

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
24 August 2006 (24.08.2006)

PCT

(10) International Publication Number
WO 2006/088920 A1

(51) International Patent Classification:

C07D 401/12 (2006.01) C07D 417/14 (2006.01)
C07D 409/14 (2006.01) C07D 413/14 (2006.01)
C07D 401/14 (2006.01) A61K 31/497 (2006.01)
C07D 405/14 (2006.01) A61P 31/00 (2006.01)
C07D 211/58 (2006.01) A61P 29/00 (2006.01)

(21) International Application Number:

PCT/US2006/005266

(22) International Filing Date:

14 February 2006 (14.02.2006)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/653,339 16 February 2005 (16.02.2005) US

(71) Applicants (for all designated States except US): **SCHERING CORPORATION** [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530 (US). **PHARMACOEPIA DRUG DISCOVERY, INC.** [US/US]; 3000 Eastpark Boulevard, Cranbury, New Jersey 08512 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **WONG, Michael, K., C.** [CA/US]; 999 Hidden Lake Drive, Apt. 3d, North Brunswick, New Jersey 08902 (US). **SHU, Youheng** [CN/US]; 1758 Talbot Road, Blue Bell, Pennsylvania 19422 (US). **YU, Wensheng** [CN/US]; 46 Woodbury Road, Edison, New Jersey 08820 (US). **ROSENBLUM, Stuart, B.** [US/US]; 16 Steven Terrace, West Orange, New Jersey 07052 (US). **KOZLOWSKI, Joseph, A.** [US/US]; 1066 Stuart Road, Princeton, New Jersey 08540 (US). **MCGUINNESS, Brian, F.** [US/US]; 16 Adams

Court, Plainsboro, New Jersey 08536 (US). **SHAO, Yuefei** [CN/US]; 38 York Drive, Princeton, New Jersey 08540 (US). **HOBBS, Douglas, W.** [US/US]; 1330 University Drive, Yardley, Pennsylvania 19067 (US).

(74) Agent: **BANERJEE, Krishna, G.**; Schering-plough Corporation, 2000 Galloping Hill Road, Patent Dept. K-6-1 1990, Kenilworth, New Jersey 07033-0530 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

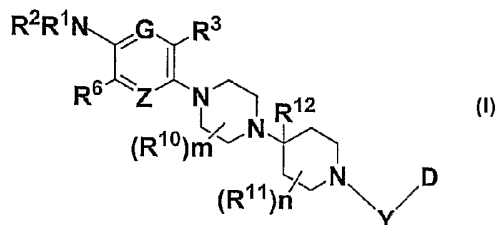
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AMINE-LINKED PYRIDYL AND PHENYL SUBSTITUTED PIPERAZINE-PIPERIDINES WITH CXCR3 ANTAGONIST ACTIVITY



(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: Chemical formula should be inserted here as it appears on the abstract in paper form. and the pharmaceutically acceptable salts, solvates and esters 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, xenograft 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.

WO 2006/088920 A1

AMINE-LINKED PYRIDYL AND PHENYL SUBSTITUTED
PIPERAZINE-PIPERIDINES WITH CXCR3 ANTAGONIST
ACTIVITY

Field of the Invention

The present invention relates to novel pyridyl and phenyl substituted piperazine-piperidines 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 xenograft rejections for example).

BACKGROUND OF THE INVENTION

Chemokines constitute a family of small cytokines that are produced in inflammation and regulate leukocyte recruitment (Baggiolini, M. *et al.*, *Adv. Immunol.*, 55 : 97-179 (1994); Springer, T. A., *Annu. Rev. Physiol.*, 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.,
5 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.

The chemokines are related in primary structure and share four
10 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, GRO α , GRO β , GRO δ , NAP-2, NAP-4), and the C-C
15 chemokines (β -chemokines), in which the first two conserved cysteines are adjacent residues (e. g., MIP-1 α , MIP-1 β , 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 (GRO α), and
20 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
25 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 1 α and 1 β (MIP-1 α and MIP-1 β) have
30 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 and characterized (Loetscher, M. *et al.*, *J. Exp. Med.*, 184 :

963-969 (1996)). 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 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, $\text{GRO}\alpha$, 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-1 α , MIP-1 β , 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 $\text{CD45RA}^{\text{low}}$, 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-1 α , MIP-1 β , 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, I. *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 (IFN δ), while the expression of IL-8 is down-regulated by

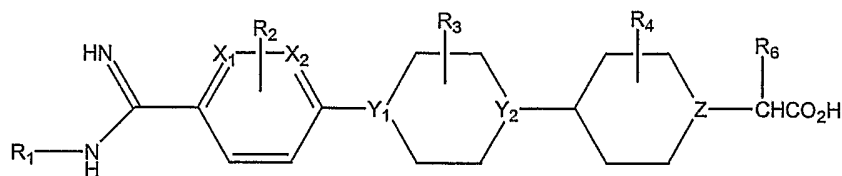
IFN δ (Luster, A. D. *et al.*, *Nature*, 315 : 672-676 (1985); Farber, J. M., *Proc. Natl. Acad. Sci. USA*, 87 : 5238-5242 (1990); Farber, J. M., *Biochem. Biophys. Res. Commun.*, 192 (1): 223-230 (1993), Liao, F. *et al.*, *J. Exp. Med.*, 182: 1301-1314 (1995); Seitz, M. *et al.*, *J. Clin. Invest.*, 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.

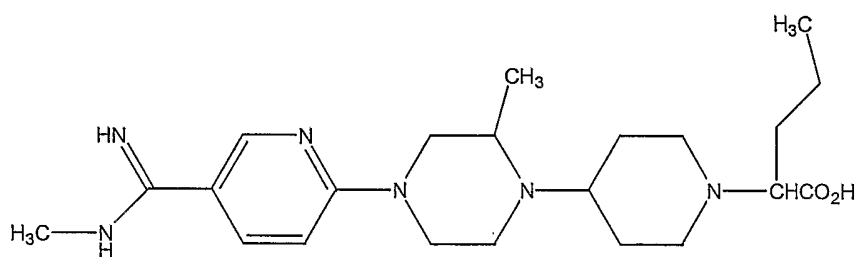
In view of these observations, it is reasonable to conclude that the formation of the characteristic infiltrates in inflammatory lesions, such as, for example, delayed-type hypersensitivity lesions, sites of viral infection and certain tumors is a process mediated via CXCR3 and regulated by CXCR3 expression. 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 (such as Crohn's disease and ulcerative colitis) 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:

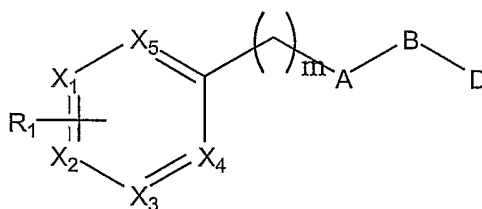


An illustrative compound of that series is:



5

Reference is also made to PCT Publication No. WO 9/20606 (Applicant: J. Uriach & CIA. S.A., Published April 29, 1999) which discloses piperazines as platelet aggregation inhibitors having the formula:



10

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.

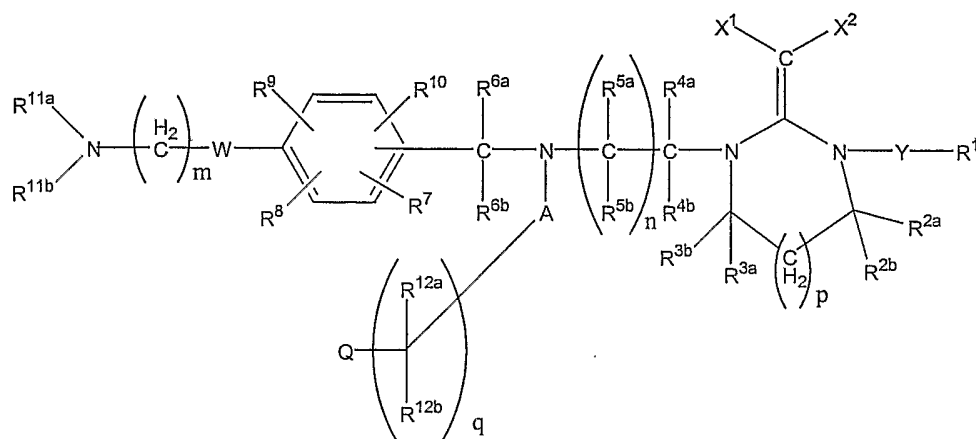
Reference is also made to PCT Publication No. WO 03/098185 A2 (Applicant: Renovar, Inc., Published November 27, 2003) which discloses methods of diagnosing and predicting organ transplant rejection by detection of chemokines, for example, CXCR3 and CCL chemokines in urine.

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

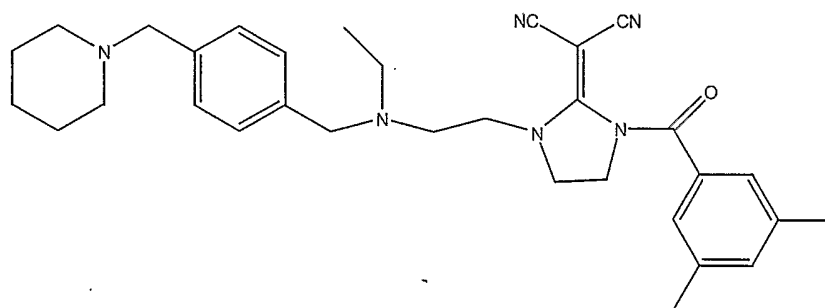
diagnosing type 2 diabetes by detecting the expression dose of a CXCR3 ligand in a biological sample.

Reference is also made to PCT Publication No. WO 02/085861
(Applicant: Millennium Pharmaceuticals, Inc. Published October 31, 2002)

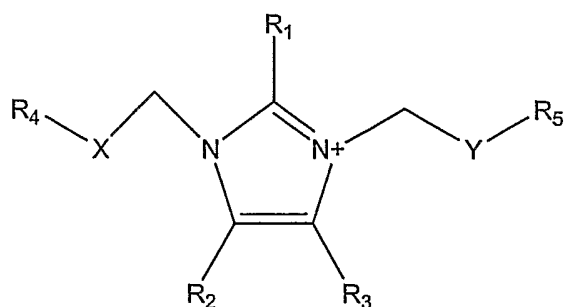
5 which discloses imidazolidine compounds and their use as CXCR3 antagonists having the formula:



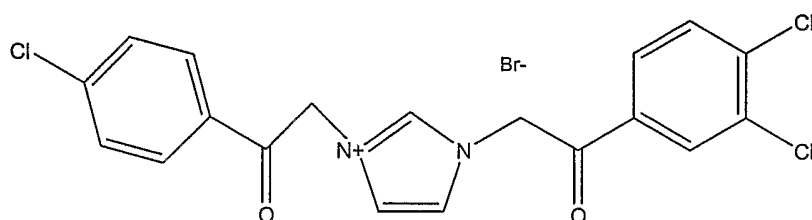
An illustrative compound of that series is:



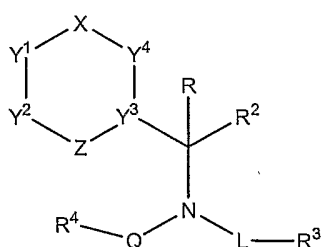
Reference is also made to PCT Publication No. WO 03/101970
(Applicant: SmithKline Beecham Corporation, Published December 11, 2003)
which discloses imidazolium compounds and their use as CXCR3 antagonists
having the formula:



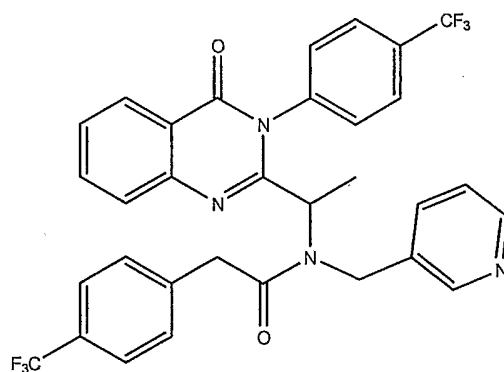
An illustrative example of that series is:



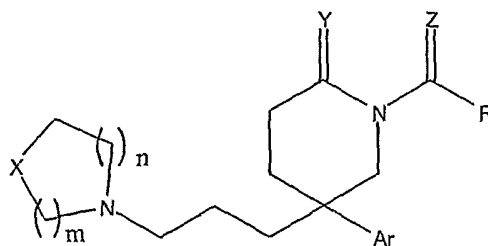
Reference is also made to US Patent Application No. US
 5 2003/0055054 A1 (Applicant: Medina et al, Published March 20, 2003) which
 discloses compounds having the formula:



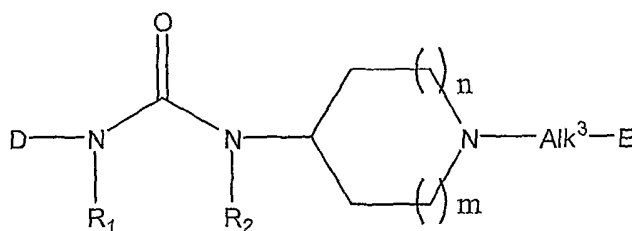
An illustrative compound of that series is:



10 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 August 28, 2003) which
 discloses compounds useful as "chemokine receptor inhibitors for the
 treatment of inflammatory diseases" having the formula:

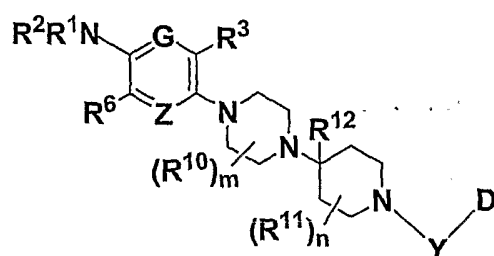


There is a need for compounds that are capable of modulating CXCR3
 activity. For example, there is a need for new treatments and therapies for
 diseases and conditions associated with CXCR3 such as inflammatory
 conditions (psoriasis and inflammatory bowel disease), autoimmune disease
 (multiple sclerosis, rheumatoid arthritis) and graft rejection (allograft and
 xenograft 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 pharmaceutically acceptable salts, solvates or esters thereof wherein:

Z is N, C(R²⁹), NO or NOH;

G is N, C(R⁴), NO or NOH;

- 5 R¹ and R² are independently absent or present, and if present each is independently selected from the group consisting of H, alkyl, alkoxy, alkenyl, carbonyl, cycloalkyl, cycloalkenyl, alkylaryl, arylalkyl, aryl, amino, alkylamino, amidinyl, carboxamido, cyano, hydroxyl, urea, -N≡CH, =NCN, -(CH₂)_qOH, -(CH₂)_qOR³¹, -(CH₂)_qNH₂, -(CH₂)_qNHR³¹, -(CH₂)_qN(R³¹)₂, -(CH₂)_qC(=O)NHR³¹,
 10 -(CH₂)_qSO₂R³¹, -(CH₂)_qNHSO₂R³¹, -(CH₂)_qSO₂NHR³¹, -C(=S)N(H)alkyl, -N(H)-S(O)₂-alkyl, -N(H)C(=O)N(H)-alkyl, -S(O)₂alkyl, -S(O)₂NH₂, -S(O)₂N(H)alkyl, -S(O)₂N(alkyl)₂, -S(O)₂aryl, -S(O)₂heteroaryl, -S(O)₂heterocyclyl, -C(=S)N(H)cycloalkyl, -C(=O)N(H)NH₂, -C(=O)alkyl, -C(=O)heteroaryl, -C(=O)heterocyclyl, -heteroaryl, heterocyclyl, and
 15 heterocyclenyl; or alternatively the N taken together with the R¹ and R² forms a heterocycl, heteroaryl or -N=C(NH₂)₂;

- R³, R⁴, R⁶ and R²⁹ moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, aralkyl, -CN, CF₃, haloalkyl, cycloalkyl, halogen, hydroxyalkyl, -N=CH-(R³¹),
 20 -C(=O)N(R³⁰)₂, -N(R³⁰)₂, -OR³⁰, -SO₂(R³¹), -N(R³⁰)C(=O)N(R³⁰)₂ and -N(R³⁰)C(=O)R³¹;

- the R¹⁰ moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclenyl, heterocyclyl, alkylaryl, arylalkyl, -CO₂H, hydroxyalkyl, -C(=O)N(R³⁰)₂, -(CH₂)_qOH, -(CH₂)_qOR³¹, -(CH₂)_qNHR³¹, -(CH₂)_qN(R³¹)₂, -OR³⁰, halogen, =O, and -C(=O)R³¹;

the R¹¹ moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, cycloalkyl, aryl,

heteroaryl, heterocyclyl, heterocyclenyl, alkylaryl, arylalkyl, hydroxyalkyl, carboxamide, CO_2H , $-(\text{CH}_2)_q\text{OH}$, $-(\text{CH}_2)_q\text{OR}^{31}$, $-(\text{CH}_2)_q\text{NHR}^{31}$, $-(\text{CH}_2)_q\text{N}(\text{R}^{31})_2$, $-\text{OR}^{30}$, halogen, = O, and $-\text{C}(=\text{O})\text{R}^{31}$;

- the R^{12} moieties can be the same or different, each being
- 5 independently selected from the group consisting of H, alkyl, $-\text{CN}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{30})_2$, $-(\text{CH}_2)_q\text{OH}$, $-(\text{CH}_2)_q\text{OR}^{31}$, $-(\text{CH}_2)_q\text{NHR}^{31}$, $-(\text{CH}_2)_q\text{N}(\text{R}^{31})_2$, and $-\text{S}(\text{O}_2)\text{R}^{31}$;

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

- 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,
- 15 alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, aminoalkyl, amidinyl, aralkyl, aralkenyl, aralkoxy, aralkoxycarbonyl, aralkylthio, aryl, aroyl, aryloxy, cyano, cycloalkyl, cycloalkenyl, formyl, guanidinyl, halogen, haloalkyl, heteroalkyl, heteroaryl, heterocyclyl, heterocyclenyl, hydroxyalkyl, hydroxamate, nitro, trifluoromethoxy, $-(\text{CH}_2)_q\text{OH}$, $-(\text{CH}_2)_q\text{OR}^{31}$, $-(\text{CH}_2)_q\text{NH}_2$, $-(\text{CH}_2)_q\text{NHR}^{31}$,
- 20 $-(\text{CH}_2)_q\text{N}(\text{R}^{31})_2$, $-(\text{CH}_2)_q\text{C}(=\text{O})\text{NHR}^{31}$, $-(\text{CH}_2)_q\text{SO}_2\text{R}^{31}$, $-(\text{CH}_2)_q\text{NH}\text{SO}_2\text{R}^{31}$, $-(\text{CH}_2)_q\text{SO}_2\text{NHR}^{31}$, $-\text{alkynylC}(\text{R}^{31})_2\text{OR}^{31}$, $-\text{C}(=\text{O})\text{R}^{30}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{30})_2$, $-\text{C}(=\text{NR}^{30})\text{NHR}^{30}$, $-\text{C}(=\text{NOH})\text{N}(\text{R}^{30})_2$, $-\text{C}(=\text{NOR}^{31})\text{N}(\text{R}^{30})_2$, $-\text{C}(=\text{O})\text{OR}^{30}$, $-\text{N}(\text{R}^{30})_2$, $-\text{N}(\text{R}^{30})\text{C}(=\text{O})\text{R}^{31}$, $-\text{NHC}(=\text{O})\text{N}(\text{R}^{30})_2$, $-\text{N}(\text{R}^{30})\text{C}(=\text{O})\text{OR}^{31}$, $-\text{N}(\text{R}^{30})\text{C}(=\text{NCN})\text{N}(\text{R}^{30})_2$, $-\text{N}(\text{R}^{30})\text{C}(=\text{O})\text{N}(\text{R}^{30})\text{SO}_2(\text{R}^{31})$, $-\text{N}(\text{R}^{30})\text{C}(=\text{O})\text{N}(\text{R}^{30})_2$,
- 25 $-\text{N}(\text{R}^{30})\text{SO}_2(\text{R}^{31})$, $-\text{N}(\text{R}^{30})\text{S}(\text{O})_2\text{N}(\text{R}^{30})_2$, $-\text{OR}^{30}$, $-\text{OC}(=\text{O})\text{N}(\text{R}^{30})_2$, $-\text{SR}^{30}$, $-\text{SO}_2\text{N}(\text{R}^{30})_2$, $-\text{SO}_2(\text{R}^{31})$, $-\text{OSO}_2(\text{R}^{31})$, and $-\text{OSi}(\text{R}^{30})_3$; 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
- 30 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, heteroalkyl, heteroaryl, heterocyclyl, heterocyclenyl, hydroxyalkyl, hydroxamate, nitro, trifluoromethoxy, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qN(R^{31})_2$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, $-alkynylC(R^{31})_2OR^{31}$, $-C(=O)R^{30}$, $-C(=O)N(R^{30})_2$, $-C(=NR^{30})NHR^{30}$, $-C(=NOH)N(R^{30})_2$, $-C(=NOR^{31})N(R^{30})_2$, $-C(=O)OR^{30}$, $-N(R^{30})_2$, $-N(R^{30})C(=O)R^{31}$, $-NHC(=O)N(R^{30})_2$, $-N(R^{30})C(=O)OR^{31}$, $-N(R^{30})C(=NCN)N(R^{30})_2$, $-N(R^{30})C(=O)N(R^{30})SO_2(R^{31})$, $-N(R^{30})C(=O)N(R^{30})_2$, $-N(R^{30})SO_2(R^{31})$, $-N(R^{30})S(O)_2N(R^{30})_2$, $-OR^{30}$, $-OC(=O)N(R^{30})_2$, $-SR^{30}$, $-SO_2N(R^{30})_2$, $-SO_2(R^{31})$, $-OSO_2(R^{31})$, and $-OSi(R^{30})_3$;

Y is selected from the group consisting of $-(CR^{13}R^{13})_r-$, $-CHR^{13}C(=O)-$, $-(CHR^{13})_rO-$, $-(CHR^{13})_rN(R^{30})-$, $-C(=O)-$, $-C(=NR^{30})-$, $-C(=N-OR^{30})-$, $-CH(C(=O)NHR^{30})-$, 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, $-CN$, $-CO_2H$, $-C(=O)R^{30}$, $-C(=O)N(R^{30})_2$, $-(CHR^{30})_qOH$, $-(CHR^{30})_qOR^{31}$, $-(CHR^{30})_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, $-NH_2$, $-N(R^{30})_2$, $-N(R^{30})C(=O)N(R^{30})_2$, $-N(R^{30})SO_2(R^{31})$, $-OH$, 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, $-(CH_2)_qOH$, $-(CH_2)_qOalkyl$, $-(CH_2)_qOalkylaryl$, $-(CH_2)_qOaryl$, $-(CH_2)_qOaralkyl$, $-(CH_2)_qOcycloalkyl$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHalkyl$, $-(CH_2)_qN(alkyl)_2$, $-(CH_2)_qNHalkylaryl$, $-(CH_2)_qNHaryl$, $-(CH_2)_qNHaralkyl$, $-(CH_2)_qNHcycloalkyl$, $-(CH_2)_qC(=O)NHalkyl$, $-(CH_2)_qC(=O)N(alkyl)_2$, $-(CH_2)_qC(=O)NHalkylaryl$, $-(CH_2)_qC(=O)NHaryl$, $-(CH_2)_qC(=O)NHaralkyl$, $-(CH_2)_qC(=O)NHcycloalkyl$, $-(CH_2)_qSO_2alkyl$, $-(CH_2)_qSO_2alkylaryl$, $-(CH_2)_qSO_2aryl$, $-(CH_2)_qSO_2aralkyl$, $-(CH_2)_qSO_2cycloalkyl$, $-(CH_2)_qNSO_2alkyl$, -

(CH₂)_qNSO₂alkylaryl, -(CH₂)_qNSO₂aryl, -(CH₂)_qNSO₂aralkyl, -
 (CH₂)_qNSO₂cycloalkyl, -(CH₂)_qSO₂NHalkyl, -(CH₂)_qSO₂NHalkylaryl, -
 (CH₂)_qSO₂NHaryl, -(CH₂)_qSO₂NHaralkyl, -(CH₂)_qSO₂NHcycloalkyl,
 heterocyclenyl, heterocyclyl, and heteroaryl;

5 the R³¹ moieties can be the same or different, each being
 independently selected from the group consisting of alkyl, alkylaryl, aryl,
 aralkyl, cycloalkyl, -(CH₂)_qOH, -(CH₂)_qOalkyl, -(CH₂)_qOalkylaryl, -(CH₂)_qOaryl,
 -(CH₂)_qOaralkyl, -(CH₂)_qOcycloalkyl, -(CH₂)_qNH₂, -(CH₂)_qNHalkyl, -
 (CH₂)_qN(alkyl)₂, -(CH₂)_qNHalkylaryl, -(CH₂)_qNHaryl, -(CH₂)_qNHaralkyl, -
 10 (CH₂)_qNHcycloalkyl, -(CH₂)_qC(=O)NHalkyl, -(CH₂)_qC(=O)N(alkyl)₂, -
 (CH₂)_qC(=O)NHalkylaryl, -(CH₂)_qC(=O)NHaryl, -(CH₂)_qC(=O)NHaralkyl, -
 (CH₂)_qC(=O)NHcycloalkyl, -(CH₂)_qSO₂alkyl, -(CH₂)_qSO₂alkylaryl, -
 (CH₂)_qSO₂aryl, -(CH₂)_qSO₂aralkyl, -(CH₂)_qSO₂cycloalkyl, -(CH₂)_qNSO₂alkyl, -
 (CH₂)_qNSO₂alkylaryl, -(CH₂)_qNSO₂aryl, -(CH₂)_qNSO₂aralkyl, -
 15 (CH₂)_qNSO₂cycloalkyl, -(CH₂)_qSO₂NHalkyl, -(CH₂)_qSO₂NHalkylaryl, -
 (CH₂)_qSO₂NHaryl, -(CH₂)_qSO₂NHaralkyl, -(CH₂)_qSO₂NHcycloalkyl,
 heterocyclenyl, heterocyclyl, and heteroaryl;

m is 0 to 4;

n is 0 to 4;

20 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
 25 alkyl groups may be optionally joined to each other to form a ring.

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

The invention provides methods of preparing compounds of Formula 1,
 30 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

5 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.,

10 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

15 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;

20 immunosuppressives (such as cyclosporins and methotrexate); steroids (including corticosteroids such as glucocorticoids); 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;

25 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

30 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,

5 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
10 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), immunosuppressives, methotrexate, azathioprine, and 6-mercaptopurines.

15 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
20 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,
25 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
30 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, azathioprine,

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, etanercept, 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.

5 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
10 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
15 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
20 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
25 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.

30 **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

5 "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:

"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

10 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, alkoxy, aryl, aryloxy, cycloalkyl,

15 cycloalkenyl, cyano, heteroaryl, heterocyclyl, heterocyclenyl, amino, aminosulfonyl, halo, carboxyl, carboxyalkyl (non-limiting example(s) include ester), alkoxy carbonyl, hydroxyalkyl, carbonyl (non-limiting example(s) include ketone), -C(=O)heterocyclyl, formyl (non-limiting example(s) include aldehyde), carboxamido (i.e. amido, -C(=O)NH₂), -C(=O)N(alkyl)₂,

20 -C(=O)NH(alkyl), -C(=O)N(cycloalkyl)₂, -C(=O)NH(cycloalkyl), -NHC(=O)alkyl, urea (e.g. -NH(C=O)NH₂, -NH(C=O)NH(alkyl), -NH(C=O)NH(alkyl)₂, -NH(C=O)NH(heteroaryl), -NH(C=O)NH(heterocyclyl)), guanidiny, -NHC(=NCN)NH₂, -NHC(=NCN)N(alkyl)₂, carbamoyl (i.e. -CO₂NH₂), NHC(=O)Oalkyl, -CO₂N(alkyl)₂, -NHC(=O))NH-S(O)₂alkyl,

25 -NHC(=O)N(alkyl)₂-S(O)₂alkyl, -NH-S(O)₂alkyl, -NH-S(O)₂heteroaryl, -N(alkyl)-S(O)₂alkyl, -NH-S(O)₂aryl, -N(alkyl)-S(O)₂aryl, -NH-S(O)₂NH₂, -NH-S(O)₂NHalkyl, -NH-S(O)₂N(alkyl)₂, alkylthiocarboxy, -S(O)₂alkyl, -S(O)₂aryl, -OS(O)₂alkyl, -OS(O)₂aryl, sulfonyl urea (non-limiting example(s) include NHC(=S)NHalkyl). Non-limiting examples of suitable alkenyl groups

30

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 and comprising about 1 to about 20 carbon atoms in the chain.

5 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
10 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, alkoxy, aryl, aryloxy, cycloalkyl, cycloalkenyl, cyano, heteroaryl, heterocyclyl, heterocyclenyl,

15 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), alkoxy, carbonyl, hydroxyalkyl, carbonyl (non-limiting example(s) include ketone), -C(=O)heterocyclyl, formyl, carboxamido (i.e. amido, -C(=O)NH₂,
20 -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 (non-limiting example(s) include -NH(C=O)NH₂, -NH(C=O)NH(alkyl), -NH(C=O)N(alkyl)₂, -NH(C=O)NH(heteroaryl), -NH(C=O)NH(heterocyclyl)), guanidinyl, -NHC(=NCN)NH₂, -NHC(=NCN)N(alkyl)₂, carbamoyl (i.e., -CO₂NH₂),
25 -NHC(=O)Oalkyl, -CO₂N(alkyl)₂, -NHC(=O)NH-S(O)₂alkyl, -NHC(=O)N(alkyl)-S(O)₂alkyl, -NH-S(O)₂alkyl, -NH-S(O)₂heteroaryl, -N(alkyl)-S(O)₂alkyl, -NH-S(O)₂aryl, -N(alkyl)-S(O)₂aryl, -NH-S(O)₂NH₂, -NH-S(O)₂NHalkyl, -NH-S(O)₂N(alkyl)₂, thio, alkylthio, alkylthiocarboxy, -S(O)alkyl, -S(O)₂alkyl, -S(O)₂aryl, -OS(O)₂alkyl, -OS(O)₂aryl, sulfonyl urea
30 (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 -NH₂ or -NH₃⁺ 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-butylnyl, 3-methylbutynyl, n-pentylnyl, 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, alkoxy, aryl, aryloxy, cycloalkyl, cycloalkenyl, cyano, heteroaryl, heterocyclyl, heterocyclenyl, -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)NH₂), -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)NH₂), -NH(C=O)NH(alkyl), -NH(C=O)NH(alkyl)₂, -NH(C=O)NH(heteroaryl), -NH(C=O)NH(heterocyclyl), -S(O)₂alkyl, and -S(O)₂aryl.

"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-Dimethylamino-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, CN, -NHSO₂alkyl, -NHSO₂aryl, -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 phenylmethylene, 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.

"Aryloxycarbonyl" means an aryl-O-C(=O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"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.

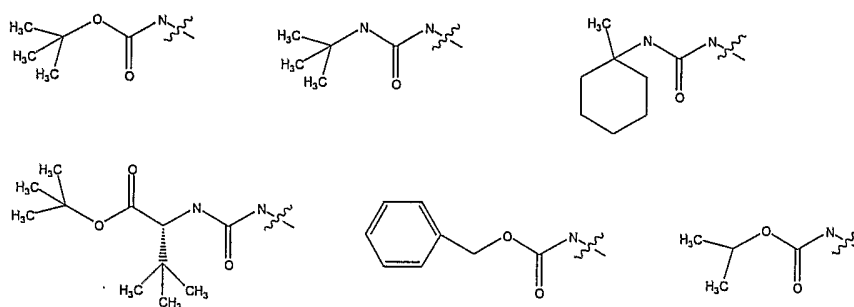
"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups

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.

- 5 "Carboxamido" means $-C(=O)NRR$ wherein R is H, alkyl, amino, aryl, cycloalkyl, heterocyclenyl, heteroaryl and carboxamido. 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
10 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
15 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 can include bicyclic cycloalkyls such as bicycloheptane.
20 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.
25 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.

5 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.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring
10 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
15 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,
20 isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyridazinyl, quinoxaliny, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinoliny, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinoliny,
25 benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl 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
30 nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. 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.

"Heterocyclenyl" means a non-aromatic 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 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. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. 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 heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic azaheterocyclenyl 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-triazolyl and the like. Non-limiting examples of suitable oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, fluorodihydrofuranyl, and the like. Non-limiting example of a suitable multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl. Non-limiting examples of suitable monocyclic thiaheterocyclenyl rings include thiophenyl, 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.

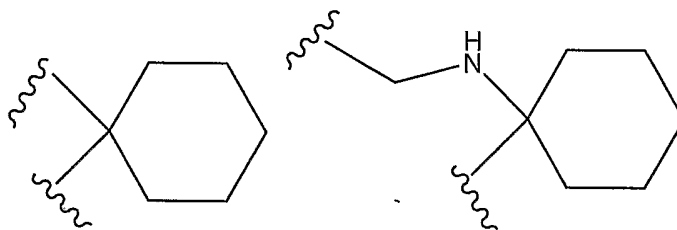
"Heteroaralkenyl" means an heteroaryl-alkenyl- group in which the
 5 heteroaryl and alkenyl are as previously described. Preferred heteroaralkenyls contain a lower alkenyl group. Non-limiting examples of suitable heteroaralkenyl groups include 2-(pyrid-3-yl)ethenyl and 2-(quinolin-3-yl)ethenyl. The bond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

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously
 10 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.

15 "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:

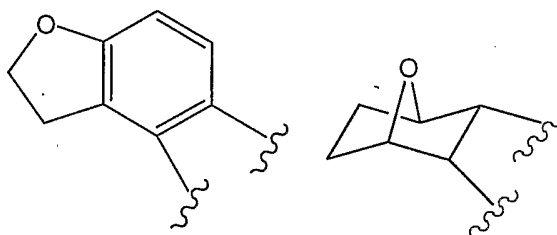


20 can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available
 25 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, heterocyclenyl, alkylaryl, alkylheteroaryl, aralkyl, aralkenyl, aralkoxy, aralkoxycarbonyl, amino, -NH(alkyl), -N(alkyl)₂,
 30 -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),
- 5 carboxamido (i.e. amido, -C(=O)NH₂), -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)NH₂), -NH(C=O)NH(alkyl), -NH(C=O)NH(alkyl)₂, -NH(C=O)NH(heteroaryl), -NH(C=O)NH(heterocyclyl), guanidiny, 10 -NHC(=NCN)NH₂, -NHC(=NCN)N(alkyl)₂, carbamoyl (i.e. -CO₂NH₂), NHC(=O)Oalkyl, -CO₂N(alkyl)₂, -NHC(=O))NH-S(O)₂alkyl, -NHC(=O)N(alkyl)₂-S(O)₂alkyl, -NH-S(O)₂alkyl, -NH-S(O)₂heteroaryl, -N(alkyl)-S(O)₂alkyl, -NH-S(O)₂aryl, -N(alkyl)-S(O)₂aryl, -NH-S(O)₂NH₂, -NH-S(O)₂NHalkyl, -NH-S(O)₂N(alkyl)₂, thio, alkylthiocarboxy, -S(O)₂alkyl, 15 -S(O)₂aryl, -OS(O)₂alkyl, -OS(O)₂aryl, sulfonyl urea (non-limiting example(s) include -NHC(=S)NHalkyl) and OSi(alkyl)₃.

"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, heterocyclyl or heterocyclenyl ring by simultaneously substituting two ring 20 hydrogen atoms on said aryl, heteroaryl, heterocyclyl or heterocyclenyl ring. Non-limiting examples include:



and the like.

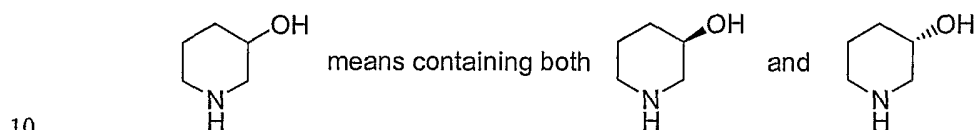
The term "optionally substituted" means optional substitution with the 25 specified groups, radicals or moieties, in available position or positions.

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 30 maximum number of such moieties is well within the knowledge of those

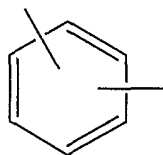
skilled in the art. Preferably, there are one to three substituents, or more preferably, one to two substituents, with at least one in the para position.

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
 5 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,

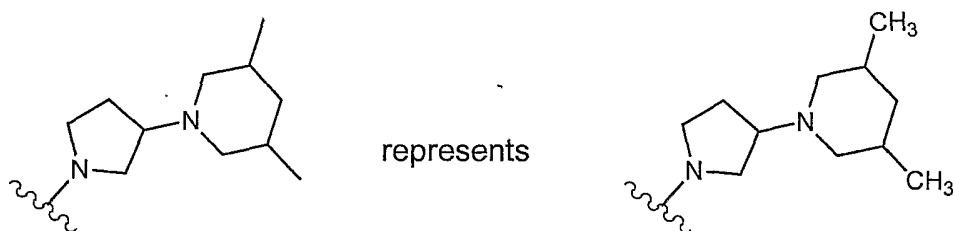


Lines drawn into the ring systems, such as, for example:



indicate that the indicated line (bond) may be attached to any of the substitutable ring carbon atoms.

15 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:



20 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,
 25 undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula 1 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
5 are incorporated herein by reference thereto.

Metabolic conjugates, for example, glucoronides and sulfates which can under reversible conversion to compounds of Formula 1 are contemplated in this application.

"Effective amount" or "therapeutically effective amount" is meant to
10 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.

15 "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
20 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 H₂O.

The compounds of Formula 1 form salts which are also within the
25 scope of this invention. Reference to a compound of Formula 1 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 contains
30 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 may be formed, for example, by reacting a compound of Formula 1 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
5 (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*
10 *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
15 reference thereto.

Exemplary acid addition salts include acetates, adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates,
20 fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, methyl sulfates, 2-naphthalenesulfonates, nicotines, nitrates, oxalates, pamoates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates,
25 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
30 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, C₁₋₄alkyl, or C₁₋₄alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C₁₋₂₀ alcohol or reactive derivative thereof, or by a 2,3-di (C₆₋₂₄)acyl glycerol.

Compounds of Formula 1, and salts, solvates 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 and prodrugs of the compounds as well as the salts and solvates 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
5 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 and prodrug of enantiomers, stereoisomers, rotamers, tautomers, racemates or
10 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.

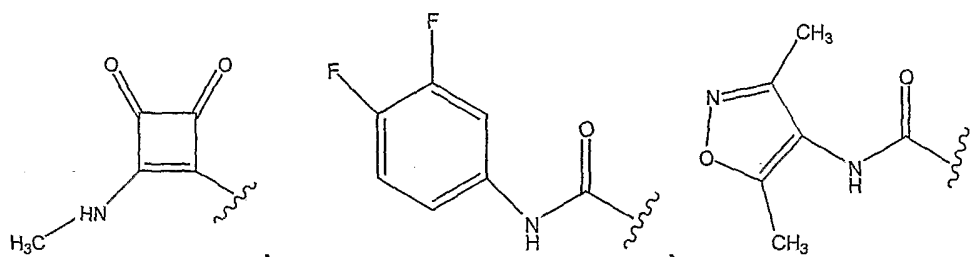
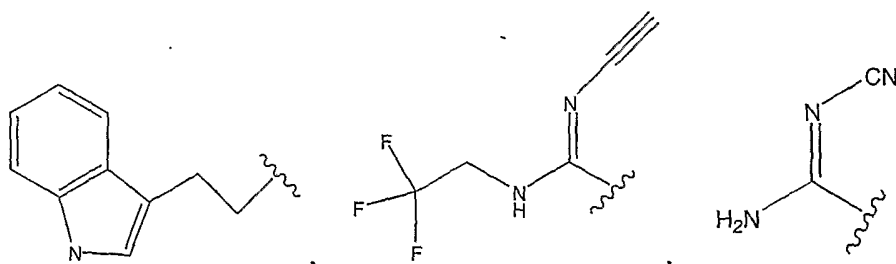
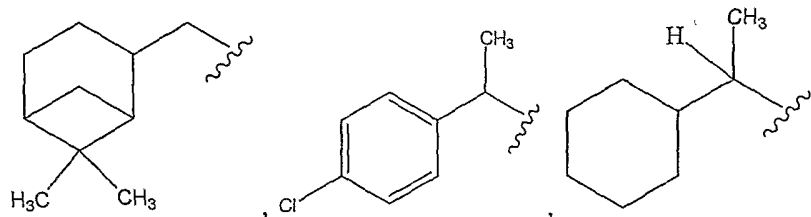
15 In one embodiment, the present invention discloses compounds of Formula 1, having CXCR3 antagonist activity, or a pharmaceutically acceptable derivative thereof, where the various definitions are given above.

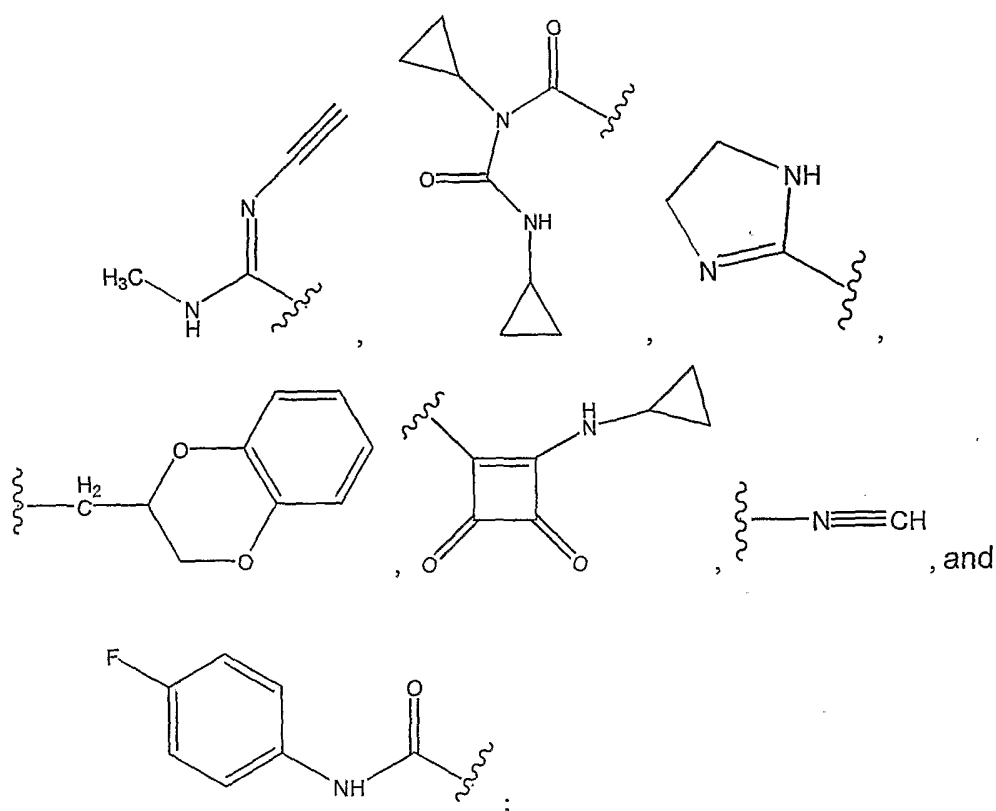
In another embodiment of the present invention, R^1 and R^2 are independently absent or present, and if present each is independently
20 selected from the group consisting of H, alkyl, aryl, amino, alkoxy, halogen, hydroxy, cycloalkyl, cycloalkenyl, arylalkyl, amidinyl, carboxamido, heteroaryl, heterocyclyl, heterocyclenyl, urea, $-S(O)_2$ alkyl, $-S(O)_2N(H)$ alkyl, $-S(O)_2$ heteroaryl, $-S(O)_2$ heterocyclyl, $-C(=O)$ heteroaryl, $-C(=O)$ heterocyclyl, $-S(O)_2N(alkyl)_2$, and $-C(=S)N(H)$ cycloalkyl.

25 In another embodiment of the present invention, R^1 and R^2 are independently absent or present, and if present each is independently selected from the group consisting of H, alkylaryl, aryl, heteroaryl, $-(CH_2)_qCF_3$, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qN(R^{31})_2$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNH SO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$,
30 $-(CH_2)_q$ -amidinyl, cyclopropyl, cyclopropylhydroxyl, cyclobutyl, cyclobutylhydroxy, cyclopentyl, and cyclopentylhydroxy; and q is an integer from 1 to 5.

