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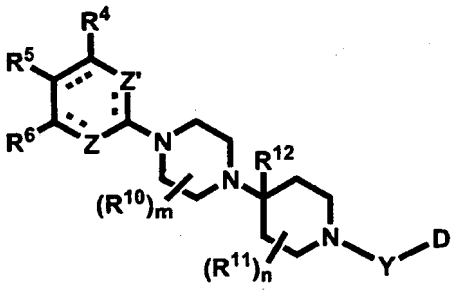

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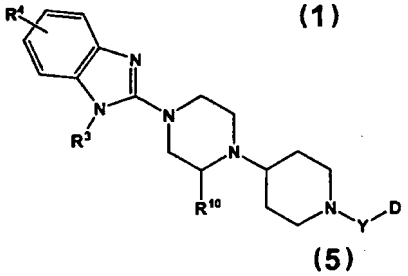

(5)

(57) Abstract: The present application discloses a compound, or enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrug of said compound, or pharmaceutically acceptable salts, solvates or esters of said compound, or of said prodrug, said compound having the general structure shown in Formula 1 or Formula 5: [Chemical formulas should be inserted here as they appear on abstract in paper form.] or a pharmaceutically acceptable salt, solvate or ester thereof. Also disclosed is a method of treating chemokine mediated diseases, such as, palliative therapy, curative therapy, prophylactic therapy of certain diseases and conditions such as inflammatory diseases (non limiting example(s) include, psoriasis), autoimmune diseases (non limiting example(s) include, rheumatoid arthritis, multiple sclerosis), graft rejection (non limiting example(s) include, allograft rejection, zenograft rejection), infectious diseases (e.g , tuberculoid leprosy), fixed drug eruptions, cutaneous delayed type hypersensitivity responses, ophthalmic inflammation, type I diabetes, viral meningitis and tumors using a compound of Formula 1.

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HETEROCYCLIC COMPOUNDS WITH CXCR3 ANTAGONIST ACTIVITY

Field Of The Invention

The present invention relates to heterocycylic compounds with CXCR3 antagonist activity, pharmaceutical compositions containing one or more such antagonists, one or more such antagonists in combination with other compounds with chemokine activity, one or more such antagonists in combination with known immunosuppressive agents, non-limiting example(s) include Methotrexate, interferon, cyclosporin, FK-506 and FTY720, methods of preparing such antagonists and methods of using such antagonists to modulate CXCR3 activity. This invention also discloses methods of using such CXCR3 antagonists for the treatment (non-limiting examples include palliative, curative and prophylactic therapies) of diseases and conditions where CXCR3 has been implicated. Diseases and conditions where CXCR3 has been implicated include but are not limited to inflammatory conditions (psoriasis and inflammatory bowel disease), autoimmune disease (multiple sclerosis, rheumatoid arthritis), fixed drug eruptions, cutaneous delayed-type hypersensitivity responses, type I diabetes, viral meningitis and tuberculoid leprosy. CXCR3 antagonist activity has also been indicated as a therapy for tumor growth suppression as well as graft rejection (allograft and zenograft rejections for example).

BACKGROUND OF THE INVENTION

Chemokines constitute a family of cytokines that are produced in inflammation and regulate leukocyte recruitment (Baggiolini, M. *et al., Adv. Immunol.*, 55: 97-179 (1994); Springer, T. A., *Annual Rev. Physio.*, 57: 827-872 (1995); and Schall, T. J. and K. B. Bacon, *Curr. Opin. Immunol*, 6: 865-873 (1994)). Chemokines are capable of selectively inducing chemotaxis of the formed elements of the blood (other than red blood cells), including

leukocytes such as neutrophils, monocytes, macrophages, eosinophils, basophils, mast cells, and lymphocytes, such as T cells and B cells. In addition to stimulating chemotaxis, other changes can be selectively induced by chemokines in responsive cells, including changes in cell shape, transient rises in the concentration of intracellular free calcium ions ($[Ca^{2+}]_i$), granule exocytosis, integrin upregulation, formation of bioactive lipids (e. g., leukotrienes) and respiratory burst, associated with leukocyte activation. Thus, the chemokines are early triggers of the inflammatory response, causing inflammatory mediator release, chemotaxis and extravasation to sites of infection or inflammation.

Chemokines are related in primary structure and share four conserved cysteines, which form disulfide bonds. Based upon this conserved cysteine motif, the family can be divided into distinct branches, including the C-X-C chemokines (α-chemokines) in which the first two conserved cysteines are separated by an intervening residue (e. g., IL-8, IP-10, Mig, I-TAC, PF4, ENA-78, GCP-2, GROα, GROß, GROδ, NAP-2, NAP-4), and the C-C chemokines (β-chemokines), in which the first two conserved cysteines are adjacent residues (e. g., MIP-1α, MIP-1ß, RANTES, MCP-1, MCP-2, MCP-3, I-309) (Baggiolini, M. and Dahinden, C. A., *Immunology Today*, 15 : 127-133 (1994)). Most CXC-chemokines attract neutrophil leukocytes. For example, the CXC-chemokines interleukin-8 (IL-8), GRO alpha (GROα), and neutrophil-activating peptide 2 (NAP-2) are potent chemoattractants and activators of neutrophils. The CXC-chemokines designated Mig (monokine induced by gamma interferon) and IP-10 (interferon-gamma inducible 10 kDa protein) are particularly active in inducing chemotaxis of activated peripheral blood lymphocytes.

CC-chemokines are generally less selective and can attract a variety of leukocyte cell types, including monocytes, eosinophils, basophils, T lymphocytes and natural killer cells. CC-chemokines such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β) have been

characterized as chemoattractants and activators of monocytes or lymphocytes, but do not appear to be chemoattractants for neutrophils.

A chemokine receptor that binds the CXC-chemokines IP-10 and Mig has been cloned, characterized (Loetscher, M. *et al., J. Exp. Med.,* 184: 963-969 (1996)) and designated CXCR3. CXCR3 is a G-protein coupled receptor with seven transmembrane-spanning domains and has been shown to be restrictively expressed in activated T cells, preferentially human Th1 cells. On binding of the appropriate ligand, chemokine receptors transduce an intracellular signal through the associated G-protein resulting in a rapid increase in intracellular calcium concentration.

The CXCR3 receptor mediates Ca^{2+} (calcium ion) mobilization and chemotaxis in response to IP-10 and Mig. CXCR3 expressing cells show no significant response to the CXC-chemokines IL-8, GROα, NAP-2, GCP-2 (granulocyte chemotactic protein-2), ENA78 (epithelial-derived neutrophil-activating peptide 78), PF4 (platelet factor 4), or the CC-chemokines MCP-1, MCP-2, MCP-3, MCP-4, MIP-Iα, MIP-1ß, RANTES, I309, eotaxin or lymphotactin. Moreover, a third ligand for CXCR3, I-TAC (Interferon-inducible T cell Alpha Chemoattractant), has also been found to bind to the receptor with high affinity and mediate functional responses (Cole, K. E. *et al., J. Exp. Med.,* 187: 2009-2021 (1998)).

The restricted expression of human CXCR3 in activated T lymphocytes and the ligand selectivity of CXCR3 are noteworthy. The human receptor is highly expressed in IL-2 activated T lymphocytes, but was not detected in resting T lymphocytes, monocytes or granulocytes (Qin, S. *et al., J. Clin. Invest.*, 101: 746-754 (1998)). Additional studies of receptor distribution indicate that it is mostly $CD3^+$ cells that express CXCR3, including cells which are $CD95^+$, $CD45RO^+$, and $CD45RA^{low}$, a phenotype consistent with previous activation, although a proportion of $CD20^+$ (B) cells and $CD56^+$ (NK) cells also express this receptor. The selective expression in activated T lymphocytes is of interest, because other receptors for chemokines which have been reported to attract lymphocytes (e. g., MCP-1, MCP-2, MCP-3, MIP-1α, MIP-1β, RANTES) are also expressed by granulocytes, such as neutrophils,

eosinophils, and basophils, as well as monocytes. These results suggest that the CXCR3 receptor is involved in the selective recruitment of effector T cells.

CXCR3 recognizes unusual CXC-chemokines, designated IP-10, Mig and I-TAC. Although these belong to the CXC-subfamily, in contrast to IL-8 and other CXC-chemokines which are potent chemoattractants for neutrophils, the primary targets of IP-10, Mig and I-TAC are lymphocytes, particularly effector cells such as activated or stimulated T lymphocytes and natural killer (NK) cells (Taub, D. D. *et al., J Exp. Med.*, 177: 18090-1814 (1993); Taub, D. D. *et al., J. Immunol.*, 155: 3877-3888 (1995); Cole, K. E. *et al., J. Exp. Med.*, 187: 2009-2021 (1998)). (NK cells are large granular lymphocytes, which lack a specific T cell receptor for antigen recognition, but possess cytolytic activity against cells such as tumor cells and virally infected cells.) Consistently, IP-10, Mig and I-TAC lack the ELR motif, an essential binding epitope in those CXC-chemokines that efficiently induce neutrophil chemotaxis (Clark-Lewis, I. *et al., J. Biol. Chem.* 266: 23128-23134 (1991); Hebert, C. A. *et al., J. Biol. Chem.*, 266 : 18989-18994 (1991); and Clark-Lewis, 1. *et al., Proc. Natl. Acad. Sci. USA*, 90 : 3574-3577 (1993)). In addition, both recombinant human Mig and recombinant human IP-10 have been reported to induce calcium flux in tumor infiltrating lymphocytes (TIL) (Liao, F. *et al., J Exp. Med*, 182: 1301-1314 (1995)). While IP-10 has been reported to induce chemotaxis of monocytes *in vitro* (Taub, D. D. *et al., J. Exp. Med.*, 177: 1809-1814 (1993), the receptor responsible has not been identified), human Mig and I-TAC appear highly selective, and do not show such an effect (Liao, F. *et al., J. Exp. Med.*, 182: 1301-1314 (1995); Cole, K. E. *et al., J. Exp. Med.*, 187: 2009-2021 (1998)). IP-10 expression is induced in a variety of tissues in inflammatory conditions such as psoriasis, fixed drug eruptions, cutaneous delayed-type hypersensitivity responses and tuberculoid leprosy as well as tumors and in animal model studies, for example, experimental glomerulonephritis, and experimental allergic encephalomyelitis. IP-10 has a potent *in vivo* antitumor effect that is T cell dependent, is reported to be an inhibitor of angiogenesis *in vivo* and can induce chemotaxis and degranulation of NK cells *in vitro*, suggesting a role as a mediator of NK cell recruitment and degranulation (in

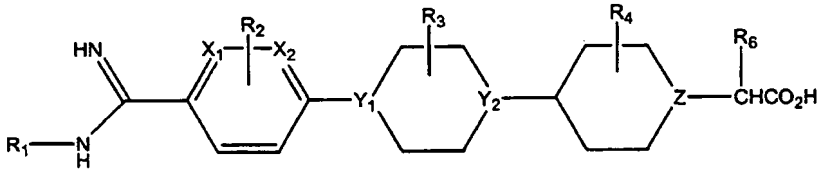
tumor cell destruction, for example) (Luster, A. D. and P. Leder, *J. Exp. Med.*, 178: 1057-1065 (1993); Luster, A. D. *et al., J Exp. Med.* 182: 219-231 (1995); Angiolillo, A. L. *et al., J. Exp. Med.*, 182: 155-162 (1995); Taub, D. D. *et al., J. Immunol.,* 155: 3877-3888 (1995)). The expression patterns of IP-10, Mig and I-TAC are also distinct from that of other CXC chemokines in that expression of each is induced by interferon-gamma (IFNδ), while the expression of IL-8 is down-regulated by IFNδ (Luster, A. D. *et al., Nature*, 315 : 672-676 (1985); Farber, J. M., *Proc. Natl. Acad. Sci. USA*, 87 : 5238-5242 (1990); Farber, J. M., *Biochem. Biophys. Res. Commun.*, 192 (1): 223-230 (1993), Liao, F. *et al., J. Exp. Med.,* 182: 1301-1314 (1995); Seitz, M. *et al., J. Clin. Invest.*, 87 : 463-469 (1991); Galy, A. H. M. and H. Spits, *J. Immunol.*, 147: 3823-3830 (1991); Cole, K. E. *et al., J. Exp. Med.*, 187 : 2009-2021 (1998)).

Chemokines are recognized as the long-sought mediators for the recruitment of lymphocytes. Several CC-chemokines were found to elicit lymphocyte chemotaxis (Loetscher, P. *et al., FASEB J.*, 8: 1055-1060 (1994)), however, they are also active on granulocytes and monocytes (Uguccioni, M. *et al., Eur. J. Immunol.*, 25 : 64-68 (1995); Baggiolini, M. and C. A. Dahinden, *Immunol. Today*, 15 : 127-133 (1994)). The situation is different for IP-10, Mig and I-TAC, which are selective in their action on lymphocytes, including activated T lymphocytes and NK cells, and which bind CXCR3, a receptor which does not recognize numerous other chemokines and which displays a selective pattern of expression.

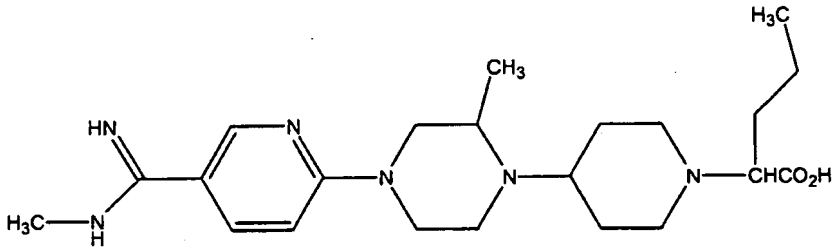
In view of these observations, it is reasonable to conclude that the formation of the characteristic infiltrates in inflammatory lesions, such as, for example, delayed-type hypersensitivity lesions, sites of viral infection and certain tumors is a process mediated via CXCR3 and regulated by CXCR3 expression. Lymphocytes, particularly T lymphocytes, bearing a CXCR3 receptor as a result of activation can be recruited into inflammatory lesions, sites of infection and/or tumors by IP-10, Mig and/or I-TAC, which can be induced locally by interferon-gamma. Thus, CXCR3 plays a role in the selective recruitment of lymphocytes, particularly effector cells such as activated or stimulated T lymphocytes. Accordingly, activated and effector T

cells have been implicated in a number of disease states such as graft-rejection, inflammation, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease and psoriasis. Thus, CXCR3 represents a promising target for the development of novel therapeutics.

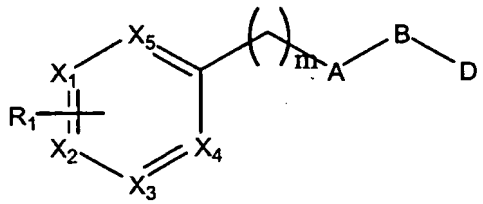
Reference is made to PCT Publication No. WO 93/10091 (Applicant: Glaxo Group Limited, Published May 27, 1993) which discloses piperidine acetic acid derivatives as inhibitors of fibrinogen-dependent blood platelet aggregation having the formula:



An illustrative compound of that series is:



Reference is also made to PCT Publication No. WO 99/20606 (Applicant: J. Uriach & CIA. S.A., Published April 29, 1999) which discloses piperazines as platelet aggregation inhibitors having the formula:

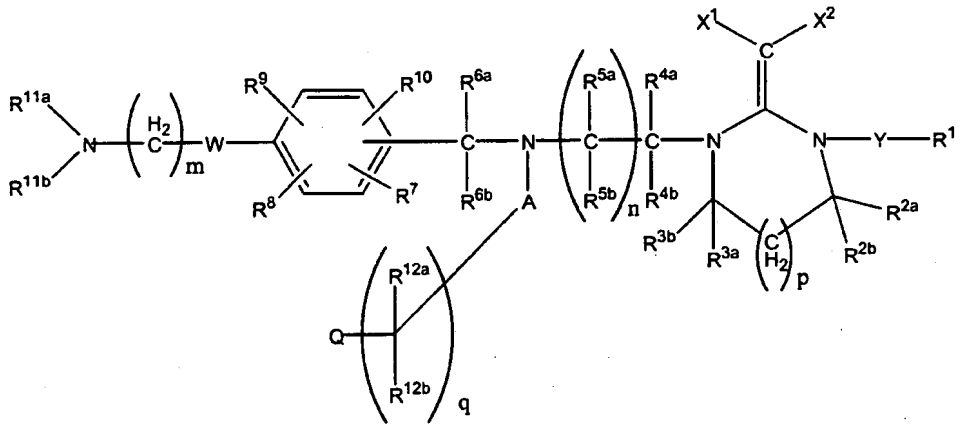


Reference is also made to US Patent Application No. US 2002/0018776 A1 (Applicant: Hancock, et al. Published February 14, 2002) which discloses methods of treating graft rejection.

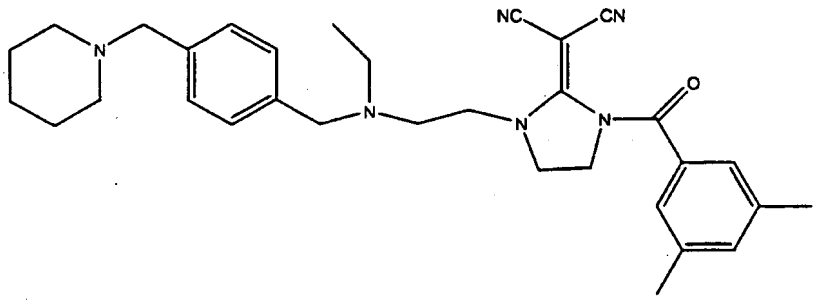
Reference is also made to PCT Publication No. WO 03/098185 A2 (Applicant: Renovar, Inc., Published November 27, 2003) which discloses methods of diagnosing and predicting organ transplant rejection by detection of chemokines, for example, CXCR3 and CCL chemokines in urine.

Reference is also made to PCT Publication No. WO 03/082335 A1 (Applicant: Sumitomo Pharmaceuticals Co. Ltd., Published October 9, 2003) which discloses methods of screening a CXCR3 ligand and methods of diagnosing type 2 diabetes by detecting the expression dose of a CXCR3 ligand in a biological sample.

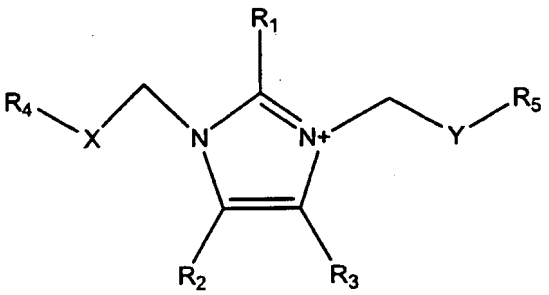
Reference is also made to PCT Publication No. WO 02/085861 (Applicant: Millennium Pharmaceuticals, Inc. Published October 31, 2002) which discloses imidazolidine compounds and their use as CXCR3 antagonists having the formula:



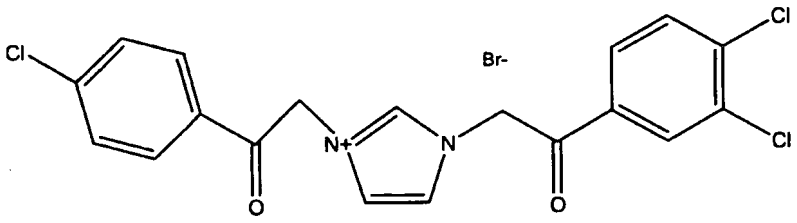
An illustrative compound of that series is:



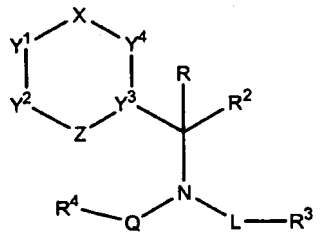
Reference is also made to PCT Publication No. WO 03/101970 (Applicant: Smithkline Beecham Corporation, Published December 11, 2003) which discloses imidazolium compounds and their use as CXCR3 antagonists having the formula:



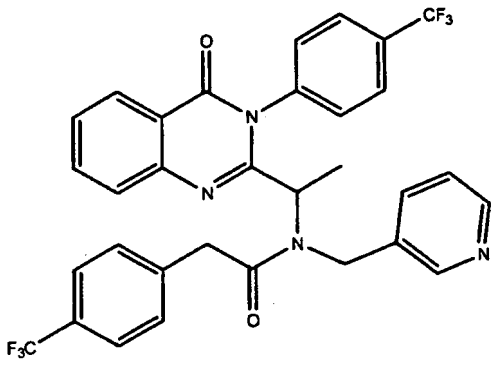
An illustrative example of that series is:



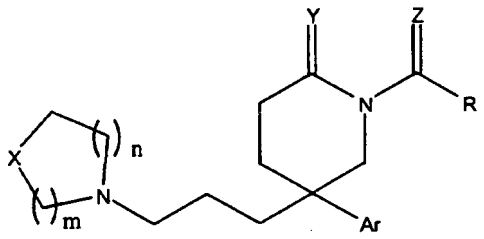
Reference is also made to US Patent Application No. US 2003/0055054 A1 (Applicant: Medina et al, Published March 20, 2003) and related patent US 6 794 379 B2 ((Applicant: Medina et al, Published September 21, 2004) which discloses compounds with CXCR3 activity having the formula:



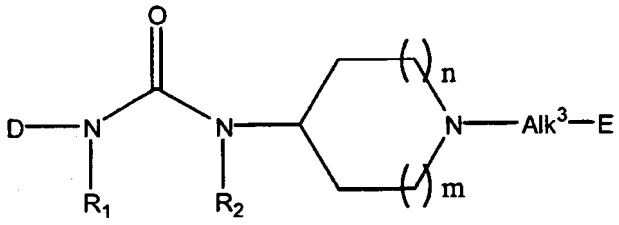
An illustrative compound of that series is:



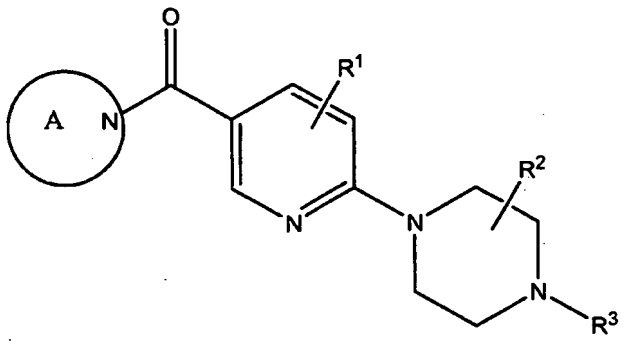
Reference is also made to US Patent No. 6,124,319 (Applicant: MacCoss *et al.*, issued September 6, 2000) which discloses compounds useful as chemokine receptor modulators having the formula:



Reference is also made to PCT Publication WO 03/070242 A1 (Applicant: CELLTECH R& D limited, Published August28, 2003) which discloses compounds useful as "chemokine receptor inhibitors for the treatment of inflammatory diseases" having the formula:

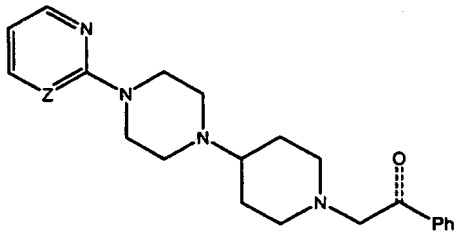


Reference is also made to PCT Publication WO 04/074287 A1, WO 04/074273 A1, WO 04/ 74278 (Applicant: AstraZeneca R & D Published February 19th 2004) which discloses pyridine derivatives, processes for their preparation and use in the modulation of autoimmune disease, having the formula:



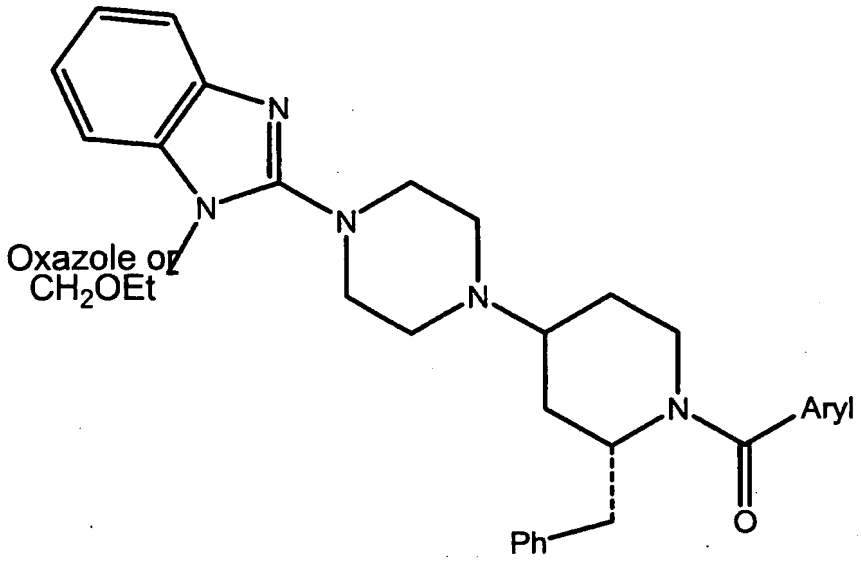
where R3 is phenyl, or a 5- or 6- membered aromatic ring with 1 or more nitrogen atoms.

Reference is also made to Yoo, K. H et al in *Archiv der Pharmazie* **2003**, *336*, 208-215 wherein unsubstituted pyridine (Z=CH) and pyrazine (Z=N) derivatives of formula:



have been reported as possessing 5-HT1A receptor affinity.

Reference is also made to PCT application WO 2004110451 (Janssen Pharmaceutica N.V., Belgium) wherein derivatives of formula:



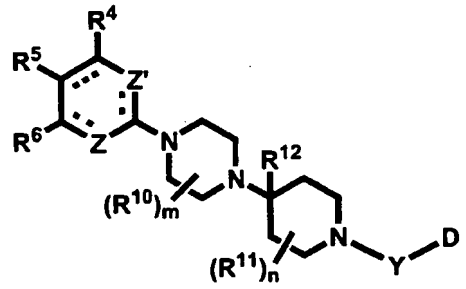
have been reported as being useful in combination with opioid analgesics.

There is a need for compounds that are capable of modulating CXCR3 activity. For example, there is a need for new treatments and therapies for diseases and conditions associated with CXCR3 such as inflammatory conditions (psoriasis and inflammatory bowel disease), autoimmune disease (multiple sclerosis, rheumatoid arthritis) and graft rejection (allograft and zenograft rejections for example) as well as infectious diseases, cancers and tumors, fixed drug eruptions, cutaneous delayed-type hypersensitivity responses, type I diabetes, viral meningitis and tuberculoid leprosy.

There is a need for methods of treatment or prevention or amelioration of one or more symptoms of diseases and conditions associated with CXCR3. There is a need for methods for modulating CXCR3 activity using the compounds provided herein.

