20

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(2,4-dichlorophenyl)-piperazin-1-yl]-ethanone:

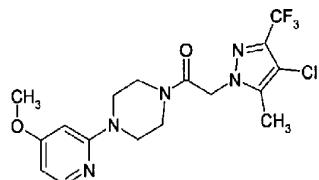


[0209] Title compound was prepared following the HATU mediated coupling protocol P,

5 wherein 1-(2,4-Dichlorophenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ¹H NMR (DMSO-*d*6, 400MHz) 7.56 (s, 1H), 7.36 (d, 1H), 7.15 (d, 1H), 5.37 (s, 2H), 3.61 (m, 4H), 3.01 (m, 2H), 2.94 (m, 2H), 2.19 (s, 3H) ppm; MS (ES) M+H expect 455.0, found = 454.9.

10

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-methoxy-pyridin-2-yl)-piperazin-1-yl]-ethanone:

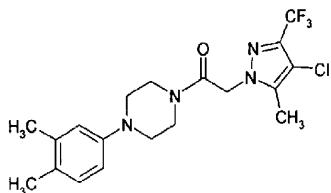


[0210] Title compound was prepared following the HATU mediated coupling protocol P,

15 wherein 1-(4-Methoxy-pyridin-2-yl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ¹H NMR (DMSO-*d*6, 400MHz) 7.92 (d, 1H), 6.67 (s 1H), 6.63 (d, 1H), 5.42 (s, 2H), 3.96 (s, 3H), 3.88 (m, 2H), 3.73 (m, 4H), 3.62 (m, 2H), 2.19 (s, 3H) ppm; MS (ES) M+H expected = 418.1, found = 418.0.

20

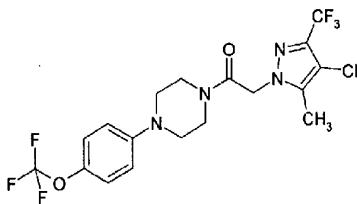
Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(3,4-dimethyl-phenyl)-piperazin1-yl]-ethanone:



[0211] Title compound was prepared following the HATU mediated coupling protocol P,
 5 wherein 1-(3,4-Dimethylphenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.03 (d, 1H), 6.94 (br s, 1H), 6.84 (br s, 1H), 5.38 (s, 2H), 3.68 (m, 4H), 3.25 (m, 2H), 3.15 (m, 2H), 2.18 (s, 6H), 2.14 (s, 3H) ppm; MS (ES) M+H expected = 415.1, found = 415.1.

10

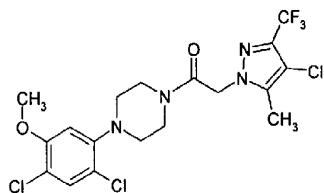
Synthesis of 2-(4-Chloro-3-trifluoromethyl-5-methyl-pyrazol-1-yl)-1-[4-(4-trifluoromethoxy-phenyl)-piperazin1-yl]-ethanone



[0212] Title compound was prepared following the HATU mediated coupling protocol P,
 15 wherein 1-(4-Trifluoromethoxyphenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.20 (d, 2H), 7.04 (d, 2H), 5.38 (s, 2H), 3.60 (m, 4H), 3.27 (m, 2H), 3.17 (m, 2H), 2.18 (s, 3H) ppm; MS (ES) M+H expected = 471.1, found = 471.0.

20

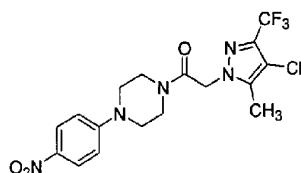
Synthesis of 2-(4-Chloro-3-trifluoromethyl-5-methyl-pyrazol-1-yl)-1-[4-(2,4-dichloro-5-methoxy-phenyl)-piperazin-1-yl]-ethanone



[0213] Title compound was prepared following the HATU mediated coupling protocol P, 5 wherein 1-(2,4-Dichloro-5-methoxyphenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.50 (s, 1H), 6.84 (s, 1H), 5.37 (s, 2H), 3.85 (s, 3H), 3.62 (m, 4H), 3.07 (m, 2H), 3.00 (m, 2H), 2.19 (s, 3H) ppm; MS (ES) M+H expected = 485.1, found = 485.0.

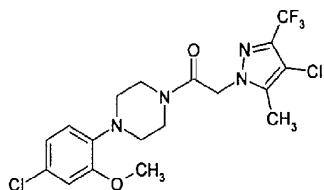
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Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-nitro-phenyl)-piperazin-1-yl]ethanone:



[0214] Title compound was prepared following the HATU mediated coupling protocol P, 15 wherein 1-(4-Nitrophenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a yellow solid: ^1H NMR (DMSO-*d*6, 400MHz) 8.05 (d, 2H), 7.01 (d, 2H), 5.38 (s, 2H), 3.62 (m, 6H), 3.52 (m, 2H), 2.19 (s, 3H) ppm; MS (ES) expect M+H = 432.1, found = 432.0.

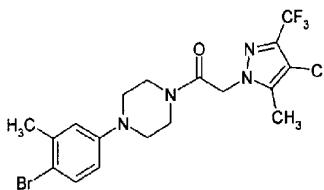
Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chloro-2-methoxy-phenyl)-piperazin-1-yl]-ethanone



[0215] Title compound was prepared following the HATU mediated coupling protocol P,
 5 wherein 1-(4-Chloro-2-methoxyphenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.02 (s, 1H), 6.93 (m, 2H), 5.36 (s, 2H), 3.82 (s, 3H), 3.60 (m, 4H), 3.03 (m, 2H), 2.95 (m, 2H), 2.19 (s, 3H) ppm; MS (ES) M+H expected = 451.1, found = 451.0.

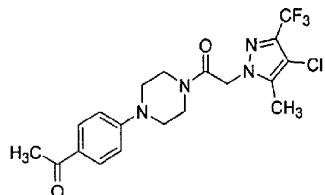
10

Synthesis of 1-[4-(4-Bromo-3-methyl-phenyl)-piperazin-1-yl]-2-(4-chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone:



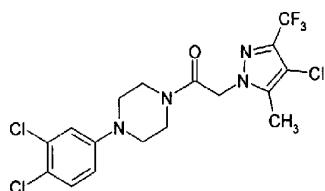
[0216] Title compound was prepared following the HATU mediated coupling protocol P,
 15 wherein 1-(4-Bromo-3-methylphenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.38 (d, 1H), 7.01 (s, 1H), 6.78 (d, 1H), 5.38 (s, 2H), 3.60 (m, 4H), 3.26 (m, 2H), 3.16 (m, 2H), 2.28 (s, 3H), 2.19 (s, 3H) ppm; MS (ES) M+H expected = 479.0, found = 478.9.

Synthesis of 1-[4-(4-Acetyl-phenyl)-piperazin-1-yl]-2-(4-chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone:



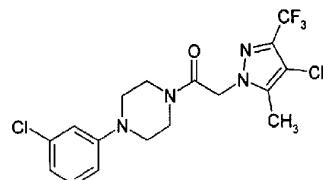
5 [0217] Title compound was prepared following the HATU mediated coupling protocol P, wherein 1-(4-Acetyl-phenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.80 (d, 1H), 6.98 (d, 2H), 5.38 (s, 2H), 3.61 (m, 4H), 3.48 (m, 2H), 3.39 (m, 2H), 2.46 (s, 3H), 2.19 (s, 3H) ppm; MS (ES) M+H expected = 429.1, found = 429.0.

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(3,4-dichlorophenyl)-piperazin-1-yl]-ethanone:



15 [0218] Title compound was prepared following the HATU mediated coupling protocol P, wherein 1-(3,4-Dichlorophenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.40 (d, 1H), 7.16 (s, 1H), 6.95 (d, 1H), 5.37 (s, 2H), 3.59 (m, 4H), 3.31 (m, 2H), 3.21 (m, 2H), 2.18 (s, 3H) ppm; MS (ES) M+H expected = 455.0, found = 455.0.

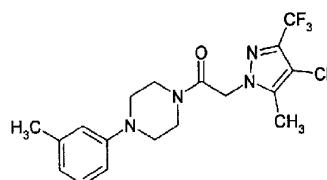
Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(3-chlorophenyl)-piperazin-1yl]-ethanone:



[0219] Title compound was prepared following the HATU mediated coupling protocol P, 5 wherein 1-(3-Chlorophenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.23 (t, 1H), 7.19 (s, 1H), 6.90 (d, 1H), 6.79 (d, 1H), 5.37 (s, 2H), 3.58 (m, 4H), 3.29 (m, 2H), 3.19 (m, 2H), 2.18 (s, 3H) ppm; MS (ES) M+H expected = 421.1, found = 421.0.

10

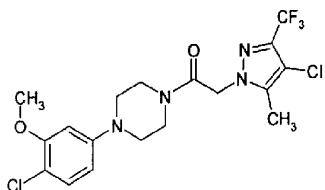
Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-(4-m-tolyl-piperazin-1-yl)-ethanone



[0220] Title compound was prepared following the HATU mediated coupling protocol P, 15 wherein 1-(3-Methylphenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.17 (t, 1H), 6.97 (br, 2H), 6.77 (d, 1H), 5.39 (s, 2H), 3.68 (m, 4H), 3.31 (m, 2H), 3.22 (m, 2H), 2.27 (s, 3H), 2.19 (s, 3H) ppm; MS (ES) M+H expected = 401.1, found = 401.1.

20

Synthesis of 1-[4-(4-Chloro-3-methoxy-phenyl)-piperazin-1-yl]-2-(4-chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone:

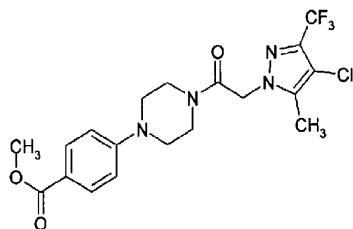


[0221] Title compound was prepared following the HATU mediated coupling protocol P,

5 wherein 1-(4-Chloro-3-methoxyphenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.21 (d, 1H), 6.74 (s, 1H), 6.56 (d, 1H), 5.39 (s, 2H), 3.82 (s, 3H), 3.63 (m, 4H), 3.30 (m, 2H), 3.19 (m, 2H), 2.19 (s, 3H) ppm; MS (ES) M+H expected = 451.1, found 451.0.

10

Synthesis of 4-[2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetyl]-piperazin-1-yl]-benzoic acid methyl ester:

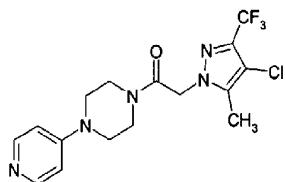


[0222] Title compound was prepared following the HATU mediated coupling protocol P,

15 wherein 4-Piperazin-1-yl-benzoic acid methyl ester and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.78 (d, 2H), 6.98 (d, 2H), 5.38 (s, 2H), 3.71 (s, 3H), 3.60 (m, 4H), 3.46 (m, 2H), 3.37 (m, 2H), 2.19 (s, 3H) ppm; MS (ES) expect M+H = 445.1, found 445.0.

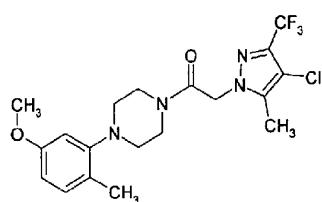
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Synthesis of 2-(4-Chloro-3,5-dimethyl-pyrazol-1-yl)-1-(4-pyridin-4-yl-piperazin-1-yl)-ethanone



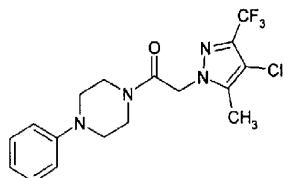
[0223] Title compound was prepared following the HATU mediated coupling protocol P, 5 wherein 1-(4-pyridyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ¹H NMR (DMSO-*d*6, 400MHz) 8.28 (d, 2H), 7.18 (d, 2H), 5.41 (s, 2H), 3.83 (m, 2H), 3.72 (m, 4H), 3.63 (m, 2H), 2.18 (s, 3H) ppm; MS (ES) M+H expected = 388.1, found = 388.0.

10 **Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(5-methoxy-2-methyl-phenyl)-piperazin-1-yl]-ethanone**



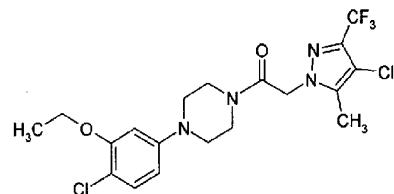
[0224] Title compound was prepared following the HATU mediated coupling protocol P, wherein 1-(3-Methoxy-5-methylphenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ¹H NMR (DMSO-*d*6, 400MHz) 7.06 (d, 1H), 6.56 (m, 2H), 5.38 (s, 2H), 3.69 (s, 3H), 3.62 (m, 4H), 2.92 (m, 2H), 2.84 (m, 2H), 2.20 (s, 3H) ppm; MS (ES) M+H expected = 431.1, found = 431.1.

Synthesis of 2-(4-Chloro-3-trifluoromethyl-5-methyl-pyrazol-1-yl)-1-(4-phenyl-piperazin-1-yl)-ethanone:



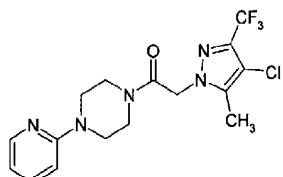
[0225] Title compound was prepared following the HATU mediated coupling protocol P, 5 wherein 1-Phenylpiperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.32 (m, 4H), 7.02 (m, 1H), 5.40 (s, 2H), 3.74 (m, 4H), 3.39 (m, 2H), 3.29 (m, 2H), 2.19 (s, 3H) ppm; MS (ES) expect M+H = 387.1, found 387.1.

10 **Synthesis of 1-[4-(4-Chloro-3-ethoxy-phenyl)-piperazin-1-yl]-2-(4-chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone:**



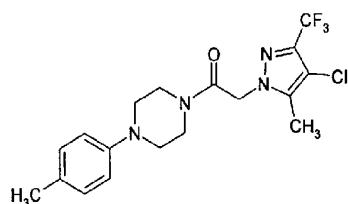
[0226] Title compound was prepared following the HATU mediated coupling protocol P, 15 wherein 1-(4-Chloro-3-ethoxyphenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.20 (d, 1H), 6.66 (s, 1H), 6.48 (d, 1H), 5.38 (s, 2H), 4.08 (q, 2H), 3.61 (m, 4H), 3.25 (m, 2H), 3.16 (m, 2H), 2.18 (s, 3H), 1.33 (t, 3H) ppm; MS (ES) M+H expected = 465.1, found 465.0.

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-(4-pyridin-2-yl-piperazin-1-yl)-ethanone:



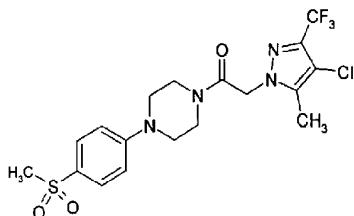
[0227] Title compound was prepared following the HATU mediated coupling protocol P, 5 wherein 1-(2-Pyridyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ¹H NMR (DMSO-*d*6, 400MHz) 8.11 (d, 1H), 7.53 (t, 1H), 6.85 (d, 1H), 6.65 (t, 1H), 5.37 (s, 2H), 3.59-3.50 (m, 8H), 2.18 (s, 3H) ppm; MS (ES) M+H expected = 388.1, found = 388.0.

10 **Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-(4-p-tolyl-piperazin-1-yl)-ethanone:**



[0228] Title compound was prepared following the HATU mediated coupling protocol P, 5 wherein 1-(4-Methylphenyl)piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ¹H NMR (DMSO-*d*6, 400MHz) 7.20 (m, 4H), 5.40 (s, 2H), 3.79 (m, 4H), 3.37 (m, 2H), 3.28 (m, 2H), 2.49 (s, 3H), 2.19 (s, 3H) ppm; MS (ES) M+H expected = 401.1, found 401.0.

Synthesis of 1-[(4-Methanesulfonyl-phenyl)-piperazine-1-yl]-2-(4-chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone

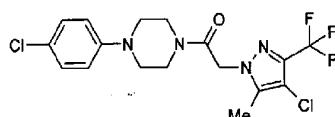


[0229] Title compound was prepared following the HATU mediated coupling protocol P,

5 wherein 1-(4-Methanesulfonyl-phenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.69 (d, 2H), 7.08 (d, 2H), 5.38 (s, 2H), 3.59 (m, 4H), 3.49 (m, 2H), 3.38 (m, 2H), 3.09 (s, 3H), 2.19 (s, 3H) ppm; MS (ES) M+H expected = 465.1, found = 465.0.

10

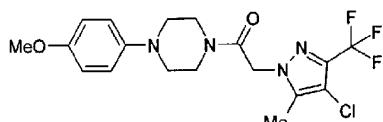
Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chlorophenyl)-piperazin-1-yl]-ethanone.



[0230] Title compound was prepared following the HATU mediated coupling protocol P,

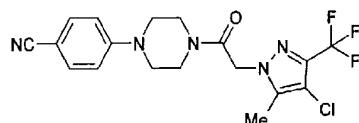
15 wherein 1-(4-Chlorophenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (CDCl₃, 400 MHz) 7.22 (d, 2H), 6.83 (d, 2H), 4.99 (s, 2H), 3.77 (m, 2H), 3.72 (m, 2H), 3.19 (m, 2H), 3.16 (m, 2H), 2.28 (s, 3H) ppm; MS (ES) M+Na expected = 443.0, found 443.0.

20 **Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-methoxy-phenyl)-piperazin-1-yl]-ethanone.**



[0231] Title compound was prepared following the HATU mediated coupling protocol P, wherein 1-(4-Methoxyphenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ¹H NMR (CDCl₃, 400 MHz) 6.88 (m, 4H), 5.00 (s, 2H), 3.78 (m, 3H), 3.76 (m, 2H), 3.70 (m, 2H), 3.08 (m, 4H), 2.30 (s, 3H) ppm; MS (ES) M+Na expected = 439.0, found 439.0.

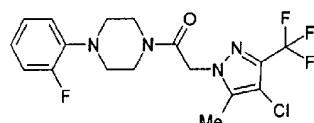
Synthesis of 4-[2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetyl]-piperazin-1-yl]-benzonitrile



10 [0232] Title compound was prepared following the HATU mediated coupling protocol P, wherein 1-(4-Cyanophenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ¹H NMR (CDCl₃, 400 MHz) 7.44 (d, 2H), 6.77 (d, 2H), 4.90 (s, 2H), 3.67 (m, 4H), 3.29 (m, 4H), 2.22 (s, 3H) ppm; MS (ES) M+Na expected = 434.0, found 434.0.

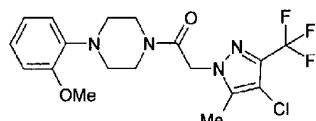
15

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(2-fluoro-phenyl)-piperazin-1-yl]-ethanone



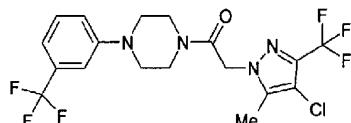
20 [0233] Title compound was prepared following the HATU mediated coupling protocol P, wherein 1-(2-Fluorophenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ¹H NMR (CDCl₃, 400 MHz) 7.02 (m, 4H), 5.00 (s, 2H), 3.80 (m, 2H), 3.70 (m, 2H), 3.53 (m, 2H), 3.25 (m, 2H), 2.30 (s, 3H) ppm; MS (ES) M+Na expected = 427.0, found 427.0.

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(2-methoxy-phenyl)-piperazin-1-yl]-ethanone



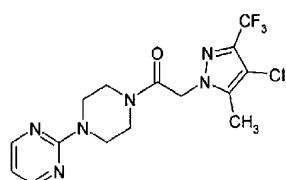
[0234] Title compound was prepared following the HATU mediated coupling protocol P, 5 wherein 1-(2-Methoxyphenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (CDCl_3 , 400 MHz) 6.62 (m, 1H), 6.48 (m, 3H), 5.01 (s, 2H), 3.73 (s, 3H), 3.61 (m, 4H), 3.43 (m, 2H), 2.31 (s, 3H) ppm; MS (ES) $\text{M}+\text{H}$ expected = 439.0, found 439.1.

10 **Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethanone.**



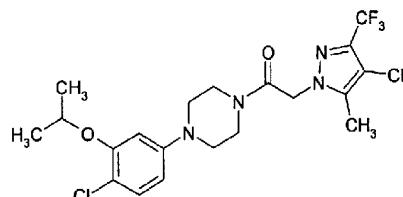
[0235] Title compound was prepared following the HATU mediated coupling protocol P, 5 wherein 1-(3-Trifluoromethylphenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (CDCl_3 , 400 MHz) 7.38 (m, 1H), 7.11 (m, 3H), 5.00 (s, 2H), 3.79 (m, 2H), 3.73 (m, 2H), 3.27 (m, 2H), 3.23 (m, 2H), 2.30 (s, 3H) ppm; MS (ES) $\text{M}+\text{H}$ expected = 455.0, found 455.0.

20 **Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-(4-pyrimidin-2-yl-piperazin-1-yl)-ethanone:**



[0236] Title compound was prepared following the HATU mediated coupling protocol P, wherein 1-(2-Pyrimidinyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: MS (ES) M+H expected = 389.1, found = 389.0; HPLC retention time = 3.99 minutes (Agilent Zorbax SB-C18, 2.1X50mm, 5 μ , 35°C) using a 4.5 minute gradient of 20% to 95% B (A = 0.1% formic acid / 5% acetonitrile / 94.9% water, B = 0.08% formic acid / 99.9% acetonitrile).

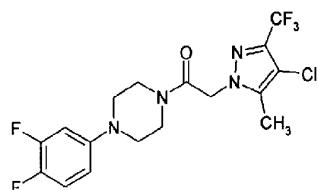
Synthesis of 1-[4-(4-Chloro-3-isopropoxy-phenyl)-piperazin-1-yl]-2-(4-chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone



10

[0237] Title compound was prepared following the HATU mediated coupling protocol P, wherein 1-(4-Chloro-3-isopropoxy-phenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ¹H NMR (DMSO-d6, 400MHz) 7.21 (d, 1H), 6.71 (s, 1H), 6.53 (d, 1H), 5.38 (s, 2H), 4.66 (m, 1H), 3.58 (m, 4H), 3.25 (m, 2H), 3.15 (m, 2H), 2.18 (s, 3H), 1.26 (d, 6H) ppm; MS (ES) M+H expected = 479.1, found = 479.0.

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(3,4-difluoro-phenyl)piperazin-1-yl]-ethanone

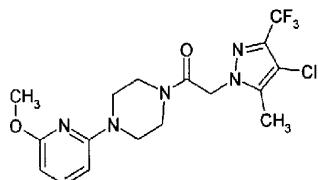


20

[0238] Title compound was prepared following the HATU mediated coupling protocol P, wherein 1-(3,4-Difluorophenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a

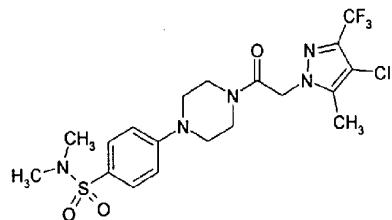
solid: ^1H NMR (DMSO-*d*6, 400MHz, not F-decoupled) 7.25 (q, 1H), 7.04 (m, 1H), 6.74 (d, 1H), 5.37 (s, 2H), 3.57 (m, 4H), 3.24 (m, 2H), 3.12 (m, 2H), 2.18 (s, 3H) ppm; MS (ES) M+H expected = 423.1, found 423.0.

5 **Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(6-methoxy-pyridin-2-yl)-piperazin-1-yl]-ethanone**



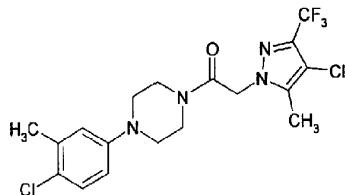
[0239] Title compound was prepared following the HATU mediated coupling protocol P, wherein 1-(6-Methoxy-pyridin-2-yl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.45 (t, 1H), 6.34 (d, 1H), 6.05 (d, 1H), 5.37 (s, 2H), 3.77 (s, 3H), 3.50 (m, 6H), 3.34 (m, 2H), 2.18 (s, 3H) ppm; MS (ES) M+H expected = 418.1, found = 418.0.

15 **Synthesis of 4-[4-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetyl]-piperazin-1-yl]-N,N-dimethyl-benzenesulfonamide:**



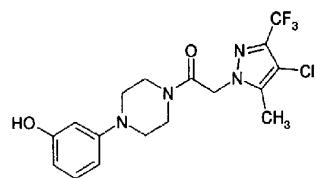
[0240] Title compound was prepared following the HATU mediated coupling protocol P, wherein N,N-Dimethyl-4-piperazin-1-yl-benzenesulfonamide and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.54 (d, 2H), 7.08 (d, 2H), 5.38 (s, 2H), 3.62 (m, 4H), 3.48 (m, 2H), 3.37 (m, 2H), 2.19 (s, 3H) ppm; MS (ES) M+H expected = 494.1, found = 494.0.

Synthesis of 1-[4-(4-Chloro-3-methyl-phenyl)-piperazin-1-yl]-2-(4-chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone



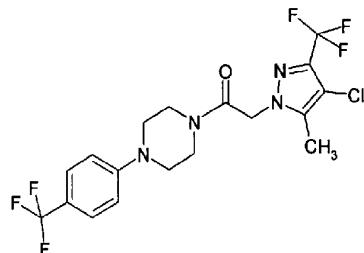
5 [0241] Title compound was prepared following the HATU mediated coupling protocol P, wherein 1-(4-Chloro-3-methylphenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.25 (d, 1H), 7.05 (s, 1H), 6.90 (d, 1H), 5.38 (s, 2H), 3.64 (m, 4H), 3.27 (m, 2H), 3.17 (m, 2H), 2.26 (s, 3H), 2.19 (s, 3H) ppm; MS (ES) M+H expected = 435.1, found = 435.0.

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(3-hydroxy-phenyl)-piperazin-1-yl]-ethanone



15 [0242] Title compound was prepared following the HATU mediated coupling protocol P, wherein 1-(3-Hydroxyphenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.10 (t, 1H), 6.66 (m, 2H), 6.45 (d, 1H), 5.39 (s, 2H), 3.74 (m, 4H), 3.33 (br, 2H), 3.24 (br, 2H), 2.19 (s, 3H) ppm; MS (ES) M+H expected = 403.1, found = 403.0.

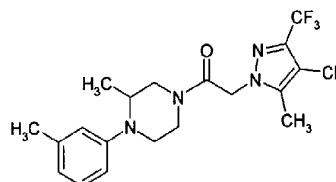
Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-ethanone



[0243] Title compound was prepared following the HATU mediated coupling protocol P, 5 wherein 1-(4-Trifluoromethylphenyl)-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.50 (d, 2H), 7.07 (d, 2H), 5.38 (s, 2H), 3.60 (m, 4H), 3.41 (m, 2H), 3.31 (m, 2H), 2.19 (s, 3H) ppm; MS (ES) M+H expected = 455.1, found = 455.0.

10

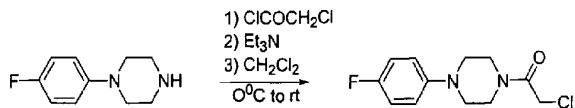
Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-(3-methyl-4-m-tolyl-piperazin-1-yl)-ethanone:



[0244] Title compound was prepared following the HATU mediated coupling protocol P, 15 wherein 1-(3-Methylphenyl)-2-methyl-piperazine and (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid were used as the coupling components, to give the product as a solid: ^1H NMR (DMSO-*d*6, 400MHz) 7.68 (br, 1H), 7.17 (br, 1H), 6.71 (br, 2H), 5.41 (m, 2H), 4.08 (m, 4H), 3.70 (m, 2H), 3.50 (br m, 2H), 2.30 (s, 3H), 2.18 (s, 3H), 1.01 (m, 3H) ppm; MS (ES) M+H expected = 415.1, found = 415.1.

20

PROTOCOL S: preparation of chloroacetyl arylpiperazines

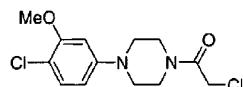
Synthesis of 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone

[0245] 1-(4-Fluorophenyl) piperazine (2.8 mmol) was dissolved in 10 mL of CH_2Cl_2 . Triethylamine (5.5 mmol) was added to it and the reaction was cooled to 0°C .

5 Chloroacetylchloride (4.2 mmol) was added to it slowly, and the reaction was warmed to room temperature overnight. After completion, the reaction was quenched with brine solution and reaction mixture was extracted with methylene chloride. The combined organic phases were washed with brine and water and dried over magnesium sulfate. The solvent was evaporated and the compound purified by column chromatography (hexane/ ethyl acetate 10 = 1.5/ 1) to afford the title compound as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 6.9-7.2 (m, 2H), 6.82-6.92 (m, 2H), 4.1 (s, 2H), 6.62-3.8 (m, 4H), 3.46-3.6 (m, 4H). ^{13}C NMR (400 MHz, CDCl_3): 164, 158, 156.2, 148.5, 118.2, 116.8, 52.6, 52.2, 48, 46, 42.1, 40.6.

Synthesis of 2-Chloro-1-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethanone

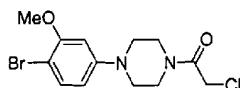
[0246] Protocol S was followed using 1-(4-chloro-phenyl) piperazine, Et_3N , chloroacetyl chloride and methylene chloride. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1.5/ 1) afforded the title compound as a white solid.

20 Synthesis of 2-Chloro-1-[4-(4-chloro-3-methoxy-phenyl)-piperazin-1-yl]-ethanone

[0247] Protocol S was followed using 1-(4-chloro-3-methoxyphenyl) piperazine, Et_3N , chloroacetyl chloride and methylene chloride. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1.5/ 1) afforded the title compounds as a white solid

25

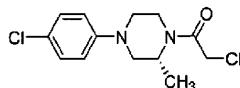
Synthesis of 2-Chloro-1-[4-(4-bromo-3-methoxy-phenyl)-piperazin-1-yl]-ethanone



[0248] Protocol S was followed using 1-(4-bromo-3-methoxyphenyl)piperazine, Et₃N, chloroacetyl chloride and methylene chloride. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1.5/ 1) afforded the title compounds as a white solid

5

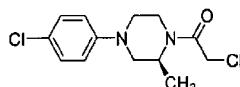
Synthesis of 2-Chloro-1-[4-(4-chloro-phenyl)-2-methyl-(R)-piperazin-1-yl]-ethanone



[0249] Protocol S was followed using 1-(4-Chloro-phenyl)-3-(R)-methyl-piperazine, Et₃N, chloroacetyl chloride and methylene chloride. Column chromatography afforded the title

10 compound

Synthesis of 2-Chloro-1-[4-(4-chloro-phenyl)-2-methyl-(S)-piperazin-1-yl]-ethanone



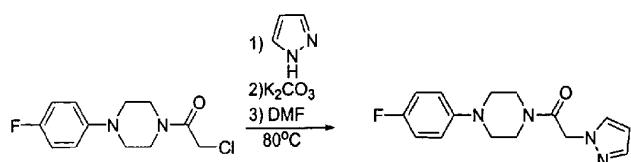
[0250] Protocol S was followed using 1-(4-Chloro-phenyl)-3-(S)-methyl-piperazine, Et₃N,

15 chloroacetyl chloride and methylene chloride. Column chromatography afforded the title compound.