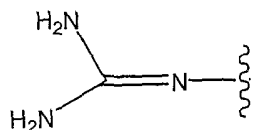
In another embodiment of the present invention, R^1 and R^2 are independently absent or present, and if present each is independently

- selected from the group consisting of H, -CH₃, fluorophenylmethylene, trifluoromethylphenylmethylene, indanyl, cyanophenylmethylene, difluorophenylmethylene, bromophenylmethylene, chlorophenylmethylene, -CH₂CH₂Ophenyl, cyclopentyl, bromochlorophenylmethylene,
- 5 fluorochlorophenylmethylene, dichlorophenylmethylene, phenylmethylene, -(CH₂)₃phenyl, -CH₂CF₃, methoxyphenylmethylene, -CH(CH₃)₂, -C₂H₅, -CH₂-cyclopropyl, -(CH₂)₂CH₃, cyclohexylmethylene, cyclohexyl, -CH₂CH₂SO₂CH₃, -CH₂-CH₂-NH₂, -CH₂CH₂OCH₃, cyclopropyl, isoxazolyl, -CH₂CH₂OH, -CH₂CH₂Ophenyl, -CH₂CH₂CH₃, -NH₂, -(CH₂)₂NH₂, pyrazolyl,
- 10 5-methyl-isoxazolyl, -CH₂CH(OCH₂CH₃)₂, -OCH₃, -NHC(=O)NH₂, chloropyridyl, pyridylmethylene, -C(=O)NHcyclopropyl, -C(=O)N(H)C₂H₅, -C(=O)N(H)CH₂CF₃, -C(=O)N(H)C(CH₃)₃, -C(=S)N(H)cyclopropyl, -C(=O)NH₂, -C(=O)N(H)CH₃, -S(O)₂CH₃, -S(O)₂N(CH₃)₂, -S(O)₂CH₂CH₃, -C(=O)CH₃, -S(O)₂(CH₂)₂CH₃, -C(=O)N(H)cyclohexyl, -C(=NH)NH₂,
- 15 -C(=O)N(H)NH₂, -C(=O)N(H)CH(CH₃)₂, thiazolyl, -C(=O)N(CH₃)₂, -S(O)₂CH₂CF₃, cyclopropyl, -S(O)₂CF₃, -CH₂CH(OCH₂CH₃)₂,

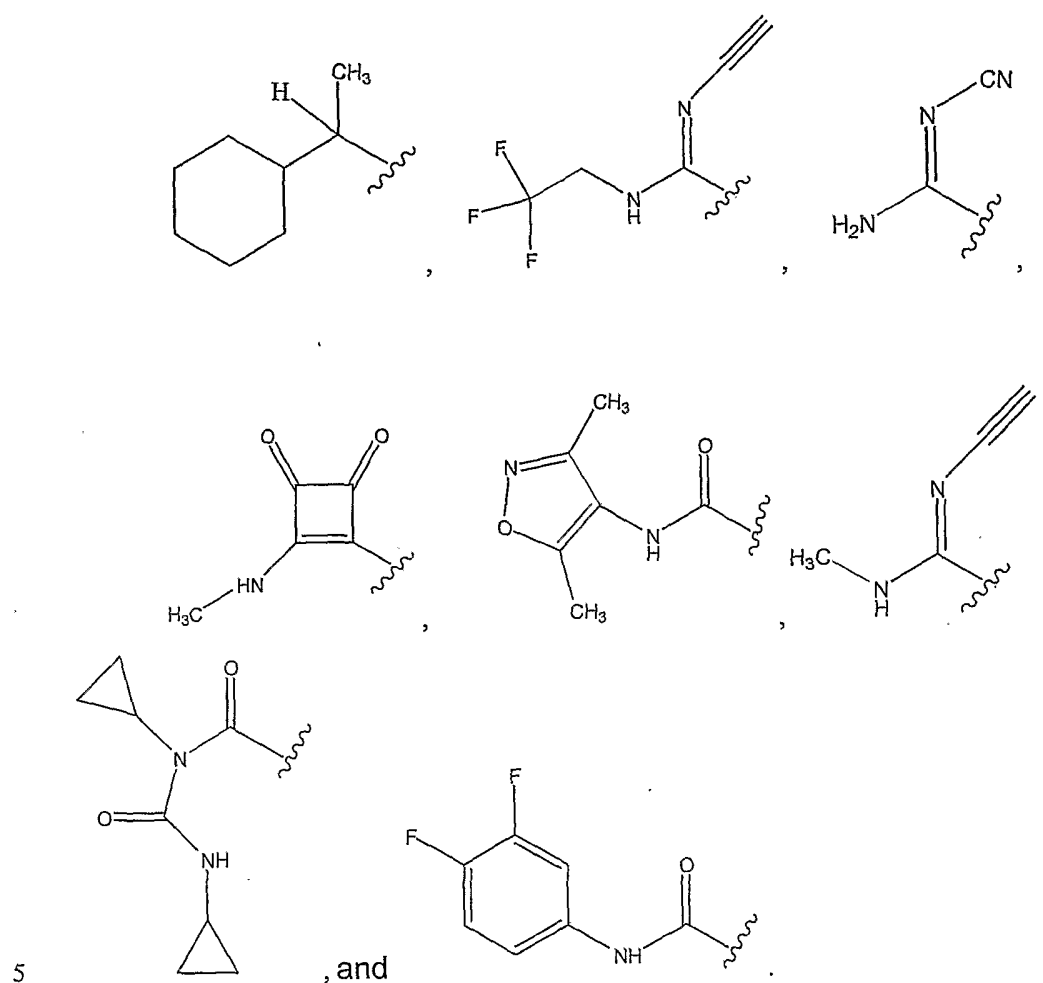




or when X is N, the N taken together with the R¹ and R² to which X is shown attached, forms a -N-cyclopropyl, -N-cyclobutyl, -N-cyclohexyl or



- 10 In another embodiment of the present invention, R¹ and R² are independently absent or present, and if present each is independently selected from the group consisting of H, -CH₃, -C₂H₅, difluorophenylmethylene, cyclopropyl, dichlorophenylmethylene, -CH(CH₃)₂, cyclohexylmethylene, cyclohexyl, isoxazolyl, difluorophenyl, -CH₂CH₂OH,
- 15 -CH₂-CH₂-N(CH₃)₂, -C(=O)N(H)cyclopropyl, -C(=O)N(H)C₂H₅, -C(=O)N(H)CH₂CF₃, -C(=O)N(H)CH(CH₃)₂, -C(=O)N(H)C(CH₃)₃, -C(=S)N(H)cyclopropyl, -C(=O)NH₂, -C(=O)N(H)CH₃, -S(O)₂CH₃, -S(O)₂N(CH₃)₂, -S(O)₂CH₂CH₃, -C(=O)CH₃, -S(O)₂(CH₂)₂CH₃, -C(=O)N(H)cyclohexyl, -C(=NH)NH₂, -C(=O)N(H)NH₂, thiazolyl,



In another embodiment of the invention, Z is N or C(R²⁹).

In another embodiment of the invention, Z is N.

In another embodiment of the invention, Z is C(H), C(alkyl),

10 C(halogen), C(CF₃) or C(N(R³⁰)₂).

In another embodiment of the invention, Z is C(alkyl), C(F) or C(NH₂).

In another embodiment of the invention, G is N or C(R⁴).

In another embodiment of the invention, G is N.

In another embodiment of the invention, G is C(R⁴).

15 In another embodiment of the invention, G is C(H), C(alkyl),

C(halogen), C(CF₃) or C(N(R³⁰)₂).

In another embodiment of the invention, G and Z are the same.

In another embodiment of the invention, G and Z are different.

In another embodiment of the invention, G and Z are both N.

In another embodiment of the invention, G is R^4 and Z is $C(R^{29})$, wherein $R^4=R^{29}$.

In another embodiment of the invention, G is N and Z is $C(R^{29})$.

In another embodiment of the invention, G is $C(R^4)$ and Z is N.

5 In another embodiment of the invention, R^3 is selected from the group consisting of H, alkyl, haloalkyl, hydroxyalkyl, halogen, $-N(R^{30})_2$, $-OR^{30}$ and $-CF_3$.

In another embodiment of the invention, R^3 is selected from the group consisting of H, $-CH_3$, $-CH_2CH_3$, cyclopropyl, $-F$, $-Cl$, OCH_3 , OCF_3 and CF_3 .

10 In another embodiment of the invention, Z is N and R^4 is selected from the group consisting of H, alkyl, hydroxyalkyl, halogen, OR^{30} , or CF_3 .

In another embodiment of the invention, R^6 is selected from the group consisting of H, alkyl, halogen, hydroxyalkyl, $-CN$, $-N(R^{30})_2$, $-OR^{30}$, $-N=CH$ -alkyl, and $-NR^{30}C(=O)$ alkyl.

15 In another embodiment of the invention, R^6 is selected from the group consisting of H, $-NH_2$, $-CH_3$, $-CN$ and $-F$.

In another embodiment of the invention, R^{10} is selected from the group consisting of H, alkyl, aralkyl, hydroxyalkyl, and carbonyl.

20 In another embodiment of the invention, R^{10} is selected from the group consisting of $-CH_3$, $-CH_2CH_3$ and $-CH_2CH_2CH_3$, and m is 0 - 2.

In another embodiment of the invention, R^{11} is selected from the group consisting of H, alkyl, hydroxyalkyl and carbonyl.

In another embodiment of the invention, R^{11} is H or $-CH_3$.

25 In another embodiment of the invention, R^{12} is selected from the group consisting of H, CN, $-C(=O)N(R^{30})_2$ and alkyl.

In another embodiment of the invention, R^{12} is selected from the group consisting of H, $-CH_3$, CN and $-CH_2CH_3$.

30 In another embodiment of the invention, the ring atoms of ring D are independently C or N and substituted by independently selected 0-4 R^{20} moieties.

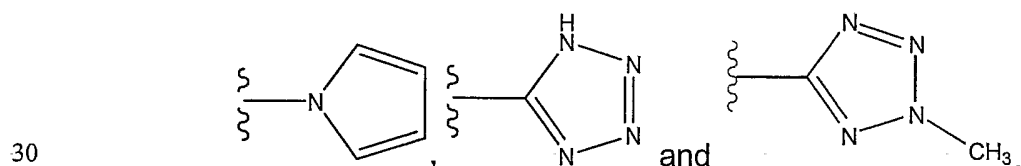
In another embodiment of the invention, ring D is a 5 to 6 membered aryl, heteroaryl, heterocyclenyl, or heterocyclyl ring and substituted by independently selected 0-4 R^{20} moieties.

In another embodiment of the invention, the R^{20} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, alkynyl, alkoxy, alkylamino, alkylheteroaryl, alkylsulfinyl, alkoxycarbonyl, aminoalkyl, amidinyl, aralkyl, aralkoxy, aryl, aryloxy, cyano, cycloalkyl, cycloalkenyl, halogen, haloalkyl, heteroalkyl, heteroaryl, heterocyclyl, hydroxyalkyl, trifluoromethyl, trifluoromethoxy, -
 5 $(CH_2)_qOR^{31}$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, $-alkynylC(R^{31})_2OR^{31}$, $-C(=O)R^{30}$, $-C(=O)N(R^{30})_2$, $-C(=O)OR^{30}$, $-N(R^{30})_2$, $-N(R^{30})C(=O)R^{31}$, $-NHC(=O)N(R^{30})_2$,
 10 $-N(R^{30})C(=O)OR^{31}$, $-N(R^{30})C(=NCN)N(R^{30})_2$, $-N(R^{30})C(=O)N(R^{30})_2$, $-N(R^{30})SO_2(R^{31})$, $-N(R^{30})SO_2N(R^{30})_2$, $-OR^{30}$, $-OC(=O)N(R^{30})_2$, $-SR^{30}$, $-SO_2N(R^{30})_2$, $-SO_2(R^{31})$, $-OSO_2(R^{31})$, and $-OSi(R^{30})_3$.

In another embodiment of the invention, the R^{20} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, amino, halogen, CN, CH_3 , CF_3 , OCF_3 , $-(CH_2)_qOR^{31}$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, $-alkynylC(R^{31})_2OR^{31}$, $-C(=O)R^{30}$, $-C(=O)OR^{30}$, $-N(R^{30})_2$, $-N(R^{30})C(=O)R^{31}$, $-NHC(=O)N(R^{30})_2$, $-N(R^{30})C(=O)OR^{31}$, $-N(R^{30})C(=NCN)N(R^{30})_2$, $-N(R^{30})C(=O)N(R^{30})_2$, $-OR^{30}$, $-OC(=O)N(R^{30})_2$, and
 20 $-OSO_2(R^{31})$.

In another embodiment of the invention, two R^{20} moieties are linked together to form a five or six membered aryl, cycloalkyl, heterocyclenyl, heterocyclyl or heteroaryl ring wherein said five or six membered aryl, cycloalkyl, heterocyclenyl, heterocyclyl, and heteroaryl ring is fused to ring D
 25 and the fused ring is optionally substituted with 0 to 4 R^{21} moieties.

In another embodiment of the invention, the R^{20} moieties can be the same or different, each being independently selected from the group consisting of H, $-CN$, $-CH_3$, $-CF_3$, $-CH_2OH$, $-CO_2H$, $-CO_2CH_3$, $-NH_2$, $-NHCH_3$, $-OCF_3$, $-OH$, F, Cl, Br, $-C(=NOH)NH_2$, $-OCH_2CH_2S(O_2)CH_3$, $-C(=O)NH_2$,



In another embodiment of the invention, Y is selected from the group consisting of: $-(\text{CHR}^{13})_r-$, $-(\text{CR}^{13}\text{R}^{13})_r-$, $-\text{C}(=\text{O})-$ and $-\text{CHR}^{13}\text{C}(=\text{O})-$.

In another embodiment of the invention, Y is selected from the group consisting of: $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{CH}_2\text{OH})-$, $-\text{C}(=\text{O})-$ and

5 $-\text{CH}(\text{CO}_2\text{alkyl})-$.

In another embodiment of the invention, m is 0-3.

In another embodiment of the invention, n is 0-2.

In another embodiment of the invention, q is 1, 2 or 3.

In another embodiment of the invention, r is 1 or 2.

10 In another embodiment of the invention, Z is N, C(H), C(alkyl), C(F) or C(NH₂);

G is N or C(R⁴);

R¹ and R² are independently absent or present, and if present each is independently selected from the group consisting of H, alkylaryl, aryl,
15 heteroaryl, $-(\text{CH}_2)_q\text{CF}_3$, $-(\text{CH}_2)_q\text{OH}$, $-(\text{CH}_2)_q\text{OR}^{31}$, $-(\text{CH}_2)_q\text{NH}_2$, $-(\text{CH}_2)_q\text{NHR}^{31}$,
 $-(\text{CH}_2)_q\text{N}(\text{R}^{31})_2$, $-(\text{CH}_2)_q\text{C}(=\text{O})\text{NHR}^{31}$, $-(\text{CH}_2)_q\text{SO}_2\text{R}^{31}$, $-(\text{CH}_2)_q\text{NHSO}_2\text{R}^{31}$,
 $-(\text{CH}_2)_q\text{SO}_2\text{NHR}^{31}$, $-(\text{CH}_2)_q$ -amidinyl, cyclopropyl, cyclopropylhydroxyl,
cyclobutyl, cyclobutylhydroxy, cyclopentyl, and cyclopentylhydroxy;

R³ is selected from the group consisting of H, alkyl, haloalkyl,
20 hydroxyalkyl, halogen, $-\text{N}(\text{R}^{30})_2$, $-\text{OR}^{30}$ and $-\text{CF}_3$;

R⁴ is selected from the group consisting of H, alkyl, haloalkyl,
hydroxyalkyl, halogen, $-\text{N}(\text{R}^{30})_2$, $-\text{OR}^{30}$ and $-\text{CF}_3$;

R⁶ is selected from the group consisting of H, alkyl, halogen,
hydroxyalkyl, $-\text{CN}$, $-\text{N}(\text{R}^{30})_2$, $-\text{OR}^{30}$, $-\text{N}=\text{CH}$ -alkyl, and $-\text{NR}^{30}\text{C}(=\text{O})\text{alkyl}$;

25 R¹⁰ is selected from the group consisting of H, alkyl, aralkyl,
hydroxyalkyl, and carbonyl;

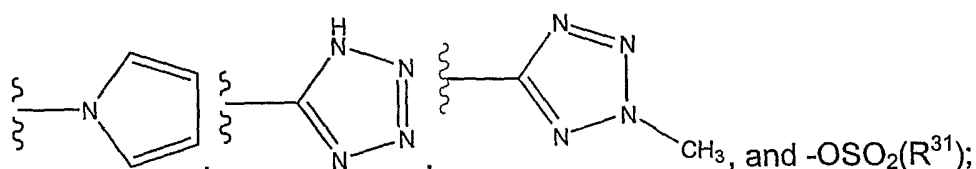
R¹¹ is selected from the group consisting of H, alkyl, hydroxyalkyl, and
carbonyl;

R¹² is selected from the group consisting of H, CN, $-\text{C}(=\text{O})\text{N}(\text{R}^{30})_2$ and
30 alkyl;

ring D is a 5 to 6 membered aryl, heteroaryl, heterocyclenyl, or
heterocyclyl ring and substituted by 0-4 R²⁰ moieties;

the R²⁰ moieties can be the same or different, each being
independently selected from the group consisting of H, alkyl, amino, halogen,

- CN, CH₃, CF₃, OCF₃, -(CH₂)_qOR³¹, -(CH₂)_qNHR³¹, -(CH₂)_qC(=O)NHR³¹, -
 (CH₂)_qSO₂R³¹, -(CH₂)_qNSO₂R³¹, -(CH₂)_qSO₂NHR³¹, -alkynylC(R³¹)₂OR³¹,
 -C(=O)R³⁰, -C(=O)OR³⁰, -N(R³⁰)₂, -N(R³⁰)C(=O)R³¹, -NHC(=O)N(R³⁰)₂,
 -N(R³⁰)C(=O)OR³¹, -N(R³⁰)C(=NCN)N(R³⁰)₂, -N(R³⁰)C(=O)N(R³⁰)₂, -OR³⁰,
 5 -OC(=O)N(R³⁰)₂,



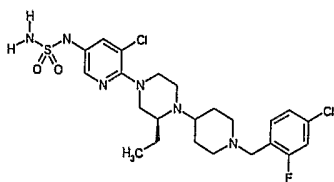
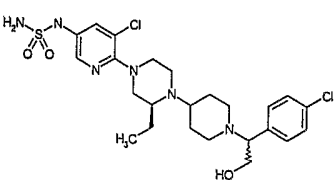
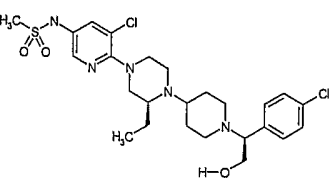
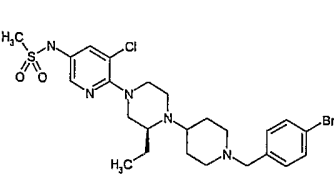
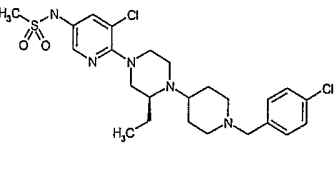
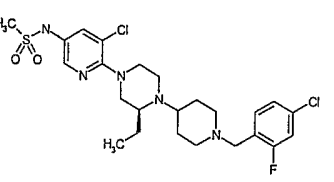
Y is selected from the group consisting of: -CH₂-, -CH(CH₃)-,
 -CH(CH₂OH)-, -C(=O)- and -CH(CO₂alkyl)-;

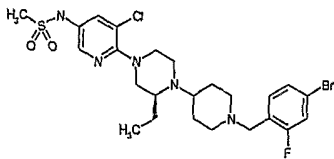
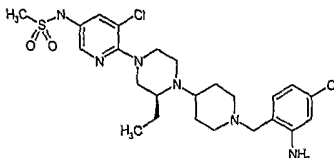
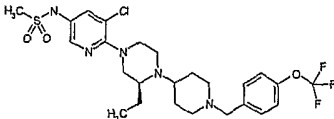
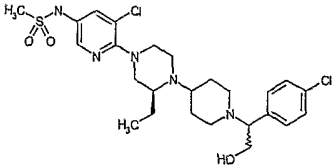
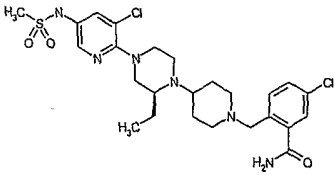
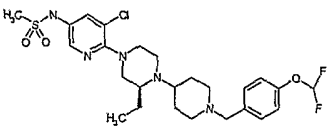
- 10 m is 0-2;
 n is 0-2;
 q is 1 or 2; and
 r is 1 or 2.

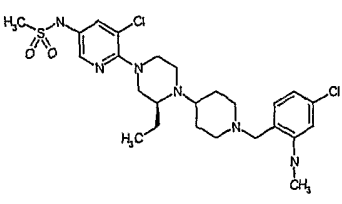
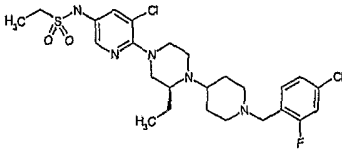
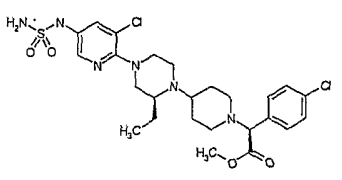
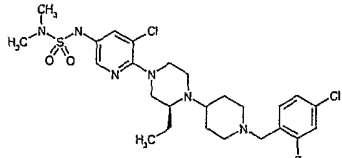
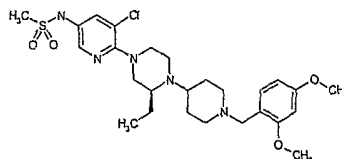
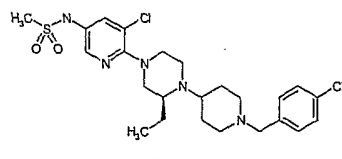
- In still another embodiment of the present invention, a compound is
 15 selected from the following structures in Table 1 below (or a pharmaceutically
 acceptable salt or solvate thereof) which are shown along with their IC₅₀
 ratings. The IC₅₀ values are rated, "A" for IC₅₀ values less than about 25
 nanomolar (nM), "B" for IC₅₀ values in the range of from about 25 to about 100
 nM and "C" for IC₅₀ values greater than about 100 nM. For example,
 20 Compound Number 1 has an IC₅₀ value of 0.8 nM.

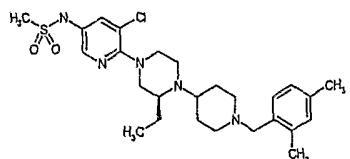
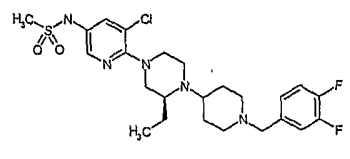
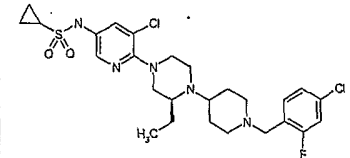
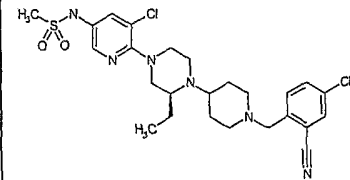
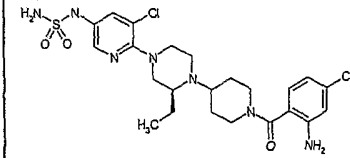
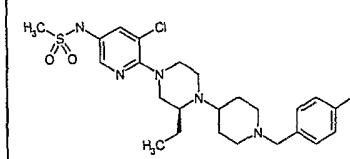
Table 1

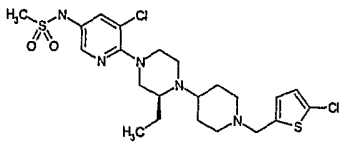
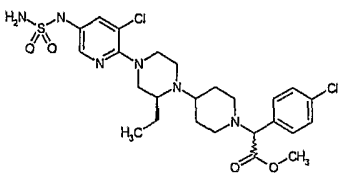
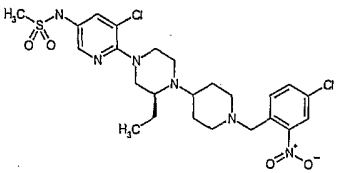
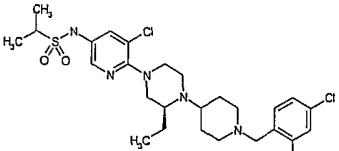
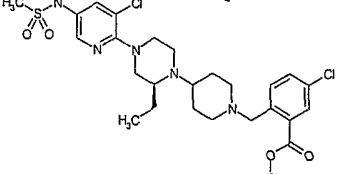
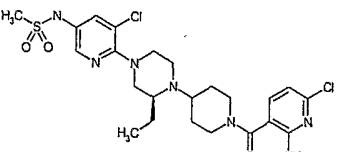
Compound No.	STRUCTURE	IC ₅₀
1		A

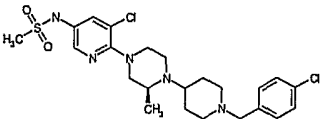
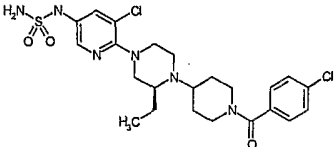
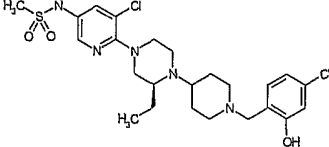
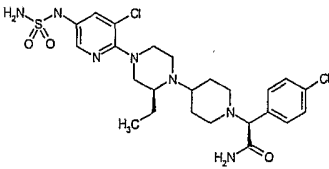
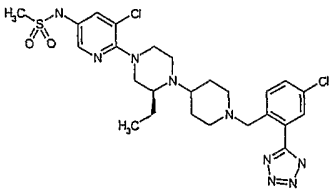
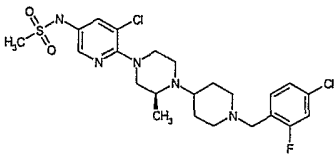
2		A
3		A
4		A
5		A
6		A
7		A

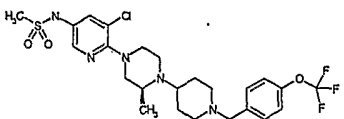
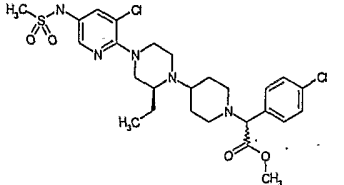
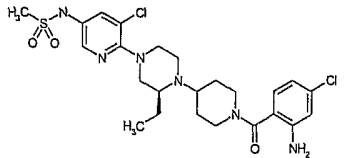
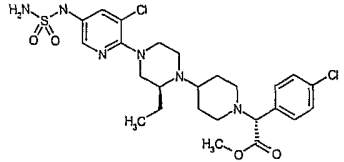
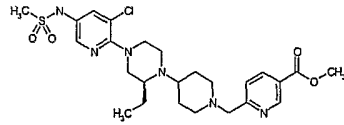
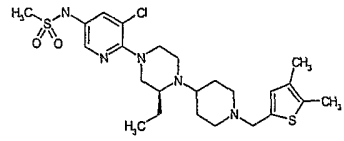
8		A
9		A
10		A
11		A
12		A
13		A

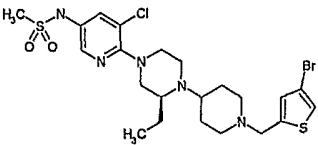
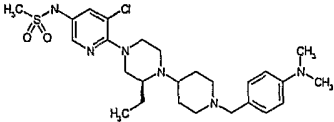
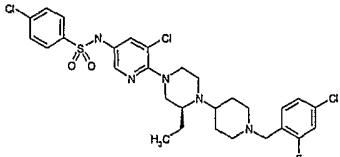
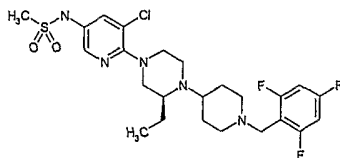
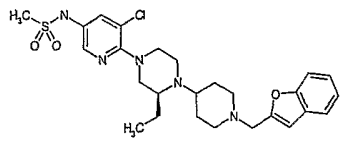
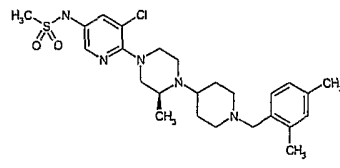
14		A
15		A
16		A
17		A
18		A
19		A

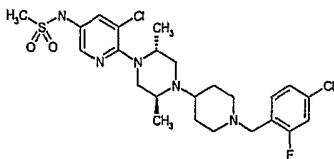
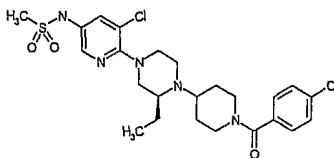
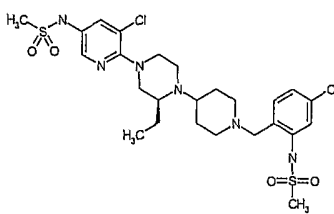
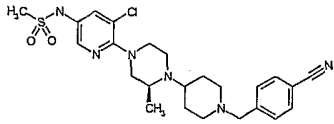
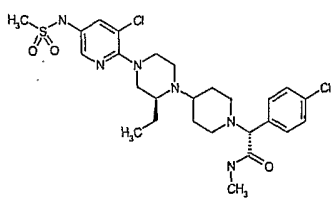
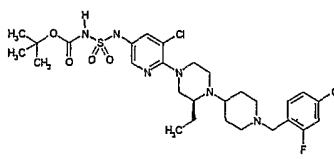
20		A
21		A
22		A
23		A
24		B
25		B

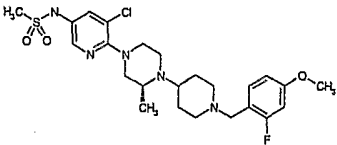
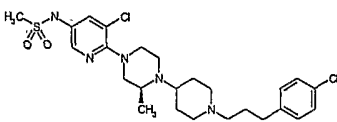
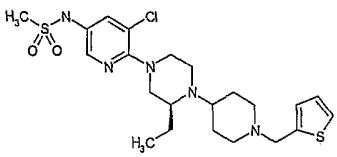
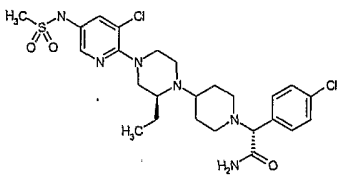
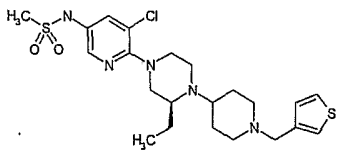
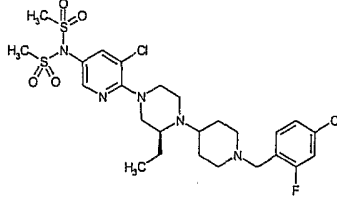
26		B
27		B
28		B
29		B
30		B
31		B

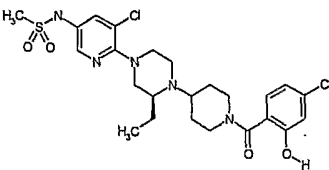
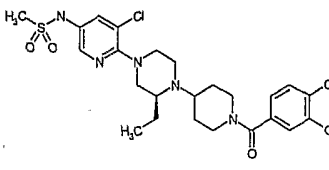
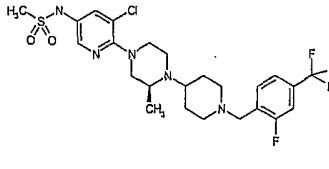
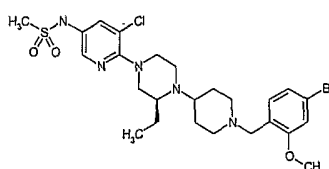
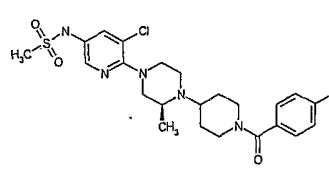
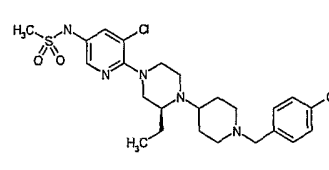
32		B
33		B
34		B
35		B
36		B
37		B

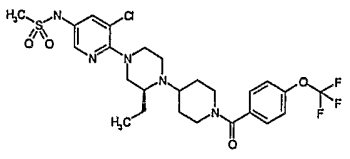
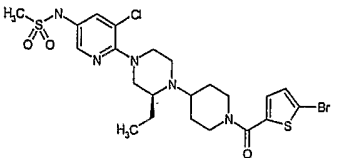
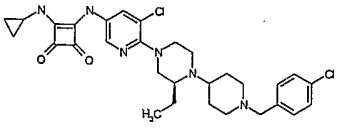
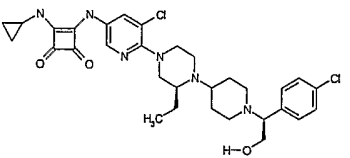
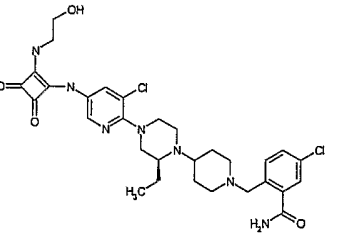
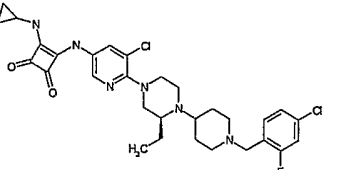
38		B
39		B
40		B
41		C
42		C
43		C

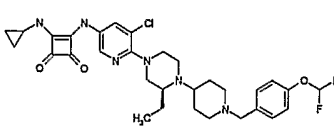
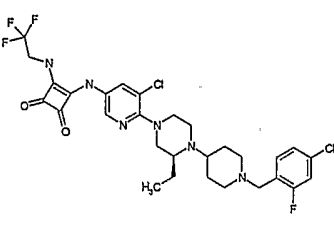
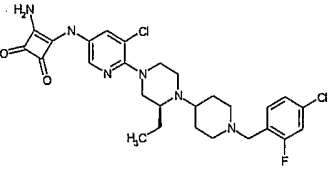
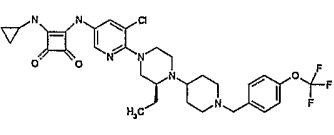
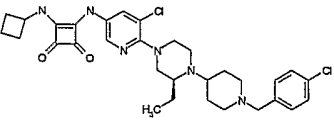
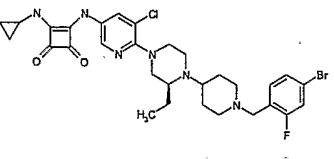
44		C
45		C
46		C
47		C
48		C
49		C

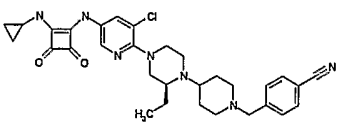
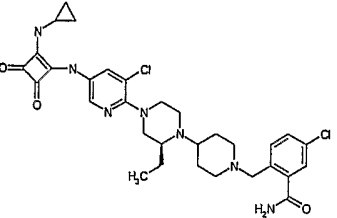
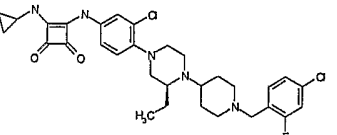
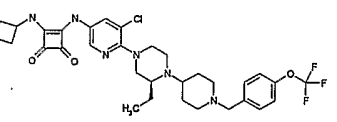
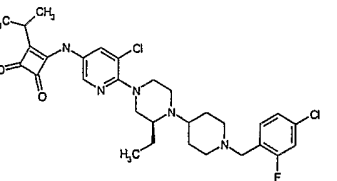
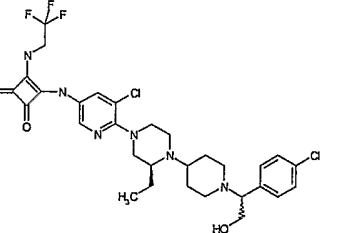
50		C
51		C
52		C
53		C
54		C
55		C

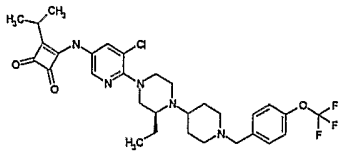
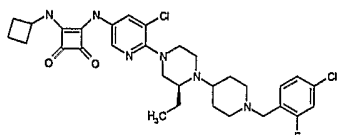
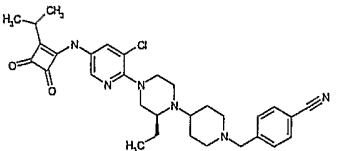
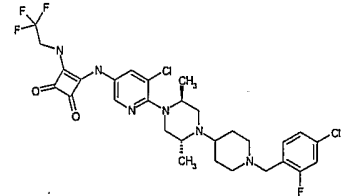
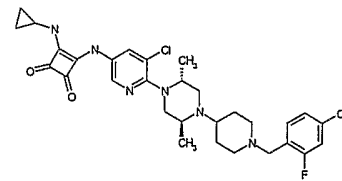
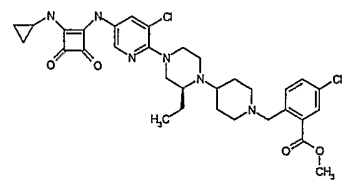
56		C
57		C
58		C
59		C
60		C
61		C

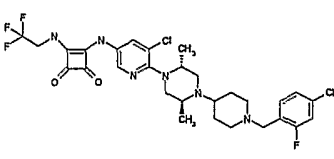
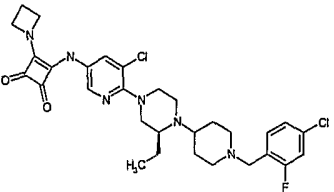
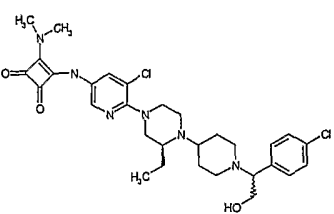
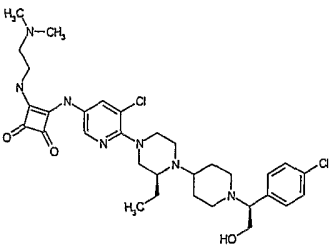
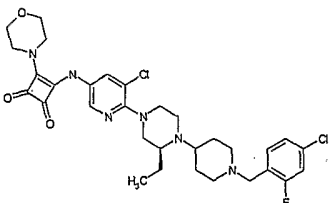
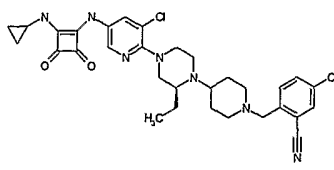
62		C
63		C
64		C
65		C
66		C
67		C

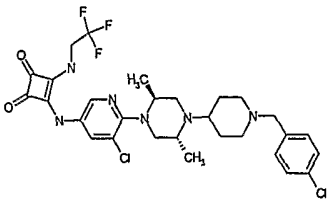
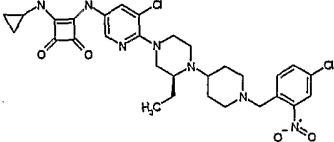
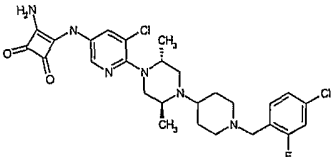
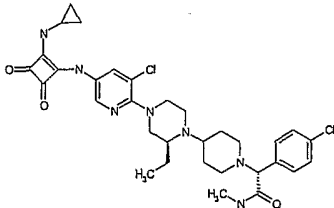
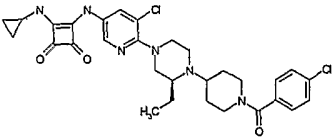
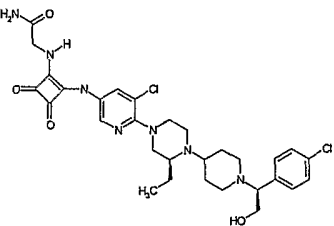
68		C
69		C
70		A
71		A
72		A
73		A

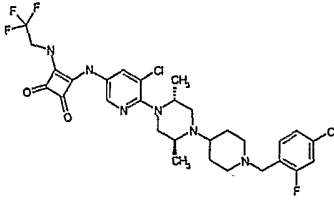
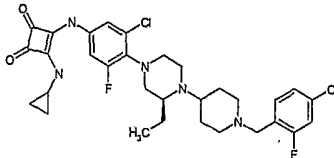
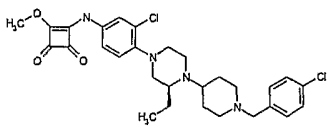
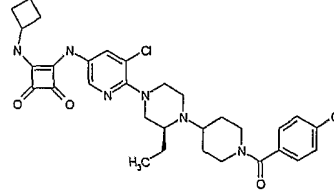
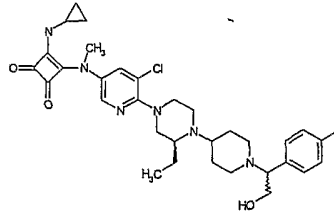
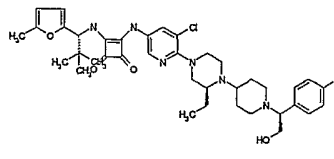
74		A
75		A
76		A
77		A
78		A
79		A

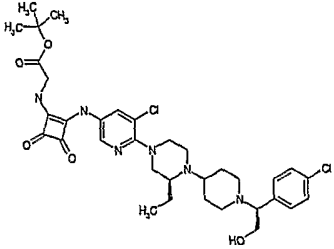
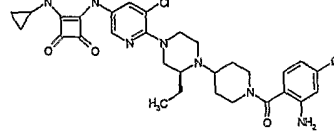
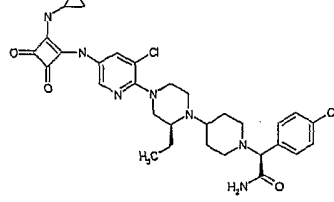
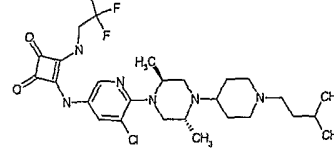
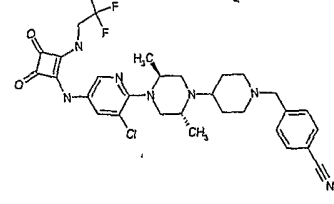
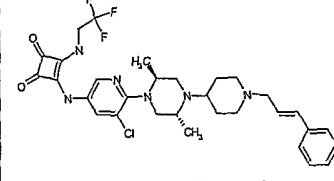
80		A
81		A
82		A
83		A
84		A
85		A

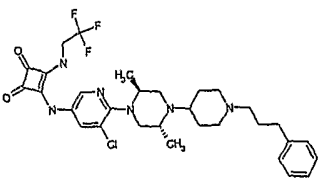
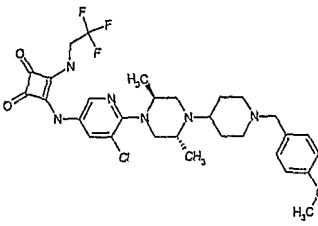
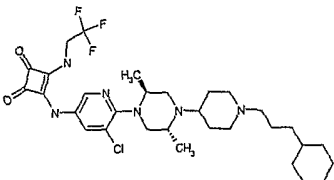
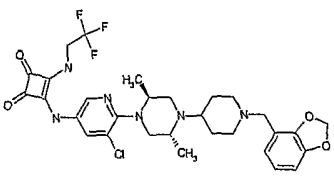
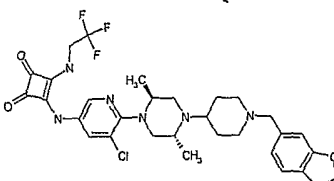
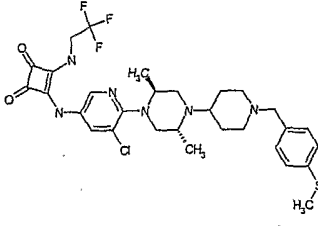
86		A
87		A
88		A
89		A
90		A
91		A

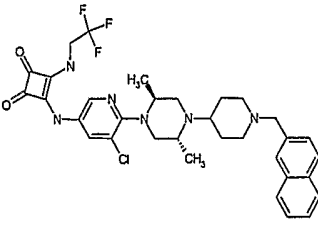
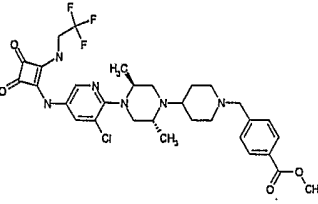
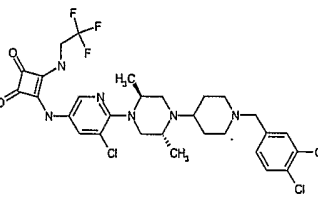
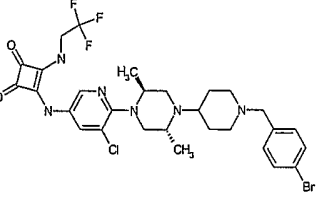
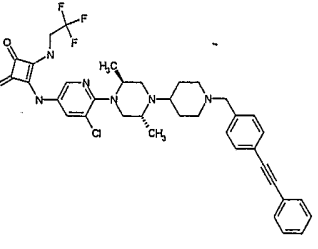
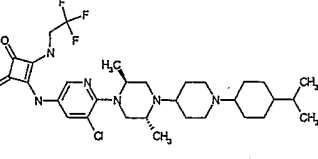
92		A
93		A
94		A
95		A
96		A
97		A

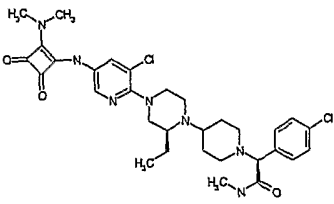
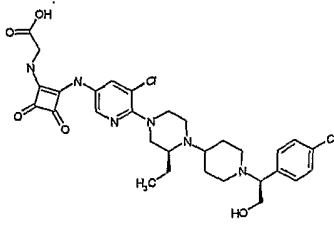
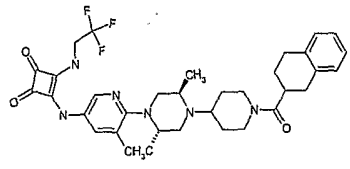
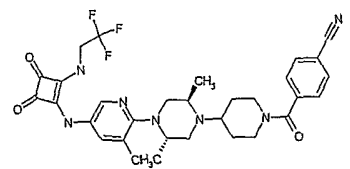
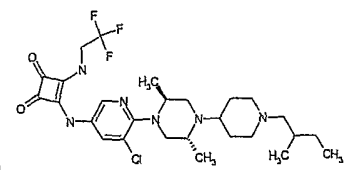
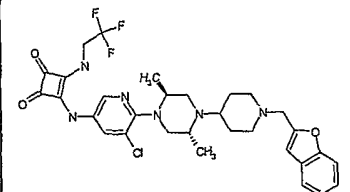
98		A
99		A
100		A
101		A
102		A
103		B

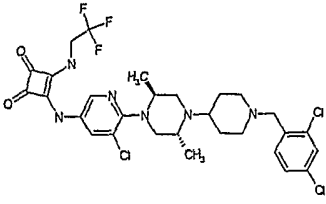
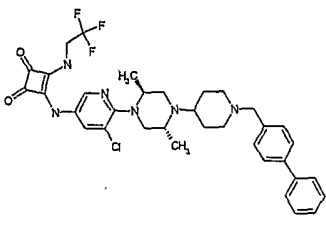
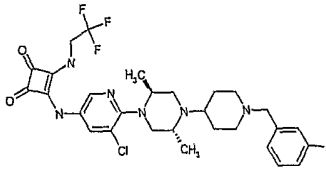
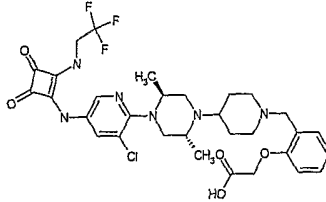
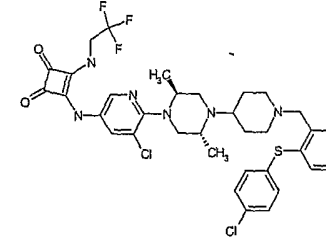
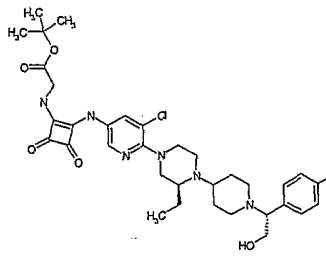
104		B
105		B
106		B
107		B
108		B
109		B