SUMMARY OF THE INVENTION

In its many embodiments, the invention provides novel compounds of the Formula 1:



Formula 1

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

---- represents a single or double bond, with the proviso that the ring comprising Z and Z' contains at least one double bond;

Z, and Z' are independently N, N(→O), NOH, or NR^3 ;

Each of R^4, R^5, and R^6 is independently selected from the group consisting of H, alkyl, alkylaryl, aralkyl, -CN, $-CF_3$, haloalkyl, cycloalkyl, halo, hydroxyalkyl, $-C(=O)N(R^{30})_2$, -C(=O)alkyl, $-OR^{30}$, $-NR^{30}S(=O)_2R^{31}$, $-N(R^{30})_2$, $-C(R^{14})(R^{15})XR^1R^2$, and G, with the proviso that R^4, R^5, and R^6 are not all simultaneously H;

or each of R^4, R^5, and R^6 taken together with the carbon atom to which they are shown attached, is independently is -(C=O);

or R^5 and R^6 together with the carbon atoms to which they are shown attached form an aryl or heteroaryl ring;

X is selected from the group consisting of N, O, alkyl, cycloalkyl, heteroaryl, heterocyclyl, and heterocyclenyl;

G is a 5-membered heteroaryl or heterocyclenyl containing at least one -C=N- moiety as part of said heteroaryl or heterocyclenyl, wherein said heteroaryl or heterocyclenyl optionally additionally contains in the ring (i.e., as ring moieties) one or more moieties which can be the same or different, each being independently selected from the group consisting of N, N(→O), O, S, S(=O) and $S(=O)_2$, further wherein each of said heteroaryl or heterocyclenyl ring is optionally independently substituted on one or more ring carbon atoms with one or more R^9 substituents, or on one or more ring nitrogen atoms with one or more R^8 substituents, wherein said R^8 and R^9 substituents can be the same or different;

R^1 and R^2 are independently absent or present, and if present each is independently selected from the group consisting of H, alkyl, alkenyl, carbonyl, cycloalkyl, cycloalkenyl, alkylaryl, arylalkyl, aryl, amino, alkylamino, amidinyl, carboxamido, cyano, urea, -CN, -N≡CH, =NCN, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qN(R^{31})_2$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNHSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, -C(=S)N(H)alkyl, -N(H)-S(O)$_2$-alkyl, -N(H)C(=O)N(H)-alkyl, -S(O)$_2$alkyl, -S(O)$_2$N(H)alkyl, -S(O)$_2$N(alkyl)$_2$, -S(O)$_2$aryl, -C(=S)N(H)cycloalkyl, $-C(=O)N(H)NH_2$, -C(=O)alkyl, -heteroaryl, heterocyclyl, and heterocyclenyl; or alternatively when X is N, the N taken together with the R^1 and R^2 forms a heterocycyl, heteroaryl or $-N=C(NH_2)_2$;

R^3 is selected from the group consisting of H, alkyl, alkylaryl, aralkyl, $-CF_3$, haloalkyl, cycloalkyl, halo, hydroxy, hydroxyalkyl, $-C(=O)N(R^{30})_2$, and $-SO_2(R^{31})$;

the R^8 moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, arylalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qC(=O)OR^{31}$, and $-(CH_2)_qSO_2NHR^{31}$;

the R^9 moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, arylalkyl, amidinyl, aryl, cycloalkyl, cyano, heteroaryl, heterocyclyl, $-C(=O)N(R^{30})_2$, $-C(=S)N(R^{30})_2$, -C(=O)alkyl, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, $-N(R^{30})_2$, $-N(R^{30})S(O_2)R^{31}$, $-N(R^{30})C(=O)N(R^{30})_2$, -OH, $-OR^{30}$, $-SO_2(R^{31})$, $-SO_2N(R^{30})_2$, =O and =S;

the R^{10} moieties can be the same or different, each being independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, heterocyclenyl, heterocyclyl, alkylaryl, arylalkyl, $-CO_2H$, $-C(=O)N(R^{30})_2$, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, -OH, $-OR^{30}$, halogen, =O, and $-C(=O)R^{31}$;

the R^{11} moieties can be the same or different, each being independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl,

heterocyclyl, heterocyclenyl, alkylaryl, arylalkyl, carboxamide, CO_2H, -$(CH_2)_qOH$, -$(CH_2)_qOR^{31}$, -OH, -OR^{30}, halogen, =O, and -$C(=O)R^{31}$;

R^{12} is selected from the group consisting of H, alkyl, -CN, -$C(=O)N(R^{30})_2$, -$(CH_2)_qOH$, -$(CH_2)_qOR^{31}$ and -$S(=O)_2R^{31}$;

ring D is a five to nine membered cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl ring having 0-4 heteroatoms independently selected from O, S or N, wherein ring D is optionally substituted with 1-5 independently selected R^{20} moieties;

R^{14} and R^{15} are the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, heteroaryl, -CN, -OH, -OR^{30}, alkylamino, -N(H)$S(=O)_2$alkyl and –N(H)C(=O)N(H)alkyl; or alternatively R^{14} and R^{15} taken together is =O, =S, =NH, =N(alkyl), =N(Oalkyl), =N(OH) or cycloalkyl;

the R^{20} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, alkynyl, alkoxy, alkylamino, alkylthiocarboxy, alkylheteroaryl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, aminoalkyl, amidinyl, aralkyl, aralkenyl, aralkoxy, aralkoxycarbonyl, aralkylthio, aryl, aroyl, aryloxy, cyano, cycloalkyl, cycloalkenyl, formyl, guanidinyl, halo, hydroxyl, haloalkoxy, haloalkyl, heteroalkyl, heteroaryl, heterocyclyl, heterocyclenyl, hydroxyalkyl, hydroxamate, nitro, -$(CH_2)_qOH$, -$(CH_2)_qOR^{31}$, -$(CH_2)_qNH_2$, -$(CH_2)_qNHR^{31}$, -$(CH_2)_qC(=O)NHR^{31}$, -$(CH_2)_qSO_2R^{31}$, -$(CH_2)_qNSO_2R^{31}$, -$(CH_2)_qSO_2NHR^{31}$, -alkynyl$C(R^{31})_2OR^{31}$, -$C(=O)R^{30}$, -$C(=O)N(R^{30})_2$, -$C(=NR^{30})NHR^{30}$, -$C(=NOH)N(R^{30})_2$, -$C(=NOR^{31})N(R^{30})_2$, -$C(=O)OR^{30}$, -$N(R^{30})_2$, -$N(R^{30})C(=O)R^{31}$, -$NHC(=O)N(R^{30})_2$, -$N(R^{30})C(=O)OR^{31}$, -$N(R^{30})C(=NCN)N(R^{30})_2$, -$N(R^{30})C(=O)N(R^{30})SO_2(R^{31})$, -$N(R^{30})C(=O)N(R^{30})_2$, -$NR^{30}S(=O)_2R^{31}$, -$N(R^{30})S(O)_2N(R^{30})_2$, -$OR^{30}$, -$OC(=O)N(R^{30})_2$, -$SR^{30}$, -$SO_2N(R^{30})_2$, -$SO_2(R^{31})$, -$OSO_2(R^{31})$, and -$OSi(R^{30})_3$; or alternatively two R^{20} moieties are linked together to form a five or six membered aryl, cycloalkyl, heterocyclyl, heterocyclenyl, or heteroaryl ring wherein said five or six membered aryl, cycloalkyl, heterocyclyl, heterocyclenyl, or heteroaryl ring is fused to ring D and the fused ring is optionally substituted with 0-4 R^{21} moieties;

the R^{21} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, alkynyl, alkoxy, alkylamino, alkylthiocarboxy, alkylheteroaryl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, aminoalkyl, amidinyl, aralkyl, aralkenyl, aralkoxy, aralkoxycarbonyl, aralkylthio, aryl, aroyl, aryloxy, carboxamido, cyano, cycloalkyl, cycloalkenyl, formyl, guanidinyl, halogen, haloalkyl, haloalkoxy, heteroalkyl, heteroaryl, heterocyclyl, heterocyclenyl, hydroxyalkyl, hydroxamate, nitro, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, -alkynyl$C(R^{31})_2OR^{31}$, $-C(=O)R^{30}$, $-C(=O)N(R^{30})_2$, $-C(=NR^{30})NHR^{30}$, $-C(=NOH)N(R^{30})_2$, $-C(=NOR^{31})N(R^{30})_2$, $-C(=O)OR^{30}$, $-N(R^{30})_2$, $-N(R^{30})C(=O)R^{31}$, $-NHC(=O)N(R^{30})_2$, $-N(R^{30})C(=O)OR^{31}$, $-N(R^{30})C(=NCN)N(R^{30})_2$, $-N(R^{30})C(=O)N(R^{30})SO_2(R^{31})$, $-N(R^{30})C(=O)N(R^{30})_2$, $-N(R^{30})SO_2(R^{31})$, $-N(R^{30})S(O)_2N(R^{30})_2$, $-OR^{30}$, $-OC(=O)N(R^{30})_2$, $-SR^{30}$, $-SO_2N(R^{30})_2$, $-SO_2(R^{31})$, $-OSO_2(R^{31})$, and $-OSi(R^{30})_3$;

Y is selected from the group consisting of a covalent bond, $-(CR^{13}R^{13})_r-$, $-CHR^{13}C(=O)-$, $-(CHR^{13})_rO-$, $-(CHR^{13})_rN(R^{30})-$, $-C(=O)-$, $-C(=NR^{30})-$, $-C(=N-OR^{30})-$, $-CH(C(=O)NHR^{30})-$, CH-heteroaryl-, $-C(R^{13}R^{13})_rC(R^{13})=C(R^{13})-$, $-(CHR^{13})_rC(=O)-$ and $-(CHR^{13})_rN(H)C(=O)-$; or alternatively Y is cycloalkyl, heterocyclenyl, or heterocyclyl wherein the cycloalkyl, heterocyclenyl, or heterocyclyl is fused with ring D;

the R^{13} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, cycloalkyl, alkoxy, aryl, heteroaryl, heterocyclenyl, heterocyclyl, spiroalkyl, -CN, $-CO_2H$, $-C(=O)R^{30}$, $-C(=O)N(R^{30})_2$, $-(CHR^{30})_qOH$, $-(CHR^{30})_qOR^{31}$, $-(CHR^{30})_qNH_2$, $-(CH\ R^{30})_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, $-NH_2$, $-N(R^{30})_2$, $-N(R^{30})C(=O)N(R^{30})_2$, $-N(R^{30})SO_2(R^{31})$, -OH, OR^{30}, $-SO_2N(R^{30})_2$, and $-SO_2(R^{31})$;

the R^{30} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, aryl, aralkyl, cycloalkyl, CN, $-(CH_2)_qOH$, $-(CH_2)_qOalkyl$, $-(CH_2)_qOalkylaryl$, $-(CH_2)_qOaryl$, $-(CH_2)_qOaralkyl$, $-(CH_2)_qOcycloalkyl$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHalkyl$, -

$(CH_2)_qN(alkyl)_2$, $-(CH_2)_qNHalkylaryl$, $-(CH_2)_qNHaryl$, $-(CH_2)_qNHaralkyl$, $-(CH_2)_qNHcycloalkyl$, $-(CH_2)_qC(=O)NHalkyl$, $-(CH_2)_qC(=O)N(alkyl)_2$, $-(CH_2)_qC(=O)NHalkylaryl$, $-(CH_2)_qC(=O)NHaryl$, $-(CH_2)_qC(=O)NHaralkyl$, $-(CH_2)_qC(=O)NHcycloalkyl$, $-(CH_2)_qSO_2alkyl$, $-(CH_2)_qSO_2alkylaryl$, $-(CH_2)_qSO_2aryl$, $-(CH_2)_qSO_2aralkyl$, $-(CH_2)_qSO_2cycloalkyl$, $-(CH_2)_qNSO_2alkyl$, $-(CH_2)_qNSO_2alkylaryl$, $-(CH_2)_qNSO_2aryl$, $-(CH_2)_qNSO_2aralkyl$, $-(CH_2)_qNSO_2cycloalkyl$, $-(CH_2)_qSO_2NHalkyl$, $-(CH_2)_qSO_2NHalkylaryl$, $-(CH_2)_qSO_2NHaryl$, $-(CH_2)_qSO_2NHaralkyl$, $-(CH_2)_qSO_2NHcycloalkyl$, heterocyclenyl, heterocyclyl, and heteroaryl;

the R^{31} moieties can be the same or different, each being independently selected from the group consisting of alkyl, alkylaryl, aryl, aralkyl, cycloalkyl, $-(CH_2)_qOH$, $-(CH_2)_qOalkyl$, $-(CH_2)_qOalkylaryl$, $-(CH_2)_qOaryl$, $-(CH_2)_qOaralkyl$, $-(CH_2)_qOcycloalkyl$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHalkyl$, $-(CH_2)_qN(alkyl)_2$, $-(CH_2)_qNHalkylaryl$, $-(CH_2)_qNHaryl$, $-(CH_2)_qNHaralkyl$, $-(CH_2)_qNHcycloalkyl$, $-(CH_2)_qC(=O)NHalkyl$, $-(CH_2)_qC(=O)N(alkyl)_2$, $-(CH_2)_qC(=O)NHalkylaryl$, $-(CH_2)_qC(=O)NHaryl$, $-(CH_2)_qC(=O)NHaralkyl$, $-(CH_2)_qC(=O)NHcycloalkyl$, $-(CH_2)_qSO_2alkyl$, $-(CH_2)_qSO_2alkylaryl$, $-(CH_2)_qSO_2aryl$, $-(CH_2)_qSO_2aralkyl$, $-(CH_2)_qSO_2cycloalkyl$, $-(CH_2)_qNSO_2alkyl$, $-(CH_2)_qNSO_2alkylaryl$, $-(CH_2)_qNSO_2aryl$, $-(CH_2)_qNSO_2aralkyl$, $-(CH_2)_qNSO_2cycloalkyl$, $-(CH_2)_qSO_2NHalkyl$, $-(CH_2)_qSO_2NHalkylaryl$, $-(CH_2)_qSO_2NHaryl$, $-(CH_2)_qSO_2NHaralkyl$, $-(CH_2)_qSO_2NHcycloalkyl$, heterocyclenyl, heterocyclyl, and heteroaryl;

m is 0 to 4;

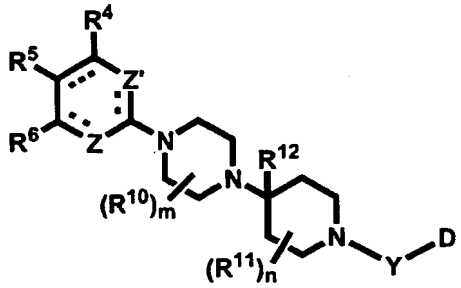
n is 0 to 4;

each q can be the same or different, each being independently selected from 1 to 5; and

r is 1 to 4;

with the proviso that there are no two adjacent double bonds in any ring, and that when a nitrogen is substituted by two alkyl groups, said two alkyl groups may be optionally joined to each other to form a ring.

The invention provides also novel compounds of the Formula 1:



Formula 1

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

---- represents a single or double bond, with the proviso that the ring comprising Z and Z' contains at least one double bond;

Z, and Z' are independently N, N(→O), NOH, or NR^3

each of R^4, R^5, and R^6 is independently selected from the group consisting of H, alkyl, alkylaryl, aralkyl, -CN, $-CF_3$, haloalkyl, cycloalkyl, halo, hydroxyalkyl, $-C(=O)N(R^{30})_2$, -C(=O)alkyl, $-OR^{30}$, $-NR^{30}S(=O)_2R^{31}$, $-N(R^{30})_2$, $-C(R^{14})(R^{15})XR^1R^2$, and G, with the proviso that R^4, R^5, and R^6 are not all simultaneously H;

or each of R^4, R^5, and R^6 taken together with the carbon atom to which they are shown attached, is independently is -(C=O);

or R^5 and R^6 together with the carbon atoms to which they are shown attached form an aryl or heteroaryl ring;

X is selected from the group consisting of N, O, alkyl, cycloalkyl, heteroaryl, heterocyclyl, and heterocyclenyl;

G is a 5-membered heteroaryl or heterocyclenyl containing at least one -C=N- moiety as part of said heteroaryl or heterocyclenyl, wherein said heteroaryl or heterocyclenyl optionally additionally contains in the ring (i.e., as ring moieties) one or more moieties which can be the same or different, each being independently selected from the group consisting of N, N(→O), O, S, S(=O) and $S(=O)_2$, further wherein each of said heteroaryl or heterocyclenyl ring is optionally independently substituted on one or more ring carbon atoms with one or more R^9 substituents, or on one or more ring nitrogen atoms with one or more R^8 substituents, wherein said R^8 and R^9 substituents can be the same or different;

R^1 and R^2 are independently absent or present, and if present each is independently selected from the group consisting of H, alkyl, alkenyl, carbonyl, cycloalkyl, cycloalkenyl, alkylaryl, arylalkyl, aryl, amino, alkylamino, amidinyl, carboxamido, cyano, urea, -CN, -N≡CH, =NCN, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qN(R^{31})_2$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNHSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, -C(=S)N(H)alkyl, -N(H)-S(O)$_2$-alkyl, -N(H)C(=O)N(H)-alkyl, -S(O)$_2$alkyl, -S(O)$_2$N(H)alkyl, -S(O)$_2$N(alkyl)$_2$, -S(O)$_2$aryl, -C(=S)N(H)cycloalkyl, $-C(=O)N(H)NH_2$, -C(=O)alkyl, -heteroaryl, heterocyclyl, and heterocyclenyl; or alternatively when X is N, the N taken together with the R^1 and R^2 forms a heterocycyl, heteroaryl or $-N=C(NH_2)_2$;

R^3 is selected from the group consisting of H, alkyl, alkylaryl, aralkyl, $-CF_3$, haloalkyl, cycloalkyl, halo, hydroxy, hydroxyalkyl, $-C(=O)N(R^{30})_2$, and $-SO_2(R^{31})$;

the R^8 moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, arylalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qC(=O)OR^{31}$, and $-(CH_2)_qSO_2NHR^{31}$;

the R^9 moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, arylalkyl, amidinyl, aryl, cycloalkyl, cyano, heteroaryl, heterocyclyl, $-C(=O)N(R^{30})_2$, $-C(=S)N(R^{30})_2$, -C(=O)alkyl, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, $-N(R^{30})_2$, $-N(R^{30})S(O_2)R^{31}$, $-N(R^{30})C(=O)N(R^{30})_2$, -OH, $-OR^{30}$, $-SO_2(R^{31})$, $-SO_2N(R^{30})_2$, =O and =S;

the R^{10} moieties can be the same or different, each being independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, heterocyclenyl, heterocyclyl, alkylaryl, arylalkyl, $-CO_2H$, $-C(=O)N(R^{30})_2$, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, -OH, $-OR^{30}$, halogen, =O, and $-C(=O)R^{31}$;

the R^{11} moieties can be the same or different, each being independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl,

heterocyclyl, heterocyclenyl, alkylaryl, arylalkyl, carboxamide, CO_2H, -$(CH_2)_qOH$, -$(CH_2)_qOR^{31}$, -OH, -OR^{30}, halogen, =O, and -$C(=O)R^{31}$;

R^{12} is selected from the group consisting of H, alkyl, -CN, -$C(=O)N(R^{30})_2$, -$(CH_2)_qOH$, -$(CH_2)_qOR^{31}$ and -$S(=O)_2R^{31}$;

ring D is a five to nine membered cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl ring having 0-4 heteroatoms independently selected from O, S or N, wherein ring D is optionally substituted with 1-5 independently selected R^{20} moieties;

R^{14} and R^{15} are the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, heteroaryl, -CN, -OH, -OR^{30}, alkylamino, -$N(H)S(=O)_2$alkyl and –N(H)C(=O)N(H)alkyl; or alternatively R^{14} and R^{15} taken together is =O, =S, =NH, =N(alkyl), =N(Oalkyl), =N(OH) or cycloalkyl;

the R^{20} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, alkynyl, alkoxy, alkylamino, alkylthiocarboxy, alkylheteroaryl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, aminoalkyl, amidinyl, aralkyl, aralkenyl, aralkoxy, aralkoxycarbonyl, aralkylthio, aryl, aroyl, aryloxy, cyano, cycloalkyl, cycloalkenyl, formyl, guanidinyl, halo, hydroxyl, haloalkoxy, haloalkyl, heteroalkyl, heteroaryl, heterocyclyl, heterocyclenyl, hydroxyalkyl, hydroxamate, nitro, -$(CH_2)_qOH$, -$(CH_2)_qOR^{31}$, -$(CH_2)_qNH_2$, -$(CH_2)_qNHR^{31}$, -$(CH_2)_qC(=O)NHR^{31}$, -$(CH_2)_qSO_2R^{31}$, -$(CH_2)_qNSO_2R^{31}$, -$(CH_2)_qSO_2NHR^{31}$, -alkynyl$C(R^{31})_2OR^{31}$, -$C(=O)R^{30}$, -$C(=O)N(R^{30})_2$, -$C(=NR^{30})NHR^{30}$, -$C(=NOH)N(R^{30})_2$, -$C(=NOR^{31})N(R^{30})_2$, -$C(=O)OR^{30}$, -$N(R^{30})_2$, -$N(R^{30})C(=O)R^{31}$, -$NHC(=O)N(R^{30})_2$, -$N(R^{30})C(=O)OR^{31}$, -$N(R^{30})C(=NCN)N(R^{30})_2$, -$N(R^{30})C(=O)N(R^{30})SO_2(R^{31})$, -$N(R^{30})C(=O)N(R^{30})_2$, -$NR^{30}S(=O)_2R^{31}$, -$N(R^{30})S(O)_2N(R^{30})_2$, -$OR^{30}$, -$OC(=O)N(R^{30})_2$, -$SR^{30}$, -$SO_2N(R^{30})_2$, -$SO_2(R^{31})$, -$OSO_2(R^{31})$, and -$OSi(R^{30})_3$; or alternatively two R^{20} moieties are linked together to form a five or six membered aryl, cycloalkyl, heterocyclyl, heterocyclenyl, or heteroaryl ring wherein said five or six membered aryl, cycloalkyl, heterocyclyl, heterocyclenyl, or heteroaryl ring is fused to ring D and the fused ring is optionally substituted with 0-4 R^{21} moieties;

the R^{21} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, alkynyl, alkoxy, alkylamino, alkylthiocarboxy, alkylheteroaryl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, aminoalkyl, amidinyl, aralkyl, aralkenyl, aralkoxy, aralkoxycarbonyl, aralkylthio, aryl, aroyl, aryloxy, carboxamido, cyano, cycloalkyl, cycloalkenyl, formyl, guanidinyl, halogen, haloalkyl, haloalkoxy, heteroalkyl, heteroaryl, heterocyclyl, heterocyclenyl, hydroxyalkyl, hydroxamate, nitro, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, -alkynyl$C(R^{31})_2OR^{31}$, $-C(=O)R^{30}$, $-C(=O)N(R^{30})_2$, $-C(=NR^{30})NHR^{30}$, $-C(=NOH)N(R^{30})_2$, $-C(=NOR^{31})N(R^{30})_2$, $-C(=O)OR^{30}$, $-N(R^{30})_2$, $-N(R^{30})C(=O)R^{31}$, $-NHC(=O)N(R^{30})_2$, $-N(R^{30})C(=O)OR^{31}$, $-N(R^{30})C(=NCN)N(R^{30})_2$, $-N(R^{30})C(=O)N(R^{30})SO_2(R^{31})$, $-N(R^{30})C(=O)N(R^{30})_2$, $-N(R^{30})SO_2(R^{31})$, $-N(R^{30})S(O)_2N(R^{30})_2$, $-OR^{30}$, $-OC(=O)N(R^{30})_2$, $-SR^{30}$, $-SO_2N(R^{30})_2$, $-SO_2(R^{31})$, $-OSO_2(R^{31})$, and $-OSi(R^{30})_3$;

Y is selected from the group consisting of $-(CR^{13}R^{13})_r-$, $-CHR^{13}C(=O)-$, $-(CHR^{13})_rO-$, $-(CHR^{13})_rN(R^{30})-$, $-C(=O)-$, $-C(=NR^{30})-$, $-C(=N-OR^{30})-$, $-CH(C(=O)NHR^{30})-$, CH-heteroaryl-, $-C(R^{13}R^{13})_rC(R^{13})=C(R^{13})-$, $-(CHR^{13})_rC(=O)-$ and $-(CHR^{13})_rN(H)C(=O)-$; or alternatively Y is cycloalkyl, heterocyclenyl, or heterocyclyl wherein the cycloalkyl, heterocyclenyl, or heterocyclyl is fused with ring D;

the R^{13} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, cycloalkyl, alkoxy, aryl, heteroaryl, heterocyclenyl, heterocyclyl, spiroalkyl, -CN, $-CO_2H$, $-C(=O)R^{30}$, $-C(=O)N(R^{30})_2$, $-(CHR^{30})_qOH$, $-(CHR^{30})_qOR^{31}$, $-(CHR^{30})_qNH_2$, $-(CH\ R^{30})_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, $-NH_2$, $-N(R^{30})_2$, $-N(R^{30})C(=O)N(R^{30})_2$, $-N(R^{30})SO_2(R^{31})$, -OH, OR^{30}, $-SO_2N(R^{30})_2$, and $-SO_2(R^{31})$;

the R^{30} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, aryl, aralkyl, cycloalkyl, CN, $-(CH_2)_qOH$, $-(CH_2)_qOalkyl$, $-(CH_2)_qOalkylaryl$, $-(CH_2)_qOaryl$, $-(CH_2)_qOaralkyl$, $-(CH_2)_qOcycloalkyl$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHalkyl$, -

$(CH_2)_qN(alkyl)_2$, $-(CH_2)_qNHalkylaryl$, $-(CH_2)_qNHaryl$, $-(CH_2)_qNHaralkyl$, $-(CH_2)_qNHcycloalkyl$, $-(CH_2)_qC(=O)NHalkyl$, $-(CH_2)_qC(=O)N(alkyl)_2$, $-(CH_2)_qC(=O)NHalkylaryl$, $-(CH_2)_qC(=O)NHaryl$, $-(CH_2)_qC(=O)NHaralkyl$, $-(CH_2)_qC(=O)NHcycloalkyl$, $-(CH_2)_qSO_2alkyl$, $-(CH_2)_qSO_2alkylaryl$, $-(CH_2)_qSO_2aryl$, $-(CH_2)_qSO_2aralkyl$, $-(CH_2)_qSO_2cycloalkyl$, $-(CH_2)_qNSO_2alkyl$, $-(CH_2)_qNSO_2alkylaryl$, $-(CH_2)_qNSO_2aryl$, $-(CH_2)_qNSO_2aralkyl$, $-(CH_2)_qNSO_2cycloalkyl$, $-(CH_2)_qSO_2NHalkyl$, $-(CH_2)_qSO_2NHalkylaryl$, $-(CH_2)_qSO_2NHaryl$, $-(CH_2)_qSO_2NHaralkyl$, $-(CH_2)_qSO_2NHcycloalkyl$, heterocyclenyl, heterocyclyl, and heteroaryl;

the R^{31} moieties can be the same or different, each being independently selected from the group consisting of alkyl, alkylaryl, aryl, aralkyl, cycloalkyl, $-(CH_2)_qOH$, $-(CH_2)_qOalkyl$, $-(CH_2)_qOalkylaryl$, $-(CH_2)_qOaryl$, $-(CH_2)_qOaralkyl$, $-(CH_2)_qOcycloalkyl$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHalkyl$, $-(CH_2)_qN(alkyl)_2$, $-(CH_2)_qNHalkylaryl$, $-(CH_2)_qNHaryl$, $-(CH_2)_qNHaralkyl$, $-(CH_2)_qNHcycloalkyl$, $-(CH_2)_qC(=O)NHalkyl$, $-(CH_2)_qC(=O)N(alkyl)_2$, $-(CH_2)_qC(=O)NHalkylaryl$, $-(CH_2)_qC(=O)NHaryl$, $-(CH_2)_qC(=O)NHaralkyl$, $-(CH_2)_qC(=O)NHcycloalkyl$, $-(CH_2)_qSO_2alkyl$, $-(CH_2)_qSO_2alkylaryl$, $-(CH_2)_qSO_2aryl$, $-(CH_2)_qSO_2aralkyl$, $-(CH_2)_qSO_2cycloalkyl$, $-(CH_2)_qNSO_2alkyl$, $-(CH_2)_qNSO_2alkylaryl$, $-(CH_2)_qNSO_2aryl$, $-(CH_2)_qNSO_2aralkyl$, $-(CH_2)_qNSO_2cycloalkyl$, $-(CH_2)_qSO_2NHalkyl$, $-(CH_2)_qSO_2NHalkylaryl$, $-(CH_2)_qSO_2NHaryl$, $-(CH_2)_qSO_2NHaralkyl$, $-(CH_2)_qSO_2NHcycloalkyl$, heterocyclenyl, heterocyclyl, and heteroaryl;

m is 0 to 4;

n is 0 to 4;

each q can be the same or different, each being independently selected from 1 to 5; and

r is 1 to 4;

with the proviso that there are no two adjacent double bonds in any ring, and that when a nitrogen is substituted by two alkyl groups, said two alkyl groups may be optionally joined to each other to form a ring.

The term "G represents a 5-membered heteroaryl or heterocyclenyl ring containing at least one -C=N- moiety" means that G represents, in a non-

limiting manner, moieties such as dihydroimidazole, imidazole, dihydrooxazole, oxazole, dihydrooxadiazole, oxadiazole, dihydrothiazole, thiazole, triazole, tetrazole and the like. These moieties may be optionally substituted on the ring carbon(s) with one or more R^9 groups as stated above, or on the ring nitrogen(s) with one or more R^8 groups as stated above.

The term "said heteroaryl or heterocyclenyl ring optionally additionally containing on the ring (i.e., as ring moieties) one or more moieties which can be the same or different, each being independently selected from the group consisting of N, N(→O), O, S, S(O) and $S(O_2)$" means that the N, N(→O), O, S, S(O) and $S(O_2)$ are present as ring 'atoms' and not as substituents.

A further feature of the invention is a pharmaceutical composition containing as active ingredient at least one compound of Formula 1 or 5 together with at least one pharmaceutically acceptable carrier or excipient.

The invention provides methods of preparing compounds of Formula 1 or 5, as well as methods for treating diseases, for example, treatment (e. g., palliative therapy, curative therapy, prophylactic therapy) of certain diseases and conditions e. g., inflammatory diseases (e. g., psoriasis, inflammatory bowel disease), autoimmune diseases (e. g., rheumatoid arthritis, multiple sclerosis), graft rejection (e. g., allograft rejection, xenograft rejection), ophthalmic inflammation or dry eye, infectious diseases and tumors. The invention provides a method of treating a CXCR3 chemokine mediated disease in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of at least one compound of Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof.