PROTOCOL T: K₂CO₃ mediated coupling reaction of chloroacetyl arylpiperazines with pyrazoles

20

Synthesis of 1-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-pyrazol-1-yl-ethanone

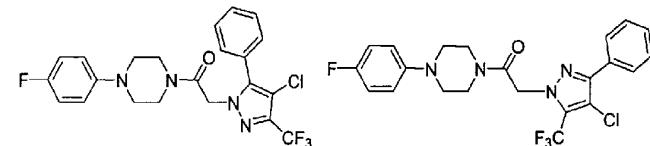


[0251] Pyrazole (112.33 mg, 1.65 mmol) was dissolved in DMF (10 mL). K₂CO₃ (228.05 mg, 1.65 mmol) and 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone (300 mg, 1.67

mmol) were added to it. The reaction was heated to 80°C for 14h. After completion, the reaction was cooled to room temperature, quenched with brine and then extracted with ethyl acetate. The organic layer was further washed with water (2X 25 mL) and brine (2X 25 mL) and dried over magnesium sulfate. The solvent was removed by rotary evaporation to give

5 the crude product which was purified by column chromatography on silica gel using a solvent mixture (hexane/ ethyl acetate = 1/1) to afford the title compound as white solid. ¹H NMR (400 MHz, CDCl₃): 7.2-7.58 (d, 2H), 6.94-7.2 (t, 2H), 6.84-6.9 (dd, 2H), 6.32-6.36 (t, 1H), 5.6 (s, 2H), 3.76-3.82 (m, 2H), 3.68-3.74 (m, 2H), 3.04-3.1 (m, 2H), 3.0-3.04 (m, 2H). ¹³C NMR (400 MHz, CDCl₃): 165, 158, 146.5, 140, 130, 118.4, 118.2, 116, 115.8, 107, 54, 51, 10 50.8 45.8, 42.8.

Synthesis of 2-(4-Chloro-5-phenyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and 2-(4-Chloro-3-phenyl-5-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone

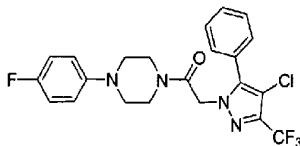


15

[0252] Protocol T was followed using 4-Chloro-5-phenyl-3-trifluoromethyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1.5/ 1) afforded a mixture of the title compounds, both as white solids

20

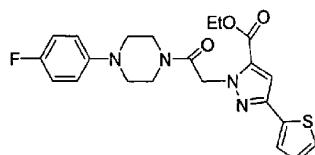
¹H NMR (400 MHz, CDCl₃): 7.44-7.54 (m, 5H), 6.94-7.2 (t, 2H), 6.84-6.9 (dd, 2H), 4.94 (s, 1H), 3.72-3.8 (m, 2H), 3.5-3.6 (m, 2H), 3.0-3.1 (m, 4H). ¹³C NMR (400 MHz, CDCl₃): 163.8, 158, 146.5, 130, 128.6, 128.2, 118.2, 114.5, 52, 50, 44.5, 42.



¹H NMR (400 MHz, CDCl₃): 7.82-7.88 (m, 2H), 7.38-7.48 (m, 3H), 6.96-7.04 (m, 2H), 6.86-6.94 (m, 2H), 5.2 (s, 1H), 3.76-3.86 (m, 2H), 3.62-3.68 (m, 2H), 3.06-3.22 (m, 4H). ¹³C NMR (400 MHz, CDCl₃): 164, 130, 128.4, 126, 118, 116.4, 52, 50, 43.8, 41.6.

5

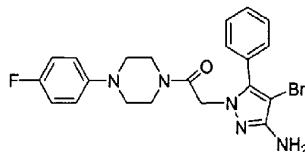
Synthesis of 2-{2-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester



[0253] Protocol T was followed using 5-Thiophen-2-yl-2H-pyrazole-3-carboxylic acid

10 ethyl ester, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1.5/ 1) afforded the title compound. ¹H NMR (400 MHz, CDCl₃): 7.32-7.36 (m, 1H), 7.22-7.26 (m, 1H), 7.08 (s, 1H), 7.02-7.08 (dd, 1H), 6.96-7.2 (m, 2H), 6.86-6.92 (m, 2H), 4.3-4.4 (q, 2H), 3.52-3.58 (m, 4H), 3.05-3.25 (m, 4H), 1.3-1.42 (m, 3H). ¹³C NMR (400MHz, CDCl₃): 164, 130, 126.8, 126.4, 120, 118.2, 115.4, 62.3, 54, 50.5, 42, 44.5, 14.6.

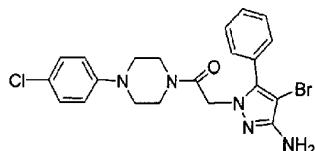
Synthesis of 2-(3-Amino-4-bromo-5-phenyl-pyrazol-1-yl)-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone



20 [0254] Protocol T was followed using 4-Bromo-5-phenyl-1H-pyrazol-3-ylamine, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 3/7) afforded the title compound as yellow solid. ¹H NMR (400 MHz, CDCl₃): 7.74-7.78 (m, 2H), 7.24-7.36 (m,

3H), 6.86-6.92 (m, 2H), 6.74-6.78 (m, 2H), 4.9 (s, 2H), 4.22 (s, 2H), 3.64-3.74 (m, 4H), 2.86-3.04 (m, 4H). ^{13}C NMR (400 MHz, CDCl_3): 164, 146.2, 144.8, 128, 126.8, 118, 114.8, 60, 50.2, 50, 48.8, 46, 42, 20.

5 **Synthesis of 2-(3-Amino-4-bromo-5-phenyl-pyrazol-1-yl)-1-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethanone**

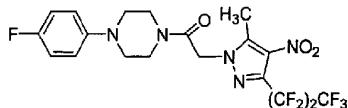


[0255] Protocol T was followed using 4-Bromo-5-phenyl-1H-pyrazol-3-ylamine, K_2CO_3 , 2-Chloro-1-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column

10 chromatography using a solvent mixture (hexane/ ethyl acetate = 1/4) afforded the title compound as white solid. ^1H NMR (400 MHz, CDCl_3): 7.7-7.8 (m, 2H), 7.24-7.3 (m, 3H), 6.8-6.92 (m, 2H), 6.74-6.78 (m, 2H), 4.9 (s, 2H), 4.2 (s, 2H), 3.6-3.7 (m, 4H), 2.86-3.04 (m, 4H). ^{13}C NMR (400 MHz, CDCl_3): 164, 146, 145, 128, 127, 118, 114.8, 60.2, 50.4, 50, 48.8, 46, 42, 22.

15

Synthesis of 1-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-(3-heptafluoropropyl-5-methyl-4-nitro-pyrazol-1-yl)-ethanone

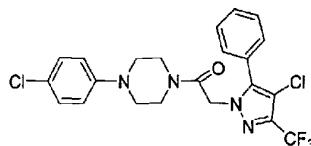


[0256] Protocol T was followed using 3-Heptafluoropropyl-5-methyl-4-nitro-1H-pyrazole,

20 K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 3/7) afforded the title compound as oil. ^1H NMR (400 MHz, CDCl_3): 6.9-7.0 (m, 2H), 6.8-6.9 (m, 2H), 5.06-5.14 (d, 2H), 3.6-3.8 (m, 4H), 3.06-3.18 (m, 4H), 2.56-2.66 (d, 3H). ^{13}C NMR (400 MHz, CDCl_3): 160, 146.2, 144, 119.2, 118, 52.2, 50.8, 50.4, 46, 42.2, 12.

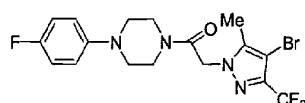
25

Synthesis of 1-[4-(4-Chloro-phenyl)-piperazin-1-yl]-2-(4-chloro-5-phenyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone



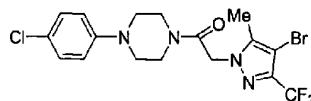
[0257] Protocol T was followed using 4-Chloro-5-phenyl-3-trifluoromethyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 2/3) afforded the title compound as white solid. ¹H NMR (400 MHz, CDCl₃): 7.82-7.84 (m, 2H), 7.4-7.48 (m, 3H), 6.9-7.04 (m, 2H), 6.88-6.94 (m, 2H), 5.22 (s, 1H), 3.76-3.88 (m, 2H), 3.6-3.68 (m, 2H), 3.1-3.22 (m, 4H). ¹³C NMR (400 MHz, CDCl₃): 164.2, 130.4, 128, 126, 118.2, 116.4, 52.2, 50, 44, 41.8.

10 **Synthesis of 1-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-(4-bromo-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone**



[0258] Protocol T was followed using 4-Bromo-5-methyl-3-trifluoromethyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 2/3) afforded the title compound as white solid. ¹H NMR (400 MHz, CDCl₃): 6.96-7 (m, 2H), 6.84-6.9 (m, 2H), 5 (s, 2H), 3.6-3.8 (m, 4H), 3.02-3.16 (m, 4H), 2.3 (s, 3H). ¹³C NMR (400 MHz, CDCl₃): 162.6, 146.5, 142, 118.5, 116, 52.2, 50.4, 46, 42.2, 15.

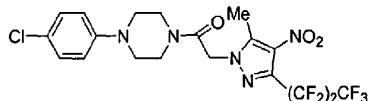
20 **Synthesis of 1-[4-(4-Chloro-phenyl)-piperazin-1-yl]-2-(4-bromo-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone**



[0259] Protocol T was followed using 4-Bromo-5-methyl-3-trifluoromethyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 2/3) afforded the title

compound as white solid. ^1H NMR (400 MHz, CDCl_3): 6.96-7.1 (m, 2H), 6.84-6.89 (m, 2H), 5.2(s, 2H), 3.6-2.3.8 (m, 4H), 3.0-3.16 (m, 4H), 2.32 (s, 3H). ^{13}C NMR (400 MHz, CDCl_3): 162, 146.4, 142.2, 118.5, 116.2, 52, 50.4, 46.2, 42.2, 15.2.

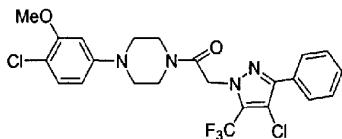
5 **Synthesis of 1-[4-(4-Chloro-phenyl)-piperazin-1-yl]-2-(3-heptafluoropropyl-5-methyl-4-nitro-pyrazol-1-yl)-ethanone**



[0260] Protocol T was followed using 3-Heptafluoropropyl-5-methyl-4-nitro-1H-pyrazole, K_2CO_3 , 2-Chloro-1-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column

10 chromatography using a solvent mixture (hexane/ ethyl acetate = 1/4, R_f = 0.81) afforded the title compound as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 6.92-7.02 (m, 2H), 6.82-6.9 (m, 2H), 5.04-5.14 (m, 2H), 3.64-3.82 (m, 4H), 3.06-3.18 (m, 4H), 2.6-2.66 (d, 3H). ^{13}C NMR (400 MHz, CDCl_3): 160.4, 146, 144.2, 119.2, 118.2, 52, 50.8, 50.6, 46, 42, 12.2.

15 **Synthesis of 1-[4-(4-Chloro-3-methoxyphenyl)-piperazin-1-yl]-2-(4-chloro-5-phenyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone**

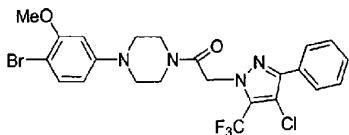


[0261] Protocol T was followed using 4-Chloro-5-phenyl-3-trifluoromethyl-1H-pyrazole, K_2CO_3 , 2-Chloro-1-[4-(4-chloro-3-methoxy-phenyl)-piperazin-1-yl]-ethanone and DMF.

20 Column chromatography using a solvent mixture (hexane/ ethyl acetate = 2/3) afforded the title compound as a white solid. ^1H NMR (400 MHz, CDCl_3): 7.4-7.52 (m, 5H), 7.18-7.22 (d, 1H), 6.44-6.48 (d, 1H), 6.36-6.42 (dd, 1H), 4.72 (s, 2H), 3.86 (s, 3H), 3.5-3.78 (m, 4H), 3.1 (s, 4H). ^{13}C NMR (400 MHz, CDCl_3) 164, 156.2, 150.4, 130.5, 130, 128.5, 110, 102.2, 56, 52, 50, 44.8, 42.

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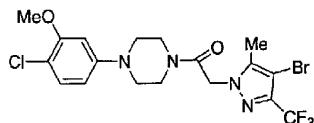
Synthesis of 1-[4-(4-Bromo-3-methoxyphenyl)-piperazin-1-yl]-2-(4-chloro-3-phenyl-5-trifluoromethyl-pyrazol-1-yl)-ethanone



[0262] Protocol T was followed using 4-Chloro-5-phenyl-3-trifluoromethyl-1H-pyrazole, K_2CO_3 , 2-Chloro-1-[4-(4-bromo-3-methoxy-phenyl)-piperazin-1-yl]-ethanone and DMF.

Column chromatography using a solvent mixture (hexane/ ethyl acetate = 2/3) afforded the title compound as a white solid. 1H NMR (400 MHz, $CDCl_3$): 7.42-7.52 (m, 4H), 7.36-7.38 (d, 1H), 6.42-6.46 (d, 1H), 6.34-6.38 (dd, 1H), 4.72 (s, 2H), 3.88 (s, 3H), 3.74-3.78 (m, 2H), 3.54-3.58 (m, 2H), 3.12-3.18 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$): 164, 156.2, 152, 132.6, 130.2, 130, 128.8, 110, 102.2, 56, 52, 50, 44.8, 42.

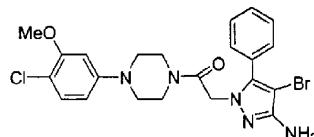
10 **Synthesis of 1-[4-(4-Chloro-3-methoxy-piperazin-1-yl)-2-(4-bromo-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone]**



[0263] Protocol T was followed using 4-Bromo-5-methyl-3-trifluoromethyl-1H-pyrazole, K_2CO_3 , 2-Chloro-1-[4-(4-chloro-3-methoxy-phenyl)-piperazin-1-yl]-ethanone and DMF.

15 Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/4) afforded the title compound as white solid. 1H NMR (400 MHz, $CDCl_3$): 7.18-7.22 (d, 1H), 6.44-6.48 (d, 1H), 6.36-6.42 (dd, 1H), 5.0 (s, 2H), 3.62-3.8 (m, 4H), 3.1-3.2 (m, 4H), 2.3 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): 162, 146.6, 142.2, 118.8, 116, 52.2, 50.4, 46.2, 42.2, 15.2.

20 **Synthesis of 2-(3-Amino-4-bromo-5-phenyl-pyrazol-1-yl)-1-[4-(4-chloro-3-methoxyphenyl)-piperazin-1-yl]-ethanone**

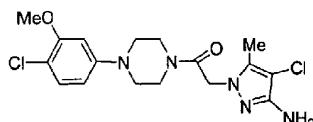


[0264] Protocol T was followed using 4-Bromo-5-phenyl-1H-pyrazol-3-ylamine, K_2CO_3 , 2-Chloro-1-[4-(4-chloro-3-methoxy-phenyl)-piperazin-1-yl]-ethanone and DMF. Column

chromatography using a solvent mixture (hexane/ ethyl acetate = 1/4) afforded the title compound as white solid. ¹H NMR (400 MHz, CDCl₃): 7.78-7.84 (d, 2H), 7.32-7.42 (m, 3H), 7.18-7.22 (d, 1H), 6.44-6.48 (d, 1H), 6.36-6.42 (dd, 1H), 4.94 (s, 2H), 4.28 (s, 2H), 3.88 (s, 3H), 3.76-3.86 (m, 4H), 3.12-3.18 (m, 4H). ¹³C NMR (400 MHz, CDCl₃): 164.6, 154.8, 5

150.2, 144.6, 130, 128.2, 128, 126.4, 109.2, 102, 56, 51, 50, 49.6, 45.6, 42.

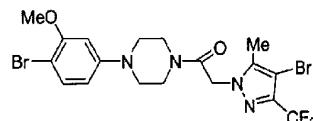
Synthesis of 2-(3-Amino-4-chloro-5-methyl-pyrazol-1-yl)-1-[4-(4-chloro-3-methoxyphenyl)-piperazin-1-yl]-ethanone



10 [0265] Protocol T was followed using 4-Chloro-5-methyl-1H-pyrazol-3-ylamine, K₂CO₃, 2-Chloro-1-[4-(4-chloro-3-methoxy-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/4) afforded the title compound as colorless oil. ¹H NMR (400 MHz, CDCl₃): 7.18-7.22 (d, 1H), 6.44-6.48 (d, 1H), 6.36-6.42 (dd, 1H), 5.0 (s, 2H), 4.24 (s, 2H), 2.4 (s, 3H), 3.76-3.86 (m, 4H), 3.12-3.18 (m, 4H). ¹³C NMR (400 MHz, CDCl₃): 164.6, 154.8, 144.6, 130.2, 130, 128.8, 109.2, 15

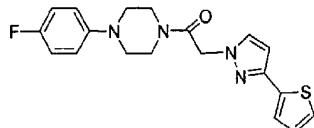
102, 56, 51, 49.6, 45.6, 42.

Synthesis of 1-[4-(4-Bromo-3-methoxy-piperazin-1-yl)-2-(4-bromo-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone



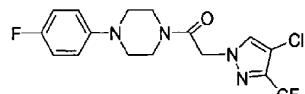
20 [0266] Protocol T was followed using 4-Bromo-5-methyl-3-trifluoromethyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-bromo-3-methoxy-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/4) afforded the title compound as white solid. ¹H NMR (400 MHz, CDCl₃): 7.38-7.4 (d, 1H), 6.44-6.46 (d, 1H), 6.26-6.4 (dd, 2H), 5.0 (s, 2H), 3.88 (s, 3H), 3.68-3.8 (m, 4H), 3.14-3.22 (m, 4H), 2.3 (s, 3H). ¹³C NMR (400 MHz, CDCl₃): 164.4, 158, 152.2, 144, 134, 110, 102.2, 56.6, 54.2, 50, 48.8, 46, 42.2, 12.

Synthesis of 1-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-(3-thiophen-2-yl-pyrazol-1-yl)-ethanone



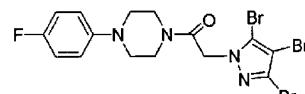
5 [0267] Protocol T was followed using 3-(2-thienyl)pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃): 7.48-7.52 (d, 1H), 7.24-7.28 (dd, 1H), 7.14-7.2 (dd, 1H), 6.98-7.2 (m, 1H), 6.88-6.96 (m, 2H), 6.78-6.84 (m, 2H), 6.46-6.52 (d, 1H), 5.0 (s, 2H), 3.64-3.8 (m, 4H), 2.94-3.1 (m, 4H). ¹³C NMR (400 MHz, CDCl₃): 164.4, 158, 152.2, 144, 134, 132, 126, 124, 123.8, 118, 116, 115.8, 102.2, 54, 51.2, 50.8, 45.8, 42.2.

Synthesis of 2-(4-Chloro-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone



15 [0268] Protocol T was followed using 4-Chloro-3-trifluoromethyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as colorless oil. ¹H NMR (400 MHz, CDCl₃): 7.64-7.68 (d, 1H), 6.98-7.4 (m, 2H), 6.86-6.92 (m, 2H), 6.98-7.2 (m, 1H), 5.4 (s, 2H), 3.78-3.84 (m, 2H), 3.68-3.92 (m, 2H), 3-3.1 (m, 4H). ¹³C NMR (400 MHz, CDCl₃): 164.4, 158, 152.2, 144, 132, 118.2, 116, 54, 50.2, 50.0, 46.0, 42.2.

Synthesis of 1-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-(3,4,5-tribromo-pyrazol-1-yl)-ethanone

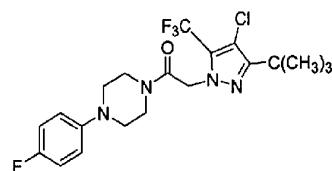


25

[0269] Protocol T was followed using 3,4,5-Tribromo-1H-pyrazole, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/4) afforded the title compound as white solid. 1H NMR (400 MHz, $CDCl_3$): 6.96-7.2 (m, 2H), 6.84-6.9 (m, 2H), 5.4 (s, 2H), 3.74-3.8 (m, 2H), 5 3.6-3.68 (m, 2H), 3.04-3.14 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$): 164.4, 158, 156, 144.2, 128, 118.4, 118.2, 116, 100, 52.8, 50.2, 50.0, 46.0, 42.2.

Synthesis of 2-(3-tert-Butyl-4-chloro-5-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone

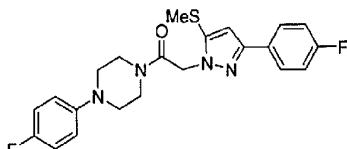
10



[0270] Protocol T was followed using 5-tert-Butyl-4-chloro-3-trifluoromethyl-1H-pyrazole, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as white solid. 1H NMR (400 MHz, $CDCl_3$): 6.94-7.22 (m, 2H), 6.84-6.92 (m, 2H), 5.3 (s, 2H), 3.68-3.8 (m, 2H), 3.6-3.68 (m, 2H), 3.04-3.2 (m, 4H), 1.4 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$): 164.8, 119, 118.4, 118.2, 116.2, 116, 54, 51, 50.8, 45.4, 42.2, 30, 29, 27.

Synthesis of 2-[3-(4-Fluoro-phenyl)-5-methylsulfanyl-pyrazol-1-yl]-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone

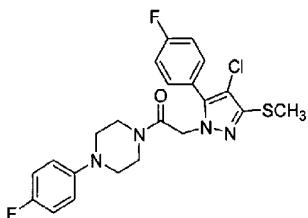
20



[0271] Protocol T was followed using 3-(4-Fluoro-phenyl)-5-methylsulfanyl-1H-pyrazole, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 2/3) afforded the title compound as white solid. 1H NMR (400 MHz, $CDCl_3$): 7.7-7.76 (m, 2H), 6.96-7.1 (m, 4H), 6.88-6.92 (m, 2H), 6.64 (s, 1H), 5.3 (s, 2H), 3.7-3.84 (m, 4H), 3.04-3.2 (m, 4H), 2.5 (s, 3H).

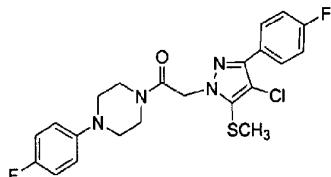
¹³C NMR (400 MHz, CDCl₃): 164.8, 152, 140, 127.4, 119, 118.4, 118.2, 116.2, 116, 108, 52.8, 52, 51.8, 45.4, 42.2, 20.

5 **Synthesis of 2-[4-Chloro-5-(4-Fluoro-phenyl)-3-methylsulfanyl-pyrazol-1-yl]-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone**



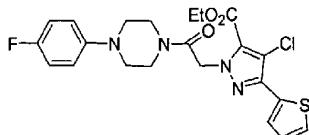
[0272] Protocol T was followed using 4-Chloro-3-(4-Fluoro-phenyl)-5-methylsulfanyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 2/3) afforded the 10 title compound as white solid. ¹H NMR (400 MHz, CDCl₃): 7.82-7.88 (m, 2H), 7.06-7.12 (m, 2H), 6.96-7.1 (m, 2H), 6.88-6.92 (m, 2H), 5.2 (s, 2H), 3.68-3.84 (m, 4H), 3.06-3.18 (m, 4H), 2.4 (s, 3H). ¹³C NMR (400 MHz, CDCl₃): 164.8, 158, 147, 135, 127.4, 127, 119, 112.4, 112.2, 110, 108.8, 52.8, 52, 51.8, 45.4, 42.2, 18.6.

15 **Synthesis of 2-[4-Chloro-3-(4-Fluoro-phenyl)-5-methylsulfanyl-pyrazol-1-yl]-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone**



[0273] Protocol T was followed using 4-Chloro-3-(4-Fluoro-phenyl)-5-methylsulfanyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. 20 Column chromatography using a solvent mixture (hexane/ ethyl acetate = 2/3) afforded the title compound as white solid. ¹H NMR (400 MHz, CDCl₃): 7.46-7.5 (m, 2H), 7.12-7.18 (m, 2H), 6.96-7.1 (m, 2H), 6.88-6.92 (m, 2H), 4.86 (s, 2H), 3.72-3.78 (m, 2H), 3.56-3.62 (m, 2H), 3.06-3.18 (m, 4H), 2.54 (s, 3H).

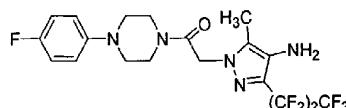
Synthesis of 2-{2-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-4-Chloro-3-thiophen-2-yl-2H-pyrazole-5-carboxylic acid ethyl ester



5 [0274] Protocol T was followed using 4-Chloro-3-Thiophen-2-yl-2H-pyrazole-5-carboxylic acid ethyl ester, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1.5/ 1: R_f = 0.62) afforded the title compound. 1H NMR (400 MHz, $CDCl_3$): 7.06-7.36 (m, 1H), 6.96-7.2 (m, 3H), 6.84-6.92 (m, 3H), 5.46 (s, 2H), 4.3-4.4 (q, 2H), 3.6-3.82 (m, 4H), 3.05-3.25 (m, 4H), 1.3-1.42 (m, 3H).

10

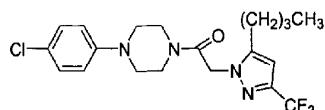
Synthesis of 2-(4-Amino-3-heptafluoropropyl-5-methyl-pyrazol-1-yl)-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone



15 [0275] Protocol T was followed using 4-Amino-3-heptafluoropropyl-5-methyl-1H-pyrazole, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/4) afforded the title compound as colorless oil. 1H NMR (400 MHz, $CDCl_3$): 6.92-7.02 (m, 4H), 5.14 (s, 2H), 3.64-3.82 (m, 4H), 3.6 (s, 2H), 3.1-3.22 (m, 4H), 2.16 (s, 3H). ^{13}C NMR (400 MHz, CD_6CO): 160.4, 158, 146, 144.2, 119.8, 118.2, 52, 50.8, 50.6, 46, 42, 12.2.

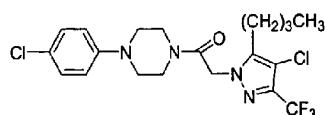
20

Synthesis of 2-(5-Butyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethanone



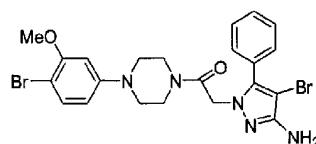
[0276] Protocol T was followed using 5-n-Butyl-3-trifluoromethyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/4) afforded the title compound as colorless oil. ¹H NMR (400 MHz, CDCl₃): 7.18-7.24 (m, 2H), 6.78-6.84 (m, 2H), 6.32 (s, 1H), 5.0 (s, 2H), 3.66-3.78 (m, 4H), 3.08-3.18 (m, 4H), 2.58-2.64 (t, 2H), 1.6-1.7 (m, 2H), 1.38-1.48 (m, 2H), 0.6-1.0 (t, 3H). ¹³C NMR (400 MHz, CDCl₃): 160.4, 150, 148, 142, 130, 126, 119.8, 103.2, 52, 50.8, 50.6, 46, 42, 30, 26, 22, 14.

10 **Synthesis of 2-(4-Chloro-5-butyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethanone**



[0277] Protocol T was followed using 4-Chloro-5-n-butyl-3-trifluoromethyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/4) afforded the title compound as colorless oil. ¹H NMR (400 MHz, CDCl₃): 7.18-7.24 (m, 2H), 6.78-6.84 (m, 2H), 5.0 (s, 2H), 3.66-3.78 (m, 4H), 3.08-3.2 (m, 4H), 2.58-2.64 (t, 2H), 1.5-1.54 (m, 2H), 1.38-1.48 (m, 2H), 0.6-1.0 (t, 3H). ¹³C NMR (400 MHz, CDCl₃): 160.4, 148, 142, 130, 128, 119.8, 52, 50.8, 50.6, 46, 42, 30.4, 26, 23, 14.

20 **Synthesis of 2-(3-Amino-4-bromo-5-phenyl-pyrazol-1-yl)-1-[4-(4-bromo-3-methoxyphenyl)-piperazin-1-yl]-ethanone**

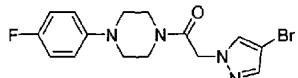


[0278] Protocol T was followed using 4-Bromo-5-phenyl-1H-pyrazol-3-ylamine, K₂CO₃, 2-Chloro-1-[4-(4-bromo-3-methoxy-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1.5) afforded the title compound as white solid. ¹H NMR (400 MHz, CDCl₃): 7.78-7.84 (d, 2H), 7.32-7.42 (m, 3H), 7.18-7.22 (d, 1H), 6.44-6.52 (d, 1H), 6.36-6.42 (dd, 1H), 4.94 (s, 2H), 4.28 (s, 2H), 3.84

(s, 3H), 3.76-3.82 (m, 4H), 3.12-3.18 (m, 4H). ^{13}C NMR (400 MHz, CDCl_3): 164.6, 154.8, 150.2, 144.6, 130, 128.8, 128.6, 126.4, 109.2, 102, 56, 51, 50, 49.6, 45.6, 42.

Synthesis of 2-(4-Bromopyrazol)-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone

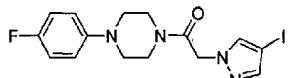
5



[0279] Protocol T was followed using 4-Bromo-1H-pyrazol, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as a white solid. ^1H NMR (400 MHz, CDCl_3): 7.52-7.58 (d, 1H), 7.48-7.52 (d, 1H), 6.95-7.0 (m, 2H), 6.82-6.92 (dd, 2H), 5.00 (s, 2H), 3.72-3.80 (t, 2H), 3.64-3.72 (t, 2H), 3.02-3.12 (m, 4H). ^{13}C NMR (400 MHz, CDCl_3): 164.6, 158.2, 156.2, 146.6, 141.6, 140.2, 130.5, 129.6, 118.2, 118.0, 115.2, 116.4, 94.2, 53.8, 50.8, 50.2, 45.4, 42.

Synthesis of 2-(4-Iodopyrazol)-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone

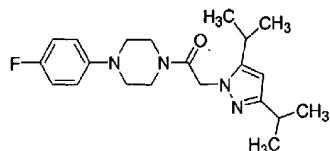
15



[0280] Protocol T was followed using 4-Iodo-1H-pyrazol, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as a white solid. ^1H NMR (400 MHz, CDCl_3): 7.58-7.62 (d, 1H), 7.52 (s, 1H), 6.95-7.1 (m, 2H), 6.84-6.92 (dd, 2H), 5.00 (s, 2H), 3.72-3.80 (t, 2H), 3.64-3.72 (t, 2H), 3.02-3.12 (m, 4H). ^{13}C NMR (400 MHz, CDCl_3): 164.6, 158.2, 156.2, 146.8, 140.8, 140.2, 130.5, 129.6, 118.2, 118.0, 115.4, 116.8, 96.0, 53.4, 51.2, 50.2, 45.2, 42.

Synthesis of 2-(3,5-Diisopropyl-pyrazol-1-yl)-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone

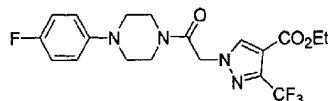
25



[0281] Protocol T was followed using 3,5-Diisopropyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as white solid. ¹H NMR (400 MHz, CDCl₃): 6.92-7.0 (m, 2H), 6.80-6.88 (dd, 2H), 5.88 (s, 1H), 4.92 (s, 2H), 3.70-3.80 (t, 4H), 2.90-3.10 (m, 4H), 1.40-1.60 (m, 12H). ¹³C NMR (400 MHz, CDCl₃): 160.6, 158.2, 150.2, 119.2, 118.0, 100.0, 50.8, 50.5, 50.2, 45.2, 42, 28.2, 26.0, 22.4.