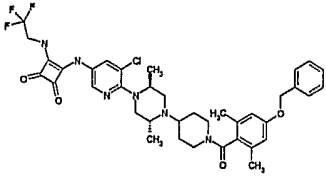
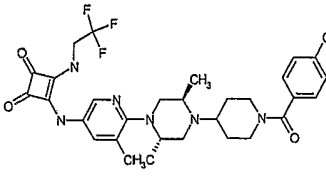
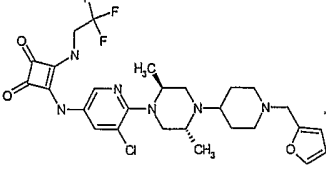
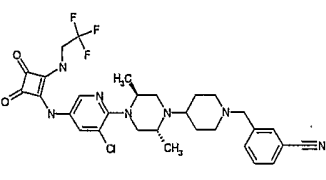
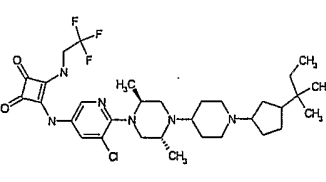
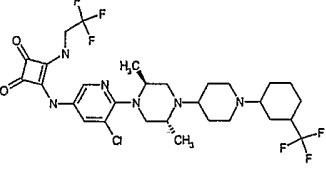
110		B
111		B
112		B
113		C
114		C
115		C

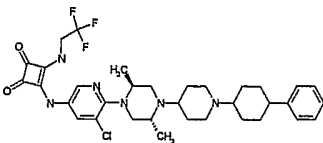
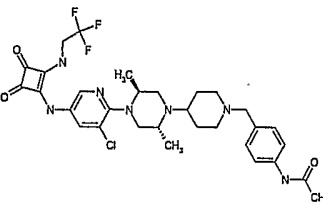
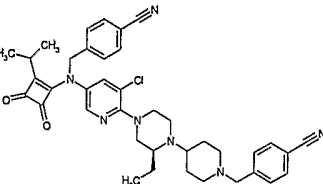
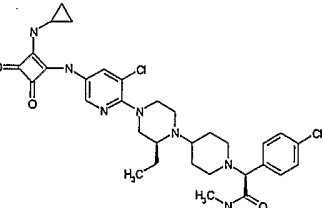
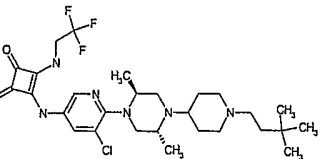
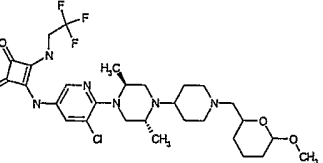
116		C
117		C
118		C
119		C
120		C
121		C

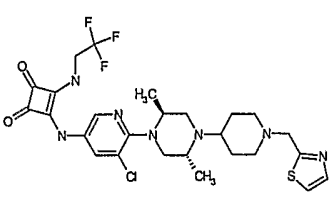
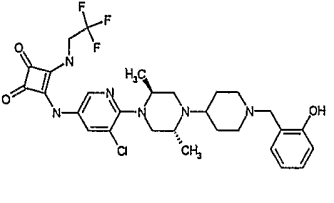
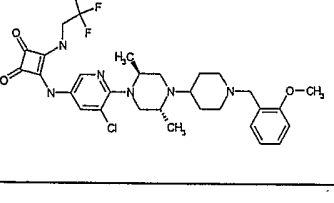
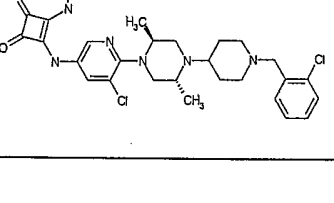
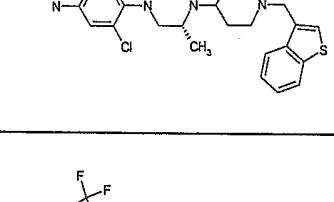
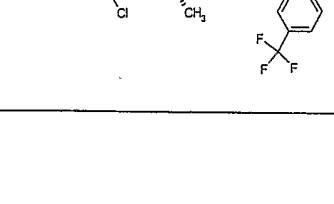
122		C
123		C
124		C
125		C
126		C
127		C

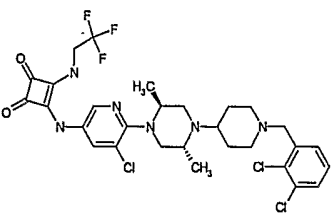
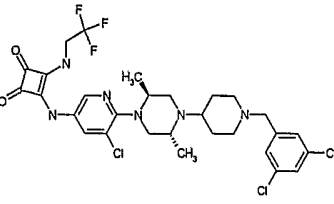
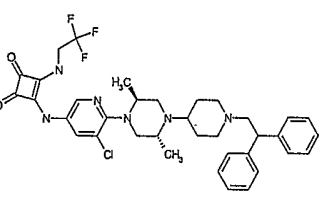
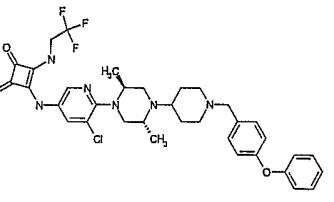
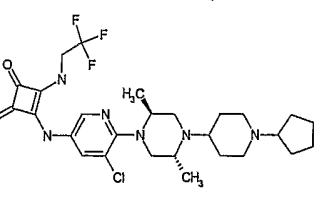
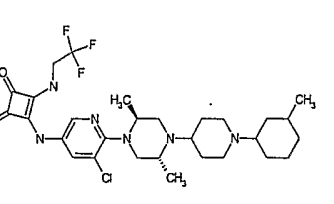
128		C
129		C
130		C
131		C
132		C
133		C

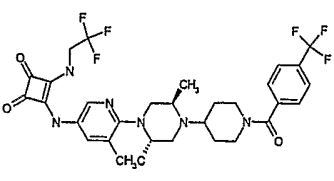
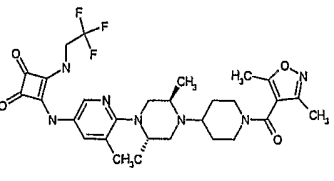
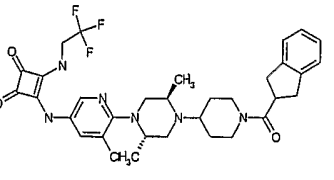
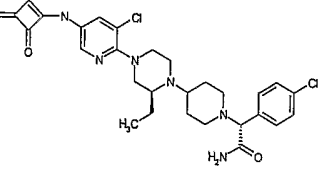
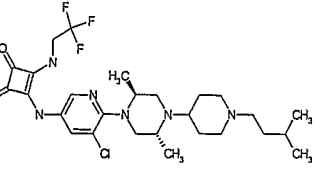
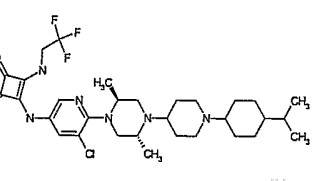
134		C
135		C
136		C
137		C
138		C
139		C

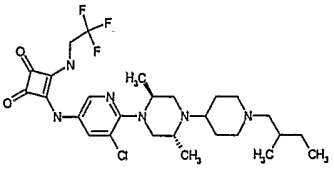
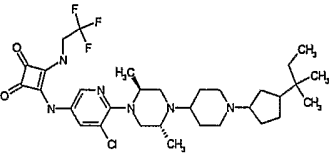
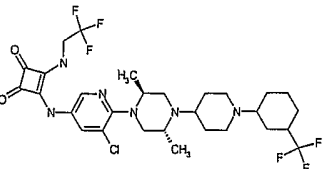
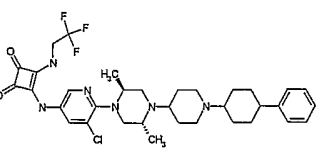
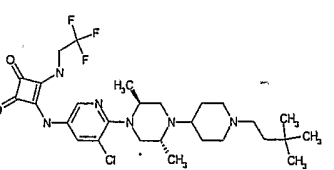
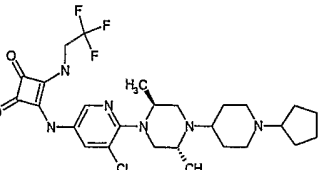
140		C
141		C
142		C
143		C
144		C
145		C

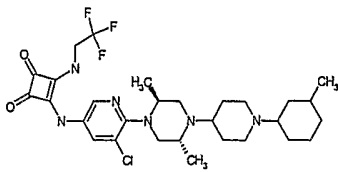
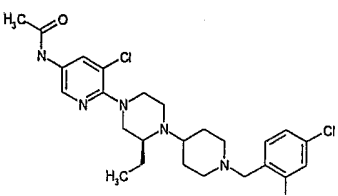
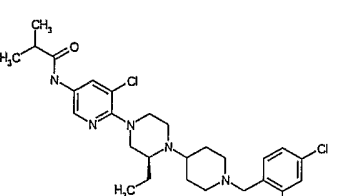
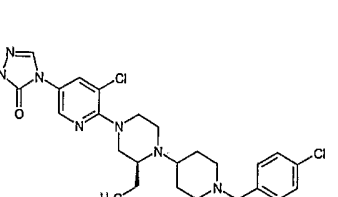
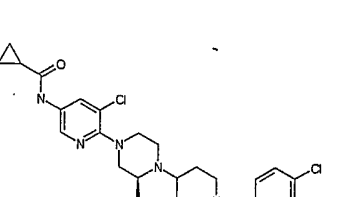
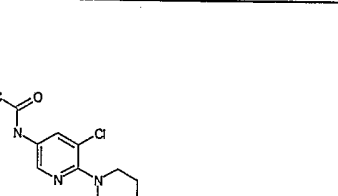
146		C
147		C
148		C
149		C
150		C
151		C

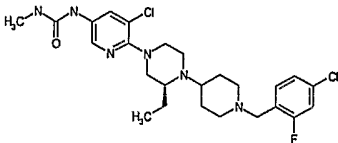
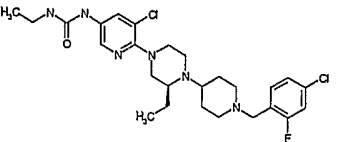
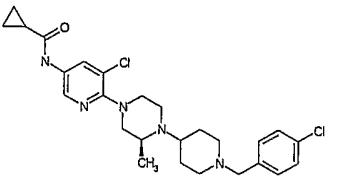
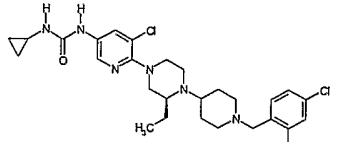
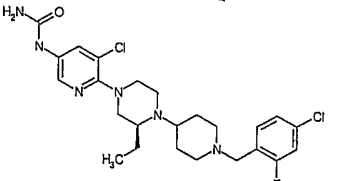
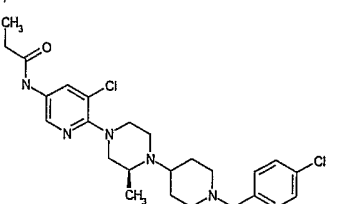
152		C
153		C
154		C
155		C
156		C
157		C

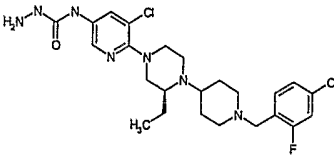
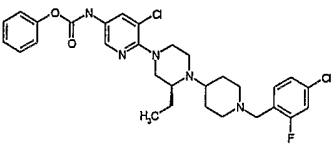
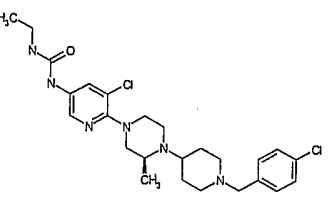
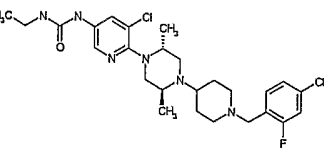
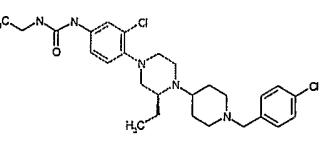
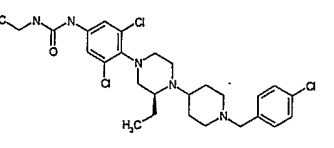
158		C
159		C
160		C
161		C
162		C
163		C

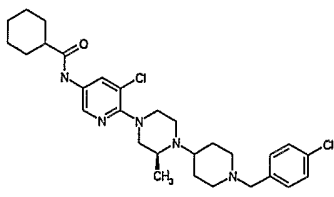
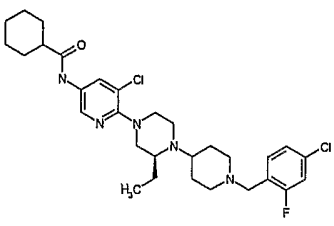
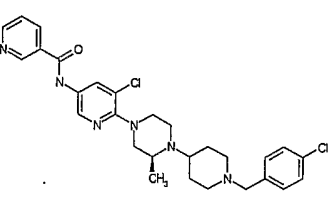
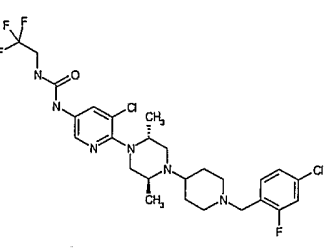
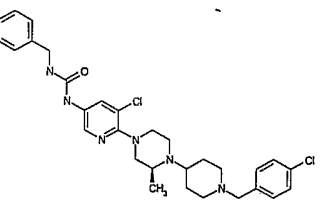
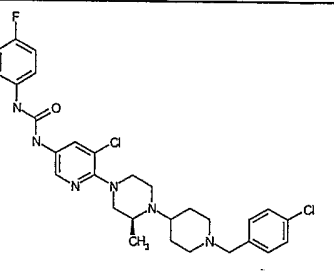
164		C
165		C
166		C
167		C
168		C
169		C

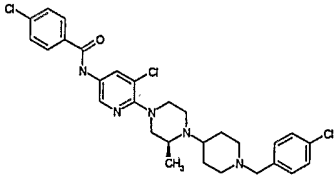
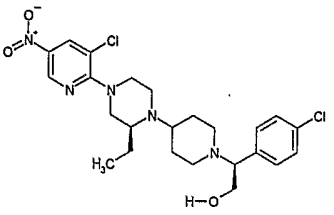
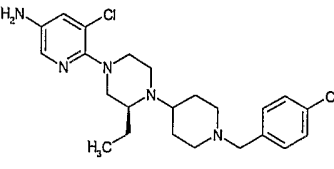
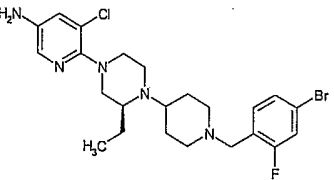
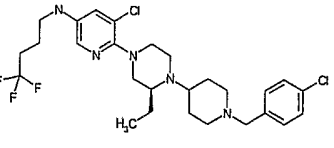
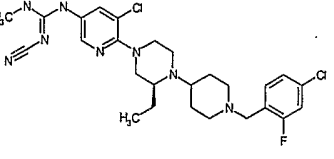
170		C
171		C
172		C
173		C
174		C
175		C

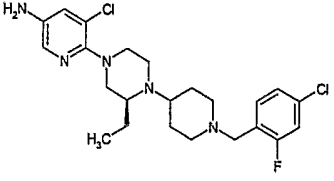
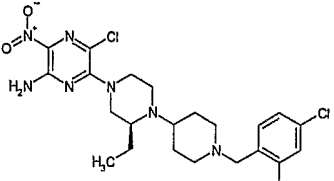
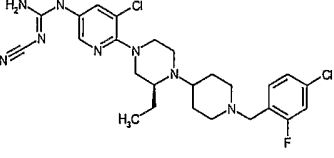
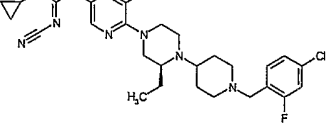
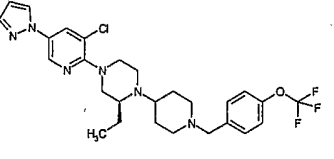
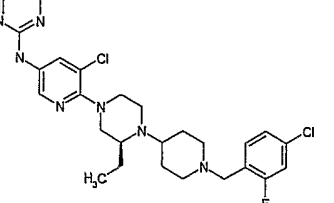
176		C
177		A
178		A
179		A
180		A
181		A

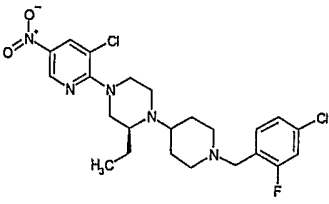
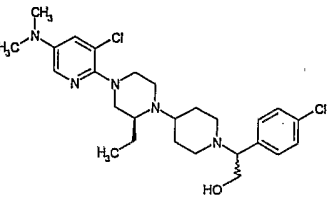
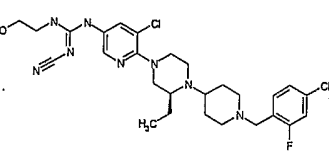
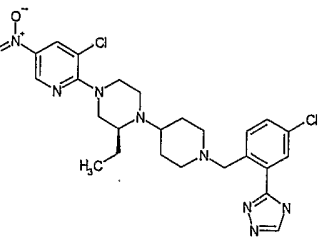
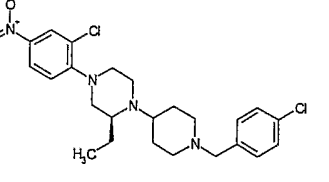
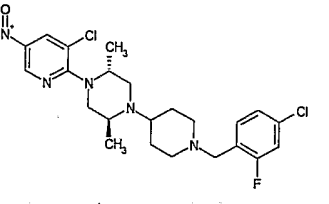
182		A
183		A
184		A
185		A
186		B
187		B

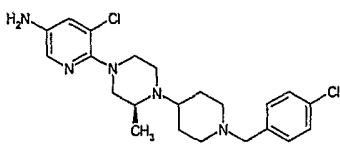
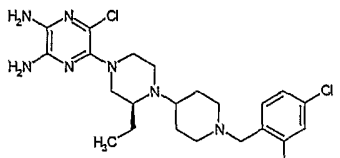
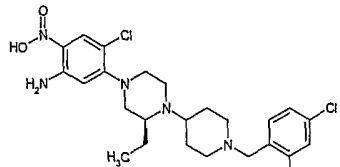
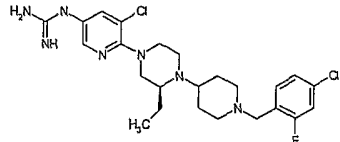
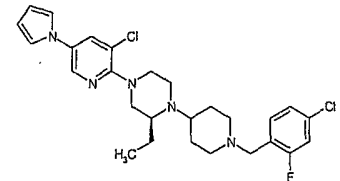
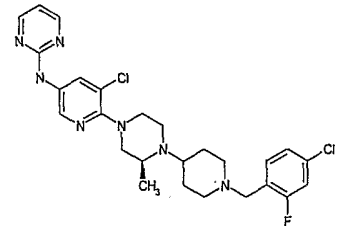
188		B
189		B
190		B
191		C
192		C
193		C

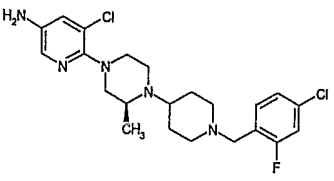
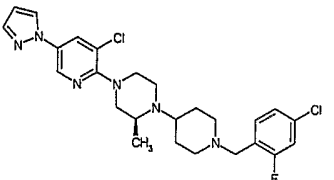
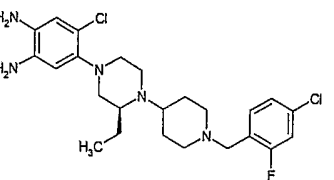
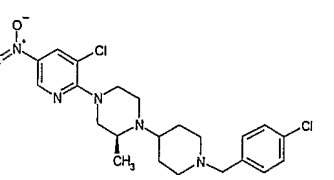
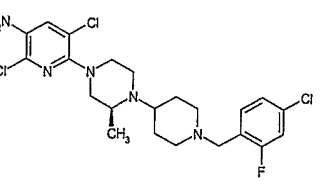
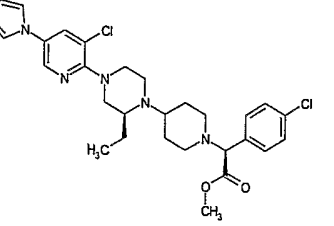
194		C
195		C
196		C
197		C
198		C
199		C

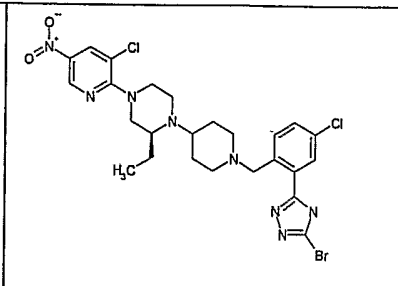
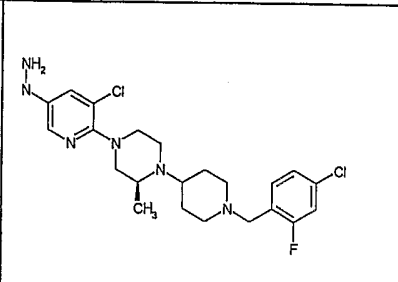
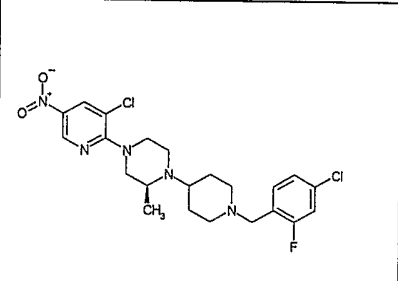
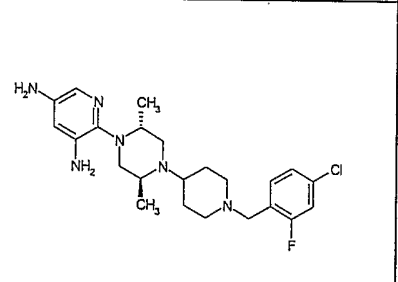
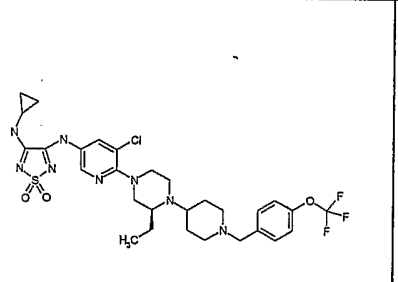
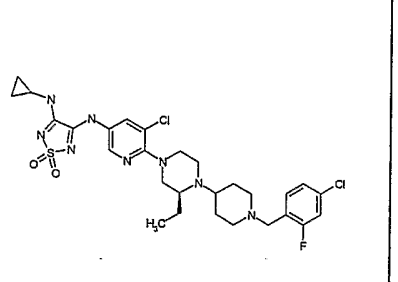
200		C
201		A
202		A
203		A
204		B
205		B

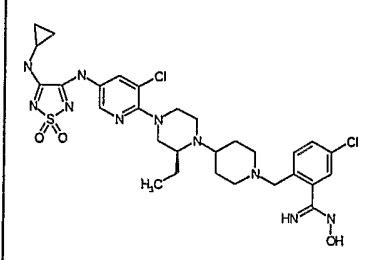
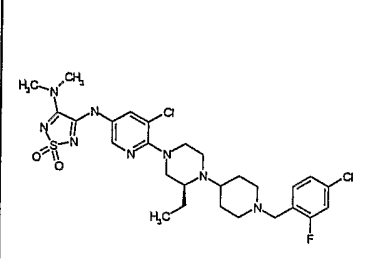
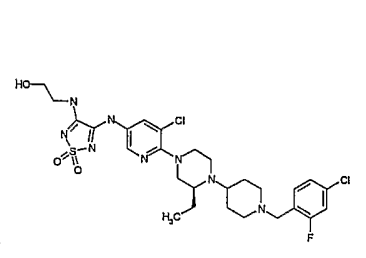
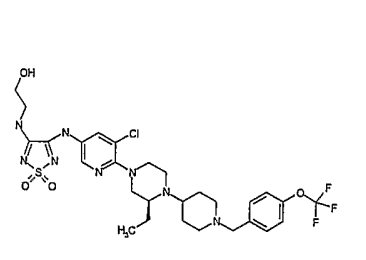
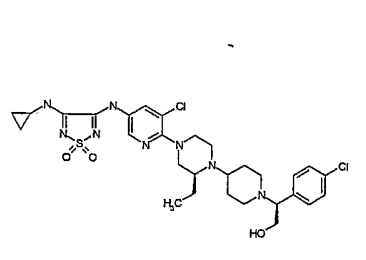
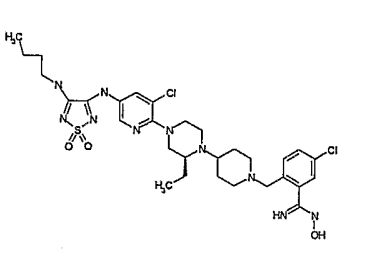
206		B
207		B
208		B
209		B
210		B
211		B

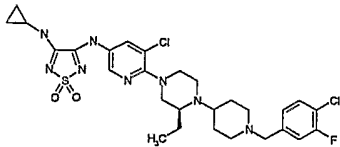
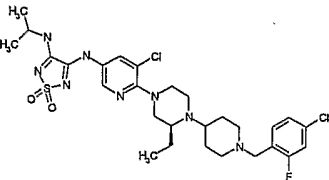
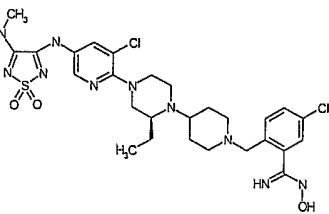
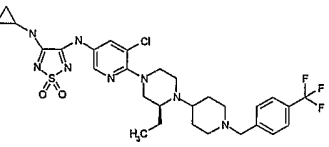
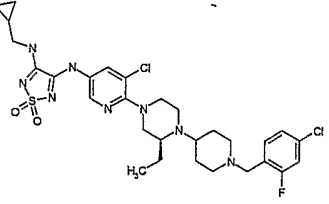
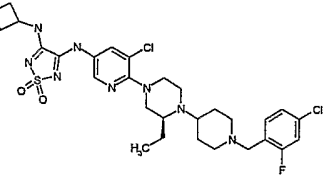
212		B
213		B
214		C
215		C
216		C
217		C

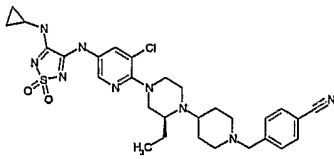
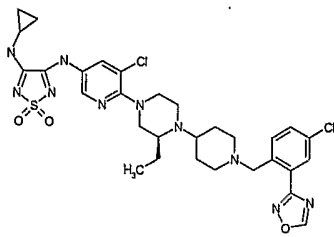
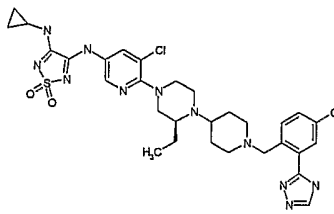
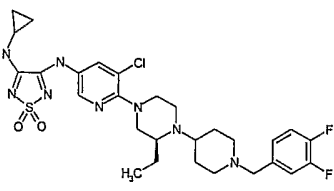
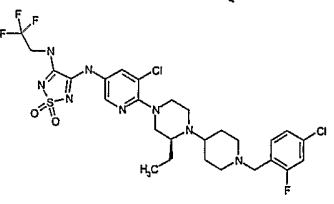
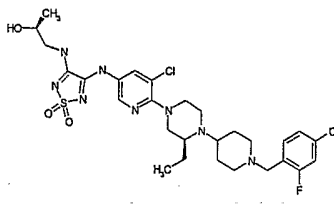
218		C
219		C
220		C
221		C
222		C
223		C

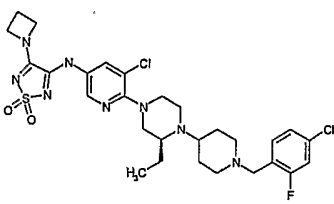
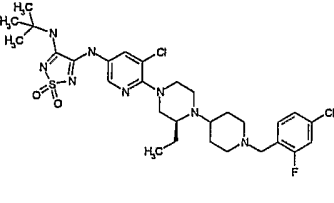
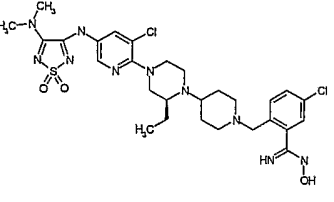
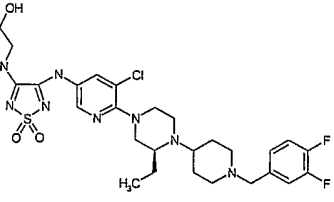
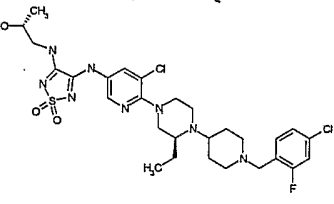
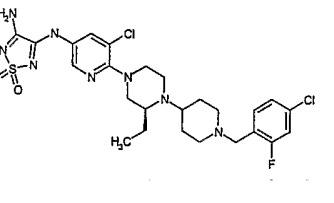
224		C
225		C
226		C
227		C
228		C
229		C

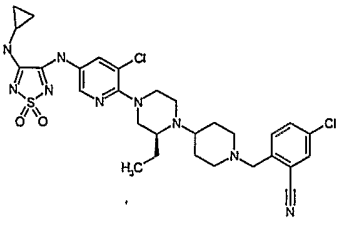
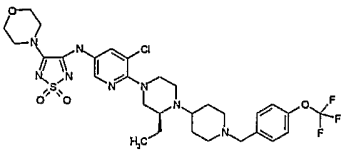
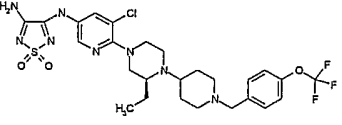
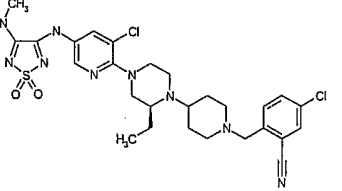
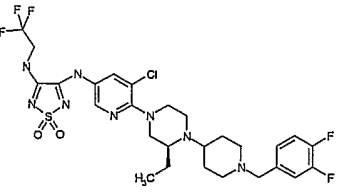
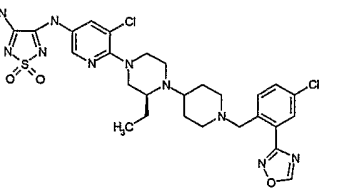
230		C
231		C
232		C
233		C
234		A
235		A

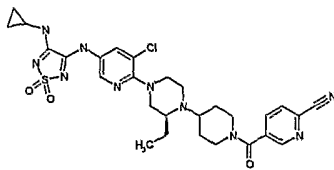
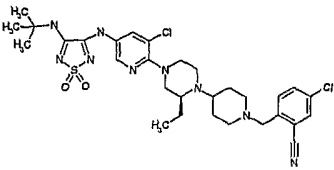
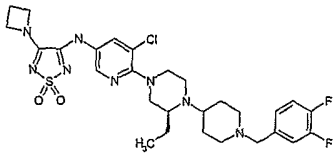
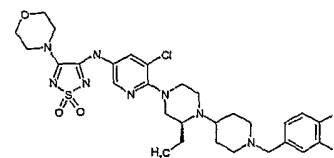
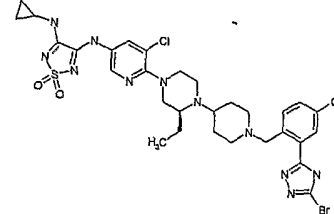
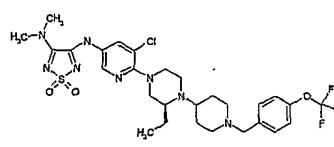
236		A
237		A
238		A
239		A
240		A
241		A

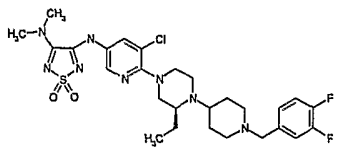
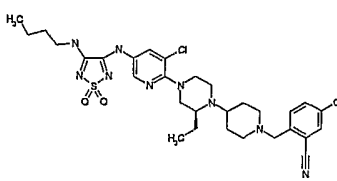
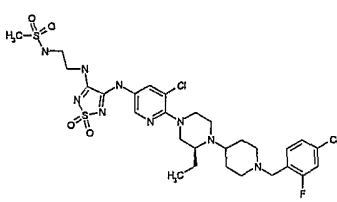
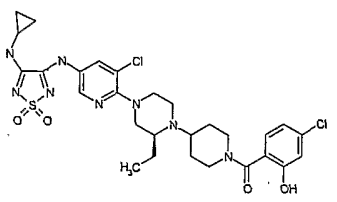
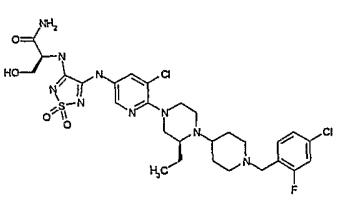
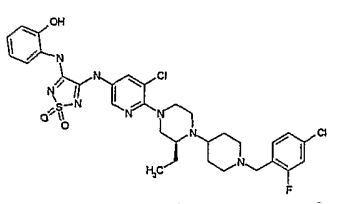
242		A
243		A
244		A
245		A
246		A
247		A

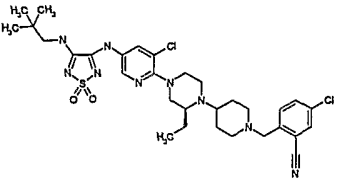
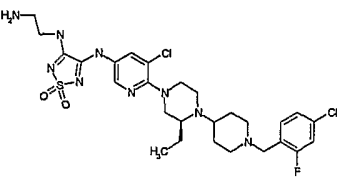
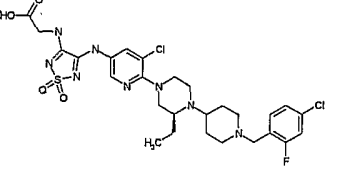
248		A
249		A
250		A
251		A
252		A
253		A

254		A
255		B
256		B
257		B
258		B
259		B

260		B
261		B
262		B
263		B
264		C
265		C

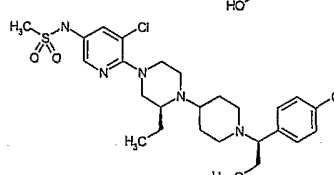
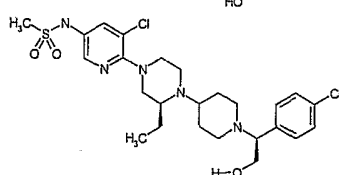
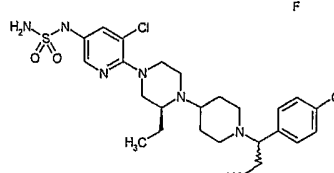
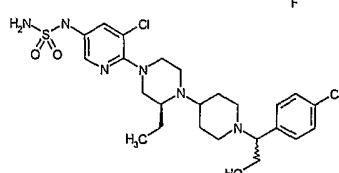
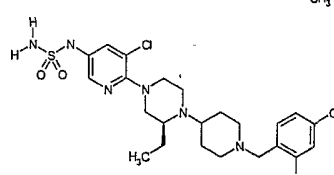
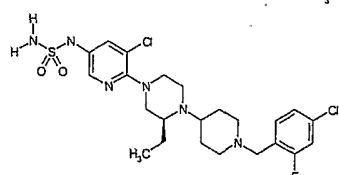
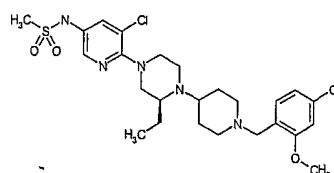
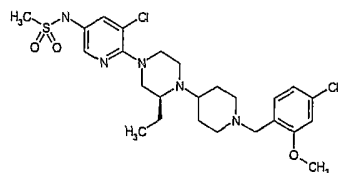
266		C
267		C
268		C
269		C
270		C
271		C

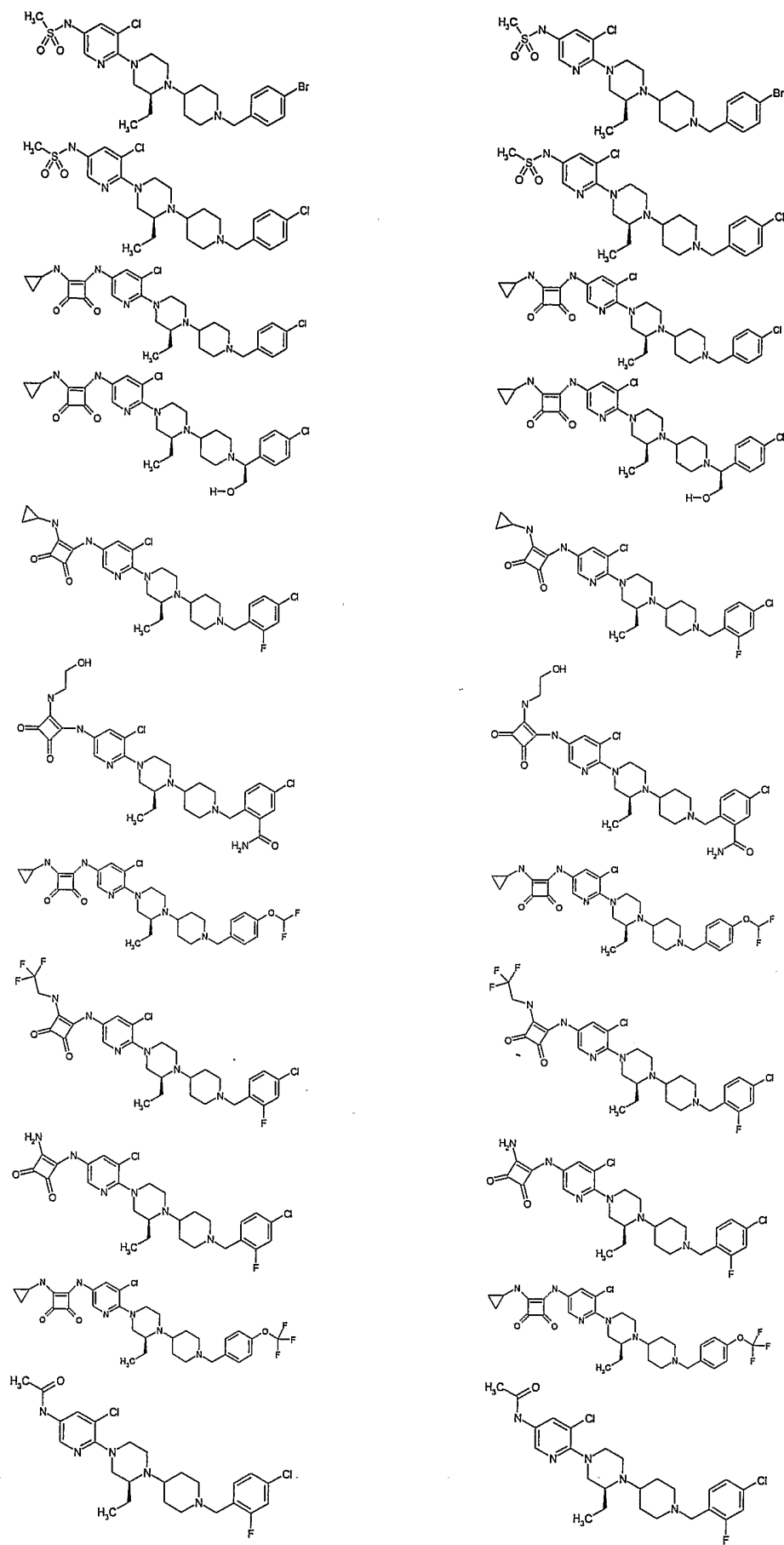
272		C
273		C
274		C
275		C
276		C
277		C

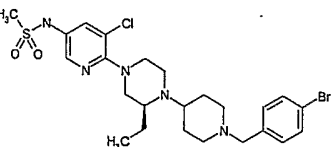
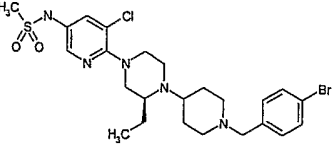
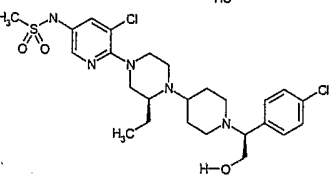
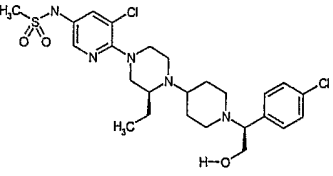
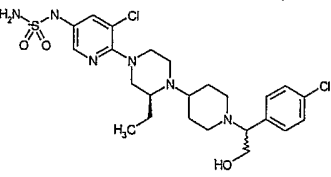
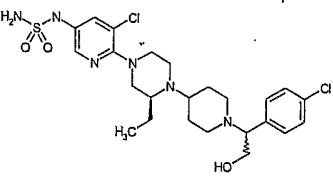
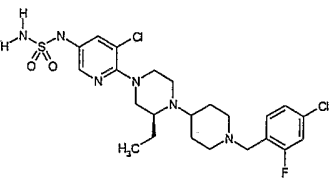
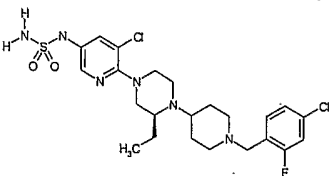
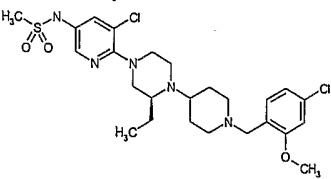
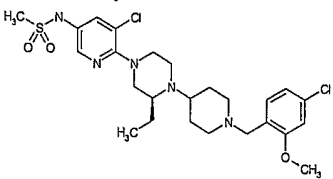
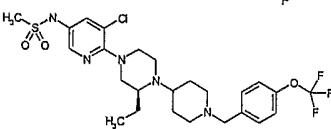
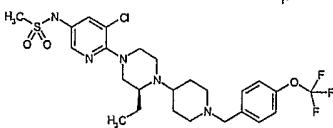
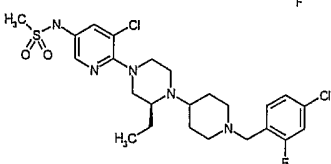
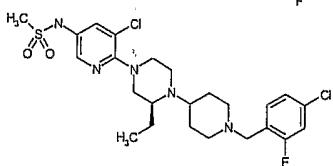
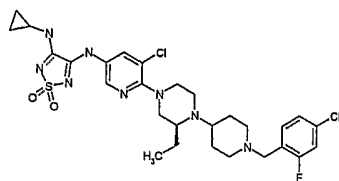
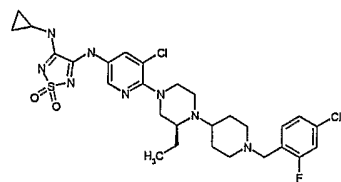
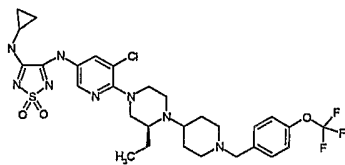
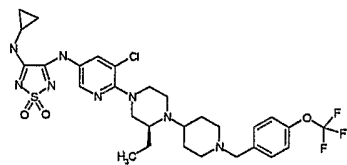
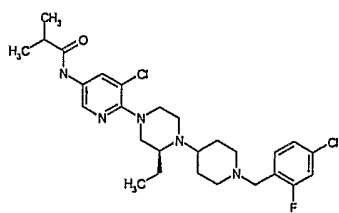
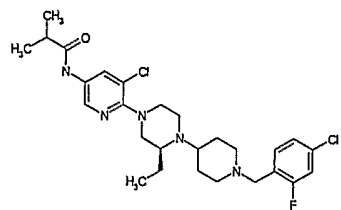
278		C
279		C
280		C

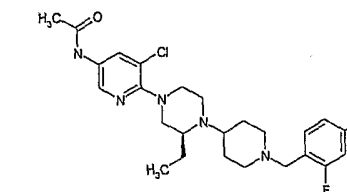
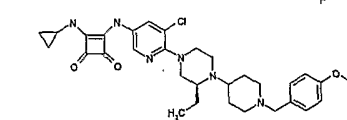
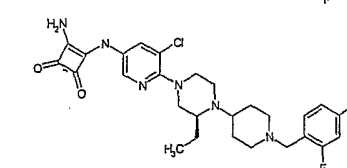
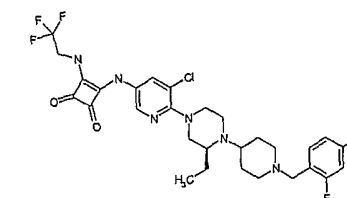
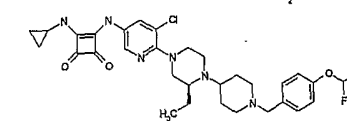
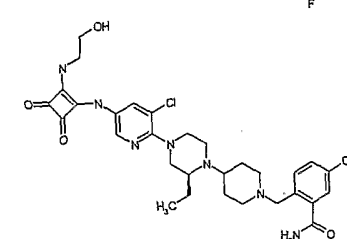
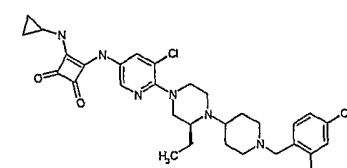
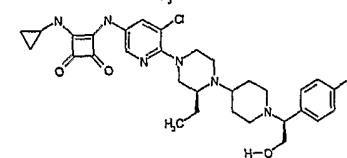
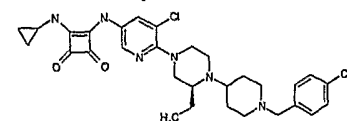
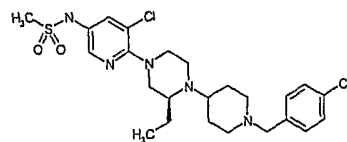
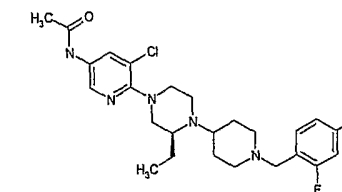
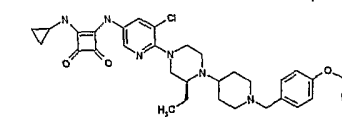
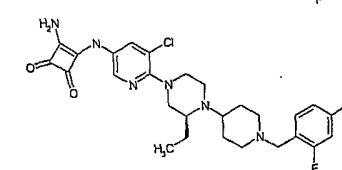
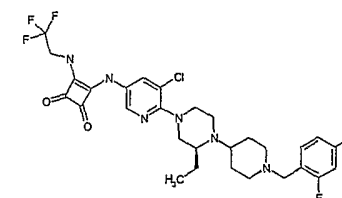
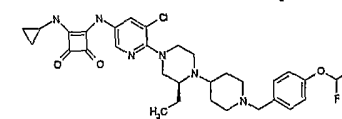
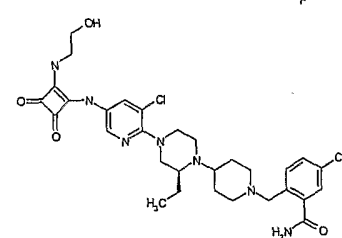
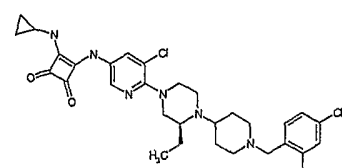
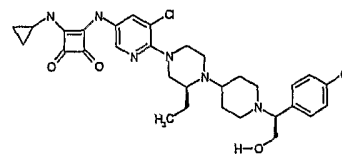
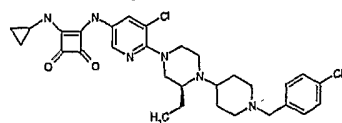
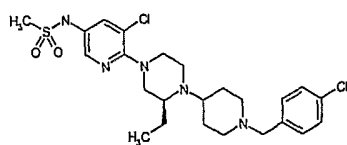
or a pharmaceutically acceptable salt, solvate or ester thereof.