The invention provides methods of treating diseases, for example, treatment (e. g., palliative therapy, curative therapy, prophylactic therapy) of certain diseases and conditions such as inflammatory diseases (e. g., psoriasis, inflammatory bowel disease), autoimmune diseases (e. g., rheumatoid arthritis, multiple sclerosis), graft rejection (e. g., allograft rejection, xenograft rejection), infectious diseases as well as cancers and tumors, fixed drug eruptions, cutaneous delayed-type hypersensitivity responses, ophthalmic inflammation or dry eye, type I diabetes, viral meningitis

and tuberculoid leprosy comprising administering: (a) a therapeutically effective amount of at least one compound according to Formula 1 or 5, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one medicament selected from the group consisting of: disease modifying antirheumatic drugs; nonsteroidal anti-inflammatory drugs; COX-2 selective inhibitors; COX-1 inhibitors; immunosuppressives (such as cyclosporins and methotrexate); steroids (including corticosteroids such as glucorticoids); PDE IV inhibitors, anti-TNF-α compounds, TNF-α-convertase (TACE) inhibitors, MMP inhibitors, cytokine inhibitors, glucocorticoids, other chemokine inhibitors such as CCR2 and CCR5, CB2-selective inhibitors, p38 inhibitors, biological response modifiers; anti-inflammatory agents and therapeutics.

The invention also provides a method of modulating (inhibiting or promoting) an inflammatory response in an individual in need of such therapy. The method comprises administering a therapeutically effective amount of a compound (e. g., small organic molecule) which inhibits or promotes mammalian CXCR3 function in an individual in need thereof. Also disclosed is a method of inhibiting or blocking T-cell mediated chemotaxis in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of a compound of Formula 1, Formula 5 or a pharmaceutically acceptable salt, solvate or ester thereof.

Also disclosed is a method of treating inflammatory bowel disease (such Crohn's disease, ulcerative colitis) in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of at least one compound of Formula 1, Formula 5 or a pharmaceutically acceptable salt, solvate or ester thereof.

Also disclosed is a method of treating inflammatory bowel disease in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of: (a) at least one compound of Formula 1, Formula 5, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: sulfasalazine, 5-aminosalicylic acid, sulfapyridine, anti-

TNF compounds, anti-IL-12 compounds, corticosteroids, glucocorticoids, T-cell receptor directed therapies (such as anti-CD3 antibodies), immunosuppresives, methotrexate, azathioprine, and 6-mercaptopurines.

Also disclosed is a method of treating graft rejection in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of at least one compound of Formula 1, Formula 5, or a pharmaceutically acceptable salt, solvate or ester thereof.

Also disclosed is a method of treating graft rejection in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of: (a) at least one compound of Formula 1, Formula 5, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: cyclosporine A, FK-506, FTY720, beta-interferon, rapamycin, mycophenolate, prednisolone, azathioprine, cyclophosphamide and an antilymphocyte globulin.

Also disclosed is a method of treating multiple sclerosis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of: (a) a therapeutically effective amount of at least one compound of Formula 1, Formula 5, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: beta-interferon, glatiramer acetate, corticosteroids, glucocorticoids, methotrexate, azothioprine, mitoxantrone, VLA-4 inhibitors, FTY720, anti-IL-12 inhibitors, and CB2-selective inhibitors.

Also disclosed is a method of treating multiple sclerosis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of: (a) a therapeutically effective amount of at least one compound of Formula 1, Formula 5, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: methotrexate, cyclosporin, leflunomide, sulfasalazine, corticosteroids, β-methasone, β-interferon, glatiramer acetate, prednisone, etonercept, and infliximab.

Also disclosed is a method of treating rheumatoid arthritis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of: (a) at least one compound of Formula 1, Formula 5, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: non-steroidal anti-inflammatory agents, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, cyclosporine, methotrexate, steroids, PDE IV inhibitors, anti-TNF-α compounds, MMP inhibitors, corticosteroids, glucocorticoids, chemokine inhibitors, CB2-selective inhibitors, caspase (ICE) inhibitors and other classes of compounds indicated for the treatment of rheumatoid arthritis.

Also disclosed is a method of treating psoriasis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of: a) at least one compound of Formula 1, Formula 5, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: immunosuppressives, cyclosporins, methotrexate, steroids, corticosteroids, anti-TNF-α compounds, anti-IL compounds, anti-IL-23 compounds, vitamin A and D compounds and fumarates.

Also disclosed is a method of treating ophthalmic inflammation (including, for e.g., uveitis, posterior segment intraocular inflammation, Sjogren's syndrome) or dry eye in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of: a) at least one compound according to Formula 1, Formula 5, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: immunosuppressives, cyclosporins, methotrexate, FK506, steroids, corticosteroids, and anti-TNF-α compounds.

Also disclosed is a method of treating a disease selected from the group consisting of: inflammatory disease, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, graft rejection, psoriasis, fixed drug eruptions, cutaneous delayed-type hypersensitivity responses, ophthalmic inflammation

(including e.g., uveitis, posterior segment intraocular inflammation, and Sjogren's syndrome), tuberculoid leprosy and cancer in a patient in need of such treatment, such method comprising administering to the patient an effective amount of at least one compound according to Formula 1, Formula 5, or a pharmaceutically acceptable salt, solvate or ester thereof.

The invention also provides a method of treating a disease selected from the group consisting of: inflammatory disease, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, graft rejection, psoriasis, fixed drug eruptions, cutaneous delayed-type hypersensitivity responses and tuberculoid leprosy, ophthalmic inflammation, type I diabetes, viral meningitis and cancer in a patient in need of such treatment, such method comprising administering to the patient an effective amount of (a) at least one compound according to Formula 1, Formula 5, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one medicament selected from the group consisting of: disease modifying antirheumatic drugs; nonsteroidal antiinflammatory drugs; COX-2 selective inhibitors; COX-1 inhibitors; immunosuppressives; steroids; PDE IV inhibitors, anti-TNF-α compounds, MMP inhibitors, corticosteroids, glucocorticoids, chemokine inhibitors, CB2-selective inhibitors, biological response modifiers; anti-inflammatory agents and therapeutics.

DETAILED DESCRIPTION OF THE INVENTION

The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "hydroxyalkyl," "haloalkyl," "alkoxy," etc.

As used above, and throughout the specification, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Acyl" means an H-C(=O)-, alkyl-C(=O)-, alkenyl-C(=O)-, alkynyl-C(=O)-, cycloalkyl-C(=O)-, cycloalkenyl-C(=O)-, or cycloalkynyl-C(=O)- group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl carbon atom. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and cyclohexanoyl.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. The alkenyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxyl, aryl, aryloxy, cycloalkyl, cycloalkenyl, cyano, heteroaryl, heterocyclyl, amino, aminosulfonyl, halo, carboxyl, carboxyalkyl (non-limiting example(s) include ester), alkoxycarbonyl, hydroxyalkyl, carbonyl (non-limiting example(s) include ketone), -C(=O)heterocyclyl, formyl (non-limiting example(s) include aldehyde), carboxamido (i.e amido, $-C(=O)NH_2$), $-C(=O)N(alkyl)_2$, -C(=O)NH(alkyl), $-C(=O)N(cycloalkyl)_2$, -C(=O)NH(cycloalkyl), -NHC(=O)alkyl, urea (*e.g* $-NH(C=O)NH_2$, -NH(C=O)NH(alkyl), $-NH(C=O)NH(alkyl)_2$, -NH(C=O)NH(heteroaryl), -NH(C=O)NH(heterocyclyl)), guanidinyl, $-NHC(=NCN)NH_2$, $-NHC(=NCN)N(alkyl)_2$, carbamoyl (i.e $-CO_2NH_2$), NHC(=O)Oalkyl, $-CO_2N(alkyl)_2$, -NHC(=O))NH-$S(O)_2$alkyl, $-NHC(=O)N(alkyl)_2$-$S(O)_2$alkyl, -NH-$S(O)_2$alkyl, -NH-$S(O)_2$heteroaryl,

-N(alkyl)-S(O)$_2$alkyl, -NH-S(O)$_2$aryl, -N(alkyl)-S(O)$_2$aryl, -NH-S(O)$_2$NH$_2$, -NH-S(O)$_2$NHalkyl, -NH-S(O)$_2$N(alkyl)$_2$, alkylthiocarboxy, -S(O)$_2$alkyl , -S(O)$_2$aryl, -OS(O)$_2$alkyl, -OS(O)$_2$aryl, sulfonyl urea (non-limiting example(s) include NHC(=S)NHalkyl). Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched or a combination thereof, and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. The alkyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxyl, aryl, aryloxy, cycloalkyl, cycloalkenyl, cyano, heteroaryl, heterocyclyl, amino, -NH(alkyl), -N(alkyl)$_2$, -NH(cycloalkyl), -N(cycloalkyl)$_2$, -NH(aryl), -N(aryl)$_2$, -NH(heteroaryl), -N(heteroaryl)$_2$, -NH(heterocyclyl), N(heterocyclyl)$_2$, halo, hydroxy, carboxyl, carboxyalkyl (non-limiting example(s) include ester), alkoxycarbonyl, hydroxyalkyl, carbonyl (non-limiting example(s) include ketone), -C(=O)heterocyclyl, formyl, carboxamido (i.e amido, -C(=O)NH$_2$, -C(=O)N(alkyl)$_2$, -C(=O)NH(alkyl), -C(=O)N(cycloalkyl)$_2$, -C(=O)NH(cycloalkyl)), -NHC(=O)alkyl, amidinyl, hydrazidyl, hydroxamate, -NHC(=O)H, -NHC(=O)alkyl, urea (*e.g* -NH(C=O)NH$_2$, -NH(C=O)NH(alkyl), -NH(C=O)NH(alkyl)$_2$, -NH(C=O)NH(heteroaryl), -NH(C=O)NH(heterocyclyl)), guanidinyl, -NHC(=NCN)NH$_2$, -NHC(=NCN)N(alkyl)$_2$, carbamoyl (i.e -CO$_2$NH$_2$), -NHC(=O)Oalkyl, -CO$_2$N(alkyl)$_2$, -NHC(=O)NH-S(O)$_2$alkyl, -NHC(=O)N(alkyl)-S(O)$_2$alkyl, -NH-S(O)$_2$alkyl, -NH-S(O)$_2$heteroaryl, -N(alkyl)-S(O)$_2$alkyl, -NH-S(O)$_2$aryl, -N(alkyl)-S(O)$_2$aryl, -NH-S(O)$_2$NH$_2$, -NH-S(O)$_2$NHalkyl, -NH-S(O)$_2$N(alkyl)$_2$, thio, alkylthio, alkylthiocarboxy,

-S(O)alkyl, -$S(O)_2$alkyl , -$S(O)_2$aryl, -$OS(O)_2$alkyl, -$OS(O)_2$aryl, sulfonyl urea (non-limiting example(s) include -NHC(=S)NHalkyl) and $OSi(alkyl)_3$. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, heptyl, nonyl, decyl, fluoromethyl, trifluoromethyl and cyclopropylmethyl.

"Alkylheteroaryl" means an alkyl-heteroaryl- group wherein the alkyl is as previously described and the bond to the parent moiety is through the heteroaryl group.

"Alkylamino" means an -NH_2 or -NH_3+ group in which one or more of the hydrogen atoms on the nitrogen is replaced by an alkyl group as defined above. The bond to the parent is through the nitrogen.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as described herein. Preferred alkylaryls comprise a lower alkyl group. Non-limiting examples of suitable alkylaryl groups include o-tolyl, p-tolyl and xylyl. The bond to the parent moiety is through the aryl.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as described herein. Non-limiting examples of suitable alkylthio groups include methylthio, ethylthio, i-propylthio and heptylthio. The bond to the parent moiety is through the sulfur.

"Alkylthiocarboxy" means an alkyl-S-C(=O)O- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the carboxy.

"Alkylsulfonyl" means an alkyl-$S(O)_2$- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Alkylsulfinyl" means an alkyl-S(O)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfinyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more

preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl, 3-methylbutynyl, n-pentynyl, and decynyl. The alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, alkoxyl, aryl, aryloxy, cycloalkyl, cycloalkenyl, cyano, heteroaryl, heterocyclyl, -NH(alkyl), -N(alkyl)$_2$, -NH(cycloalkyl), -N(cycloalkyl)$_2$, -NH(aryl), -N(aryl)$_2$, -NH(heteroaryl), -N(heteroaryl)$_2$, -NH(heterocyclyl), N(heterocyclyl)$_2$, alkoxycarbonyl, hydroxyalkyl, carbonyl (non-limiting example(s) include ketone), -C(=O)heterocyclyl, carboxamido (i.e amido, -C(=O)NH$_2$), -C(=O)N(alkyl)$_2$, -C(=O)NH(alkyl), -C(=O)N(cycloalkyl)$_2$, -C(=O)NH(cycloalkyl), alkylC(=O)NH-, -NHC(=O)alkyl, urea (*e.g* -NH(C=O)NH$_2$), -NH(C=O)NH(alkyl), -NH(C=O)NH(alkyl)$_2$, -NH(C=O)NH(heteroaryl), -NH(C=O)NH(heterocyclyl), -S(O)$_2$alkyl, and -S(O)$_2$aryl.-

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, heptoxy and methylhydroxy. The bond to the parent moiety is through the ether oxygen.

"Alkoxycarbonyl" means an alkyl-O-C(=O)- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aminoalkyl" means an amine-alkyl- group in which alkyl is as previously defined. Preferred aminoalkyls contain lower alkyl. Non-limiting examples of suitable aminoalkyl groups include aminomethyl and 2-Dimethlylamino-2-ethyl. The bond to the parent moiety is through the alkyl.

"Amidinyl" means –C(=NR)NHR group. The R groups are defined as H, alkyl, alkylaryl, heteroaryl, hydroxyl, alkoxy, amino, ester, -NHSO$_2$alkyl, -NHSO$_2$Aryl, -NHC(=O)NHalkyl, and –NHalkyl. The bond to the parent moiety is through the carbon.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group attached to the aryl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Aralkenyl" means an aryl-alkenyl- group in which the aryl and alkenyl are as previously described. Preferred aralkenyls contain a lower alkenyl group. Non-limiting examples of suitable aralkenyl groups include 2-phenethenyl and 2-naphthylethenyl. The bond to the parent moiety is through the alkenyl.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Aralkoxy" means an aralkyl-O- group in which the aralkyl group is as described above. The bond to the parent moiety is through the oxygen group.

"Aralkoxycarbonyl" means an aralkyl-O-C(=O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aroyl" means an aryl-C(=O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- and 2-naphthoyl.

"Aryl" (sometimes abbreviated "Ar") means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

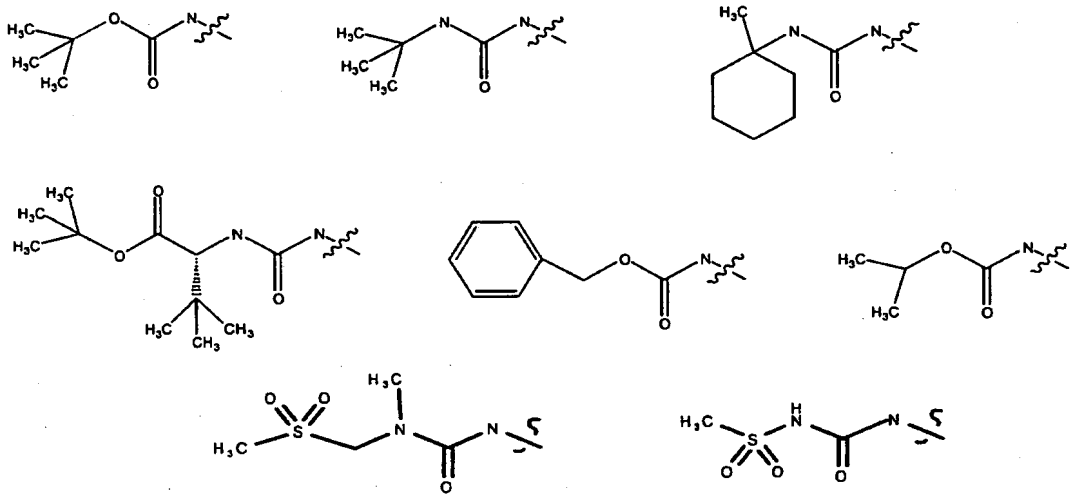
"Arylsulfonyl" means an aryl-$S(O)_2$- group. The bond to the parent moiety is through the sulfonyl.

"Arylsulfinyl" means an aryl-S(O)- group. The bond to the parent moiety is through the sulfinyl.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Carboxyalkyl" means an alkyl-C(=O)O- group. The bond to the parent moiety is through the carboxy.

Carbamates and urea substituents refer to groups with oxygens and nitrogens respectively adjacent an amide; representative carbamate and urea substituents include the following:



"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalin, norbornyl, adamantyl and the like.

"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl. The term "cycloalkenyl" additionally means moieties such as cyclobutenedione, cyclopentenone, cyclopentenedione and the like.

"Halogen" (or halo) means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"Haloalkyl" means an alkyl as defined above wherein one or more hydrogen atoms on the alkyl is replaced by a halo group defined above. Non-limiting examples include trifluoromethyl, 2,2,2-trifluoroethyl, 2-chloropropyl and alike.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. The nitrogen or sulfur atom of the heteroaryl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl,

benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like.

"Heterocyclenyl" means a partially unsaturated monocyclic or partially unsaturated multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heterocyclenyls contain about 5 to about 6 ring atoms and 1-3 double bonds. Preferred heterocyclenyls also contain at least one -C=N as part of the ring. The "heterocyclenyl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. The nitrogen or sulfur atom of the heteroaryl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable heterocyclenyls include dihydroimidazole, dihydrooxazole, dihydrooxadiazole, dihydrothiazole, and the like.

"Heterocyclyl" (or heterocycloalkyl) means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, oxazolidinyl, imidazolidinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl,

tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like. Also included are ring systems comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Non-limiting examples of suitable monocyclic azaheterocyclic (i.e., azaheterocyclyl) groups include 1,2,3,4- tetrahydropyridine, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridine, 1,4,5,6-tetrahydropyrimidine, dihydro-2-pyrrolinyl, dihydro-3-pyrrolinyl, dihydro-2-imidazolinyl, dihydro-2-pyrazolinyl, dihydro-4,5-trizolyl and the like. Non-limiting examples of suitable oxaheterocyclic (i.e., oxaheterocyclyl) groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, fluorodihydrofuranyl, and the like. Non-limiting example of a suitable multicyclic oxaheterocyclic group is 7-oxabicyclo[2.2.1]heptenyl. Non-limiting examples of suitable monocyclic thiaheterocyclic (i.e., thiaheterocyclyl) rings include dihydrothiophenyl, dihydrothiopyranyl, and the like.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, 2-(furan-3-yl)ethyl and quinolin-(3-yl)methyl. The bond to the parent moiety is through the alkyl.

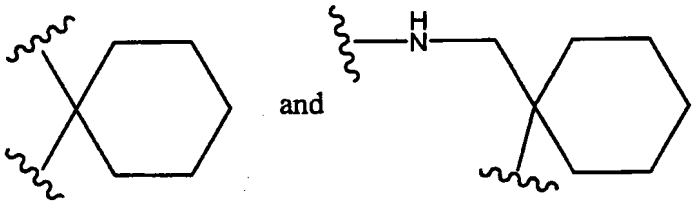
"Heteroaralkenyl" means an heteroaryl-alkenyl- group in which the heteroaryl and alkenyl are as previously described. Preferred heteroaralkenyls contain a lower alkenyl group. Non-limiting examples of suitable heteroaralkenyl groups include 2-(pyrid-3-yl)ethenyl and 2-(quinolin-3-yl)ethenyl. The bond to the parent moiety is through the alkenyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl. The bond to the parent moiety is through the alkyl.

"Hydroxamate" means an alkyl-C(=O)NH-O- group. The bond to the parent moiety is through the oxygen group.

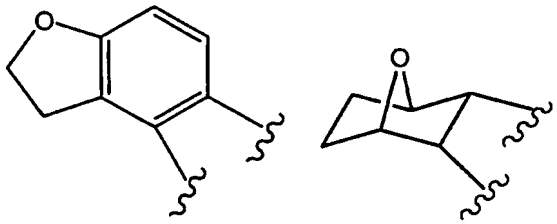
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, alkoxyl, aryl, aroyl, aryloxy, cycloalkyl, cycloalkenyl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl, aralkyl, aralkenyl, aralkoxy, aralkoxycarbonyl, amino, -NH(alkyl), -N(alkyl)$_2$, -NH(cycloalkyl), -N(cycloalkyl)$_2$, -NH(aryl), -N(aryl)$_2$, -NH(heteroaryl), -N(heteroaryl)$_2$, -NH(heterocyclyl), N(heterocyclyl)$_2$, halo, hydroxy, carboxyl, carboxyalkyl (non-limiting example(s) include ester), cyano, alkoxycarbonyl, hydroxyalkyl, carbonyl (non-limiting example(s) include ketone), -C(=O)heterocyclyl, formyl (non-limiting example(s) include aldehyde), carboxamido (i.e amido, -C(=O)NH$_2$), -C(=O)N(alkyl)$_2$, -C(=O)NH(alkyl), -C(=O)N(cycloalkyl)$_2$, -C(=O)NH(cycloalkyl), alkylC(=O)NH-, –amidino, hydrazido, hydroxamate, -NHC(=O)H, -NHC(=O)alkyl, urea (*e.g* -NH(C=O)NH$_2$), -NH(C=O)NH(alkyl), -NH(C=O)NH(alkyl)$_2$, -NH(C=O)NH(heteroaryl), -NH(C=O)NH(heterocyclyl), guanidinyl, -NHC(=NCN)NH$_2$, -NHC(=NCN)N(alkyl)$_2$, carbamoyl (i.e -CO$_2$NH$_2$), -NHC(=O)Oalkyl, -CO$_2$N(alkyl)$_2$, -NHC(=O)NH-S(O)$_2$alkyl, -NHC(=O)N(alkyl)$_2$-S(O)$_2$alkyl, -NH-S(O)$_2$alkyl, -NH-S(O)$_2$heteroaryl, -N(alkyl)-S(O)$_2$alkyl, -NH-S(O)$_2$aryl, -N(alkyl)-S(O)$_2$aryl, -NH-S(O)$_2$NH$_2$, -NH-S(O)$_2$NHalkyl, -NH-S(O)$_2$N(alkyl)$_2$,thio, alkylthiocarboxy, -S(O)$_2$alkyl , -S(O)$_2$aryl, -OS(O)$_2$alkyl, -OS(O)$_2$aryl, sulfonyl urea (non-limiting example(s) include -NHC(=S)NHalkyl) and OSi(alkyl)$_3$.

"Spiroalkyl" means an alkylene group wherein two carbon atoms of an alkyl group are attached to one carbon atom of a parent molecular group thereby forming a carbocyclic or heterocyclic ring of three to eleven atoms. Representative structures include examples such as:



The spiroalkyl groups of this invention can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein.

"Ring system substituent" also means a cyclic ring of 3 to 7 ring atoms of which may contain 1 or 2 heteroatoms, attached to an aryl, heteroaryl, or heterocyclyl ring by simultaneously substituting two ring hydrogen atoms on said aryl, heteroaryl, heterocyclyl ring. Non-limiting examples include:



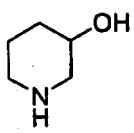
, and the like.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties, in available position or positions.

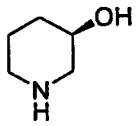
With reference to the number of moieties (non-limiting example(s) include, substituents, groups or rings) in a compound, unless otherwise defined, the phrases "one or more" and "at least one" mean that, there can be as many moieties as chemically permitted, and the determination of the maximum number of such moieties is well within the knowledge of those skilled in the art. Preferably, there are one to three substituents, or more preferably, one to two substituents, with at least one in the para position.

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

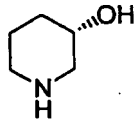
The straight line —— as a bond generally indicates a mixture of, or either of, the possible isomers, non-limiting example(s) include, containing (R)- and (S)- stereochemistry. For example,



means containing both

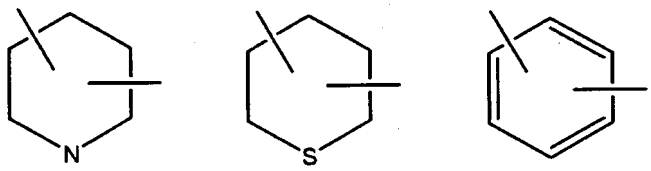


and



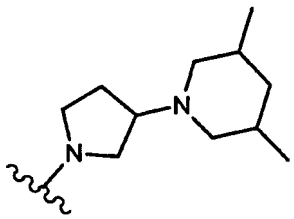
A dashed line (----) represents an optional bond.

Lines drawn into the ring systems, such as, for example:

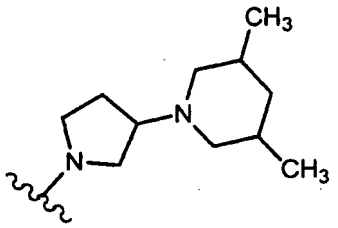


indicate that the indicated line (bond) may be attached to any of the substitutable ring atoms, non limiting examples include carbon, nitrogen and sulfur ring atoms.

As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom, unless stated otherwise. For example:



represents



It should also be noted that any heteroatom with unsatisfied valences in the text, schemes, examples, structural formulae, and any Tables herein is assumed to have the hydrogen atom or atoms to satisfy the valences.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula 1, Formula 5, or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) Volume 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed.,

American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Metabolic conjugates", for example, glucuronides and sulfates which can undergo reversible conversion to compounds of Formula 1 or Formula 5 are contemplated in this application.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective to antagonize CXCR3 and thus produce the desired therapeutic effect in a suitable patient.

"Mammal" means humans and other mammalian animals.

"Patient" includes both human and animals.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O. In general, the solvated forms are equivalent to the unsolvated forms and are intended to be encompassed within the scope of this invention.

The compounds of Formula 1 or Formula 5 can form salts which are also within the scope of this invention. Reference to a compound of Formula 1 or 5 herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula 1 or 5 contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable

(non-limiting example(s) include, non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula 1 or 5 may be formed, for example, by reacting a compound of Formula 1 or 5 with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization. Acids (and bases) which are generally considered suitable for the formation of pharmaceutically useful salts from basic (or acidic) pharmaceutical compounds are discussed, for example, by S. Berge *et al, Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al, The Practice of Medicinal Chemistry* (1996), Academic Press, New York; in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website); and P. Heinrich Stahl, Camille G. Wermuth (Eds.), *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, (2002) Int'l. Union of Pure and Applied Chemistry, pp. 330-331. These disclosures are incorporated herein by reference thereto.

Exemplary acid addition salts include acetates, adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, methyl sulfates, 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pamoates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates, sulfonates (such as those mentioned herein), tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) undecanoates, and the like.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, aluminum salts, zinc salts, salts with organic bases (for example, organic amines) such as benzathines, diethylamine,

dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, piperazine, phenylcyclohexylamine, choline, tromethamine, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (non-limiting example(s) include methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (non-limiting example(s) include dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (non-limiting example(s) include decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (non-limiting example(s) include benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

Compounds of Formula 1 or 5, and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

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

It should also be noted that throughout the specification and Claims appended hereto any formula, compound, moiety or chemical illustration with unsatisfied valences is assumed to have the hydrogen atom to satisfy the valences unless the context indicates a bond.

In one embodiment, the present invention discloses compounds of Formula 1 or 5, having CXCR3 antagonist activity, or a pharmaceutically acceptable derivative thereof, where the various definitions are given above.

In another embodiment of the present invention, in formula 1, Z and Z' are independently N or NR^3.

In another embodiment, in formula 1, Z is N, and Z' is N or NR^3.

In another embodiment, in formula 1, R^3 is alkyl or cycloalkyl.

In another embodiment, in formula 1, R^3 is methyl or cyclopropyl.

In another embodiment, in formula 1, R^4 is selected from the group consisting of H, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and $-C(=O)N(R^{30})_2$, wherein each R^{30} independently is H or alkyl, or wherein R^4 together with the carbon atom to which it is shown attached is -C(=O)-.

In another embodiment, in formula 1, R^4 is selected from the group consisting of H, F, Cl, alkyl, CF_3, -Oalkyl, $-OCF_3$, and -C(=O)N(H)alkyl ; or wherein R^4 together with the carbon atom to which it is shown attached is –C(=O).

In another embodiment, in formula 1, R^4 is selected from the group consisting of H, Cl, CF_3, and -C(=O)N(H)alkyl; or wherein R^4 together with the carbon atom to which it is shown attached is –C(=O).

In another embodiment, in Formula 1, R^5 and R^6 independently are selected from the group consisting H, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, $-C(=O)N(R^{30})_2$ and G, wherein each R^{30} independently is H or alkyl, or wherein R^5 and R^6 together with the carbon atoms to which they are shown attached are aryl or heteroaryl.

In another embodiment, in Formula 1, R^5 and R^6 independently are selected from the group consisting H, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, $-C(=O)N(R^{30})_2$ and G, wherein each R^{30} independently is H or alkyl, or wherein R^5 and R^6 together with the carbon atoms to which they are shown attached are heteroaryl.

In another embodiment, in Formula 1, R^5 and R^6 independently are selected from the group consisting of H, F, $-CH_3$, $-CF_3$, -OH, $-OCH_3$,

$-OCF_3$, $-C(=O)NHCH_2$-aryl, oxazole, thiazole, and oxadiazole, wherein the "aryl" part of $-C(=O)NHCH_2$-aryl, and each of said oxazole, thiazole and oxadiazole are optionally substituted; or wherein R^5 and R^6 together with the carbon atoms to which they are shown attached are pyridyl or imidazolyl, each of which is optionally substituted.