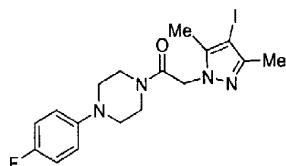
Synthesis of 1-[2-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester

10 **1H-pyrazole-4-carboxylic acid ethyl ester**



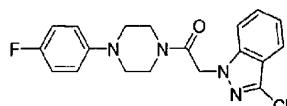
[0282] Protocol T was followed using 3-Trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as colorless oil. ¹H NMR (400 MHz, CDCl₃): 8.15 (s, 1H), 6.98-7.04 (m, 2H), 6.86-6.92 (m, 2H), 5.1 (s, 2H), 4.28-4.38 (q, 2H), 3.78-3.84 (m, 2H), 3.62-3.74 (m, 2H), 3.04-3.2 (m, 4H), 1.3-1.4 (t, 3H). ¹³C NMR (400 MHz, CDCl₃): 163.4, 160.5, 159.2, 156.2, 147, 137.2, 119, 118.8, 116, 115.8, 61, 54, 50.8, 50.0, 45.0, 42.2, 14.2.

20 **Synthesis of 1-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-(4-iodo-3,5-dimethyl-pyrazol-1-yl)-ethanone**



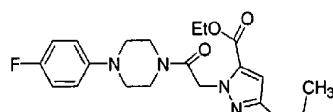
[0283] Protocol T was followed using 4-Iodo-3,5-dimethyl-pyrazole, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as a white solid. 1H NMR (400 MHz, $CDCl_3$): 6.95-7.1 (m, 2H), 6.84-6.92 (dd, 2H), 5.00 (s, 2H), 3.62-3.82 (m, 4H), 3.02-3.12 (m, 4H), 2.22-2.32 (d, 6H). ^{13}C NMR (400 MHz, $CDCl_3$): 165, 158.2, 156.2, 150.2, 146.8, 141.8, 118.8, 115.4, 115.2, 52.8, 51.6, 50.2, 45.2, 42, 14.8, 12.6.

Synthesis of 2-(3-Chloro-indazol-1-yl)-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone



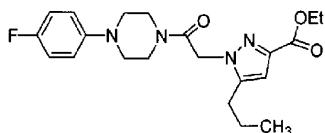
10 [0284] Protocol T was followed using 3-Chloro-1H-indazole, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/4) afforded the title compound as a white solid. 1H NMR (400 MHz, $CDCl_3$): 7.64-7.70 (m, 1H), 7.38-7.48 (m, 2H), 7.18-7.26 (m, 2H), 6.94-7.0 (m, 2H), 6.82-6.88 (dd, 2H), 5.2 (s, 2H), 3.72-3.82 (m, 4H), 3.02-3.08 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$): 165, 158.2, 142.8, 134.8, 128.8, 128.4, 122, 121.6, 118.8, 118.6, 115.4, 115.2, 110.6, 110.0, 51.8, 50.6, 50.2, 45.2, 42.

Synthesis of 2-[2-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl]-5-propyl-2H-pyrazole-3-carboxylic acid ethyl ester



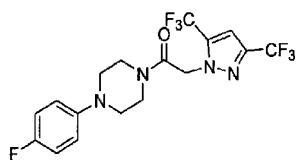
20 [0285] Protocol T was followed using 5-Propyl-2H-pyrazole-3-carboxylic acid ethyl ester, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as a white solid. 1H NMR (400 MHz, $CDCl_3$): 6.94-7.0 (m, 2H), 6.82-6.90 (dd, 2H), 6.7 (s, 1H), 5.5 (s, 2H), 4.26-4.32 (q, 2H), 3.62-3.82 (m, 4H), 3.04-3.18 (m, 4H), 2.58-2.64 (t, 2H), 1.64-1.74 (m, 2H), 1.34-1.38 (t, 3H), 0.96-1.0 (t, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): 165, 160, 156.2, 152.4, 146.8, 132.8, 118.2, 118.1, 115.8, 115.4, 110.2, 61, 53, 50.6, 50.2, 45, 42, 30, 22.8, 14.2, 14.

Synthesis of 2-{2-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-propyl-2H-pyrazole-5-carboxylic acid ethyl ester



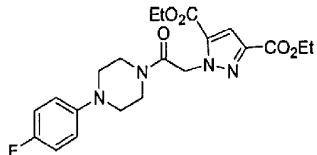
5 [0286] Protocol T was followed using 5-Propyl-2H-pyrazole-3-carboxylic acid ethyl ester, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as white solid. 1H NMR (400 MHz, $CDCl_3$): 6.94-7.0 (m, 2H), 6.82-6.90 (dd, 2H), 6.2 (s, 1H), 5.06 (s, 2H), 4.34-4.40 (q, 2H), 3.62-3.8 (m, 4H), 3.02-3.12 (m, 4H), 2.54-10 2.60 (t, 2H), 1.64-1.78 (m, 2H), 1.34-1.38 (t, 3H), 0.98-1.4 (t, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): 165, 160, 156.4, 152.2, 146.6, 132.8, 118.4, 118.2, 115.8, 115.4, 113.2, 61, 53, 50.6, 50.2, 45.2, 42, 28, 21.8, 14.2, 14.

Synthesis of 2-(3,5-Bis-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone



15 [0287] Protocol T was followed using 3,5-Bis-trifluoromethyl-1H-pyrazole, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as a white solid. 1H NMR (400 MHz, $CDCl_3$): 6.94-7.0 (m, 2H), 6.92 (s, 1H), 6.82-7.90 (dd, 2H), 5.2 (s, 2H), 3.72-3.8 (t, 2H), 3.58-3.66 (t, 2H), 3.12-3.18 (t, 2H), 3.02-3.12 (t, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): 162.2, 158.2, 156.4, 146.5, 118.4, 116.2, 115.8, 113.2, 60.4, 53.2, 50.6, 50.2, 45.2, 42.2, 21.2, 14.2.

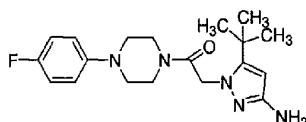
25 **Synthesis of 1-{2-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-1H-pyrazole-3,5-dicarboxylic acid diethyl ester**



[0288] Protocol T was followed using 1H-Pyrazole-3,5-dicarboxylic acid diethyl ester, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃): 7.38 (s, 1H), 6.94-7.0 (m, 2H), 6.82-7.90 (dd, 2H), 5.54 (s, 2H), 4.36-4.42 (q, 2H), 4.26-4.32 (q, 2H), 3.60-3.80 (m, 4H), 3.02-3.20 (m, 4H), 1.22-1.42 (m, 6H). ¹³C NMR (400 MHz, CDCl₃): 164.2, 162.2, 158.2, 157.4, 156.2, 148.5, 144.4, 134.2, 118.4, 116.2, 115.8, 114.2, 62, 61.8, 54.2, 50.6, 50.2, 45.2, 42.2, 14.6, 14.2.

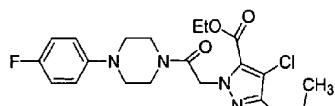
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Synthesis of 2-(3-Amino-4-*t*-butyl-pyrazol-1-yl)-1-[4-(4-fluorophenyl)-piperazin-1-yl]-ethanone



[0289] Protocol T was followed using 5-*tert*-Butyl-1H-pyrazol-3-ylamine, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 3/7: R_f = 0.49) afforded the title compound as colorless oil. ¹H NMR (400 MHz, CDCl₃): 6.92-7.98 (l, 2H), 6.82-6.88 (dd, 2H), 4.84 (s, 2H), 3.95 (s, 2H), 3.70-3.90 (m, 4H), 2.95-3.10 (m, 4H), 1.25 (s, 9H).

20 **Synthesis of 2-[2-(4-(4-Fluoro-phenyl)-piperazin-1-yl)-2-oxo-ethyl]-4-chloro-5-propyl-2H-pyrazole-3-carboxylic acid ethyl ester**



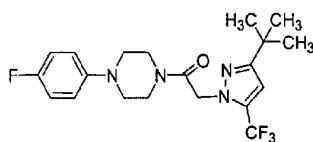
[0290] Protocol T was followed using 4-Chloro-5-Propyl-2H-pyrazole-3-carboxylic acid ethyl ester, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF.

Column chromatography using a solvent mixture (hexane/ ethyl acetate = 3/7) afforded the title compound as a white solid. ^1H NMR (400 MHz, CDCl_3): 6.94-7.0 (m, 2H), 6.82-6.90 (dd, 2H), 5.0 (s, 2H), 4.36-4.40 (q, 2H), 3.62-3.82 (m, 4H), 3.04-3.18 (m, 4H), 2.58-2.66 (t, 2H), 1.64-1.76 (m, 2H), 1.34-1.38 (t, 3H), 0.94-1.0 (t, 3H). ^{13}C NMR (400 MHz, CDCl_3): 5

165, 160.2, 156.2, 152.4, 147, 133, 118.4, 118.2, 115.8, 115.4, 112.2, 61, 53, 50.6, 50.2, 45, 42, 30, 22.8, 14.4, 14.2.

Synthesis of 2-(3-tert-Butyl-5-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone

10

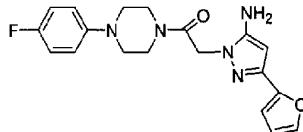


[0291] Protocol T was followed using 5-tert-Butyl-3-trifluoromethyl-1H-pyrazole, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as a colorless oil. ^1H NMR (400 MHz, CDCl_3): 6.92-7.08 (t, 2H), 6.82-6.88 (dd, 2H), 6.52 (s, 1H), 5.08 (s, 2H), 3.70-3.80 (m, 2H), 3.58-3.68 (m, 2H), 3.05-3.15 (m, 4H), 1.3

15 (s, 9H). ^{13}C NMR (400 MHz, CDCl_3): 164, 161.2, 158.2, 156.4, 147.2, 118.4, 118.2, 115.8, 115.4, 108.2, 54, 50.6, 50.2, 45, 44, 30.

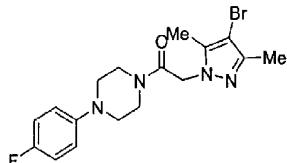
Synthesis of 2-(5-Amino-3-furan-2-yl-pyrazol-1-yl)-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone

20



[0292] Protocol T was followed using 3-Furan-2-yl-2H-pyrazol-5-ylamine, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using 100% ethyl acetate afforded the title compound as a white solid. ^1H NMR (400 MHz, CD_3CO): 7.48-7.52 (m, 1H), 6.98-7.06 (m, 2H), 6.52-6.56 (m, 2H), 6.44-6.48 (m, 2H), 5.74 (s, 1H), 4.98 (s, 2H), 3.68-3.88 (m, 4H), 3.12-3.24 (m, 4H). MS (ES) $\text{M}+\text{H}$ expected = 369.4, found 370.1.

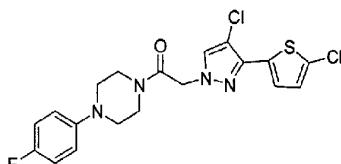
Synthesis of 1-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-(4-bromo-3,5-dimethyl-pyrazol-1-yl)-ethanone



5 [0293] Protocol T was followed using 4-Bromo-3, 5-dimethyl-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃): 6.95-7.1 (m, 2H), 6.84-6.92 (dd, 2H), 4.90 (s, 2H), 3.62-3.82 (m, 4H), 3.02-3.12 (m, 4H), 2.24-2.34 (d, 6H). ¹³C NMR (400 MHz, CDCl₃): 165, 158.4, 156.6, 150.6, 146.8, 141.4, 119, 115.6, 115.2, 52.6, 51.6, 50.4, 45.2, 42.2, 14.8, 12.6.

10

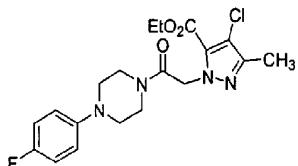
Synthesis of 2-[4-Chloro-3-(5-chloro-thiophen-2-yl)-pyrazol-1-yl]-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone



15 [0294] Protocol T was followed using 4-Chloro-3-(5-chloro-thiophen-2-yl)-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 2/3) afforded the title compound as yellow solid. ¹H NMR (400 MHz, CDCl₃): 7.58 (s, 1H), 7.38-7.42 (d, 1H), 6.94-7.1 (m, 2H), 6.84-6.88 (dd, 2H), 4.96 (s, 2H), 3.62-3.81 (m, 4H), 3.02-3.14 (m, 4H). ¹³C NMR (400 MHz, CDCl₃): 165, 158.8, 156.8, 142.4, 131, 126.8, 124.8, 119, 116, 115.6, 54, 52, 51.6, 46, 42.6.

20

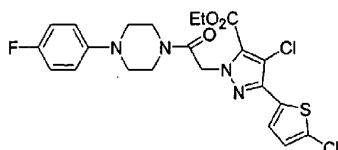
Synthesis of 4-Chloro-2-[2-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl]-5-methyl-2H-pyrazole-3-carboxylic acid ethyl ester



[0295] Protocol T was followed using 4-Chloro-5-methyl-2H-pyrazole-3-carboxylic acid ethyl ester, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF.

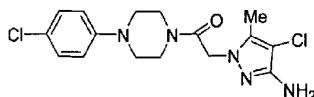
Column chromatography using a solvent mixture (hexane/ ethyl acetate = 2/3) afforded the title compound as a white solid. 1H NMR (400 MHz, $CDCl_3$): 6.94-7.1 (m, 2H), 6.84-6.88 (dd, 2H), 5.04 (s, 2H), 4.38-4.44 (q, 2H), 3.62-3.80 (m, 4H), 3.02-3.14 (m, 4H), 2.3 (s, 3H), 1.36-1.42 (t, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): 182, 165, 119, 116.2, 116, 61.4, 52.3, 51, 50.8, 45.8, 42.6, 14.4, 10.

Synthesis of 4-Chloro-5-(5-chloro-thiophen-2-yl)-2-[2-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl]-2H-pyrazole-3-carboxylic acid ethyl ester



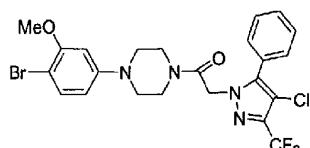
[0296] Protocol T was followed using 4-Chloro-5-(5-chloro-thiophen-2-yl)-2H-pyrazole-3-carboxylic acid ethyl ester, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 2/3) afforded the title compound as a yellow solid. 1H NMR (400 MHz, $CDCl_3$): 7.46-7.48 (m, 1H), 6.94-7.1 (m, 2H), 6.84-6.92 (m, 3H), 5.4 (s, 2H), 4.34-4.4 (q, 2H), 3.62-3.81 (m, 4H), 3.04-3.24 (m, 4H), 1.36-1.44 (m, 3H). MS (ES) $M+H$ expected = 511.41, found 511.

Synthesis of 2-(3-Amino-4-chloro-5-methyl-pyrazol-1-yl)-1-[4-(4-chlorophenyl)-piperazin-1-yl]-ethanone



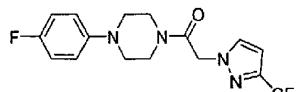
[0297] Protocol T was followed using 4-Chloro-5-methyl-1H-pyrazol-3-ylamine, K_2CO_3 , 2-Chloro-1-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/4) afforded the title compound as a colorless oil. 1H NMR (400 MHz, $CDCl_3$): 7.18-7.22 (d, 1H), 6.78-6.84 (d, 2H), 4.8 (s, 2H), 4.4 (s, 2H), 3.72-3.82 (m, 4H), 3.08-3.18 (m, 4H), 2.14 (s, 3H).

Synthesis of 1-[4-(4-Bromo-3-methoxyphenyl)-piperazin-1-yl]-2-(4-chloro-5-phenyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone



[0298] Protocol T was followed using 4-Chloro-5-phenyl-3-trifluoromethyl-1H-pyrazole, K_2CO_3 , 2-Chloro-1-[4-(4-bromo-3-methoxy-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 2/3: R_f = 0.58) afforded the title compound as a white solid. 1H NMR (400 MHz, $CDCl_3$): 7.81-7.86 (m, 1H), 7.36-7.44 (m, 4H), 6.42-6.48 (d, 1H), 6.34-6.38 (dd, 2H), 5.2 (s, 2H), 3.88 (s, 3H), 3.62-3.82 (m, 4H), 3.12-3.22 (m, 4H).

Synthesis of 1-[4-(4-Fluorophenyl)-piperazin-1-yl]-2-(3-trifluoromethyl-pyrazol)-ethanone

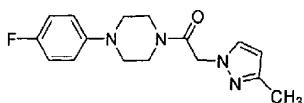


[0299] Protocol T was followed using 3-trifluoromethyl-1H-pyrazole, K_2CO_3 , 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as a white solid. 1H NMR (400 MHz, $CDCl_3$): 7.54-7.60 (m, 1H), 6.94-7.0 (m, 2H), 6.80-6.88 (m, 2H), 6.52-6.58

(d, 1H), 5.2 (s, 2H), 3.72-3.80 (t, 2H), 3.62-3.72 (t, 2H), 3.02-3.12 (m, 4H). MS (ES) M+H expected 356.33, found 357.1.

Synthesis of 1-[4-(4-Fluorophenyl)-piperazin-1-yl]-2-(3-methyl-pyrazol)-ethanone

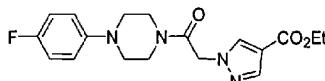
5



[0300] Protocol T was followed using 3-methyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃): 7.38-7.41 (m, 1H), 6.94-7.0 (m, 2H), 6.80-6.88 (m, 2H), 6.08-6.10 (d, 1H), 4.95 (s, 2H), 3.74-3.82 (t, 2H), 3.62-3.72 (t, 2H), 3.0-3.1 (m, 4H), 2.28 (s, 3H). MS (ES) M+H expected 302.05, found 303.1.

Synthesis of 1-[2-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl]-1H-pyrazole-4-carboxylic acid ethyl ester

15



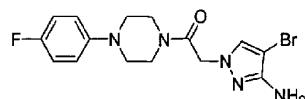
[0301] Protocol T was followed using 1H-Pyrazole-4-carboxylic acid ethyl ester, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃): 8.2 (s, 1H), 7.92 (s, 1H), 6.94-7.0 (m, 2H), 6.82-6.88 (m, 2H), 5.0 (s, 2H), 4.1-4.2 (q, 2H), 3.74-3.82 (t, 2H), 3.62-3.72 (t, 2H), 3.0-3.12 (m, 4H), 1.28-1.42 (t, 3H). MS (ES) M+H expected 360.39, found 361.1.

Synthesis of 1-[4-(4-Fluorophenyl)-piperazin-1-yl]-2-(4-methyl-pyrazol)-ethanone

25 [0302] Protocol T was followed using 4-methyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as a white solid. ¹H NMR

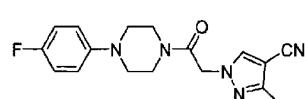
(400 MHz, CDCl₃): 7.26-7.32 (m, 1H), 6.94-7.0 (m, 2H), 6.80-6.88 (m, 2H), 5.0 (s, 2H), 3.62-3.82 (m, 4H), 3.0-3.1 (m, 4H), 2.1 (s, 3H). MS (ES) M+H expected 302.35, found 303.1.

5 **Synthesis of 1-[4-(4-Fluorophenyl)-piperazin-1-yl]-2-(3-amino-4-bromopyrazole)-ethanone**



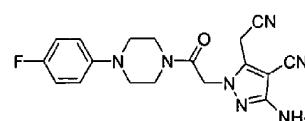
[0303] Protocol T was followed using 4-bromo-3-aminopyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 3/7) afforded the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃): 7.23 (s, 1H), 6.94-7.0 (m, 2H), 6.80-6.88 (m, 2H), 4.9 (s, 2H), 4.2 (s, 2H), 3.72-3.82 (m, 4H), 3.0-3.14 (m, 4H). MS (ES) M+H expected 382.24, found 382.

15 **Synthesis of 1-[4-(4-Fluorophenyl)-piperazin-1-yl]-2-(3-amino-4-cyanopyrazole)-ethanone**



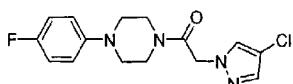
[0304] Protocol T was followed using 3-amino-4-cyano-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 3/7) afforded the title compound as a solid. ¹H NMR (400 MHz, CDCl₃): 7.48 (s, 1H), 6.96-7.2 (m, 2H), 6.86-6.92 (m, 2H), 4.96 (s, 2H), 4.88 (s, 2H), 3.78-3.86 (m, 4H), 3.08-3.16 (m, 4H). MS (ES) M+H expected 328.25, found 329.1

25 **Synthesis of 3-Amino-5-cyanomethyl-1-{2-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-1H-pyrazole-4-carbonitrile**



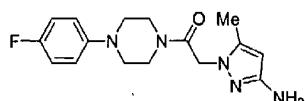
[0305] Protocol T was followed using 5-amino-3-cyanomethyl-1H-pyrazole-4-carbonitrile, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 3/2) afforded the title compound as white solid. ¹H NMR (400 MHz, CDCl₃): 6.96-7.2 (m, 2H), 6.86-6.92 (m, 2H), 5.2 (s, 2H), 4.86 (s, 2H), 3.78-3.86 (m, 4H), 3.7 (s, 2H), 3.08-3.16 (m, 4H). MS (ES) M+H expected 367.39, found 368.1.

Synthesis of 1-[4-(4-Fluorophenyl)-piperazin-1-yl]-2-(4-chloro-pyrazol)-ethanone



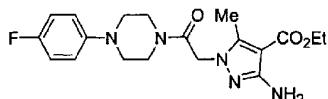
10 [0306] Protocol T was followed using 4-chloro-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 3/2) afforded the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃): 7.54-7.56 (d, 2H), 7.46 (s, 1H), 6.94-7.2 (m, 2H), 6.84-6.88 (m, 2H), 4.98 (s, 2H), 3.62-3.82 (m, 4H), 3.0-3.1 (m, 4H). MS (ES) M+H expected 322.77, found 323.1

Synthesis of 2-(3-Amino-5-methyl-pyrazol-1-yl)-1-[4-(4-fluorophenyl)-piperazin-1-yl]-ethanone



20 [0307] Protocol T was followed using 5-methyl-1H-pyrazol-3-ylamine, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/4) afforded the title compound as a colorless oil. ¹H NMR (400 MHz, CDCl₃): 7.12-7.18 (m, 3H), 7.0-7.08 (t, 2H), 4.8 (s, 2H), 5.1 (s, 2H), 3.78-3.88 (m, 4H), 3.18-3.38 (m, 4H), 2.28 (s, 3H). MS (ES) M+H expected 317.37, found 318.1

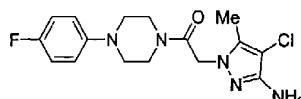
Synthesis of 3-Amino-1-{2-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-5-methyl-1H-pyrazole-4-carboxylic acid ethyl ester



[0308] Protocol T was followed using 3-Amino-5-methyl-1H-pyrazole-4-carboxylic acid ethyl ester, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/4) afforded the title compound as a colorless oil. ¹H NMR (400 MHz, CDCl₃): 6.94-7.1 (m, 2H), 6.84-6.88 (m, 2H), 5.52 (s, 2H), 4.78 (s, 2H), 4.24-4.32 (q, 2H), 3.74-3.82 (m, 4H), 3.0-3.1 (m, 4H), 2.3 (s, 3H), 1.31-1.38 (t, 3H). MS (ES) M+H expected 389.43, found 390.1.

Synthesis of 2-(3-Amino-4-chloro-5-methyl-pyrazol-1-yl)-1-[4-(4-fluorophenyl)-

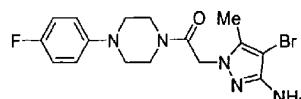
10 piperazin-1-yl]-ethanone



[0309] Protocol T was followed using 4-Chloro-5-methyl-1H-pyrazol-3-ylamine, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/4) afforded the title compound as colorless oil. ¹H NMR (400 MHz, CDCl₃): 7.02-7.08 (m, 2H), 6.94-7.0 (t, 2H), 4.85 (s, 2H), 4.2 (s, 2H), 3.80-3.88 (m, 4H), 3.14-3.34 (m, 4H), 2.34 (s, 3H). MS (ES) M+H expected 317.37, found 318.1. MS (ES) M+H expected 351.81, found 352.1.

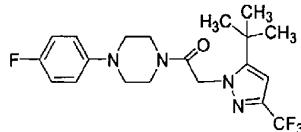
Synthesis of 2-(3-Amino-4-bromo-5-methyl-pyrazol-1-yl)-1-[4-(4-fluorophenyl)-

20 piperazin-1-yl]-ethanone



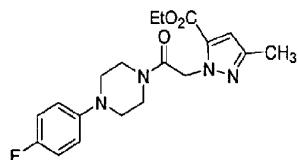
[0310] Protocol T was followed using 4-Bromo-5-methyl-1H-pyrazol-3-ylamine, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography ethyl acetate afforded the title compound as a colorless oil. ¹H NMR (400 MHz, CDCl₃): 6.94-7.02 (m, 2H), 6.82-6.88 (t, 2H), 4.84 (s, 2H), 4.1 (s, 2H), 3.72-3.78 (m, 4H), 3.04-3.08 (m, 4H), 2.16 (s, 3H). MS (ES) M+H expected 317.37, found 318.1. MS (ES) M+H expected 396.27, found 396.

Synthesis of 2-(5-tert-Butyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone



5 [0311] Protocol T was followed using 5-tert-Butyl-3-trifluoromethyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as a colorless oil. ¹H NMR (400 MHz, CDCl₃): 6.94-7.08 (t, 2H), 6.82-6.88 (dd, 2H), 6.32 (s, 1H), 5.14 (s, 2H), 3.62-3.80 (m, 4H), 3.05-3.18 (m, 4H), 1.35 (s, 9H). MS (ES) 10 M+H expected 412.43, found 413.1

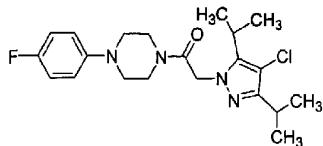
Synthesis of 2-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl]-5-methyl-2H-pyrazole-3-carboxylic acid ethyl ester



15 [0312] Protocol T was followed using 5-methyl-2H-pyrazole-3-carboxylic acid ethyl ester, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1) afforded the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃): 6.94-7.0 (m, 2H), 6.84-6.88 (dd, 2H), 6.58 (s, 1H), 5.04 (s, 2H), 4.3-4.38 (q, 2H), 3.62-3.80 (m, 4H), 3.02-3.14 (m, 4H), 2.3 (s, 3H), 1.32-1.38 (t, 3H). ¹³C NMR (400 MHz, CDCl₃): 180, 165, 119, 116.2, 116, 109, 61.8, 52, 51.5, 50.8, 45.8, 42.6, 14.4, 10.2.

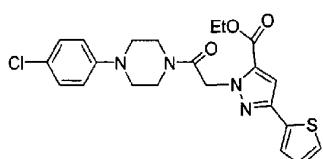
Synthesis of 2-(3,5-Diisopropyl-4-chloro-pyrazol-1-yl)-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone

25



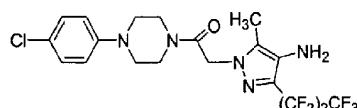
[0313] Protocol T was followed using 3,5-Diisopropyl-4-chloro-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1, R_f = 0.76) afforded the title compound as white solid. MS (ES) M+H expected = 406.9, found 407.1.

Synthesis of 2-[2-[4-(4-Chloro-phenyl)-piperazin-1-yl]-2-oxo-ethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester



[0314] Protocol T was followed using 5-Thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester, K₂CO₃, 2-Chloro-1-[4-(4-Chloro-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1.5/ 1) afforded the title compound. ¹H NMR (400 MHz, CDCl₃): 7.34-7.38 (m, 1H), 7.24-7.26 (m, 1H), 7.12 (s, 1H), 7.04-7.08 (dd, 1H), 6.96-7.2 (m, 2H), 6.88-6.94 (m, 2H), 4.32-4.42 (q, 2H), 3.52-3.58 (m, 4H), 3.05-3.35 (m, 4H), 1.32-1.42 (m, 3H). ¹³C NMR (400MHz, CDCl₃): 164.2, 128, 126.8, 126.6, 120.2, 118.4, 115.2, 62.5, 54.2, 50.5, 42.6, 44, 14.6.

Synthesis of 2-(4-Amino-3-heptafluoropropyl-5-methyl-pyrazol-1-yl)-1-[4-(4-chlorophenyl)-piperazin-1-yl]-ethanone

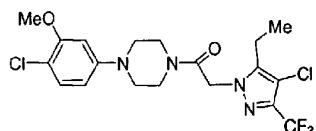


[0315] Protocol T was followed using 4-Amino-3-heptafluoropropyl-5-methyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethanone and DMF.

Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/4, R_f = 0.42) afforded the title compound as colorless oil. ^1H NMR (400 MHz, CDCl_3): 6.88-6.94 (d, 2H), 7.22-7.26 (d, 2H), 4.98 (s, 2H), 3.64-3.82 (m, 4H), 3.1-3.22 (m, 4H), 2.98 (s, 2H), 2.18 (s, 3H). MS (ES) $\text{M}+\text{H}$ expected = 501.82, found 502.1.

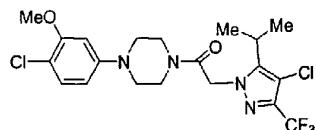
5

Synthesis of 1-[4-(4-Chloro-3-methoxy-phenyl)-piperazin-1-yl]-2-(4-chloro-5-ethyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone:



10 [0316] Protocol T was followed using 4-Chloro-5-ethyl-3-trifluoromethyl-1-H-pyrazol, K_2CO_3 , 1-[4-(4-Chloro-3-methoxyphenyl)-piperazine-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 2/3, R_f = 0.53) afforded the title compound as white solid. ^1H NMR (400 MHz, CDCl_3): 7.18-7.22 (d, 2H), 6.38-6.48 (m, 2H), 4.98 (s, 2H), 3.86 (s, 3H), 3.66-3.76 (m, 4H), 3.1-3.2 (m, 4H), 2.66-2.74 (q, 2H), 1.18-1.28 (m, 3H). MS (ES) $\text{M}+\text{H}$ expected = 464.82, found 465.

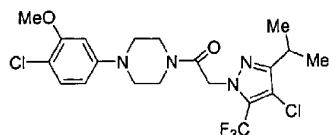
Synthesis of 2-(4-Chloro-5-isopropyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chloro-3-methoxy-phenyl)-piperazin-1-yl]-ethanone:



20 [0317] Protocol T was followed using 4-Chloro-5-isopropyl-3-trifluoromethyl-1-H-pyrazol, K_2CO_3 , 1-[4-(4-Chloro-3-methoxyphenyl)-piperazine-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 5.5/4.5, R_f = 0.52) afforded the title compound as white solid. ^1H NMR (400 MHz, CDCl_3): 7.19-7.22 (d, 2H), 6.42-6.48 (m, 2H), 5.18 (s, 2H), 3.88 (s, 3H), 3.56-3.78 (m, 4H), 3.22-3.44 (m, 4H), 3.04-3.14 (m, 1H), 1.44-1.48 (d, 6H). ^{13}C NMR (400MHz, CDCl_3): 164.2, 154.8, 151, 130, 109.8, 102, 56.2, 54, 50.5, 50, 45.2, 42.6, 26.2, 22.1.