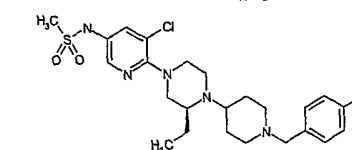
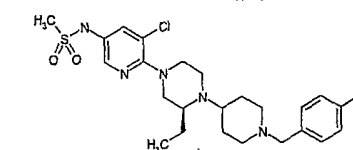
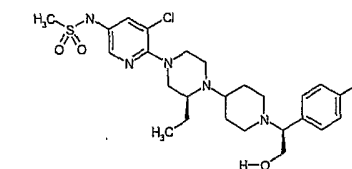
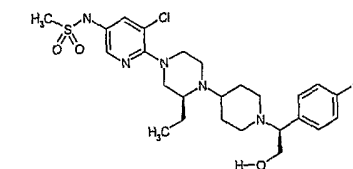
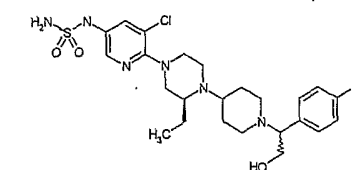
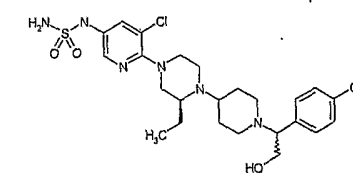
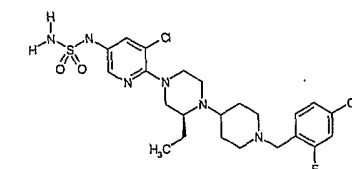
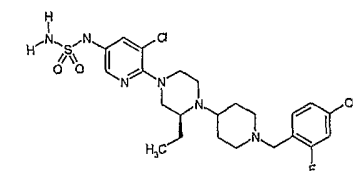
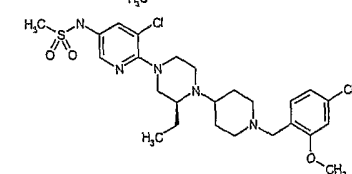
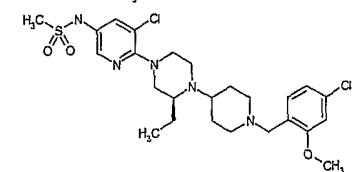
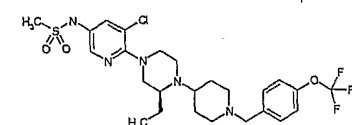
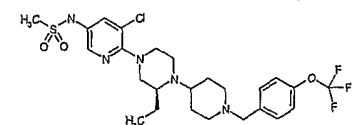
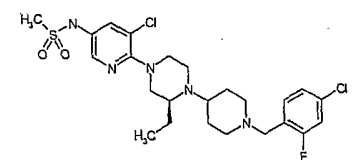
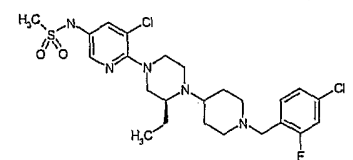
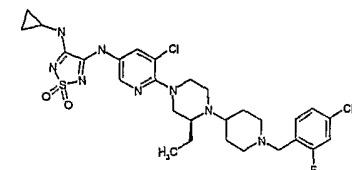
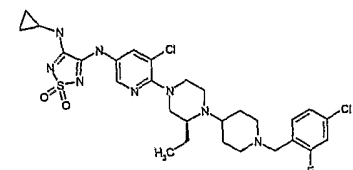
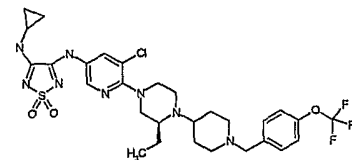
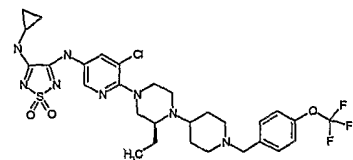
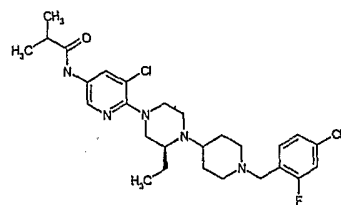
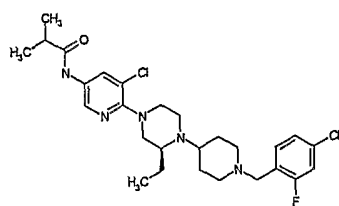
For example, the compound according to Formula 1 can be selected from the group consisting of compounds of the formulae:

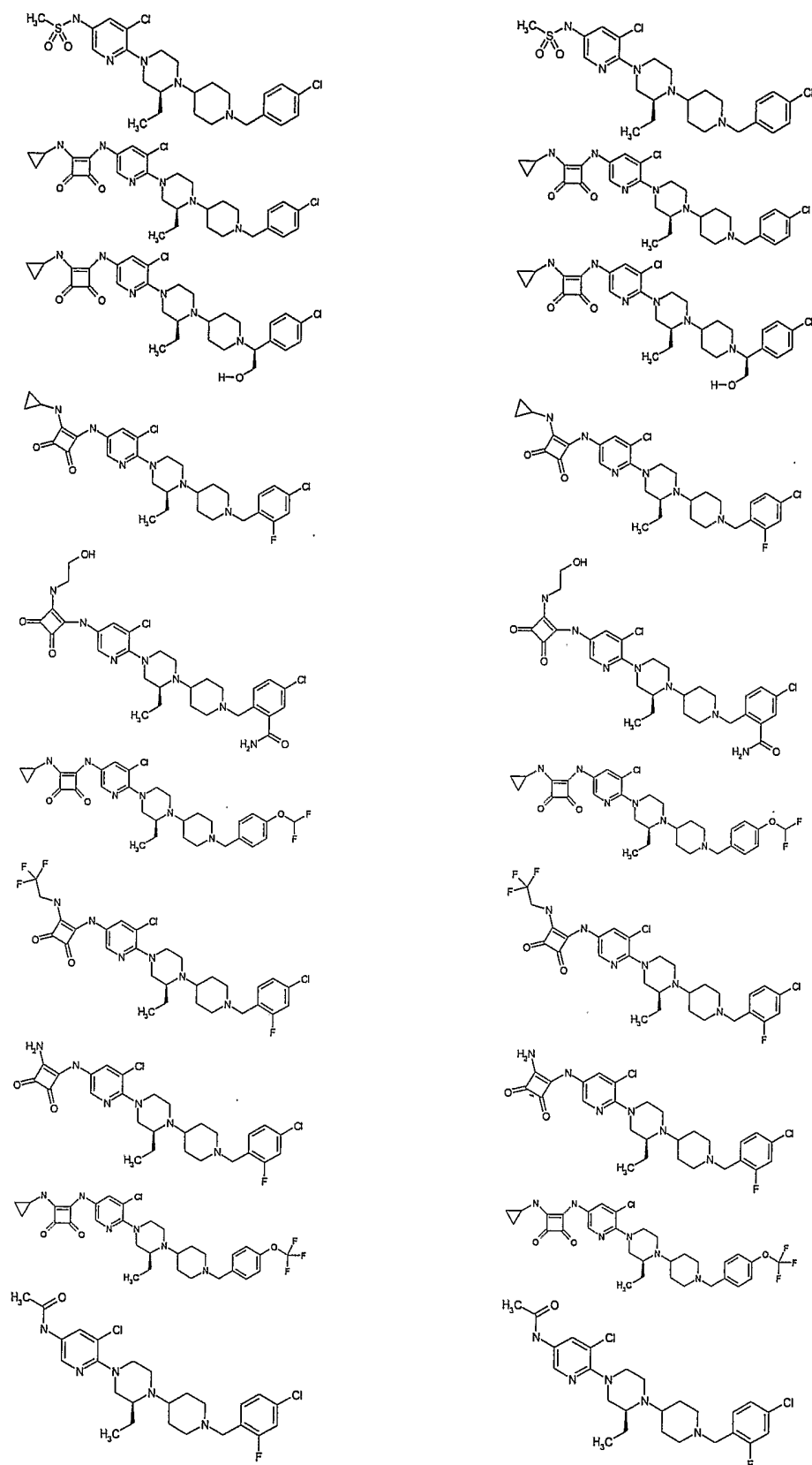


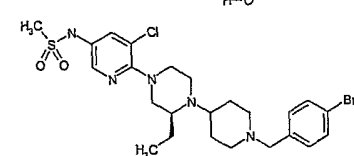
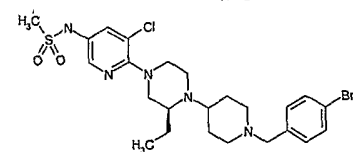
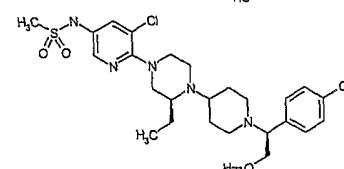
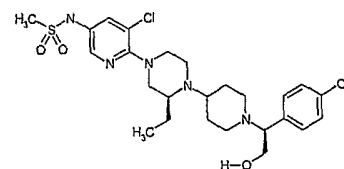
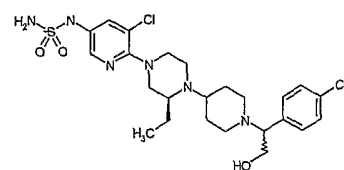
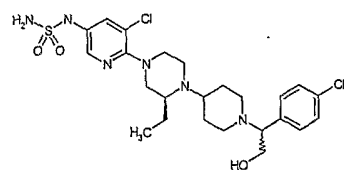
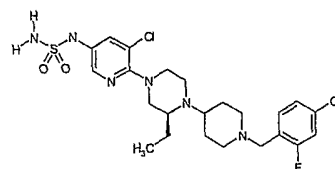
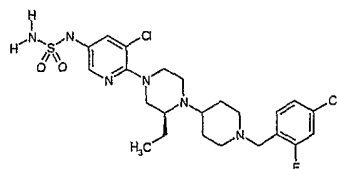
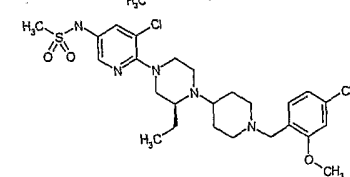
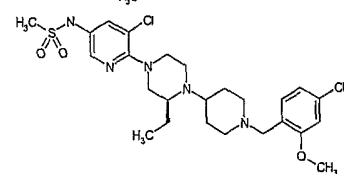
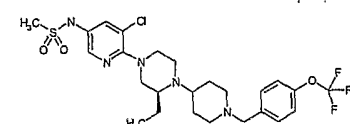
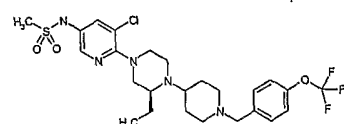
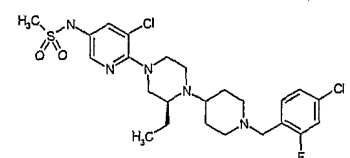
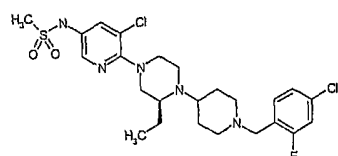
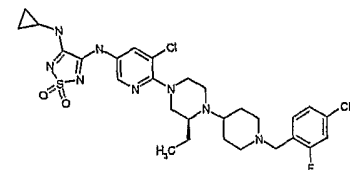
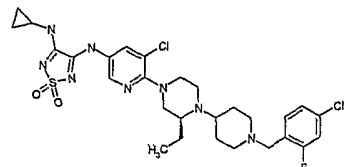
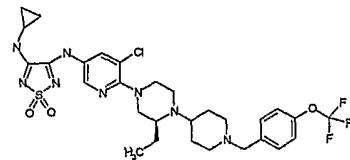
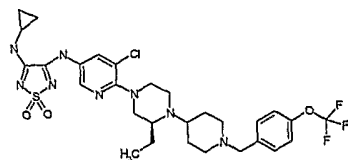
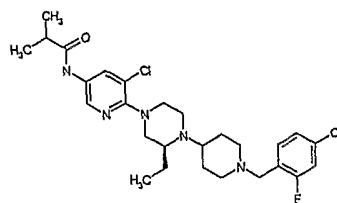
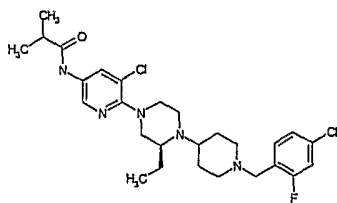


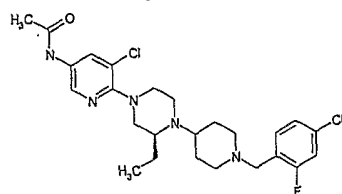
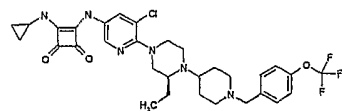
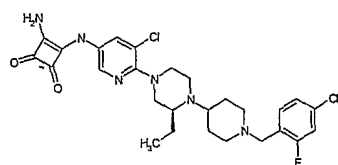
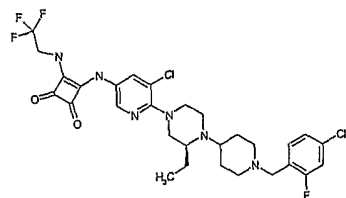
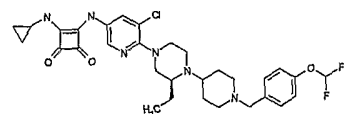
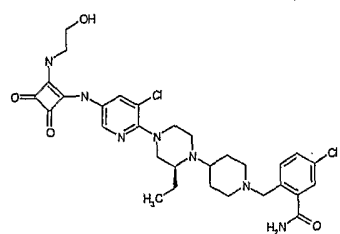
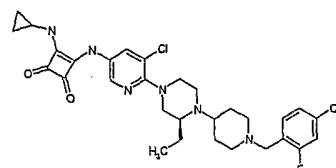
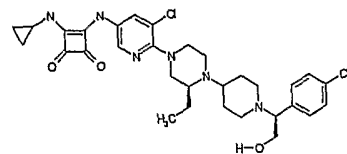
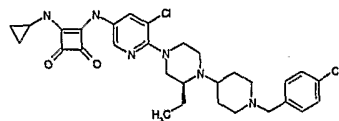
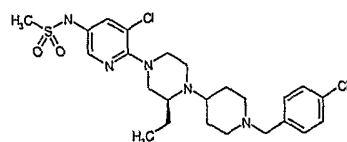
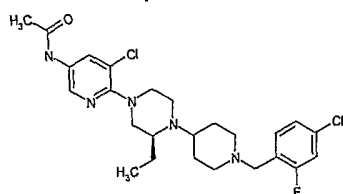
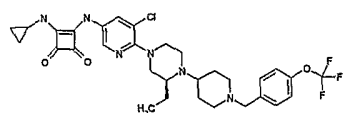
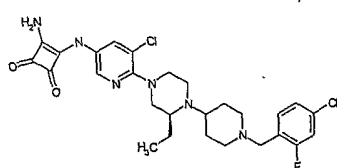
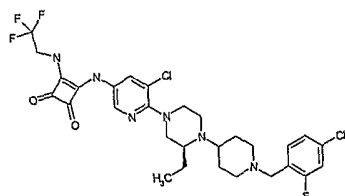
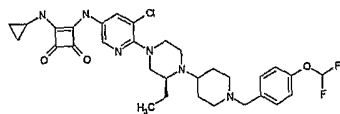
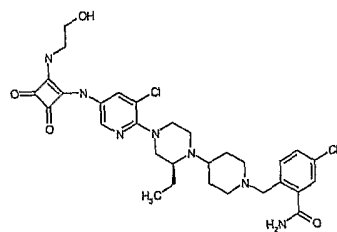
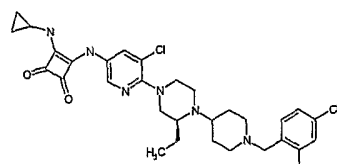
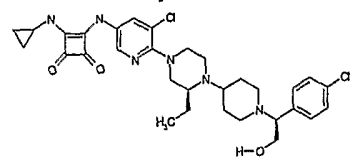
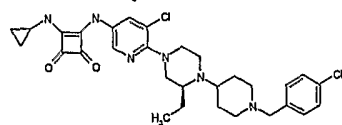
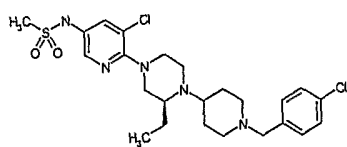


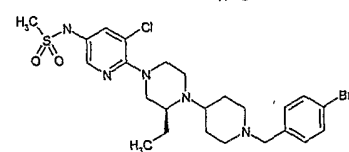
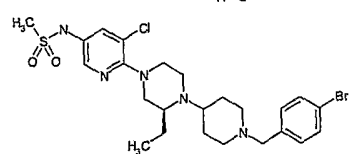
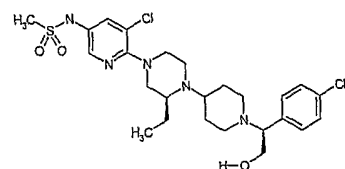
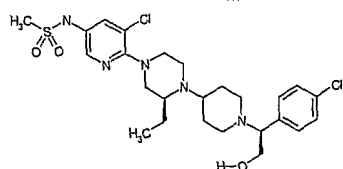
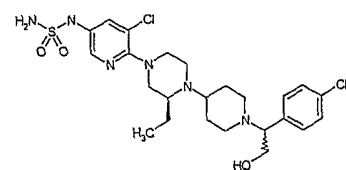
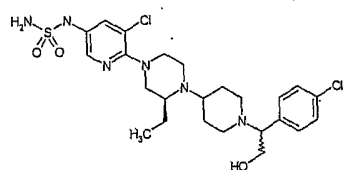
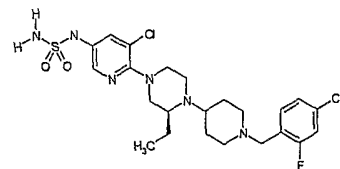
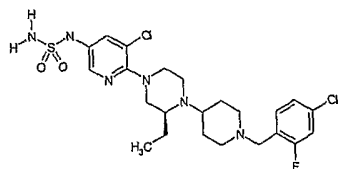
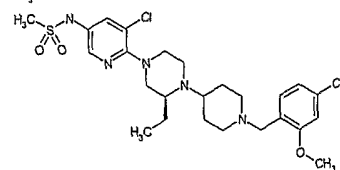
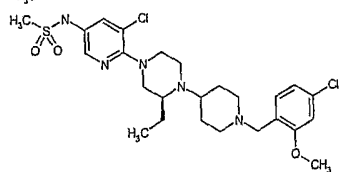
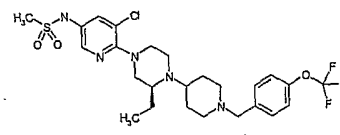
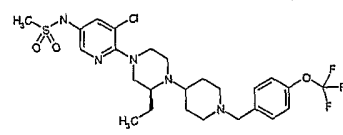
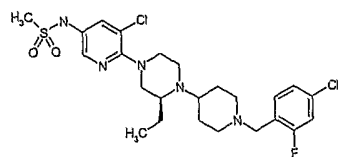
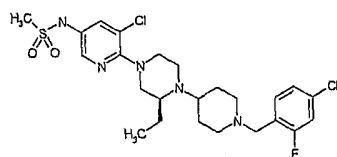
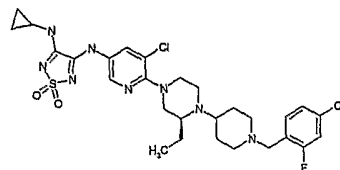
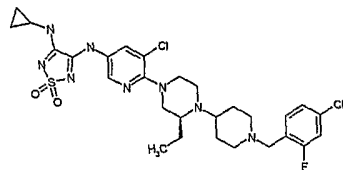
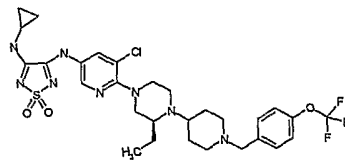
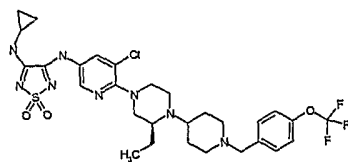
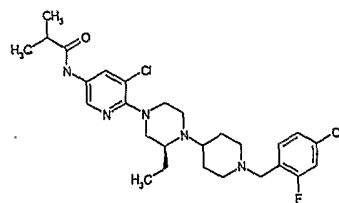
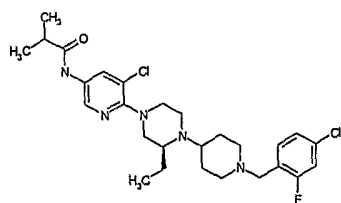


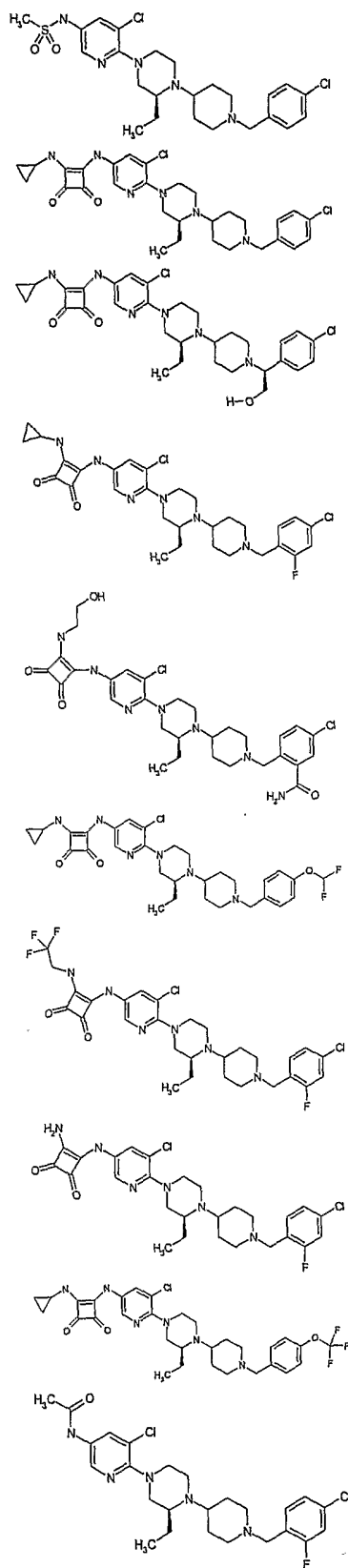
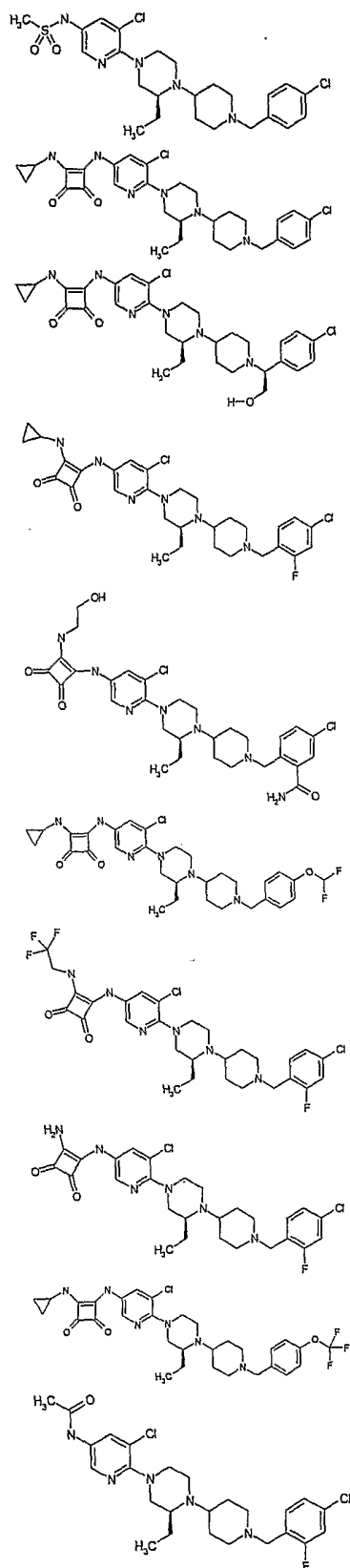


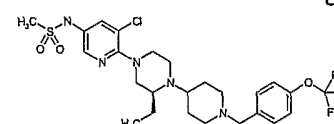
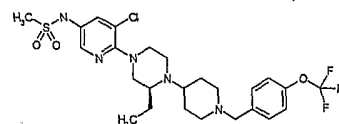
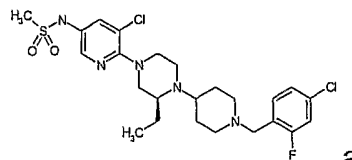
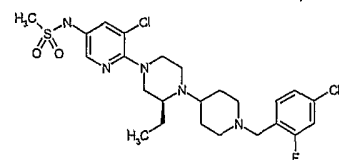
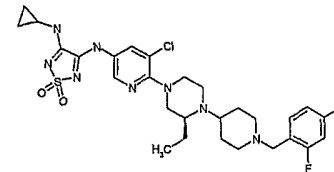
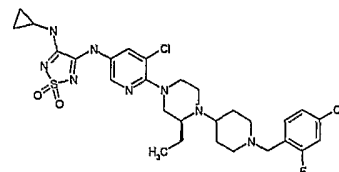
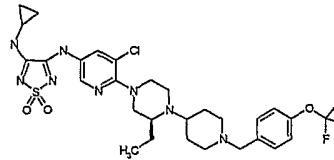
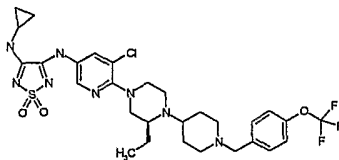
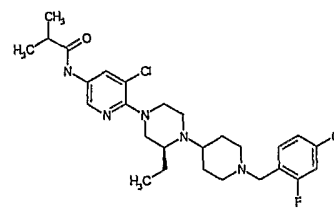
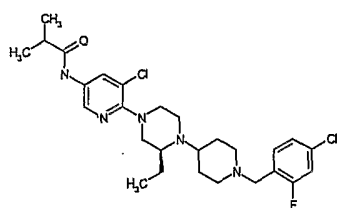










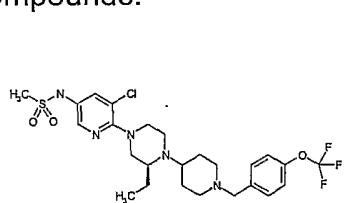


and

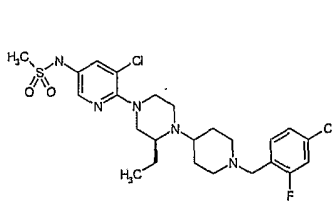
or pharmaceutically acceptable salts, solvates or esters thereof.

In yet another aspect, this invention discloses the following compounds:

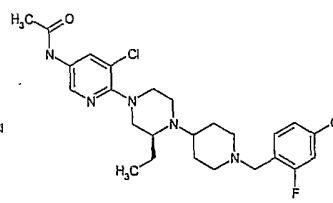
5



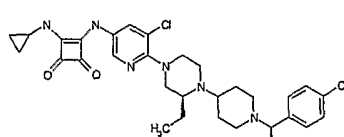
(2 nM)



(2 nM)

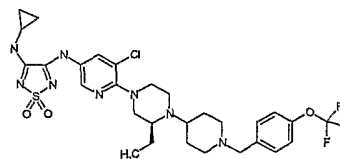


(1.2 nM)



(1 nM)

and



(1.3 nM)

10 or pharmaceutically acceptable salts, solvates or esters thereof. The human IC_{50} values (in nM) for the above compounds have been set forth above underneath their chemical structures.

In yet another aspect, the compound according to Formula 1 is 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.

5 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
10 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
15 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
20 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
25 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
30 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
5 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
10 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
15 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
20 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
25 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.

30 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 hydrophilic 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.

Glidants - materials that prevent caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidants 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 method can further comprise 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 glucocorticoids); 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 disease can be an inflammatory disease (e.g., psoriasis, inflammatory bowel disease)

Another embodiment of this invention is directed to 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 Formula 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

Another embodiment of this invention is directed to 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 according to Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof.

Another embodiment of this invention is directed to 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), immunosuppressives, methotrexate, azathioprine, and 6-mercaptopurines.

Another embodiment of this invention is directed to 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 Formula 1, or a pharmaceutically acceptable salt, solvate or ester thereof.

Another embodiment of this invention is directed to a 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: cyclosporine A, FK-506, FTY720, beta-interferon, rapamycin, mycophenolate, prednisolone, azathioprine, cyclophosphamide and an antilymphocyte globulin.

Another embodiment of this invention is directed to 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 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, azathioprine, mitoxantrone, VLA-4 inhibitors, FTY720, anti-IL-12 inhibitors, and CB2-selective inhibitors.

Another embodiment of this invention is directed to 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 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, etanercept, and infliximab.

Another embodiment of this invention is directed to 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 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,

5 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.

Another embodiment of this invention is directed to a method of
10 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 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:

15 immunosuppressives, cyclosporins, methotrexate, steroids, corticosteroids, anti-TNF- α compounds, anti-IL compounds, anti-IL-23 compounds, vitamin A and D compounds and fumarates.

Another embodiment of this invention is directed to a method of treating ophthalmic inflammation (including, for e.g., uveitis, posterior segment
20 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
25 group consisting of: immunosuppressives, cyclosporins, methotrexate, FK506, steroids, corticosteroids, and anti-TNF- α compounds.

Another embodiment of this invention is directed to a method of treating a disease selected from the group consisting of: inflammatory disease, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease,
30 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.

Another embodiment of this invention is directed to 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 inventive compounds disclosed above.

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

DBU= 1,8-diazabicyclo[5.4.0]undec-7-ene

DBN= 1,5-diazabicyclo[4.3.0]non-5-ene

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

HATU =

N-(Diethylamino)-1H-1,2,3-triazolo[4,5-b]pyridine-1-ylmethylene]-N-methylmethanaminium Hexafluorophosphate N-oxide

HOBT= 1-hydroxybenzotriazole

DCC= dicyclohexylcarbodiimide

Dibal-H= diisobutylaluminum hydride

DBPD = 2-(Di-*t*-butylphosphino)biphenyl

DMF = Dimethylformamide

LAH= lithium aluminum hydride

NaBH(OAc)₃= sodium triacetoxymborohydride

NaBH₄= sodium borohydride

NaBH₃CN= sodium cyanoborohydride

LDA= lithium diisopropylamide

5 p-TsOH= p-toluenesulfonic acid

p-TsCl= p-toluenesulfonyl chloride

PPTS = pyridinium p-toluenesulfonate

m-CPBA= m-Chloroperbenzoic acid

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

10 CSA= camphorsulfonic acid

NaHMDS= sodium hexamethyl disilylazide

HRMS= High Resolution Mass Spectrometry

HPLC= High Performance Liquid Chromatography

LRMS= Low Resolution Mass Spectrometry

15 nM= nanomolar

K_i= Dissociation Constant for substrate/receptor complex

pA₂= -logEC₅₀, as defined by J. Hey, *Eur. J. Pharmacol.*, (1995), Vol. 294, 329-335.

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

20 Tr= Triphenylmethyl

Tris= Tris (hydroxymethyl)aminomethane

GENERAL SYNTHESIS

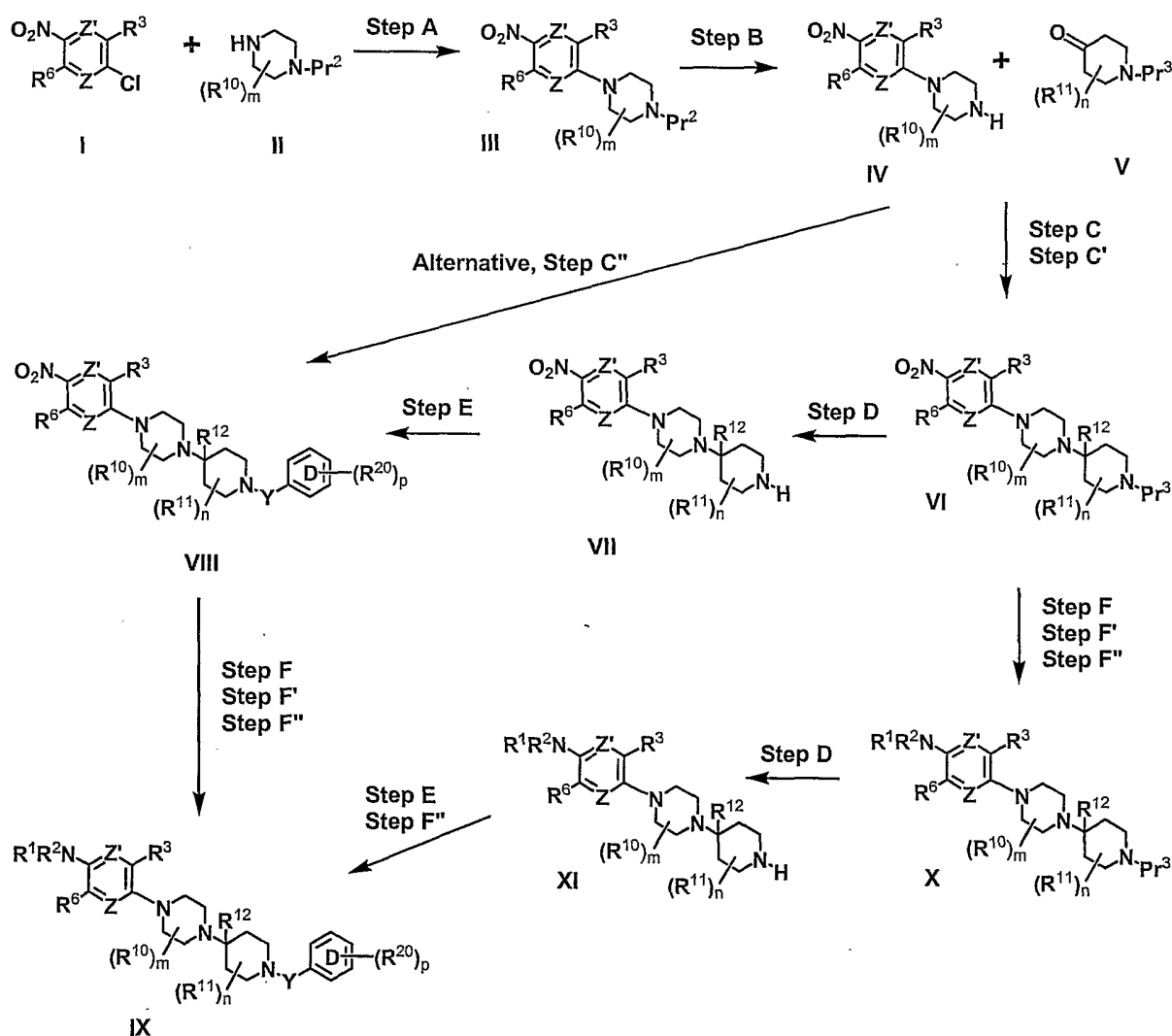
Compounds of the present invention can be prepared by a number of ways evident to one skilled in the art. Preferred methods include, but are not limited to, the general synthetic procedures described herein. One skilled in the art will recognize that one route will be optimal depending on the choice 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. One such method for the preparation of compounds of general Formula 1 where variables [R¹⁷, R¹⁸, R³, R⁶, R¹⁰, R¹¹, R¹², R²⁰, Y, Z, Q, L, m, n, w and p] are as defined above, is shown in scheme 1. **Pr²** and **Pr³** are protecting

groups exemplified below. Alternative methodology for introduction of an arylamine moiety is well known in the open literature.

The prepared compounds may be analyzed for their composition and purity as well as characterized by standard analytical techniques such as, for example, elemental analysis, NMR, mass spectroscopy, and IR spectroscopy.

10

Scheme 1



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.

5 One skilled in the art will recognize that the synthesis of compounds of Formula 1 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). Suitable protecting groups for carboxylic acids include methyl, ethyl, isopropyl, or benzyl ester and the like. Suitable protecting
10 groups for an amine (**Pr**² or **Pr**³) include methyl, benzyl, ethoxyethyl, t-butoxycarbonyl, phthaloyl and the like. 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
15 Formula 1 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,
20 dimethylformamide and the like. 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 1 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
25 reactive carbonyl (e.g. aldehyde or ketone) under reductive amination conditions. Suitable reducing reagents of the intermediate imine are sodium borohydride, sodium triacetoxyborohydride and the like at 0°C to 100°C. Suitable solvents for the reaction are halogenated hydrocarbons, ethereal solvents, dimethylformamide and the like. Another such method is, but not
30 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 the like. Suitable solvents for the reaction are halogenated hydrocarbons,

ethereal solvents, dimethylformamide and the like. 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 1 may require the reduction of a reducible functional group. Suitable reducing reagents include sodium borohydride, lithium aluminum hydride, diborane and the like at -20°C to 100°C. Suitable solvents for the reaction are halogenated hydrocarbons, ethereal solvents, dimethylformamide and the like.

One skilled in the art will recognize that the synthesis of compounds of Formula 1 may require the oxidation of a functional group. Suitable oxidizing reagents include oxygen, hydrogen peroxide, m-chloroperoxybenzoic acid and the like at -20°C to 100°C. Suitable solvents for the reaction are halogenated hydrocarbons, ethereal solvents, water and the like.

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 the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

General Description of Scheme 1

Step A

An appropriately substituted 2-halo-5-nitropyridine, 1-halo-4-nitrophenyl, or a suitable coupling analog of structure I is allowed to react with an optionally substituted or protected piperazine of structure II to afford a compound of general structure III. Preferably the reaction is carried out in a solvent such as dioxane in the presence of a base such as triethylamine, diisopropylethylamine, potassium carbonate or cesium carbonate. Optionally, catalysts such as palladium acetate may be added and the reaction heated to a temperature between 30°C and 150°C.

Step B

If the product of step A is a protected piperazine of structure III, deprotection is required. When Pr^2 is an optionally substituted benzyl group, deprotection can be effected by reaction under a pressure of hydrogen gas in the presence of a suitable 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 or hydrogen chloride.

Step C

5 A piperazine of structure **IV** is allowed to react with a ketone of structure **V** in the presence of a reducing agent to afford a compound of structure **VI** where R¹² is hydrogen. General conditions for the reductive amination reaction are described herein.

Step C'

10 A piperazine of structure **IV** is allowed to react with a ketone with structure **V** in the presence of a reducing agent to form a compound of structure **VI** where R¹² is a cyanide residue. Typical conditions are the reaction of an equimolar quantity of a piperazine of structure **IV** and a ketone of structure **V** in the presence of titanium isopropoxide in a halogenated
15 solvent such as methylene chloride for 1-48 hours. Subsequent addition of a cyanide source such as dimethylaluminum cyanide affords a compound of structure **VI** where R¹² is a cyanide residue.

Step C''

 A piperazine of structure **IV** is allowed to react with a ketone of
20 structure **V** in the presence of a reducing reagent to afford a compound of structure **VIII** where R¹² is hydrogen. General conditions for the reductive amination reaction are described above.

Step D

 A protected piperidine of structure **VI** or **X** is deprotected to provide the
25 secondary amine of structure **VII** or **XI**, respectively. When **Pr**³ is an optionally substituted benzyl group, deprotection can be effected by reaction under a pressure of hydrogen gas in the presence of a suitable 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
30 can be effected with a strong acid such as trifluoroacetic acid or hydrogen chloride.

Step E

 A secondary amine of structure **VII** or **XI** is either alkylated or acylated to provide compounds of structures **VIII** or **IX**, respectively. General methods

for such alkylations and acylations are described above and are well known to those skilled in the art.

Step F

A nitro compound of structure **VI** or **VIII** is allowed to react with an appropriate reducing reagent such as tin(II) chloride in a solvent such as ethanol or ethyl acetate to afford the corresponding amine.

Step F'

A compound of structures **VIII** and **VI** can be functionalized by methods as alkylation, acylation, or sulfonylation to provide compounds of structures **X** or **IX**. General methods for such alkylations, acylations, and sulfonylations are described above and are well known to those skilled in the art.

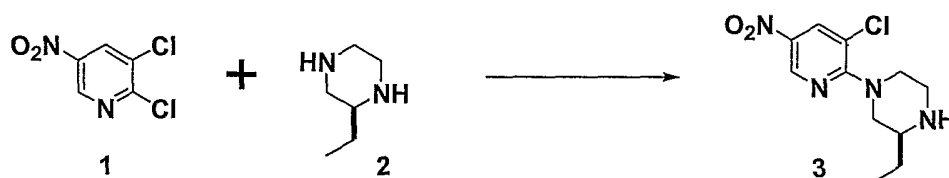
Step F''

Optionally, functional group manipulation or multi-step elaboration of a compound of structure **VI** or **XI** may be done to provide additional related compounds of structures **VI** or **XI**, respectively.

PREPARATIVE EXAMPLES

The following Preparative Examples are intended to illustrate, but not to limit, the scope of the invention.

Preparative Example 1



2,3-Dichloro-5-nitropyridine (**1**) was prepared from commercially available 2-hydroxy-5-nitropyridine (Aldrich) according to the procedure of Koch and Schnatterer, in *Synthesis* **1990**, 499-501.

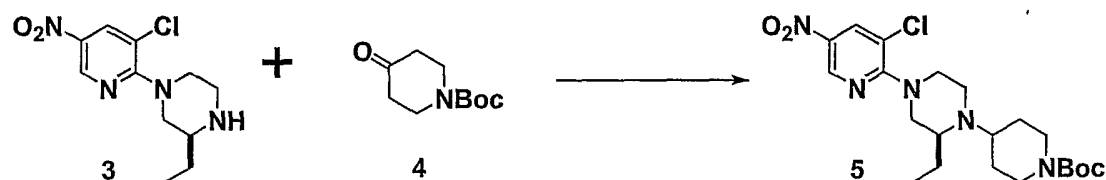
2(S)-Ethylpiperazine (**2**) was prepared from commercially available starting materials by analogy to the procedure of Kiely and Priebe, in *Org. Prep. Proc. Int.* **1990**, 22, 761-768.

Solid 2,3-dichloro-5-nitropyridine (**1**, 20 g, 88 mmol) was finely ground and added portion wise over ~15 min to a stirred solution of 2(S)-ethylpiperazine (**2**, 11 g, 90%; 10 g, 8.8 mmol) and triethylamine (14 mL, 9.7 g, 96 mmol) in dichloromethane (400 mL). The reaction mixture was stirred at room temperature for 24 hours. The solvent was removed by rotary

evaporation under reduced pressure and the resulting brown liquid was adsorbed onto ~75 g silica gel. Purification by silica gel chromatography [2.5% (7 M ammonia in methanol) in dichloromethane) gave piperazinylpiperidine **3** as a yellow-orange semi-solid (17 g, 72% yield). MS:

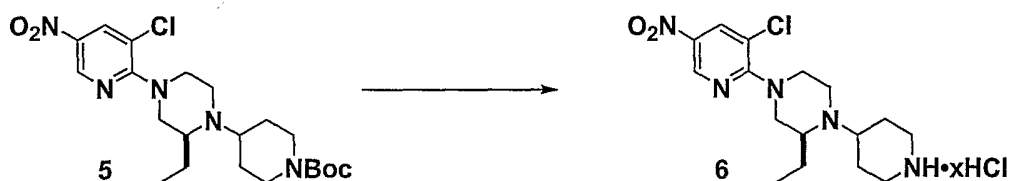
5 $[M + H]^+ = 271$.

Preparative Example 2

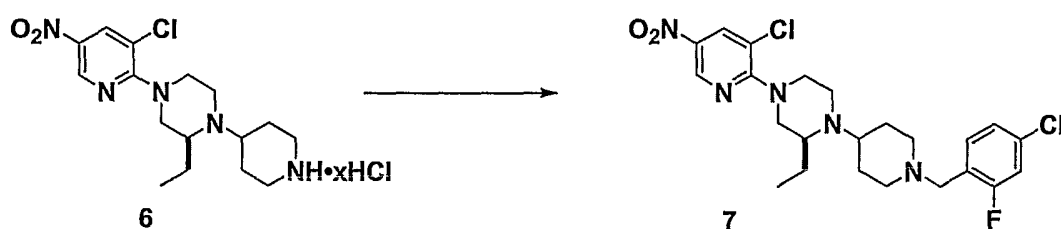


To a solution of the secondary amine **3** (12.2 g, 40.8 mmol) in dry
 10 1,2-dichloroethane (100 mL) was added a solution of
 1-(*t*-butoxycarbonyl)-4-piperidone (**4**, 12.2 g, 61.2 mmol) in dry
 1,2-dichloroethane (40 mL). The orange solution was stirred at room
 temperature for 30 min, cooled to 0°C with an external ice-water bath, and
 then heated at 70°C for 18 hours. The reaction mixture was diluted with
 15 dichloromethane (100 mL) and washed successively with saturated aqueous
 NaHCO₃ (2 x 100 mL), water (1 x 100 mL), and brine (1 x 100 mL). The
 organic layer was dried over anhydrous magnesium sulfate, filtered, and
 concentrated under reduced pressure to yield a brown oil (30 g). Purification
 of the oil by silica gel chromatography (1.5% (7 M ammonia in methanol) in
 20 dichloromethane) gave **5** (16.2 g, 82% yield) as a yellow-brown solid. MS: $[M + H]^+ = 454$.

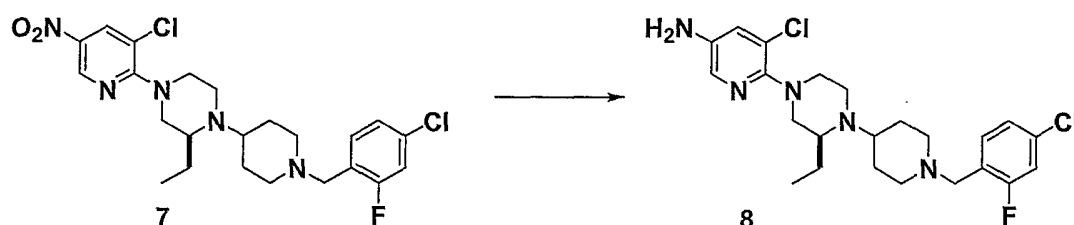
Preparative Example 3



25 A solution of **5** (5.5 g, 12 mmol) and hydrogen chloride (15 mL, 4 M in
 dioxane; 61 mmol) in methanol (200 mL) was stirred at room temperature for
 15 hours. The solvent was evaporated under reduced pressure to give **6** as a
 pale yellow solid (4.90 g, 95% yield, based on •2HCl salt). MS: $[M + H]^+ =$
 354.