In another embodiment, in Formula 1, R^5 and R^6 independently are selected from the group consisting of H, $-CH_3$, $-CF_3$, and $-C(=O)NHCH_2$-aryl, wherein said aryl is optionally substituted; or wherein R^5 and R^6 together with the carbon atoms to which they are shown attached are pyridyl or imidazolyl, each of which is optionally substituted.

In another embodiment, in Formula 1, m is 1.

In another embodiment, in Formula 1, R^{10} is alkyl.

In another embodiment, in Formula 1, R^{10} is methyl or ethyl.

In another embodiment, in Formula 1, n is zero.

In another embodiment, in Formula 1, R^{12} is H.

In another embodiment, in Formula 1, Y is selected from the group consisting of $-(CR^{13}R^{13})_r-$ and $-C(=O)-$.

In another embodiment, in Formula 1, Y is $-CH_2-$ or $-C(=O)-$.

In another embodiment, in Formula 1, ring D is a five to nine membered aryl or heteroaryl ring having 1-2 N atoms, wherein said ring D is optionally substituted with 1-5 R^{20} moieties independently selected from the group consisting of halo, cyano, alkyl, hydroxy, haloalkyl, alkoxy, haloalkoxy, $-C(=O)N(R^{30})_2$, $-NR^{30}S(=O)_2R^{31}$, and $-N(R^{30})_2$.

In another embodiment, in Formula 1, ring D is phenyl or pyridyl, wherein ring D is optionally substituted with 1-2 R^{20} moieties independently selected from the group consisting of F, Cl, -CN, -OH, alkyl, $-CF_3$, -Oalkyl, $-OCF_3$, -C(=O)NHalkyl, $-NH_2$, and $-NHS(=O)_2$alkyl.

In another embodiment, in Formula 1, ring D is phenyl or pyridyl, wherein ring D is optionally substituted with 1-2 R^{20} moieties independently selected from the group consisting of F, Cl, -CN, $-CF_3$, $-OCF_3$, and $-NH_2$.

In another embodiment, in Formula 1:

Z is N, and Z' is N or NR^3;

R^3 is alkyl or cycloalkyl;

R^4 is selected from the group consisting of H, halo, haloalkyl, and $-C(=O)N(R^{30})_2$, wherein each R^{30} independently is H or alkyl, or wherein R^4 together with the carbon atom to which it is shown attached is -C(=O)-;

R^5 and R^6 independently are selected from the group consisting of H, alkyl, haloalkyl, and $-C(=O)N(R^{30})_2$, wherein each R^{30} independently is H or alkyl , or wherein R^5 and R^6 together with the carbon atoms to which they are shown attached are heteroaryl;

R^{10} is alkyl;

m is 1;

n is zero;

R^{12} is H;

Y is selected from the group consisting of $-(CR^{13}R^{13})_r-$ and -C(=O)-;

ring D is a five to nine membered aryl or heteroaryl ring having 1-2 N atoms, wherein said ring D is unsubstituted or substituted with 1-5 R^{20} moieties independently selected from the group consisting of halo, cyano, alkyl, hydroxy, haloalkyl, alkoxy, haloalkoxy, $-C(=O)N(R^{30})_2$, $-NR^{30}S(=O)_2R^{31}$, and $-N(R^{30})_2$.

In another embodiment, in Formula 1:

Z is N, and Z' is N or NR^3;

R^3 is alkyl or cycloalkyl;

R^4 is selected from the group consisting of H, F, Cl, alkyl, CF_3, -Oalkyl, $-OCF_3$, and -C(=O)NHalkyl ; or wherein R^4 together with the carbon atom to which it is shown attached is –C(=O);

R^5 and R^6 independently are selected from the group consisting of H, F, -alkyl, $-CF_3$, -OH, -Oalkyl, $-OCF_3$, $-C(=O)NHCH_2$-aryl, and G; wherein said aryl is optionally substituted; or wherein R^5 and R^6 together with the carbon atoms to which they are shown attached are pyridyl or imidazolyl, each of which is optionally substituted;

R^{10} is alkyl;

Y is $–CH_2-$ or -C(=O)-; and

ring D is phenyl or pyridyl, wherein ring D is ring D is phenyl or pyridyl, wherein ring D is optionally substituted with 1-2 R^{20} moieties independently selected from the group consisting of F, Cl, -CN, -OH, alkyl, CF_3, -Oalkyl, -OCF_3, -C(=O)NHalkyl, $-NH_2$, and $-NHS(=O)_2$alkyl.

In another embodiment, in Formula 1:

Z is N, and Z' is N or NR^3;

R^3 is methyl or cyclopropyl;

R^4 is selected from the group consisting of H, Cl, $-CF_3$, and -C(=O)NHalkyl ; or wherein R^4 together with the carbon atom to which it is shown attached is –C(=O);

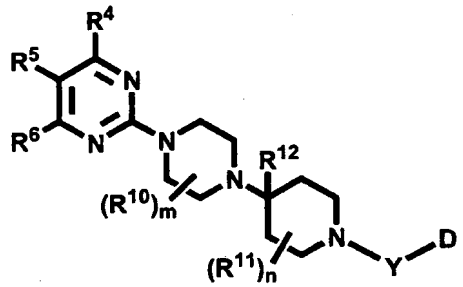
R^5 and R^6 independently are selected from the group consisting of H, alkyl, $-CF_3$, $-C(=O)NHCH_2$-aryl, oxazole, thiazole, and oxadiazole, wherein each of said aryl, oxazole, thiazole and oxadiazole is optionally substituted; or wherein R^5 and R^6 together with the carbon atoms to which they are shown attached are pyridyl or imidazolyl, each of which is optionally substituted;

R^{10} is alkyl;

Y is $–CH_2$- or -C(=O)-; and

ring D is phenyl or pyridyl, wherein ring D is ring D is phenyl or pyridyl, wherein ring D is optionally substituted with 1-2 R^{20} moieties independently selected from the group consisting of F, Cl, CH_3, -CN, $-CF_3$, $-OCF_3$, and $-NH_2$.

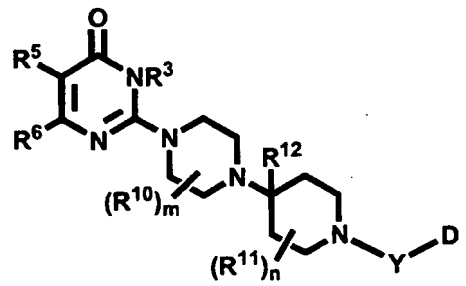
In another embodiment, the compound of Formula 1 is represented by structural formula 2 :



Formula 2

or a pharmaceutically acceptable salt, solvate, or ester thereof.

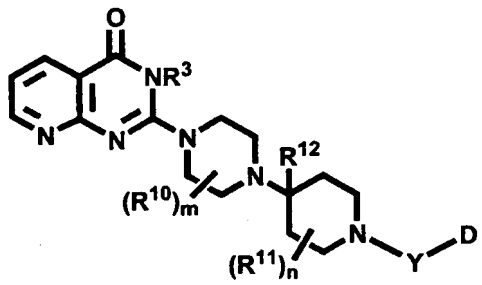
In another embodiment, the compound of Formula 1 is respresented by structural formula 3:



Formula 3

or a pharmaceutically acceptable salt, solvate, or ester thereof.

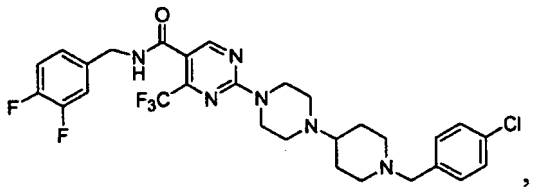
In another embodiment, the compound of Formula 3 above is represented by Formula 4:



Formula 4

or a pharmaceutically acceptable salt, solvate, or ester thereof.

In another embodiment, the compound of Formula 1 is selected from the group consisting of :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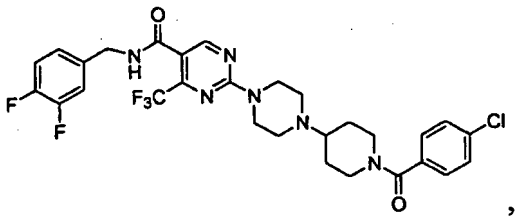
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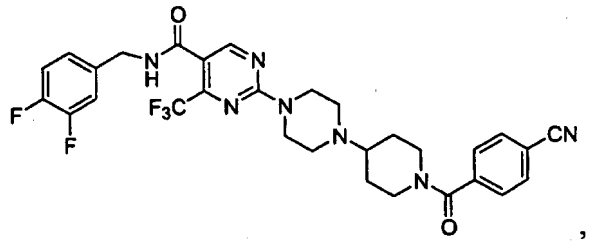
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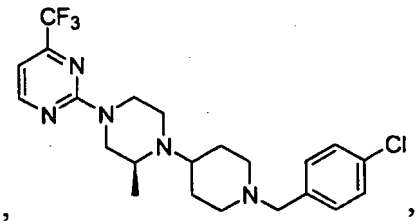
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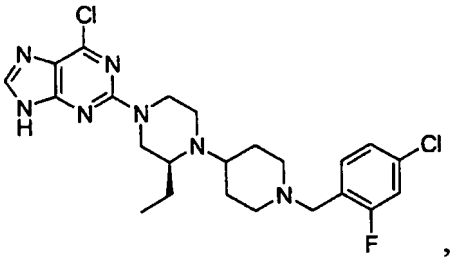
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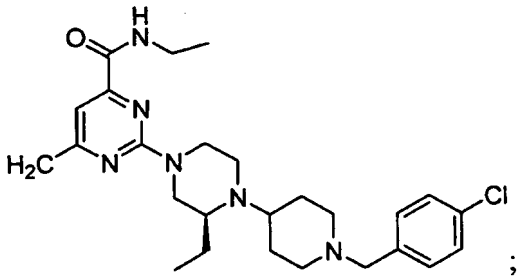
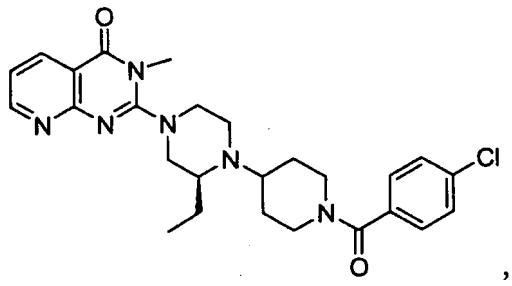

;

or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, the compound of Formula 1 is selected from the group consisting of :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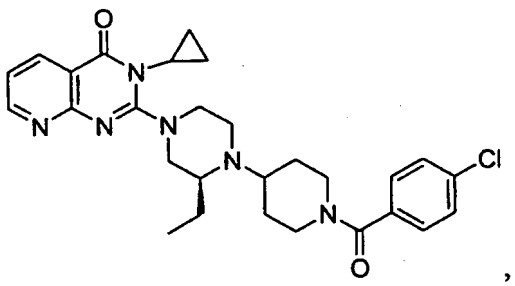
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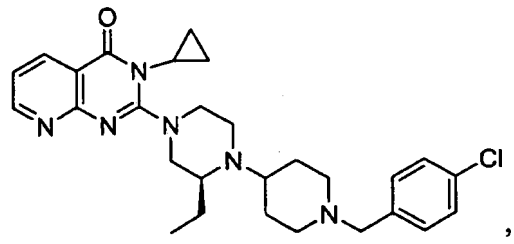
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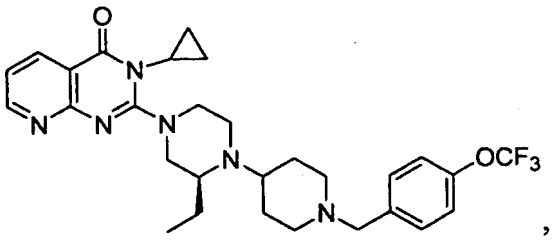
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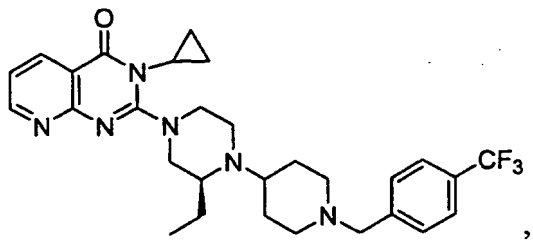
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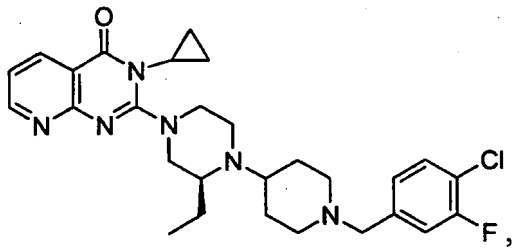
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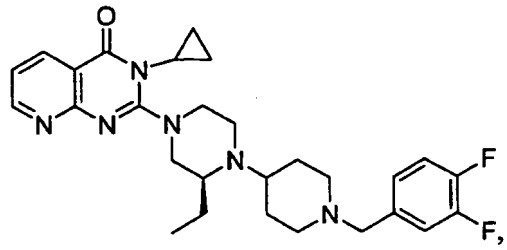
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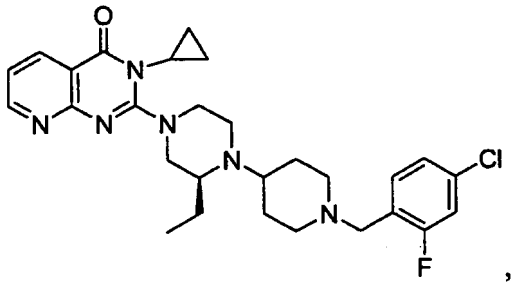
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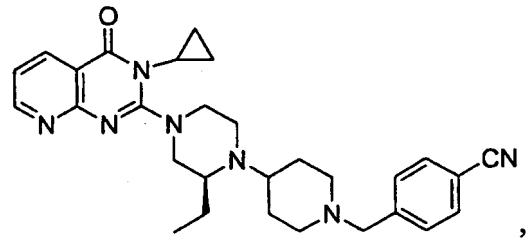
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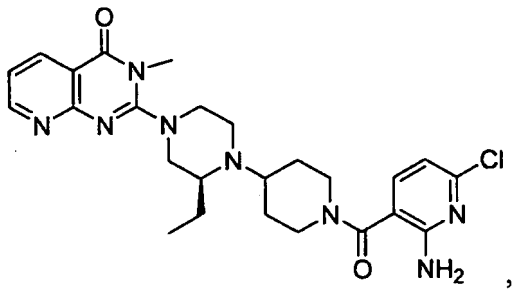
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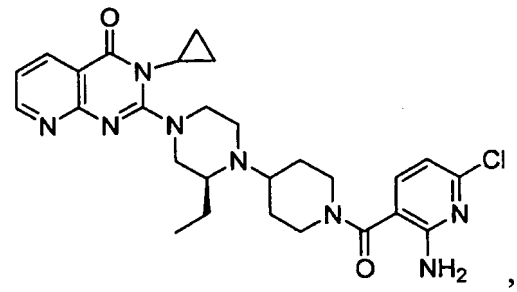
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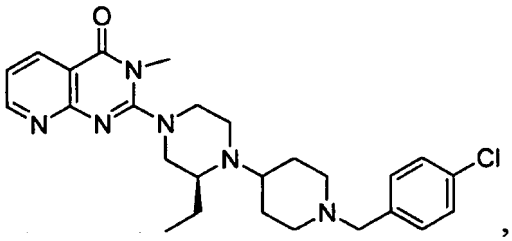
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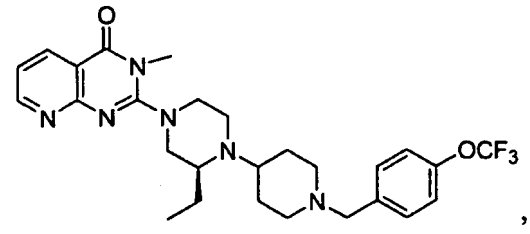
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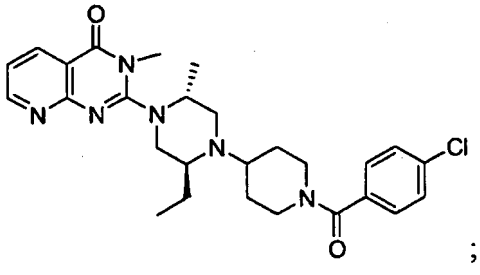
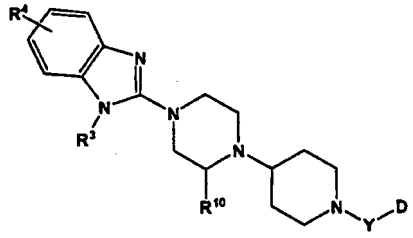

;

or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, the present invention provides a compound of the formula 5



Formula 5

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

R^3 is selected from the group consisting of H, alkyl, alkylaryl, aralkyl, $-CF_3$, haloalkyl, cycloalkyl, halo, hydroxy, hydroxyalkyl, $-C(=O)N(R^{30})_2$, and $-SO_2(R^{31})$;

R^4 is selected from the group consisting of H, alkyl, alkylaryl, aralkyl, -CN, CF_3, haloalkyl, cycloalkyl, halo, hydroxyalkyl, $-C(=O)N(R^{30})_2$, -C(=O)alkyl, $-OR^{30}$, $-NR^{30}S(=O)_2R^{31}$, $-N(R^{30})_2$, $-C(R^{14})(R^{15})-XR^1R^2$, and G;

X is selected from the group consisting of N, O, alkyl, cycloalkyl, heteroaryl, heterocyclyl, and heterocyclenyl;

G is a 5-membered heteroaryl or heterocyclenyl containing at least one -C=N- moiety as part of said heteroaryl or heterocyclenyl, wherein said heteroaryl or heterocyclenyl optionally additionally contains in the ring (i.e., as ring moieties) one or more moieties which can be the same or different, each being independently selected from the group consisting of N, N(→O), O, S, S(=O) and $S(=O)_2$, further wherein each of said heteroaryl or heterocyclenyl ring is optionally independently substituted on one or more ring carbon atoms with one or more R^9 substituents, or on one or more ring nitrogen atoms with one or more R^8 substituents, wherein said R^8 and R^9 substituents can be the same or different;

R^1 and R^2 are independently absent or present, and if present each is independently selected from the group consisting of H, alkyl, alkenyl, carbonyl, cycloalkyl, cycloalkenyl, alkylaryl, arylalkyl, aryl, amino, alkylamino, amidinyl, carboxamido, cyano, urea, -CN, -(+)N≡CH, =NCN, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qN(R^{31})_2$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNHSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, -C(=S)N(H)alkyl, -N(H)-$S(O)_2$-alkyl, -N(H)C(=O)N(H)-alkyl, $-S(O)_2$alkyl, $-S(O)_2N(H)$alkyl, $-S(O)_2N(alkyl)_2$,

-S(O)$_2$aryl, -C(=S)N(H)cycloalkyl, -C(=O)N(H)NH$_2$, -C(=O)alkyl, -heteroaryl, heterocyclyl, and heterocyclenyl; or alternatively when X is N, the N taken together with the R^1 and R^2 forms a heterocycyl, heteroaryl or -N=C(NH$_2$)$_2$;

the R^8 moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, arylalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, -(CH$_2$)$_q$OH, -(CH$_2$)$_q$OR^{31}, -(CH$_2$)$_q$NH$_2$, -(CH$_2$)$_q$NHR^{31}, -(CH$_2$)$_q$C(=O)NHR^{31}, -(CH$_2$)$_q$SO$_2$R^{31}, -(CH$_2$)$_q$NSO$_2$R^{31}, -(CH$_2$)$_q$C(=O)OR^{31}, and -(CH$_2$)$_q$SO$_2$NHR^{31};

the R^9 moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, arylalkyl, amidinyl, aryl, cycloalkyl, cyano, heteroaryl, heterocyclyl, -C(=O)N(R^{30})$_2$, -C(=S)N(R^{30})$_2$, -C(=O)alkyl, -(CH$_2$)$_q$OH, -(CH$_2$)$_q$OR^{31}, -(CH$_2$)$_q$NH$_2$, -(CH$_2$)$_q$NHR^{31}, -(CH$_2$)$_q$C(=O)NHR^{31}, -(CH$_2$)$_q$SO$_2$R^{31}, -(CH$_2$)$_q$NSO$_2$R^{31}, -(CH$_2$)$_q$SO$_2$NHR^{31}, -N(R^{30})$_2$, -N(R^{30})S(O$_2$)R^{31}, -N(R^{30}) C(=O)N(R^{30})$_2$, -OH, -OR^{30}, -SO$_2$(R^{31}), -SO$_2$N(R^{30})$_2$, =O and =S;

R^{10} is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, heterocyclenyl, heterocyclyl, alkylaryl, arylalkyl, -CO$_2$H, -C(=O)N(R^{30})$_2$, -(CH$_2$)$_q$OH, -(CH$_2$)$_q$OR^{31}, -OH, -OR^{30}, halogen, =O, and -C(=O)R^{31};

ring D is a five to nine membered cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl ring having 0-4 heteroatoms independently selected from O, S or N, wherein ring D is optionally substituted with 1-5 independently selected R^{20} moieties;

R^{14} and R^{15} are the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, heteroaryl, -CN, -OH, -OR^{30}, alkylamino, -N(H)S(=O)$_2$alkyl and –N(H)C(=O)N(H)alkyl; or alternatively R^{14} and R^{15} taken together is =O, =S, =NH, =N(alkyl), =N(Oalkyl), =N(OH) or cycloalkyl;

the R^{20} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, alkynyl, alkoxy, alkylamino, alkylthiocarboxy, alkylheteroaryl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, aminoalkyl, amidinyl, aralkyl, aralkenyl, aralkoxy,

aralkoxycarbonyl, aralkylthio, aryl, aroyl, aryloxy, cyano, cycloalkyl, cycloalkenyl, formyl, guanidinyl, halo, haloalkoxy, haloalkyl, heteroalkyl, heteroaryl, heterocyclyl, heterocyclenyl, hydroxyalkyl, hydroxamate, nitro, -$(CH_2)_qOH$, -$(CH_2)_qOR^{31}$, -$(CH_2)_qNH_2$, -$(CH_2)_qNHR^{31}$, -$(CH_2)_qC(=O)NHR^{31}$, -$(CH_2)_qSO_2R^{31}$, -$(CH_2)_qNSO_2R^{31}$, -$(CH_2)_qSO_2NHR^{31}$, -alkynyl$C(R^{31})_2OR^{31}$, -$C(=O)R^{30}$, -$C(=O)N(R^{30})_2$, -$C(=NR^{30})NHR^{30}$, -$C(=NOH)N(R^{30})_2$, -$C(=NOR^{31})N(R^{30})_2$, -$C(=O)OR^{30}$, -$N(R^{30})_2$, -$N(R^{30})C(=O)R^{31}$, -$NHC(=O)N(R^{30})_2$, -$N(R^{30})C(=O)OR^{31}$, -$N(R^{30})C(=NCN)N(R^{30})_2$, -$N(R^{30})C(=O)N(R^{30})SO_2(R^{31})$, -$N(R^{30})C(=O)N(R^{30})_2$, -$N(R^{30})SO_2(R^{31})$, -$N(R^{30})S(O)_2N(R^{30})_2$, -$OR^{30}$, -$OC(=O)N(R^{30})_2$, -$SR^{30}$, -$SO_2N(R^{30})_2$, -$SO_2(R^{31})$, -$OSO_2(R^{31})$, and -$OSi(R^{30})_3$; or alternatively two R^{20} moieties are linked together to form a five or six membered aryl, cycloalkyl, heterocyclyl, heterocyclenyl, or heteroaryl ring wherein said five or six membered aryl, cycloalkyl, heterocyclyl, heterocyclenyl, or heteroaryl ring is fused to ring D and the fused ring is optionally substituted with 0-4 R^{21} moieties;

the R^{21} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, alkynyl, alkoxy, alkylamino, alkylthiocarboxy, alkylheteroaryl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, aminoalkyl, amidinyl, aralkyl, aralkenyl, aralkoxy, aralkoxycarbonyl, aralkylthio, aryl, aroyl, aryloxy, carboxamido, cyano, cycloalkyl, cycloalkenyl, formyl, guanidinyl, halogen, haloalkyl, haloalkoxy, heteroalkyl, heteroaryl, heterocyclyl, heterocyclenyl, hydroxyalkyl, hydroxamate, nitro, -$(CH_2)_qOH$, -$(CH_2)_qOR^{31}$, -$(CH_2)_qNH_2$, -$(CH_2)_qNHR^{31}$, -$(CH_2)_qC(=O)NHR^{31}$, -$(CH_2)_qSO_2R^{31}$, -$(CH_2)_qNSO_2R^{31}$, -$(CH_2)_qSO_2NHR^{31}$, -alkynyl$C(R^{31})_2OR^{31}$, -$C(=O)R^{30}$, -$C(=O)N(R^{30})_2$, -$C(=NR^{30})NHR^{30}$, -$C(=NOH)N(R^{30})_2$, -$C(=NOR^{31})N(R^{30})_2$, -$C(=O)OR^{30}$, -$N(R^{30})_2$, -$N(R^{30})C(=O)R^{31}$, -$NHC(=O)N(R^{30})_2$, -$N(R^{30})C(=O)OR^{31}$, -$N(R^{30})C(=NCN)N(R^{30})_2$, -$N(R^{30})C(=O)N(R^{30})SO_2(R^{31})$, -$N(R^{30})C(=O)N(R^{30})_2$, -$N(R^{30})SO_2(R^{31})$, -$N(R^{30})S(O)_2N(R^{30})_2$, -$OR^{30}$, -$OC(=O)N(R^{30})_2$, -$SR^{30}$, -$SO_2N(R^{30})_2$, -$SO_2(R^{31})$, -$OSO_2(R^{31})$, and -$OSi(R^{30})_3$;

Y is selected from the group consisting of a covalent bond, -$(CR^{13}R^{13})_r$-, -$CHR^{13}C(=O)$-, -$(CHR^{13})_rO$-, -$(CHR^{13})_rN(R^{30})$-, -$C(=O)$-, -$C(=NR^{30})$-, -C(=N-

OR^{30})-, -CH(C(=O)NHR^{30})-, CH-heteroaryl-, -C($R^{13}R^{13}$)$_r$C(R^{13})=C(R^{13})-, -(CHR^{13})$_r$C(=O)- and -(CHR^{13})$_r$N(H)C(=O)-; or alternatively Y is cycloalkyl, heterocyclenyl, or heterocyclyl wherein the cycloalkyl, heterocyclenyl, or heterocyclyl is fused with ring D;

the R^{30} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, aryl, aralkyl, cycloalkyl, CN, -$(CH_2)_q$OH, -$(CH_2)_q$Oalkyl, -$(CH_2)_q$Oalkylaryl, -$(CH_2)_q$Oaryl, -$(CH_2)_q$Oaralkyl, -$(CH_2)_q$Ocycloalkyl, -$(CH_2)_q$NH$_2$, -$(CH_2)_q$NHalkyl, -$(CH_2)_q$N(alkyl)$_2$, -$(CH_2)_q$NHalkylaryl, -$(CH_2)_q$NHaryl, -$(CH_2)_q$NHaralkyl, -$(CH_2)_q$NHcycloalkyl, -$(CH_2)_q$C(=O)NHalkyl, -$(CH_2)_q$C(=O)N(alkyl)$_2$, -$(CH_2)_q$C(=O)NHalkylaryl, -$(CH_2)_q$C(=O)NHaryl, -$(CH_2)_q$C(=O)NHaralkyl, -$(CH_2)_q$C(=O)NHcycloalkyl, -$(CH_2)_q$SO$_2$alkyl, -$(CH_2)_q$SO$_2$alkylaryl, -$(CH_2)_q$SO$_2$aryl, -$(CH_2)_q$SO$_2$aralkyl, -$(CH_2)_q$SO$_2$cycloalkyl, -$(CH_2)_q$NSO$_2$alkyl, -$(CH_2)_q$NSO$_2$alkylaryl, -$(CH_2)_q$NSO$_2$aryl, -$(CH_2)_q$NSO$_2$aralkyl, -$(CH_2)_q$NSO$_2$cycloalkyl, -$(CH_2)_q$SO$_2$NHalkyl, -$(CH_2)_q$SO$_2$NHalkylaryl, -$(CH_2)_q$SO$_2$NHaryl, -$(CH_2)_q$SO$_2$NHaralkyl, -$(CH_2)_q$SO$_2$NHcycloalkyl, heterocyclenyl, heterocyclyl, and heteroaryl;

the R^{31} moieties can be the same or different, each being independently selected from the group consisting of alkyl, alkylaryl, aryl, aralkyl, cycloalkyl, -$(CH_2)_q$OH, -$(CH_2)_q$Oalkyl, -$(CH_2)_q$Oalkylaryl, -$(CH_2)_q$Oaryl, -$(CH_2)_q$Oaralkyl, -$(CH_2)_q$Ocycloalkyl, -$(CH_2)_q$NH$_2$, -$(CH_2)_q$NHalkyl, -$(CH_2)_q$N(alkyl)$_2$, -$(CH_2)_q$NHalkylaryl, -$(CH_2)_q$NHaryl, -$(CH_2)_q$NHaralkyl, -$(CH_2)_q$NHcycloalkyl, -$(CH_2)_q$C(=O)NHalkyl, -$(CH_2)_q$C(=O)N(alkyl)$_2$, -$(CH_2)_q$C(=O)NHalkylaryl, -$(CH_2)_q$C(=O)NHaryl, -$(CH_2)_q$C(=O)NHaralkyl, -$(CH_2)_q$C(=O)NHcycloalkyl, -$(CH_2)_q$SO$_2$alkyl, -$(CH_2)_q$SO$_2$alkylaryl, -$(CH_2)_q$SO$_2$aryl, -$(CH_2)_q$SO$_2$aralkyl, -$(CH_2)_q$SO$_2$cycloalkyl, -$(CH_2)_q$NSO$_2$alkyl, -$(CH_2)_q$NSO$_2$alkylaryl, -$(CH_2)_q$NSO$_2$aryl, -$(CH_2)_q$NSO$_2$aralkyl, -$(CH_2)_q$NSO$_2$cycloalkyl, -$(CH_2)_q$SO$_2$NHalkyl, -$(CH_2)_q$SO$_2$NHalkylaryl, -$(CH_2)_q$SO$_2$NHaryl, -$(CH_2)_q$SO$_2$NHaralkyl, -$(CH_2)_q$SO$_2$NHcycloalkyl, heterocyclenyl, heterocyclyl, and heteroaryl;

each q can be the same or different, each being independently selected from 1 to 5; and

r is 1 to 4;

with the proviso that there are no two adjacent double bonds in any ring, and that when a nitrogen is substituted by two alkyl groups, said two alkyl groups may be optionally joined to each other to form a ring.