Synthesis of 2-(4-Chloro-3-isopropyl-5-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chloro-3-methoxy-phenyl)-piperazin-1-yl]-ethanone:

5

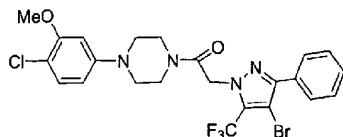


[0318] Protocol T was followed using 4-Chloro-3-isopropyl-5-trifluoromethyl-1-H-pyrazol, K₂CO₃, 1-[4-(4-Chloro-3-methoxyphenyl)-piperazine-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate =2/3, R_f = 0.45) afforded the title compound as white solid. ¹H NMR (400 MHz, CDCl₃): 7.19-7.22 (d, 2H), 6.38-6.48 (m, 2H), 5 (s, 2H), 3.86 (s, 3H), 3.62-3.78 (m, 4H), 3.08-3.18 (m, 4H), 2.98-3.04 (m, 1H), 1.35-1.41 (d, 6H). ¹³C NMR (400MHz, CDCl₃): 163.8, 154.8, 150.5, 130, 109.8, 102, 56.4, 52.8, 50, 49.8, 45.2, 42.6, 26.8, 20.

15 **Synthesis of 2-(4-Chloro-3-n-propyl-5-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chloro-3-methoxy-phenyl)-piperazin-1-yl]-ethanone:**

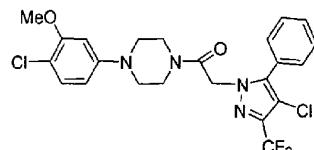
[0319] Protocol T was followed using 4-Chloro-3-n-propyl-5-trifluoromethyl-1-H-pyrazol, K₂CO₃, 1-[4-(4-Chloro-3-methoxyphenyl)-piperazine-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate =3/7, R_f = 0.78) afforded the title compound as white solid. ¹H NMR (400 MHz, CDCl₃): 7.22-7.24 (d, 2H), 6.42-6.48 (m, 2H), 5.7 (s, 2H), 3.8 (s, 3H), 3.72-3.78 (m, 4H), 3.22-3.42 (m, 4H), 2.66-2.72 (t, 2H), 1.58-1.68 (m, 2H), 0.98-1.02 (t, 3H). ¹³C NMR (400MHz, CDCl₃): 164, 154.8, 150.5, 130, 109.8, 102.2, 56.4, 52.8, 50, 49.8, 45.2, 42.6, 26, 21.8, 14.

Synthesis of 1-[4-(4-Chloro-3-methoxyphenyl)-piperazin-1-yl]-2-(4-bromo-3-phenyl-5-trifluoromethyl-pyrazol-1-yl)-ethanone



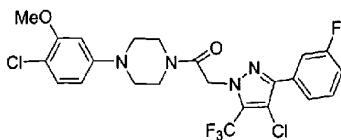
5 [0320] Protocol T was followed using 4-Bromo-3-phenyl-5-trifluoromethyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-chloro-3-methoxy-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 1/1, R_f = 0.51) afforded the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃): 7.42-7.52 (m, 5H), 7.18-7.22 (d, 1H), 6.38-6.42 (dd, 1H), 6.46-6.48 (d, 1H), 4.94 (s, 2H), 3.88 (s, 3H), 3.5-10 3.78 (m, 4H), 3.18 (s, 4H).

Synthesis of 1-[4-(4-Chloro-3-methoxyphenyl)-piperazin-1-yl]-2-(4-chloro-5-phenyl-3-trifluoromethyl-pyrazol-1-yl)-ethanone



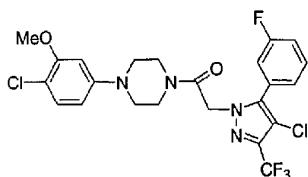
15 [0321] Protocol T was followed using 4-Chloro-5-phenyl-3-trifluoromethyl-1H-pyrazole, K₂CO₃, 2-Chloro-1-[4-(4-chloro-3-methoxy-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 2/3, R_f = 0.92) afforded the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃): 7.78-7.84 (m, 2H), 7.36-7.52 (m, 4H), 6.38-6.48 (m, 2H), 5.2 (s, 2H), 3.88 (s, 3H), 3.62-3.78 (m, 4H), 3.18-20 3.26 (s, 4H). ¹³C NMR (400 MHz, CDCl₃) 164.4, 156, 150.4, 130.4, 130, 128.6, 110.2, 102.4, 56.4, 52, 50.4, 44.6, 42.

25 **Synthesis of 1-[4-(4-Chloro-3-methoxyphenyl)-piperazin-1-yl]-2-(4-chloro-3-[3-Fluoro-phenyl]-5-trifluoromethyl-pyrazol-1-yl)-ethanone**



[0322] Protocol T was followed using 4-Chloro-3-[3-Fluorophenyl]-5-trifluoromethyl-1H-pyrazole, K_2CO_3 , 2-Chloro-1-[4-(4-chloro-3-methoxy-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 2/3, R_f = 0.51) afforded the title compound as a white solid. 1H NMR (400 MHz, $CDCl_3$): 7.44-7.52 (m, 1H), 7.18-7.28 (m, 4H), 6.38-6.48 (m, 2H), 4.94 (s, 2H), 3.84 (s, 3H), 3.52-3.78 (m, 4H), 3.12 (s, 4H).

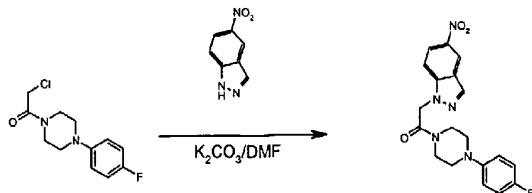
10 **Synthesis of 1-[4-(4-Chloro-3-methoxyphenyl)-piperazin-1-yl]-2-(4-chloro-5-[3-Fluoro-phenyl]-3-trifluoromethyl-pyrazol-1-yl)-ethanone**



[0323] Protocol T was followed using 4-Chloro-5-[3-Fluorophenyl]-3-trifluoromethyl-1H-pyrazole, K_2CO_3 , 2-Chloro-1-[4-(4-chloro-3-methoxy-phenyl)-piperazin-1-yl]-ethanone and DMF. Column chromatography using a solvent mixture (hexane/ ethyl acetate = 2/3, R_f = 0.59) afforded the title compound as a white solid. 1H NMR (400 MHz, $CDCl_3$): 7.64-7.68 (d, 1H), 7.56-7.62 (d, 1H), 7.36-7.42 (m, 1H), 7.22-7.24 (m, 2H), 7.08-7.12 (m, 1H), 6.42-6.52 (m, 2H), 5.2 (s, 2H), 3.9 (s, 3H), 3.62-3.82 (m, 4H), 3.12-3.22 (m, 4H).

20 **PROTOCOL U: for the K_2CO_3 mediated coupling reaction of chloroacetyl substituted arylpiperazines with novel heteraryl ring systems**

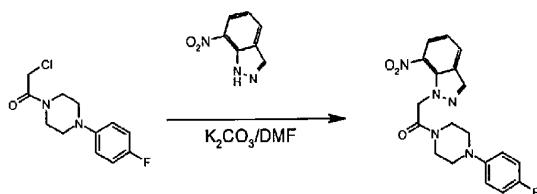
Synthesis of 1-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-[5-nitro-indazol-1-yl]-ethanone



[0324] 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone (0.834g, 3.3mmol) was taken in dry DMF (15mL) and dry potassium carbonate (1.6g, 11.6mmol) was added to it and the reaction mixture stirred at room temperature for 1h under nitrogen. 5-Nitro-1H-indazole (0.5g, 2.9 mmol) in DMF (2mL) was then added to the mixture through a syringe. The reaction was heated at 70°C for 14h, cooled and then quenched with water and extracted with ethyl acetate. Drying of the organic layer with Na_2SO_4 followed by concentration afforded material that on purification on neutral alumina column (pet ether/ethyl acetate) gave title compound as a pale yellow solid.

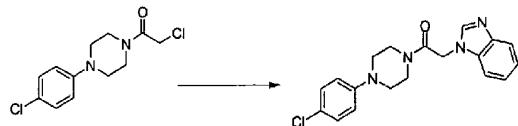
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Synthesis of 1-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-[7-nitro-indazol-1-yl]-ethanone



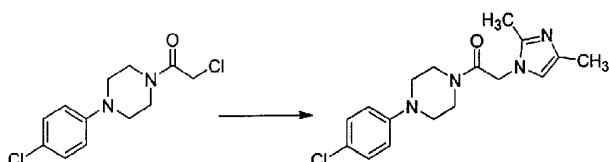
[0325] 2-Chloro-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone (0.834g, 3.3mmol) was taken in dry DMF (15mL) and dry potassium carbonate (1.6g, 11.6mmol) was added to it and the reaction mixture stirred at room temperature for 1h under nitrogen. 7-Nitro-1H-indazole (0.5g, 2.9 mmol) in DMF (2mL) was then added to the mixture through a syringe. The reaction was then heated at 70°C for 14h, cooled and then quenched with water and extracted with ethyl acetate. Drying of the organic layer with Na_2SO_4 followed by concentration afforded material that was purified on neutral alumina column (pet ether/ethyl acetate). The resulting solid was recrystallized from DCM/pet ether to obtain pure product as a pale yellow solid.

Synthesis of 2-Benzimidazol-1-yl-1-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethanone



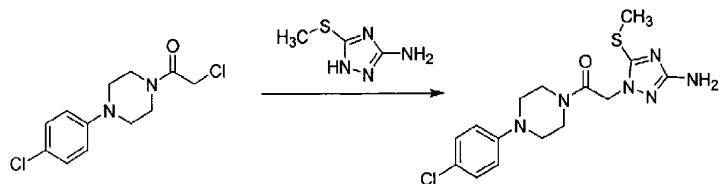
[0326] Benzimidazole (0.785g, 0.7mmol) was taken in dry DMF (15ml) and dry potassium carbonate (340mg) and KI (20mg) was added to it and the reaction mixture stirred at room temperature for 1h under nitrogen. 2-Chloro-1-[4-(4-chlorophenyl)-piperazin-1-yl]-ethanone (200mg, 1.1mmol) in DMF (5ml) was then added to the mixture through a syringe. The reaction was then heated at 140°C for 14h, cooled and then quenched with water and extracted with ethyl acetate. Drying of the organic layer with Na₂SO₄ followed by concentration gave material that on purification by flash chromatography (CHCl₃/MeOH) afforded pure product: ¹H NMR (300 MHz, CDCl₃): δ 8.10-7.65 (m, 4H), 7.26 (d, 2H), 6.83 (d, 2H), 4.99 (s, 2H), 3.79-3.66 (m, 4H), 3.14 (br, 4H).

Synthesis of 1-[4-(4-Chlorophenyl)-piperazin-1-yl]-2-(2,4-dimethyl-imidazol-1-yl)-ethanone



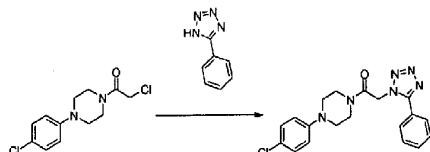
[0327] 2,4-dimethylimidazole (0.633g, 0.7mmol) was taken up in dry DMF (15ml) and dry potassium carbonate (340mg) and KI (20mg) was added and the reaction mixture was stirred at room temperature for 1h under nitrogen. 2-Chloro-1-[4-(4-chlorophenyl)-piperazin-1-yl]-ethanone (200mg, 1.1mmol) in DMF (5ml) was then added to the mixture through a syringe. The reaction was then heated at 140°C for 14h, cooled and quenched with water and extracted with ethyl acetate. Drying of the organic layer with Na₂SO₄ followed by concentration gave material that was purified on a silica gel column (CHCl₃/MeOH): ¹H NMR (300 MHz, CDCl₃): δ 7.25 (d, 2H), 6.80 (d, 2H), 6.53 (s, 1H), 4.62 (s, 2H), 3.78 (br, 2H), 3.59 (br, 2H), 3.21 (br, 4H), 2.31 (s, 3H), 2.17 (s, 1H).

25 **Synthesis of 2-(5-Amino-3-methylsulfanyl-[1,2,4]triazol-1-yl)-1-[4-(4-chlorophenyl)-piperazin-1-yl]-ethanone**



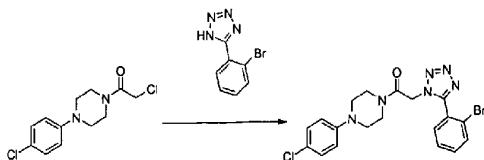
[0328] 5-Methylsulfanyl-2H-[1,2,4]triazol-3-ylamine (0.216g, 1.7mmol) was taken in dry DMF (15ml) and dry potassium carbonate (800mg) and KI (20mg) was added to it and the reaction mixture stirred at room temperature for 1h under nitrogen. 2-Chloro-1-[4-(4-chlorophenyl)-piperazin-1-yl]-ethanone (500mg, 1.8mmol) in DMF (5ml) was then added to the mixture through a syringe. The reaction was then heated at 140°C for 14h, cooled and then quenched with water and extracted with ethyl acetate. Drying of the organic layer with Na₂SO₄ followed by concentration afforded crude product that was purified by column chromatography (CHCl₃/MeOH): ¹H NMR (300 MHz, DMSO-*d*6): δ 7.24 (d, 2H), 6.98 (d, 2H), 6.24 (s, 2H), 4.84 (s, 2H), 3.57 (m, 4H), 3.21 (m, 2H), 3.13 (m, 2H), 2.37 (s, 3H).

Synthesis of 2-[5-(2-Bromo-phenyl)-tetrazol-1-yl]-1-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethanone



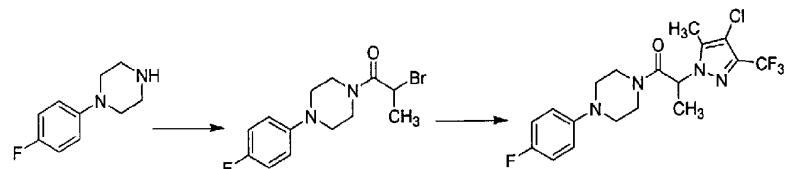
[0329] 5-phenyl-1H-tetrazole (0.1216g, 0.832mmol) was taken in dry DMF (15ml) and dry potassium carbonate (400mg) and KI (20mg) was added to it and the reaction mixture stirred at room temperature for 1h under nitrogen. 2-Chloro-1-[4-(4-chlorophenyl)-piperazin-1-yl]-ethanone (250mg, 0.92mmol) in DMF (5ml) was then added to the mixture through a syringe. The reaction was then heated at 140°C for 14h, cooled and quenched with water and extracted with ethyl acetate. Drying of the organic layer with Na₂SO₄ followed by concentration afforded material that was further purified by flash column chromatography (ethyl acetate/pet ether): ¹H NMR (300 MHz, CDCl₃): δ 8.17 (br, 2H), 7.49 (br, 3H), 7.24 (br, 2H), 6.85 (br, 2H), 5.60 (s, 2H), 3.82 (m, 2H), 3.71 (m, 2H), 3.19 (m, 4H).

25 **Synthesis of 2-[5-(2-Bromo-phenyl)-tetrazol-1-yl]-1-[4-(4-chloro-phenyl)-piperazin-**

1-yl]-ethanone

[0330] 5-(2-Bromo-phenyl)-1H-tetrazole (0.374 g, 1.66 mmol) was taken in dry DMF (15 mL) and dry potassium carbonate (800 mg) and KI (20 mg) was added to it and stirred at rt for 1 h under nitrogen. 2-Chloro-1-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethanone (500 mg, 1.8 mmol) in DMF (5 mL) was then added to the mixture through a syringe. The reaction was then heated at 140°C for 14 h, cooled and quenched with water and extracted with ethyl acetate. Drying of the organic layer with Na₂SO₄ followed by concentration afforded material that was further purified by flash column chromatography (ethyl acetate/pet ether):

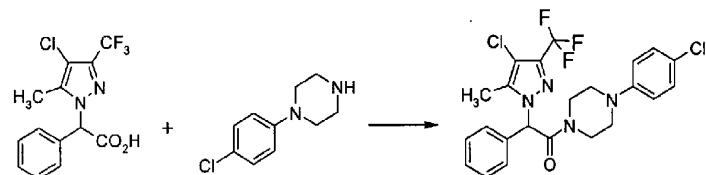
10 ¹H NMR (300 MHz, CDCl₃): δ 7.90 (d, 1H), 7.74 (d, 1H), 7.45 (t, 1H), 7.35 (t, 1H), 7.25 (d, 2H), 6.87 (d, 2H), 5.65 (s, 2H), 3.84 (m, 2H), 3.73 (m, 2H), 3.20 (m, 4H).

Preparation of compounds with modified linker regions**15 *α*-substituted acetyl linkers****Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-propan-1-one**

20 [0331] 1-(4-Fluorophenyl)-piperazine (1g, 5.5mmol) dissolved in dry CH₂Cl₂ (20ml) was cooled to 0°C and triethylamine (1.66g, 16.5mmol) was added to it. 2-bromopropionyl chloride (1.14g, 6.6mol) was added slowly and the reaction mixture stirred for another 1h at the same temperature. The mixture was washed with sodium bicarbonate and brine and dried (Na₂SO₄). Evaporation of the solvent afforded the intermediate alkyl bromide (0.68g,

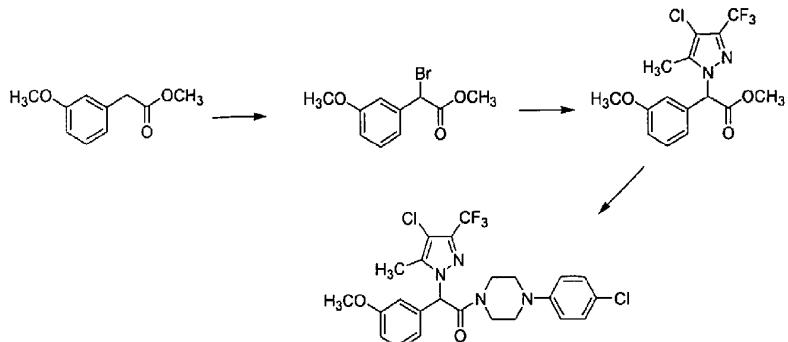
3.7mmol) which was taken into dry DMF (20ml). Potassium carbonate (2.1g) was added. After stirring for 1h at room temperature under nitrogen, 3-Methyl-4-chloro-5-trifluoromethyl- (1H)-pyrazole (1.3g, 4.1 mmol) in DMF (5ml) was then added to the mixture through a syringe. The reaction was then heated at 70°C for 14h, cooled and quenched with 5 water and extracted with ethyl acetate. Drying of the organic layer over Na₂SO₄ followed by concentration afforded material that was purified on a neutral alumina column (chloroform/methanol).

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chloro-phenyl)-piperazin-1-yl]-2-phenyl-ethanone



[0332] To 4-Chloro-5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl] phenylacetic acid (0.1 g, 0.00036 mol) and 1-(4-chlorophenyl) piperazine (0.060 g, 0.00031 mol) in 20 ml of dry CH₂Cl₂ was added 0.2 ml of triethylamine and the reaction mixture stirred at room 15 temperature for 30 min. TBTU (0.1 g, 0.00031 mol) was then added and the reaction mixture was stirred at room temperature for 17 h. The reaction mixture was diluted with 60 ml of CH₂Cl₂ and washed with saturated aqueous NaHCO₃ (2 × 50 ml), brine and then dried over sodium sulfate. The crude product obtained after concentration was purified by column 20 chromatography to give the product as an off white solid: ¹H NMR (CDCl₃, 300MHz) 7.40- 6.61 (m, 10H), 3.99 (m, 1H), 3.80 (m, 1H), 3.50-2.81 (m, 6H), 1.90 (s, 3H) ppm; MS (ES) M+H expected = 497.1, found 497.2.

Synthesis of 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chloro-phenyl)-piperazin-1-yl]-2-(3-methoxy-phenyl)-ethanone



[0333] AIBN (10 mg) was added to a solution of (3-Methoxy-phenyl)-acetic acid methyl ester (2g, 11mmol) in CCl₄ (30ml). The solution was then heated to reflux and NBS (2.3g, 13mmol) was added in portions. After complete addition the reaction mixture was refluxed 5 for 4h. After cooling, solid residue was filtered off and the filtrate concentrated to yield product Bromo-(3-methoxy-phenyl)-acetic acid methyl ester, that was washed repeatedly with pet ether.

[0334] 4-Chloro-3-methyl-5-trifluoromethyl-1H-pyrazole (610mg, 3.3mmol) was taken into dry CH₃CN (15ml), dry potassium carbonate (1.15g) was added to this and the resulting 10 mixture stirred at room temperature for 1h under nitrogen. Bromo-(3-methoxy-phenyl)-acetic acid methyl ester (900mg, 2.8mmol) in CH₃CN (5ml) was then added to the mixture through a syringe. The reaction was then heated at reflux for 10h, cooled and then filtered through a celite filter bed. The filtrate was concentrated to obtain (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-(3-methoxy-phenyl)-acetic acid ethyl ester that was purified by 15 column chromatography on silica (pet ether/ethyl acetate)

[0335] (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-(3-methoxy-phenyl)-acetic acid methyl ester was then dissolved in THF (20 ml) and LiOH (0.39g) in water (5ml) were added. The mixture was stirred at room temperature for 4h. After this period the THF was 20 completely evaporated from the reaction mixture under vacuum. The remaining aqueous layer was extracted with ethyl acetate (3x 5 ml) and the organic layer was discarded. The aqueous layer was cooled in ice and neutralized by using concentrated HCl. This neutral aqueous layer was extracted with ethyl acetate (3x10ml), the organic layer dried over Na₂SO₄, concentrated and purified by flash chromatography (CHCl₃/MeOH) to yield (4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-(3-methoxy-phenyl)-acetic acid

[0336] This compound (90mg, 0.275mmol) was taken into dry CH₂Cl₂ (10ml) and cooled to 0°C. To this cold mixture was first added 4-chlorophenyl-piperazine (0.059g, 0.31mmol) followed by the addition of T3P (0.35g, 0.55mmol, 50% solution in EtOAc). The reaction was left overnight at room temperature. The mixture was diluted with CH₂Cl₂, and then 5 washed sequentially with saturated NaHCO₃ solution, brine, dried over Na₂SO₄, and concentrated to afford the crude product. Purification by column chromatography on neutral alumina yielded 2-(4-Chloro-5-methyl-3-trifluoromethyl-pyrazol-1-yl)-1-[4-(4-chlorophenyl)-piperazin-1-yl]-2-(3-methoxy-phenyl)-ethanone: ¹H NMR (300 MHz, CDCl₃): δ 7.37-7.21 (m, 3H), 6.96-6.79 (m, 4H), 6.60 (s, 1H), 5.31 (s, 1H), 3.99 (m, 1H), 3.80 (s, 3H), 10 3.79 (m, 1H), 3.46 (m, 2H), 3.24 (m, 1H), 3.13 (m, 2H), 2.91 (m, 1H), 1.95 (s, 3H).

EXAMPLE 2

[0337] This example illustrates the activity associated with representative compounds of 15 the invention.

Materials and Methods

A. Cells

CCR1 expressing cells

a. THP-1 cells

20 [0338] THP-1 cells were obtained from ATCC and cultured as a suspension in RPMI-1640 medium supplemented with 2 mM L-glutamine, 1.5 g/L sodium bicarbonate, 4.5 g/L glucose, 10 mM HEPES, 1 mM sodium pyruvate, 0.05% 2-mercaptoethanol and 10% FBS. Cells were grown under 5% CO₂/95% air, 100% humidity at 37°C and subcultured twice weekly at 1:5 and harvested at 1 x 10⁶ cells/ml. THP-1 cells express CCR1 and can be used in CCR1 25 binding and functional assays.

b. Isolated human monocytes

[0339] Monocytes were isolated from human buffy coats using the Miltenyi bead isolation system (Miltenyi, Auburn, CA). Briefly, following a Ficoll gradient separation to isolate 30 peripheral blood mononuclear cells, cells were washed with PBS and the red blood cells lysed using standard procedures. Remaining cells were labeled with anti-CD14 antibodies coupled to magnetic beads (Miltenyi Biotech, Auburn, CA). Labeled cells were passed

through AutoMACS (Miltenyi, Auburn, CA) and positive fraction collected. Monocytes express CCR1 and can be used in CCR1 binding and functional assays.

B. Assays

5 *Inhibition of CCR1 ligand binding*

[0340] CCR1 expressing cells were centrifuged and resuspended in assay buffer (20 mM HEPES pH 7.1, 140 mM NaCl, 1 mM CaCl₂, 5 mM MgCl₂, and with 0.2% bovine serum albumin) to a concentration of 2.2 x 10⁵ cells/ml for THP-1 cells and 1.1 x 10⁶ for monocytes. Binding assays were set up as follows. First, 0.09 ml of cells (1 x 10⁵ THP-1 cells/well or 5 x 10⁵ monocytes) was added to the assay plates containing the compounds, giving a final concentration of ~2-10 µM each compound for screening (or part of a dose response for compound IC₅₀ determinations). Then 0.09 ml of ¹²⁵I labeled MIP-1 α (obtained from Amersham; Piscataway, NJ) diluted in assay buffer to a final concentration of ~50 pM, yielding ~30,000 cpm per well, was added, the plates sealed and incubated for approximately 15 3 hours at 4°C on a shaker platform. Reactions were aspirated onto GF/B glass filters pre-soaked in 0.3% polyethyleneimine (PEI) solution, on a vacuum cell harvester (Packard Instruments; Meriden, CT). Scintillation fluid (50 µl; Microscint 20, Packard Instruments) was added to each well, the plates were sealed and radioactivity measured in a Top Count scintillation counter (Packard Instruments). Control wells containing either diluent only (for 20 total counts) or excess MIP-1 α or MIP-1 β (1 µg/ml, for non-specific binding) were used to calculate the percent of total inhibition for compound. The computer program Prism from GraphPad, Inc. (San Diego, Ca) was used to calculate IC₅₀ values. IC₅₀ values are those concentrations required to reduce the binding of labeled MIP-1 α to the receptor by 50%.

25 *Calcium mobilization*

[0341] To detect the release of intracellular stores of calcium, cells (THP-1 or monocytes) were incubated with 3 µM of INDO-1AM dye (Molecular Probes; Eugene, OR) in cell media for 45 minutes at room temperature and washed with phosphate buffered saline (PBS). After INDO-1AM loading, the cells were resuspended in flux buffer (Hank's balanced salt solution 30 (HBSS) and 1% FBS). Calcium mobilization was measured using a Photon Technology International spectrophotometer (Photon Technology International; New Jersey) with excitation at 350 nm and dual simultaneous recording of fluorescence emission at 400 nm and

490 nm. Relative intracellular calcium levels were expressed as the 400 nm/490 nm emission ratio. Experiments were performed at 37°C with constant mixing in cuvettes each containing 10⁶ cells in 2 ml of flux buffer. The chemokine ligands may be used over a range from 1 to 100 nM. The emission ratio was plotted over time (typically 2-3 minutes). Candidate ligand 5 blocking compounds (up to 10 µM) were added at 10 seconds, followed by chemokines at 60 seconds (i.e., MIP-1α; R&D Systems; Minneapolis, MN) and control chemokine (i.e., SDF-1α; R&D Systems; Minneapolis, MN) at 150 seconds. .

Chemotaxis assays

10 [0342] Chemotaxis assays were performed using 5 µm pore polycarbonate, polyvinylpyrrolidone-coated filters in 96-well chemotaxis chambers (Neuroprobe; Gaithersburg, MD) using chemotaxis buffer (Hank's balanced salt solution (HBSS) and 1% FBS). CCR1 chemokine ligands (i.e., MIP-1α, Leukotactin; R&D Systems; Minneapolis, MN) are used to evaluate compound mediated inhibition of CCR1 mediated migration. Other 15 chemokines (i.e., SDF-1α; R&D Systems; Minneapolis, MN) are used as specificity controls. The lower chamber was loaded with 29 µl of chemokine (i.e., 0.1 nM MIP-1α) and varying amounts of compound; the top chamber contained 100,000 THP-1 or monocyte cells in 20 µl. The chambers were incubated 1-2 hours at 37°C, and the number of cells in the lower chamber quantified either by direct cell counts in five high powered fields per well or by the 20 CyQuant assay (Molecular Probes), a fluorescent dye method that measures nucleic acid content and microscopic observation.

Identification of inhibitors of CCR1

A. Assay

25 [0343] To evaluate small organic molecules that prevent the receptor CCR1 from binding ligand, an assay was employed that detected radioactive ligand (i.e., MIP-1α or leukotactin) binding to cells expressing CCR1 on the cell surface (for example, THP-1 cells or isolated human monocytes). For compounds that inhibited binding, whether competitive or not, fewer radioactive counts are observed when compared to uninhibited controls.

30 [0344] THP-1 cells and monocytes lack other chemokine receptors that bind the same set of chemokine ligands as CCR1 (i.e., MIP-1α, MPIF-1, Leukotactin, etc.). Equal numbers of cells were added to each well in the plate. The cells were then incubated with radiolabeled

MIP-1 α . Unbound ligand was removed by washing the cells, and bound ligand was determined by quantifying radioactive counts. Cells that were incubated without any organic compound gave total counts; non-specific binding was determined by incubating the cells with unlabeled ligand and labeled ligand. Percent inhibition was determined by the equation:

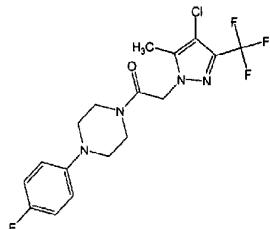
5 % inhibition = $(1 - [(sample\ cpm) - (nonspecific\ cpm)] / [(total\ cpm) - (nonspecific\ cpm)]) \times 100.$

B. Inhibitors from a compound library identified using CCR1 expressing cells

[0345] In a screen of a set of compounds, the normalized standard deviation was 17%,
 10 indicating that inhibitory activity of 34% or more was significant; again, a 40% threshold was used. These pooled compound plates yielded 39 wells that exhibited greater than 40% inhibition of MIP-1 α binding. When screened a second time as pooled compound plates, 14 of these wells decreased ligand by greater than 40%. To determine which of the compounds in each well inhibited CCR1 ligation of MIP-1 α , the pools were deconvoluted by testing each 15 of the compounds individually for inhibitory activity in the assay. Because some compounds may act together to inhibit binding and deconvolution assays only tested compounds individually, compounds that were effective in combination but not singly were not found in this experiment. Testing the compounds singly identified inhibitory candidates:

20 **C. Inhibitor from compound library identified using CCR1-expressing cells**

[0346] CCX-105 was identified from the compound screening effort.



Dose Response Curves

25 [0347] To ascertain a candidate compound's affinity for CCR1 as well as confirm its ability to inhibit ligand binding, inhibitory activity was titrated over a 1×10^{-10} to 1×10^{-4} M range of

compound concentrations. In the assay, the amount of compound was varied; while cell number and ligand concentration were held constant. Compound CCX-105 was titered and found to be a potent inhibitor of CCR1 specific chemokine binding (see Table, for compound 1.001).

5

CCR1 functional assays

[0348] CCR1 is a seven transmembrane, G-protein linked receptor. A hallmark of signaling cascades induced by the ligation of some such receptors is the pulse-like release of calcium ions from intracellular stores. Calcium mobilization assays were performed to 10 determine if the candidate CCR1 inhibitory compounds were able to also block aspects of CCR1 signaling. Candidate compounds able to inhibit ligand binding and signaling with an enhanced specificity over other chemokine and non-chemokine receptors were desired.