Preparative Example 4

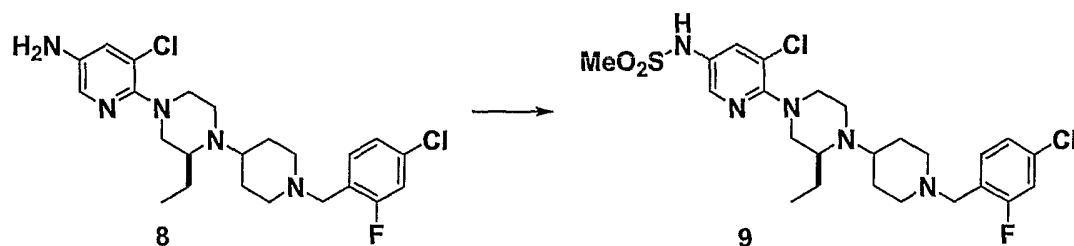
To a solution of **6** (315 mg, 0.74 mmol based on $\cdot 2\text{HCl}$ salt) and triethylamine (493 μL , 360 mg, 3.6 mmol) in dry DMF (2 mL) was added a solution of 2-fluoro-4-chlorobenzyl bromide (168 μL , 219 mg, 0.98 mmol) in DMF (0.5 mL). The reaction mixture was stirred at room temperature for 18 hours, after which it was diluted with ethyl acetate (50 mL) and washed with water (10 mL). The aqueous phase was extracted with ethyl acetate (2 x 10 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a light brown oil. Purification by silica gel chromatography (1 $\rightarrow$ 2% (7 M ammonia in methanol) in dichloromethane) gave **7** as a yellow oil (309 mg, 84% yield). MS: $[\text{M} + \text{H}]^+ = 496$.

Preparative Example 5

Solid, anhydrous tin(II) chloride (14 g, 74 mmol) was added portion wise to a solution of **7** (7.32 g, 15 mmol) in absolute ethanol (140 mL). The suspension was stirred at room temperature for 2 hours. Solvent was removed under reduced pressure to afford an orange-brown residue that was then partitioned between 0.4 M aqueous sodium hydroxide solution (500 mL) and dichloromethane (500 mL). The aqueous layer was extracted further with dichloromethane (4 x 100 mL). The combined extracts were washed with brine (~250 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give an orange solid. Purification of the solid by silica gel chromatography (5% (7 M ammonia in methanol) in

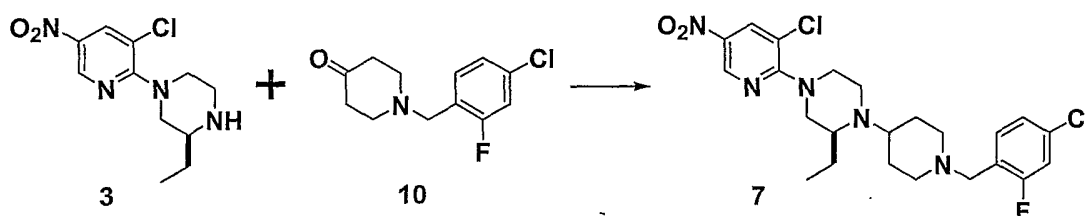
dichloromethane) gave **8** as an orange-brown solid (4.1 g, 60% yield). MS: $[M + H]^+ = 466$.

Preparative Example 6. Preparation of Table 1 Compound No. 7



To an ice-cold solution of **8** (47 mg) in dichloromethane (500 μ L) was added a solution of methanesulfonyl chloride (446 μ L, 0.68 M in 1,2-dichloroethane), dropwise over 5 min. The reaction mixture was stirred at 0°C for 1 hour and at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate (50 mL) and was washed with 1 N aqueous sodium hydroxide (25 mL), water (25 mL), and brine (25 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification of the resulting brown gum by preparative TLC (10% (7 M ammonia in methanol) in dichloromethane) gave **9** as a white solid (38 mg, 70% yield). MS: $[M + H]^+ = 544$.

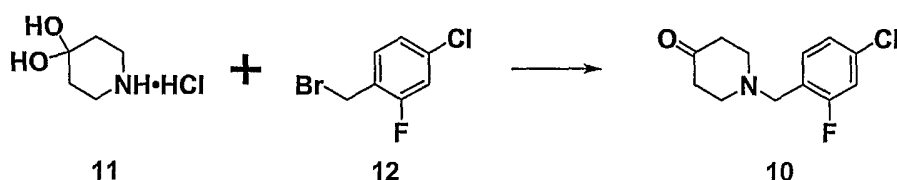
Preparative Example 7



A solution of secondary amine **3** (5.04 g, 18.6 mmol) and ketone **10** (6.75 g, 27.9 mmol) in 1,2-dichloroethane (50 mL) was stirred at room temperature for 8 hours. The solution was cooled to 0°C and sodium triacetoxyborohydride (7.89 g, 37.2 mmol) was added portion wise. The reaction mixture was stirred at 0°C for 30 min, room temperature for 2 hours, and 70°C for 15 hours. The mixture was allowed to cool to room temperature, and was then partitioned between dichloromethane (500 mL) and water (400 mL). The organic layer was removed, and the pH of the aqueous layer was adjusted to neutrality with 0.4 M aqueous sodium hydroxide. The neutralized aqueous solution was extracted with dichloromethane (4 x 250 mL). The

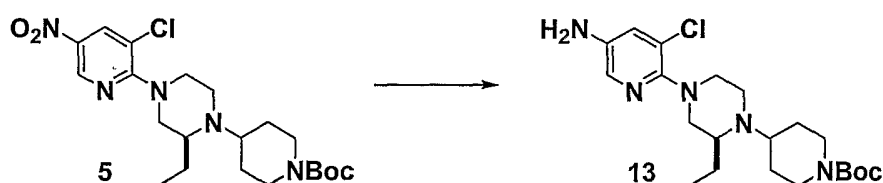
combined organic solutions were washed with brine (500 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield a red-brown oil. Purification by silica gel chromatography (3:1 ethyl acetate–dichloromethane, then 5% (7 M ammonia in methanol) in dichloromethane) gave **7** as a yellow-orange syrup (7.32 g, 78% yield). MS: $[M + H]^+ = 496$.

Preparative Example 8.



A mixture of piperidine hydrate hydrochloride (**11**, 13.7 g, 90 mmol) and potassium carbonate (31 g, 224 mmol) in DMF (100 mL) was stirred at room temperature for 30 min. Neat 2-fluoro-4-chlorobenzyl bromide (**12**, 20.0 g, 90 mmol) was added, and the reaction mixture was stirred for 2 days. Solids were then removed by filtration through a sintered glass funnel. The filtrate was partitioned between diethyl ether (100 mL) and water (100 mL). The aqueous layer was extracted with diethyl ether (50 mL). The combined organic phases were washed with water (50 mL), 10% aqueous sodium thiosulfate (50 mL), and brine (50 mL), then dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced to afford **10** (20.9 g, 97% yield). MS: $[M + H]^+ = 242$.

Preparative Example 9



The nitro compound **5** (4.0 g, 8.8 mmol) was dissolved in absolute ethanol (60 mL). Anhydrous tin(II) chloride (8.4 g, 44 mmol) was added in small portions, and the reaction mixture was stirred at room temperature for 2 days. The reaction mixture was poured into ice-cold 10% aqueous sodium hydroxide solution (100 mL) and was then stirred for 30 min. The slurry was extracted with ethyl acetate (2 x 150 mL). The combined organic phases were washed successively with water (100 mL) and brine (100 mL), dried over

anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield a light yellow solid. Purification by silica gel chromatography (5% (7 M ammonia in methanol) in dichloromethane) gave amine **13** as an off-white solid (1.65 g, 50% yield).

5 Preparative Example 10



A solution of amine **13** (1.8 g, 4.3 mmol) and triethylamine (1 mL, 0.73 g, 7.2 mmol) in dry dichloromethane (50 mL) was cooled to 0 °C and methanesulfonyl chloride (0.7 mL, 1.0 g, 8.9 mmol) was added. The reaction mixture was stirred and allowed to warm to room temperature over 1 hour. The reaction mixture was diluted with dichloromethane (50 mL) and was washed successively with 1 N sodium bicarbonate solution (50 mL) and brine (50 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to yield 2.4 g of a brown solid.

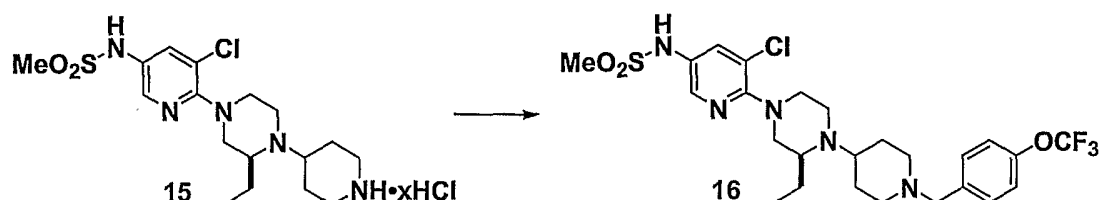
The brown solid was dissolved in methanol (50 mL) and a solution of lithium hydroxide monohydrate (906 mg, 22 mmol) in water (20 mL) was added. The reaction solution was stirred overnight at room temperature. The volatile solvent was evaporated under reduced pressure to yield an off-white suspension. The suspension was extracted with ethyl acetate (2 x 100 mL) and the extracts were washed successively with 1 N aqueous sodium bicarbonate solution (50 mL) and brine (50 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield a pale yellow solid, purification of which by silica gel chromatography (5% (7 M ammonia in methanol) in dichloromethane) gave **14** as a yellow solid (2.05 g, 96% yield). MS: $[M + H]^+ = 501$.

Preparative Example 11



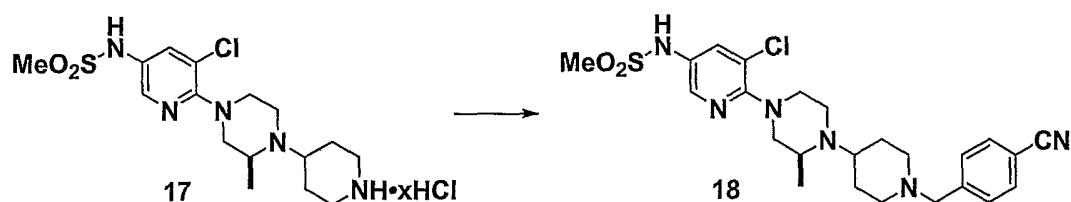
Carbamate **14** (2.3 g, 4.6 mmol) was dissolved in methanol (45 mL) and hydrogen chloride (10 mL, 4 N in dioxane, 40 mmol) was added. The solution was stirred for 3 hours at room temperature. The solvent was evaporated under reduced pressure to give amine salt **15** as a yellow solid (2.45 g). MS: $[M + H]^+ = 402$.

Preparative Example 12. Preparation of Table 1 Compound No. 10



Amine salt **15** (102 mg, 0.200 mmol, based on $\cdot 3\text{HCl}$ salt), diisopropylethylamine (1 mL, 740 mg, 5.7 mmol), and 4-(trifluoromethoxy)benzaldehyde (57 μL , 76 mg, 0.400 mmol) were dissolved in dichloromethane (5 mL) and the resulting solution was stirred at room temperature for 30 min. The solution was cooled to 0°C , and solid sodium triacetoxyborohydride (85 mg, 0.400 mmol) was added. The reaction was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane (50 mL) and washed with water (25 mL) and brine (25 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to give a brown oil. Purification of the crude product by silica gel chromatography (8% (7 M ammonia in methanol) in dichloromethane) gave **16** as a beige solid (89 mg, 77% yield). MS: $[M + H]^+ = 576$.

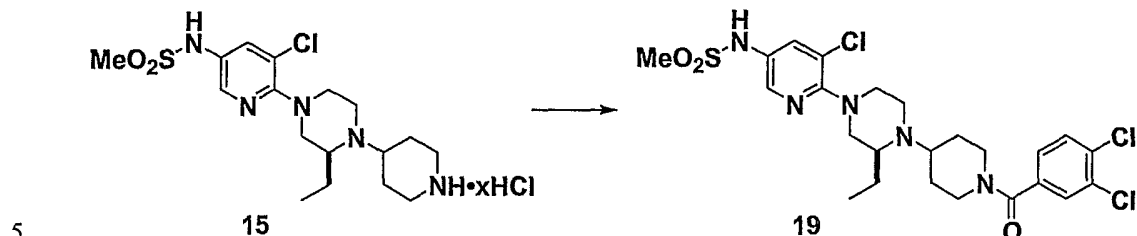
Preparative Example 13. Preparation of Table 1 Compound No. 53



Amine salt **17** (92 mg, 0.200 mmol, based on $\cdot 2\text{HCl}$ salt), diisopropylethylamine (1 mL, 740 mg, 5.7 mmol), and 4-cyanobenzyl bromide (78 mg, 0.40 mmol) were dissolved in N,N-dimethylacetamide (2 mL) and stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with water (2 x 25 mL) and brine (25 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered,

and concentrated to give an orange-brown solid. Purification by silica gel chromatography (5% (7 M ammonia in methanol) in dichloromethane) gave **18** (88 mg, 88% yield). MS: $[M + H]^+ = 503$.

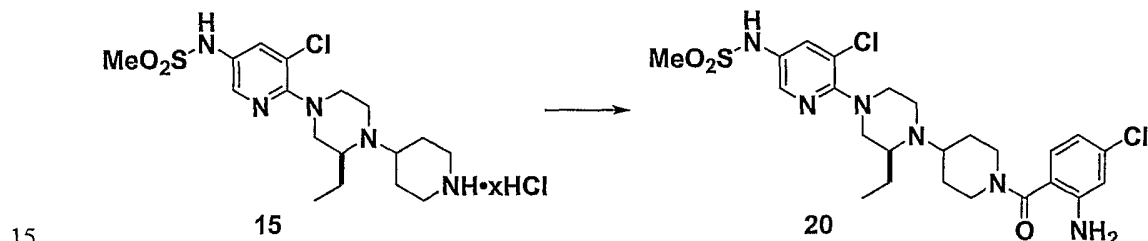
Preparative Example 14. Preparation of Table 1 Compound No. 63



Amine salt **15** (50 mg, 98 μ mol based on $\cdot 3HCl$ salt) and triethylamine (57 μ L, 42 mg, 410 μ mol) were dissolved in dichloromethane (300 μ L) and 3,4-dichlorobenzoyl chloride (23 mg, 110 μ mol) was added. The reaction was allowed to proceed for 20 hours at room temperature. The solvent was evaporated under reduced pressure to afford a brown residue. Subsequent purification of the residue by preparative TLC (10% (7 M ammonia in methanol) in dichloromethane) gave amide **19** (28 mg, 57% yield). MS: $[M + H]^+ = 503$.

10

Preparative Example 15. Preparation of Table 1 Compound No. 40



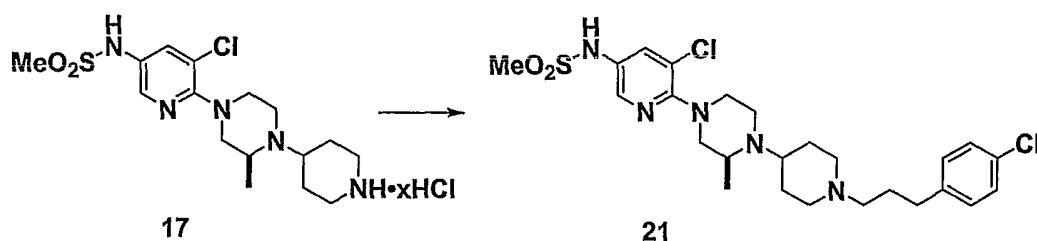
Amine salt **15** (50 mg, 98 μ mol based on $\cdot 3HCl$ salt) was suspended in DMF (1 mL) and diisopropylethylamine (90 μ L, 68 mg, 0.50 mmol), 2-amino-4-chlorobenzoic acid (23 mg, 0.135 mmol), DECI (26 mg, 0.135 mmol), and HOBT (18 mg, 0.135 mmol) were added sequentially. The stirred reaction mixture was heated with stirring at 70°C. The reaction mixture was partitioned in ethyl acetate (40 mL) and water (10 mL). The aqueous layer was extracted further with ethyl acetate (2 x 30 mL) and the combined organic layers were then washed with brine (30 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give a brown oil. Purification by preparative TLC (10% (7 M ammonia in methanol)

20

25

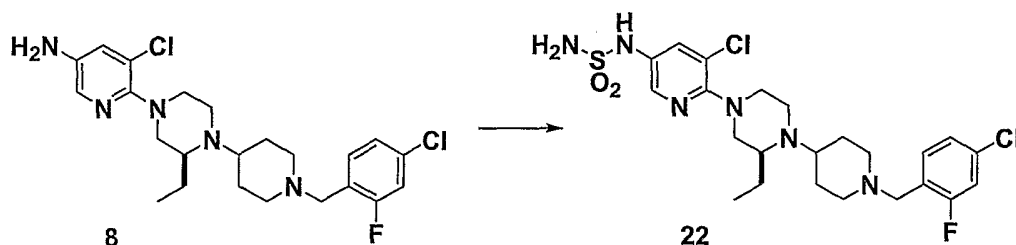
in dichloromethane) afforded the amide **20** (35 mg, 64% yield). MS: $[M + H]^+ = 555$.

Preparative Example 16. Preparation of Table 1 Compound No. 57



5 Amine salt **17** (39 mg, 0.078 mmol, based on $\cdot 3HCl$ salt), cesium carbonate (65 mg, 0.200 mmol), and 1-chloro-3-(4-chlorophenyl)propane (18 mg, 0.094 mmol) were dissolved in N,N-dimethylacetamide (1 mL) and stirred at 90°C for 18 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL) and washed with water (2 x 25 mL) and
 10 brine (25 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to give an orange-brown solid. Purification by HPLC (acetonitrile/water gradient) gave alkylated amine **21** (20 mg, 57% yield). MS: $[M + H]^+ = 540$.

Preparative Example 17. Preparation of Table 1 Compound No. 2

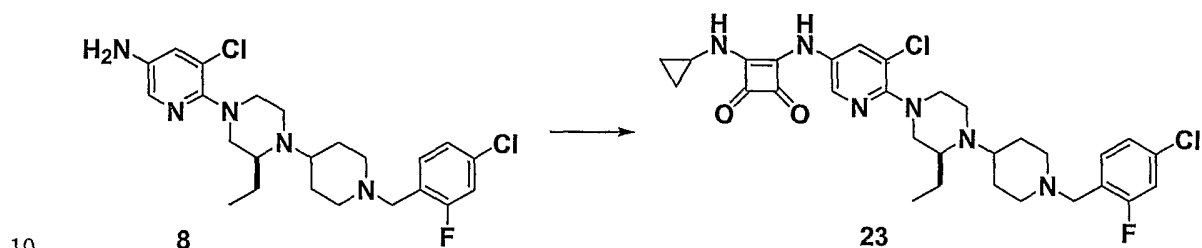


15 To a solution of ice-cold chlorosulfonyl isocyanate (31 μ L, 50 mg, 0.35 mmol) in dry dichloromethane (0.900 mL) was added dropwise a solution of *t*-butanol (34 μ L, 26 mg, 0.35 mmol) in dichloromethane (0.350 mL). The clear, colorless solution was stirred at 0°C for 30 min, then was added
 20 dropwise by syringe to an ice-cold solution of amine **8** (110 mg, 0.236 mmol) and triethylamine (49 μ L, 36 mg, 0.35 mmol) in dichloromethane (0.790 mL). The reaction mixture was stirred at 0°C for 10 min and at room temperature for a further 20 hours. The solvent was then evaporated under reduced pressure to afford an off-white solid.

25 The solid was suspended in methanol (2 mL) and hydrogen chloride solution (0.5 mL, 4 M in dioxane, 2 mmol) was added. The clear solution was

stirred at room temperature for 15 hours. The solvent was evaporated and the residue was partitioned between ethyl acetate (30 mL) and water (20 mL). The aqueous layer was neutralized with 1 N aqueous sodium hydroxide and extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with brine (~30 mL), dried over anhydrous magnesium sulfate, filtered, and evaporated to give an off-white solid. Purification by preparative TLC (10% (7 M ammonia in methanol) in dichloromethane) gave sulfamide **22** as an off-white solid (54 mg, 42% yield). MS: $[M + H]^+ = 545$.

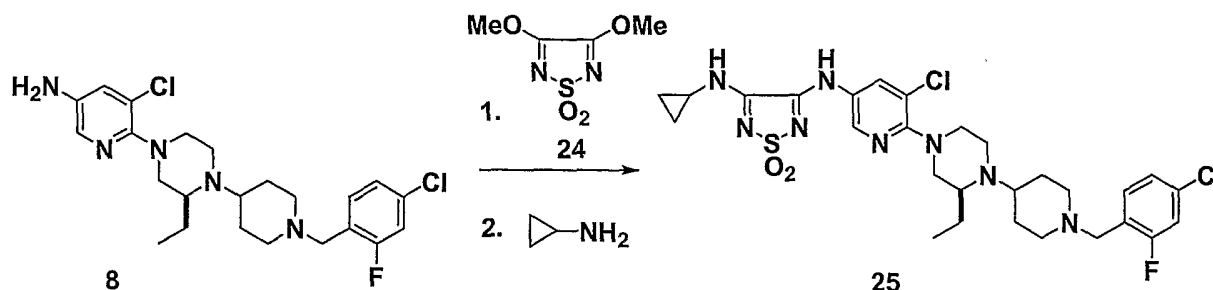
Preparative Example 18. Preparation of Table 1 Compound No. 73



3,4-Diethoxycyclobutenedione (93 μ L, 107 mg, 0.628 mmol, Aldrich) was added to a solution of amine **8** (266 mg, 0.571 mmol) in absolute ethanol (2.0 mL) and the reaction mixture was stirred at room temperature for 2 days.

Cyclopropylamine (60 μ L, 49 mg, 0.856 mmol) was added to the reaction mixture described above in step F', and the reaction was allowed to proceed for 14 hours at room temperature. The solvent was allowed to evaporate under a stream of nitrogen to afford a brown residue. Purification of the residue by reverse-phase HPLC (0–100% acetonitrile-water gradient) gave the daminocyclobutenedione **23** (203 mg, 59% yield). MS: $[M + H]^+ = 601$.

Preparative Example 19. Preparation of Table 1 Compound No. 235:

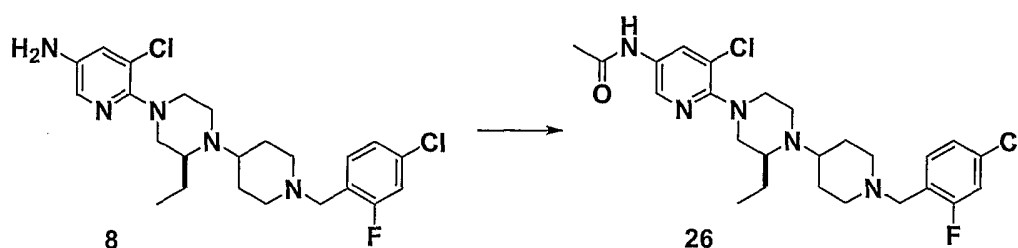


3,4-Dimethoxy-1,2,5-thiadiazole-1,1-dioxide (**24**) was prepared according to the method of Carmack et al., in *J. Org. Chem.* **1975**, *40*, 2743.

An admixture of amine **8** (32 mg, 0.067 mmol) and **24** (36 mg, 0.200 mmol) was dissolved in methanol (150 μ L) and DMF (20 μ L) was added. The reaction mixture was stirred at room temperature for 18 hours.

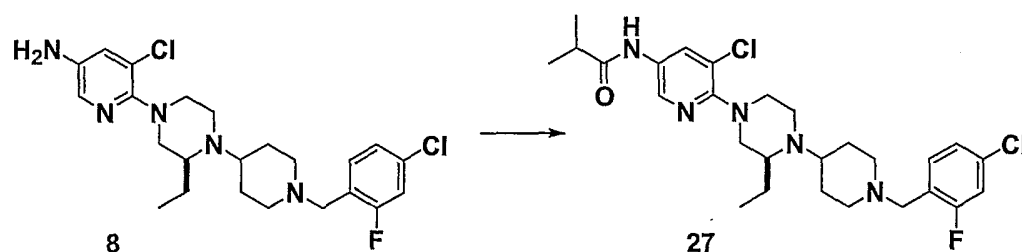
Cyclopropylamine (23 μ L, 19 mg, 0.335 mmol) was added to the reaction mixture described above in step F', and the reaction was allowed to proceed for 2 days at room temperature. The solvent was allowed to evaporate under a stream of nitrogen to afford a brown residue. Purification of the residue by reverse-phase HPLC (0 $\rightarrow$ 100% acetonitrile-water gradient) gave **25** (18 mg, 43% yield). MS: $[M + H]^+ = 637$.

Preparative Example 20. Preparation of Table 1 Compound No. 177



A solution of amine **8** (47 mg, 0.1 mmol) and triethylamine (15 μ L, 11 mg, 0.1 mmol) in dry dichloromethane (3 mL) was cooled to 0°C and acetyl chloride (7 μ L, 8 mg, 0.1 mmol) was added. The reaction mixture was stirred at 0°C for 1 hour and at room temperature overnight. The reaction mixture was diluted with dichloromethane (25 mL) and was washed successively with 1 N sodium bicarbonate solution (10 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (5% (7 M ammonia in methanol) in dichloromethane) gave amide **26** as a white solid (40 mg, 78% yield). MS: $[M + H]^+ = 508$.

Preparative Example 21. Preparation of Table 1 Compound No. 178

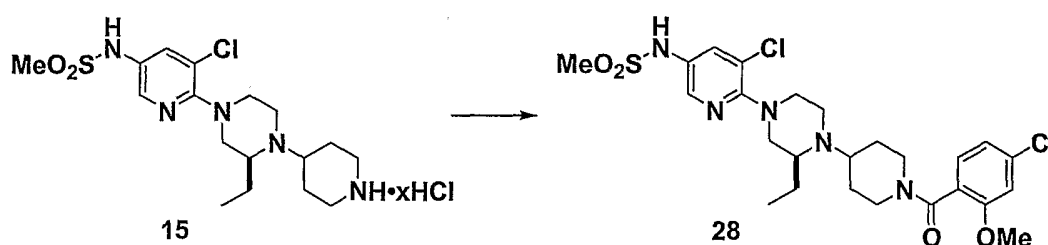


A solution of amine **8** (47 mg, 0.1 mmol) and triethylamine (15 μ L, 11 mg, 0.1 mmol) in dry dichloromethane (3 mL) was cooled to 0°C and

isobutyryl chloride (11 μ L, 11 mg, 0.1 mmol) was added. The reaction mixture was stirred at 0°C for 1 hour and at room temperature overnight. The reaction mixture was diluted with dichloromethane (25 mL) and was washed successively with 1 N sodium bicarbonate solution (10 mL) and brine (10 mL).

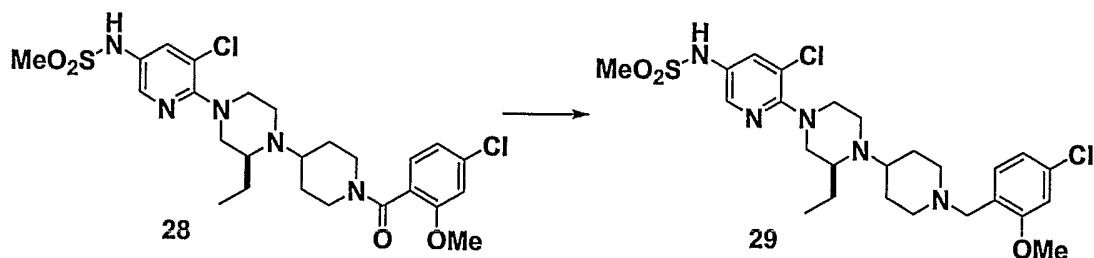
- 5 The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (5% (7 M ammonia in methanol) in dichloromethane) gave amide **27** as a white solid (41 mg, 77% yield). MS: $[M + H]^+ = 536$.

10 **Preparative Example 22**



- Amine salt **15** (204 mg, 400 μ mol based on $\cdot 3\text{HCl}$ salt) was suspended in DMF (4 mL) and diisopropylethylamine (0.5 mL, 372 mg, 2.9 mmol),
15 2-methoxy-4-chlorobenzoic acid (112 mg, 0.600 mmol), DECI (115 mg, 0.599 mmol), and HOBT (81 mg, 0.600 mmol) were added successively. The reaction mixture was heated with stirring at 70°C. The reaction mixture was partitioned in ethyl acetate (100 mL) and water (50 mL). The aqueous layer was extracted further with ethyl acetate (2 x 25 mL), and the combined
20 organic layers were then washed with brine (50 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give a brown oil. Purification by preparative TLC (5% (7 M ammonia in methanol) in dichloromethane) afforded amide **28** (180 mg, 64% yield). MS: $[M + H]^+ = 570$.

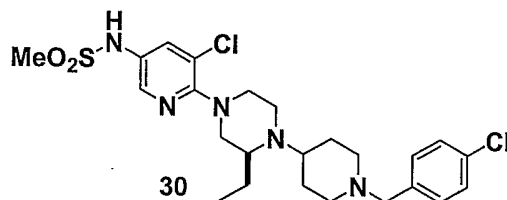
- 25 **Preparative Example 23.** Preparation of Table 1 Compound No. 1



Borane-methyl sulfide complex (320 μ L, 10 M in THF, 3.2 mmol) was added to a solution of amide **28** (180 mg, 0.32 mmol) in THF (4 mL). The solution was stirred at reflux for 4 hours, cooled to room temperature, and diluted with ethyl acetate (50 mL). The organic solution was washed sequentially with 1 N aqueous hydrochloric acid, 1 N aqueous sodium hydroxide, water, and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure.

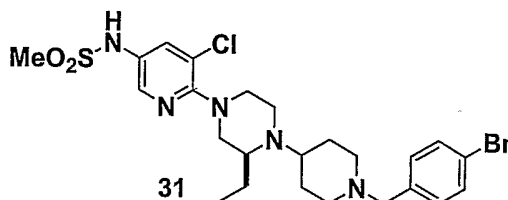
Purification by silica gel chromatography (5% (7 M ammonia in methanol) in dichloromethane) gave substituted benzylamine **29** (130 mg, 74% yield). MS: $[M + H]^+ = 556$.

Preparative Example 24. Preparation of Table 1 Compound No. 6



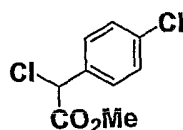
Compound **30** was prepared by the same method shown for Preparative Examples 4 through 6, using 4-chlorobenzyl chloride in place of 2-fluoro-4-chlorobenzyl bromide. MS: $[M + H]^+ = 526$.

Preparative Example 25. Preparation of Table 1 Compound No. 5



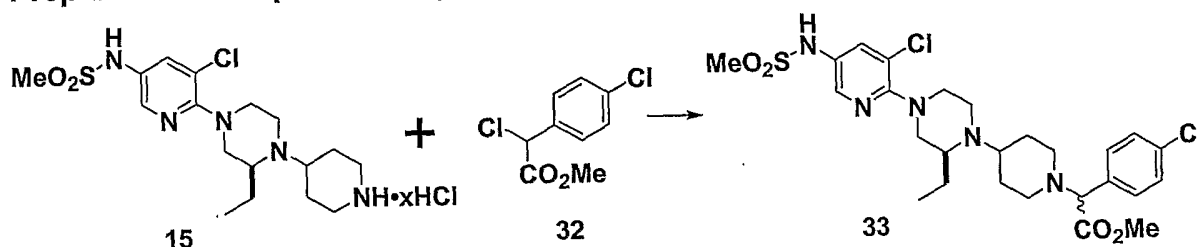
Compound **31** was prepared by the same method shown for Preparative Example 12, using 4-bromobenzaldehyde in place of 4-(trifluoromethoxy)benzaldehyde. MS: $[M + H]^+ = 570$.

Preparative Example 26. Preparation of Methyl 2-chloro-2-(4-chlorophenyl)acetate (**32**).

**32**

Neat thionyl chloride (66 mL, 108 g, 0.911 mol) was added to solid *p*-chloromandelic acid (20 g, 0.107 mol, Aldrich) and the mixture was stirred at 70°C for 19 hours. The majority of the volatile components was removed by evaporation under reduced pressure, and residual thionyl chloride was removed by co-evaporation with toluene (2 x 200 mL). The remaining pale yellow liquid was cooled to 0°C and methanol (100 mL) was added slowly. The resulting solution was stirred at room temperature for 8 hours. The solvent was evaporated under reduced pressure to give a pale yellow crude product. Purification of the crude product by silica gel chromatography (19:1 hexanes-ether) gave ester **32** (15.5 g, 67% yield).

Preparative Example 27. Preparation of Table 1 Compound No. 39:

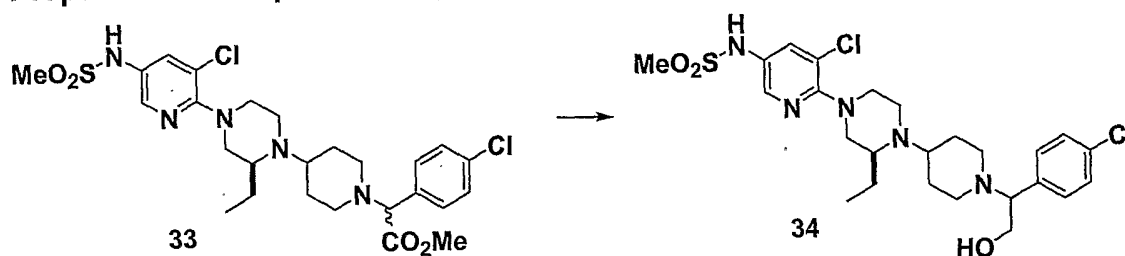


15

Compound **33** was prepared by the same method shown for Preparative Example 13, using Compound **32** in place of 4-cyanobenzyl bromide. Optionally, the stereoisomers of **33** may be separated by HPLC.

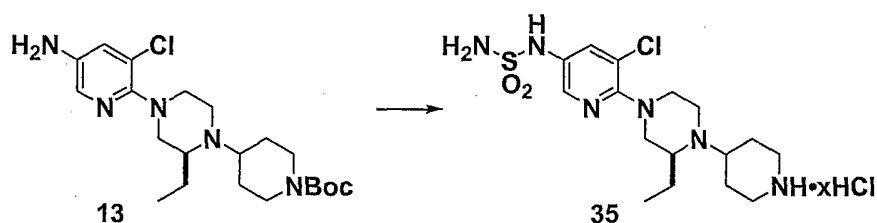
MS: $[M + H]^+ = 584$.

Preparative Example 28. Preparation of Table 1 Compound No. 11



Lithium borohydride (308 μ L, 2.0 M in THF; 0.616 mmol) was added to a solution of ester **33** (180 mg) in THF (1.5 mL) at 0°C. The reaction mixture was stirred at 0°C for 30 min and at room temperature for 24 hours. An additional portion of lithium borohydride (600 μ L, 2.0 M in THF; 1.2 mmol) and THF (2 mL) was added and the reaction was allowed to proceed for a further 14 hours. The reaction mixture was diluted with ethyl acetate (50 mL) and water (~10 mL) was cautiously added. 1 N aqueous hydrochloric acid was added dropwise until effervescence was no longer observed. The aqueous layer was adjusted to pH 7 with 0.5 M aqueous sodium hydroxide and then extracted further with ethyl acetate (3 x 25 mL). The combined organic layers were washed with brine (~30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (10% (7 M ammonia in methanol) in dichloromethane) to give alcohol **34** as a white solid (140 mg, 82% yield). Optionally, the stereoisomers of **34** may be separated by HPLC. MS: $[M + H]^+ = 556$.

Preparative Example 29. Preparation of Amine Salt 35.

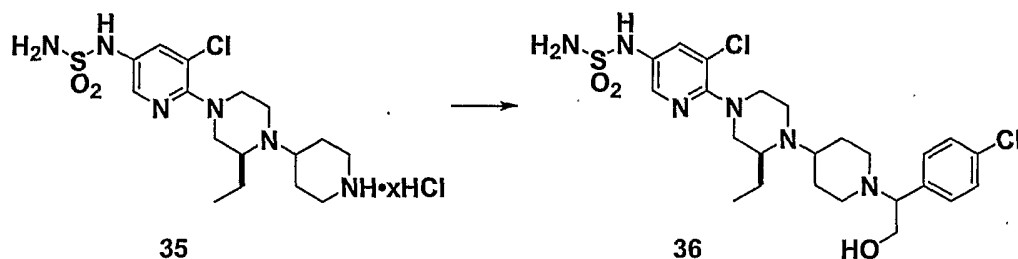


To a solution of ice-cold chlorosulfonyl isocyanate (92 μ L, 150 mg, 1.06 mmol) in dry dichloromethane (2.6 mL) was added dropwise a solution of *t*-butanol (101 μ L, 79 mg, 1.06 mmol) in dichloromethane (1 mL). The clear, colorless solution was stirred at 0°C for 30 min, then was added dropwise by syringe over 10 min to an ice-cold solution of amine **13** (225 mg, 0.53 mmol) and triethylamine (147 μ L, 107 mg, 1.06 mmol) in dichloromethane (1.8 mL). The reaction mixture was stirred at 0°C for 30 min and at room temperature for a further 18 hours. The solvent was then evaporated under reduced pressure to afford a brown solid.

The solid was suspended in methanol (3 mL) and hydrogen chloride solution (1.5 mL, 4 M in dioxane, 6 mmol) was added. The solution was stirred at room temperature for 18 hours. The solvent was evaporated to give

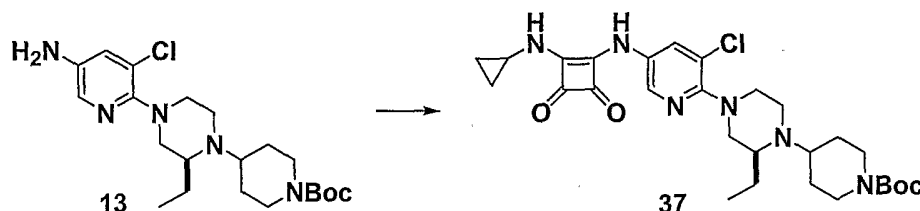
35 (205 mg, 75% yield), which was used without further purification. MS: $[M + H]^+ = 403$.

Preparative Example 30. Preparation of Table 1 Compound No. 3



Amine salt **35** was converted to **36** according to methods outlined for Preparative Examples 27 and 28. MS: $[M + H]^+ = 557$.

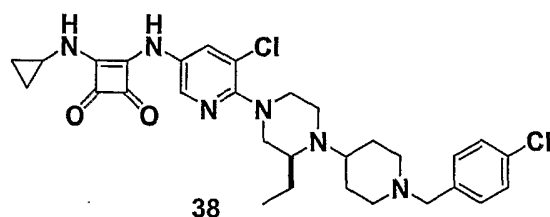
Preparative Example 31. Preparation of Table 1 Compound No. 37.



3,4-Diethoxycyclobutenedione (340 μ L, 390 mg, 2.30 mmol, Aldrich) was added to a solution of amine **13** (750 mg, 1.77 mmol) in absolute ethanol (12 mL) and the reaction mixture was stirred at room temperature for 2 days. Step F'.

Cyclopropylamine (240 μ L, 200 mg, 3.5 mmol) was added to the reaction mixture, which was stirred for 14 hours at room temperature. The solvent was removed under reduced pressure afford a brown residue. Purification of the residue by silica gel chromatography (5% (7 M ammonia in methanol) in dichloromethane) gave **37** (541 mg, 55% yield). MS: $[M + H]^+ = 559$.

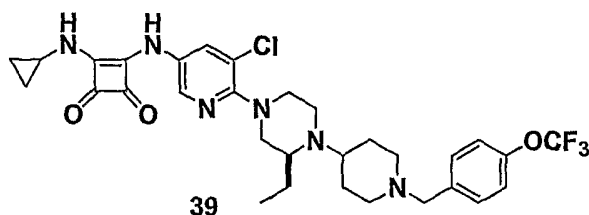
Preparative Example 32. Preparation of Table 1 Compound No. 70



Compound **38** was prepared from carbamate **37** by sequential application of methods illustrated for Preparative Examples 11 and 13,

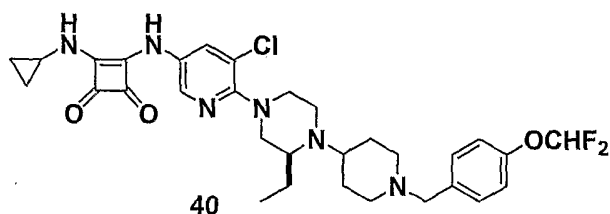
substituting 4-chlorobenzyl chloride for 4-cyanobenzyl bromide. MS: $[M + H]^+ = 583$.

Preparative Example 33. Preparation of Table 1 Compound No. 77



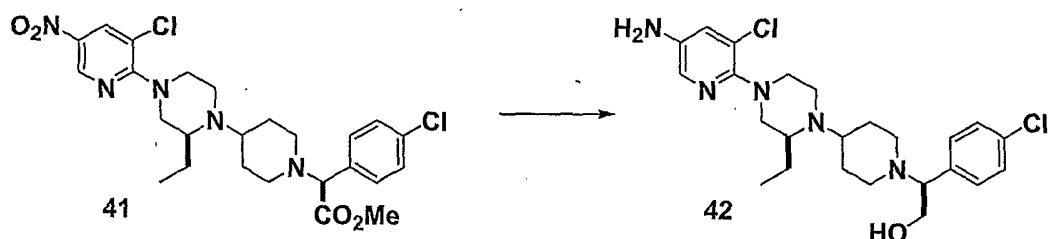
Compound **39** was prepared from carbamate **37** by sequential application of methods illustrated for Preparative Examples 11 and 13, substituting 4-(trifluoromethoxy)benzyl bromide for 4-cyanobenzyl bromide. MS: $[M + H]^+ = 633$.

Preparative Example 34. Preparation of Table 1 Compound No. 74



Compound **40** was prepared from carbamate **37** by sequential application of methods illustrated for Preparative Examples 11 and 13, substituting 4-(difluoromethoxy)benzyl bromide for 4-cyanobenzyl bromide. MS: $[M + H]^+ = 615$.

Preparative Example 35. Preparation of Table 1 Compound No. 42.

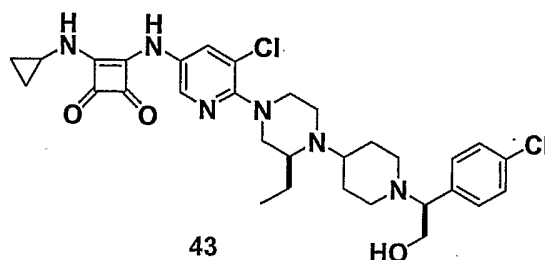


Ester **41** was prepared from amine salt **6** according to the method for Preparative Example 4, substituting Compound **32** for 2-fluoro-4-chlorobenzyl bromide. MS: $[M + H]^+ = 536$.

Lithium borohydride (2 mL, 2.0 M in THF, 4 mmol) was added to a solution of ester **41** (205 mg, 0.382 mmol) in dry THF (1 mL) at 0°C. The reaction was allowed to proceed for 0°C for 30 min and at room temperature for 24 hours. Water (20 mL) and ethyl acetate (20 mL) were added and the mixture was stirred for 30 min. The aqueous layer was extracted with ethyl

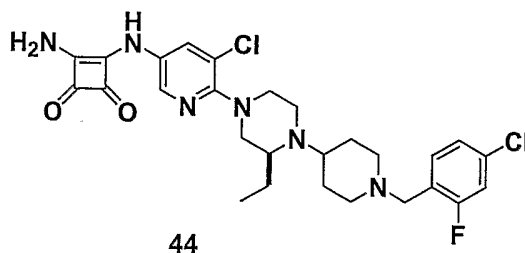
acetate (3 x 20 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (10% (7 M ammonia in methanol) in dichloromethane) gave alcohol **42** (94 mg, 50% yield). MS: $[M + H]^+ = 478$.

Preparative Example 36. Preparation of Table 1 Compound No. 71



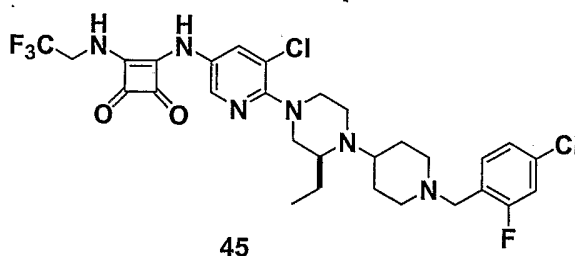
Compound **43** was prepared from amine **42** by the method outlined for Preparative Example 18. MS: $[M + H]^+ = 613$.

Preparative Example 37. Preparation of Table 1 Compound No. 76



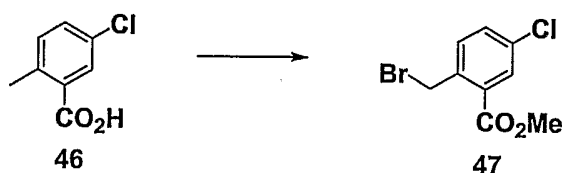
Compound **44** was prepared from amine **8** by the method outlined for Preparative Example 18, substituting ammonium hydroxide for cyclopropylamine. MS: $[M + H]^+ = 561$.

Preparative Example 38. Preparation of Table 1 Compound No. 75



Compound **45** was prepared from amine **8** by the method outlined for Preparative Example 18, substituting 2,2,2-trifluoroethylamine for cyclopropylamine. MS: $[M + H]^+ = 643$.