In another embodiment, in Formula 5, R^3 is alkyl or cycloalkyl.

In another embodiment, in Formula 5, R^3 is alkyl, cycloalkyl, aralkyl, or heterocyclyl.

In another embodiment, in Formula 5, R^3 is methyl or cyclopropyl.

In another embodiment, in Formula 5, R^4 is selected from the group consisting of H, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and $-C(=O)N(R^{30})_2$, wherein each R^{30} independently is H or alkyl, or wherein R^4 together with the carbon atom to which it is attached is -C(=O).

In another embodiment, in Formula 5, R^4 is selected from the group consisting of H, F, Cl, alkyl, CF_3, -Oalkyl, $-OCF_3$, and -C(=O)NHalkyl; or wherein R^4 together with the carbon atom to which it is shown attached is –C(=O).

In another embodiment, in Formula 5, R^{10} is alkyl or cycloalkyl.

In another embodiment, in Formula 5, R^{10} is methyl or ethyl.

In another embodiment, in Formula 5, Y is selected from the group consisting of $-(CR^{13}R^{13})_r-$ and -C(=O)-.

In another embodiment, in Formula 5, Y is $–CH_2-$ or -C(=O)-.

In another embodiment, in Formula 5, ring D is a five to nine membered aryl or heteroaryl ring having 1-2 N atoms, wherein said ring D is optionally substituted with 1-5 R^{20} moieties independently selected from the group consisting of halo, cyano, alkyl, hydroxy, haloalkyl, alkoxy, haloalkoxy, $-C(=O)N(R^{30})_2$, $-NR^{30}S(=O)_2R^{31}$, and $-N(R^{30})_2$.

In another embodiment, in Formula 5, ring D is phenyl or pyridyl, wherein ring D is optionally substituted with 1-2 R^{20} moieties independently selected from the group consisting of F, Cl, -CN, -OH, -alkyl, CF_3, -Oalkyl, $-OCF_3$, -C(=O)NHalkyl, $-NH_2$, and $–NHS(=O)_2$alkyl.

In another embodiment, in Formula 5:

R^3 is alkyl or cycloalkyl;

R^4 is selected from the group consisting of H, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and -C(=O)N(R^{30})$_2$, wherein each R^{30} independently is H or alkyl, or wherein R^4 together with the carbon atom to which it is attached is -C(=O)-;

R^{10} is alkyl;

Y is selected from the group consisting of -($CR^{13}R^{13}$)$_r$– and -C(=O)-; and

ring D is a five to nine membered aryl or heteroaryl ring having 1-2 N atoms, wherein said ring D is optionally substituted with 1-5 R^{20} moieties independently selected from the group consisting of halo, cyano, alkyl, hydroxy, haloalkyl, alkoxy, haloalkoxy, -C(=O)N(R^{30})$_2$, -NR^{30}S(=O)$_2R^{31}$, and -N(R^{30})$_2$.

In another embodiment, in Formula 5:

R^3 is methyl or cyclopropyl;

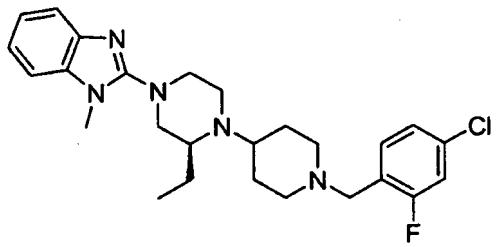
R^4 is selected from the group consisting of H, F, Cl, alkyl, CF_3, -O alkyl, -OCF_3, and -C(=O)NHalkyl; or wherein R^4 together with the carbon atom to which it is shown attached is
–C(=O);

R^{10} is methyl or ethyl;

Y is –CH_2- or -C(=O)-; and

ring D is phenyl or pyridyl, wherein ring D is optionally substituted with 1-2 R^{20} moieties independently selected from the group consisting of F, Cl, -CN, -OH, alkyl, CF_3, -Oalkyl, -OCF_3, -C(=O)NHalkyl, -NH_2, and –NHS(=O)$_2$alkyl.

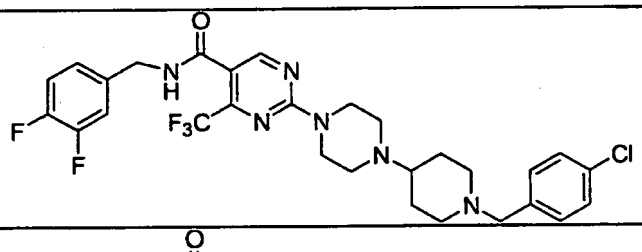
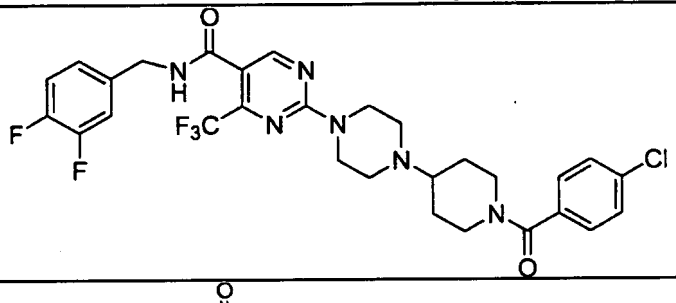
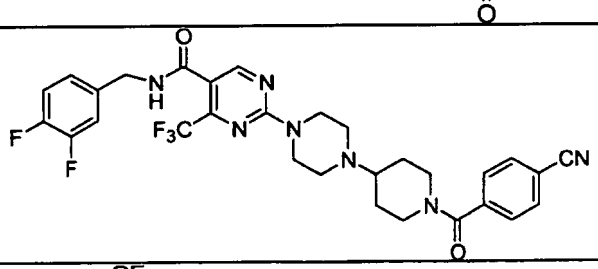
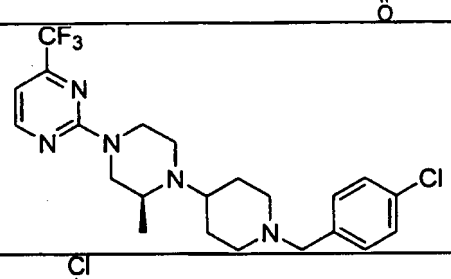
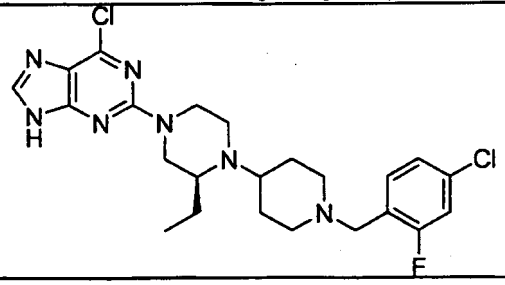
In another embodiment, the compound of Formual 5 is

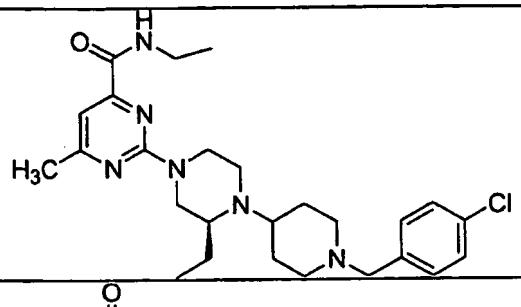
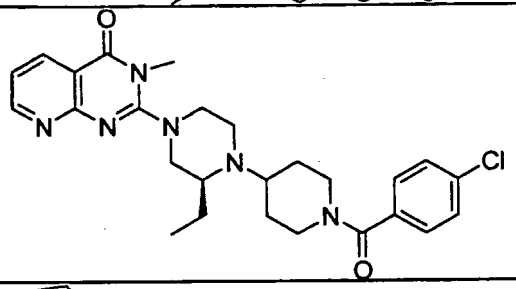
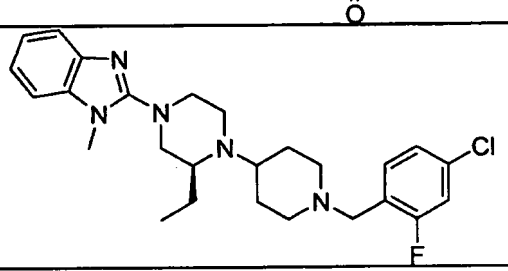
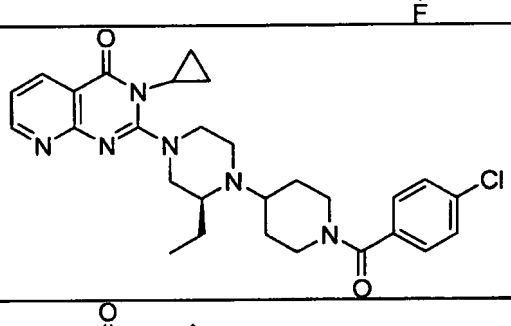
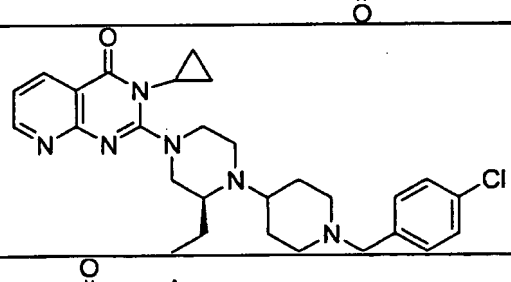
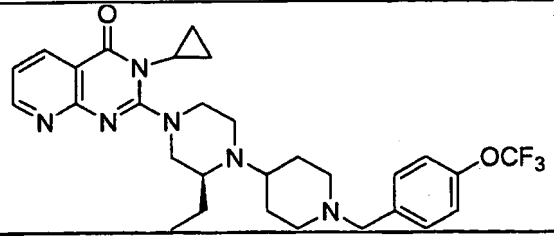


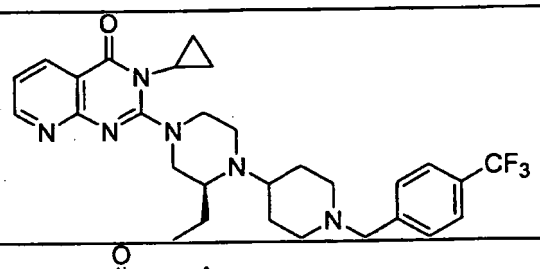
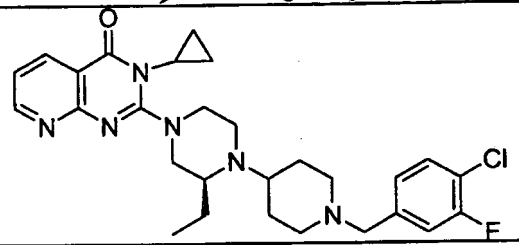
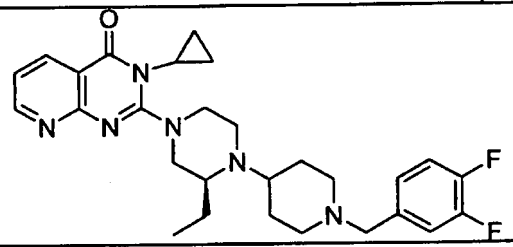
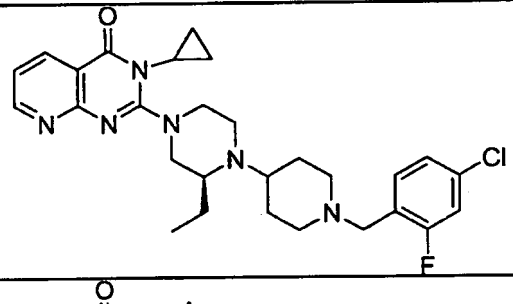
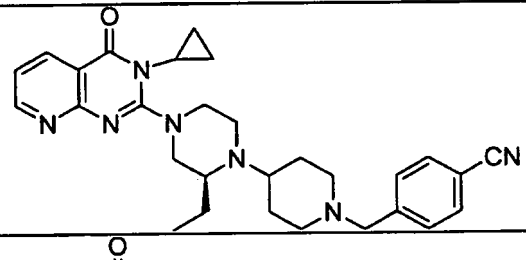
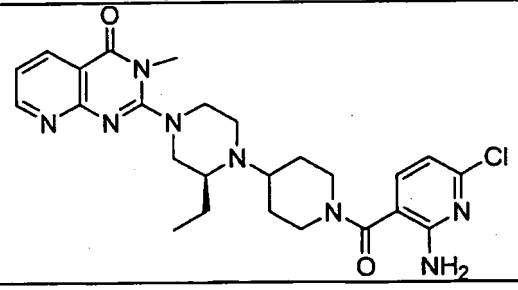
or a pharmaceutically acceptable salt or solvate thereof.

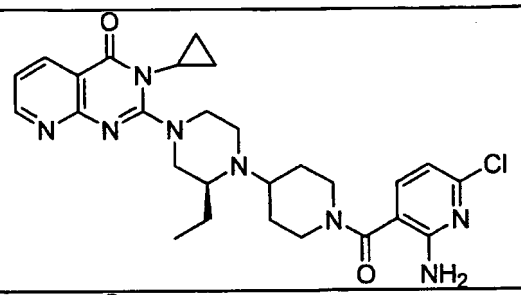
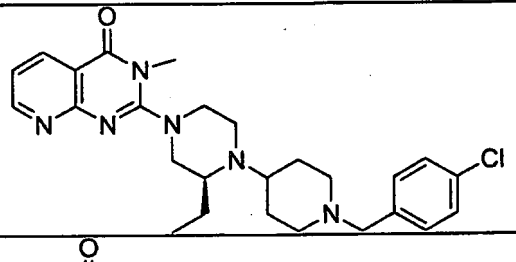
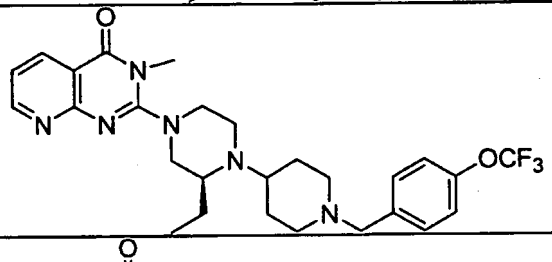
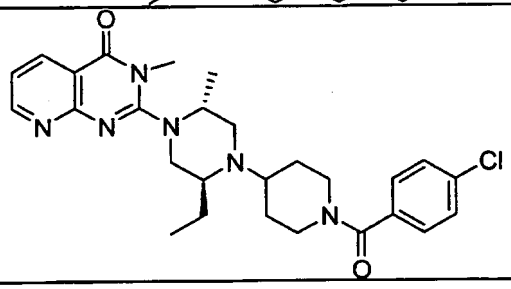
Table 1 below lists compounds of Formula 1 or 5 which are shown along with their IC_{50} ratings. The IC_{50} values are rated, "A" for IC_{50} values less than about 25 nanomolar (nM), "B" for IC_{50} values in the range of from about 25 to about 100 nM and "C" for IC_{50} values greater than about 100 nM.

Table 1

Compound Number	STRUCTURE	M +H	IC50 rating (human)
2		610.0	C
3			C
4		603.6	C
5		454.9	C
7		493.4	C

8		486.1	C
9		496.0	B
10		471.0	C
11		522.1	B
12		508.1	A
13		557.6	A

14		541.6	A
15		526.1	A
16		509.6	A
17		526.1	A
18		498.6	A
19		512.0	C

20		538.1	B
21		482.0	A
22		531.6	A
23		510.1	C

In yet another aspect, the compound according to Formula 1 can be in purified form.

In another embodiment, this invention provides a pharmaceutical composition comprising at least one compound of Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof in combination with at least one pharmaceutically acceptable carrier.

In still another embodiment, the invention provides a pharmaceutical composition of Formula 1, further comprising at least one additional agent, drug, medicament, antibody and/or inhibitor for treating a CXCR3 chemokine receptor mediated disease.

When administering a combination therapy to a patient in need of such administration, the therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising the therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. The amounts of the various actives in such combination therapy may be different amounts (different dosage amounts) or same amounts (same dosage amounts). Thus, for non-limiting illustration purposes, a compound of Formula III and an additional therapeutic agent may be present in fixed amounts (dosage amounts) in a single dosage unit (e.g., a capsule, a tablet and the like). A commercial example of such single dosage unit containing fixed amounts of two different active compounds is VYTORIN® (available from Merck Schering-Plough Pharmaceuticals, Kenilworth, New Jersey).

In yet another embodiment, the present invention discloses methods for preparing pharmaceutical compositions comprising the inventive heterocyclic substituted piperazine compounds of Formula 1 as an active ingredient. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, i.e. oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Powders and tablets may be comprised of from about 5 to about 95 percent inventive composition. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose,

polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum and the like. Sweetening and flavoring agents and preservatives may also be included where appropriate. Some of the terms noted above, namely disintegrants, diluents, lubricants, binders and the like, are discussed in more detail below.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize the therapeutic effects, i.e. anti-inflammatory activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

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

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

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

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

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

Preferably the compound is administered orally.

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

The quantity of the inventive active composition in a unit dose of preparation may be generally varied or adjusted from about 1.0 milligram to about 1,000 milligrams, preferably from about 1.0 to about 950 milligrams, more preferably from about 1.0 to about 500 milligrams, and typically from about 1 to about 250 milligrams, according to the particular application. The actual dosage employed may be varied depending upon the patient's age, sex, weight and severity of the condition being treated. Such techniques are well known to those skilled in the art.

Generally, the human oral dosage form containing the active ingredients can be administered 1 or 2 times per day. The amount and frequency of the administration will be regulated according to the judgment of the attending clinician. A generally recommended daily dosage regimen for oral administration may range from about 1.0 milligram to about 1,000 milligrams per day, in single or divided doses.

Some useful terms are described below:

Capsule - refers to a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredients. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

Tablet- refers to a compressed or molded solid dosage form containing the active ingredients with suitable diluents. The tablet can be prepared by

compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

Oral gels- refers to the active ingredients dispersed or solubilized in a hydrophillic semi-solid matrix.

Powders for constitution - refers to powder blends containing the active ingredients and suitable diluents which can be suspended in water or juices.

Diluent - refers to substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn, rice and potato; and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 10 to about 90% by weight of the total composition, preferably from about 25 to about 75%, more preferably from about 30 to about 60% by weight, even more preferably from about 12 to about 60%.

Disintegrants - refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

Binders - refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose

and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

Lubricant - refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d'l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

Glidents - materials that prevent caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidents include silicon dioxide and talc. The amount of glident in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

Coloring agents - excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

Bioavailability - refers to the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control.

Conventional methods for preparing tablets are known. Such methods include dry methods such as direct compression and compression of granulation

produced by compaction, or wet methods or other special procedures. Conventional methods for making other forms for administration such as, for example, capsules, suppositories and the like are also well known.

It will be apparent to those skilled in the art that many modifications, variations and alterations to the present disclosure, both to materials and methods, may be practiced. Such modifications, variations and alterations are intended to be within the spirit and scope of the present invention.

As stated earlier, the invention includes tautomers, enantiomers and other stereoisomers of the compounds also. Thus, as one skilled in the art knows, certain imidazole compounds may exist in tautomeric forms. Such variations are contemplated to be within the scope of the invention. Certain compounds of the present invention may exist in multiple crystalline forms or amorphous forms. All physical forms of the current invention are contemplated.

Compounds of this invention which contain unnatural proportions of atomic isotopes (i.e. "radiolabeled compounds") whether their use is therapeutic, diagnostic or as a research reagent are contemplated under this invention.

Another embodiment of the invention discloses the use of the pharmaceutical compositions disclosed above for treatment of diseases of a CXCR3 chemokine receptor mediated disease in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of at least one compound according to Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof.

In another embodiment, the method is directed to administering to the patient (a) an effective amount of at least one compound according to Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one additional agent, drug, medicament, antibody and/or inhibitor for treating a CXCR3 chemokine receptor mediated disease, in combination with a pharmaceutically acceptable carrier.

In another embodiment, at least one compound of Formula 1 binds to a CXCR3 receptor.

The invention provides methods of preparing compounds of Formula 1, as well as methods for treating diseases, for example, treatment (e. g., palliative therapy, curative therapy, prophylactic therapy) of certain diseases and conditions e. g., inflammatory diseases (e. g., psoriasis, inflammatory bowel disease), autoimmune diseases (e. g., rheumatoid arthritis, multiple sclerosis), graft rejection (e. g., allograft rejection, xenograft rejection), ophthalmic inflammation or dry eye, infectious diseases and tumors. The invention provides a method of treating a CXCR3 chemokine mediated disease in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of at least one compound of Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof.

The invention provides methods of treating diseases, for example, treatment (e. g., palliative therapy, curative therapy, prophylactic therapy) of certain diseases and conditions such as inflammatory diseases (e. g., psoriasis, inflammatory bowel disease), autoimmune diseases (e. g., rheumatoid arthritis, multiple sclerosis), graft rejection (e. g., allograft rejection, xenograft rejection), infectious diseases as well as cancers and tumors, fixed drug eruptions, cutaneous delayed-type hypersensitivity responses, ophthalmic inflammation or dry eye, type I diabetes, viral meningitis and tuberculoid leprosy comprising administering: (a) a therapeutically effective amount of at least one compound according to Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one medicament selected from the group consisting of: disease modifying antirheumatic drugs; nonsteroidal anti-inflammatory drugs; COX-2 selective inhibitors; COX-1 inhibitors; immunosuppressives (such as cyclosporins and methotrexate); steroids (including corticosteroids such as glucorticoids); PDE IV inhibitors, anti-TNF-α compounds, TNF-α-convertase (TACE) inhibitors, MMP inhibitors, cytokine inhibitors, glucocorticoids, other chemokine inhibitors such as CCR2 and CCR5, CB2-selective inhibitors, p38 inhibitors, biological response modifiers; anti-inflammatory agents and therapeutics.

The invention also provides a method of modulating (inhibiting or promoting) an inflammatory response in an individual in need of such therapy. The method comprises administering a therapeutically effective amount of a compound (e. g., small organic molecule) which inhibits or promotes mammalian CXCR3 function in an individual in need thereof. Also disclosed is a method of inhibiting or blocking T-cell mediated chemotaxis in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of a compound of Formula 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

Also disclosed is a method of treating inflammatory bowel disease (such Crohn's disease, ulcerative colitis) in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of at least one compound of Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof.

Also disclosed is a method of treating inflammatory bowel disease in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of: (a) at least one compound of Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: sulfasalazine, 5-aminosalicylic acid, sulfapyridine, anti-TNF compounds, anti-IL-12 compounds, corticosteroids, glucocorticoids, T-cell receptor directed therapies (such as anti-CD3 antibodies), immunosuppresives, methotrexate, azathioprine, and 6-mercaptopurines.

Also disclosed is a method of treating graft rejection in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of at least one compound of Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof.

Also disclosed is a method of treating graft rejection in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of: (a) at least one compound of Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting

of: cyclosporine A, FK-506, FTY720, beta-interferon, rapamycin, mycophenolate, prednisolone, azathioprine, cyclophosphamide and an antilymphocyte globulin.

Also disclosed is a method of treating multiple sclerosis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of: (a) a therapeutically effective amount of at least one compound of Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: beta-interferon, glatiramer acetate, corticosteroids, glucocorticoids, methotrexate, azothioprine, mitoxantrone, VLA-4 inhibitors, FTY720, anti-IL-12 inhibitors, and CB2-selective inhibitors.

Also disclosed is a method of treating multiple sclerosis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of: (a) a therapeutically effective amount of at least one compound of Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: methotrexate, cyclosporin, leflunomide, sulfasalazine, corticosteroids, β-methasone, β-interferon, glatiramer acetate, prednisone, etonercept, and infliximab.

Also disclosed is a method of treating rheumatoid arthritis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of: (a) at least one compound of Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: non-steroidal anti-inflammatory agents, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, cyclosporine, methotrexate, steroids, PDE IV inhibitors, anti-TNF-α compounds, MMP inhibitors, corticosteroids, glucocorticoids, chemokine inhibitors, CB2-selective inhibitors, caspase (ICE) inhibitors and other classes of compounds indicated for the treatment of rheumatoid arthritis.

Also disclosed is a method of treating psoriasis in a patient in need of such treatment the method comprising administering to the patient a

therapeutically effective amount of: a) at least one compound of Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: immunosuppressives, cyclosporins, methotrexate, steroids, corticosteroids, anti-TNF-α compounds, anti-IL compounds, anti-IL-23 compounds, vitamin A and D compounds and fumarates.

Also disclosed is a method of treating ophthalmic inflammation (including, for e.g., uveitis, posterior segment intraocular inflammation, Sjogren's syndrome) or dry eye in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of: a) at least one compound according to Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: immunosuppressives, cyclosporins, methotrexate, FK506, steroids, corticosteroids, and anti-TNF-α compounds.

Also disclosed is a method of treating a disease selected from the group consisting of: inflammatory disease, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, graft rejection, psoriasis, fixed drug eruptions, cutaneous delayed-type hypersensitivity responses, ophthalmic inflammation (including e.g., uveitis, posterior segment intraocular inflammation, and Sjogren's syndrome), tuberculoid leprosy and cancer in a patient in need of such treatment, such method comprising administering to the patient an effective amount of at least one compound according to Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof.

The invention also provides a method of treating a disease selected from the group consisting of: inflammatory disease, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, graft rejection, psoriasis, fixed drug eruptions, cutaneous delayed-type hypersensitivity responses and tuberculoid leprosy, ophthalmic inflammation, type I diabetes, viral meningitis and cancer in a patient in need of such treatment, such method comprising administering to the patient an effective amount of (a) at least one compound according to Formula 1, or a pharmaceutically acceptable salt, solvate or ester

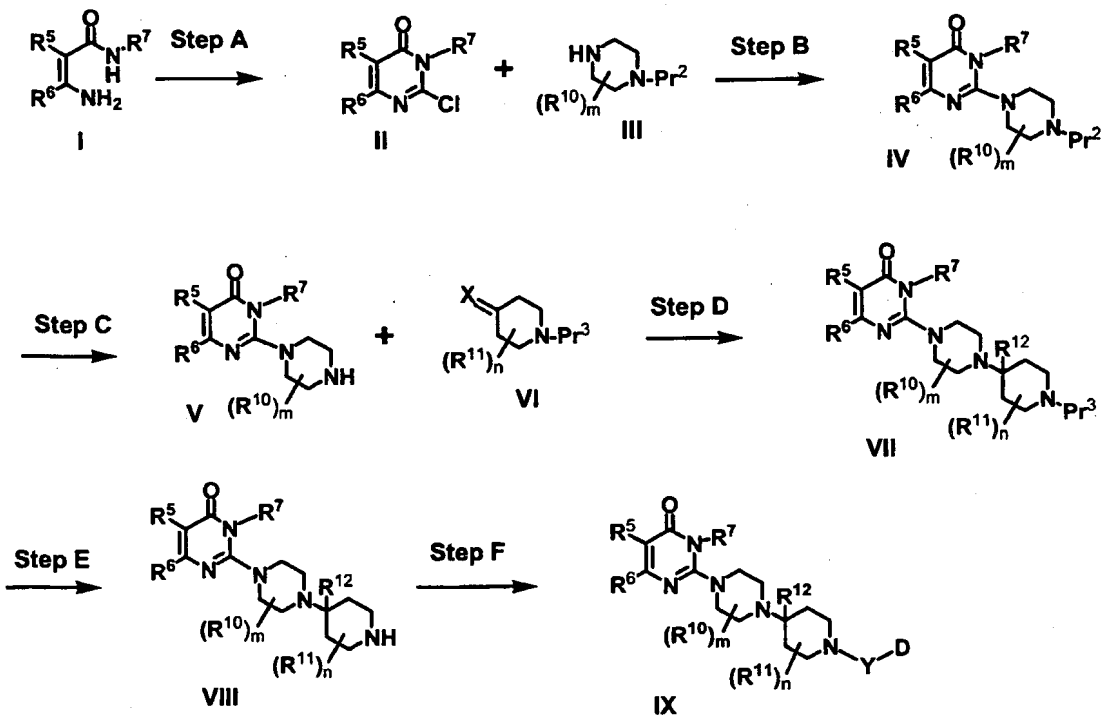
thereof concurrently or sequentially with (b) at least one medicament selected from the group consisting of: disease modifying antirheumatic drugs; nonsteroidal antiinflammatory drugs; COX-2 selective inhibitors; COX-1 inhibitors; immunosuppressives; steroids; PDE IV inhibitors, anti-TNF-α compounds, MMP inhibitors, corticosteroids, glucocorticoids, chemokine inhibitors, CB2-selective inhibitors, biological response modifiers; anti-inflammatory agents and therapeutics.