[0349] Calcium ion release in response to CCR1 chemokine ligands (i.e., MIP-1 α , MPIF-1, Leukotactin, etc.) was measured using the calcium indicator INDO-1. THP-1 cells or 15 monocytes were loaded with INDO-1/AM and assayed for calcium release in response to CCR1 chemokine ligand (i.e., MIP-1 α) addition. To control for specificity, non-CCR1 ligands, specifically bradykinin, was added, which also signals via a seven transmembrane receptor. Without compound, a pulse of fluorescent signal will be seen upon MIP-1 α addition. If a compound specifically inhibits CCR1-MIP-1 α signaling, then little or no signal 20 pulse will be seen upon MIP-1 α addition, but a pulse will be observed upon bradykinin addition. However, if a compound non-specifically inhibits signaling, then no pulse will be seen upon both MIP-1 α and bradykinin addition.

[0350] As shown below, CCX-105 was able to significantly and specifically inhibit signaling from CCR1.

Table 2. Inhibition of calcium signaling

Compound	MIP-1 α ¹	Bradykinin ¹	Comments
CCX-105	-	+	Specific inhibition

¹+, pulse observed, -, no pulse observed, n.s., non-specific signal (see main text)

25

[0351] One of the primary functions of chemokines is their ability to mediate the migration of chemokine receptor-expressing cells, such as white blood cells. To confirm that CCX-105 inhibited not only CCR1 specific binding and signaling (at least as determined by calcium mobilization assays), but also CCR1 mediated migration, a chemotaxis assay was employed.

5 THP-1 myelomonocytic leukemia cells, which resemble monocytes, as well as freshly isolated monocytes, were used as targets for chemoattraction by CCR1 chemokine ligands (i.e., MIP-1 α , CCL15/leukotactin). Cells were placed in the top compartment of a microwell migration chamber, while MIP-1 α (or other potent CCR1 chemokine ligand) and increasing concentrations of CCX-105 or other candidate compound was loaded in the lower chamber.

10 In the absence of inhibitor, cells will migrate to the lower chamber in response to the chemokine agonist; if a compound inhibited CCR1 function, then the majority of cells will remain in the upper chamber. To ascertain a candidate compound's affinity for CCR1 as well as to confirm its ability to inhibit CCR1 mediated cell migration, inhibitory activity was titrated over a 1×10^{-10} to 1×10^{-4} M range of compound concentrations in this chemotaxis

15 assay. In this assay, the amount of compound was varied; while cell number and chemokine agonist concentrations were held constant. After the chemotaxis chambers were incubated 1-2 hours at 37°C, the responding cells in the lower chamber were quantified by labeling with the CyQuant assay (Molecular Probes), a fluorescent dye method that measures nucleic acid content, and by measuring with a Spectrafluor Plus (Tecan). The computer program Prism

20 from GraphPad, Inc. (San Diego, Ca) was used to calculate IC₅₀ values. IC₅₀ values are those compound concentrations required to inhibit the number of cells responding to a CCR1 agonist by 50%.

In Vivo Efficacy

25 *rabbit model of destructive joint inflammation*

A study was conducted to evaluate the effects of CCX-105 on inhibiting the inflammatory response of rabbits to an intra-articular injection of the bacterial membrane component lipopolysaccharide (LPS). This study design mimics the destructive joint inflammation seen in arthritis. Intra-articular injection of LPS causes an acute inflammatory

30 response characterized by the release of cytokines and chemokines, many of which have been identified in rheumatoid arthritic joints. Marked increases in leukocytes occur in synovial fluid and in synovium in response to elevation of these chemotactic mediators.¹ Selective

antagonists of chemokine receptors have shown efficacy in this model (see Podolin, et al., *J. Immunol.* **169**(11):6435-6444 (2002)).

In a rabbit LPS study conducted essentially as described in Podolin, et al. *ibid.*, female New Zealand rabbits (approximately 2 kilograms) were treated intra-articularly in one knee

5 with LPS (10 ng) together with either vehicle only (phosphate buffered saline with 1% DMSO) or with addition of CCX-105 (dose 1 = 50 μ M or dose 2 = 100 μ M) in a total volume of 1.0 mL. Sixteen hours after the LPS injection, knees were lavaged and cells counts performed. Beneficial effects of treatment were determined by histopathologic evaluation of synovial inflammation. The following inflammation scores were used for the histopathologic

10 evaluation: 1 - minimal, 2 - mild, 3 - moderate, 4 - moderate-marked. As shown below, CCX-105 was able to significantly and specifically inhibit the inflammatory response in this in vivo assay.

15 **Table 3.**
CCX-105 efficacy in a rabbit model of destructive joint inflammation

synovium inflammation score	
Vehicle	3
CCX-105 (dose 1)	2
CCX-105 (dose 2)	1

Evaluation of compound 1.028 in a rat model of collagen induced arthritis

A 17 day developing type II collagen arthritis study was conducted to evaluate the

20 effects of compound 1.028 on arthritis induced clinical ankle swelling. Rat collagen arthritis is an experimental model of polyarthritis that has been widely used for preclinical testing of numerous anti-arthritis agents (see Trentham, et al., *J. Exp. Med.* **146**(3):857-868 (1977), Bendele, et al., *Toxicologic Pathol.* **27**:134-142 (1999), Bendele, et al., *Arthritis Rheum.* **42**:498-506 (1999)). The hallmarks of this model are reliable onset and progression of

25 robust, easily measurable polyarticular inflammation, marked cartilage destruction in association with pannus formation and mild to moderate bone resorption and periosteal bone proliferation.

Female Lewis rats (approximately 0.2 kilograms) were anesthetized with isoflurane and injected with Freund's Incomplete Adjuvant containing 2 mg/ml bovine type II collagen

30 at the base of the tail and two sites on the back on days 0 and 6 of this 17 day study.

Compound 1.028 was dosed daily in a sub-cutaneous manner from day 0 till day 17 at a dose

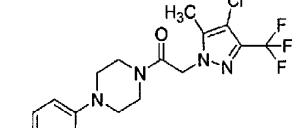
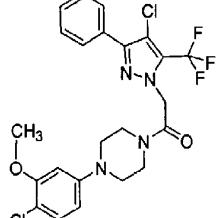
of 25 mg/kg and a volume of 1 ml/kg in the following vehicle (20% N,N-dimethylacetamide, 75% corn oil, 5% Tween-80). Caliper measurements of the ankle joint diameter were taken, and reducing joint swelling was taken as a measure of efficacy. As shown below, compound 1.028 was able to significantly and specifically inhibit the arthritis induced ankle swelling in this *in vivo* assay.

Table 4.
Efficacy of compound 1.028 in a rat collagen induced arthritis assay

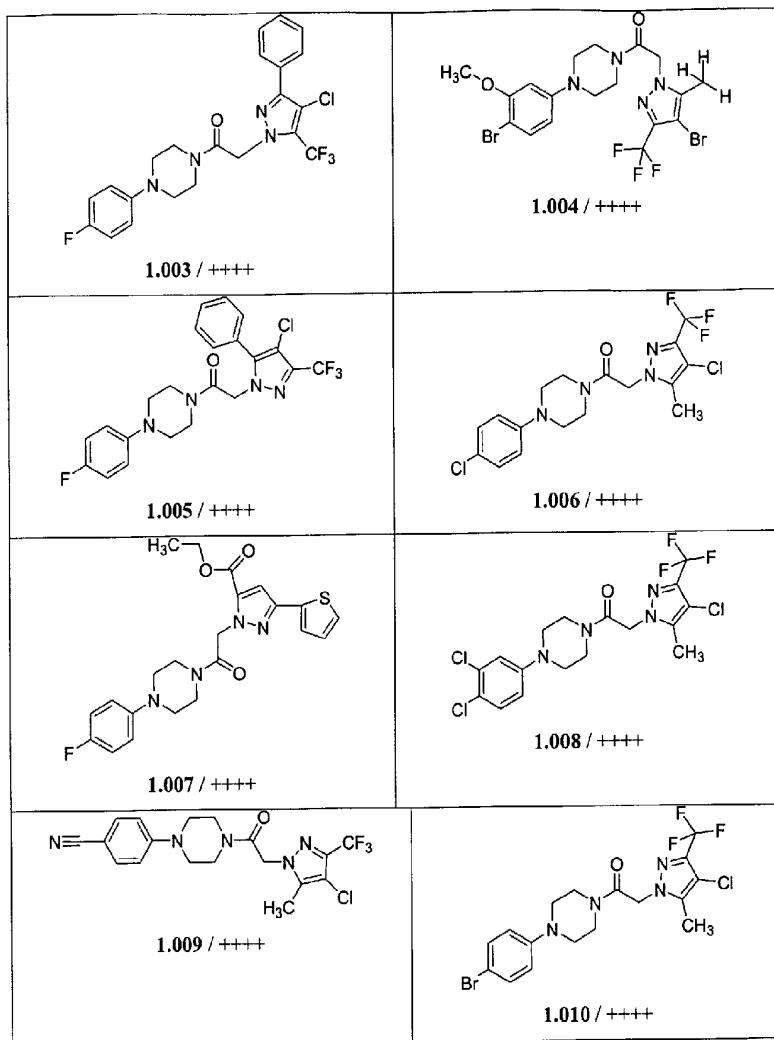
change in joint diameter day9-day17	
Vehicle	15.7% +/- 2.0%
Normal	0% +/- 0.3%
Compound 1.028	9.1% +/- 1.8%

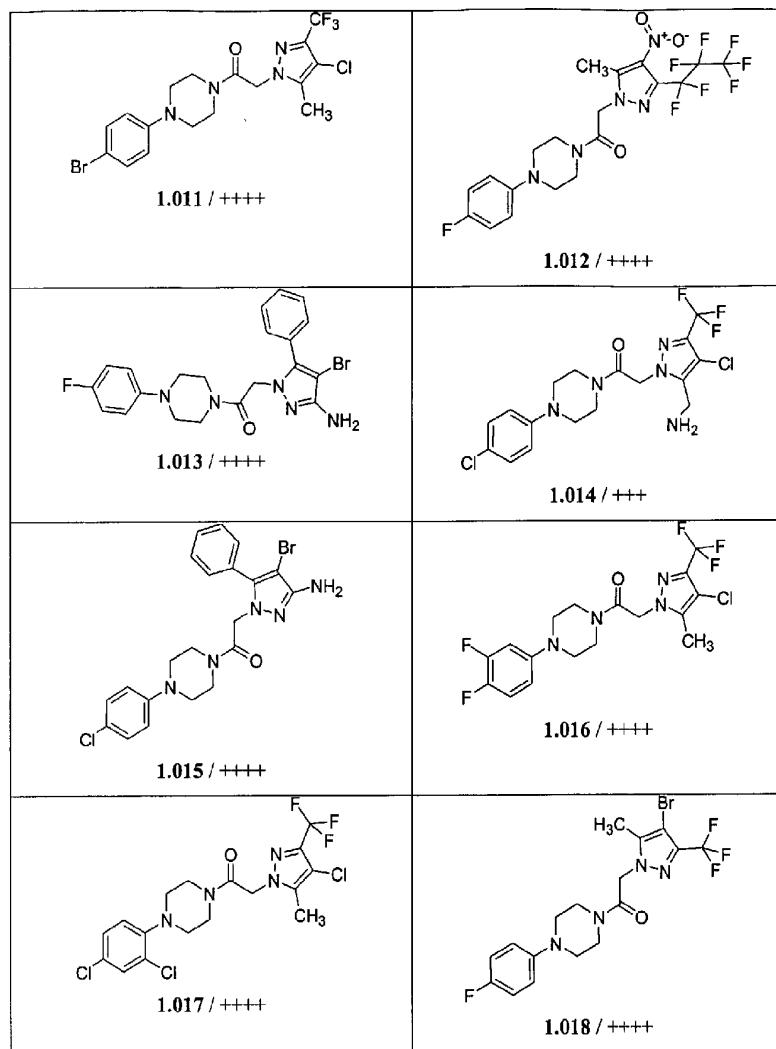
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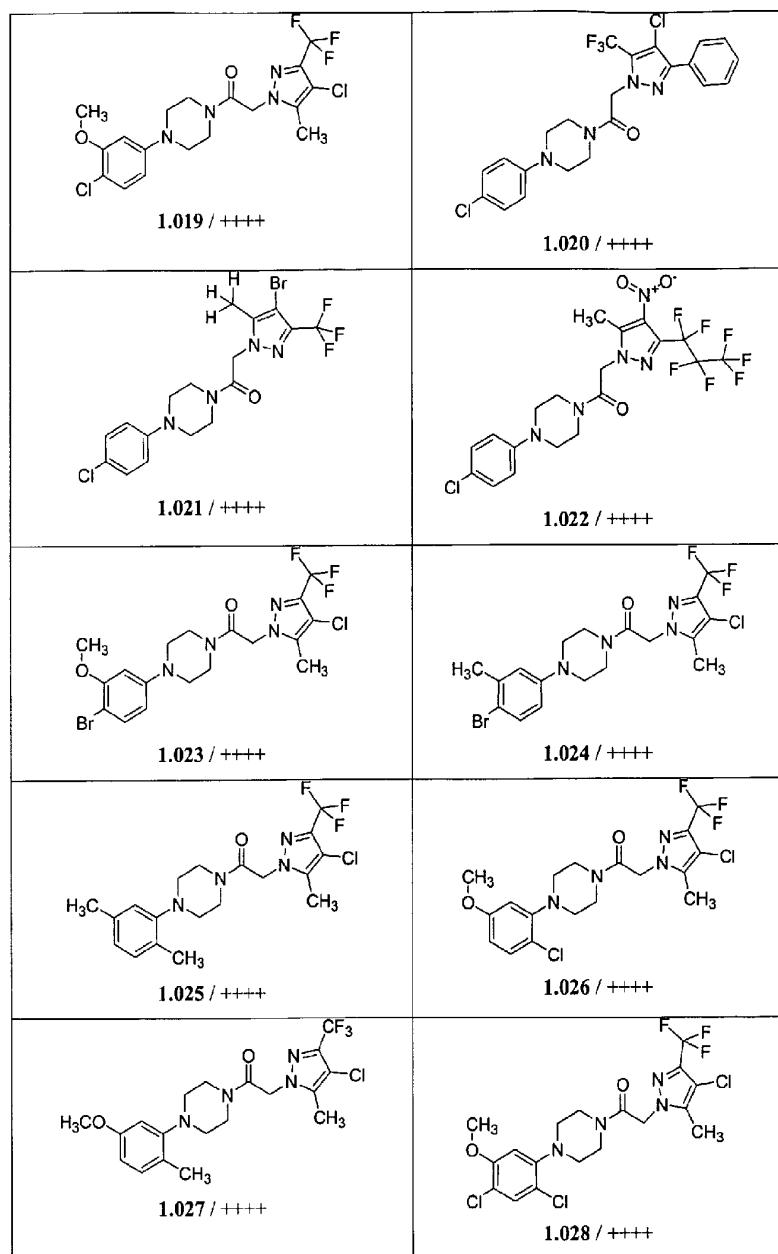
[0352] In the table below, structures and activity are provided for representative compounds described herein. Activity is provided as follows for either or both of the chemotaxis assay and/or binding assay, described above: +, $IC_{50} > 12.5 \mu M$; ++, $2500 nM < IC_{50} < 12.5 \mu M$; +++, $500 nM < IC_{50} < 2500 nM$; and +++++, $IC_{50} < 500 nM$.

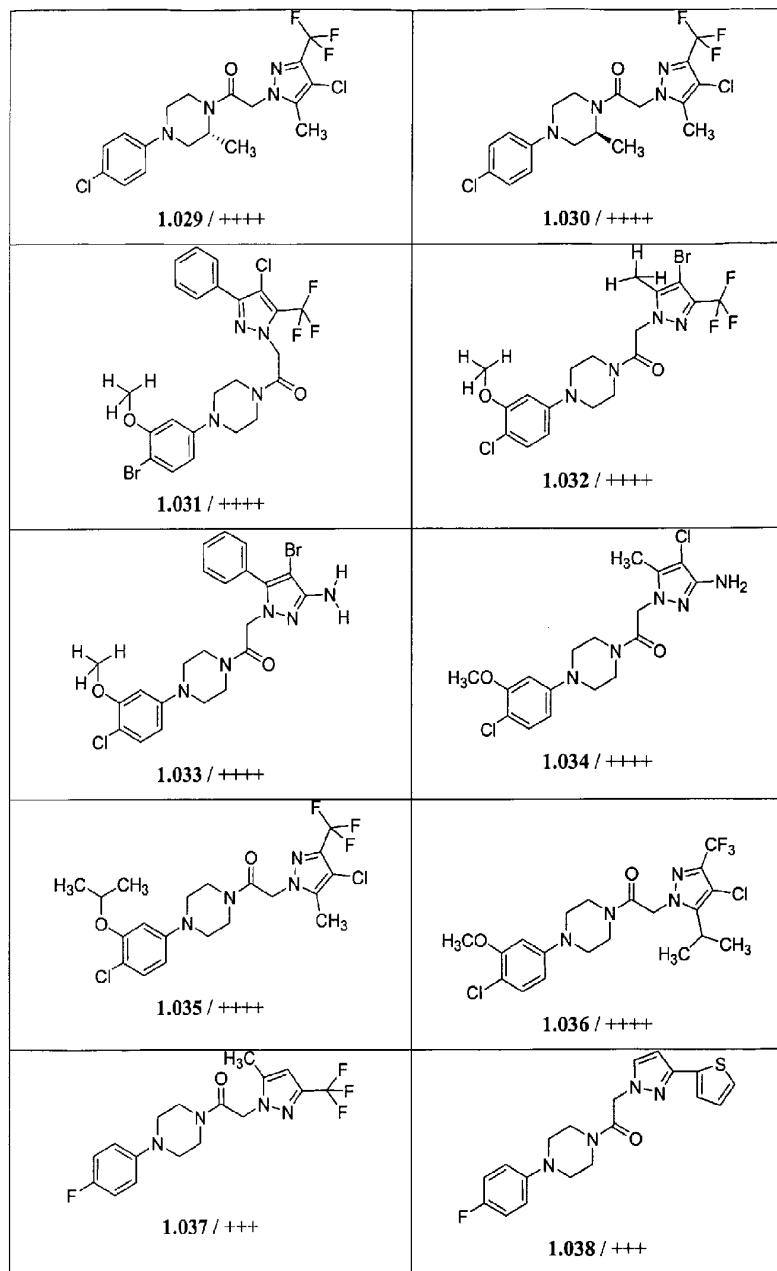
Structure	Structure
 CCX 105	 1.002 / +++++

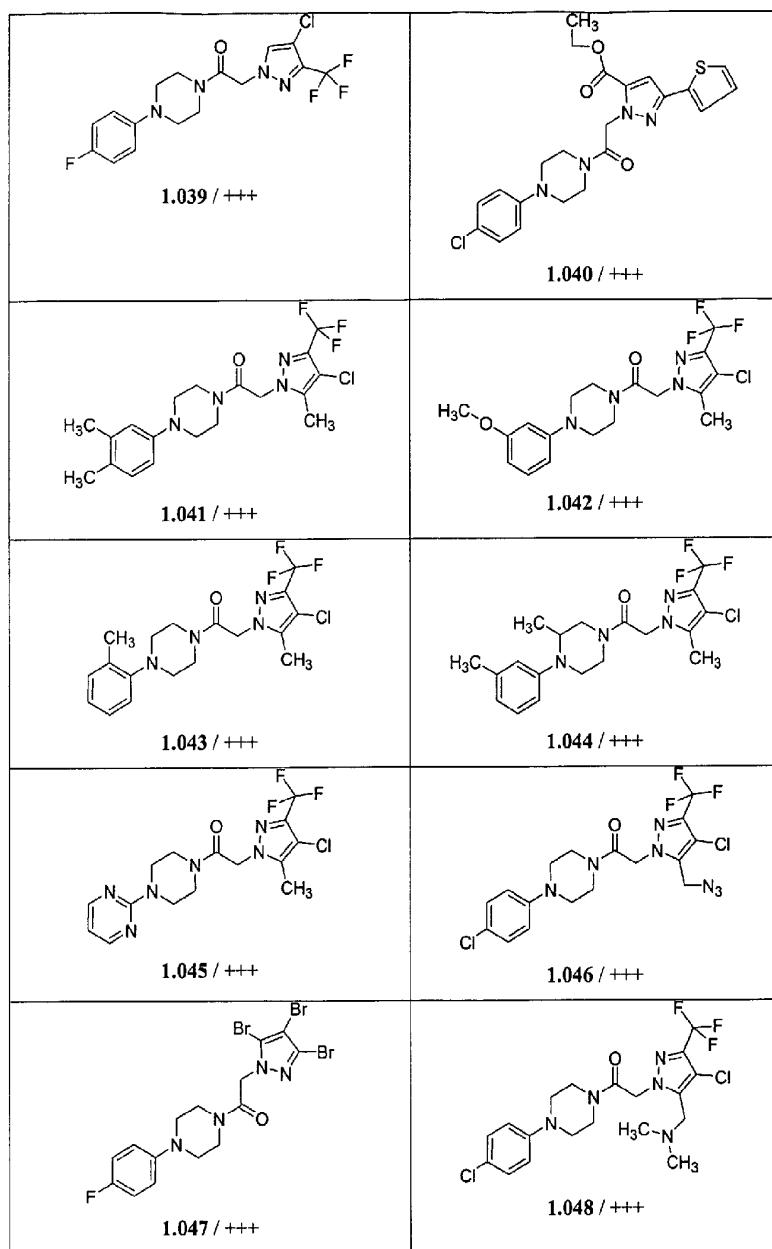
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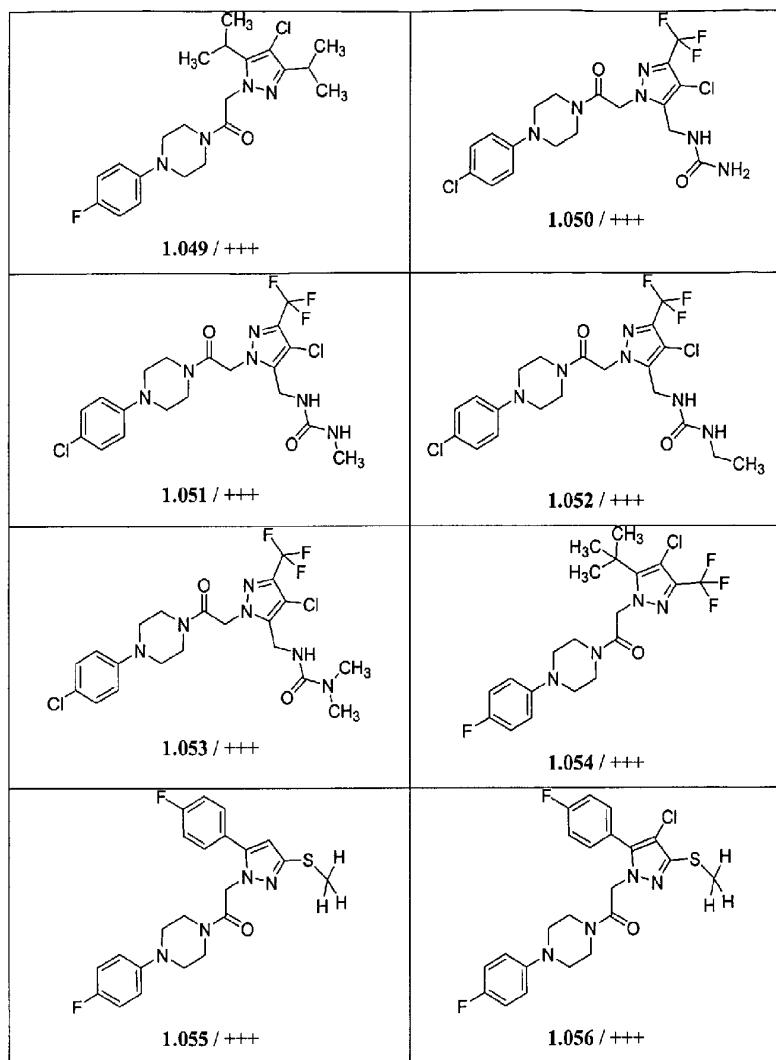