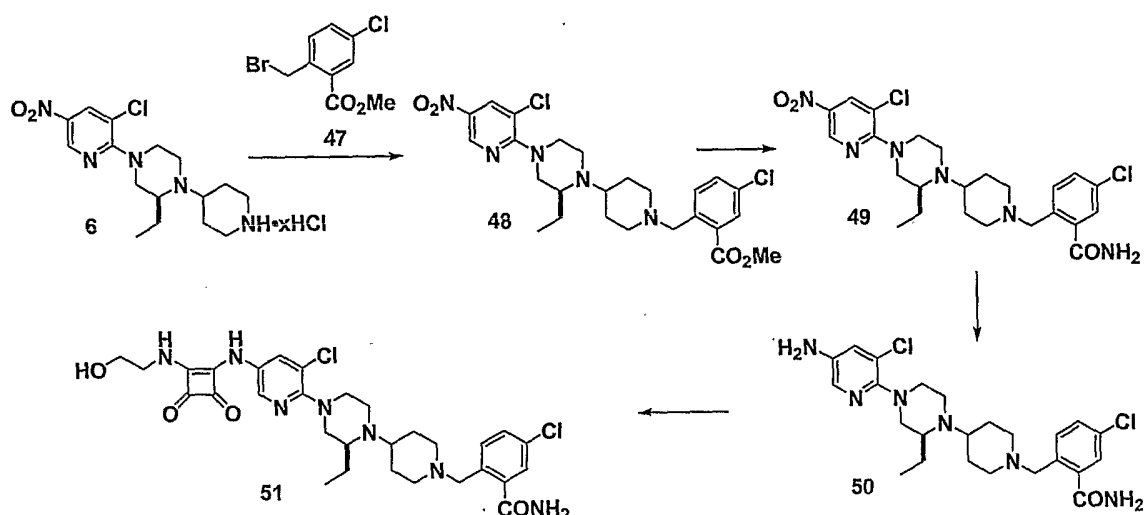
Preparative Example 39. Preparation of Bromide 47.



5-Chloro-2-methylbenzoic acid (**46**, 5.0 g, 29.3 mmol) was suspended in dichloromethane (30 mL) and thionyl chloride (3.2 mL, 5.2 g, 44 mmol) was added. The solution was stirred at room temperature for 1 hour. Methanol
5 was added and the reaction was allowed to proceed for a further 16 hours. The volatile components were evaporated under reduced pressure. The resulting residue was taken up again in methanol (30 mL) and pyridine (5 mL) was added. The solution was stirred at room temperature for 2 days. The solvent was evaporated under reduced pressure. The residue was dissolved
10 in dichloromethane and washed with water. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated to afford methyl 5-chloro-2-methylbenzoate (5.3 g, 96% yield) that was used in the following step without further purification.

N-Bromosuccinimide (5.3 g, 30 mmol) and benzoyl peroxide (343 mg, 1.4 mmol) were added sequentially to a solution of methyl
15 5-chloro-2-methylbenzoate (5.2 g, 28 mmol) in carbon tetrachloride (180 mL). The reaction mixture was stirred at 70°C for 24 hours, then allowed to cool to room temperature, and was washed with saturated aqueous sodium bisulfite solution. The aqueous layer was extracted with dichloromethane. The
20 combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford bromide **47** (6.4 g, 50% purity, remainder starting material).

Preparative Example 40. Preparation of Table 1 Compound No. 72

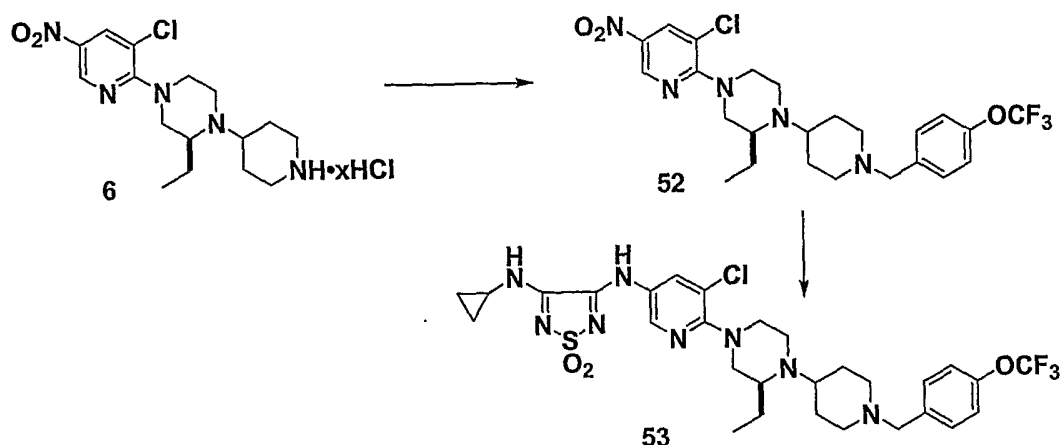


To a solution of amine salt **6** (250 mg, 0.54 mmol based on $\cdot 3\text{HCl}$ salt) and diisopropylethylamine (500 μL , 371 mg, 2.9 mmol) in dry dichloromethane (2 mL) was added bromide **47** (262 mg, 50% purity, 131 mg, 0.5 mmol). The reaction mixture was stirred at room temperature for 18 hours. Evaporation of the solvent under reduced pressure gave a brown oil that was purified by silica gel chromatography (2% (7 M ammonia in methanol) in dichloromethane) to give **48** as a yellow oil (257 mg, 89% yield). MS: $[\text{M} + \text{H}]^+ = 536$.

Ester **48** (252 mg, 0.471 mmol) was dissolved in ammonia solution (4 mL, 7 M in methanol, 28 mmol, Acros Organics) and the solution was heated overnight at 70°C in a pressure vessel. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was taken up again in ammonia solution (4 mL, 7 M in methanol, 28 mmol, Acros Organics) and the solution was heated at 70°C for a further 3 days. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure to give amide **49** (245 mg, 100% yield). MS: $[\text{M} + \text{H}]^+ = 521$.

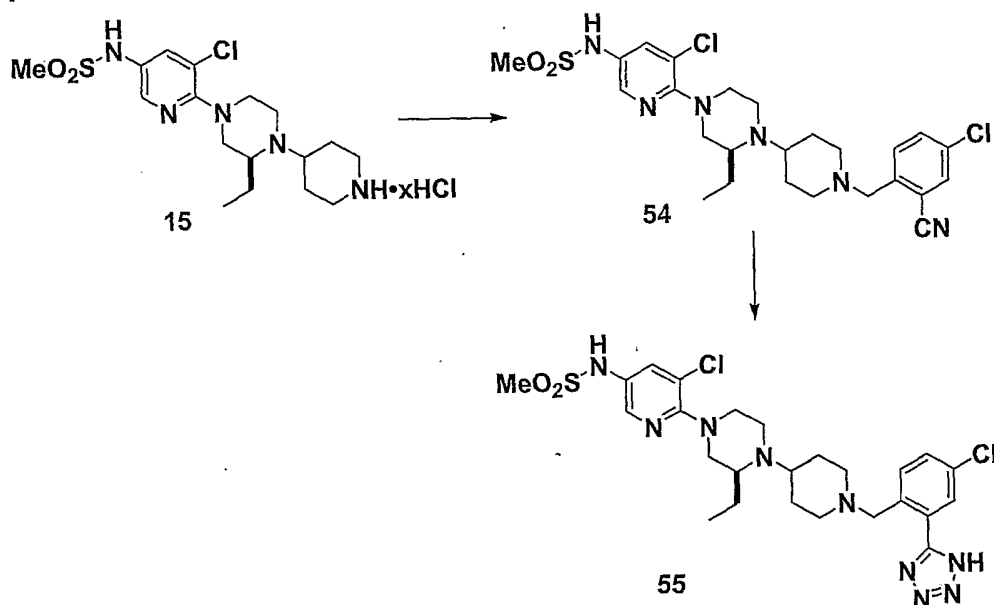
Amide **49** was converted to **51** by sequential application of methods outlined in Preparative Examples 9 and 18, substituting ethanolamine for cyclopropylamine in the last step. MS: $[\text{M} + \text{H}]^+ = 630$.

Preparative Example 41. Preparation of Table 1 Compound No. 234



Amine salt **6** was converted into **52** according to the method presented in Preparative Example 4, using 4-(trifluoromethoxy)benzyl bromide in place of 2-fluoro-4-chlorobenzyl bromide. Nitro compound **52** was transformed into **53** by sequential application of methods presented in Preparative Examples 5 and 19. MS: $[\text{M} + \text{H}]^+ = 669$.

Preparative Example 42. Preparation of Table 1 Compound No. 36



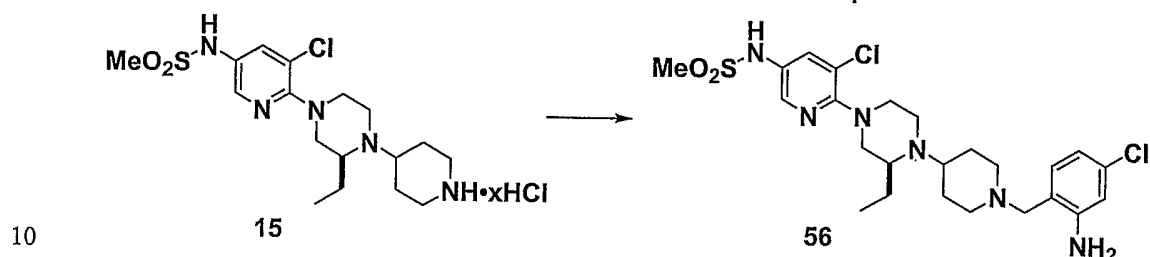
2-Cyano-4-chlorobenzyl bromide was prepared from 5-chloro-2-methylbenzonitrile (Matrix Scientific) by the method given in Preparative Example 39.

Amine salt **15** was converted to **54** by the method given in Preparative Example 13, substituting 2-cyano-4-chlorobenzyl bromide for 4-cyanobenzyl bromide.

The nitrile **54** (102 mg, 0.185 mmol) was then dissolved in DMF (1.8 mL) and triethylamine hydrochloride (77 mg, 0.560 mmol) and sodium azide

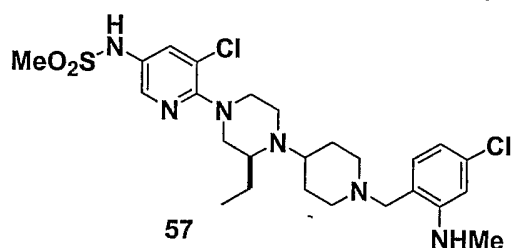
(84 mg, 1.3 mmol) were added sequentially. The reaction mixture was stirred at 80°C for 18 hours. A second portion of sodium azide (84 mg, 1.3 mmol) was added and the reaction mixture was stirred for a further 2 days at 80°C and 2 days at room temperature. The reaction mixture was diluted with
 5 dichloromethane (100 mL), and the solvents were evaporated under reduced pressure. Residual DMF was removed by co-evaporation with toluene (2 x 50 mL). The residue was purified by preparative TLC (20% methanol–dichloromethane) to provide **55** (28 mg). MS: $[M + H]^+ = 594$.

Preparative Example 43. Preparation of Table 1 Compound No. 9



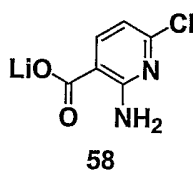
Amine salt **15** was converted to **56** first by application of the method shown in Preparative Example 12, substituting 4-chloro-2-nitrobenzaldehyde (Aldrich) for 4-(trifluoromethoxy)benzaldehyde, and then by following the reduction procedure shown in Preparative Example 35. MS: $[M + H]^+ = 541$.

15 **Preparative Example 44.** Preparation of Table 1 Compound No. 14



Compound **57** was prepared from amine **56** using the method shown for Preparative Example 12, substituting paraformaldehyde for 4-(trifluoromethoxy)benzaldehyde and omitting diisopropylethylamine. MS:
 20 $[M + H]^+ = 555$.

Preparative Example 45. Lithium 2-amino-6-chloronicotinate (**58**).



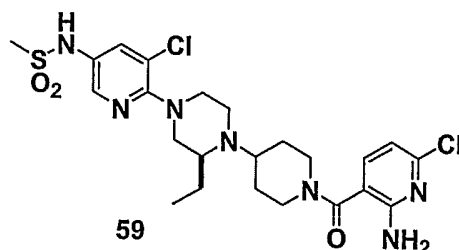
A solution of 2,5-dichloronicotinic acid (20.2 g, 0.105 mol, Aldrich) in methanol (500 mL) was cooled to 0°C and neat thionyl chloride (38 mL, 63 g,

0.525 mol) was added over ~30 min. The reaction mixture was stirred at 0°C for 1 hour. The cooling bath was removed, the reaction temperature was allowed to warm to room temperature, and the reaction was allowed to stir for an additional 2 days at room temperature. The solvent was removed under reduced pressure to give an off-white residue. The residue was dissolved in ether (~500 mL) and the resulting solution was washed successively with saturated aqueous sodium bicarbonate solution (~300 mL), water (~300 mL), and brine (~300 mL). The organic layer was separated, dried over anhydrous magnesium sulfate, and filtered. Removal of the solvent under reduced pressure yielded methyl 2,5-dichloronicotinate (21.0 g, 97% yield) as a white solid.

Performed in duplicate on identical scales in two pressure vessels, methyl 2,5-dichloronicotinate (4.5 g, 22 mmol) was dissolved in ammonia solution (250 mL, 0.5 M in 1,4-dioxane; 0.125 mol). The pressure vessels were sealed and heated at (85 ± 5) °C for 9 days. The two reaction mixtures were allowed to cool to room temperature, then combined and concentrated under reduced pressure to yield a white solid. Dissolution of the solid in 1:1 acetone-methanol (~500 mL), followed by adsorption onto silica gel (25 g) and then purification by flash column chromatography (25:10:1 hexanes-dichloromethane-ether), gave methyl 2-amino-5-chloronicotinate (6.08 g, 75% yield).

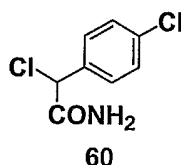
A solution of LiOH·H₂O (1.38 g, 33 mmol) in water (33 mL) was added in one portion to a suspension of methyl 2-amino-5-chloronicotinate (6.08 g, 27 mmol) in methanol (110 mL). The reaction mixture was stirred at 70°C for 24 hours, and gradually became homogeneous. The solvents were removed under reduced pressure, and after the resulting white solid was dried under vacuum (<1 mmHg) to constant weight, lithium 2-amino-5-chloronicotinate (**58**) was obtained (5.51 g, 95% yield).

Preparative Example 46. Preparation of Table 1 Compound No. 31



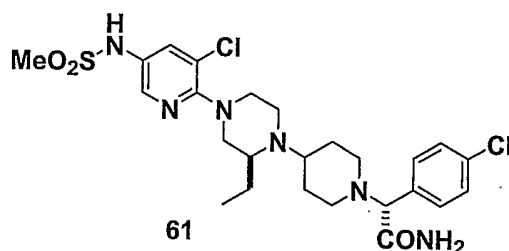
The amide **59** was prepared from amine salt **15** following the method for Preparative Example 15, substituting the carboxylate salt **58** for 2-amino-4-chlorobenzoic acid. MS: $[M + H]^+ = 556$.

5 Preparative Example 47.

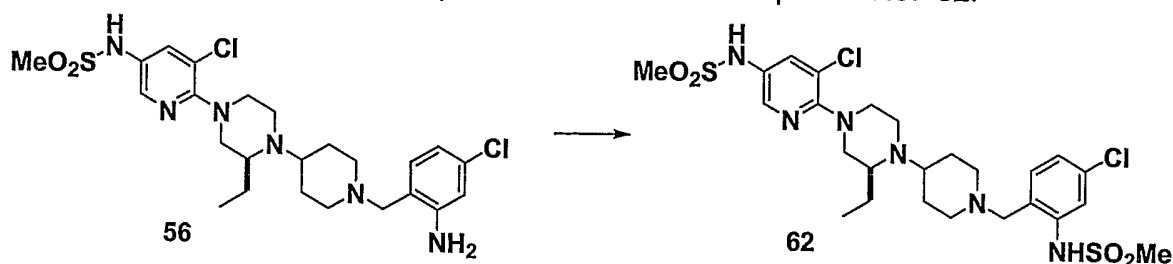


Neat thionyl chloride (50 mL, 81 g, 0.69 mol) was added to solid *p*-chloromandelic acid (9.3 g, 0.050 mol, Aldrich) and the mixture was stirred at 70°C for 19 hours. The majority of the volatile components was removed by evaporation under reduced pressure, and residual thionyl chloride was removed by co-evaporation with toluene (2 x 200 mL). The remaining pale yellow liquid was cooled to 0°C and ammonia solution (50 mL, 0.5 M in dioxane, 25 mmol) was added slowly. The resulting solution was stirred at room temperature for 2 days. The solvent was evaporated under reduced pressure to give a pale yellow residue. Crystallization from dichloromethane–hexanes gave amide **60** (10.0 g, 98% yield).

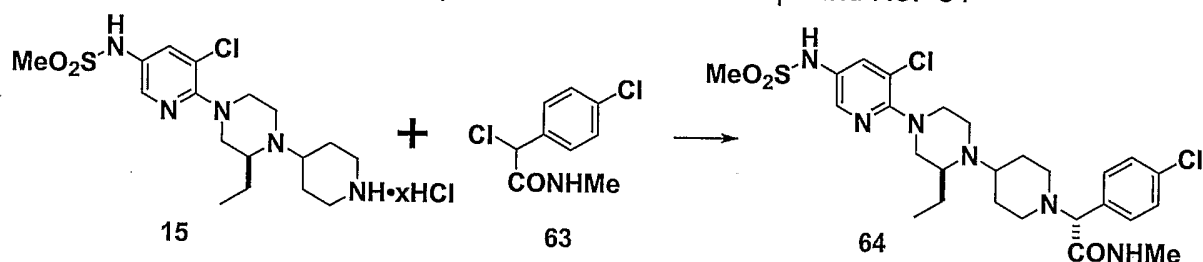
Preparative Example 48. Preparation of Table 1 Compound No. 31



Compound **61** was prepared from amine salt **15** by the method shown in Preparative Example 13, substituting the chloro-amide **60** for 4-cyanobenzyl bromide. MS: $[M + H]^+ = 569$.

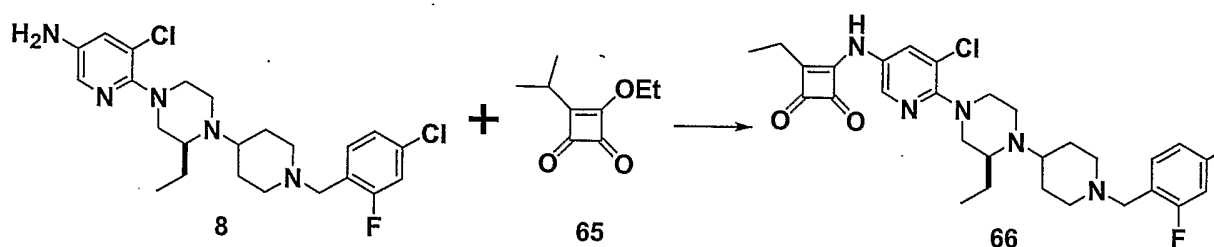
Preparative Example 49. Preparation of Table 1 Compound No. 52:

The sulfonamide **62** was prepared from amine **56** following the procedure for Preparative Example 10. MS: $[M + H]^+ = 619$.

Preparative Example 50. Preparation of Table 1 Compound No. 54

Chloro-amide **63** was prepared from *p*-chloromandelic acid (Aldrich) via the method given for Preparative Example 47, substituting methylamine for ammonia.

Compound **64** was prepared from amine salt **15** following the procedure given in Preparative Example 13, substituting the chloro-amide **63** for 4-cyanobenzyl bromide. MS: $[M + H]^+ = 583$.

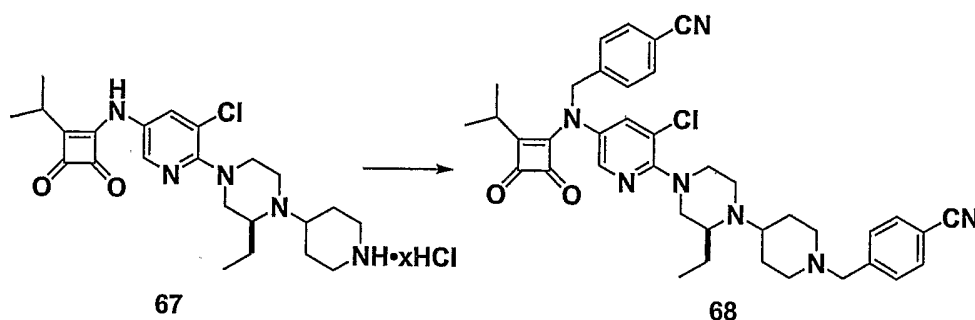
Preparative Example 51. Preparation of Table 1 Compound No. 84

2-Ethoxy-3-isopropylcyclobutene-1,2-dione (**65**) was prepared from 2,3-diethoxycyclobutene-1,2-dione (Aldrich) using the procedure of Moore et al., given in *J. Org. Chem.* **1996**, 61, 6009-6012.

Solid **8** (48 mg, 0.10 mmol) was added to a solution of **65** (52 mg, 0.31 mmol) in absolute ethanol (0.2 mL). The resulting solution was stirred at room temperature for 2 days. The solvent was evaporated under reduced pressure

and the residue was purified by reverse-phase HPLC (0 → 100% acetonitrile–water gradient) to give **66** (32 mg, 53% yield). MS: $[M + H]^+ = 588$.

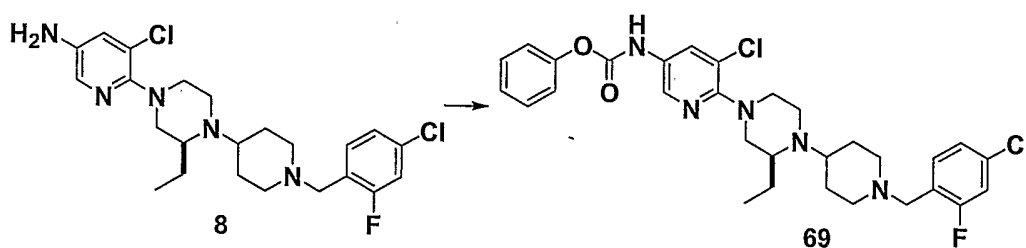
Preparative Example 52. Preparation of Table 1 Compound No. 148



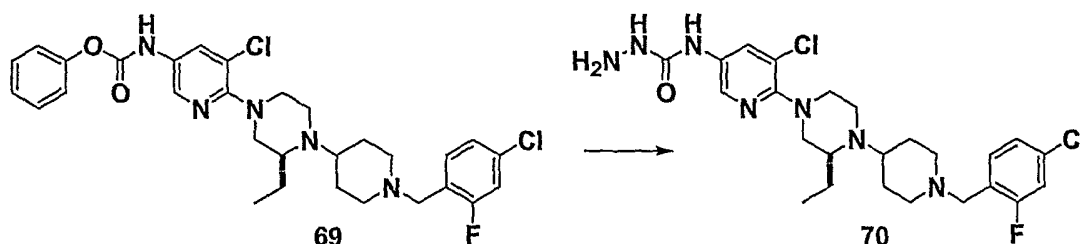
Compound **67** was prepared from amine **13**, first by reaction with **65** according to the method given in Preparative Example 51 and then by following the method given in Preparative Example 11.

Amine salt **67** (40 mg, 0.077 mmol, based on •2HCl salt) and triethylamine (62 μ L, 45 mg, 0.45 mmol) were dissolved in DMF (0.250 mL). *p*-Cyanobenzyl bromide (21 mg, 0.11 mmol) was added and the reaction mixture was stirred at room temperature for 20 hours. The reaction mixture was filtered and purified directly by reverse-phase HPLC (0 → 100% acetonitrile–water gradient) to give **68** (10 mg, 19% yield). MS: $[M + H]^+ = 676$.

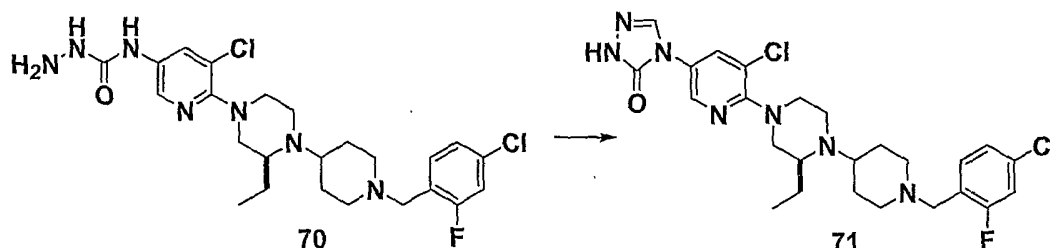
Preparative Example 53. Preparation of Table 1 Compound No. 189



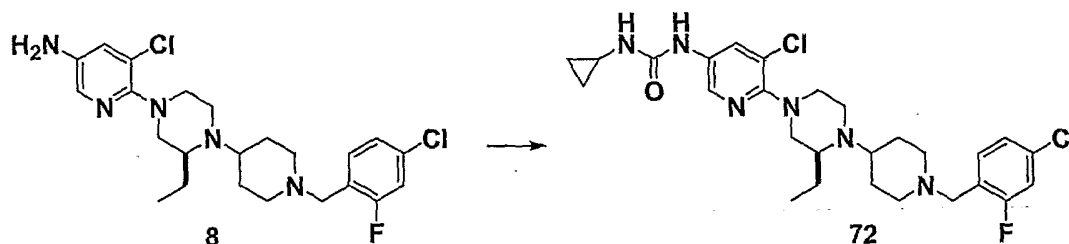
Phenyl chloroformate (90 mL, 111 mg, 0.71 mmol) was added dropwise over 5 min to an ice-cold solution of amine **8** (300 mg, 0.644 mmol) in 3:1 dichloromethane–pyridine (4 mL). The reaction mixture was allowed to warm to room temperature over 10 min, then stirred for a further 18 hours at room temperature. Solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (2 → 5% (7 M ammonia in methanol) in dichloromethane) to give **69** (280 mg, 74% yield). MS: $[M + H]^+ = 586$.

Preparative Example 54. Preparation of Table 1 Compound No. 188

Carbamate **69** and anhydrous hydrazine (75 μ L, 77 mg, 2.4 mmol) were dissolved in 1,4-dioxane (1 mL) and heated at reflux for 3 hours, then cooled to room temperature and partitioned between ethyl acetate (50 mL) and water (20 mL). The organic layer was washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to give semicarbazide **70** (62 mg, 50% yield). MS: $[M + H]^+ = 524$.

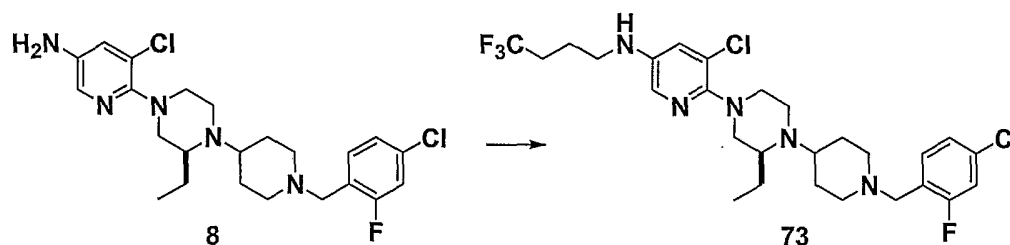
Preparative Example 55. Preparation of Table 1 Compound No. 179

Formamidine acetate (62 mg, 0.60 mmol) was added to a solution of semicarbazide **70** (62 mg, 0.12 mmol) in DMF (0.250 mL) and the reaction mixture was stirred at 130°C for 18 hours. The reaction mixture was cooled to room temperature, diluted with dichloromethane (20 mL), and washed with brine (5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give a brown residue. Purification by preparative TLC (10% (7 M ammonia in methanol) in dichloromethane) gave triazolone **71** (23 mg, 37% yield). MS: $[M + H]^+ = 534$.

Preparative Example 56. Preparation of Table 1 Compound No. 185

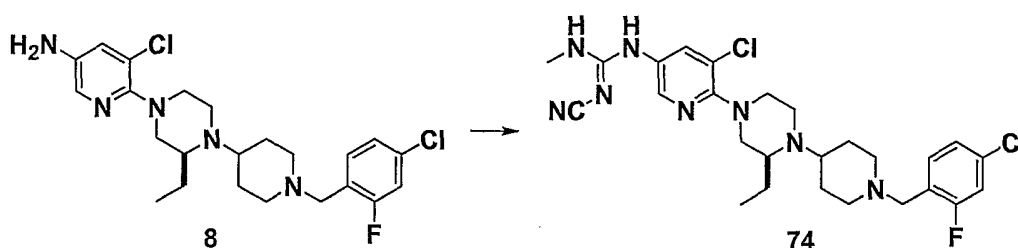
1,17-Carbonyldiimidazole (49 mg, 0.30 mmol, Aldrich) was added to a solution of amine **8** (47 mg, 0.10 mmol) in THF (1 mL). The solution was stirred overnight at room temperature. Excess cyclopropylamine (25 μ L, 21 mg, 0.36 mmol) was added and the reaction was allowed to proceed for a further 5 hours. The reaction mixture was diluted with ethyl acetate (25 mL) and washed sequentially with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield a yellow-orange oil. Purification by preparative TLC (5% (7 M ammonia in methanol) in dichloromethane) gave urea **72** (27 mg, 50% yield). MS: $[M + H]^+ = 549$.

Preparative Example 57. Preparation of Table 1 Compound No. 204



Sodium hydride (5 mg, 60% dispersion in oil, 2.8 mg, 0.12 mmol) was added to a solution of **8** (40 mg, 0.09 mmol) in dry DMF (350 μ L). The reaction was allowed to proceed at room temperature for 4 days. The reaction mixture was diluted with ethyl acetate (50 mL) and washed sequentially with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Preparative TLC separation (10% (7 M ammonia in methanol) in dichloromethane) gave alkylated amine **73** (6 mg, 12% yield). MS: $[M + H]^+ = 558$.

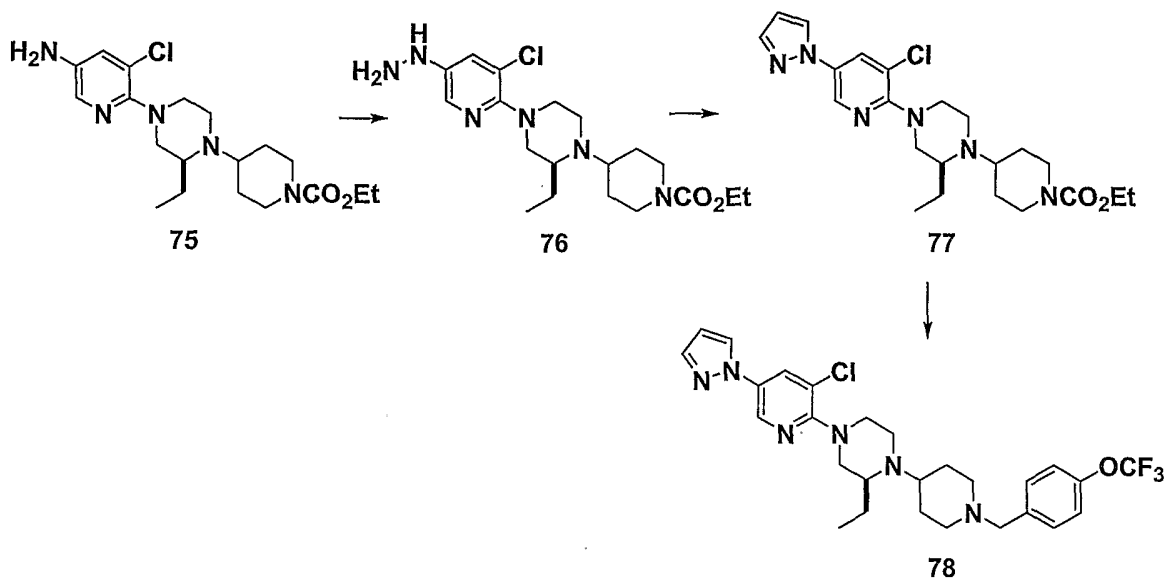
Preparative Example 58. Preparation of Table 1 Compound No. 205



Diphenyl cyanocarbonimidate (25 mg, 0.10 mmol, Aldrich) was added to a solution of **8** (40 mg, 0.09 mmol) and triethylamine (14 μ L, 10 mg, 0.10

mmol) in 1,2-dichloroethane (100 μ L). The reaction mixture was stirred at room temperature for 27 hours. Excess methylamine (400 μ L, 2.0 M in THF, 0.8 mmol) was added and the solution was stirred at room temperature for 24 hours. Evaporation of the solvent under reduced pressure followed by
 5 purification by preparative TLC (10% (7 M ammonia in methanol) in dichloromethane) gave **74** (30 mg, 64% yield). MS: $[M + H]^+ = 547$.

Preparative Example 59. Preparation of Table 1 Compound No. 210

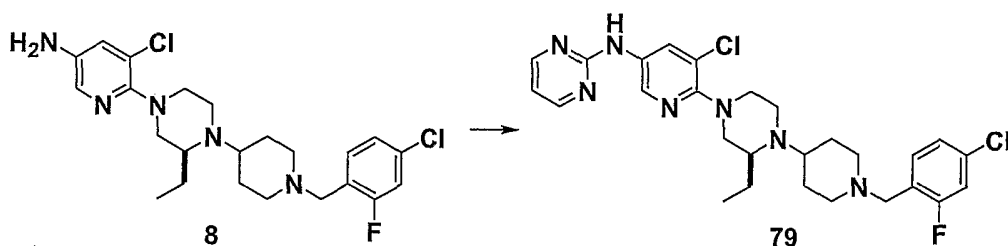


Amine **75** was prepared from the combination of **3** and 1-carbethoxy-4-piperidone (Aldrich) according to the method shown in Preparative Example 2,
 10 followed by application of the procedure of Preparative Example 9.

Amine **75** (1.10 g, 2.8 mmol) was dissolved in concentrated hydrochloric acid (10 mL) and the solution was cooled to -10°C . Sodium nitrite (211 mg, 3.1 mmol), dissolved in water (1 mL) was added dropwise into
 15 the reaction mixture. Tin(II) chloride (2.6 g, 13 mmol) was dissolved in concentrated hydrochloric acid (5 mL), cooled to -10°C , and added dropwise to the reaction mixture. The solution was allowed to warm to room temperature and was stirred for a further 30 min. The reaction mixture was cooled to 0°C and 20% aqueous sodium hydroxide solution (20 mL) was
 20 added cautiously. The aqueous solution was extracted with ethyl acetate (100 mL), the organic layer washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. Silica gel chromatography (5% (7 M ammonia in methanol) in dichloromethane) gave **76** (310 mg). MS: $[M + H]^+ = 411$.

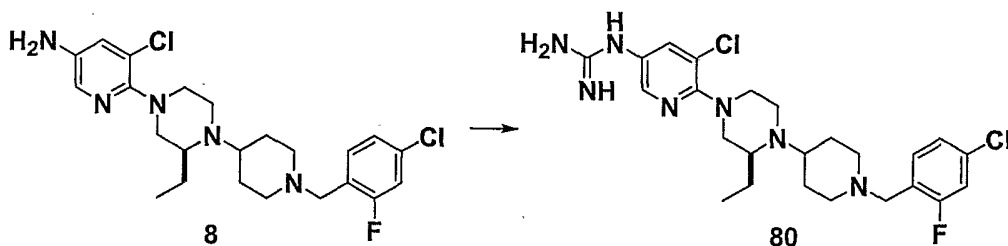
Hydrazine **76** (310 mg, 0.76 mmol) was dissolved in 1:1 ethanol/water (6 mL). Concentrated hydrochloric acid (0.1 mL) and 1,1,3,3-tetraethoxypropane (0.220 mL, 200 mg, 0.91 mmol) were added. The mixture was heated at reflux overnight, then cooled to room temperature, diluted with ethyl acetate (50 mL), and washed sequentially with saturated aqueous sodium bicarbonate solution (3 x 25 mL), water (25 mL) and brine (25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give **77**. The carbamate **77** was dissolved in 1,2-dichloroethane (1 mL) and iodotrimethylsilane (0.64 mL, 896 mg, 4.5 mmol) was added. The solution was stirred at 70°C overnight, then cooled to room temperature and diluted with methanol (1 mL). Solvent was removed under reduced pressure to give a brown oil. Sequential application of methods given in Preparative Examples 11 and 12 gave **78** (50 mg, 33% yield from **75**). MS: $[M + H]^+ = 549$.

Preparative Example 60. Preparation of Table 1 Compound No. 211



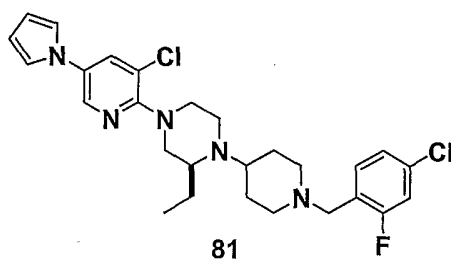
2-Chloropyrimidine (35 mg, 0.30 mmol), palladium acetate (45 mg, 0.30 mmol), 2-(di-*t*-butylphosphino)biphenyl (60 mg, 0.20 mmol, Strem Chemicals), and cesium carbonate (100 mg, 0.30 mmol) and amine **8** (47 mg, 0.10 mmol) were added sequentially into 1,4-dioxane (1.0 mL). The mixture was heated at 110°C overnight, cooled to room temperature, and applied directly to a silica gel column. Elution with 2% (7 M ammonia in methanol) in dichloromethane gave **79** (10 mg, 18% yield). MS: $[M + H]^+ = 544$.

Preparative Example 61. Preparation of Table 1 Compound No. 221



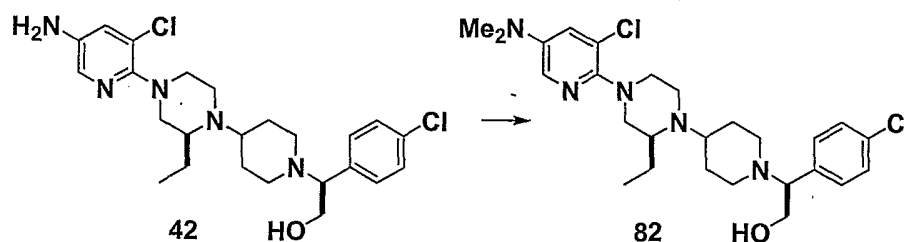
1,3-Bis(*t*-butoxycarbonyl)-2-methyl-2-thiopseudourea (30 mg, 0.10 mmol, Aldrich), mercury(II) chloride (27 mg, 0.10 mmol), and triethylamine (300 μ L, 216 mg, 2.1 mmol) were added sequentially to a solution of **8** (47 mg, 0.10 mmol) in DMF (1 mL). The reaction was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (50 mL) and washed sequentially with water (25 mL) and brine (25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give a brown oil. The oil was dissolved in ethyl acetate (1 mL) and hydrogen chloride (1.0 mL, 4 M solution in 1,4-dioxane, 4 mmol) was added. The solution was stirred at room temperature for 18 hours. The solvent was evaporated and the residue was purified by reverse-phase HPLC to give **80** (38 mg, 75% yield). MS: $[M + H]^+ = 508$.

Preparative Example 62. Preparation of Table 1 Compound No. 222



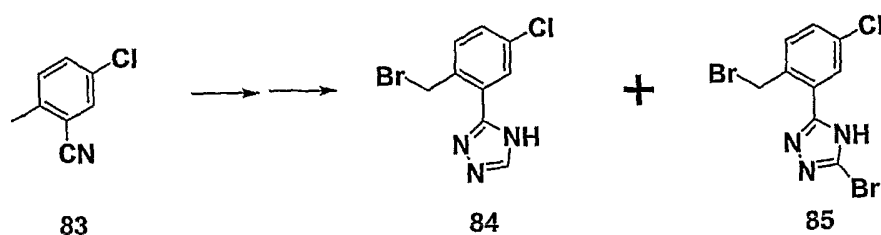
Compound **81** was prepared from amine **8** by the procedure of Josey, in *Org. Synth., Collective Vol. 5*, p. 716. MS: $[M + H]^+ = 516$.

Preparative Example 63. Preparation of Table 1 Compound No. 213



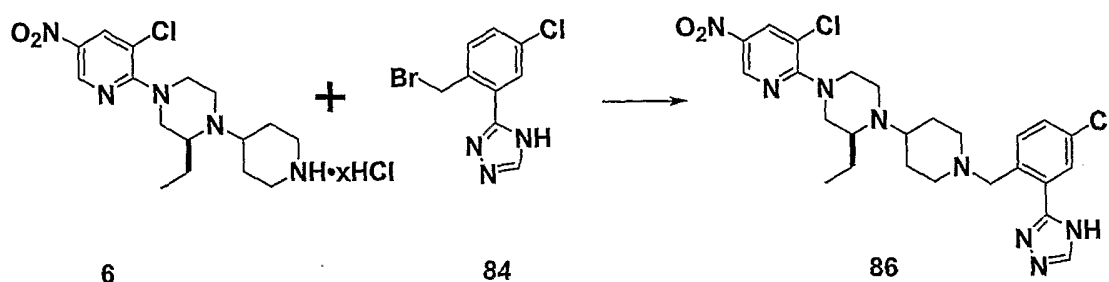
The amine **42** (100 mg, 0.210 mmol) was dissolved in dichloromethane (2 mL). Excess paraformaldehyde (63 mg) was added and the mixture was stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (443 mg, 2.09 mmol) was then added and the reaction was stirred overnight at room temperature. Work-up was carried out as described in Preparative Example 7 to afford **82** (28 mg, 26% yield). MS: $[M + H]^+ = 506$.

Preparative Example 64. Preparation of Intermediates **84** and **85**.

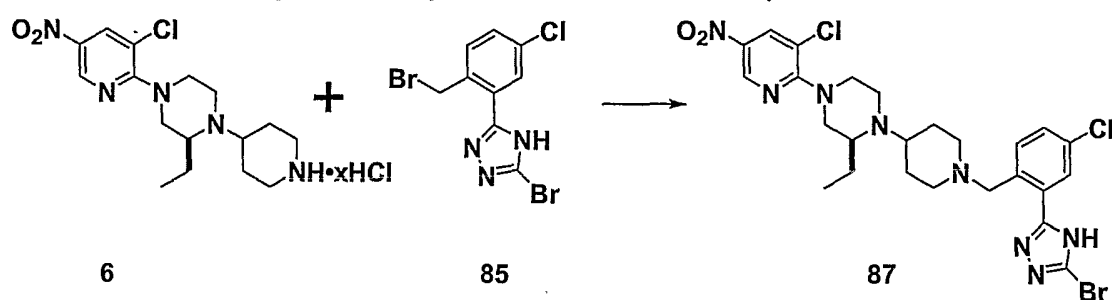


5-Chloro-2-methylbenzonitrile (**83**) was converted to 2-cyano-4-chlorobenzyl bromide by the method given in Preparative Example 39. A mixture of 2-cyano-4-chlorobenzyl bromide and sodium methoxide (13.2 mL, 0.5 M in MeOH, 6.6 mmol) in methanol (6 mL) was stirred for 2 hours at 25°C. To this was added formyl hydrazide (409 mg, 6.75 mmol) in methanol at 25°C. The reaction mixture was stirred at the temperature for 1 hour and then at reflux for 4 days. The reaction mixture was cooled, poured into water, and neutralized by addition of 1 N HCl solution. The organic layers were extracted with ethyl acetate and the combined organic solutions were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residual material was purified by SiO₂ column chromatography. Then, a mixture of the purified material (206 mg, 1.06 mmol), N-bromosuccinimide (567 mg, 3.19 mmol) and benzoyl peroxide (7.7 mg, 0.03 mmol) in carbon tetrachloride (15 mL) was stirred under nitrogen for 15 minutes at 25°C. The reaction mixture was heated to reflux for 3 hours. The reaction mixture was cooled and the precipitate was filtered. The filtrate was concentrated under reduced pressure and the residue was purified by preparative TLC (3% MeOH in CH₂Cl₂) to afford **84** (64 mg, 22%) and **85** (72 mg, 20%). MS (**84**): M+H = 272, MS (**85**): M+H = 350.

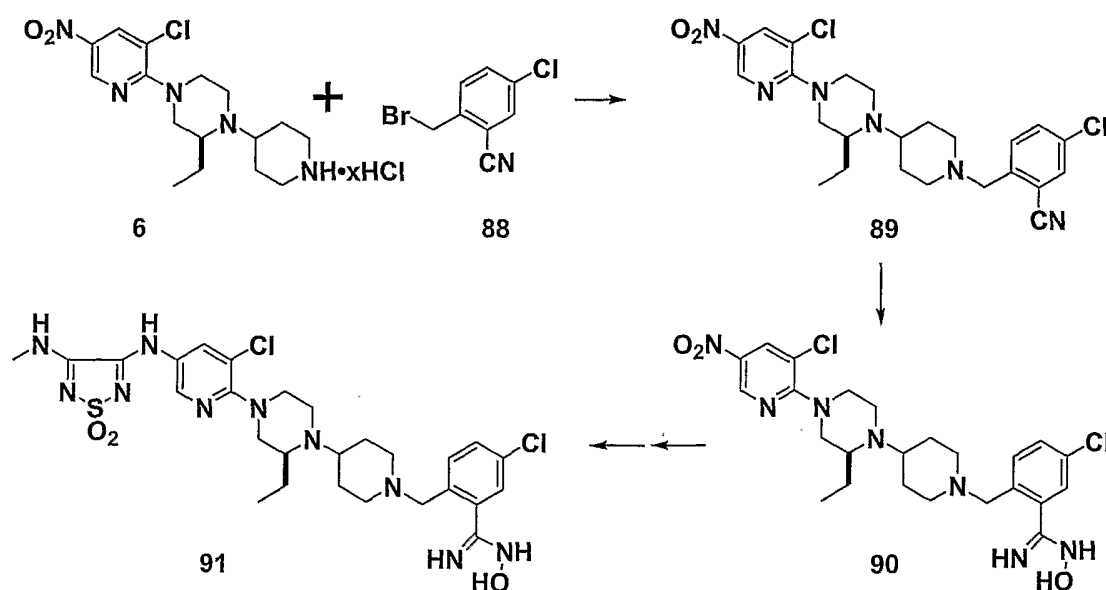
Preparative Example 65. Preparation of Table 1 Compound No. 215:



Amine salt **6** was combined with **84** according to the method given in Preparative Example 13 to afford **86**.