Another embodiment of the invention discloses a method of making the substituted pyridine compounds, disclosed above.

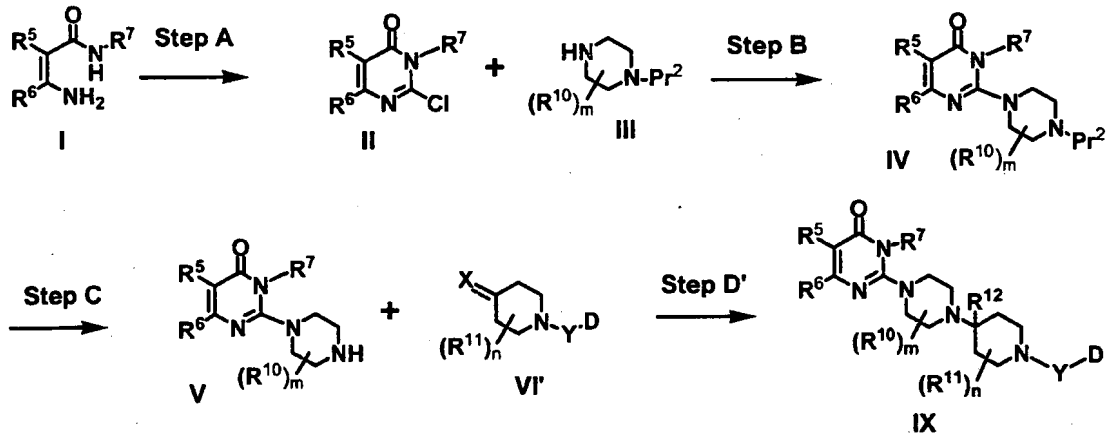
GENERAL SYNTHESIS

Compounds of the present invention can be prepared by a number of ways evident to one skilled in the art of organic synthesis. Preferred methods include, but are not limited to, the general synthetic procedures described herein. One skilled in the art will recognize that one route will be optimal depending on the choice of appendage substituents. Additionally, one skilled in the art will recognize that in some cases the order of steps has to be controlled to avoid functional group incompatibilities. One skilled in the art will recognize that a more convergent route (i.e. non-linear or preassembly of certain portions of the molecule) is a more efficient method of assembly of the target compounds. Two such methods for the preparation of compounds of general formula **IX** were variables **[R^5, R^6, R^7, R^{10}, R^{11}, R^{12}, Y, D, m, n, and p]** are as defined above, are shown in scheme 1 and Scheme 2. **Pr^2** and **Pr^3** are optional protecting groups exemplified below.

Scheme 1. Method A



Scheme 2. Method B.



The starting material and reagents used in preparing compounds described are either available from commercial suppliers such as Aldrich Chemical Co. (Wisconsin, USA) and Acros Organics Co. (New Jersey, USA) or were prepared by literature methods known to those skilled in the art.

One skilled in the art will recognize that the synthesis of compounds of formula **IX** may require the need for the protection of certain functional groups

(i.e. derivatization for the purpose of chemical compatibility with a particular reaction condition). A suitable protecting group for an amine (Pr^2, Pr^3) is methyl, benzyl, ethoxyethyl, t-butoxycarbonyl, phthaloyl and alike. All protecting groups can be appended to and removed by literature methods known to those skilled in the art.

One skilled in the art will recognize that the synthesis of compounds of formula **IX** may require the construction of an amide bond. Methods include but are not limited to the use of a reactive carboxy derivative (e.g. acid halide, or ester at elevated temperatures) or the use of an acid with a coupling reagent (e.g. DECI, DCC) with an amine at 0 °C to 100 °C Suitable solvents for the reaction are halogenated hydrocarbons, ethereal solvents, dimethylformamide and alike. The reaction may be conducted under pressure or in a sealed vessel.

One skilled in the art will recognize that the synthesis of compounds of formula **IX** may require the construction of an amine bond. One such method is, but not limited to, the reaction of a primary or secondary amine with a carbonyl containing compound (e.g. aldehyde or ketone) under reductive amination conditions known in the art. Suitable reducing reagents of the intermediate imine are sodium borohydride, sodium triacetoxyborohydride and alike at 0 °C to 100 °C. Suitable solvents for the reaction are halogenated hydrocarbons, ethereal solvents, dimethylformamide and alike. Another such method is, but not limited to, the reaction of a primary or secondary amine with a reactive alkylating agent such as an alkyl halide, benzyl halide, mesylate, tosylate or alike. Suitable solvents for the reaction are halogenated hydrocarbons, ethereal solvents, dimethylformamide and alike. The reaction may be conducted under pressure or in a sealed vessel at 0 °C to 100 °C.

One skilled in the art will recognize that the synthesis of compounds of formula **IX** may require the reduction of a reducible functional group. Suitable reducing reagents include sodium borohydride, lithium aluminum hydride, diborane and alike at -20 °C to 100 °C. Suitable solvents for the reaction are halogenated hydrocarbons, ethereal solvents, dimethylformamide and alike.

One skilled in the art will recognize that the synthesis of compounds of formula **IX** may require the oxidation of a functional group. Suitable oxidizing reagents include oxygen, hydrogen peroxide, m-chloroperoxybenzoic acid and alike at -20 °C to 100 °C. Suitable solvents for the reaction are halogenated hydrocarbons, ethereal solvents, water and alike.

The starting materials and the intermediates of a reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and alike. Such materials can be characterized using conventional means, including physical constants and spectral data.

General Description of Methods A & B

Step A. Cyclization of aminoaryl carboxylic amide

A compound of formula **I** is reacted with triphosgene followed by phosphorus oxychloride to form a compound of general formula **II**. Preferably the reaction is carried out in a solvent such as dichloromethane or neat.

Step B. Amination of a 2-halo quinazolinone derivative

A 2-halo quinazolinone derivative of formula II is reacted with a piperazine of formula III to form a compound of general formula **IV**. Preferably the reaction is carried out in a solvent such as dioxane in the presence of a base such as potassium carbonate or cesium carbonate.

Step C.

A protected piperazine of structure **IV** is deprotected to provide the secondary amine of structure **V**. When Pr^2 is benzyl or substituted benzyl deprotection can be effected by reaction under a pressure of hydrogen gas in the presence of a catalyst such as palladium. When Pr^2 is ethoxyethyl deprotection can be effected by reaction with trimethylsilyl iodide. When Pr^2 is

t-butoxycarbonyl deprotection can be effected with a strong acid such as trifluoroacetic acid.

Step D

A piperazine of structure **V** is reacted with a ketone of structure **VI** in the presence of a reducing agent to form a compound of structure **VII** were R^{12} is hydrogen. General conditions for the reductive amination reaction are described above.

Step D'

A piperazine of structure **V** is reacted with a ketone of structure **VI'** in the presence of a reducing agent to form a compound of structure **IX** were R^{12} is hydrogen. Typical conditions are the reaction of an equi-molar quantity of a piperazine of structure **IV** and a ketone of structure in the presence of titanium isopropoxide in a halogenated solvent such as methylene chloride for 1-48 h. Subsequent addition of a cyanide source such as dimethylaluminum cyanide affords a compound of structure **VI** were R^{12} is a cyanide residue.

Step E

A protected piperidine of structure **VII** is deprotected to provide the secondary amine of structure **VIII**. When Pr^2 is benzyl or substituted benzyl deprotection can be effected by reaction under a pressure of hydrogen gas in the presence of a catalyst such as palladium. When Pr^2 is ethoxyethyl deprotection can be effected by reaction with trimethylsilyl iodide. When Pr^2 is t-butoxycarbonyl deprotection can be effected with a strong acid such as trifluoroacetic acid.

Step F

A secondary piperidine of formula **VIII** is either alkylated or acylated to provide compounds of formula **IX**. General methods for such alkyations and acylations are described above and are well known to those skilled in the art.

Compounds of formula **IX** can be prepared by the general methods outlined in schemes 1 and 2. Synthesis of the specifically exemplified compounds, were prepared as described in detailed below. The following **EXAMPLES** are being provided to further illustrate the present invention. They are for illustrative purposes only; the scope of the invention is not to be considered limited in any way thereby.

EXAMPLES

Unless otherwise stated, the following abbreviations have the stated meanings in the Examples below:

EDCI= 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

HOBT= 1-hydroxybenzotriazole

DCC= dicyclohexylcarbodiimide

Dibal-H= diisobutylaluminum hydride

LAH= lithium aluminum hydride

$NaBH(OAc)_3$= sodium triacetoxyborohydride

$NaBH_4$= sodium borohydride

$NaBH_3CN$= sodium cyanoborohydride

LDA= lithium diisopropylamide

p-TsOH= p-toluenesulfonic acid

m-CPBA= m-Chloroperbenzoic acid

TMAD= N,N,N',N'-tetramethylazodicarboxamide

CSA= camphorsulfonic acid

NaHMDS= sodium hexamethyl disilylazide

HRMS= High Resolution Mass Spectrometry

HPLC= High Performance Liquid Chromatography

LRMS= Low Resolution Mass Spectrometry

nM= nanomolar

Ki= Dissociation Constant for substrate/receptor complex

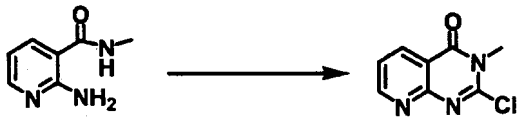
pA2= $-\log EC_{50}$, as defined by J. Hey, *Eur. J. Pharmacol.*, (1995), Vol. 294, 329-335.

Ci/mmol= Curie/mmol (a measure of specific activity)

Tr= Triphenylmethyl

Tris= Tris (hydroxymethyl)aminomethane

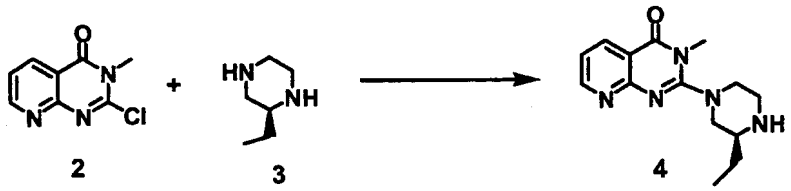
Example 1, Step A, Method A and Method B



1 2

A 500 ml round bottomed flask was charged with methyl 2-aminopyridine 3-carboxamide **1** (4.5 g, 29.76 mmol) and 1,2-dichloroethane (150 ml). The resulting solution was cooled to -40 °C while triphosgene (7 g, 23.59 mmol) was slowly added. Triethylamine (4.4 g, 43.48 mmol) was then added via a syringe dropwise at this temperature. The reaction mixture was stirred at -40 °C for two hours before warming up gradually to room temperature and maintained at this temperature overnight. The suspension was treated with water (100 ml) and saturated sodium carbonate (100 ml) and separated. The aqueous solution was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated on rotavapor. The residue was dried under house vacuum to provide a deep tan solid (4.1 g). This material was mixed with phosphorus oxychloride (50 ml) in a 250 ml flask. The resulting suspension was refluxed for 4 hours. The excess phosphorus oxychloride was removed by distillation under reduced pressure. The residue was dissolved in methylene dichloride (200 ml) and poured into ice (50 g). The suspension was neutralized with saturated sodium carbonate solution and separated. The organic layer was dried over sodium sulfate, concentrated, and dried under vacuum to afford a black gel (1.4 g), which was used directly for the next reaction without purification.

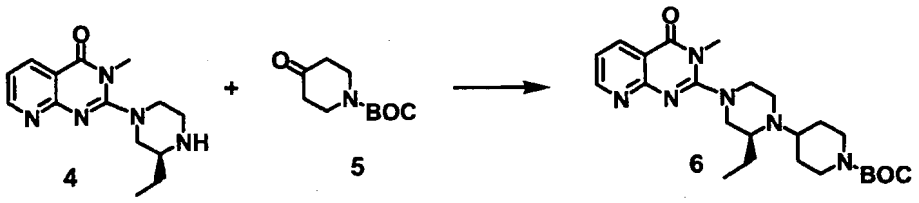
Example 2, Step B, Method A and Method B



2 3 4

A round bottomed flask was charged with crude **2** (1.4 g, ~7 mmol), 2-S-ethyl piperazine (prepared as per Williams et al J. Med. Chem **1996**, *39*, 1345; 80% active, 1.6 g, ~11 mmol), cesium carbonate (4.2 g, 12.9 mmol) and 1,4 dioxane (40 ml). The resulting suspension was stirred at room temperature for 5 days, diluted with methylene chloride (~ 200 ml), and filtered through celite. The filtrate was washed once with water and then concentrated to an oil. The crude product was purified by silica gel chromatography using a methanol/methylene chloride eluent (5% to 10% MeOH) to afford 0.7 g (9% from compound **1**) of the title compound.

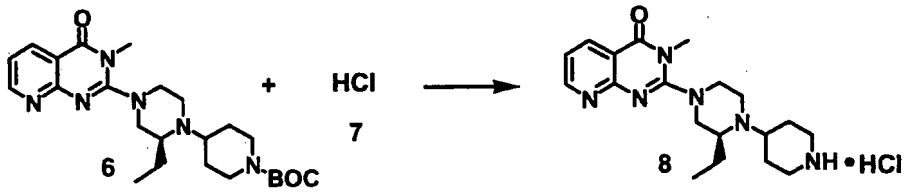
Example 3. Step D, Method A



4 5 6

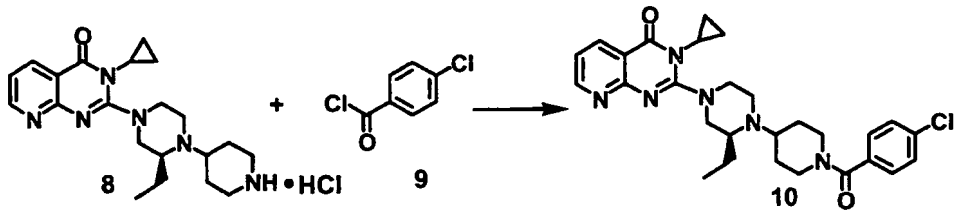
A 250 ml round-bottomed flask was charged with **4** (0.77g, 2.56 mmol), **5** (1.4 g, 7.03 mmol), sodium triacetoxyborohydride (1.4 g, 6.6 mmol), and 1,2-dichloroethane (100 ml). The resulting suspension was stirred at room temperature for 5 days, and then quenched with 1.0 M sodium hydroxide solution. After separation, the aqueous solution was extracted with dichloromethane. The combined organic solutions were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica flash chromatography using 5% methanol in dichloromethane as the eluent to afford the title compound as a gel (0.25 g, 21%).

Example 4. Step E, Method A



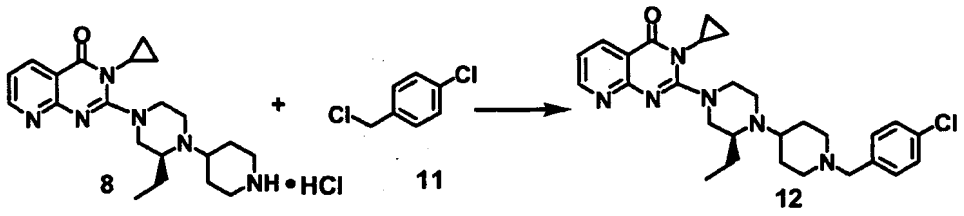
The starting materials **6** (250 mg, 0.548 mmol), hydrochloride (5 ml of 4.0 M in dioxane, 20 mmol), and methanol (15 ml) were charged in a 50 ml round-bottomed flask. The resulting solution was stirred at room temperature for 20 hours before concentrated under reduced pressure. The residue was dried under vacuum to provide a white solid as an HCl salt for the next reaction directly.

Example 5. Step F, Method A



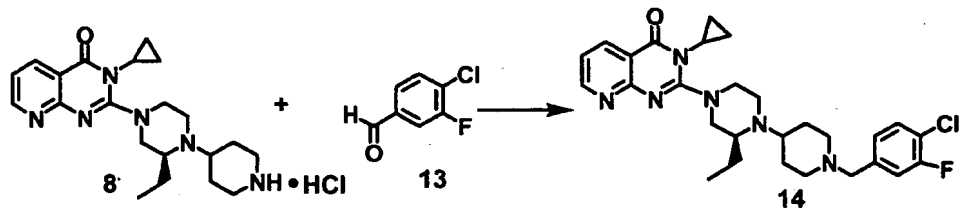
A mixture of **8** (17 mg, 0.044 mmol), 4-chlorobenzoyl chloride (20 mg, 0.11 mmol), triethylamine (0.2 ml, ~1.4 mmol), and dichloromethane (3 ml) was stirred at room temperature for 3 days. The reaction was then quenched with 1.0 M sodium hydroxide (1 ml), the organic layer separated. The aqueous solution was re-extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, concentrated in vacuo, and purified by silica preparative TLC (5% methanol in dichloromethane as the eluent) to afford the title compound as a wax (5 mg, 22%). MS [M+H]=522.1

Example 6. Step F, Method A



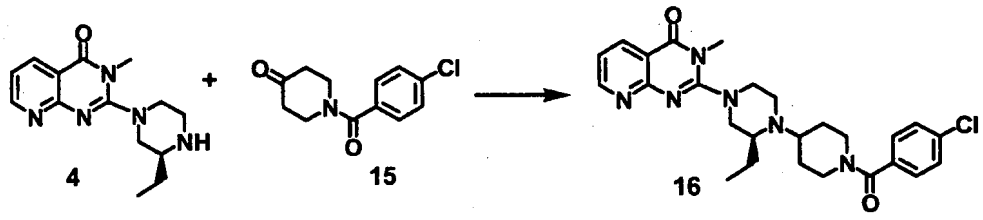
Starting materials **8** (20 mg, 0.048 mmol), 4-chlorobenzyl chloride (17 mg, 0.106 mmol), sodium iodide (10 mg, 0.067 mmol), triethylamine (0.3 ml, ~ 2.1 mmol), and DMF (3 ml) were added to a 25 ml round-bottomed flask. The suspension was stirred at room temperature for 2 days, diluted with ethyl acetate (10 ml), and washed with 1.0 M sodium hydroxide and water. The solution was dried with sodium sulfate, concentrated on vacuum, and purified by silica preparative TLC (5% methanol in dichloromethane as the eluent) to provide the title compound as a white foam (10 mg, 41%). MS [M+H]=508.1

Example 7. Step F, Method A



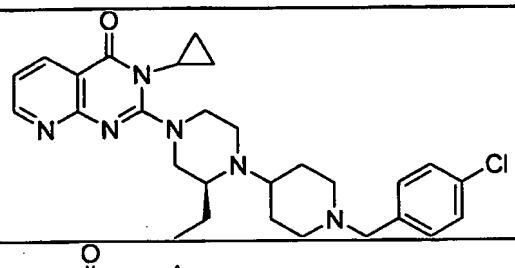
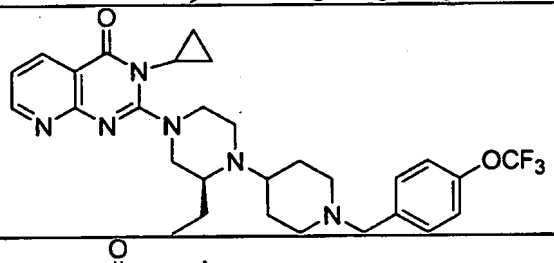
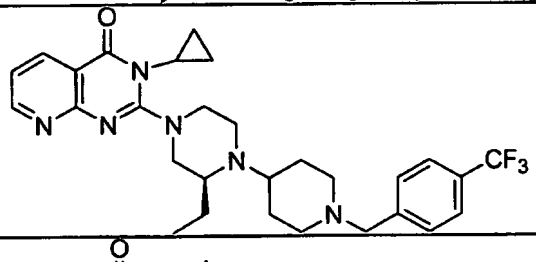
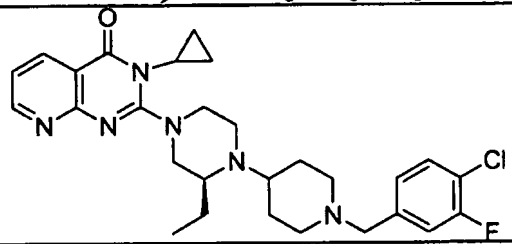
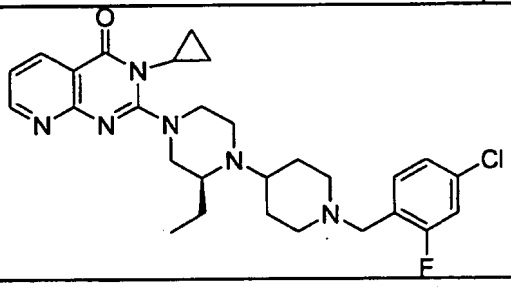
A 50 ml round-bottomed flask was charged with **8** (17 mg, 0.041 mmol), 4-chloro-3-fluorobenzaldehyde (28 mg, 0.17 mmol), sodium triacetoxyborohydride (30 mg, 0.145 mmol), triethylamine (0.3 ml, ~2.1 mmol), and 1,2-dichloromethane (5 ml). The suspension was stirred at room temperature for 20 hours, diluted with ethyl acetate (10 ml), and washed with 1.0 M sodium hydroxide and water. The solution was dried with sodium sulfate, concentrated on vacuum, and purified by silica preparative TLC (5% methanol in dichloromethane as the eluent) to provide the title compound as a white gel (7 mg, 33%). MS [M+H]=526.1

Example 8. Step D', Method B



A 25 ml round-bottomed flask was charged with **4** (38 mg, 0.14 mmol), **15** (50 mg, 0.21 mmol), sodium triacetoxyborohydride (46 mg, 0.22 mmol), and 1,2-dichloroethane (5 ml). The resulting suspension was stirred at room temperature for two days and then additional **4** (60 mg, 0.25 mmol) and sodium triacetoxy-borohydride (50 mg, 1.09 mmol) were added. The suspension was allowed to stir for two more days and a third batch of **4** (60 mg, 0.25 mmol) and sodium triacetoxyborohydride (50 mg, 1.09 mmol) were added. After stirring for an additional 3 days, the reaction mixture was treated with 1.0 M sodium hydroxide and the organic layer separated. The aqueous phase was extracted again with dichloromethane. The combined organic layers were dried with sodium sulfate and concentrated under reduced pressure. The residue was purified by silica flash chromatography using 3% methanol and 0.1% diethylamine in ethyl acetate as the eluent to afford the title compound as a white foam(21 mg, 31%). MS [M+H]=496.1

The Table below lists numerical IC_{50} values of some representative compounds of the present invention:

Compound Number	STRUCTURE	IC50 (nM)
12		1.9
13		2.8
14		5.6
15		1.8
17		2.5

Biological Examples:

The inventive compounds can readily be evaluated to determine activity at The CXCR3 receptors by known methods, such as, for example, Development of Human CXCR3 (N-delta 4) Binding Assay.

Cloning and expression of human CXCR3 (N-delta 4):

The DNA encoding human CXCR3 was cloned by PCR using human genomic DNA (Promega, Madison, WI) as a template. The PCR primers were designed based on the published sequence of human orphan receptor GPR9 (1) with incorporated restriction sites, a Kozak consensus sequence, CD8 leader and Flag tag. The PCR product was subcloned into the mammalian expression vector pME18Sneo, a derivative of the SR-alpha expression vector (designated as pME18Sneo-hCXCR3 (N-delta 4).

IL-3-dependent mouse pro-B cells Ba/F3 were transfected by electroporation in 0.4 ml Dulbecco's PBS containing 4 X 10^6 cells with 20 µg of pME18Sneo-hCXCR3 (N-delta 4) plasmid DNA. Cells were pulsed at 400 Volts, 100 OHMs, 960 µFd. The transfected cells were under selection with 1 mg/ml G418 (Life Technologies, Gaithersburg, MD). G418-resistant Ba/F3 clones were screened for CXCR3 expression by specific binding of [^{125}I] IP-10 (NEN Life Science Products, Boston, MA).

Preparation of Ba/F3-hCXCR3 (N-delta 4) membranes

Ba/F3 cells expressing human CXCR3 (N-delta 4) were pelleted and resuspended in the lysis buffer containing 10 mM HEPES , pH 7.5 and Complete® protease inhibitors (1 tablet per 100 ml) (Boehringer Mannheim, Indianapolis, IN) at a cell density of 20 x 10^6 cells per ml. After 5 minutes incubation on ice, cells were transferred to 4639 cell disruption bomb (Parr Instrument, Moline, IL) and applied with 1,500 psi of nitrogen for 30 minutes on ice. Large cellular debris was removed by centrifugation at 1,000 x g. Cell membrane in the supernatant was sedimented at 100,000 x g. The membrane was resuspended in the lysis buffer supplemented with 10% sucrose and stored at –80 °C. Total protein concentration of the membrane was determined by BCA method from Pierce (Rockford, IL).

Human CXCR3 (N-delta 4) scintillation proximity assay (SPA)

For each assay point, 2 µg of membrane was preincubated for 1 hr with 300 µg wheat germ agglutinin (WGA) coated SPA beads (Amersham, Arlington Heights, IL) in the binding buffer (50 mM HEPES, 1 mM $CaCl_2$, 5 mM $MgCl_2$, 125 mM NaCl, 0.002% NaN_3, 1.0% BSA) at room temperature. The beads were spun down, washed once, resuspended in the binding buffer and

transferred to a 96-well Isoplate (Wallac, Gaithersburg, MD). 25 pM of [^{125}I] IP-10 with tested compounds in a series of titration were added to start the reaction. After 3 hr reaction at room temperature, the amount of [^{125}I] IP-10 bound to the SPA beads was determined with a Wallac 1450 Microbeta counter.

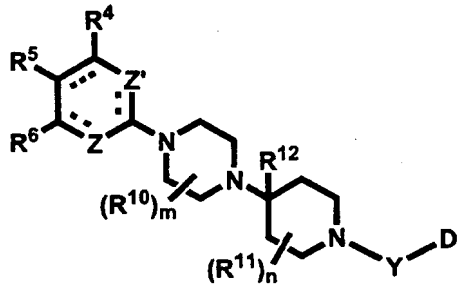
The Ki values for the various example compounds of the present invention are given in the afore-mentioned Table 1. From these values, it would be apparent to the skilled artisan that the compounds of the invention have excellent utility CXCR3 antagonists.