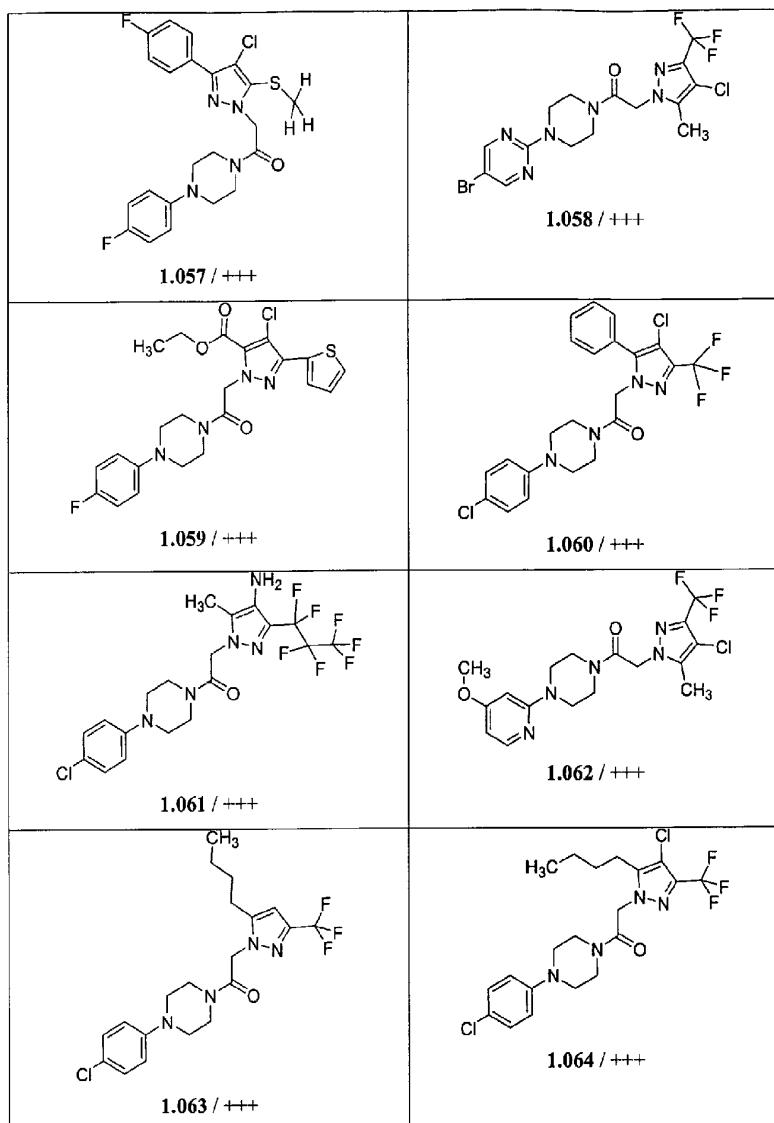


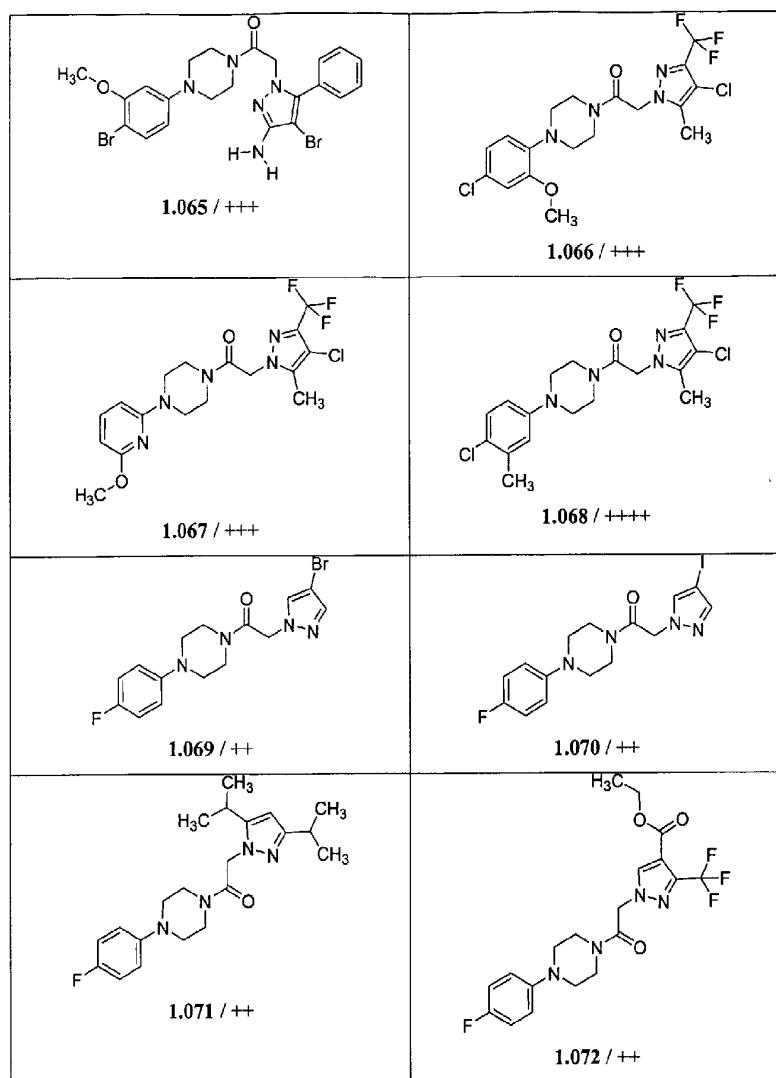


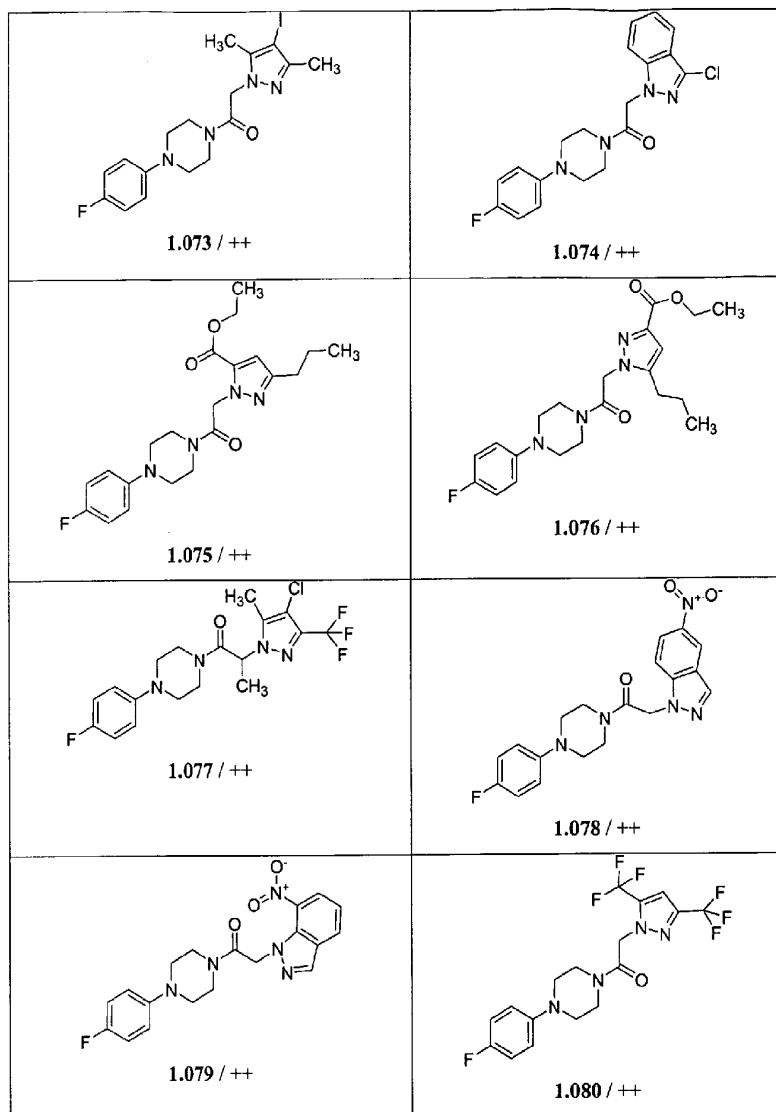


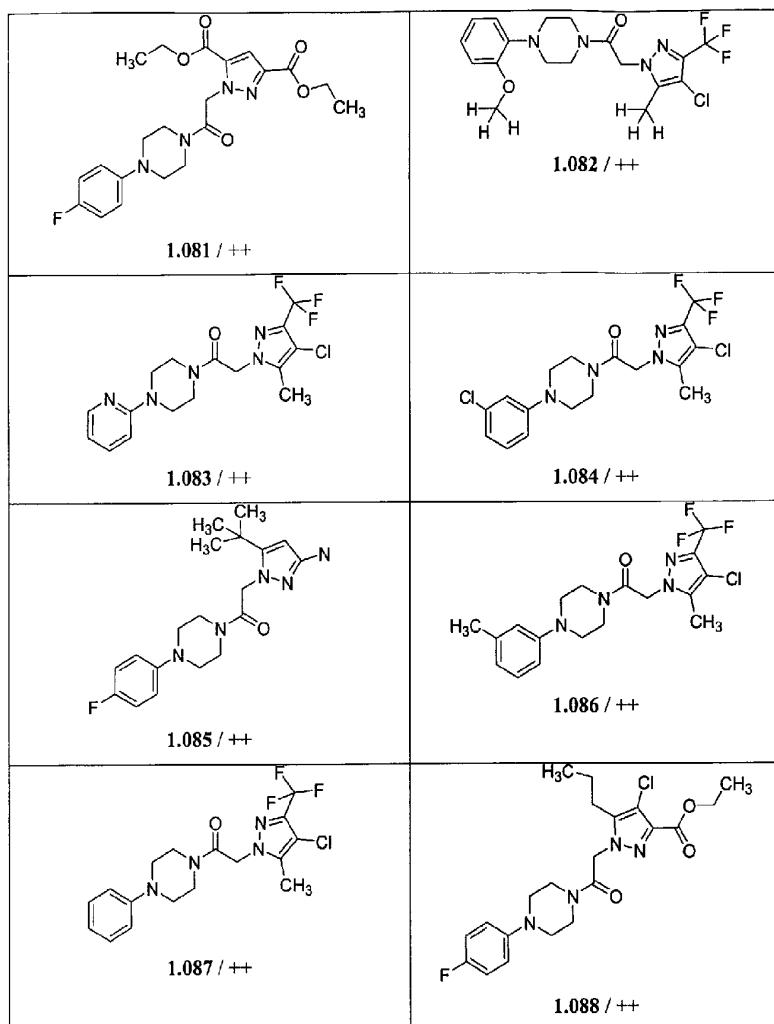


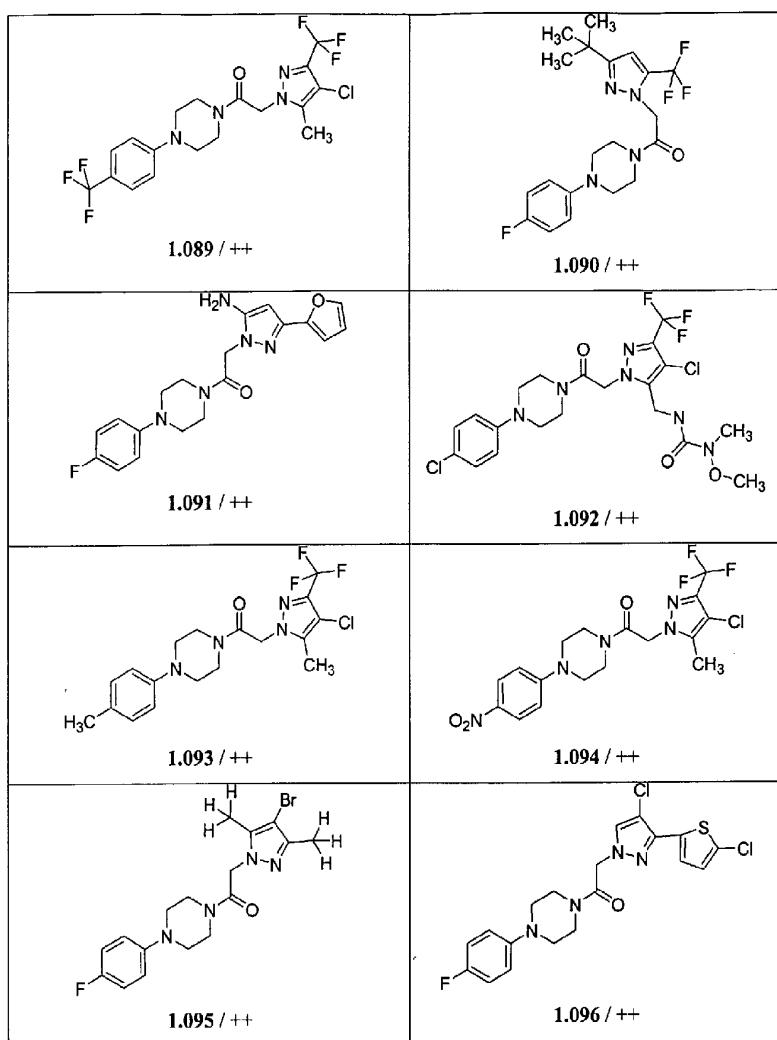


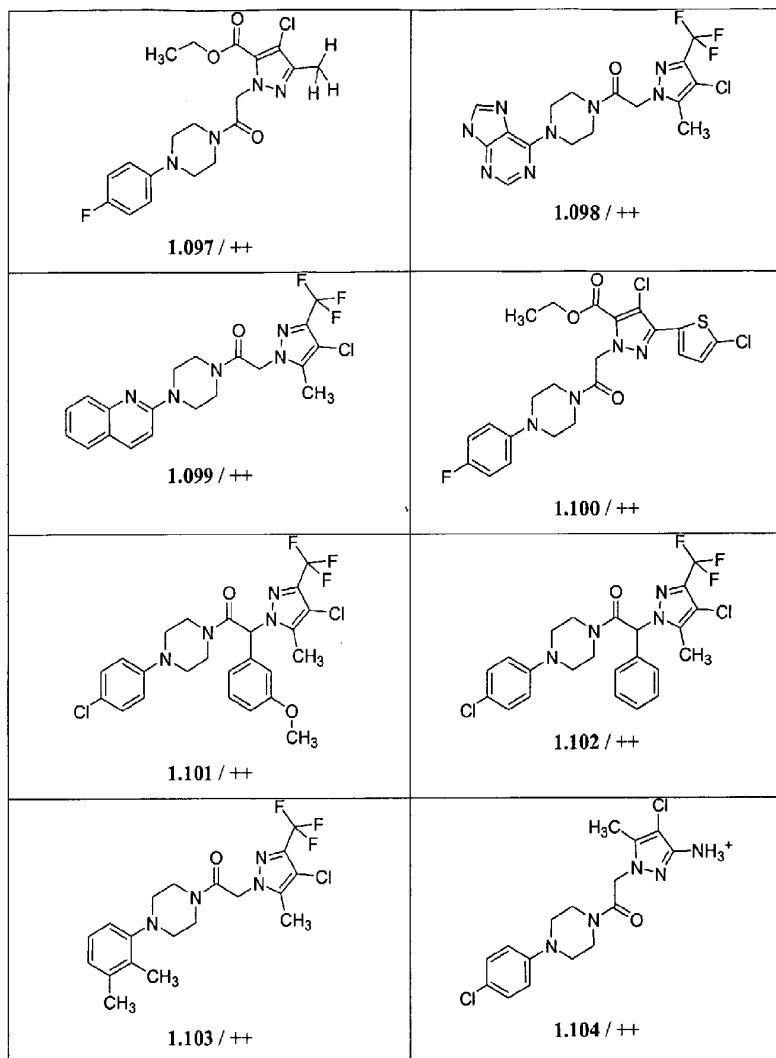


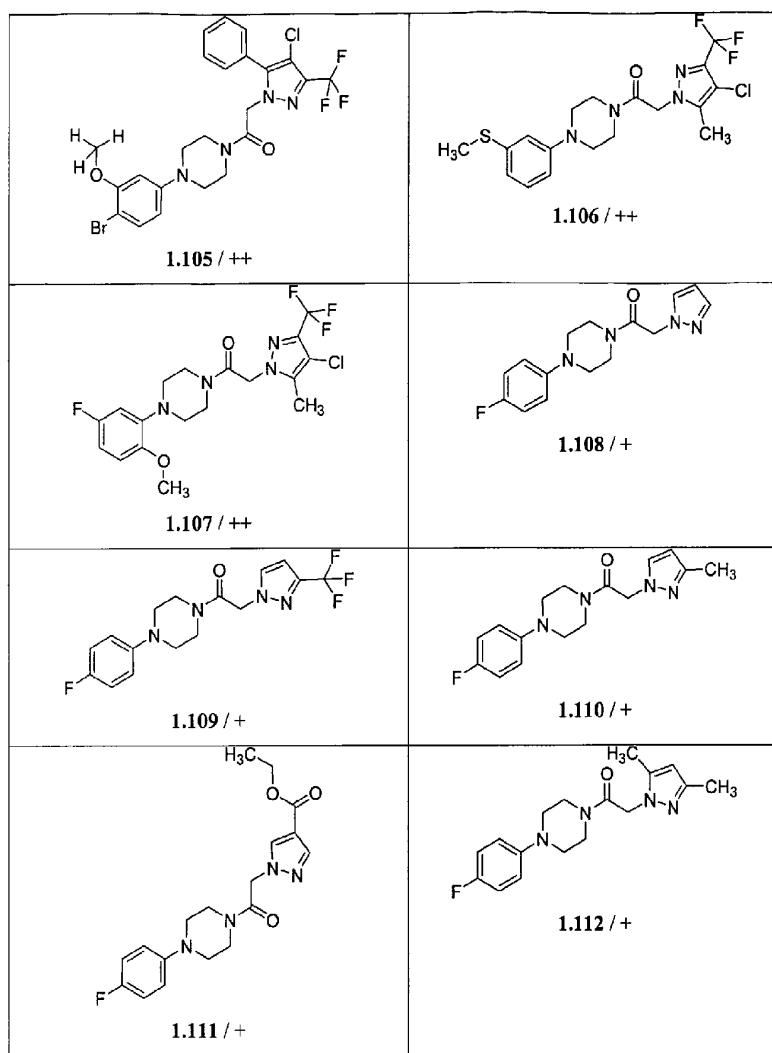


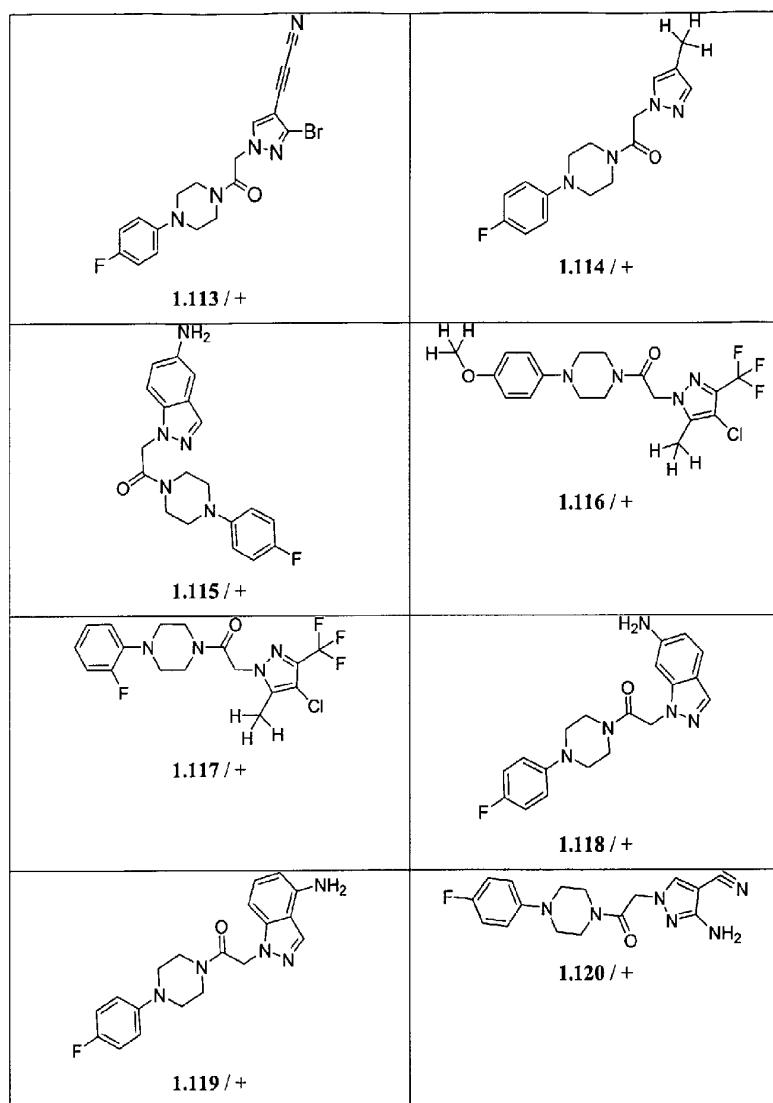


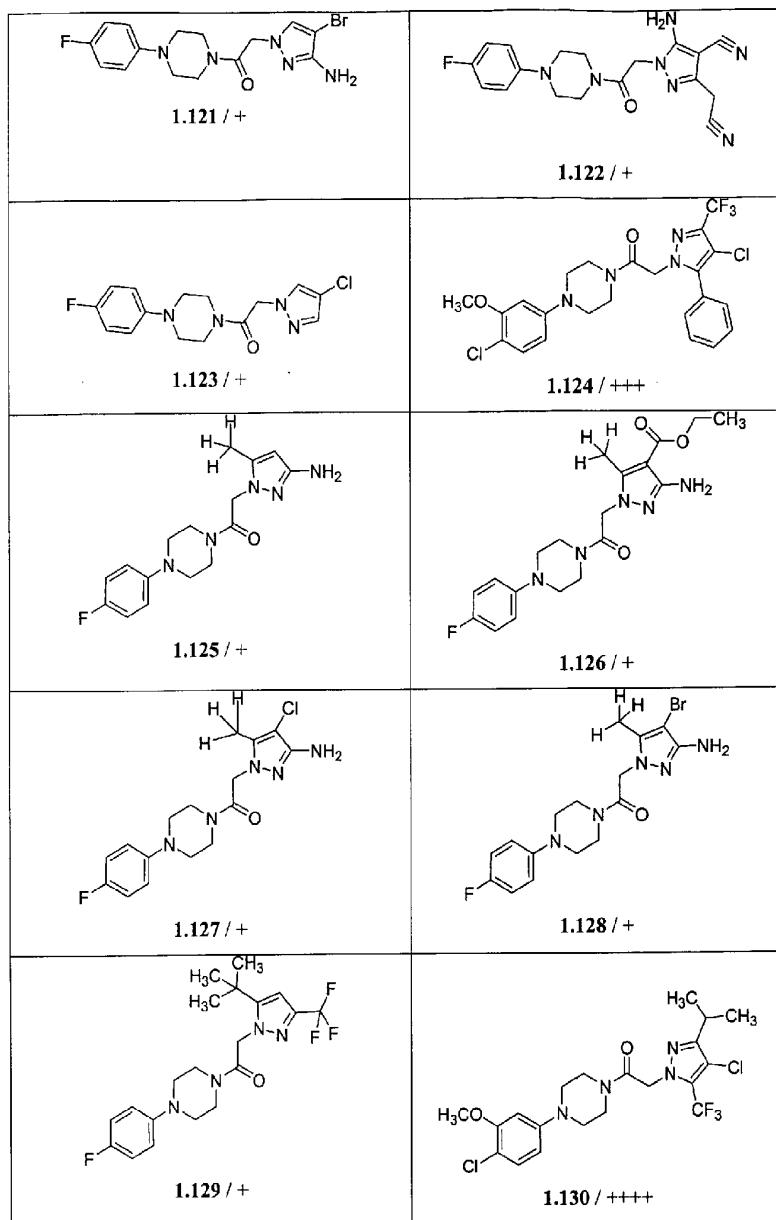


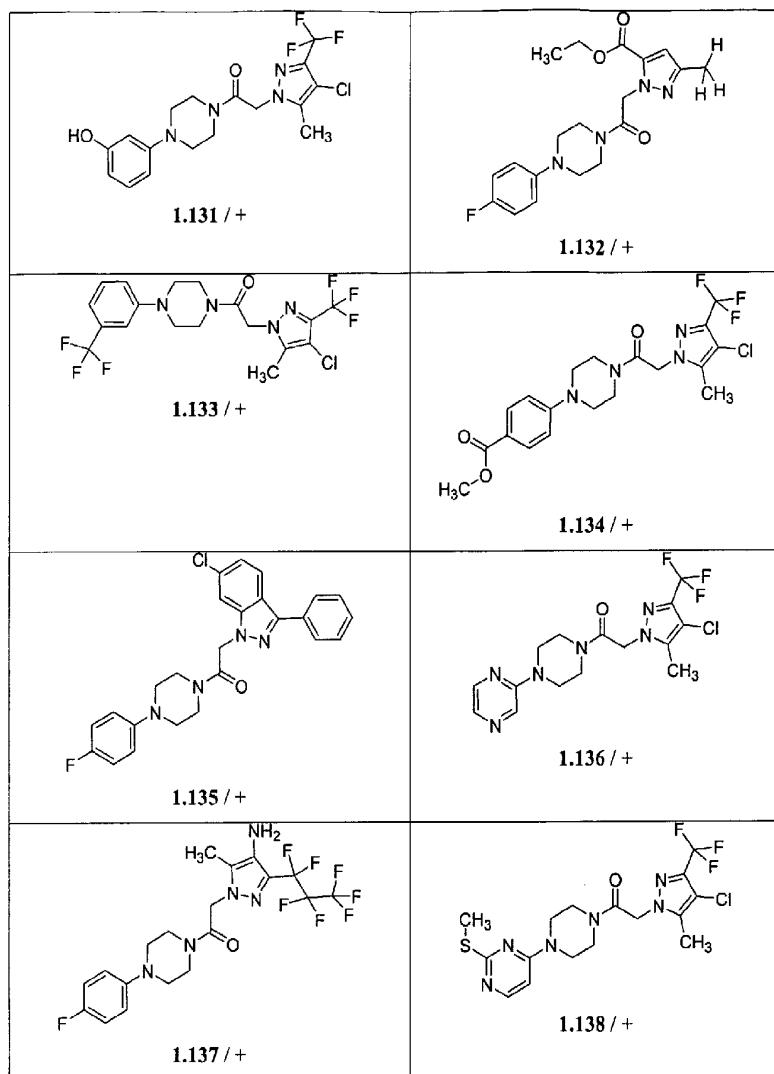


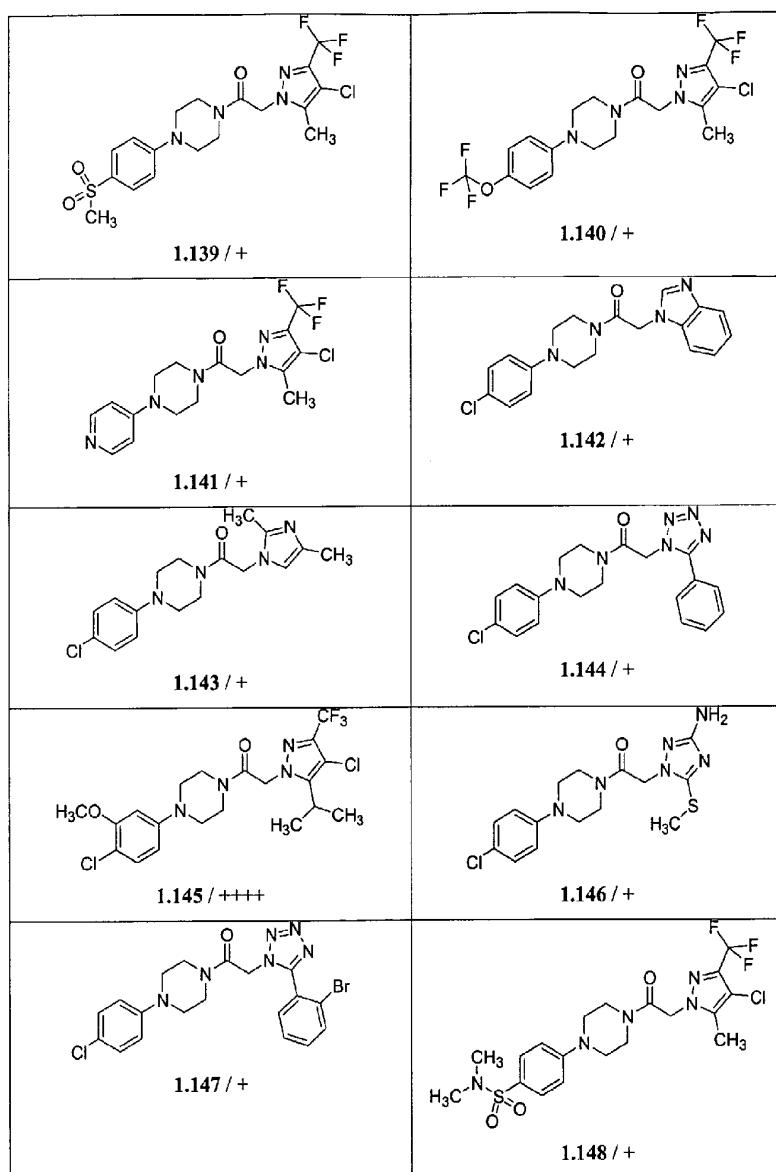


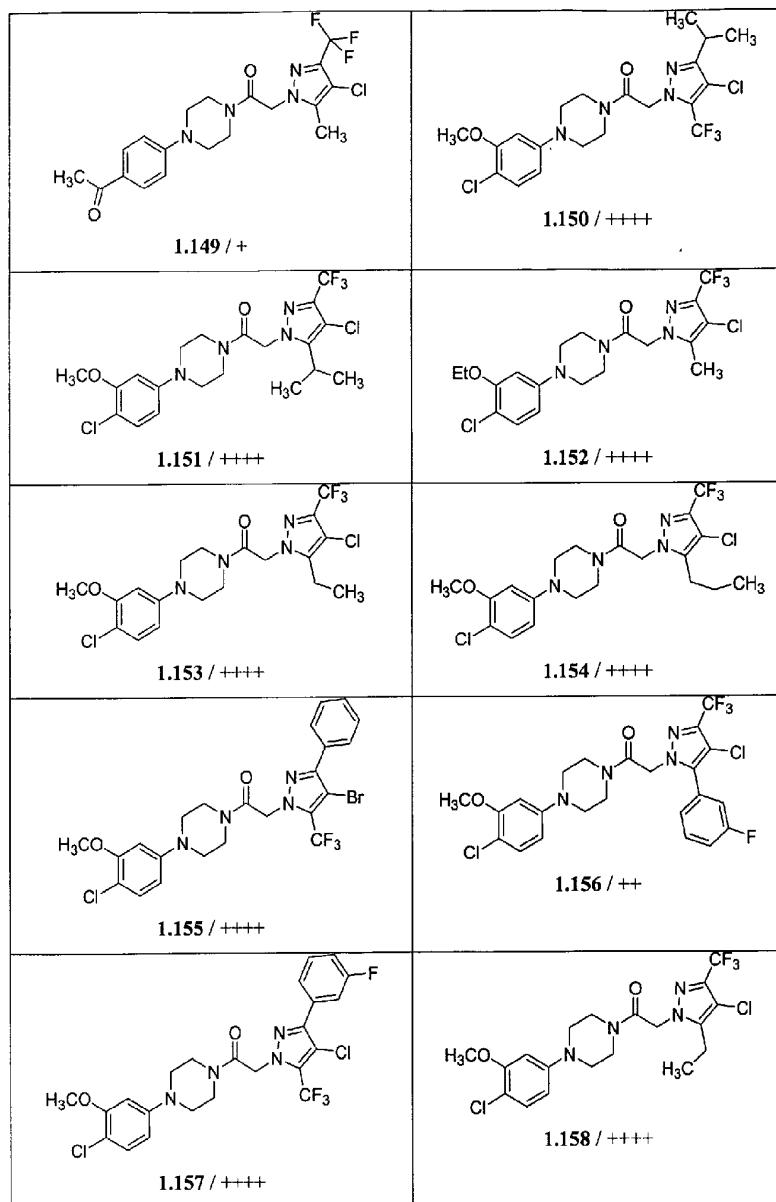








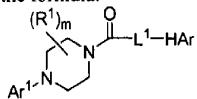




[0353] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent 5 applications cited herein are hereby incorporated by reference for all purposes.

The claims defining the invention are as follows:

1. A compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein

5 L^1 is a $-CH_2-$ group;

the subscript m is an integer of from 0 to 2;

each R^1 is a substituent independently selected from the group consisting of C_{1-4} alkyl and C_{1-4} haloalkyl;

10 Ar^1 is selected from the group consisting of phenyl, pyridyl, pyrazinyl, and pyridazinyl, each of which is optionally substituted with from one to three R^2 substituents independently selected from the group consisting of halogen, $-OR^c$, $-OC(O)R^c$, $-NR^cR^d$, $-SR^c$, $-R^e$, $-CN$, $-NO_2$, $-CO_2R^c$, $-CONR^cR^d$, $-C(O)R^c$, $-OC(O)NR^cR^d$, $-NR^dC(O)R^c$, $-NR^dC(O)_2R^c$, $-NR^c-C(O)NR^cR^d$, $-S(O)R^c$, $-S(O)_2R^c$, $-NR^cS(O)_2R^e$, $-S(O)_2NR^cR^d$, $-N_3$, $-X^2OR^c$, $-X^2OC(O)R^c$, $-X^2NR^cR^d$, $-X^2SR^c$, $-X^2CN$, $-X^2NO_2$, $-X^2CO_2R^c$, $-X^2CONR^cR^d$, $-X^2C(O)R^c$, $-X^2OC(O)NR^cR^d$, $-X^2NR^dC(O)R^c$, $-X^2NR^dC(O)_2R^c$, $-X^2NR^cC(O)NR^cR^d$, $-X^2S(O)R^c$, $-X^2S(O)_2R^c$, $-X^2NR^cS(O)_2R^e$, $-X^2S(O)_2NR^cR^d$ and $-X^2N_3$, wherein X^2 is C_{1-4} alkylene, and each R^c and R^d is independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl, and C_{2-8} alkynyl, and each R^c is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl, and C_{2-8} alkynyl, and each of R^c , R^d and R^e is optionally further substituted with from one to three members selected from the group consisting of OH , $O(C_{1-8}$ alkyl), SH , $S(C_{1-8}$ alkyl), CN , NO_2 , NH_2 , $NH(C_{1-8}$ alkyl) and $N(C_{1-8}$ alkyl) $_2$;

15 $HArc$ is a heteroaryl group selected from the group consisting of pyrazolyl and benzopyrazolyl each of which is linked through a ring member nitrogen atom to the remainder of the molecule and is substituted with from one to three R^3 substituents independently selected from the group consisting of halogen, phenyl, thienyl, furanyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, triazolyl, tetrazolyl, oxadiazolyl, $-OR^h$, $-OC(O)R^f$, NR^fR^g , $-SR^f$, $-R^h$, $-CN$, $-NO_2$, $-CO_2R^f$, $-CONR^fR^g$, $-C(O)R^f$, $-OC(O)NR^fR^g$, $-NR^gC(O)R^f$, $-NR^gC(O)_2R^h$, $-NR^fC(O)NR^fR^g$, $-S(O)R^h$, $-S(O)_2R^h$, $-NR^fS(O)_2R^h$, $-S(O)_2NR^fR^g$, $-NR^fS(O)_2R^h$, $-NR^fS(O)_2NR^fR^g$, $-N_3$, $-X^3OR^f$, $-X^3OC(O)R^f$, $-X^3NR^fR^g$, $-X^3SR^f$, $-X^3CN$, $-X^3NO_2$, $-X^3CO_2R^f$, $-X^3CONR^fR^g$, $-X^3C(O)R^f$, $-X^3OC(O)NR^fR^g$, $-X^3NR^gC(O)R^f$, $-X^3NR^gC(O)_2R^h$, $-X^3NR^fC(O)NR^fR^g$, $-X^3S(O)R^h$, $-X^3S(O)_2R^h$, $-X^3NR^fS(O)_2R^h$, and $-X^3S(O)_2NR^fR^g$

wherein X^3 is C_{1-4} alkylene, each R^f and R^g is independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl, and C_{2-8} alkynyl, and each R^h is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl, and C_{2-8} alkynyl, and wherein any phenyl, thienyl, furanyl, 5 pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, triazolyl, tetrazolyl or oxadiazolyl substituents present are optionally substituted with from one to three substituents selected from the group consisting of halogen, $-OR^f$, $-NR^fR^g$, $-R^h$, $-CN$, $-NO_2$, $-CO_2R^f$, $-CONR^fR^g$, $-C(O)R^f$, $-X^3OR^f$, $-X^3NR^fR^g$, $-X^3NR^fS(O)_2R^h$ and $-X^3S(O)_2NR^fR^g$;

10 with the proviso that the compound is other than CAS Reg. No. 492422-98-7, 1-[[4-bromo-5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl]-4-(5-chloro-2-methylphenyl)-piperazine; CAS Reg. No. 351986-92-0, 1-[[4-chloro-5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl]-4-(4-fluorophenyl)-piperazine; and CAS Reg. No. 356039-23-1, 1-[(3,5-dimethyl-4-nitro-1H-pyrazol-1-yl)acetyl]-4-(4-fluorophenyl)-15 piperazine.

2. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ar^1 is selected from the group consisting of:

- (i) phenyl, substituted with from 1 to 3 R^2 groups,
- (ii) pyridinyl, substituted with from 1 to 3 R^2 groups; and
- 20 (iii) pyrazinyl, substituted with from 1 to 3 R^2 groups;

wherein each R^2 is a member independently selected from the group consisting of halogen, $-OR^c$, $-OC(O)R^c$, $-NR^cR^d$, $-SR^c$, $-R^e$, $-CN$, $-NO_2$, $-CO_2R^c$, $-CONR^cR^d$, $-C(O)R^c$, $-OC(O)NR^cR^d$, $-NR^dC(O)R^c$, $-NR^dC(O)_2R^c$, $-NR^c-C(O)NR^cR^d$, $-S(O)R^c$, $-S(O)_2R^c$, $-NR^cS(O)_2R^c$, $-S(O)_2NR^cR^d$ and $-N_3$, wherein each R^c and R^d is independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl and C_{2-8} alkynyl, and each R^e is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl and C_{2-8} alkynyl.

3. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ar^1 is selected from the group consisting of:

- (i) phenyl substituted with from 1 to 3 R^2 groups;
- (ii) pyridinyl substituted with from 1 to 3 R^2 groups; and
- 30 (iii) pyrazinyl, substituted with from 1 to 3 R^2 groups;

wherein each R^2 is a member independently selected from the group consisting of halogen, $-X^2OR^c$, $-X^2OC(O)R^c$, $-X^2NR^cR^d$, $-X^2SR^c$, $-X^2CN$, $-X^2NO_2$, $-X^2CO_2R^c$, $-X^2CONR^cR^d$, $-X^2C(O)R^c$, $-X^2OC(O)NR^cR^d$, $-X^2NR^dC(O)R^c$, $-X^2NR^dC(O)_2R^c$,

-X²NR^cC(O)NR^cR^d, -X²S(O)R^c, -X²S(O)₂R^c, -X²NR^cS(O)₂R^c, -X²S(O)NR^cR^d and -X²N₃, wherein each R^c and R^d is independently selected from hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, and each R^c is independently selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl.

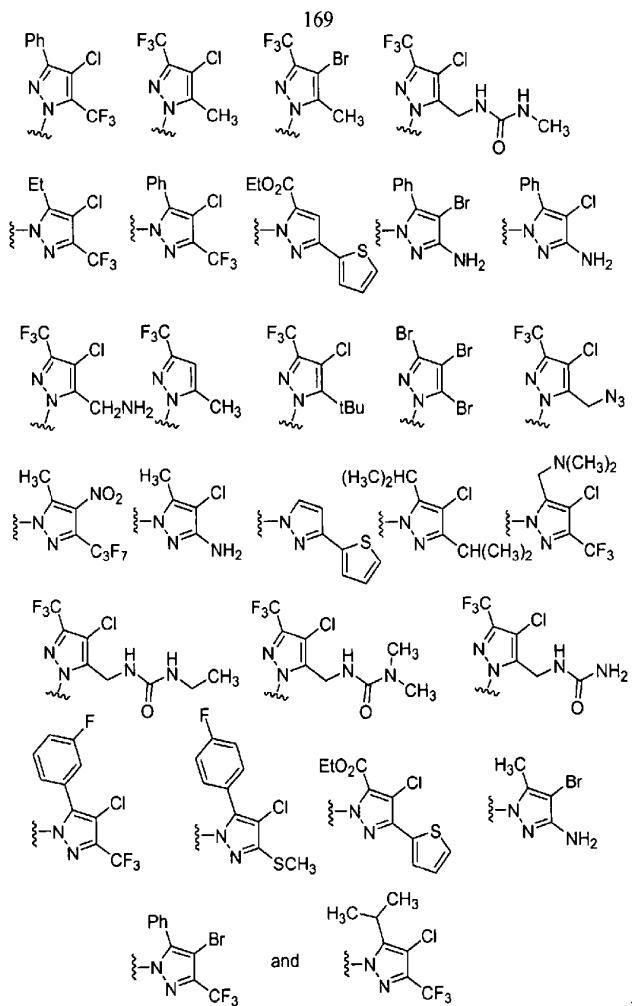
4. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ar¹ is phenyl substituted with from 1 to 3 R² groups.

5. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein HAr is a member selected from the group consisting of pyrazolyl and benzopyrazolyl each of which is optionally substituted with from one to three-R³ groups independently selected from the group consisting of halogen, phenyl, thienyl, -OR^h, -COR^f, -CO₂R^f, -CONR^fR^g, -NO₂, -R^h, -CN, -SR^f, -S(O)R^h, -S(O)₂R^h and -NR^fR^g, wherein R^f and R^g are each independently selected from the group consisting of H, C₁₋₈ alkyl, C₃₋₆ cycloalkyl and C₁₋₈ haloalkyl, and each R^h is independently selected from the group consisting of C₁₋₈ alkyl, C₃₋₆ cycloalkyl and C₁₋₈ haloalkyl.

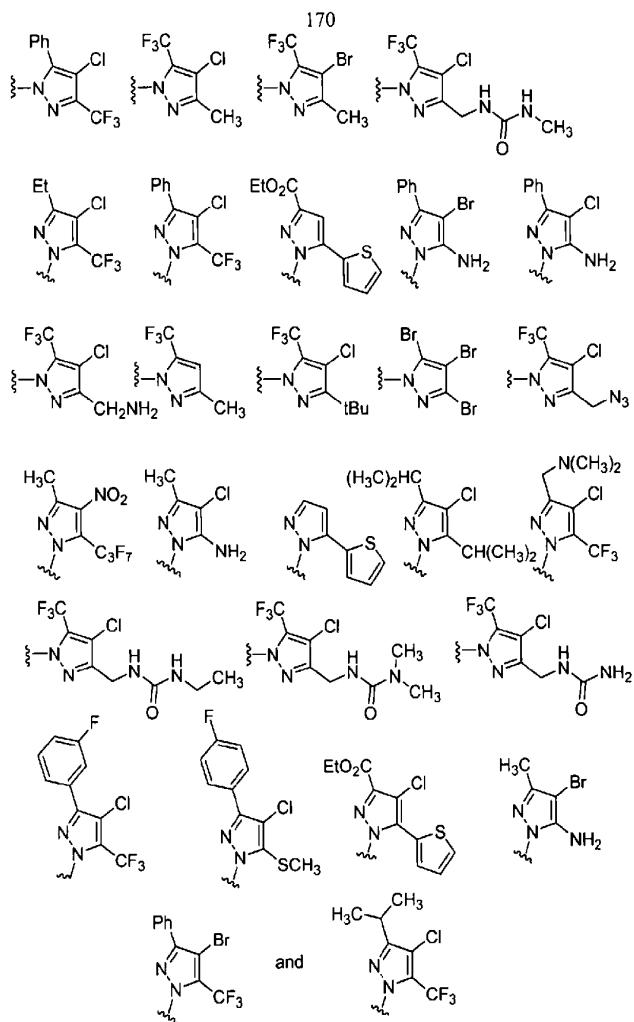
6. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein HAr is pyrazolyl or benzopyrazolyl, each of which is optionally substituted with from one to three R³ groups independently selected from the group consisting of halogen, phenyl, thienyl, -OR^h, -CO₂R^f, -COR^f, -CONR^fR^g, -NO₂, -R^h, -CN, -SR^f, -S(O)R^h, -S(O)₂R^h and -NR^fR^g, wherein each R^f and R^g is independently selected from the group consisting of H, C₁₋₈ alkyl and C₁₋₈ haloalkyl, and each R^h is independently selected from the group consisting of C₁₋₈ alkyl and C₁₋₈ haloalkyl.

7. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein HAr is selected from the group consisting of:

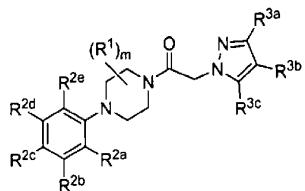
2003236500 28 Nov 2008



8. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein HAr is selected from the group consisting of:



9. A compound of claim 1, or a pharmaceutically acceptable salt thereof, having the formula:



wherein the subscript m is an integer of from 0 to 2;

each R¹ is a member selected from the group consisting of C₁₋₄ alkyl and C₁₋₄ haloalkyl;

R^{2a}, R^{2b}, R^{2c}, R^{2d} and R^{2e} are each members independently selected from the group consisting of hydrogen, halogen, -OR^c, -OC(O)R^c, -NR^cR^d, -SR^c, -R^e, -CN, -NO₂, -CO₂R^c, -CONR^cR^d, -C(O)R^c, -OC(O)NR^cR^d, -NR^dC(O)R^c, -NR^dC(O)₂R^c, -NR^cC(O)NR^cR^d, -S(O)R^c, -S(O)₂R^c, -NR^cS(O)₂R^c, -S(O)₂NR^cR^d, -N₃, -X²OR^c, -X²OC(O)R^c, -X²NR^cR^d, -X²SR^c, -X²CN, -X²NO₂, -X²CO₂R^c, -X²CONR^cR^d, -X²C(O)R^c, -X²OC(O)NR^cR^d, -X²NR^dC(O)R^c, -X²NR^dC(O)₂R^c, -X²NR^cC(O)NR^cR^d, -X²S(O)R^c, -X²S(O)₂R^c, -X²NR^cS(O)₂R^c and -X²N₃, wherein X² is C₁₋₄ alkylene, and each R^c and R^d is independently selected from hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, and each R^e is independently selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, and each of R^c, R^d and R^e is optionally further substituted with from one to three members selected from the group consisting of OH, O(C₁₋₈ alkyl), SH, S(C₁₋₈ alkyl), CN, NO₂, NH₂, NH(C₁₋₈ alkyl) and N(C₁₋₈ alkyl)₂;

R^{3a}, R^{3b} and R^{3c} are each members independently selected from the group consisting of hydrogen, halogen, phenyl, thieryl, -OR^h, -OC(O)R^f, -NR^fR^g, -SR^f, -R^h, -CN, -NO₂, -CO₂R^f, -CONR^fR^g, -C(O)R^f, -OC(O)NR^fR^g, -NR^gC(O)R^f, -NR^gC(O)₂R^h, -NR^fC(O)NR^fR^g, -S(O)R^h, -S(O)₂R^h, -NR^fS(O)₂R^h, -S(O)₂NR^fR^g, -NR^fS(O)₂R^h, -NR^fS(O)₂NR^fR^g, -X³OR^f, -X³OC(O)R^f, -X³NR^fR^g, -X³SR^f, -X³CN, -X³NO₂, -X³CO₂R^f, -X³CONR^fR^g, -X³C(O)R^f, -X³OC(O)NR^fR^g, -X³NR^gC(O)R^f, -X³NR^gC(O)₂R^h, -X³NR^fC(O)NR^fR^g, -X³S(O)R^h, -X³NR^fS(O)₂R^h and -X³S(O)₂NR^fR^g wherein X³ is C₁₋₄ alkylene, each R^f and R^g is independently selected from hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, and each R^h is independently selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl, and wherein any phenyl or thieryl group present is optionally substituted with from one to three substituents selected from the group consisting of halogen, -OR^f, -NR^fR^g, -R^h, -CN, -NO₂, -CO₂R^f, -CONR^fR^g, -C(O)R^f, -X³OR^f, -X³NR^fR^g, -X³NR^fS(O)₂R^h and -X³S(O)₂NR^fR^g.

10. A compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein m is 0 or 1; and at least one of R^{2a} and R^{2c} is hydrogen.

11. A compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein at least one of R^{3a}, R^{3b} and R^{3c} is selected from the group consisting of halogen and C₁₋₄ haloalkyl.

12. A compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R^{2d} is hydrogen and at least two of R^{3a} , R^{3b} and R^{3c} are selected from the group consisting of halogen and C_{1-4} haloalkyl.

13. A compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein R^{2e} is selected from the group consisting of F, Cl, Br, CN, NO_2 , CO_2CH_3 , $C(O)CH_3$ and $S(O)_2CH_3$, and each of R^{3a} , R^{3b} and R^{3c} is other than hydrogen.

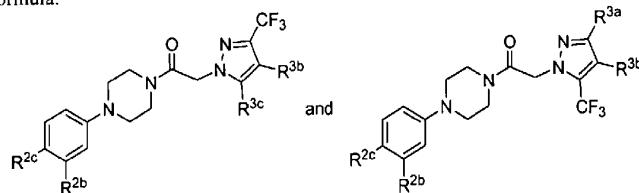
14. A compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein m is 0 or 1; and R^{2a} and R^{2e} are each hydrogen.

15. A compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein at least one of R^{3a} , R^{3b} and R^{3c} is selected from the group consisting of halogen and C_{1-4} haloalkyl.

16. A compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein each of R^{3a} , R^{3b} and R^{3c} is other than hydrogen.

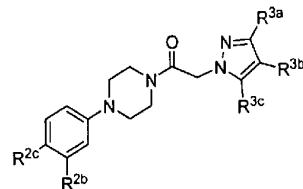
17. A compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein m is 0 or 1; R^{2b} and R^{2e} are each hydrogen.

18. A compound of claim 9, or a pharmaceutically acceptable salt thereof, having the formula:



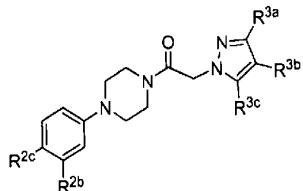
19. A compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein R^{3c} and R^{3a} are each independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl.

20. A compound of claim 9, or a pharmaceutically acceptable salt thereof, having the formula:



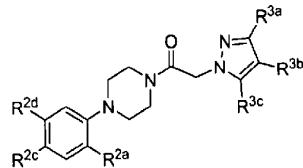
wherein R^{2c} is halogen, cyano or nitro; R^{2b} is R^e or $-OR^c$; R^{3a} is selected from the group consisting of NH_2 , CF_3 , SCH_3 , Ph and thieryl; R^{3b} is chloro or bromo; and R^{3c} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl.

21. A compound of claim 9, or a pharmaceutically acceptable salt thereof, having
5 the formula:



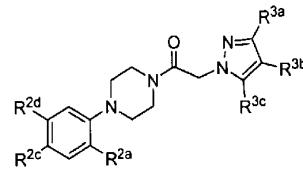
wherein R^{2c} is halogen, cyano or nitro; R^{2b} is R^e or $-OR^c$; R^{3a} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl; R^{3c} is selected from the group consisting of NH_2 , CF_3 , SCH_3 , Ph and thieryl; and R^{3b} is chloro or bromo.

10 22. A compound of claim 9, or a pharmaceutically acceptable salt thereof, having
the formula:



wherein R^{2a} is other than hydrogen; R^{2c} is halogen, cyano or nitro; R^{2d} is R^e or $-OR^c$; R^{3a} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl; R^{3b} is chloro or bromo; and R^{3c} is selected from the group consisting of NH_2 , CF_3 , SCH_3 , Ph and thieryl.

23. A compound of claim 9, or a pharmaceutically acceptable salt thereof, having
the formula:



20 wherein R^{2a} is other than hydrogen; R^{2c} is halogen, cyano or nitro; R^{2d} is R^e or $-OR^c$; R^{3a} is selected from the group consisting of NH_2 , CF_3 , SCH_3 , Ph and thieryl; R^{3b} is chloro or bromo; and R^{3c} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl.

24. A compound of claim 17, or a pharmaceutically acceptable salt thereof, wherein at least one of R^{3a} , R^{3b} and R^{3c} is selected from the group consisting of halogen and C_{1-4} haloalkyl.
25. A compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein each of R^{3a} , R^{3b} and R^{3c} is other than hydrogen.
26. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof.
27. A method of treating CCR1-mediated diseases or conditions comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 25 or a pharmaceutically acceptable salt thereof, or a composition of claim 26.
28. A method in accordance with claim 27, wherein said CCR1-mediated disease or condition is selected from an inflammatory condition, an immunoregulatory disorder, rheumatoid arthritis, multiple sclerosis, transplant rejection, dermatitis, eczema, urticaria, vasculitis, inflammatory bowel disease, food allergy and encephalomyelitis.
29. Use of a compound of any one of claims 1 to 26 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating CCR1-mediated diseases or conditions.
30. Use according to claim 29 wherein said CCR1-mediated disease or condition is selected from an inflammatory condition, an immunoregulatory disorder, rheumatoid arthritis, multiple sclerosis, transplant rejection, dermatitis, eczema, urticaria, vasculitis, inflammatory bowel disease, food allergy and encephalomyelitis.

25 Dated 20 November, 2008

Chemocentryx, Inc.