Preparative Example 66. Preparation of Table 1 Compound No. 230

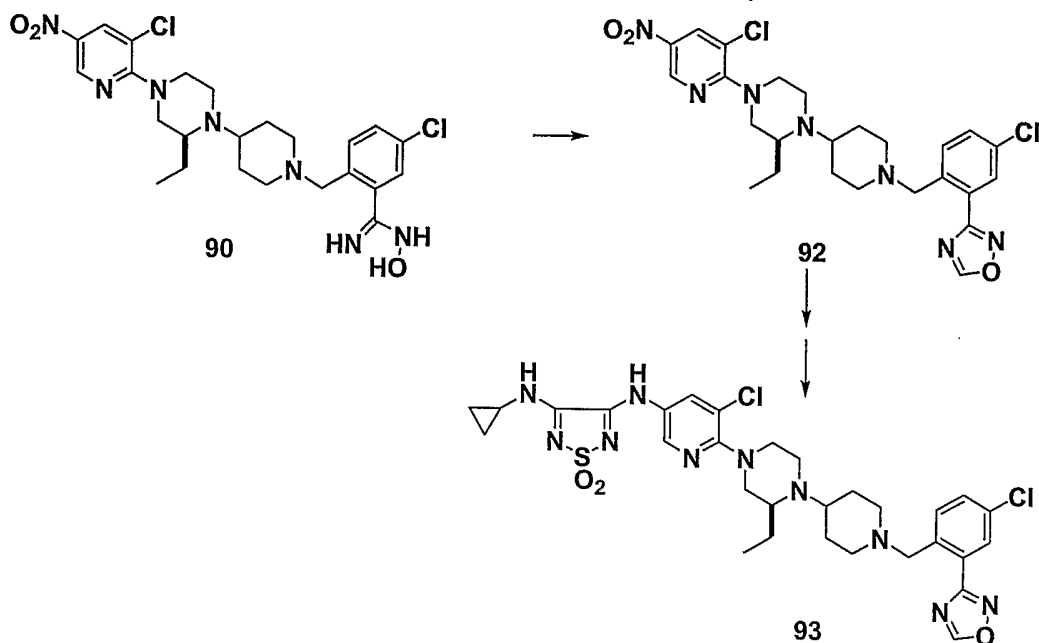
Amine salt **6** was combined with **85** according to the method given in Preparative Example 13 to afford **87**.

Preparative Example 67. Preparation of Table 1 Compound No. 236

Bromide **88**, prepared from 5-chloro-2-methylbenzonitrile (Matrix Scientific) was combined with amine salt **6** according to the method of Preparative Example 13 to give **89**. Nitrile **89** (377 mg, 0.75 mmol) was then dissolved in absolute ethanol (3 mL). Hydroxylamine hydrochloride (150 mg, 1.5 mmol) and diisopropylethylamine (261 μ L, 194 mg, 1.5 mmol) were added. The reaction mixture was stirred at reflux for 16 hours. The reaction mixture was cooled to room temperature, neutralized with saturated sodium bicarbonate solution, and extracted with ethyl acetate. The organic solution was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to give **90** as a yellow solid. Purification by silica gel chromatography (8% (7 M ammonia in methanol) in dichloromethane) gave **90** (167 mg, 42% yield). MS: $[M + H]^+ = 536$.

The nitro compound **90** was converted to **91** following procedures given in Preparative Examples 5 and 19, substituting methylamine for cyclopropylamine in the final step. MS: $[M + H]^+ = 651$.

Preparative Example 68. Preparation of Table 1 Compound No. 249

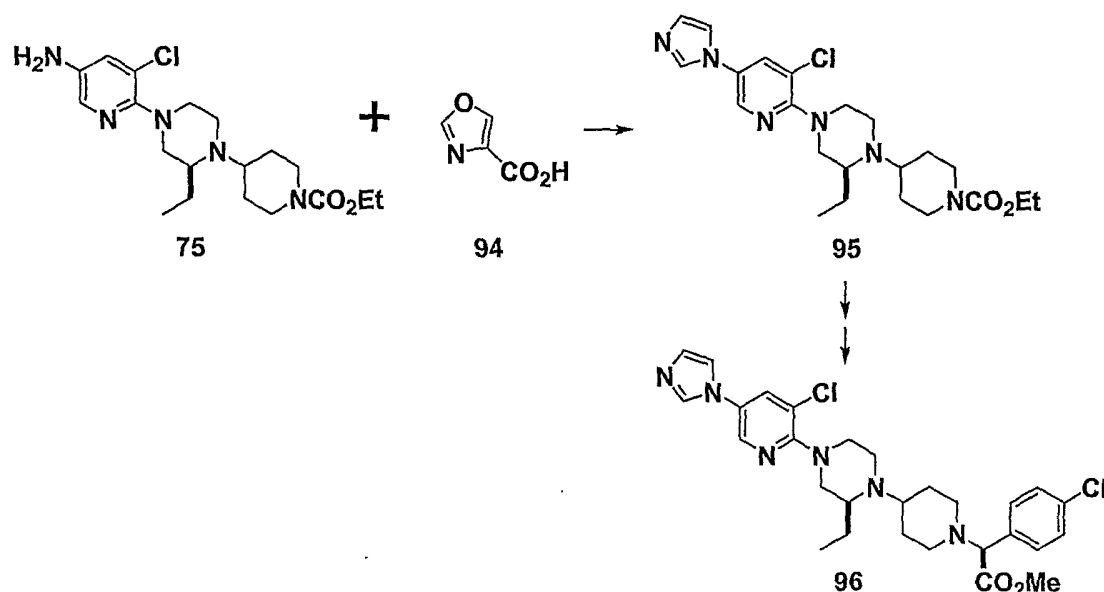


5

Compound **90** (500 mg, 0.900 mmol) was dissolved in triethyl orthoformate (3 mL) and pyridinium *p*-toluenesulfonate (250 mg) was added. The mixture was stirred at 70°C overnight, then cooled to room temperature, diluted with dichloromethane, and washed with brine. The organic solution was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to give **92**. The nitro compound **92** was converted to **93** following procedures given in Preparative Examples 5 and 19. MS: $[M + H]^+ = 687$.

10

Preparative Example 69. Preparation of Table 1 Compound No. 229

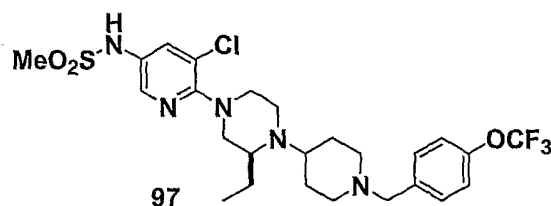


Compound **75** was prepared from the combination of **3** with 1-carbethoxy-4-piperidone (Aldrich) according to the method given in Preparative Example 2, followed by application of the procedure given in Preparative Example 9.

Oxazole-4-carboxylic acid (**94**) was prepared according to the procedure of Schöllkopf *et al.* in *Liebigs Ann. Chem.* **1979**, 1370-1387.

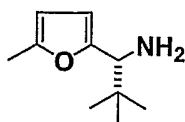
The combination of **75** and **94** to give **95** was carried out by the procedure of Cornforth and Cornforth in *J. Chem. Soc.* **1947**, 96-102. Compound **95** was converted to **96** by sequential application of methods given in Preparative Examples 59, 11, and 13, but substituting chloro-ester **32** for 4-cyanobenzyl bromide in the final step. MS: $[M + H]^+ = 557$.

Preparative Example 70. Preparation of Table 1 Compound No. 10

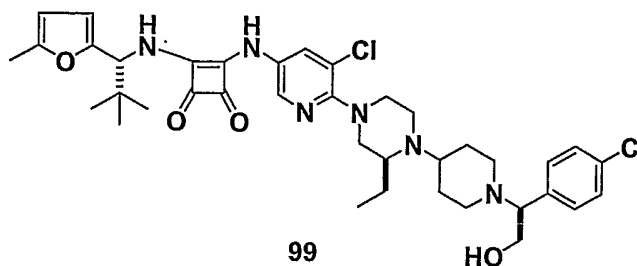


Compound **97** was prepared by the same method shown for Preparative Examples 4 through 6, using 4-(trifluoromethoxy)benzyl bromide in place of 2-fluoro-4-chlorobenzyl bromide. MS: $[M + H]^+ = 576$.

Preparative Example 71. Preparation of Table 1 Compound No. 109



98

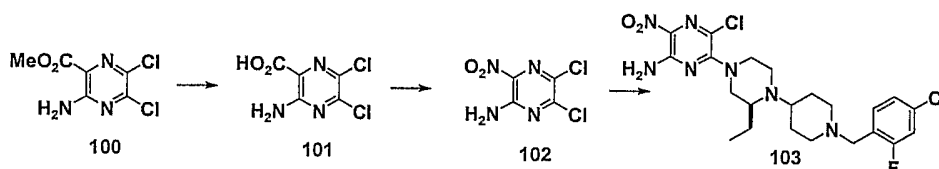


99

Amine **98** was prepared according to the method of Taveras *et al.* in WO 03/080053 and WO 04/011418.

- Compound **99** was prepared from amine **42** by the method outlined for
 5 Preparative Example 18, but using amine **98** in place of cyclopropylamine in the final step. MS: $[M + H]^+ = 723$.

Preparative Example 72. Preparation of Table 1 Compound No. 207

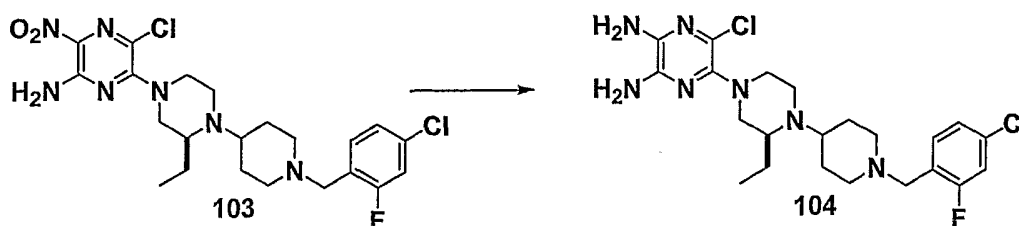


- A suspension of **100** (3.6 g, 16 mmol, Aldrich) and sodium hydroxide
 10 (1.6 g, 39 mmol) in water (30 mL) was heated at reflux for 15 min. The solution was filtered, allowed to cool to room temperature, and was acidified with 1 N hydrochloric acid. The precipitated solid **101** (1.2 g, 36% yield) was collected by filtration, air-dried, and dried further under vacuum.

- A solution of **101** (1.1 g, 5.3 mmol) in concentrated sulfuric acid (9 mL)
 15 was cooled to 0 °C and a 1:1 (v/v) nitric acid–sulfuric acid mixture (680 µL) was added. The reaction mixture was stirred at room temperature for 3 hours, then poured into ice (~150 mL). The precipitated solid was collected by filtration and then dissolved in ethyl acetate. The organic solution was neutralized with saturated aqueous sodium carbonate solution, dried over
 20 anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give **102** (619 mg, 56% yield).

The nitro compound was then converted to **103** by sequential application of procedures given in Preparative Examples 1 and 7. MS: $[M + H]^+ = 496$.

- 25 **Preparative Example 73.** Preparation of Table 1 Compound No. 219



A solution of **103** (60 mg, 0.12 mmol) in 4:1 ethanol–water (8 mL) was treated with calcium chloride dehydrate (80 mg, 0.54 mmol) and iron powder (200 mg, 3.6 mmol) at room temperature. The resulting suspension was stirred at reflux for 2 hours, cooled to room temperature, and diluted with methanol. The solids were removed by filtration and the filtrate was concentrated under reduced pressure to give a brown gum. Purification by silica gel chromatography (10% (7 M ammonia in methanol) in dichloromethane) gave **104** (45 mg, 78% yield). MS: $[M + H]^+ = 482$.

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 a 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 4×10^6 cells with 20 μ g of pME18Sneo-hCXCR3 (N-delta 4) plasmid DNA. Cells were pulsed at 400 Volts, 100 OHMs, 960 μ Fd. 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 $[^{125}\text{I}]$ 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 20×10^6 cells per ml. After 5 minute
5 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
10 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 CaCl₂, 5 mM MgCl₂,
15 125 mM NaCl, 0.002% NaN₃, 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 [¹²⁵I] IP-10 with tested compounds in a series of titration were added to start the
20 reaction. After 3 hr reaction at room temperature, the amount of [¹²⁵I] IP-10 bound to the SPA beads was determined with a Wallac 1450 Microbeta counter.

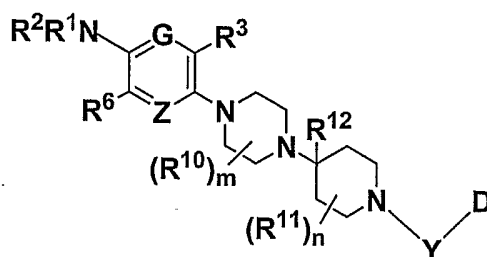
The Ki ratings for the various compounds of the present invention are given in the afore-mentioned Table 1. From these ratings and value ranges, it
25 would be apparent to the skilled artisan that the compounds of the invention have excellent utility as CXCR3 receptor antagonists.

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
30 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 pharmaceutically acceptable salts, solvates or esters thereof wherein:

Z is N, C(R²⁹), NO or NOH;

G is N, C(R⁴), NO or NOH;

- R¹ and R² are independently absent or present, and if present each is independently selected from the group consisting of H, alkyl, alkoxy, alkenyl, carbonyl, cycloalkyl, cycloalkenyl, alkylaryl, arylalkyl, aryl, amino, alkylamino, amidinyl, carboxamido, cyano, hydroxyl, urea, -N≡CH, =NCN, -(CH₂)_qOH, -(CH₂)_qOR³¹, -(CH₂)_qNH₂, -(CH₂)_qNHR³¹, -(CH₂)_qN(R³¹)₂, -(CH₂)_qC(=O)NHR³¹, -(CH₂)_qSO₂R³¹, -(CH₂)_qNHSO₂R³¹, -(CH₂)_qSO₂NHR³¹, -C(=S)N(H)alkyl, -N(H)-S(O)₂-alkyl, -N(H)C(=O)N(H)-alkyl, -S(O)₂alkyl, -S(O)₂NH₂, -S(O)₂N(H)alkyl, -S(O)₂N(alkyl)₂, -S(O)₂aryl, -S(O)₂heteroaryl, -S(O)₂heterocyclyl, -C(=S)N(H)cycloalkyl, -C(=O)N(H)NH₂, -C(=O)alkyl, -C(=O)heteroaryl, -C(=O)heterocyclyl, -heteroaryl, heterocyclyl, and heterocyclenyl; or alternatively the N taken together with the R¹ and R² forms a heterocycl, heteroaryl or -N=C(NH₂)₂;

- R³, R⁴, R⁶ and R²⁹ moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, aralkyl, -CN, CF₃, haloalkyl, cycloalkyl, halogen, hydroxyalkyl, -N=CH-(R³¹), -C(=O)N(R³⁰)₂, -N(R³⁰)₂, -OR³⁰, -SO₂(R³¹), -N(R³⁰)C(=O)N(R³⁰)₂ and -N(R³⁰)C(=O)R³¹;

the R¹⁰ moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclenyl, heterocyclyl, alkylaryl, arylalkyl, -CO₂H,

hydroxyalkyl, $-\text{C}(=\text{O})\text{N}(\text{R}^{30})_2$, $-(\text{CH}_2)_q\text{OH}$, $-(\text{CH}_2)_q\text{OR}^{31}$, $-(\text{CH}_2)_q\text{NHR}^{31}$, $-(\text{CH}_2)_q\text{N}(\text{R}^{31})_2$, $-\text{OR}^{30}$, halogen, $=\text{O}$, and $-\text{C}(=\text{O})\text{R}^{31}$;

the R^{11} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, alkylaryl, arylalkyl, hydroxyalkyl, carboxamide, CO_2H , $-(\text{CH}_2)_q\text{OH}$, $-(\text{CH}_2)_q\text{OR}^{31}$, $-(\text{CH}_2)_q\text{NHR}^{31}$, $-(\text{CH}_2)_q\text{N}(\text{R}^{31})_2$, $-\text{OR}^{30}$, halogen, $=\text{O}$, and $-\text{C}(=\text{O})\text{R}^{31}$;

the R^{12} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, $-\text{CN}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{30})_2$, $-(\text{CH}_2)_q\text{OH}$, $-(\text{CH}_2)_q\text{OR}^{31}$, $-(\text{CH}_2)_q\text{NHR}^{31}$, $-(\text{CH}_2)_q\text{N}(\text{R}^{31})_2$, and $-\text{S}(\text{O}_2)\text{R}^{31}$;

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 unsubstituted or optionally substituted with 1-5 independently selected R^{20} moieties;

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, halogen, haloalkyl, heteroalkyl, heteroaryl, heterocyclyl, heterocyclenyl, hydroxyalkyl, hydroxamate, nitro, trifluoromethoxy, $-(\text{CH}_2)_q\text{OH}$, $-(\text{CH}_2)_q\text{OR}^{31}$, $-(\text{CH}_2)_q\text{NH}_2$, $-(\text{CH}_2)_q\text{NHR}^{31}$, $-(\text{CH}_2)_q\text{N}(\text{R}^{31})_2$, $-(\text{CH}_2)_q\text{C}(=\text{O})\text{NHR}^{31}$, $-(\text{CH}_2)_q\text{SO}_2\text{R}^{31}$, $-(\text{CH}_2)_q\text{NHSO}_2\text{R}^{31}$, $-(\text{CH}_2)_q\text{SO}_2\text{NHR}^{31}$, $-\text{alkynylC}(\text{R}^{31})_2\text{OR}^{31}$, $-\text{C}(=\text{O})\text{R}^{30}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{30})_2$, $-\text{C}(=\text{NR}^{30})\text{NHR}^{30}$, $-\text{C}(=\text{NOH})\text{N}(\text{R}^{30})_2$, $-\text{C}(=\text{NOR}^{31})\text{N}(\text{R}^{30})_2$, $-\text{C}(=\text{O})\text{OR}^{30}$, $-\text{N}(\text{R}^{30})_2$, $-\text{N}(\text{R}^{30})\text{C}(=\text{O})\text{R}^{31}$, $-\text{NHC}(=\text{O})\text{N}(\text{R}^{30})_2$, $-\text{N}(\text{R}^{30})\text{C}(=\text{O})\text{OR}^{31}$, $-\text{N}(\text{R}^{30})\text{C}(=\text{NCN})\text{N}(\text{R}^{30})_2$, $-\text{N}(\text{R}^{30})\text{C}(=\text{O})\text{N}(\text{R}^{30})\text{SO}_2(\text{R}^{31})$, $-\text{N}(\text{R}^{30})\text{C}(=\text{O})\text{N}(\text{R}^{30})_2$, $-\text{N}(\text{R}^{30})\text{SO}_2(\text{R}^{31})$, $-\text{N}(\text{R}^{30})\text{S}(\text{O})_2\text{N}(\text{R}^{30})_2$, $-\text{OR}^{30}$, $-\text{OC}(=\text{O})\text{N}(\text{R}^{30})_2$, $-\text{SR}^{30}$, $-\text{SO}_2\text{N}(\text{R}^{30})_2$, $-\text{SO}_2(\text{R}^{31})$, $-\text{OSO}_2(\text{R}^{31})$, and $-\text{OSi}(\text{R}^{30})_3$; 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 R²¹ moieties;

the R²¹ 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, heteroalkyl, heteroaryl, heterocyclyl, heterocyclenyl, hydroxyalkyl, hydroxamate, nitro, trifluoromethoxy, -(CH₂)_qOH, -(CH₂)_qOR³¹, -(CH₂)_qNH₂, -(CH₂)_qNHR³¹, -(CH₂)_qN(R³¹)₂, -(CH₂)_qC(=O)NHR³¹, -(CH₂)_qSO₂R³¹, -(CH₂)_qNSO₂R³¹, -(CH₂)_qSO₂NHR³¹, -alkynylC(R³¹)₂OR³¹, -C(=O)R³⁰, -C(=O)N(R³⁰)₂, -C(=NR³⁰)NHR³⁰, -C(=NOH)N(R³⁰)₂, -C(=NOR³¹)N(R³⁰)₂, -C(=O)OR³⁰, -N(R³⁰)₂, -N(R³⁰)C(=O)R³¹, -NHC(=O)N(R³⁰)₂, -N(R³⁰)C(=O)OR³¹, -N(R³⁰)C(=NCN)N(R³⁰)₂, -N(R³⁰)C(=O)N(R³⁰)SO₂(R³¹), -N(R³⁰)C(=O)N(R³⁰)₂, -N(R³⁰)SO₂(R³¹), -N(R³⁰)S(O)₂N(R³⁰)₂, -OR³⁰, -OC(=O)N(R³⁰)₂, -SR³⁰, -SO₂N(R³⁰)₂, -SO₂(R³¹), -OSO₂(R³¹), and -OSi(R³⁰)₃;

Y is selected from the group consisting of -(CR¹³R¹³)_r-, -CHR¹³C(=O)-, -(CHR¹³)_rO-, -(CHR¹³)_rN(R³⁰)-, -C(=O)-, -C(=NR³⁰)-, -C(=N-OR³⁰)-, -CH(C(=O)NHR³⁰)-, CH-heteroaryl-, -C(R¹³R¹³)_rC(R¹³)=C(R¹³)-, -(CHR¹³)_rC(=O)- and -(CHR¹³)_rN(H)C(=O)-; or alternatively Y is cycloalkyl, heterocyclenyl, or heterocyclyl wherein the cycloalkyl, heterocyclenyl, or heterocyclyl is fused with ring D;

the R¹³ 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, -CO₂H, -C(=O)R³⁰, -C(=O)N(R³⁰)₂, -(CHR³⁰)_qOH, -(CHR³⁰)_qOR³¹, -(CHR³⁰)_qNH₂, -(CHR³⁰)_qNHR³¹, -(CH₂)_qC(=O)NHR³¹, -(CH₂)_qSO₂R³¹, -(CH₂)_qNSO₂R³¹, -(CH₂)_qSO₂NHR³¹, -NH₂, -N(R³⁰)₂, -N(R³⁰)C(=O)N(R³⁰)₂, -N(R³⁰)SO₂(R³¹), -OH, OR³⁰, -SO₂N(R³⁰)₂, and -SO₂(R³¹);

the R³⁰ moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, aryl, aralkyl, cycloalkyl, CN, -(CH₂)_qOH, -(CH₂)_qOalkyl, -(CH₂)_qOalkylaryl, -(CH₂)_qOaryl, -(CH₂)_qOaralkyl, -(CH₂)_qOcycloalkyl, -(CH₂)_qNH₂, -(CH₂)_qNHalkyl,

- $-(CH_2)_qN(alkyl)_2$, $-(CH_2)_qNHalkylaryl$, $-(CH_2)_qNHaryl$, $-(CH_2)_qNHaralkyl$, -
 $(CH_2)_qNHcycloalkyl$, $-(CH_2)_qC(=O)NHalkyl$, $-(CH_2)_qC(=O)N(alkyl)_2$, -
 $(CH_2)_qC(=O)NHalkylaryl$, $-(CH_2)_qC(=O)NHaryl$, $-(CH_2)_qC(=O)NHaralkyl$, -
 $(CH_2)_qC(=O)NHcycloalkyl$, $-(CH_2)_qSO_2alkyl$, $-(CH_2)_qSO_2alkylaryl$, -
5 $(CH_2)_qSO_2aryl$, $-(CH_2)_qSO_2aralkyl$, $-(CH_2)_qSO_2cycloalkyl$, $-(CH_2)_qNSO_2alkyl$, -
 $(CH_2)_qNSO_2alkylaryl$, $-(CH_2)_qNSO_2aryl$, $-(CH_2)_qNSO_2aralkyl$, -
 $(CH_2)_qNSO_2cycloalkyl$, $-(CH_2)_qSO_2NHalkyl$, $-(CH_2)_qSO_2NHalkylaryl$, -
 $(CH_2)_qSO_2NHaryl$, $-(CH_2)_qSO_2NHaralkyl$, $-(CH_2)_qSO_2NHcycloalkyl$,
heterocyclenyl, heterocyclyl, and heteroaryl;
- 10 the R^{31} moieties can be the same or different, each being
independently selected from the group consisting of alkyl, alkylaryl, aryl,
aralkyl, cycloalkyl, $-(CH_2)_qOH$, $-(CH_2)_qOalkyl$, $-(CH_2)_qOalkylaryl$, $-(CH_2)_qOaryl$,
 $-(CH_2)_qOaralkyl$, $-(CH_2)_qOcycloalkyl$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHalkyl$, -
 $(CH_2)_qN(alkyl)_2$, $-(CH_2)_qNHalkylaryl$, $-(CH_2)_qNHaryl$, $-(CH_2)_qNHaralkyl$, -
15 $(CH_2)_qNHcycloalkyl$, $-(CH_2)_qC(=O)NHalkyl$, $-(CH_2)_qC(=O)N(alkyl)_2$, -
 $(CH_2)_qC(=O)NHalkylaryl$, $-(CH_2)_qC(=O)NHaryl$, $-(CH_2)_qC(=O)NHaralkyl$, -
 $(CH_2)_qC(=O)NHcycloalkyl$, $-(CH_2)_qSO_2alkyl$, $-(CH_2)_qSO_2alkylaryl$, -
 $(CH_2)_qSO_2aryl$, $-(CH_2)_qSO_2aralkyl$, $-(CH_2)_qSO_2cycloalkyl$, $-(CH_2)_qNSO_2alkyl$, -
 $(CH_2)_qNSO_2alkylaryl$, $-(CH_2)_qNSO_2aryl$, $-(CH_2)_qNSO_2aralkyl$, -
20 $(CH_2)_qNSO_2cycloalkyl$, $-(CH_2)_qSO_2NHalkyl$, $-(CH_2)_qSO_2NHalkylaryl$, -
 $(CH_2)_qSO_2NHaryl$, $-(CH_2)_qSO_2NHaralkyl$, $-(CH_2)_qSO_2NHcycloalkyl$,
heterocyclenyl, heterocyclyl, and heteroaryl;

m is 0 to 4;

n is 0 to 4;

- 25 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
30 alkyl groups may be optionally joined to each other to form a ring.

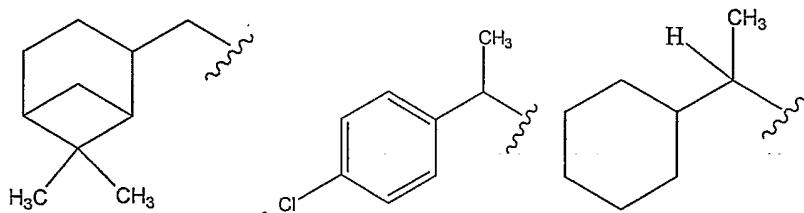
2. The compound according to Claim 1, wherein R^1 and R^2 are
independently absent or present, and if present each is independently
selected from the group consisting of H, alkyl, aryl, amino, alkoxy, halogen,
hydroxy, cycloalkyl, cycloalkenyl, arylalkyl, amidinyl, carboxamido, heteroaryl,

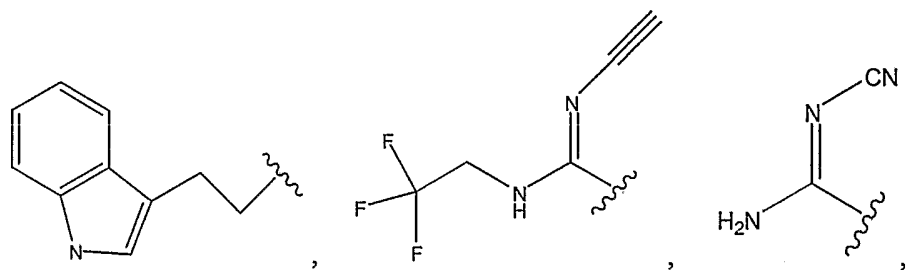
heterocyclyl, heterocyclenyl, urea, $-\text{S}(\text{O})_2\text{alkyl}$, $-\text{S}(\text{O})_2\text{N}(\text{H})\text{alkyl}$,
 $-\text{S}(\text{O})_2\text{heteroaryl}$, $-\text{S}(\text{O})_2\text{heterocyclyl}$, $-\text{C}(=\text{O})\text{heteroaryl}$, $-\text{C}(=\text{O})\text{heterocyclyl}$,
 $-\text{S}(\text{O})_2\text{N}(\text{alkyl})_2$, and $-\text{C}(=\text{S})\text{N}(\text{H})\text{cycloalkyl}$.

3. The compound according to Claim 1, wherein R^1 and R^2 are
 5 independently absent or present, and if present each is independently
 selected from the group consisting of H, alkylaryl, aryl, heteroaryl, $-(\text{CH}_2)_q\text{CF}_3$,
 $-(\text{CH}_2)_q\text{OH}$, $-(\text{CH}_2)_q\text{OR}^{31}$, $-(\text{CH}_2)_q\text{NH}_2$, $-(\text{CH}_2)_q\text{NHR}^{31}$, $-(\text{CH}_2)_q\text{N}(\text{R}^{31})_2$,
 $-(\text{CH}_2)_q\text{C}(=\text{O})\text{NHR}^{31}$, $-(\text{CH}_2)_q\text{SO}_2\text{R}^{31}$, $-(\text{CH}_2)_q\text{NHSO}_2\text{R}^{31}$, $-(\text{CH}_2)_q\text{SO}_2\text{NHR}^{31}$,
 $-(\text{CH}_2)_q\text{-amidinyl}$, cyclopropyl, cyclopropylhydroxyl, cyclobutyl,
 10 cyclobutylhydroxy, cyclopentyl, and cyclopentylhydroxy; and
 q is an integer from 1 to 5.

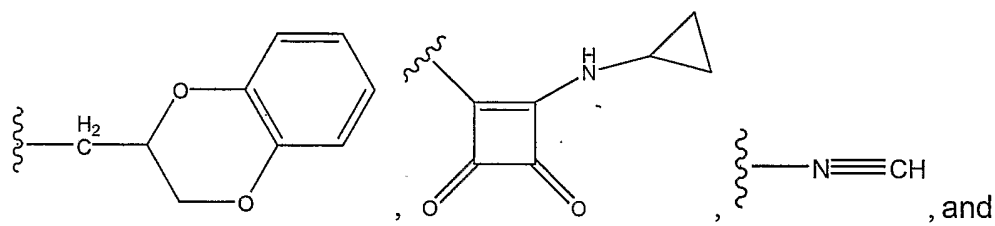
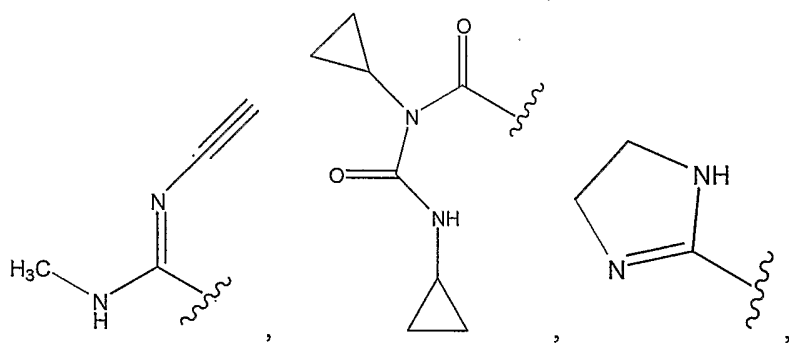
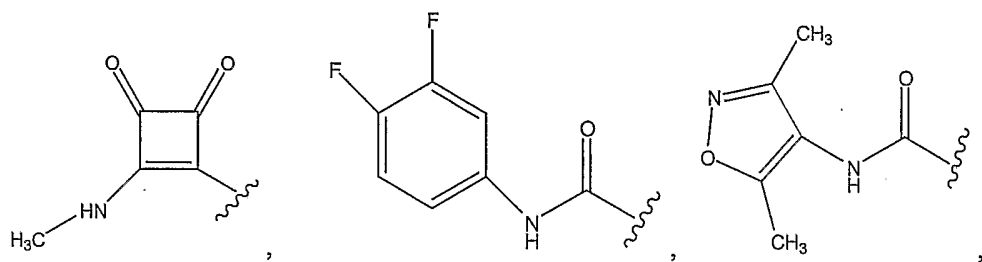
4. The compound according to Claim 1, wherein R^1 and R^2 are
 independently absent or present, and if present each is independently
 selected from the group consisting of H, $-\text{CH}_3$, fluorophenylmethylene,
 15 trifluoromethylphenylmethylene, indanyl, cyanophenylmethylene,
 difluorophenylmethylene, bromophenylmethylene, chlorophenylmethylene,
 $-\text{CH}_2\text{CH}_2\text{Ophenyl}$, cyclopentyl, bromochlorophenylmethylene,
 fluorochlorophenylmethylene, dichlorophenylmethylene, phenylmethylene,
 $-(\text{CH}_2)_3\text{phenyl}$, $-\text{CH}_2\text{CF}_3$, methoxyphenylmethylene, $-\text{CH}(\text{CH}_3)_2$, $-\text{C}_2\text{H}_5$,
 20 $-\text{CH}_2\text{-cyclopropyl}$, $-(\text{CH}_2)_2\text{CH}_3$, cyclohexylmethylene, cyclohexyl, $-\text{CH}_2\text{CH}_2\text{SO}_2\text{CH}_3$,
 $-\text{CH}_2\text{-CH}_2\text{-NH}_2$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, cyclopropyl, isoxazolyl,
 $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{Ophenyl}$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{NH}_2$, $-(\text{CH}_2)_2\text{NH}_2$, pyrazolyl,
 5-methyl-isoxazolyl, $-\text{CH}_2\text{CH}(\text{OCH}_2\text{CH}_3)_2$, $-\text{OCH}_3$, $-\text{NHC}(=\text{O})\text{NH}_2$,
 chloropyridyl, pyridylmethylene, $-\text{C}(=\text{O})\text{NHcyclopropyl}$, $-\text{C}(=\text{O})\text{N}(\text{H})\text{C}_2\text{H}_5$,
 25 $-\text{C}(=\text{O})\text{N}(\text{H})\text{CH}_2\text{CF}_3$, $-\text{C}(=\text{O})\text{N}(\text{H})\text{C}(\text{CH}_3)_3$, $-\text{C}(=\text{S})\text{N}(\text{H})\text{cyclopropyl}$,
 $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{N}(\text{H})\text{CH}_3$, $-\text{S}(\text{O})_2\text{CH}_3$, $-\text{S}(\text{O})_2\text{N}(\text{CH}_3)_2$, $-\text{S}(\text{O})_2\text{CH}_2\text{CH}_3$,
 $-\text{C}(=\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2(\text{CH}_2)_2\text{CH}_3$, $-\text{C}(=\text{O})\text{N}(\text{H})\text{cyclohexyl}$, $-\text{C}(=\text{NH})\text{NH}_2$,
 $-\text{C}(=\text{O})\text{N}(\text{H})\text{NH}_2$, $-\text{C}(=\text{O})\text{N}(\text{H})\text{CH}(\text{CH}_3)_2$, thiazolyl, $-\text{C}(=\text{O})\text{N}(\text{CH}_3)_2$,
 $-\text{S}(\text{O})_2\text{CH}_2\text{CF}_3$, cyclopropyl, $-\text{S}(\text{O})_2\text{CF}_3$, $-\text{CH}_2\text{CH}(\text{OCH}_2\text{CH}_3)_2$,

30

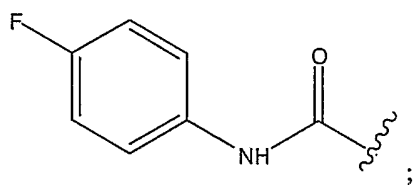




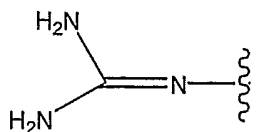
5



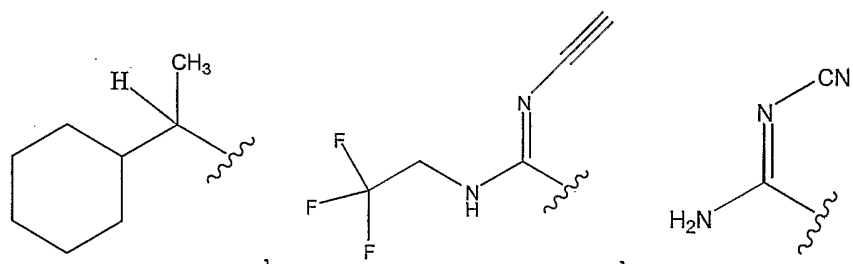
10



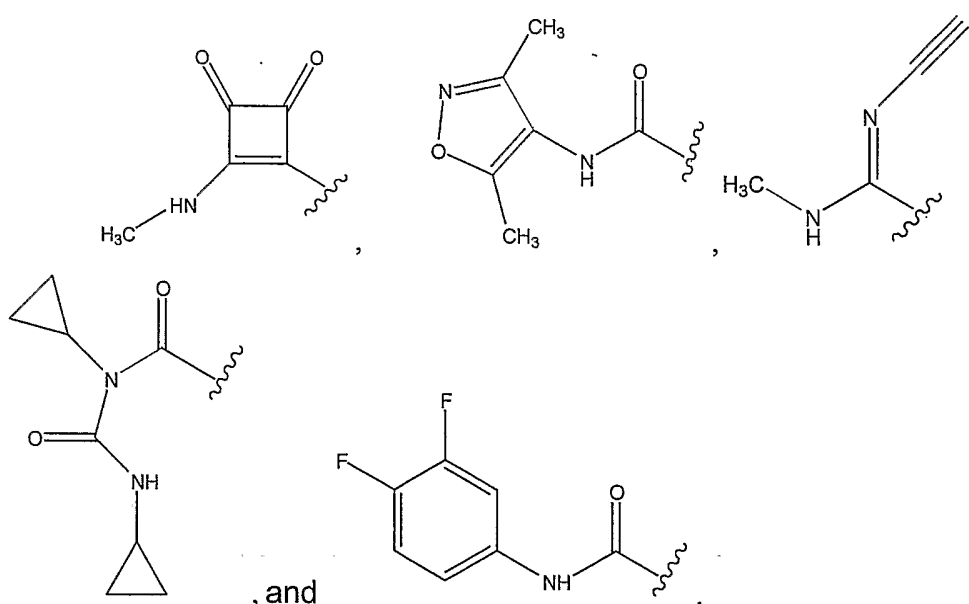
or when X is N, the N taken together with the R¹ and R² to which X is shown attached, forms a -N-cyclopropyl, -N-cyclobutyl, -N-cyclohexyl or



5. The compound according to Claim 1, wherein R¹ and R² are
 5 independently absent or present, and if present each is independently
 selected from the group consisting of H, -CH₃, -C₂H₅,
 difluorophenylmethylene, cyclopropyl, dichlorophenylmethylene, -CH(CH₃)₂,
 cyclohexylmethylene, cyclohexyl, isoxazolyl, difluorophenyl, -CH₂CH₂OH,
 -CH₂-CH₂-N(CH₃)₂, -C(=O)N(H)cyclopropyl, -C(=O)N(H)C₂H₅,
 10 -C(=O)N(H)CH₂CF₃, -C(=O)N(H)CH(CH₃)₂, -C(=O)N(H)C(CH₃)₃,
 -C(=S)N(H)cyclopropyl, -C(=O)NH₂, -C(=O)N(H)CH₃, -S(O)₂CH₃,
 -S(O)₂N(CH₃)₂, -S(O)₂CH₂CH₃, -C(=O)CH₃, -S(O)₂(CH₂)₂CH₃,
 -C(=O)N(H)cyclohexyl, -C(=NH)NH₂, -C(=O)N(H)NH₂, thiazolyl,



15



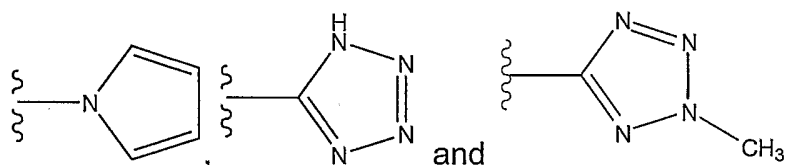
6. The compound according to Claim 1, wherein Z is N or C(R²⁹).
7. The compound according to Claim 6, wherein Z is N.
8. The compound according to Claim 6, wherein Z is C(H), C(alkyl),
 5 C(halogen), C(CF₃) or C(N(R³⁰)₂).
9. The compound according to Claim 8, wherein Z is C(alkyl), C(F) or C(NH₂).
10. The compound according to claim 1, wherein G is N or C(R⁴).
11. The compound according to claim 10, wherein G is N.
- 10 12. The compound according to claim 10, wherein G is C(R⁴).
13. The compound according to claim 10, wherein G is C(H), C(alkyl), C(halogen), C(CF₃) or C(N(R³⁰)₂).
14. The compound according to claim 1, wherein G and Z are the same.
15. The compound according to claim 1, wherein G and Z are different.
- 15 16. The compound according to claim 14, wherein G and Z are N.
17. The compound according to claim 14, wherein G is R⁴ and Z is C(R²⁹), wherein R⁴=R²⁹.
18. The compound according to claim 15, wherein G is N and Z is C(R²⁹).
19. The compound according to claim 15, wherein G is C(R⁴) and Z is N.
- 20 20. The compound according to Claim 1, wherein R³ is selected from the group consisting of H, alkyl, haloalkyl, hydroxyalkyl, halogen, -N(R³⁰)₂, -OR³⁰ and -CF₃.
21. The compound according to Claim 20, wherein R³ is selected from the group consisting of H, -CH₃, -CH₂CH₃, cyclopropyl, -F, -Cl, OCH₃, OCF₃ and
 25 CF₃.
22. The compound according to claim 1, wherein Z is N and R⁴ is selected from the group consisting of H, alkyl, hydroxyalkyl, halogen, OR³⁰, or CF₃.
23. The compound according to Claim 1, wherein R⁶ is selected from the group consisting of H, alkyl, halogen, hydroxyalkyl, -CN, -N(R³⁰)₂, -OR³⁰,
 30 -N=CH-alkyl, and -NR³⁰C(=O)alkyl.
24. The compound according to Claim 23, wherein R⁶ is selected from the group consisting of H, -NH₂, -CH₃, -CN and -F.
25. The compound according to Claim 1, wherein R¹⁰ is selected from the group consisting of H, alkyl, aralkyl, hydroxyalkyl, and carbonyl.

26. The compound according to Claim 25, wherein R^{10} is selected from the group consisting of $-CH_3$, $-CH_2CH_3$ and $-CH_2CH_2CH_3$, and m is 0 - 2.
27. The compound according to Claim 1, wherein R^{11} is selected from the group consisting of H, alkyl, hydroxyalkyl and carbonyl.
- 5 28. The compound according to Claim 27, wherein R^{11} is H or $-CH_3$.
29. The compound according to Claim 1, wherein R^{12} is selected from the group consisting of H, CN, $-C(=O)N(R^{30})_2$ and alkyl.
30. The compound according to Claim 29, wherein R^{12} is selected from the group consisting of H, $-CH_3$, CN and $-CH_2CH_3$.
- 10 31. The compound according to Claim 1, wherein the ring atoms of ring D are independently C or N and substituted by independently selected 0-4 R^{20} moieties.
32. The compound according to Claim 1, wherein ring D is a 5 to 6 membered aryl, heteroaryl, heterocyclenyl, or heterocyclyl ring and
- 15 substituted by independently selected 0-4 R^{20} moieties.
33. The compound according to Claim 1, wherein the R^{20} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, alkylaryl, alkynyl, alkoxy, alkylamino, alkylheteroaryl, alkylsulfinyl, alkoxy carbonyl, aminoalkyl, amidinyl, aralkyl, aralkoxy, aryl,
- 20 aryloxy, cyano, cycloalkyl, cycloalkenyl, halogen, haloalkyl, heteroalkyl, heteroaryl, heterocyclyl, hydroxyalkyl, trifluoromethyl, trifluoromethoxy, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, $-alkynylC(R^{31})_2OR^{31}$, $-C(=O)R^{30}$, $-C(=O)N(R^{30})_2$, $-C(=O)OR^{30}$, $-N(R^{30})_2$, $-N(R^{30})C(=O)R^{31}$, $-NHC(=O)N(R^{30})_2$,
- 25 $-N(R^{30})C(=O)OR^{31}$, $-N(R^{30})C(=NCN)N(R^{30})_2$, $-N(R^{30})C(=O)N(R^{30})_2$, $-N(R^{30})SO_2(R^{31})$, $-N(R^{30})SO_2N(R^{30})_2$, $-OR^{30}$, $-OC(=O)N(R^{30})_2$, $-SR^{30}$, $-SO_2N(R^{30})_2$, $-SO_2(R^{31})$, $-OSO_2(R^{31})$, and $-OSi(R^{30})_3$.
34. The compound according to Claim 1, wherein the R^{20} moieties can be the same or different, each being independently selected from the group
- 30 consisting of H, alkyl, amino, halogen, CN, CH_3 , CF_3 , OCF_3 , $-(CH_2)_qOR^{31}$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, $-alkynylC(R^{31})_2OR^{31}$, $-C(=O)R^{30}$, $-C(=O)OR^{30}$, $-N(R^{30})_2$, $-N(R^{30})C(=O)R^{31}$, $-NHC(=O)N(R^{30})_2$, $-N(R^{30})C(=O)OR^{31}$,

$-N(R^{30})C(=NCN)N(R^{30})_2$, $-N(R^{30})C(=O)N(R^{30})_2$, $-OR^{30}$, $-OC(=O)N(R^{30})_2$, and $-OSO_2(R^{31})$.

35. The compound according to Claim 1, wherein two R^{20} moieties are linked together to form a five or six membered aryl, cycloalkyl, heterocyclenyl, heterocyclyl or heteroaryl ring wherein said five or six membered aryl, cycloalkyl, heterocyclenyl, heterocyclyl, and heteroaryl ring is fused to ring D and the fused ring is optionally substituted with 0 to 4 R^{21} moieties.

36. The compound according to Claim 1, wherein the R^{20} moieties can be the same or different, each being independently selected from the group consisting of H, -CN, -CH₃, -CF₃, -CH₂OH, -CO₂H, -CO₂CH₃, -NH₂, -NHCH₃, -OCF₃, -OH, F, Cl, Br, -C(=NOH)NH₂, -OCH₂CH₂S(O₂)CH₃, -C(=O)NH₂,



37. The compound according to Claim 1, wherein Y is selected from the group consisting of: $-(CHR^{13})_r-$, $-(CR^{13}R^{13})_r-$, $-C(=O)-$ and $-CHR^{13}C(=O)-$.

38. The compound according to Claim 1, wherein Y is selected from the group consisting of: $-CH_2-$, $-CH(CH_3)-$, $-CH(CH_2OH)-$, $-C(=O)-$ and $-CH(CO_2alkyl)-$.