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

CLAIMS

What is claimed is:

1. A compound having the general structure shown in Formula 1



Formula 1

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

⎯⎯ represents a single or double bond, with the proviso that the ring comprising Z and Z' contains at least one double bond;

Z, and Z' are independently N, N(→O), NOH, or NR^3 ;

Each of R^4, R^5, and R^6 is independently selected from the group consisting of H, alkyl, alkylaryl, aralkyl, -CN, $-CF_3$, haloalkyl, cycloalkyl, halo, hydroxyalkyl, $-C(=O)N(R^{30})_2$, -C(=O)alkyl, $-OR^{30}$, $-NR^{30}S(=O)_2R^{31}$, $-N(R^{30})_2$, $-C(R^{14})(R^{15})XR^1R^2$, and G, with the proviso that R^4, R^5, and R^6 are not all simultaneously H;

or each of R^4, R^5, and R^6 taken together with the carbon atom to which they are shown attached, is independently is -(C=O);

or R^5 and R^6 together with the carbon atoms to which they are shown attached form an aryl or heteroaryl ring;

X is selected from the group consisting of N, O, alkyl, cycloalkyl, heteroaryl, heterocyclyl, and heterocyclenyl;

G is a 5-membered heteroaryl or heterocyclenyl containing at least one -C=N- moiety as part of said heteroaryl or heterocyclenyl, wherein said heteroaryl or heterocyclenyl optionally additionally contains in the ring (i.e., as ring moieties) one or more moieties which can be the same or different, each being independently selected from the group consisting of N, N(→O), O, S, S(=O) and $S(=O)_2$, further wherein each of said heteroaryl or heterocyclenyl

ring is optionally independently substituted on one or more ring carbon atoms with one or more R^9 substituents, or on one or more ring nitrogen atoms with one or more R^8 substituents, wherein said R^8 and R^9 substituents can be the same or different;

R^1 and R^2 are independently absent or present, and if present each is independently selected from the group consisting of H, alkyl, alkenyl, carbonyl, cycloalkyl, cycloalkenyl, alkylaryl, arylalkyl, aryl, amino, alkylamino, amidinyl, carboxamido, cyano, urea, -CN, -N≡CH, =NCN, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qN(R^{31})_2$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNHSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, -C(=S)N(H)alkyl, -N(H)-$S(O)_2$-alkyl, -N(H)C(=O)N(H)-alkyl, -$S(O)_2$alkyl, -$S(O)_2$N(H)alkyl, -$S(O)_2$N(alkyl)$_2$, -$S(O)_2$aryl, -C(=S)N(H)cycloalkyl, $-C(=O)N(H)NH_2$, -C(=O)alkyl, -heteroaryl, heterocyclyl, and heterocyclenyl; or alternatively when X is N, the N taken together with the R^1 and R^2 forms a heterocycyl, heteroaryl or $-N=C(NH_2)_2$;

R^3 is selected from the group consisting of H, alkyl, alkylaryl, aralkyl, $-CF_3$, haloalkyl, cycloalkyl, halo, hydroxy, hydroxyalkyl, $-C(=O)N(R^{30})_2$, and $-SO_2(R^{31})$;

the R^8 moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, arylalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qC(=O)OR^{31}$, and $-(CH_2)_qSO_2NHR^{31}$;

the R^9 moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, arylalkyl, amidinyl, aryl, cycloalkyl, cyano, heteroaryl, heterocyclyl, $-C(=O)N(R^{30})_2$, $-C(=S)N(R^{30})_2$, -C(=O)alkyl, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, $-N(R^{30})_2$, $-N(R^{30})S(O_2)R^{31}$, $-N(R^{30})C(=O)N(R^{30})_2$, -OH, $-OR^{30}$, $-SO_2(R^{31})$, $-SO_2N(R^{30})_2$, =O and =S;

the R^{10} moieties can be the same or different, each being independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl,

heterocyclenyl, heterocyclyl, alkylaryl, arylalkyl, $-CO_2H$, $-C(=O)N(R^{30})_2$, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, -OH, $-OR^{30}$, halogen, =O, and $-C(=O)R^{31}$;

the R^{11} moieties can be the same or different, each being independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, alkylaryl, arylalkyl, carboxamide, CO_2H, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, -OH, $-OR^{30}$, halogen, =O, and $-C(=O)R^{31}$;

R^{12} is selected from the group consisting of H, alkyl, -CN, $-C(=O)N(R^{30})_2$, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$ and $-S(=O)_2R^{31}$;

ring D is a five to nine membered cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl ring having 0-4 heteroatoms independently selected from O, S or N, wherein ring D is optionally substituted with 1-5 independently selected R^{20} moieties;

R^{14} and R^{15} are the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, heteroaryl, -CN, -OH, $-OR^{30}$, alkylamino, $-N(H)S(=O)_2$alkyl and –N(H)C(=O)N(H)alkyl; or alternatively R^{14} and R^{15} taken together is =O, =S, =NH, =N(alkyl), =N(Oalkyl), =N(OH) or cycloalkyl;

the R^{20} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, alkynyl, alkoxy, alkylamino, alkylthiocarboxy, alkylheteroaryl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, aminoalkyl, amidinyl, aralkyl, aralkenyl, aralkoxy, aralkoxycarbonyl, aralkylthio, aryl, aroyl, aryloxy, cyano, cycloalkyl, cycloalkenyl, formyl, guanidinyl, halo, hydroxyl, haloalkoxy, haloalkyl, heteroalkyl, heteroaryl, heterocyclyl, heterocyclenyl, hydroxyalkyl, hydroxamate, nitro, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, -alkynyl$C(R^{31})_2OR^{31}$, $-C(=O)R^{30}$, $-C(=O)N(R^{30})_2$, $-C(=NR^{30})NHR^{30}$, $-C(=NOH)N(R^{30})_2$, $-C(=NOR^{31})N(R^{30})_2$, $-C(=O)OR^{30}$, $-N(R^{30})_2$, $-N(R^{30})C(=O)R^{31}$, $-NHC(=O)N(R^{30})_2$, $-N(R^{30})C(=O)OR^{31}$, $-N(R^{30})C(=NCN)N(R^{30})_2$, $-N(R^{30})C(=O)N(R^{30})SO_2(R^{31})$, $-N(R^{30})C(=O)N(R^{30})_2$, $-NR^{30}S(=O)_2R^{31}$, $-N(R^{30})S(O)_2N(R^{30})_2$, $-OR^{30}$, $-OC(=O)N(R^{30})_2$, $-SR^{30}$, $-SO_2N(R^{30})_2$, $-SO_2(R^{31})$, $-OSO_2(R^{31})$, and $-OSi(R^{30})_3$; or alternatively two R^{20} moieties are linked

together to form a five or six membered aryl, cycloalkyl, heterocyclyl, heterocyclenyl, or heteroaryl ring wherein said five or six membered aryl, cycloalkyl, heterocyclyl, heterocyclenyl, or heteroaryl ring is fused to ring D and the fused ring is optionally substituted with 0-4 R^{21} moieties;

the R^{21} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, alkynyl, alkoxy, alkylamino, alkylthiocarboxy, alkylheteroaryl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, aminoalkyl, amidinyl, aralkyl, aralkenyl, aralkoxy, aralkoxycarbonyl, aralkylthio, aryl, aroyl, aryloxy, carboxamido, cyano, cycloalkyl, cycloalkenyl, formyl, guanidinyl, halogen, haloalkyl, haloalkoxy, heteroalkyl, heteroaryl, heterocyclyl, heterocyclenyl, hydroxyalkyl, hydroxamate, nitro, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, -alkynylC$(R^{31})_2OR^{31}$, $-C(=O)R^{30}$, $-C(=O)N(R^{30})_2$, $-C(=NR^{30})NHR^{30}$, $-C(=NOH)N(R^{30})_2$, $-C(=NOR^{31})N(R^{30})_2$, $-C(=O)OR^{30}$, $-N(R^{30})_2$, $-N(R^{30})C(=O)R^{31}$, $-NHC(=O)N(R^{30})_2$, $-N(R^{30})C(=O)OR^{31}$, $-N(R^{30})C(=NCN)N(R^{30})_2$, $-N(R^{30})C(=O)N(R^{30})SO_2(R^{31})$, $-N(R^{30})C(=O)N(R^{30})_2$, $-N(R^{30})SO_2(R^{31})$, $-N(R^{30})S(O)_2N(R^{30})_2$, $-OR^{30}$, $-OC(=O)N(R^{30})_2$, $-SR^{30}$, $-SO_2N(R^{30})_2$, $-SO_2(R^{31})$, $-OSO_2(R^{31})$, and $-OSi(R^{30})_3$;

Y is selected from the group consisting of a covalent bond, $-(CR^{13}R^{13})_r-$, $-CHR^{13}C(=O)-$, $-(CHR^{13})_rO-$, $-(CHR^{13})_rN(R^{30})-$, $-C(=O)-$, $-C(=NR^{30})-$, $-C(=N-OR^{30})-$, $-CH(C(=O)NHR^{30})-$, CH-heteroaryl-, $-C(R^{13}R^{13})_rC(R^{13})=C(R^{13})-$, $-(CHR^{13})_rC(=O)-$ and $-(CHR^{13})_rN(H)C(=O)-$; or alternatively Y is cycloalkyl, heterocyclenyl, or heterocyclyl wherein the cycloalkyl, heterocyclenyl, or heterocyclyl is fused with ring D;

the R^{13} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, cycloalkyl, alkoxy, aryl, heteroaryl, heterocyclenyl, heterocyclyl, spiroalkyl, -CN, $-CO_2H$, $-C(=O)R^{30}$, $-C(=O)N(R^{30})_2$, $-(CHR^{30})_qOH$, $-(CHR^{30})_qOR^{31}$, $-(CHR^{30})_qNH_2$, $-(CH\ R^{30})_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, $-NH_2$, $-N(R^{30})_2$, $-N(R^{30})C(=O)N(R^{30})_2$, $-N(R^{30})SO_2(R^{31})$, -OH, OR^{30}, $-SO_2N(R^{30})_2$, and $-SO_2(R^{31})$;

the R^{30} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, aryl, aralkyl, cycloalkyl, CN, $-(CH_2)_qOH$, $-(CH_2)_qOalkyl$, $-(CH_2)_qOalkylaryl$, $-(CH_2)_qOaryl$, $-(CH_2)_qOaralkyl$, $-(CH_2)_qOcycloalkyl$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHalkyl$, $-(CH_2)_qN(alkyl)_2$, $-(CH_2)_qNHalkylaryl$, $-(CH_2)_qNHaryl$, $-(CH_2)_qNHaralkyl$, $-(CH_2)_qNHcycloalkyl$, $-(CH_2)_qC(=O)NHalkyl$, $-(CH_2)_qC(=O)N(alkyl)_2$, $-(CH_2)_qC(=O)NHalkylaryl$, $-(CH_2)_qC(=O)NHaryl$, $-(CH_2)_qC(=O)NHaralkyl$, $-(CH_2)_qC(=O)NHcycloalkyl$, $-(CH_2)_qSO_2alkyl$, $-(CH_2)_qSO_2alkylaryl$, $-(CH_2)_qSO_2aryl$, $-(CH_2)_qSO_2aralkyl$, $-(CH_2)_qSO_2cycloalkyl$, $-(CH_2)_qNSO_2alkyl$, $-(CH_2)_qNSO_2alkylaryl$, $-(CH_2)_qNSO_2aryl$, $-(CH_2)_qNSO_2aralkyl$, $-(CH_2)_qNSO_2cycloalkyl$, $-(CH_2)_qSO_2NHalkyl$, $-(CH_2)_qSO_2NHalkylaryl$, $-(CH_2)_qSO_2NHaryl$, $-(CH_2)_qSO_2NHaralkyl$, $-(CH_2)_qSO_2NHcycloalkyl$, heterocyclenyl, heterocyclyl, and heteroaryl;

the R^{31} moieties can be the same or different, each being independently selected from the group consisting of alkyl, alkylaryl, aryl, aralkyl, cycloalkyl, $-(CH_2)_qOH$, $-(CH_2)_qOalkyl$, $-(CH_2)_qOalkylaryl$, $-(CH_2)_qOaryl$, $-(CH_2)_qOaralkyl$, $-(CH_2)_qOcycloalkyl$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHalkyl$, $-(CH_2)_qN(alkyl)_2$, $-(CH_2)_qNHalkylaryl$, $-(CH_2)_qNHaryl$, $-(CH_2)_qNHaralkyl$, $-(CH_2)_qNHcycloalkyl$, $-(CH_2)_qC(=O)NHalkyl$, $-(CH_2)_qC(=O)N(alkyl)_2$, $-(CH_2)_qC(=O)NHalkylaryl$, $-(CH_2)_qC(=O)NHaryl$, $-(CH_2)_qC(=O)NHaralkyl$, $-(CH_2)_qC(=O)NHcycloalkyl$, $-(CH_2)_qSO_2alkyl$, $-(CH_2)_qSO_2alkylaryl$, $-(CH_2)_qSO_2aryl$, $-(CH_2)_qSO_2aralkyl$, $-(CH_2)_qSO_2cycloalkyl$, $-(CH_2)_qNSO_2alkyl$, $-(CH_2)_qNSO_2alkylaryl$, $-(CH_2)_qNSO_2aryl$, $-(CH_2)_qNSO_2aralkyl$, $-(CH_2)_qNSO_2cycloalkyl$, $-(CH_2)_qSO_2NHalkyl$, $-(CH_2)_qSO_2NHalkylaryl$, $-(CH_2)_qSO_2NHaryl$, $-(CH_2)_qSO_2NHaralkyl$, $-(CH_2)_qSO_2NHcycloalkyl$, heterocyclenyl, heterocyclyl, and heteroaryl;

m is 0 to 4;

n is 0 to 4;

each q can be the same or different, each being independently selected from 1 to 5; and

r is 1 to 4;

with the proviso that there are no two adjacent double bonds in any ring, and that when a nitrogen is substituted by two alkyl groups, said two alkyl groups may be optionally joined to each other to form a ring.

2. The compound according to Claim 1, wherein Z and Z' are independently N or NR^3.

3. The compound according to Claim 2, wherein Z is N, and Z' is N or NR^3.

4. The compound according to any one of Claims 1, 2, or 3, wherein R^3 is alkyl, cycloalkyl, aralkyl, or heterocyclyl.

5. The compound according to Claim 4, wherein R^3 is methyl or cyclopropyl.

6. The compound according to any one of Claims 1-4, wherein R^4 is selected from the group consisting of H, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and $-C(=O)N(R^{30})_2$, wherein each R^{30} independently is H or alkyl, or wherein R^4 together with the carbon atom to which it is shown attached is -C(=O)-.

7. The compound of Claim 6, wherein R^4 is selected from the group consisting of H, F, Cl, alkyl, CF_3, -Oalkyl, $-OCF_3$, and -C(=O)N(H)alkyl ; or wherein R^4 together with the carbon atom to which it is shown attached is –C(=O).

8. The compound of Claim 7, wherein R^4 is selected from the group consisting of H, Cl, CF_3, and -C(=O)N(H)alkyl; or wherein R^4 together with the carbon atom to which it is shown attached is –C(=O).

9. The compound according to any one of Claims 1-8, wherein R^5 and R^6 independently are selected from the group consisting of H, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, $-C(=O)N(R^{30})_2$ and G, wherein each R^{30} independently is H or alkyl, or wherein R^5 and R^6 together with the carbon atoms to which they are shown attached are aryl or heteroaryl.

10. A compound according to Claim 9, wherein R^5 and R^6 independently are selected from the group consisting of H, F, $-CH_3$, $-CF_3$, -OH, $-OCH_3$, $-OCF_3$, $-C(=O)NHCH_2$-aryl, oxazole, thiazole, and oxadiazole, wherein the "aryl" part of $-C(=O)NHCH_2$-aryl, and each of said oxazole, thiazole and oxadiazole are optionally substituted; or wherein R^5 and R^6 together with the

carbon atoms to which they are shown attached are pyridyl or imidazolyl, each of which is optionally substituted.

11. A compound according to Claim 10, wherein R^5 and R^6 independently are selected from the group consisting of H, $-CH_3$, $-CF_3$, and $-C(=O)NHCH_2$-aryl, wherein said aryl is optionally substituted; or wherein R^5 and R^6 together with the carbon atoms to which they are shown attached are pyridyl or imidazolyl, each of which is optionally substituted.

12. The compound according to any one of Claims 1-11, wherein m is 1.

13. The compound according to any of Claims 1-12, wherein R^{10} is alkyl.

14. The compound according to Claim 13, wherein R^{10} is methyl or ethyl.

15. The compound according to any one of Claims 1-14, wherein n is zero.

16. The compound according to any one of Claims 1-15, wherein R^{12} is H.

17. The compound according to any one of Claims 1-16, wherein Y is selected from the group consisting of $-(CR^{13}R^{13})_r-$ and $-C(=O)-$.

18. The compound according to Claim 17, wherein Y is $-CH_2-$ or $-C(=O)-$.

19. The compound according to any one of Claims 1-18, wherein ring D is a five to nine membered aryl or heteroaryl ring having 1 to 2 N atoms, wherein said ring D is optionally substituted with 1 to 5 R^{20} moieties independently selected from the group consisting of halo, cyano, alkyl, hydroxy, haloalkyl, alkoxy, haloalkoxy, $-C(=O)N(R^{30})_2$, $-NR^{30}S(=O)_2R^{31}$, and $-N(R^{30})_2$.

20. The compound according to Claim 19, wherein ring D is phenyl or pyridyl, wherein ring D is optionally substituted with 1 to 2 R^{20} moieties independently selected from the group consisting of F, Cl, -CN, -OH, alkyl, $-CF_3$, -Oalkyl, $-OCF_3$, $-C(=O)NH$alkyl, $-NH_2$, and $-NHS(=O)_2$alkyl.

21. The compound according to Claim 20, wherein ring D is phenyl or pyridyl, wherein ring D is optionally substituted with 1-2 R^{20} moieties independently selected from the group consisting of F, Cl, -CN, $-CF_3$, $-OCF_3$, and $-NH_2$.

22. The compound according to Claim 1, wherein:

Z is N, and Z' is N or NR^3;

R^3 is alkyl or cycloalkyl;

R^4 is selected from the group consisting of H, halo, haloalkyl, and $-C(=O)N(R^{30})_2$, wherein each R^{30} independently is H or alkyl, or wherein R^4 together with the carbon atom to which it is shown attached is -C(=O)-;

R^5 and R^6 independently are selected from the group consisting of H, alkyl, haloalkyl, $-C(=O)N(R^{30})_2$ and G, wherein each R^{30} independently is H or alkyl , or wherein R^5 and R^6 together with the carbon atoms to which they are shown attached are heteroaryl;

R^{10} is alkyl;

m is 1;

n is zero;

R^{12} is H;

Y is selected from the group consisting of $-(CR^{13}R^{13})_r-$ and -C(=O)-;

ring D is a five to nine membered aryl or heteroaryl ring having 1-2 N atoms, wherein said ring D is unsubstituted or substituted with 1-5 R^{20} moieties independently selected from the group consisting of halo, cyano, alkyl, hydroxy, haloalkyl, alkoxy, haloalkoxy, $-C(=O)N(R^{30})_2$, $-NR^{30}S(=O)_2R^{31}$, and $-N(R^{30})_2$.

23. The compound according to Claim 22, wherein:

R^3 is alkyl or cycloalkyl;

R^4 is selected from the group consisting of H, F, Cl, alkyl, CF_3, -Oalkyl, $-OCF_3$, and -C(=O)NHalkyl ; or wherein R^4 together with the carbon atom to which it is shown attached is –C(=O);

R^5 and R^6 independently are selected from the group consisting of H, F, -alkyl, $-CF_3$, -OH, -Oalkyl, $-OCF_3$, $-C(=O)NHCH_2$-aryl, and G; wherein said aryl is optionally substituted; or wherein R^5 and R^6 together with the carbon atoms to which they are shown attached are pyridyl or imidazolyl, each of which is optionally substituted;

R^{10} is alkyl;

Y is $-CH_2-$ or -C(=O)-; and

ring D is phenyl or pyridyl, wherein ring D is ring D is phenyl or pyridyl, wherein ring D is optionally substituted with 1-2 R^{20} moieties independently

selected from the group consisting of F, Cl, -CN, -OH, alkyl, CF_3, -Oalkyl, -OCF_3, -C(=O)NHalkyl, $-NH_2$, and $-NHS(=O)_2$alkyl.

24. The compound according to Claim 23, wherein:

R^3 is methyl or cyclopropyl;

R^4 is selected from the group consisting of H, Cl, $-CF_3$, and -C(=O)NHalkyl ; or wherein R^4 together with the carbon atom to which it is shown attached is –C(=O);

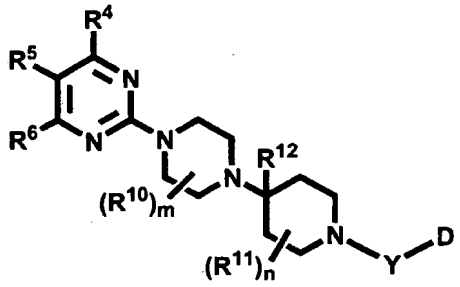
R^5 and R^6 independently are selected from the group consisting of H, alkyl, $-CF_3$, $-C(=O)NHCH_2$-aryl, oxazole, thiazole, and oxadiazole, wherein each of said aryl, oxazole, thiazole and oxadiazole is optionally substituted; or wherein R^5 and R^6 together with the carbon atoms to which they are shown attached are pyridyl or imidazolyl, each of which is optionally substituted;

R^{10} is alkyl;

Y is $-CH_2-$ or -C(=O)-; and

ring D is phenyl or pyridyl, wherein ring D is optionally substituted with 1-2 R^{20} moieties independently selected from the group consisting of F, Cl, CH_3, -CN, $-CF_3$, $-OCF_3$, and $-NH_2$.

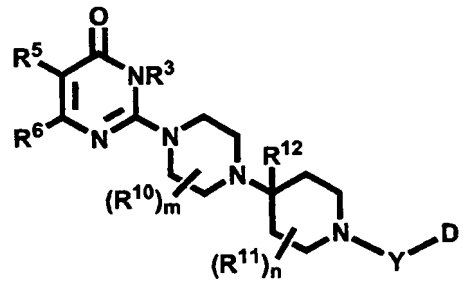
25. The compound according to any one of Claims 1, 23, and 24, wherein said compound is represented by structural formula 2 :



Formula 2

or a pharmaceutically acceptable salt, solvate, or ester thereof.

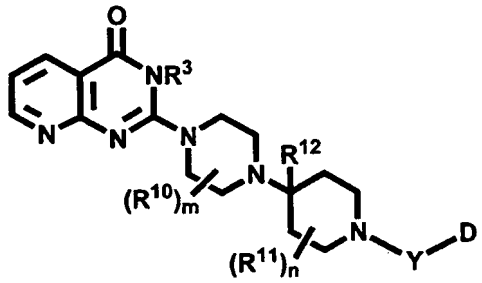
26. The compound according to any one of Claims 1, 23, and 24, wherein said compound is represented by structural formula 3:



Formula 3

or a pharmaceutically acceptable salt, solvate, or ester thereof.

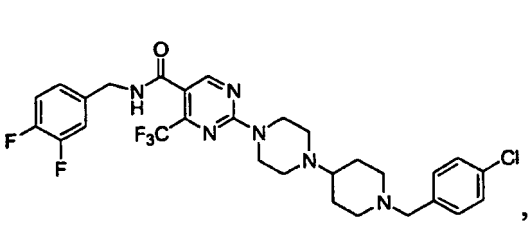
27. The compound according to Claim 26, wherein Formula (IV) is represented by Formula 4:



Formula 4

or a pharmaceutically acceptable salt, solvate, or ester thereof.

28. The compound according to any one of Claims 1, and 23-25, selected from the group consisting of :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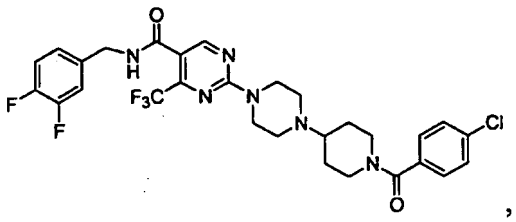
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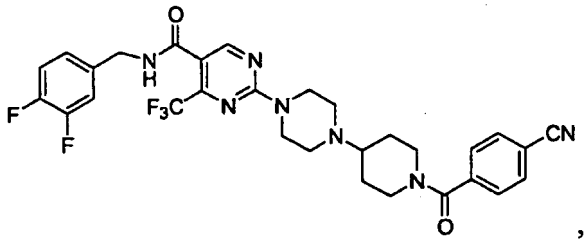
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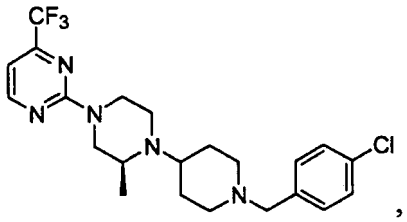
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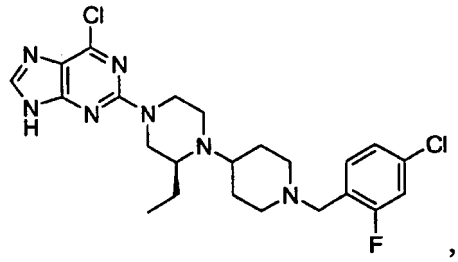
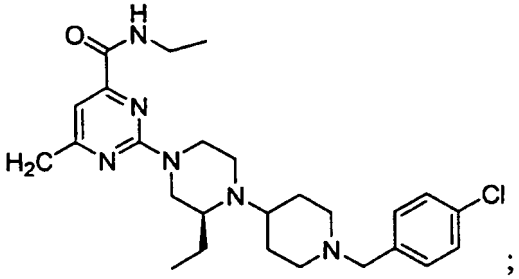
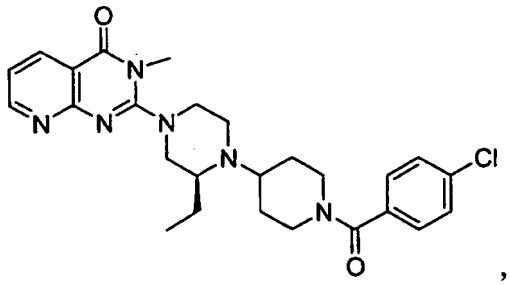

, and

;

or a pharmaceutically acceptable salt or solvate thereof.

29. The compound according to any one of Claims 1, and 26-27, selected from the group consisting of :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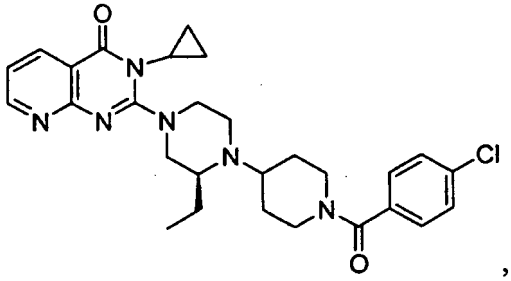
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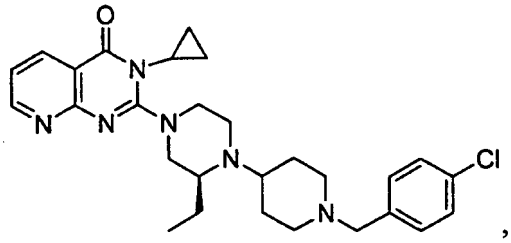
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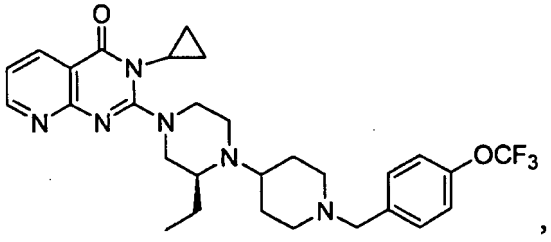
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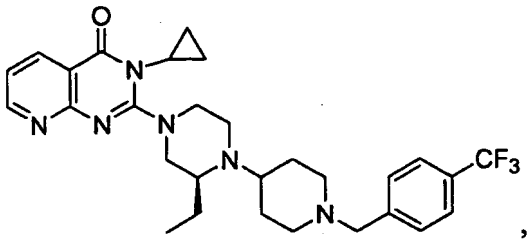
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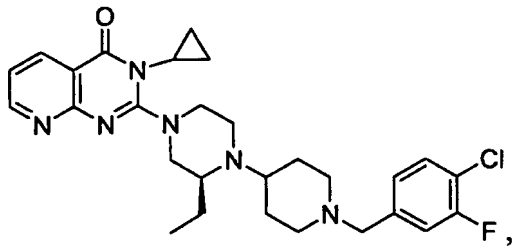
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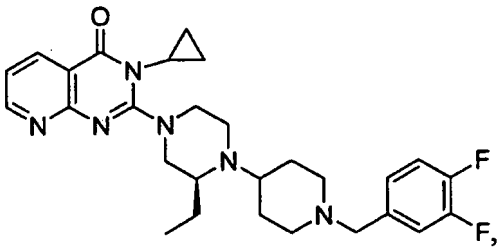
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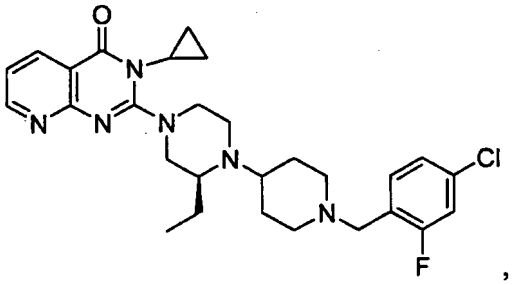
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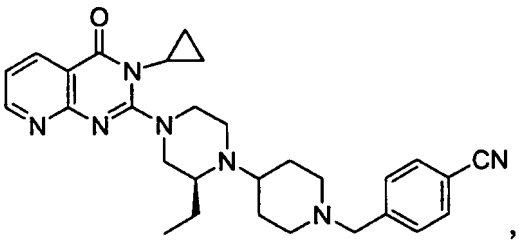
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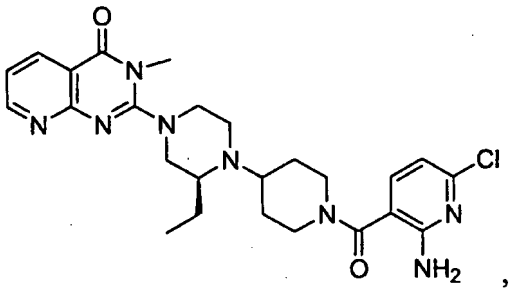
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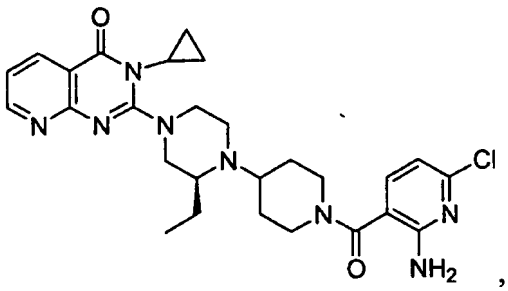
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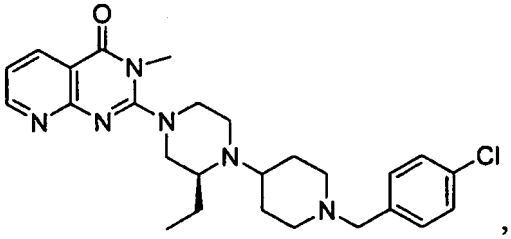
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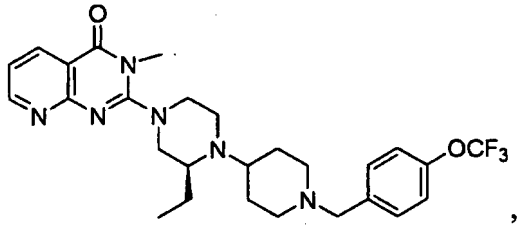
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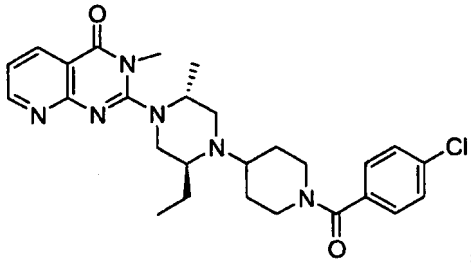
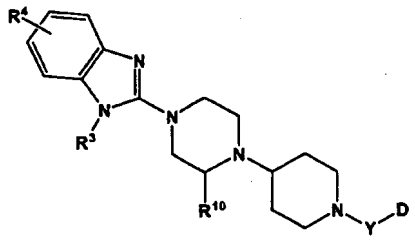

;

or a pharmaceutically acceptable salt or solvate thereof.