Patent Attorneys for the Applicant/Nominated Person

SPRUSON & FERGUSON

Figure 1

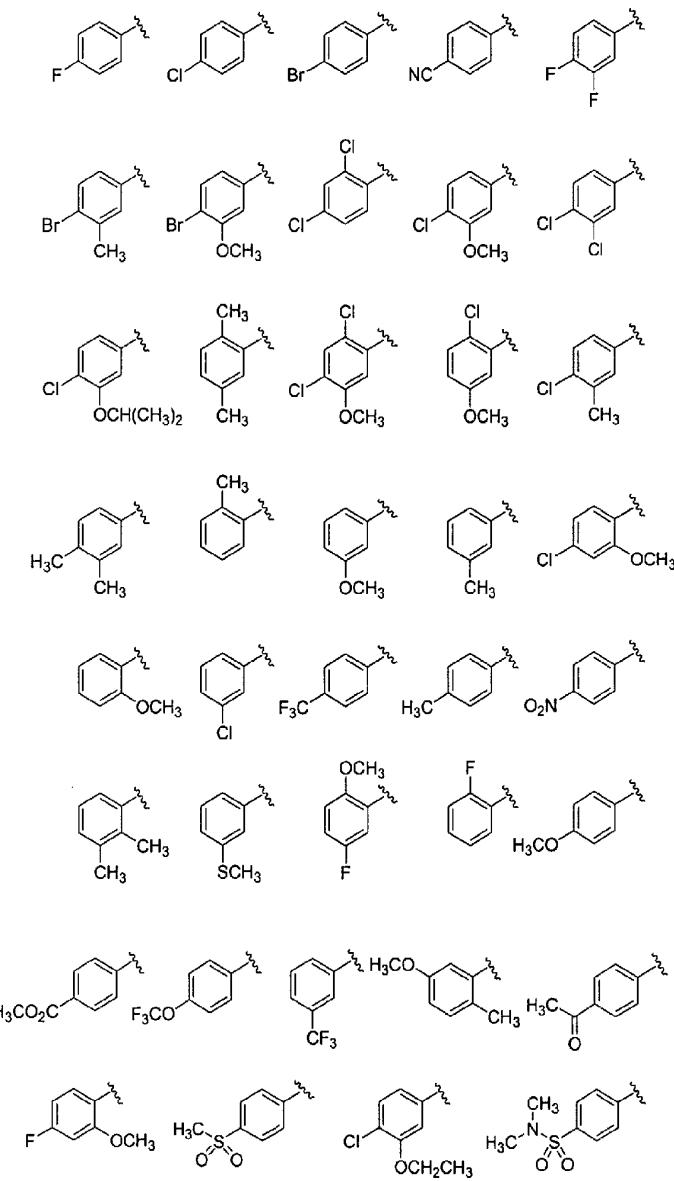


Figure 2

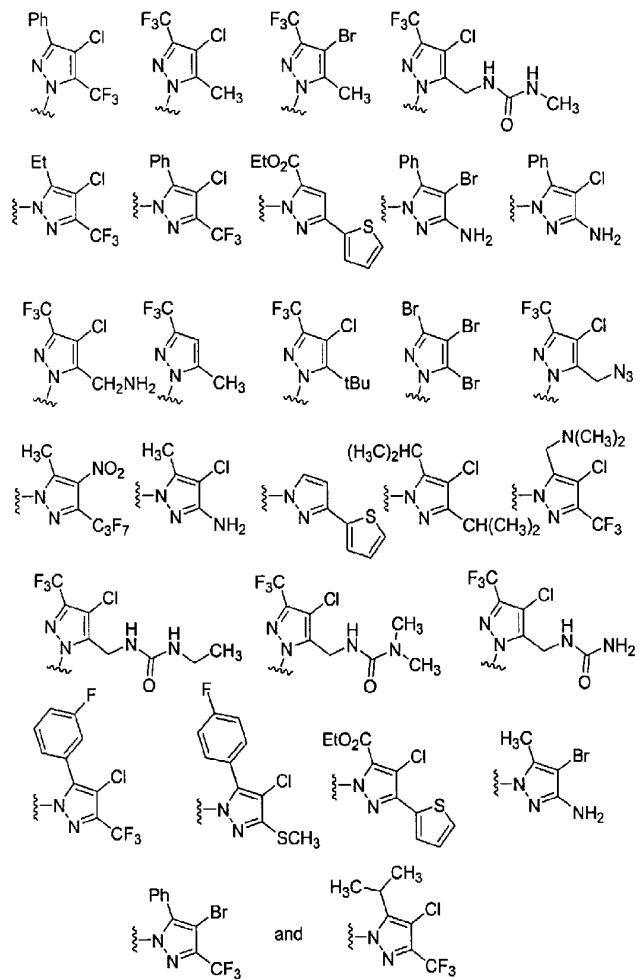


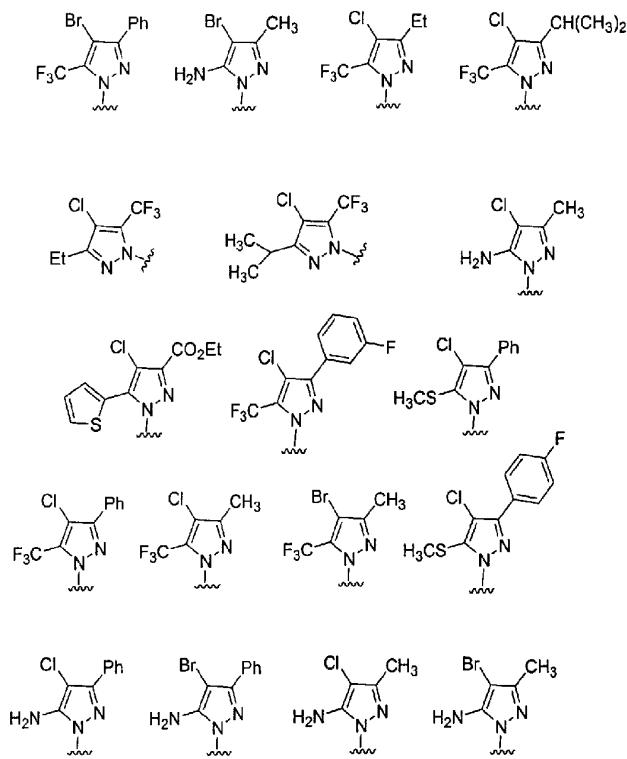
Figure 3

Figure 4A

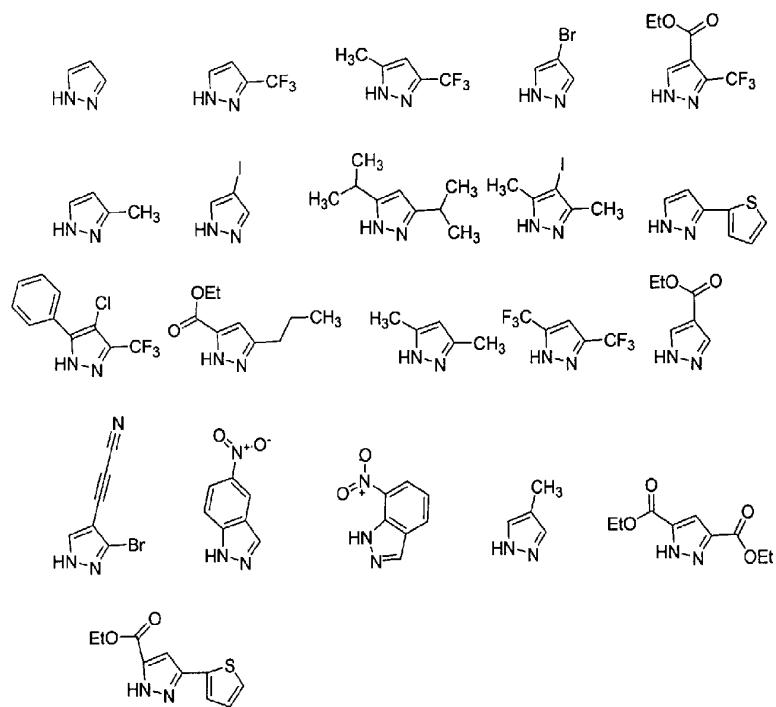


Figure 4B

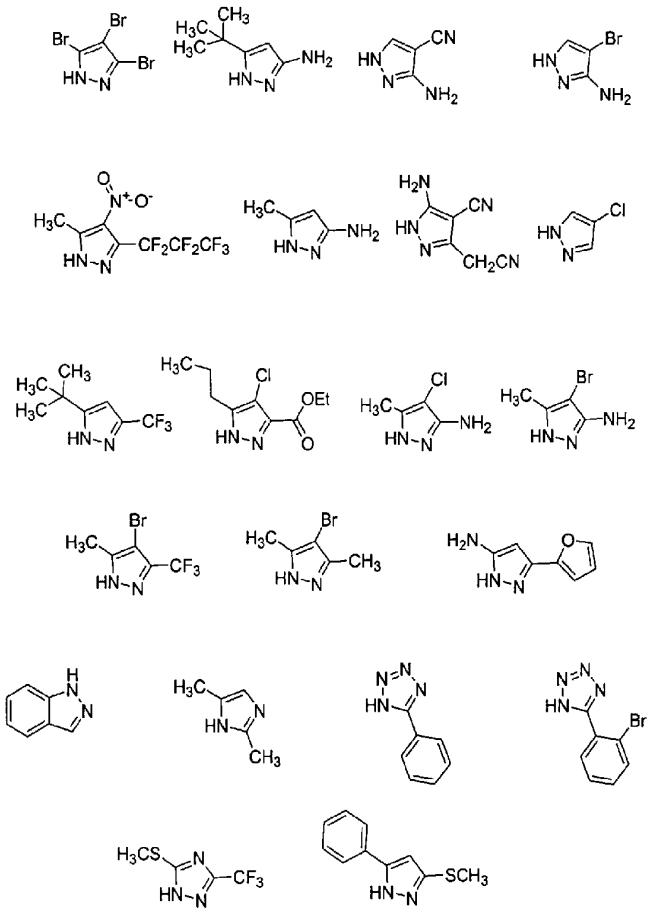


Figure 4C

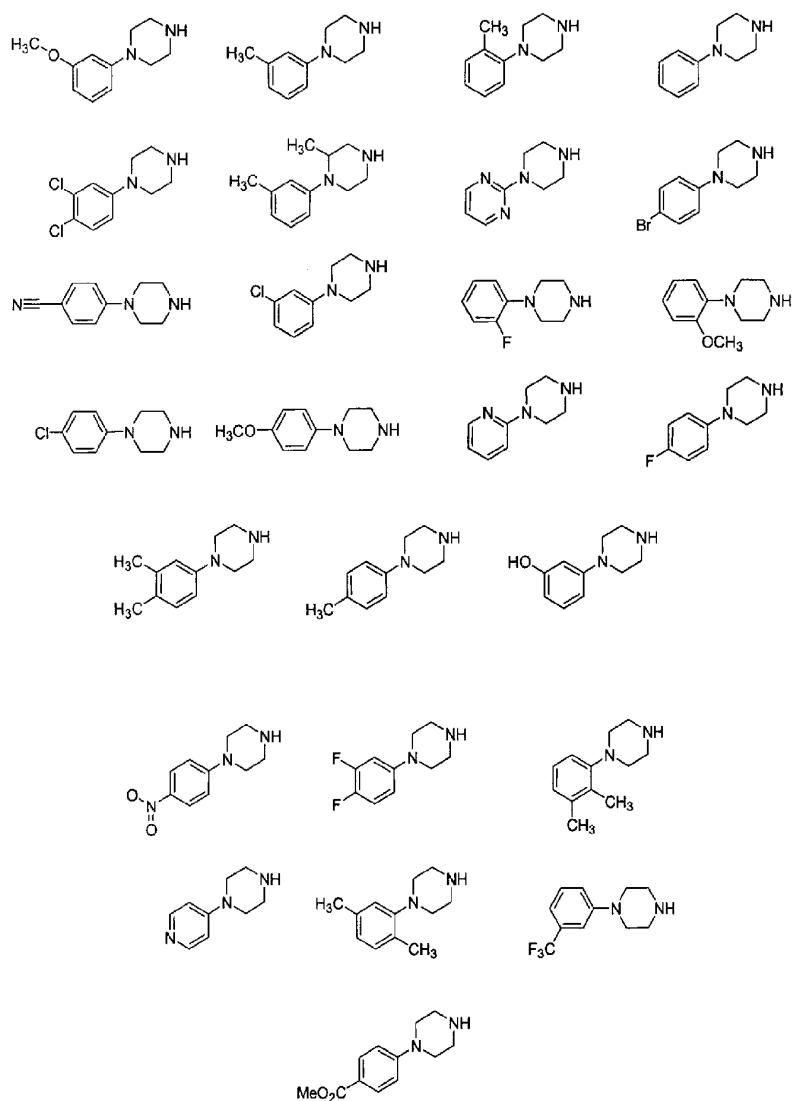


FIGURE 5A

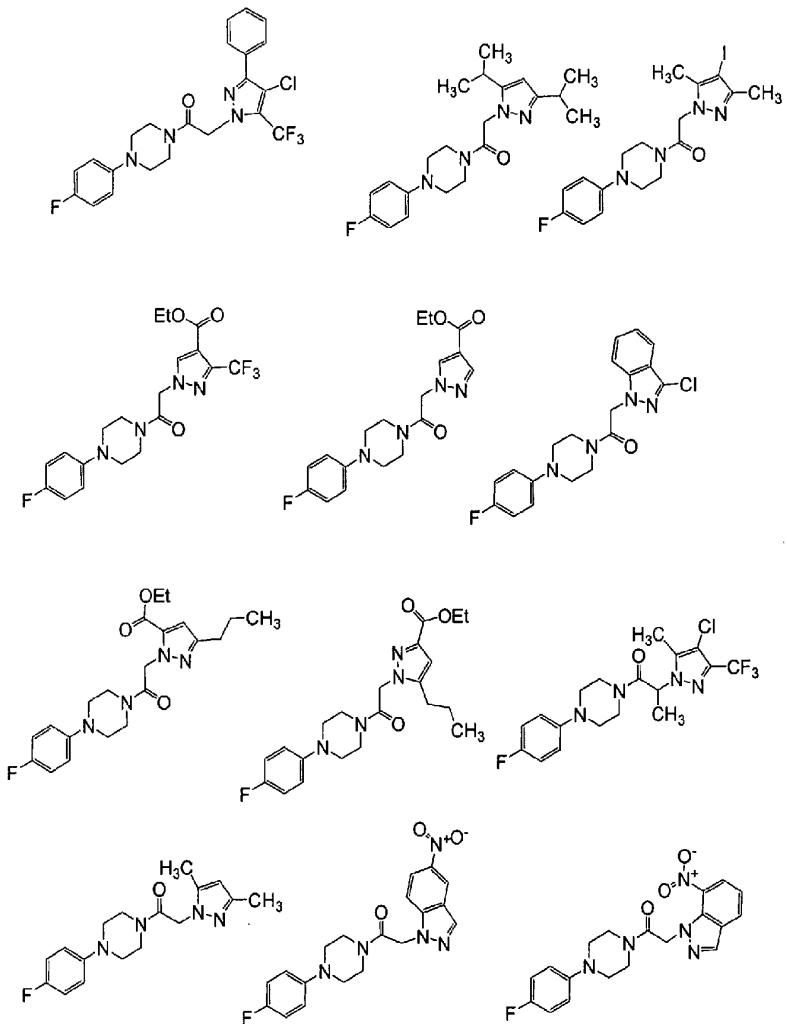


FIGURE 5B

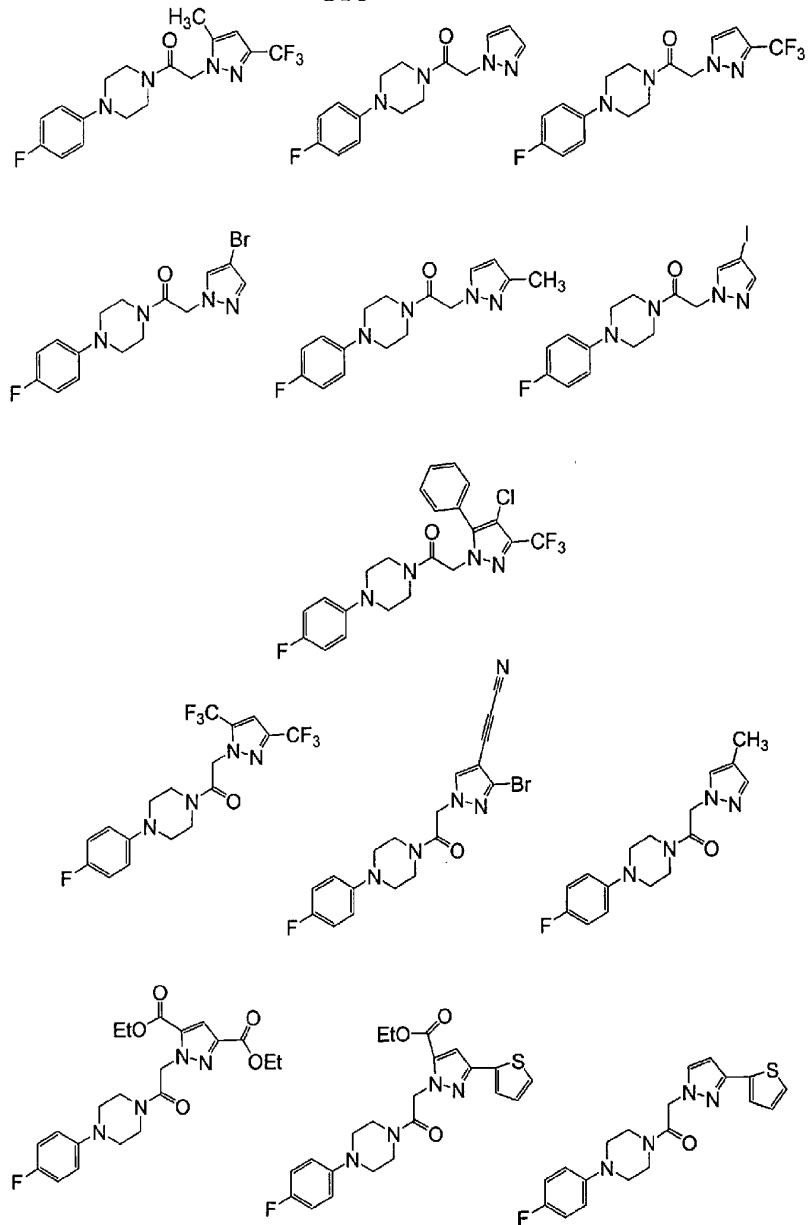


FIGURE 5C

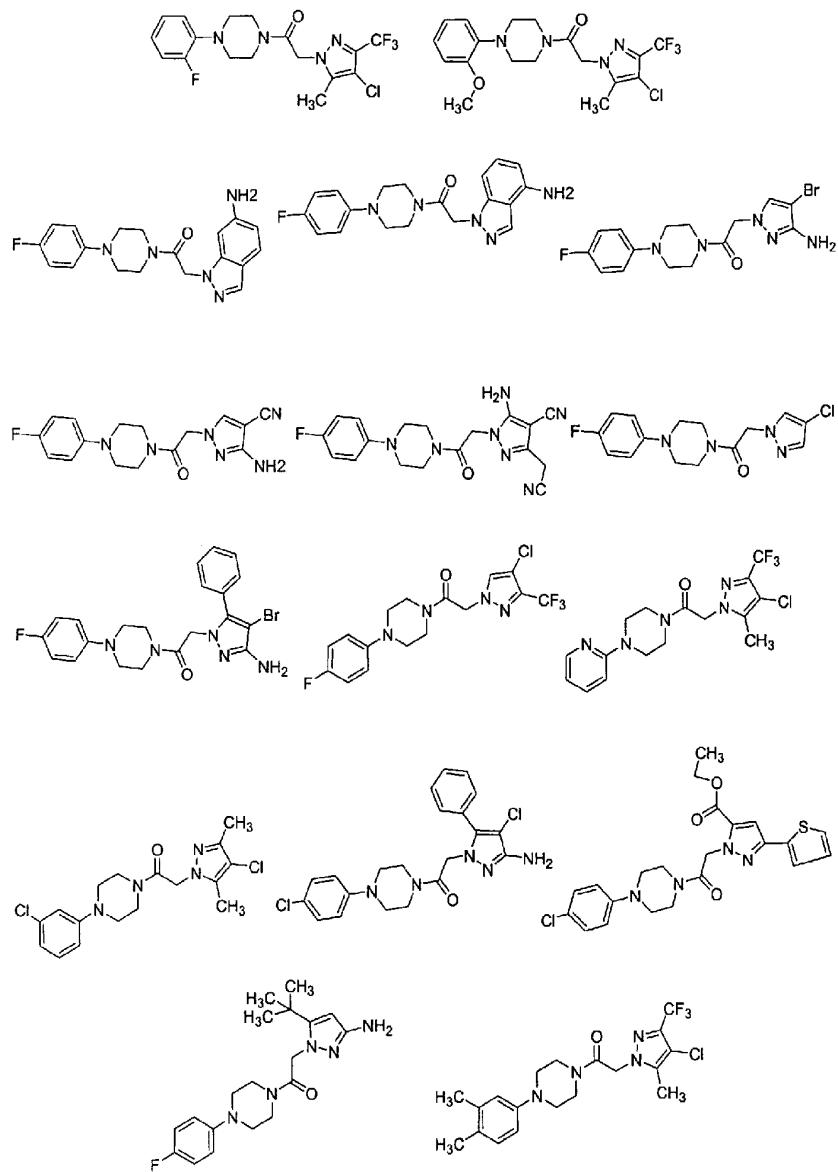


FIGURE 5D

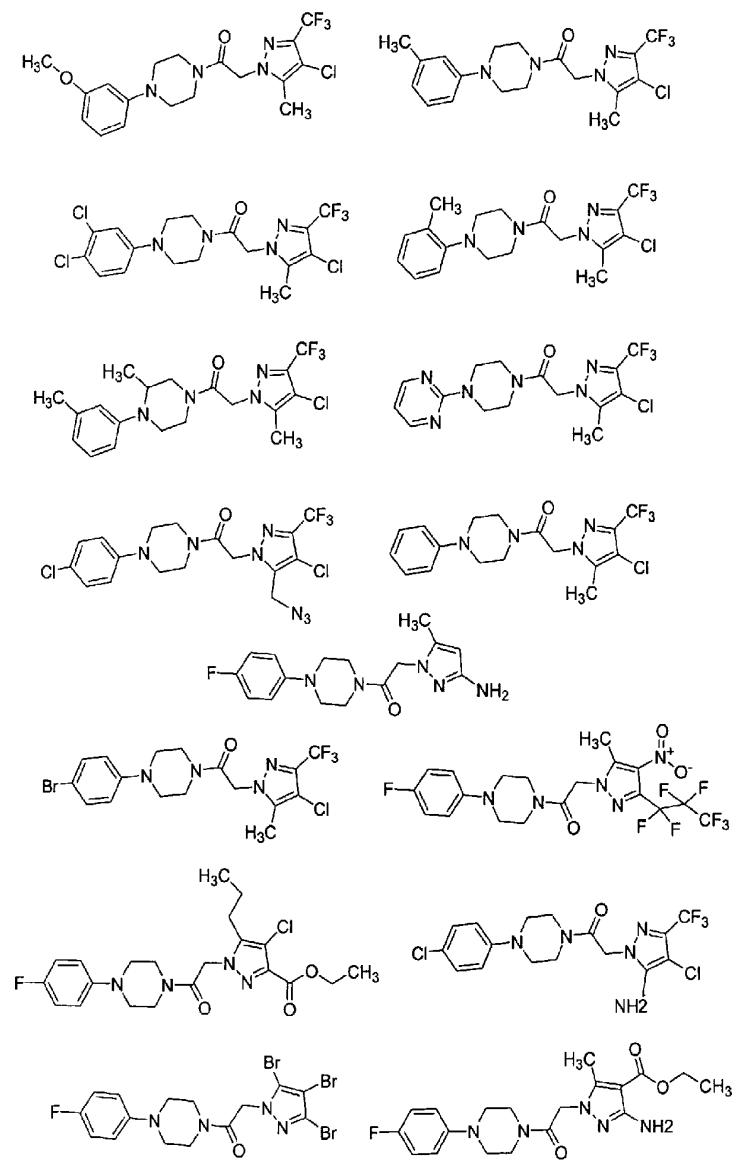


FIGURE 5E

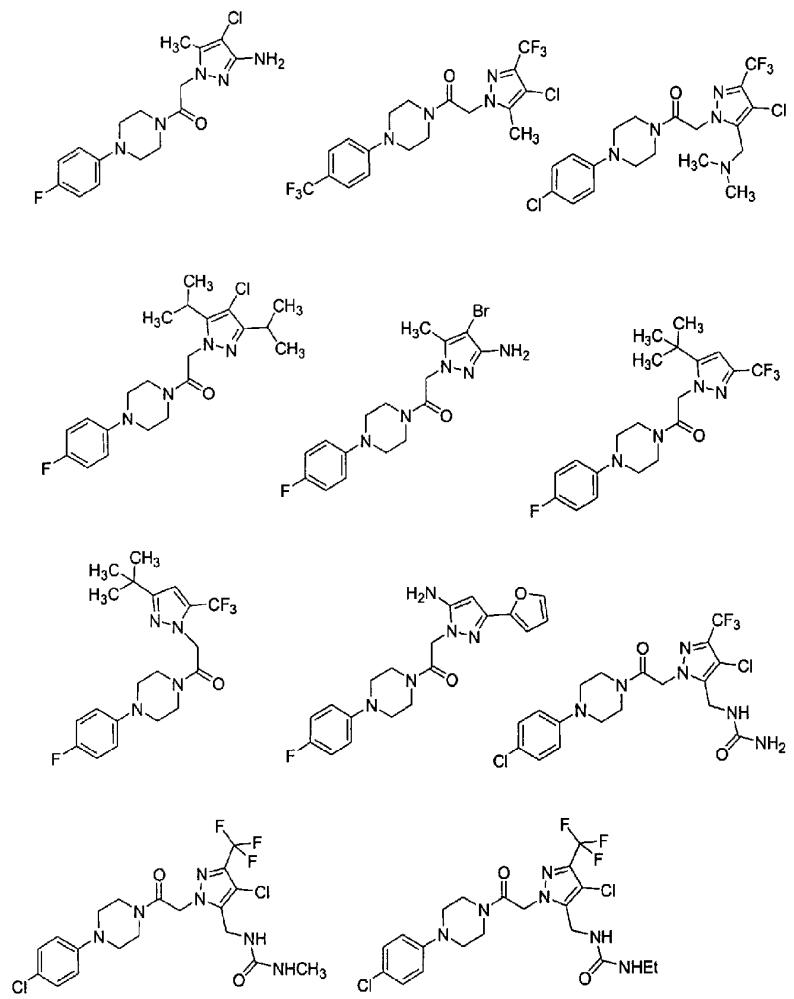


FIGURE 5F

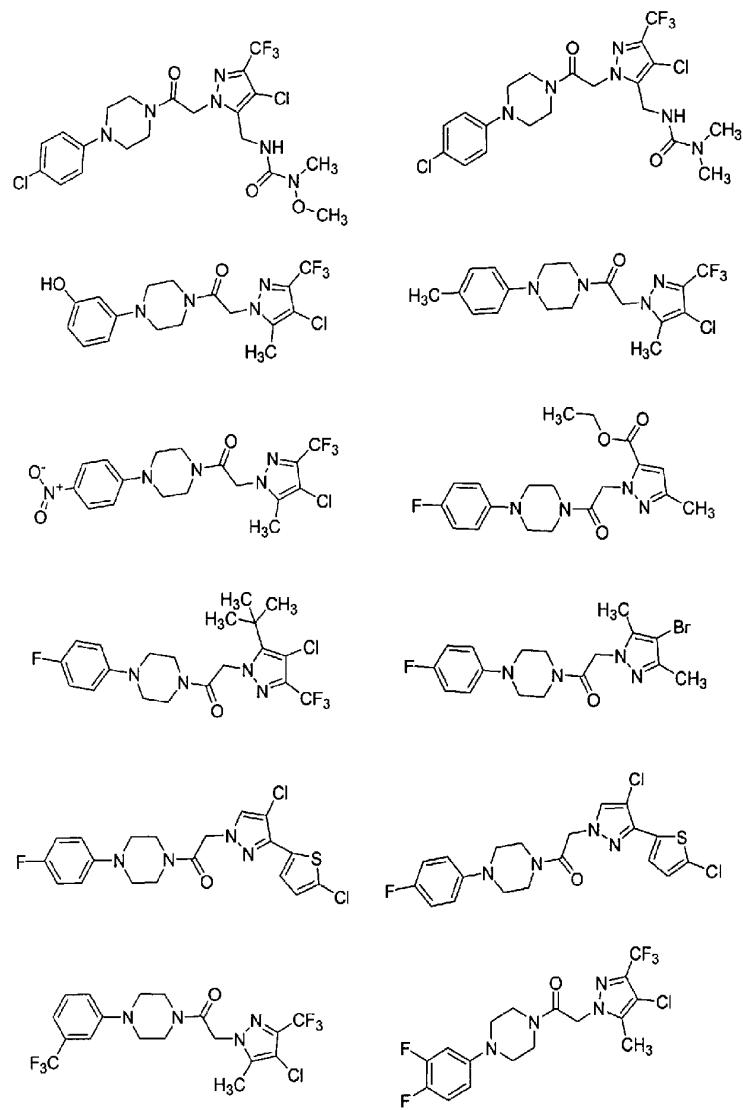


FIGURE 5G

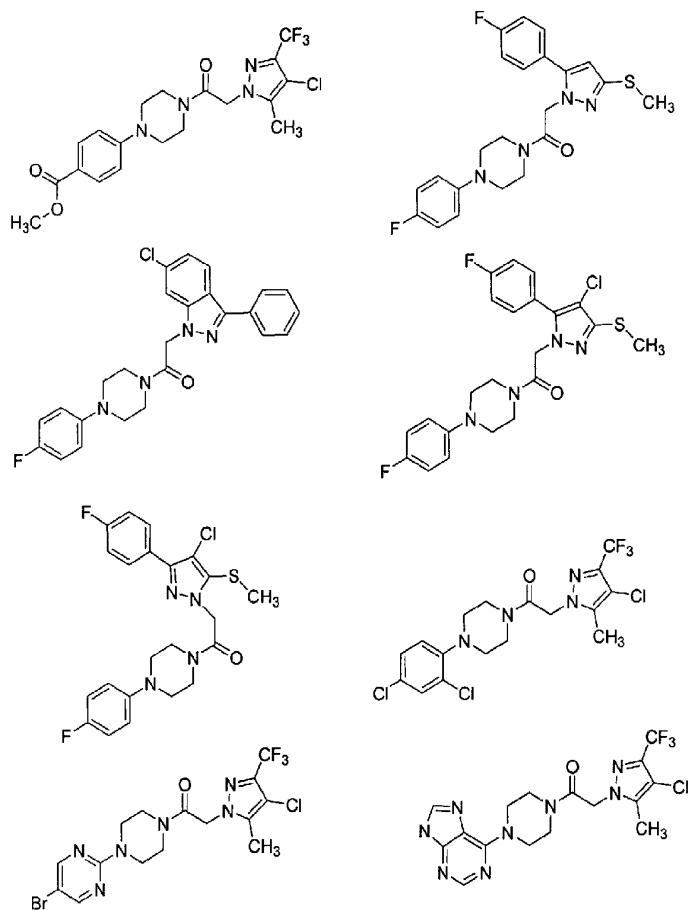


FIGURE 5H

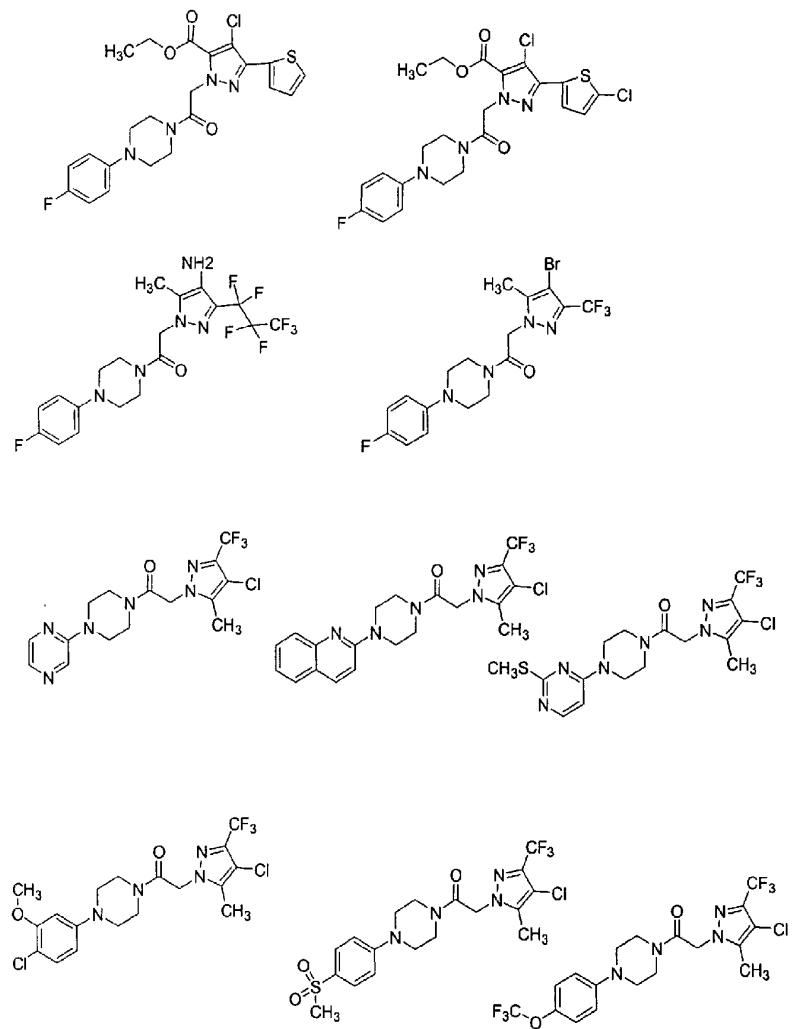


FIGURE 5I

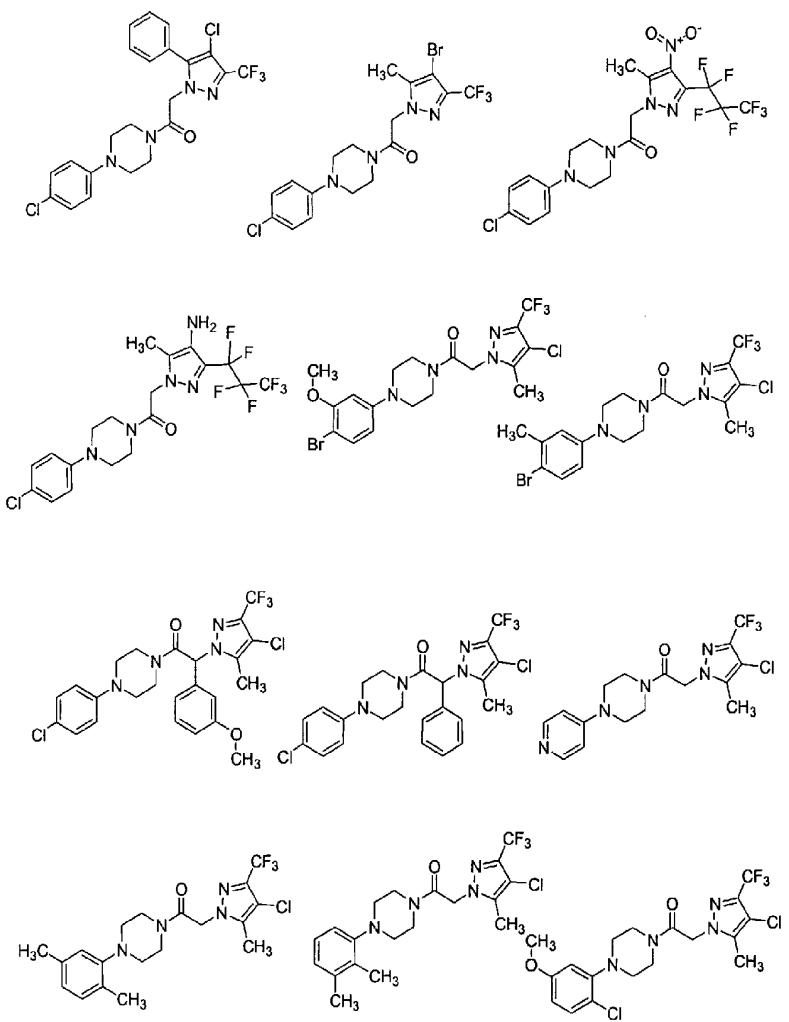


FIGURE 5J

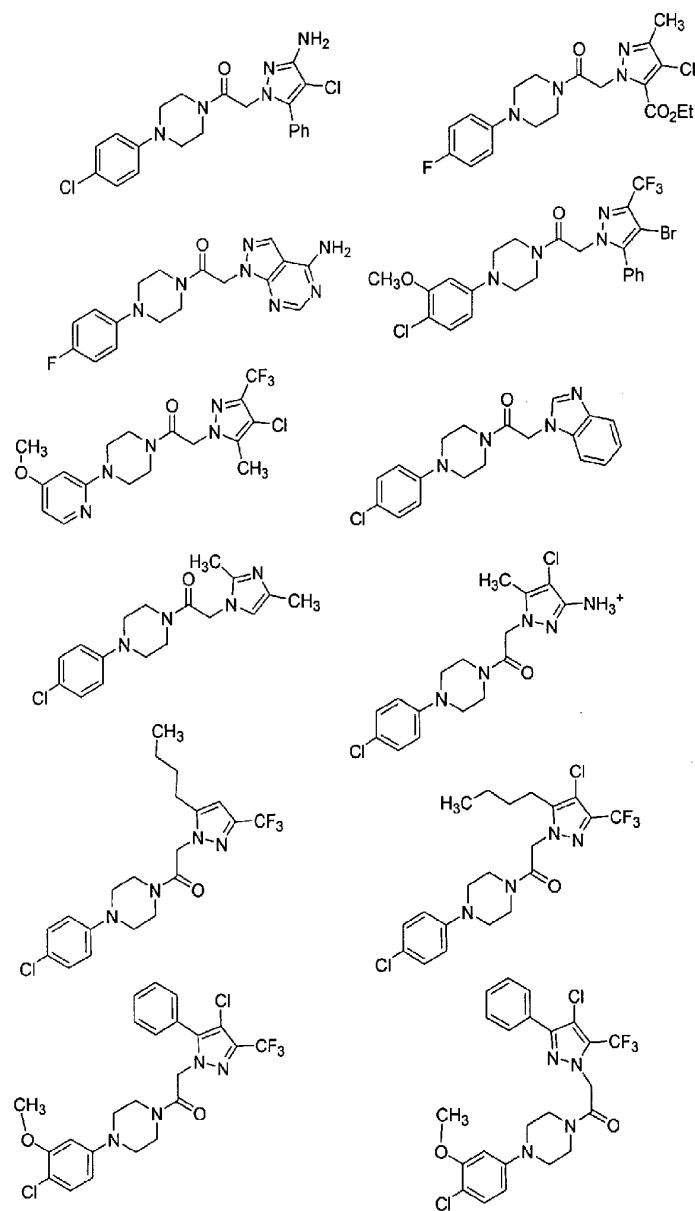


FIGURE 5K

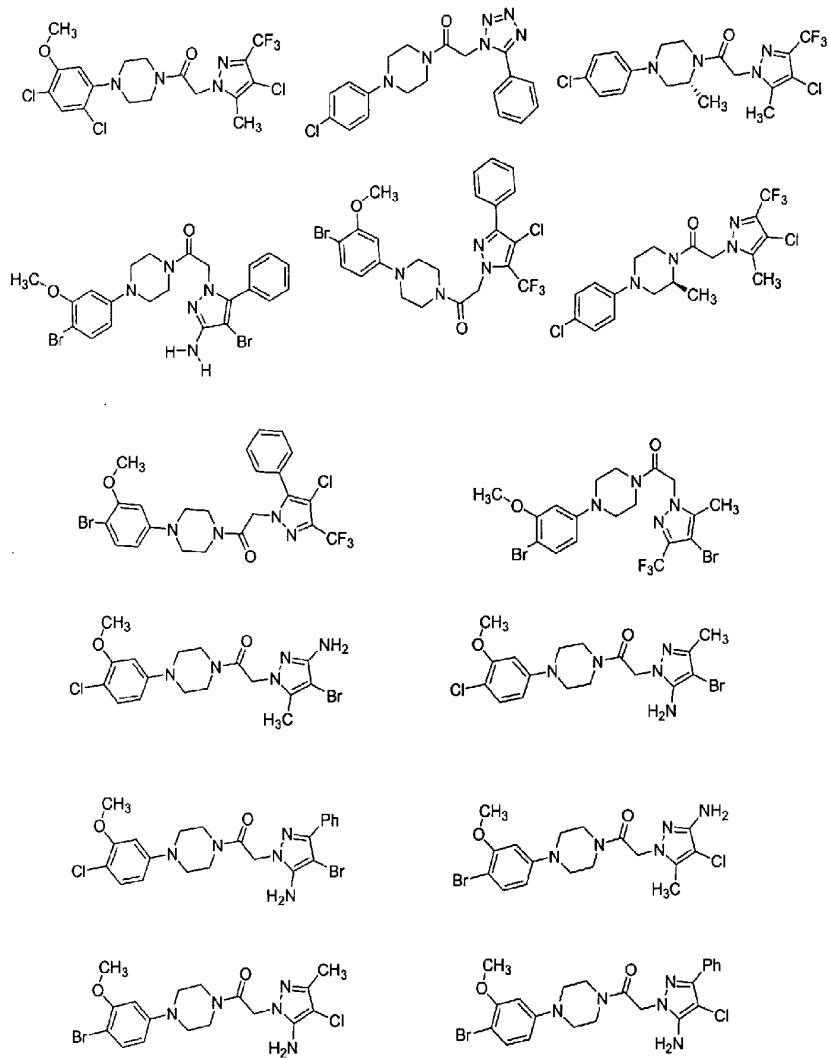


FIGURE 5L

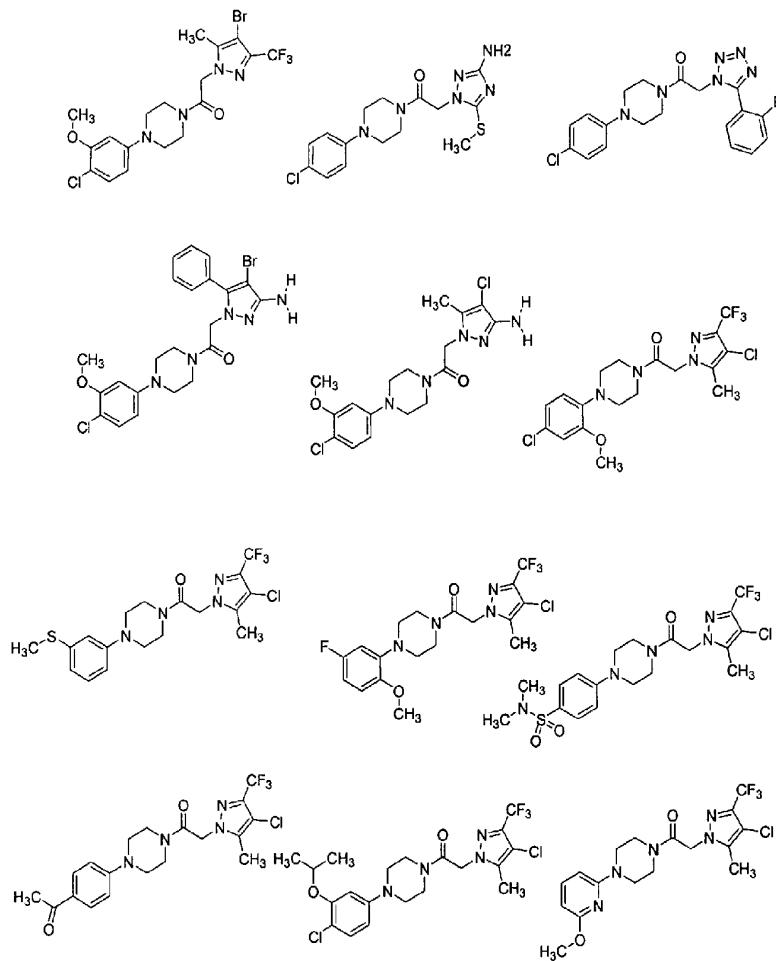


FIGURE 5M

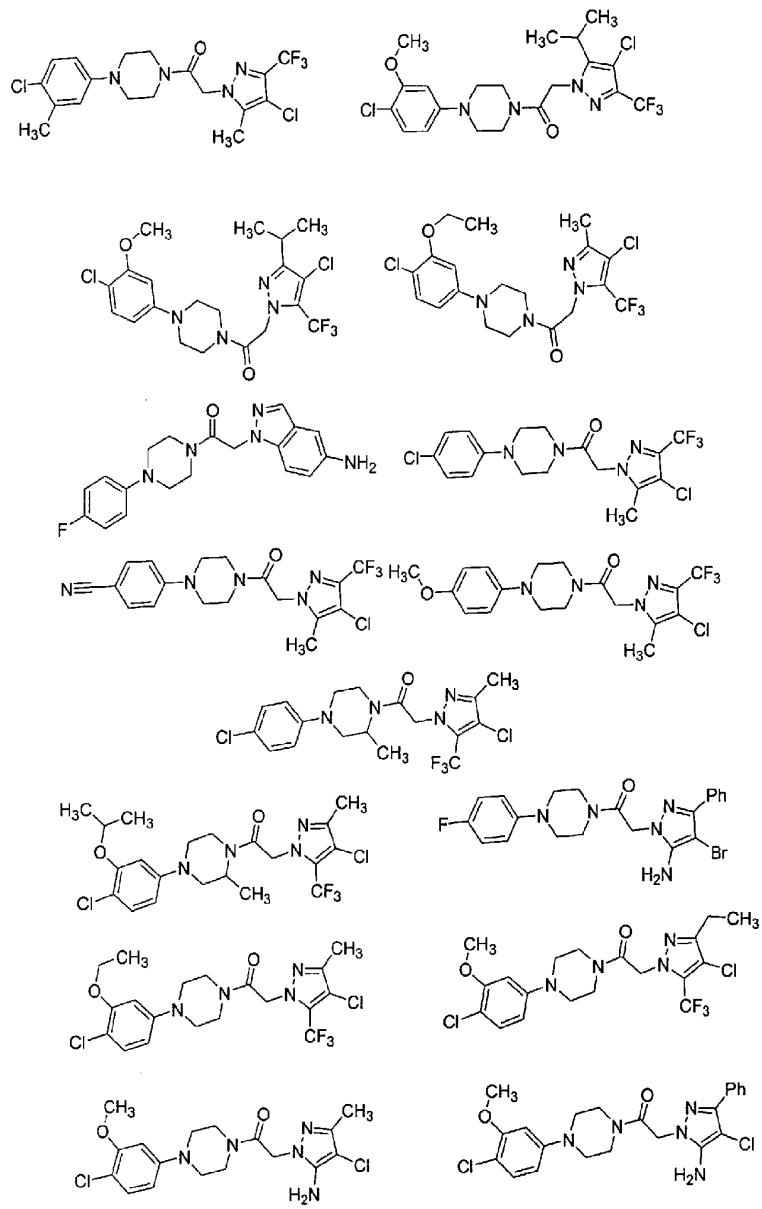


FIGURE 5N