30. A compound of the formula 5



Formula 5

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

R^3 is selected from the group consisting of H, alkyl, alkylaryl, aralkyl, $-CF_3$, haloalkyl, cycloalkyl, halo, hydroxy, hydroxyalkyl, $-C(=O)N(R^{30})_2$, and $-SO_2(R^{31})$;

R^4 is selected from the group consisting of H, alkyl, alkylaryl, aralkyl, -CN, CF_3, haloalkyl, cycloalkyl, halo, hydroxyalkyl, $-C(=O)N(R^{30})_2$, -C(=O)alkyl, $-OR^{30}$, $-NR^{30}S(=O)_2R^{31}$, $-N(R^{30})_2$, $-C(R^{14})(R^{15})-XR^1R^2$, and G;

X is selected from the group consisting of N, O, alkyl, cycloalkyl, heteroaryl, heterocyclyl, and heterocyclenyl;

G is a 5-membered heteroaryl or heterocyclenyl containing at least one -C=N- moiety as part of said heteroaryl or heterocyclenyl, wherein said heteroaryl or heterocyclenyl optionally additionally contains in the ring (i.e., as ring moieties) one or more moieties which can be the same or different, each being independently selected from the group consisting of N, N(→O), O, S, S(=O) and $S(=O)_2$, further wherein each of said heteroaryl or heterocyclenyl ring is optionally independently substituted on one or more ring carbon atoms with one or more R^9 substituents, or on one or more ring nitrogen atoms with one or more R^8 substituents, wherein said R^8 and R^9 substituents can be the same or different;

R^1 and R^2 are independently absent or present, and if present each is independently selected from the group consisting of H, alkyl, alkenyl, carbonyl, cycloalkyl, cycloalkenyl, alkylaryl, arylalkyl, aryl, amino, alkylamino, amidinyl, carboxamido, cyano, urea, -CN, -(+)N≡CH, =NCN, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qN(R^{31})_2$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNHSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, -C(=S)N(H)alkyl, -N(H)-$S(O)_2$-alkyl, -N(H)C(=O)N(H)-alkyl, $-S(O)_2$alkyl, $-S(O)_2N(H)$alkyl, $-S(O)_2N(alkyl)_2$,

-$S(O)_2$aryl, -C(=S)N(H)cycloalkyl, -C(=O)N(H)NH_2, -C(=O)alkyl, -heteroaryl, heterocyclyl, and heterocyclenyl; or alternatively when X is N, the N taken together with the R^1 and R^2 forms a heterocycyl, heteroaryl or -N=C$(NH_2)_2$;

the R^8 moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, arylalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, -$(CH_2)_q$OH, -$(CH_2)_q$$OR^{31}$, -$(CH_2)_q$$NH_2$, -$(CH_2)_q$$NHR^{31}$, -$(CH_2)_q$C(=O)$NHR^{31}$, -$(CH_2)_q$$SO_2R^{31}$, -$(CH_2)_q$$NSO_2R^{31}$, -$(CH_2)_q$C(=O)$OR^{31}$, and -$(CH_2)_q$$SO_2NHR^{31}$;

the R^9 moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, arylalkyl, amidinyl, aryl, cycloalkyl, cyano, heteroaryl, heterocyclyl, -C(=O)N$(R^{30})_2$, -C(=S)N$(R^{30})_2$, -C(=O)alkyl, -$(CH_2)_q$OH, -$(CH_2)_q$$OR^{31}$, -$(CH_2)_q$$NH_2$, -$(CH_2)_q$$NHR^{31}$, -$(CH_2)_q$C(=O)$NHR^{31}$, -$(CH_2)_q$$SO_2R^{31}$, -$(CH_2)_q$$NSO_2R^{31}$, -$(CH_2)_q$$SO_2NHR^{31}$, -N$(R^{30})_2$, -N$(R^{30})$$S(O_2)R^{31}$, -N$(R^{30})$ C(=O)N$(R^{30})_2$, -OH, -OR^{30}, -$SO_2(R^{31})$, -$SO_2N(R^{30})_2$, =O and =S;

R^{10} is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, heterocyclenyl, heterocyclyl, alkylaryl, arylalkyl, -CO_2H, -C(=O)N$(R^{30})_2$, -$(CH_2)_q$OH, -$(CH_2)_q$$OR^{31}$, -OH, -$OR^{30}$, halogen, =O, and -C(=O)R^{31};

ring D is a five to nine membered cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclenyl or heterocyclyl ring having 0-4 heteroatoms independently selected from O, S or N, wherein ring D is optionally substituted with 1-5 independently selected R^{20} moieties;

R^{14} and R^{15} are the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, heteroaryl, -CN, -OH, -OR^{30}, alkylamino, -N(H)S(=O)$_2$alkyl and –N(H)C(=O)N(H)alkyl; or alternatively R^{14} and R^{15} taken together is =O, =S, =NH, =N(alkyl), =N(Oalkyl), =N(OH) or cycloalkyl;

the R^{20} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, alkynyl, alkoxy, alkylamino, alkylthiocarboxy, alkylheteroaryl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, aminoalkyl, amidinyl, aralkyl, aralkenyl, aralkoxy,

aralkoxycarbonyl, aralkylthio, aryl, aroyl, aryloxy, cyano, cycloalkyl, cycloalkenyl, formyl, guanidinyl, halo, haloalkoxy, haloalkyl, heteroalkyl, heteroaryl, heterocyclyl, heterocyclenyl, hydroxyalkyl, hydroxamate, nitro, -$(CH_2)_qOH$, -$(CH_2)_qOR^{31}$, -$(CH_2)_qNH_2$, -$(CH_2)_qNHR^{31}$, -$(CH_2)_qC(=O)NHR^{31}$, -$(CH_2)_qSO_2R^{31}$, -$(CH_2)_qNSO_2R^{31}$, -$(CH_2)_qSO_2NHR^{31}$, -alkynyl$C(R^{31})_2OR^{31}$, -$C(=O)R^{30}$, -$C(=O)N(R^{30})_2$, -$C(=NR^{30})NHR^{30}$, -$C(=NOH)N(R^{30})_2$, -$C(=NOR^{31})N(R^{30})_2$, -$C(=O)OR^{30}$, -$N(R^{30})_2$, -$N(R^{30})C(=O)R^{31}$, -$NHC(=O)N(R^{30})_2$, -$N(R^{30})C(=O)OR^{31}$, -$N(R^{30})C(=NCN)N(R^{30})_2$, -$N(R^{30})C(=O)N(R^{30})SO_2(R^{31})$, -$N(R^{30})C(=O)N(R^{30})_2$, -$N(R^{30})SO_2(R^{31})$, -$N(R^{30})S(O)_2N(R^{30})_2$, -$OR^{30}$, -$OC(=O)N(R^{30})_2$, -$SR^{30}$, -$SO_2N(R^{30})_2$, -$SO_2(R^{31})$, -$OSO_2(R^{31})$, and -$OSi(R^{30})_3$; or alternatively two R^{20} moieties are linked together to form a five or six membered aryl, cycloalkyl, heterocyclyl, heterocyclenyl, or heteroaryl ring wherein said five or six membered aryl, cycloalkyl, heterocyclyl, heterocyclenyl, or heteroaryl ring is fused to ring D and the fused ring is optionally substituted with 0-4 R^{21} moieties;

the R^{21} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkenyl, alkylaryl, alkynyl, alkoxy, alkylamino, alkylthiocarboxy, alkylheteroaryl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, aminoalkyl, amidinyl, aralkyl, aralkenyl, aralkoxy, aralkoxycarbonyl, aralkylthio, aryl, aroyl, aryloxy, carboxamido, cyano, cycloalkyl, cycloalkenyl, formyl, guanidinyl, halogen, haloalkyl, haloalkoxy, heteroalkyl, heteroaryl, heterocyclyl, heterocyclenyl, hydroxyalkyl, hydroxamate, nitro, -$(CH_2)_qOH$, -$(CH_2)_qOR^{31}$, -$(CH_2)_qNH_2$, -$(CH_2)_qNHR^{31}$, -$(CH_2)_qC(=O)NHR^{31}$, -$(CH_2)_qSO_2R^{31}$, -$(CH_2)_qNSO_2R^{31}$, -$(CH_2)_qSO_2NHR^{31}$, -alkynyl$C(R^{31})_2OR^{31}$, -$C(=O)R^{30}$, -$C(=O)N(R^{30})_2$, -$C(=NR^{30})NHR^{30}$, -$C(=NOH)N(R^{30})_2$, -$C(=NOR^{31})N(R^{30})_2$, -$C(=O)OR^{30}$, -$N(R^{30})_2$, -$N(R^{30})C(=O)R^{31}$, -$NHC(=O)N(R^{30})_2$, -$N(R^{30})C(=O)OR^{31}$, -$N(R^{30})C(=NCN)N(R^{30})_2$, -$N(R^{30})C(=O)N(R^{30})SO_2(R^{31})$, -$N(R^{30})C(=O)N(R^{30})_2$, -$N(R^{30})SO_2(R^{31})$, -$N(R^{30})S(O)_2N(R^{30})_2$, -$OR^{30}$, -$OC(=O)N(R^{30})_2$, -$SR^{30}$, -$SO_2N(R^{30})_2$, -$SO_2(R^{31})$, -$OSO_2(R^{31})$, and -$OSi(R^{30})_3$;

Y is selected from the group consisting of a covalent bond, -$(CR^{13}R^{13})_r$-, -$CHR^{13}C(=O)$-, -$(CHR^{13})_rO$-, -$(CHR^{13})_rN(R^{30})$-, -$C(=O)$-, -$C(=NR^{30})$-, -C(=N-

OR^{30})-, -CH(C(=O)NHR^{30})-, CH-heteroaryl-, -C($R^{13}R^{13}$)$_r$C(R^{13})=C(R^{13})-, -(CHR^{13})$_r$C(=O)- and -(CHR^{13})$_r$N(H)C(=O)-; or alternatively Y is cycloalkyl, heterocyclenyl, or heterocyclyl wherein the cycloalkyl, heterocyclenyl, or heterocyclyl is fused with ring D;

the R^{30} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, aryl, aralkyl, cycloalkyl, CN, -$(CH_2)_q$OH, -$(CH_2)_q$Oalkyl, -$(CH_2)_q$Oalkylaryl, -$(CH_2)_q$Oaryl, -$(CH_2)_q$Oaralkyl, -$(CH_2)_q$Ocycloalkyl, -$(CH_2)_q$NH$_2$, -$(CH_2)_q$NHalkyl, -$(CH_2)_q$N(alkyl)$_2$, -$(CH_2)_q$NHalkylaryl, -$(CH_2)_q$NHaryl, -$(CH_2)_q$NHaralkyl, -$(CH_2)_q$NHcycloalkyl, -$(CH_2)_q$C(=O)NHalkyl, -$(CH_2)_q$C(=O)N(alkyl)$_2$, -$(CH_2)_q$C(=O)NHalkylaryl, -$(CH_2)_q$C(=O)NHaryl, -$(CH_2)_q$C(=O)NHaralkyl, -$(CH_2)_q$C(=O)NHcycloalkyl, -$(CH_2)_q$SO$_2$alkyl, -$(CH_2)_q$SO$_2$alkylaryl, -$(CH_2)_q$SO$_2$aryl, -$(CH_2)_q$SO$_2$aralkyl, -$(CH_2)_q$SO$_2$cycloalkyl, -$(CH_2)_q$NSO$_2$alkyl, -$(CH_2)_q$NSO$_2$alkylaryl, -$(CH_2)_q$NSO$_2$aryl, -$(CH_2)_q$NSO$_2$aralkyl, -$(CH_2)_q$NSO$_2$cycloalkyl, -$(CH_2)_q$SO$_2$NHalkyl, -$(CH_2)_q$SO$_2$NHalkylaryl, -$(CH_2)_q$SO$_2$NHaryl, -$(CH_2)_q$SO$_2$NHaralkyl, -$(CH_2)_q$SO$_2$NHcycloalkyl, heterocyclenyl, heterocyclyl, and heteroaryl;

the R^{31} moieties can be the same or different, each being independently selected from the group consisting of alkyl, alkylaryl, aryl, aralkyl, cycloalkyl, -$(CH_2)_q$OH, -$(CH_2)_q$Oalkyl, -$(CH_2)_q$Oalkylaryl, -$(CH_2)_q$Oaryl, -$(CH_2)_q$Oaralkyl, -$(CH_2)_q$Ocycloalkyl, -$(CH_2)_q$NH$_2$, -$(CH_2)_q$NHalkyl, -$(CH_2)_q$N(alkyl)$_2$, -$(CH_2)_q$NHalkylaryl, -$(CH_2)_q$NHaryl, -$(CH_2)_q$NHaralkyl, -$(CH_2)_q$NHcycloalkyl, -$(CH_2)_q$C(=O)NHalkyl, -$(CH_2)_q$C(=O)N(alkyl)$_2$, -$(CH_2)_q$C(=O)NHalkylaryl, -$(CH_2)_q$C(=O)NHaryl, -$(CH_2)_q$C(=O)NHaralkyl, -$(CH_2)_q$C(=O)NHcycloalkyl, -$(CH_2)_q$SO$_2$alkyl, -$(CH_2)_q$SO$_2$alkylaryl, -$(CH_2)_q$SO$_2$aryl, -$(CH_2)_q$SO$_2$aralkyl, -$(CH_2)_q$SO$_2$cycloalkyl, -$(CH_2)_q$NSO$_2$alkyl, -$(CH_2)_q$NSO$_2$alkylaryl, -$(CH_2)_q$NSO$_2$aryl, -$(CH_2)_q$NSO$_2$aralkyl, -$(CH_2)_q$NSO$_2$cycloalkyl, -$(CH_2)_q$SO$_2$NHalkyl, -$(CH_2)_q$SO$_2$NHalkylaryl, -$(CH_2)_q$SO$_2$NHaryl, -$(CH_2)_q$SO$_2$NHaralkyl, -$(CH_2)_q$SO$_2$NHcycloalkyl, heterocyclenyl, heterocyclyl, and heteroaryl;

each q can be the same or different, each being independently selected from 1 to 5; and

r is 1 to 4;

with the proviso that there are no two adjacent double bonds in any ring, and that when a nitrogen is substituted by two alkyl groups, said two alkyl groups may be optionally joined to each other to form a ring.

31. The compound according to Claim 30, wherein R^3 is alkyl, cycloalkyl, aralkyl, or heterocyclyl.

32. The compound according to Claim 31, wherein R^3 is methyl or cyclopropyl.

33. The compound according to any one of Claims 30-32, wherein R^4 is selected from the group consisting of H, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and $-C(=O)N(R^{30})_2$, wherein each R^{30} independently is H or alkyl, or wherein R^4 together with the carbon atom to which it is attached is -C(=O)-.

34. The compound according to Claim 33, wherein R^4 is selected from the group consisting of H, F, Cl, alkyl, CF_3, -Oalkyl, $-OCF_3$, and -C(=O)NHalkyl; or wherein R^4 together with the carbon atom to which it is shown attached is –C(=O).

35. The compound according to any one of Claims 30-32, wherein R^{10} is alkyl or cycloalkyl.

36. The compound according to Claim 35, wherein R^{10} is methyl or ethyl.

37. The compound according to any one of Claims 30-34, wherein Y is selected from the group consisting of $-(CR^{13}R^{13})_r-$ and -C(=O)-.

38. The compound according to Claim 37, wherein Y is $–CH_2-$ or -C(=O)-.

39. The compound according to any one of Claims 30-38, wherein ring D is a five to nine membered aryl or heteroaryl ring having 1-2 N atoms, wherein said ring D is optionally substituted with 1-5 R^{20} moieties independently selected from the group consisting of halo, cyano, alkyl, hydroxy, haloalkyl, alkoxy, haloalkoxy, $-C(=O)N(R^{30})_2$, $-NR^{30}S(=O)_2R^{31}$, and $-N(R^{30})_2$.

40. The compound according to Claim 39, wherein ring D is phenyl or pyridyl, wherein ring D is optionally substituted with 1-2 R^{20} moieties independently selected from the group consisting of F, Cl, -CN, -OH, -alkyl, CF_3, -Oalkyl, $-OCF_3$, -C(=O)NHalkyl, $-NH_2$, and $–NHS(=O)_2$alkyl.

41. The compound according to Claim 30, wherein:

R^3 is alkyl or cycloalkyl;

R^4 is selected from the group consisting of H, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and -C(=O)N(R^{30})$_2$, wherein each R^{30} independently is H or alkyl, or wherein R^4 together with the carbon atom to which it is attached is -C(=O)-;

R^{10} is alkyl;

Y is selected from the group consisting of -($CR^{13}R^{13}$)$_r$– and -C(=O)-; and

ring D is a five to nine membered aryl or heteroaryl ring having 1-2 N atoms, wherein said ring D is optionally substituted with 1-5 R^{20} moieties independently selected from the group consisting of halo, cyano, alkyl, hydroxy, haloalkyl, alkoxy, haloalkoxy, -C(=O)N(R^{30})$_2$, -NR^{30}S(=O)$_2R^{31}$, and -N(R^{30})$_2$.

42. The compound according to Claim 41, wherein:

R^3 is methyl or cyclopropyl;

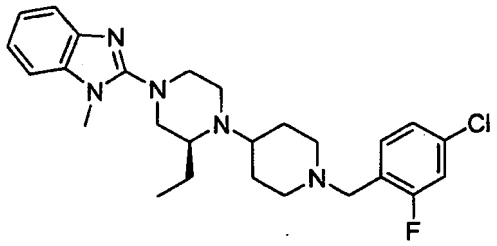
R^4 is selected from the group consisting of H, F, Cl, alkyl, CF_3, -O alkyl, -OCF_3, and -C(=O)NHalkyl; or wherein R^4 together with the carbon atom to which it is shown attached is –C(=O);

R^{10} is methyl or ethyl;

Y is –CH_2- or -C(=O)-; and

ring D is phenyl or pyridyl, wherein ring D is optionally substituted with 1-2 R^{20} moieties independently selected from the group consisting of F, Cl, -CN, -OH, alkyl, CF_3, -Oalkyl, -OCF_3, -C(=O)NHalkyl, -NH_2, and –NHS(=O)$_2$alkyl.

43. The compound according to any one of Claims 30, and 41-42, wherein said compound is



or a pharmaceutically acceptable salt or solvate thereof.

44. A compound according to any one of Claims 1, 22-30 and 41-43, in purified form.

45. A pharmaceutical composition comprising at least one compound of any one of Claims 1, 28-30, and 43, or a pharmaceutically acceptable salt, solvate or ester thereof, in combination with at least one pharmaceutically acceptable carrier.

46. The pharmaceutical composition of Claim 45, further comprising at least one additional agent, drug, medicament, antibody and/or inhibitor for treating a CXCR3 chemokine receptor mediated disease.

47. A method of treating a CXCR3 chemokine receptor mediated disease in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of at least one compound according to any one of Claims 1, 28-30, and 43, or a pharmaceutically acceptable salt, solvate or ester thereof.

48. A method according to Claim 47, further comprising administering concurrently or sequentially at least one additional agent, drug, medicament, antibody and/or inhibitor for treating a CXCR3 chemokine receptor mediated disease, in combination with a pharmaceutically acceptable carrier.

49. The method according to Claim 47, wherein the compound binds to a CXCR3 receptor.

50. The method according to Claim 47, further comprising administering concurrently or sequentially at least one medicament selected from the group consisting of: disease modifying antirheumatic drugs, nonsteroidal anti-inflammatory drugs, COX-2 selective inhibitors, COX-1 inhibitors, immunosuppressives, steroids, beta agonists, muscarinic antagonists, PDE IV inhibitors, anti-TNF-α compounds, TNF-alpha-convertase inhibitors, cytokine inhibitors, MMP inhibitors, glucocorticoids, corticosteroids, chemokine inhibitors, CB2-selective inhibitors, p38 inhibitors, biological response modifiers, anti-inflammatory agents and therapeutics.

51. The method according to Claim 47, wherein the disease is an inflammatory or immune disease.

52. The method according to Claim 51, wherein said inflammatory or immune disease is selected from the group consisting of neurodegenerative disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, juvenile rheumatoid arthritis, atherosclerosis, vasculitis, chronic heart failure, cerebrovascular ischemia, encephalitis, meningitis, hepatitis, nephritis, glomerulonephritis, sepsis, sarcoidosis, psoriasis, eczema, urticaria, type I diabetes, asthma, conjunctivitis, ophthalmic inflammation, otitis, allergic rhinitis, chronic obstructive pulmonary disease, sinusitis, dermatitis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, Behcet's syndrome, pulmonary fibrosis, endometriosis, gout, cancer, cachexia, a viral infection, a bacterial infection, an organ transplant condition, a skin transplant condition, and a graft versus host disease.

53. A method of inhibiting or blocking T-cell mediated chemotaxis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of at least one compound according to any one of Claims 1, 28-30, and 43, or a pharmaceutically acceptable salt, solvate or ester thereof.

54. A method of treating inflammatory bowel disease in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of at least one compound according to any one of Claims 1, 28-30, and 43, or a pharmaceutically acceptable salt, solvate or ester thereof.

55. The method according to Claim 54, further comprising administering concurrently or sequentially at least one compound selected from the group consisting of: sulfasalazine, 5-aminosalicylic acid, sulfapyridine, anti-TNF compounds, anti-IL-12 compounds, corticosteroids, glucocorticoids, T-cell receptor directed therapies, immunosuppresives, methotrexate, azathioprine, and 6-mercaptopurines.

56. A method of treating or preventing graft rejection in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of at least one compound according to any one of Claims 1, 28-30, and 43, or a pharmaceutically acceptable salt, solvate or ester thereof.

57. The method according to Claim 55, further comprising administering concurrently or sequentially at least one compound selected from the group consisting of: cyclosporine A, FK-506, FTY720, beta-interferon, rapamycin, mycophenolate, prednisolone, azathioprene, cyclophosphamide and an antilymphocyte globulin.

58. A method of treating multiple sclerosis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of: (a) at least one compound according to any one of Claims 1, 28-30, and 43, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: beta-interferon, glatiramer acetate, glucocorticoids, glucocorticoids, methotrexate, azothioprine, mitoxantrone, VLA-4 inhibitors, FTY720, anti-IL-12 compounds, and CB2-selective inhibitors.

59. A method of treating multiple sclerosis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of: a) at least one compound according to any one of Claims 1, 28-30, and 43, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: methotrexate, cyclosporin, leflunomide, sulfasalazine, corticosteroids, β-methasone, β-interferon, glatiramer acetate, prednisone, etonercept, and infliximab.

60. A method of treating rheumatoid arthritis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of: (a) at least one compound according to any one of Claims 1, 28-30, and 43, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: non-steroidal anti-inflammatory agents, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, cyclosporine, methotrexate, steroids, PDE IV inhibitors, anti-TNF-α compounds, MMP inhibitors, corticosteroids, glucocorticoids, chemokine inhibitors, CB2-selective inhibitors, caspase (ICE) inhibitors and other classes of compounds indicated for the treatment of rheumatoid arthritis.

61. A method of treating psoriasis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of: a) at least one compound according to any one of Claims 1, 28-30, and 43, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: immunosuppressives, cyclosporins, methotrexate, steroids, corticosteroids, anti-TNF-α compounds, anti-IL compounds, anti-IL-23 compounds, vitamin A and D compounds and fumarates.

62. A method of treating ophthalmic inflammation or dry eye in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of: a) at least one compound according to any one of Claims 1, 28-30, and 43, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: immunosuppressives, cyclosporins, methotrexate, FK506, steroids, corticosteroids, and anti-TNF-α compounds.

63. A method according to Claim 52, further comprising administering to the patient concurrently or sequentially at least one medicament selected from the group consisting of: disease modifying antirheumatic drugs, nonsteroidal anti-inflammatory drugs, COX-2 selective inhibitors, COX-1 inhibitors, immunosuppressives, steroids, beta agonists, muscarinic antagonists, PDE IV inhibitors, anti-TNF-α compounds, TNF-alpha-convertase inhibitors, cytokine inhibitors, MMP inhibitors, glucocorticoids, corticosteroids, chemokine inhibitors, CB2-selective inhibitors, p38 inhibitors, biological response modifiers, anti-inflammatory agents and therapeutics.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/026039

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 A61K31/495 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	YOO ET AL: "Synthesis of hetero-aryl-piperazines and hetero-aryl-bipiperidines with a restricted side chain and their affinities for 5-HT1A receptor" ARCHIV DER PHARMAZIE, VCH VERLAGSGESELLSCHAFT MBH, WEINHEIM, DE, vol. 336, no. 4/5, 2003, pages 208-215, XP002425606 ISSN: 0365-6233 cited in the application page 209; compound 13B	1-63
Y	WO 2006/088921 A (SCHERING CORP [US]; PHARMACOPEIA DRUG DISCOVERY [US]; ROSENBLUM STUART) 24 August 2006 (2006-08-24) page 1; examples 1-492	1-63

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 May 2008	13/05/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bourghida, E

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/026039

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/088919 A (SCHERING CORP [US]; PHARMACOPEIA DRUG DISCOVERY [US]; MCGUINNESS BRIAN) 24 August 2006 (2006-08-24) page 1; examples 1-461	1-63

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/026039

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 47-63 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/026039

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006088921 A	24-08-2006	AR 054224 A1	13-06-2007
		AU 2006214380 A1	24-08-2006
		CA 2598458 A1	24-08-2006
		CN 101142209 A	12-03-2008
		EP 1856098 A2	21-11-2007
		KR 20070107060 A	06-11-2007
WO 2006088919 A	24-08-2006	AR 055195 A1	08-08-2007
		AU 2006214378 A1	24-08-2006
		CA 2598457 A1	24-08-2006
		EP 1856097 A2	21-11-2007
		KR 20070107056 A	06-11-2007

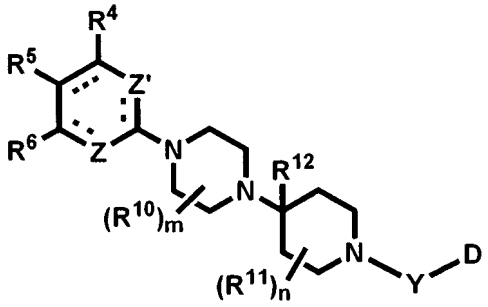
HKP0921985

名称:

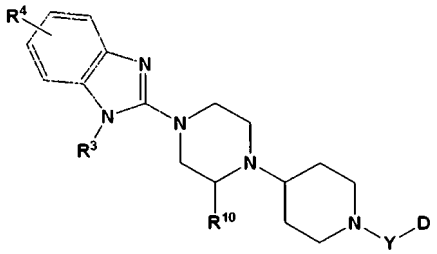
具 CXCR3 拮抗活性的杂环化合物

摘要:

本申请公开了一种化合物，或该化合物的对映异构体、立体异构体、旋转异构体、互变异构体、外消旋体或前药，或该化合物或该前药的医药学上可接受的盐、溶剂化物或酯，该化合物具有式 1 或式 5 中所示的一般结构：



式 1



式 5

或其医药学上可接受的盐、溶剂化物或酯。本申请也公开了一种使用

式 1 化合物来治疗趋化因子介导的疾病的方法，诸如某些疾病及病状的减轻性疗法、治愈性疗法、预防性疗法，这种疾病及病状诸如发炎性疾病(非限制性实施例包括牛皮癣)、自身免疫疾病(非限制性实施例包括类风湿性关节炎、多发性硬化症)、移植排斥(非限制性实施例包括同种异体移植排斥、异种移植排斥)、感染性疾病(例如，类结核型麻疯)、固定型药疹、皮肤迟发型超敏反应、眼科炎症、I 型糖尿病、病毒性脑膜炎及肿瘤。