39. The compound according to Claim 1, wherein m is 0-3.

40. The compound according to Claim 1, wherein n is 0-2.

41. The compound according to Claim 1, wherein q is 1, 2 or 3.

42. The compound according to Claim 1, wherein r is 1 or 2.

43. The compound according to Claim 1, wherein Z is N, C(H), C(alkyl), C(F) or C(NH₂);

G is N or C(R⁴);

R^1 and R^2 are independently absent or present, and if present each is independently selected from the group consisting of H, alkylaryl, aryl, heteroaryl, $-(CH_2)_qCF_3$, $-(CH_2)_qOH$, $-(CH_2)_qOR^{31}$, $-(CH_2)_qNH_2$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_q-N(R^{31})_2$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNHSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, $-(CH_2)_q$ -amidinyl, cyclopropyl, cyclopropylhydroxyl, cyclobutyl, cyclobutylhydroxy, cyclopentyl, and cyclopentylhydroxy;

R^3 is selected from the group consisting of H, alkyl, haloalkyl, hydroxyalkyl, halogen, $-N(R^{30})_2$, $-OR^{30}$ and $-CF_3$;

R^4 is selected from the group consisting of H, alkyl, haloalkyl, hydroxyalkyl, halogen, $-N(R^{30})_2$, $-OR^{30}$ and $-CF_3$;

5 R^6 is selected from the group consisting of H, alkyl, halogen, hydroxyalkyl, $-CN$, $-N(R^{30})_2$, $-OR^{30}$, $-N=CH$ -alkyl, and $-NR^{30}C(=O)$ alkyl;

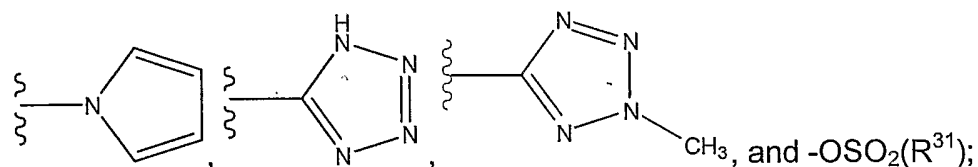
R^{10} is selected from the group consisting of H, alkyl, aralkyl, hydroxyalkyl, and carbonyl;

10 R^{11} is selected from the group consisting of H, alkyl, hydroxyalkyl, and carbonyl;

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

ring D is a 5 to 6 membered aryl, heteroaryl, heterocyclenyl, or heterocyclyl ring and substituted by 0-4 R^{20} moieties;

15 the R^{20} moieties can be the same or different, each being independently selected from the group consisting of H, alkyl, amino, halogen, CN, CH_3 , CF_3 , OCF_3 , $-(CH_2)_qOR^{31}$, $-(CH_2)_qNHR^{31}$, $-(CH_2)_qC(=O)NHR^{31}$, $-(CH_2)_qSO_2R^{31}$, $-(CH_2)_qNSO_2R^{31}$, $-(CH_2)_qSO_2NHR^{31}$, $-alkynylC(R^{31})_2OR^{31}$, $-C(=O)R^{30}$, $-C(=O)OR^{30}$, $-N(R^{30})_2$, $-N(R^{30})C(=O)R^{31}$, $-NHC(=O)N(R^{30})_2$,
20 $-N(R^{30})C(=O)OR^{31}$, $-N(R^{30})C(=NCN)N(R^{30})_2$, $-N(R^{30})C(=O)N(R^{30})_2$, $-OR^{30}$, $-OC(=O)N(R^{30})_2$,



Y is selected from the group consisting of: $-CH_2-$, $-CH(CH_3)-$,
25 $-CH(CH_2OH)-$, $-C(=O)-$ and $-CH(CO_2alkyl)-$;

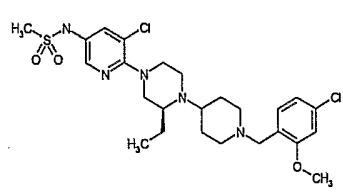
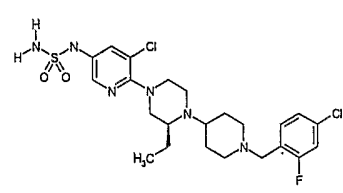
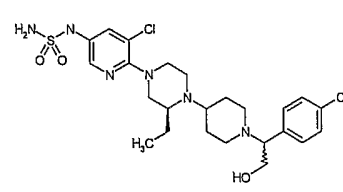
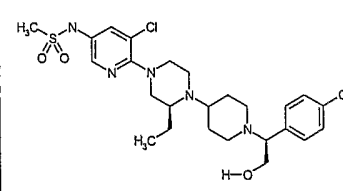
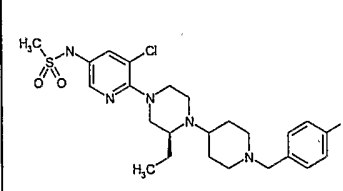
m is 0-2;

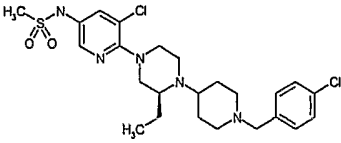
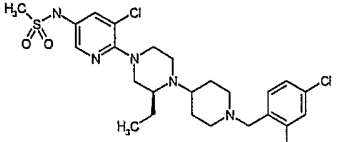
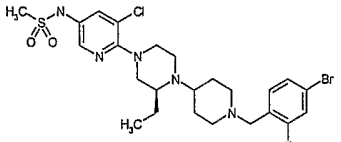
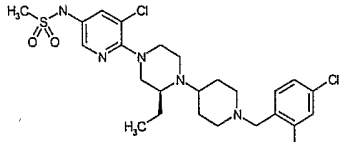
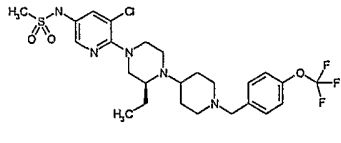
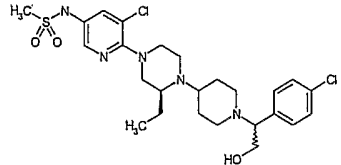
n is 0-2;

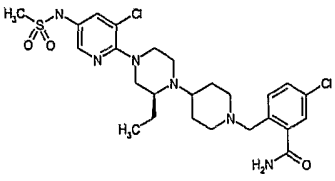
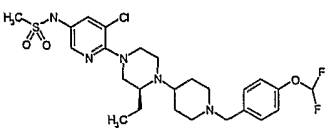
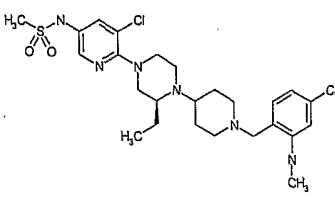
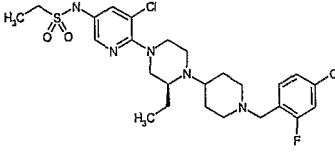
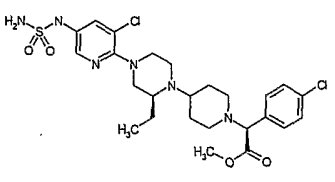
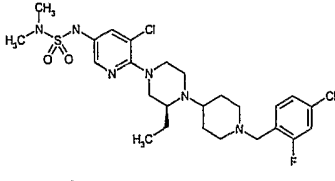
q is 1 or 2; and

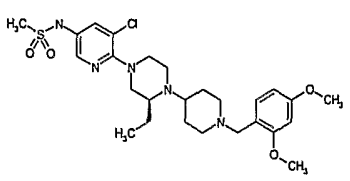
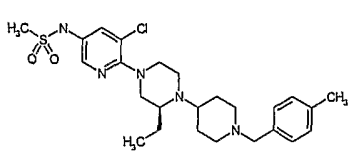
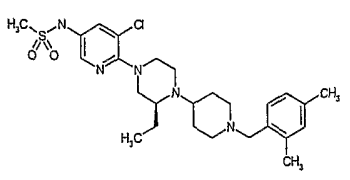
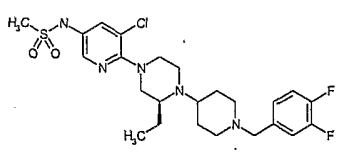
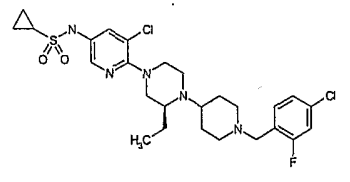
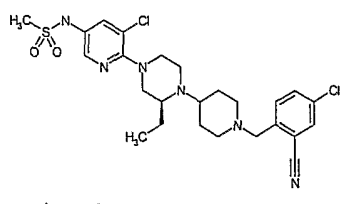
r is 1 or 2.

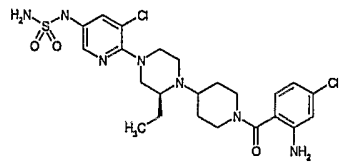
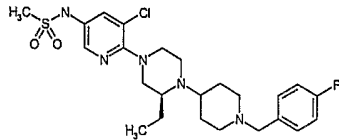
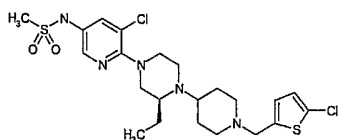
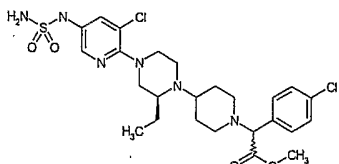
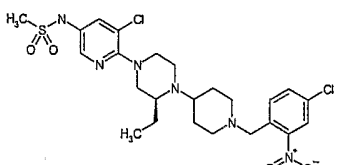
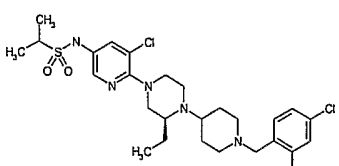
30 44. The compound according to Claim 1, selected from the group consisting of:

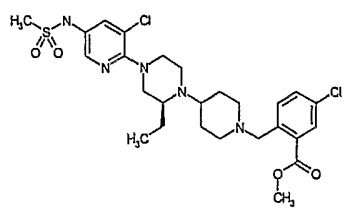
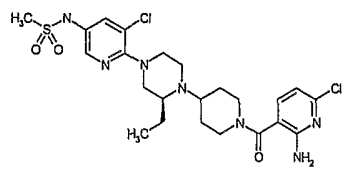
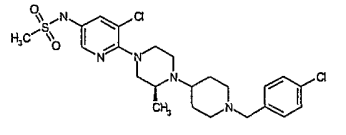
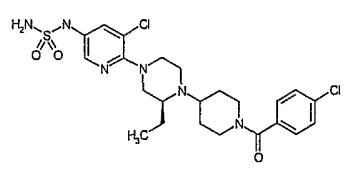
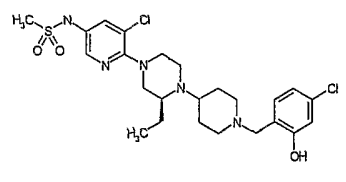
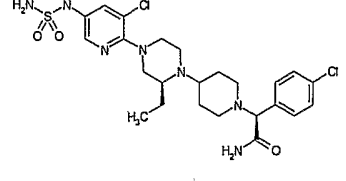
Compound No.	STRUCTURE
1	
2	
3	
4	
5	

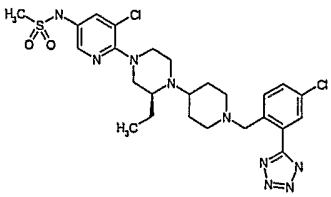
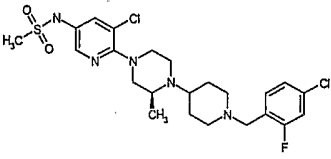
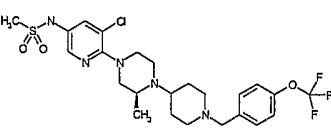
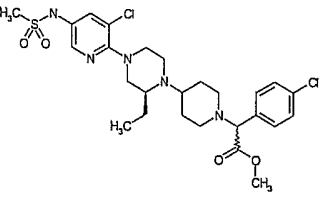
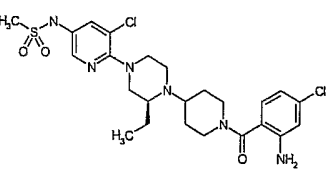
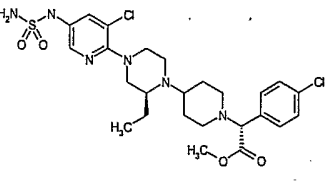
6	
7	
8	
9	
10	
11	

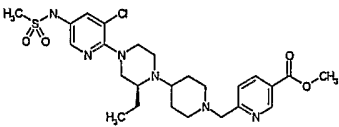
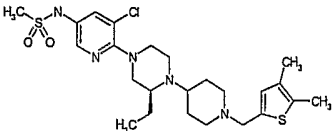
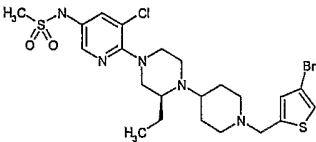
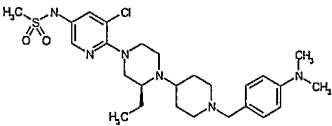
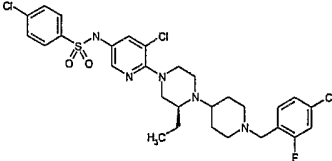
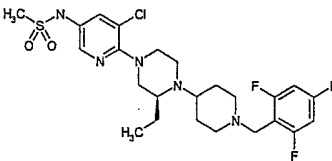
12	
13	
14	
15	
16	
17	

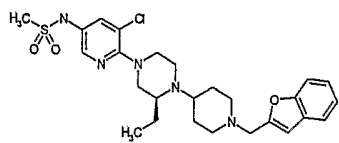
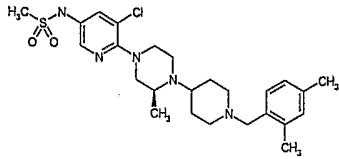
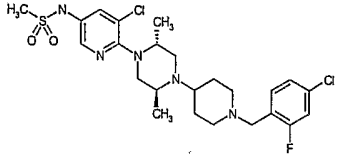
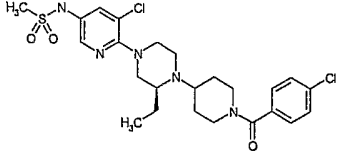
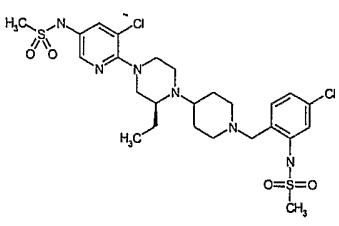
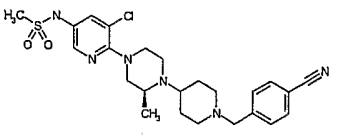
18	
19	
20	
21	
22	
23	

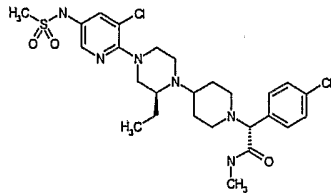
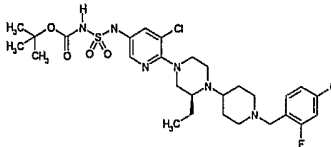
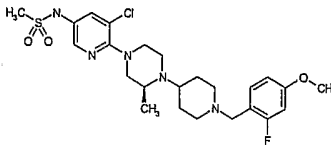
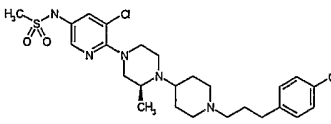
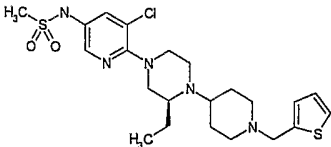
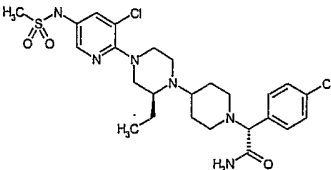
24	
25	
26	
27	
28	
29	

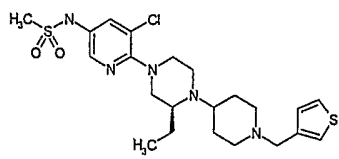
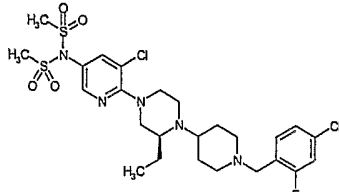
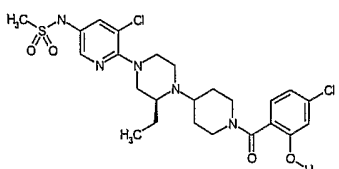
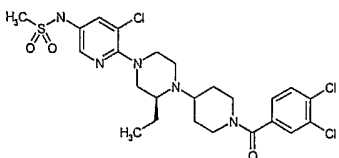
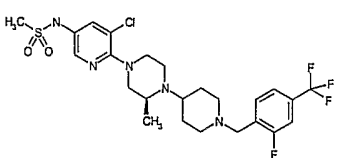
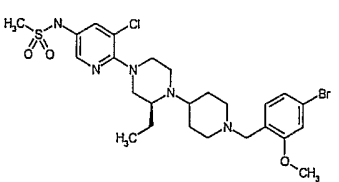
30	
31	
32	
33	
34	
35	

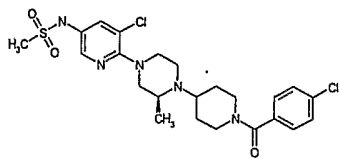
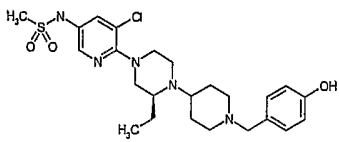
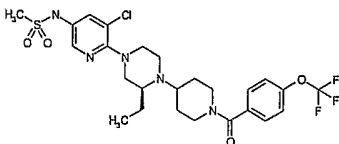
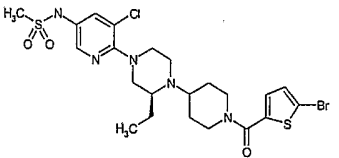
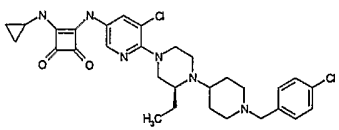
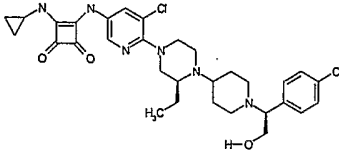
36	
37	
38	
39	
40	
41	

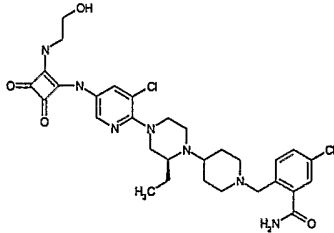
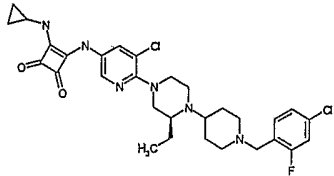
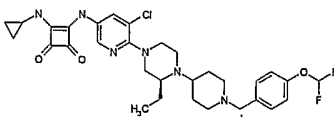
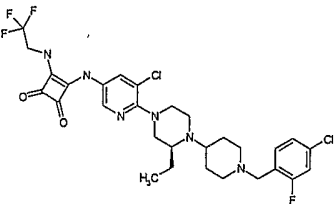
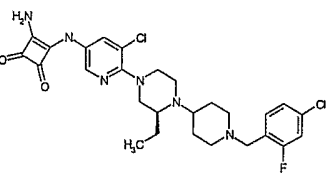
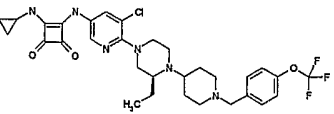
42	
43	
44	
45	
46	
47	

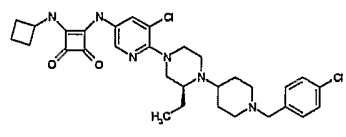
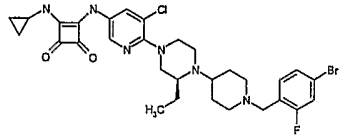
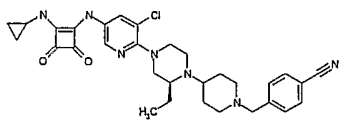
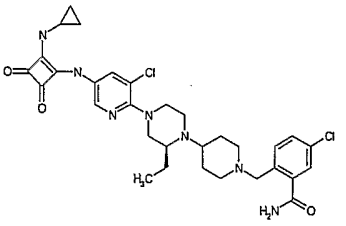
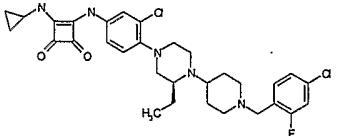
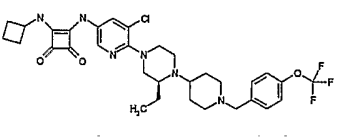
48	
49	
50	
51	
52	
53	

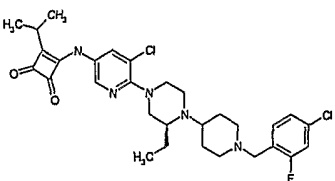
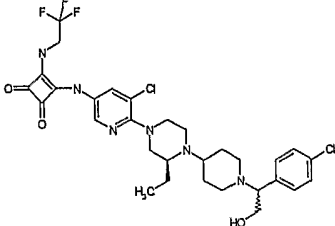
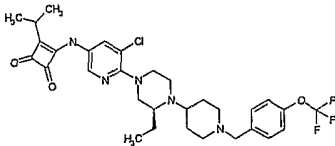
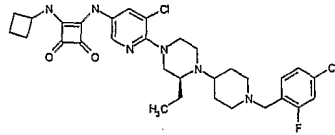
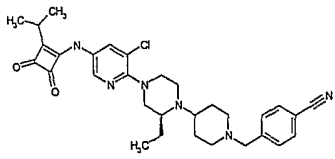
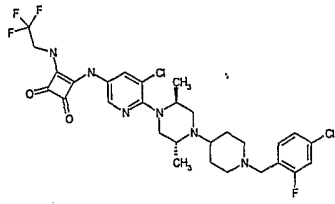
54	
55	
56	
57	
58	
59	

60	
61	
62	
63	
64	
65	

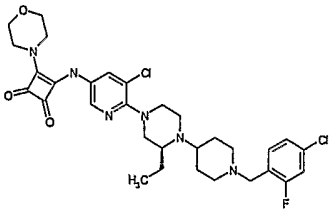
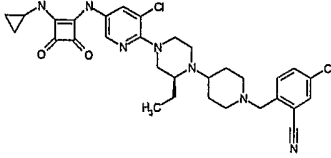
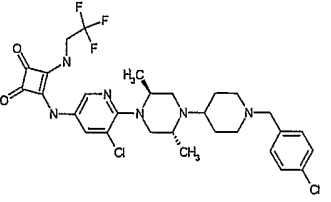
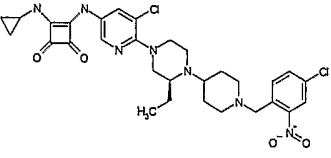
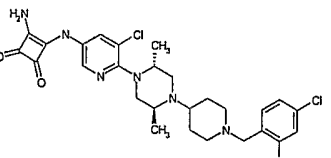
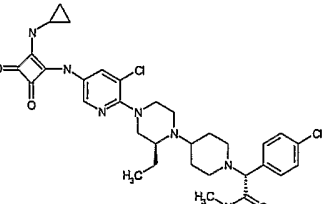
66	
67	
68	
69	
70	
71	

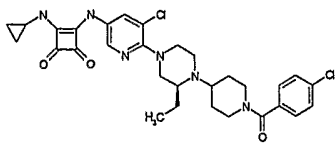
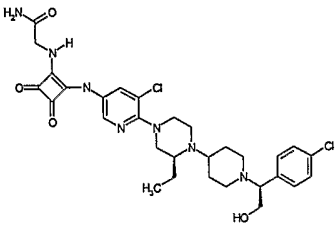
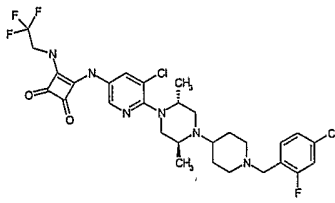
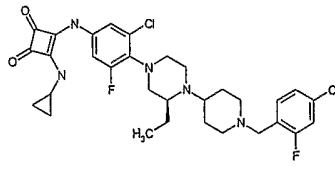
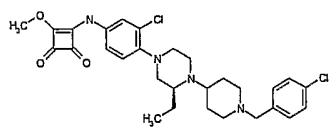
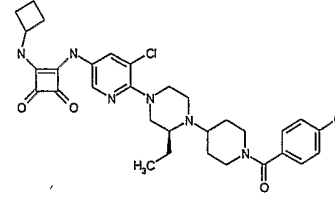
72	
73	
74	
75	
76	
77	

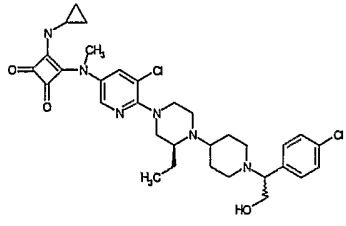
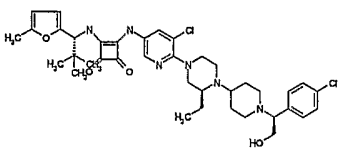
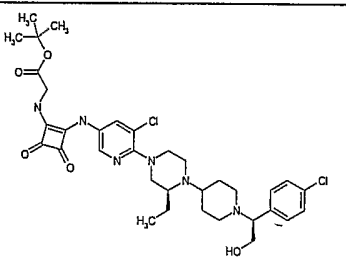
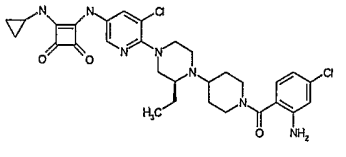
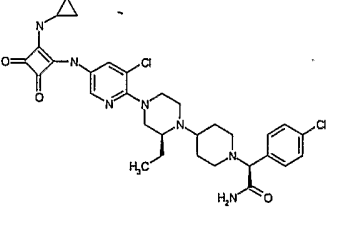
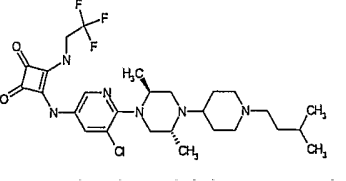
78	
79	
80	
81	
82	
83	

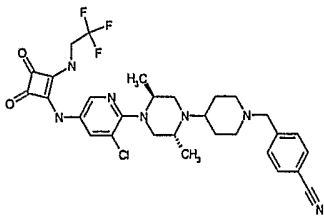
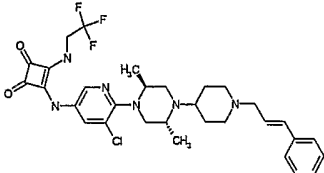
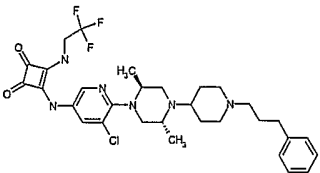
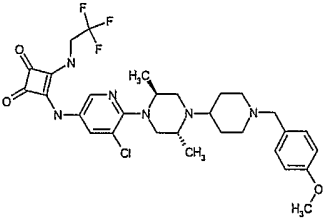
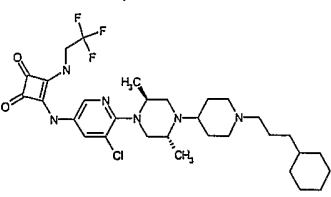
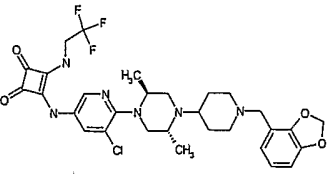
84	
85	
86	
87	
88	
89	

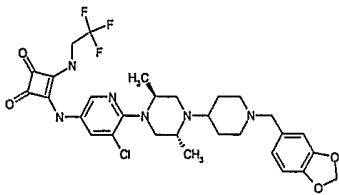
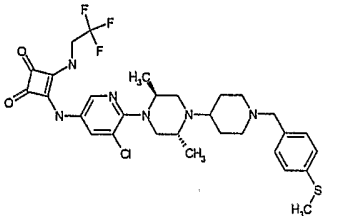
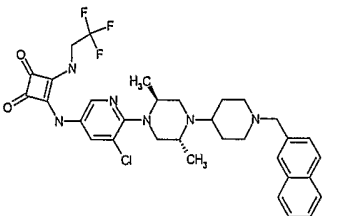
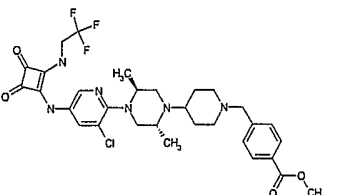
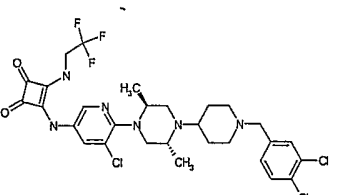
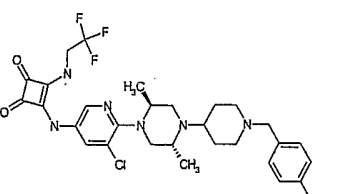
90	
91	
92	
93	
94	
95	

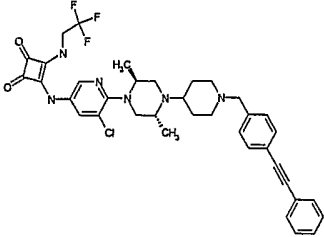
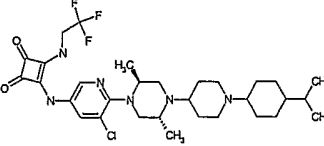
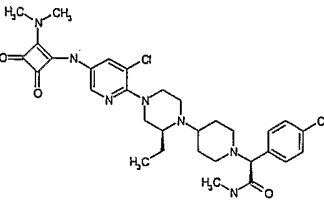
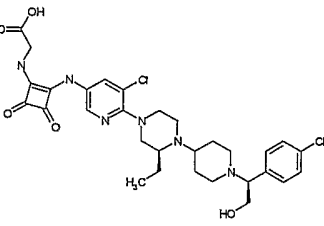
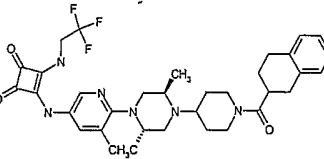
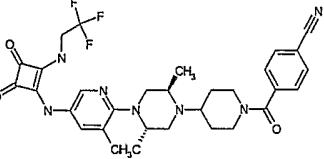
96	
97	
98	
99	
100	
101	

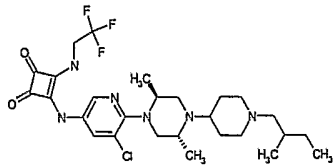
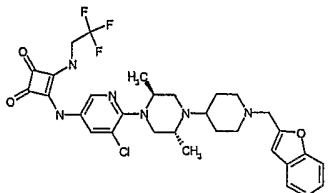
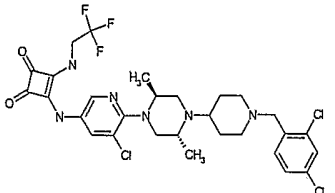
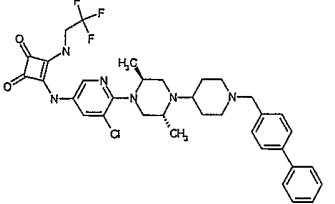
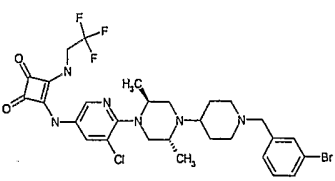
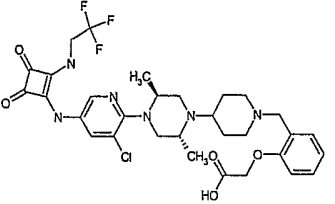
102	
103	
104	
105	
106	
107	

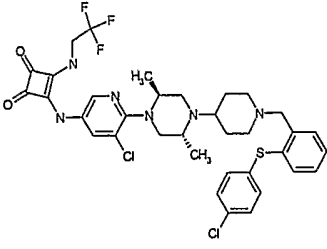
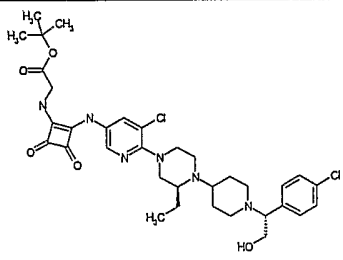
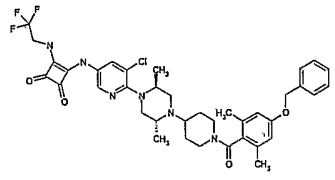
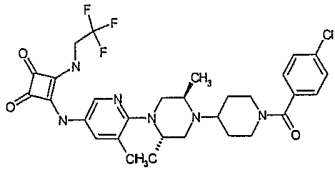
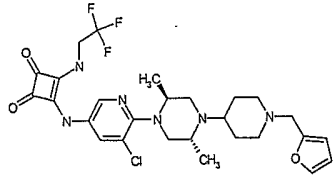
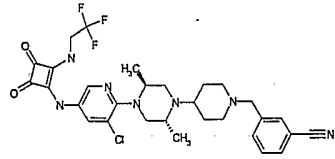
108	
109	
110	
111	
112	
113	

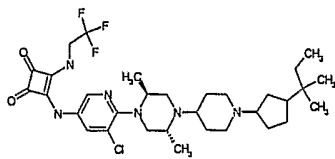
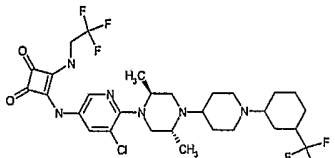
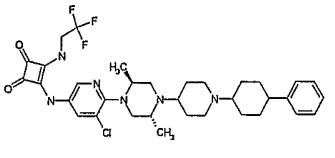
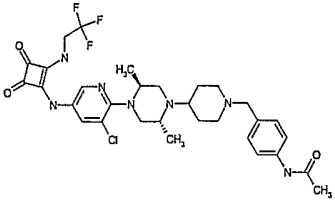
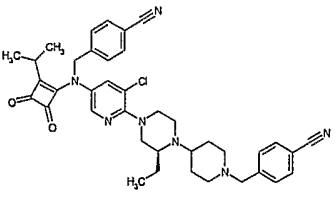
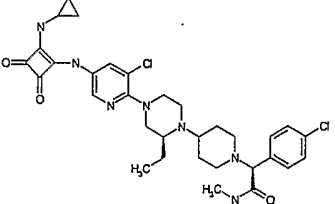
114	
115	
116	
117	
118	
119	

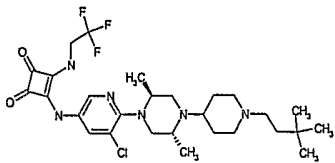
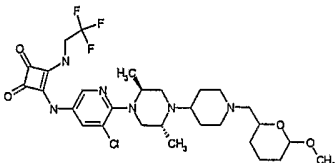
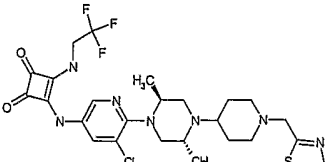
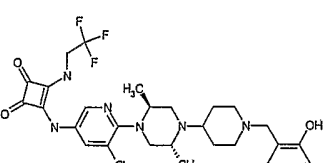
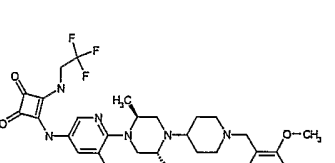
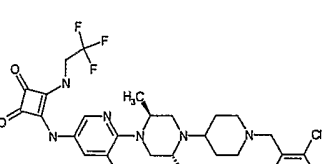
120	
121	
122	
123	
124	
125	

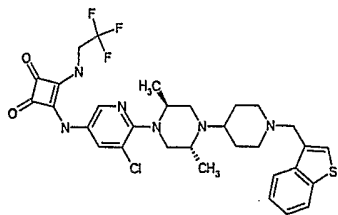
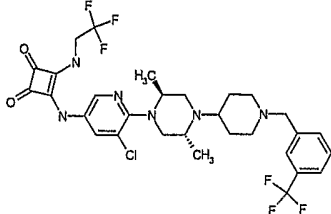
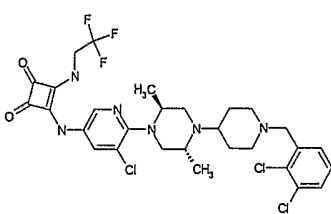
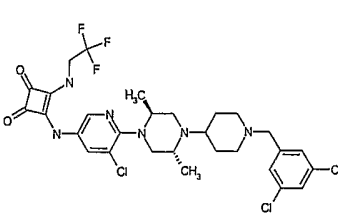
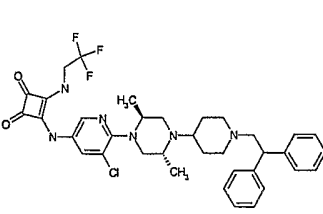
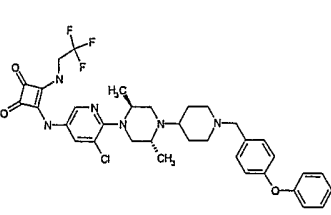
126	
127	
128	
129	
130	
131	

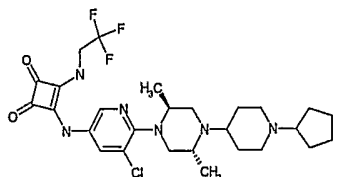
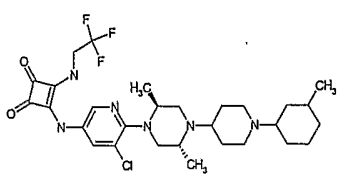
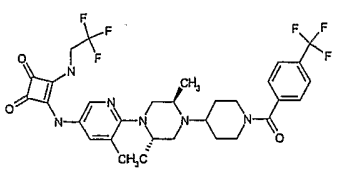
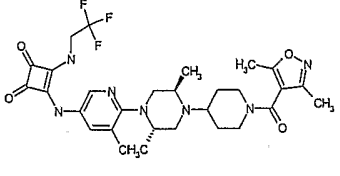
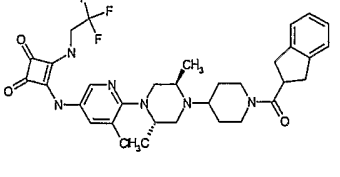
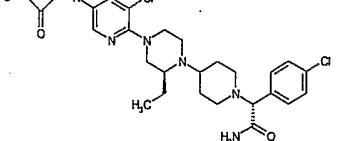
132	
133	
134	
135	
136	
137	

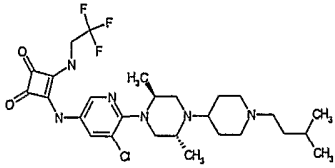
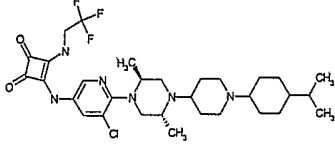
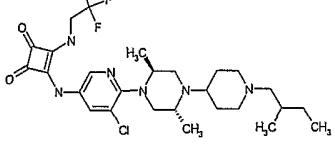
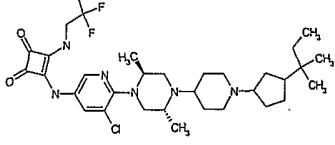
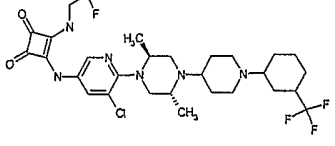
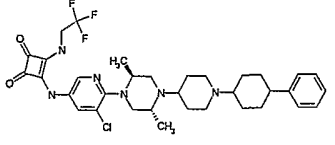
138	
139	
140	
141	
142	
143	

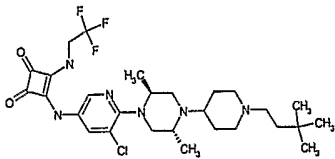
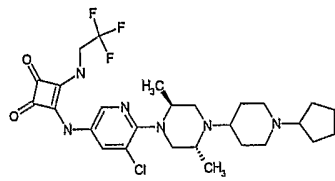
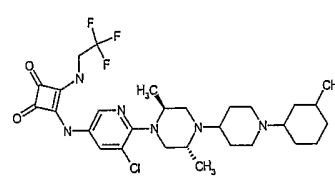
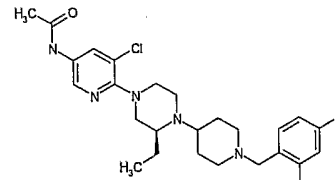
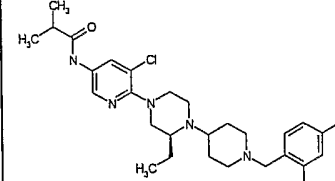
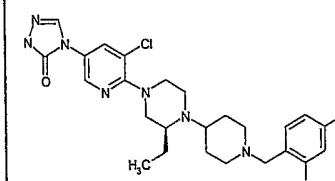
144	
145	
146	
147	
148	
149	

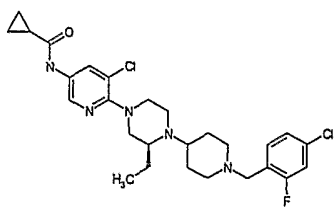
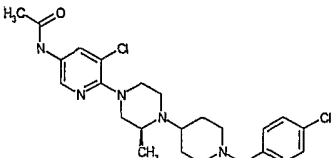
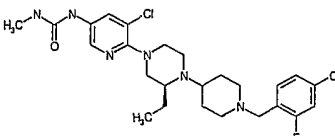
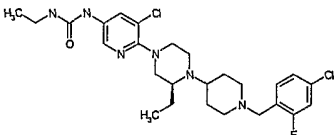
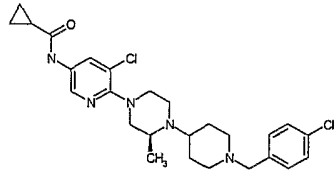
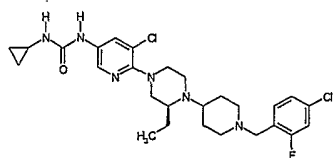
150	
151	
152	
153	
154	
155	

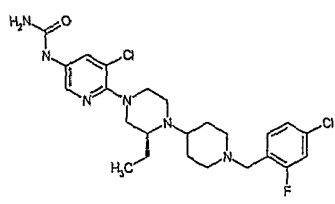
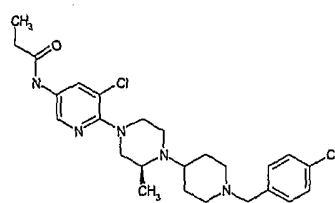
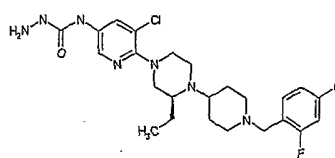
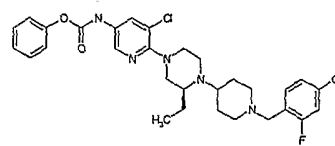
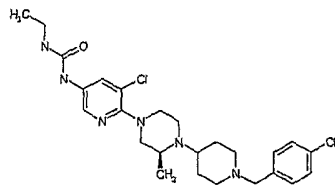
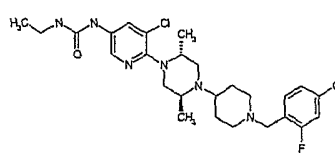
156	
157	
158	
159	
160	
161	

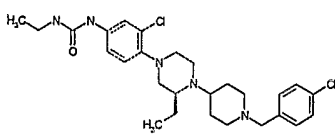
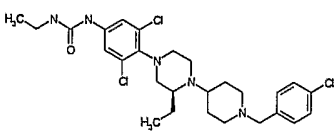
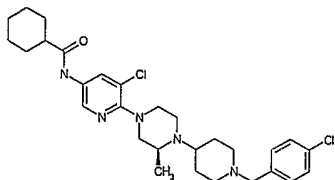
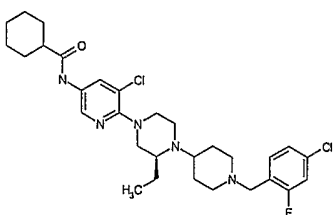
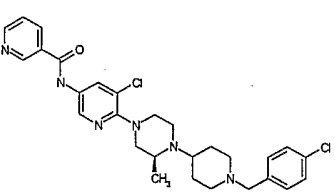
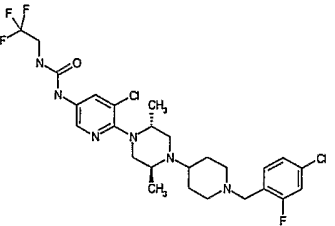
162	
163	
164	
165	
166	
167	

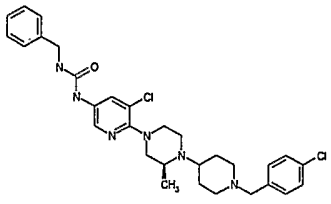
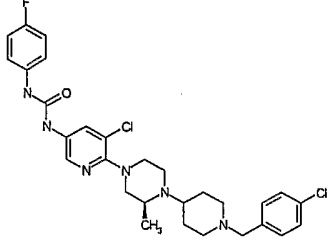
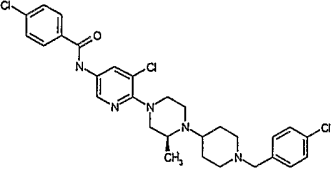
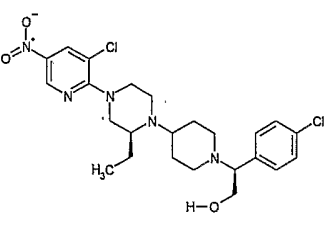
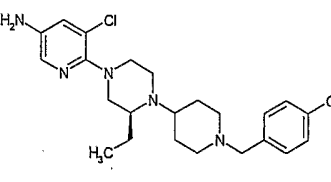
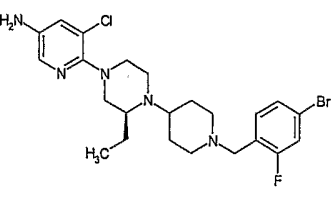
168	
169	
170	
171	
172	
173	

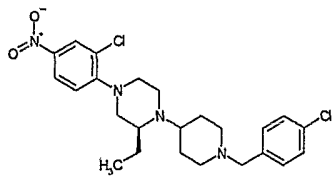
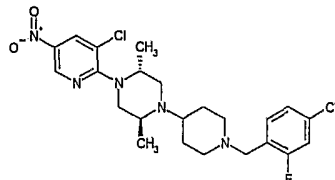
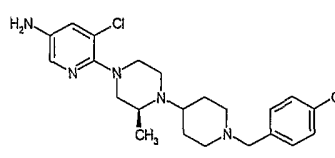
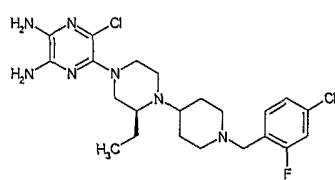
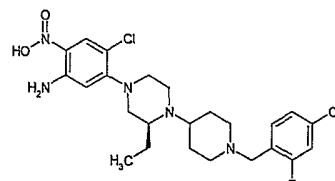
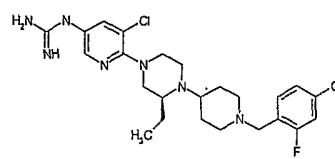
174	
175	
176	
177	
178	
179	

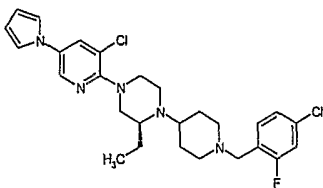
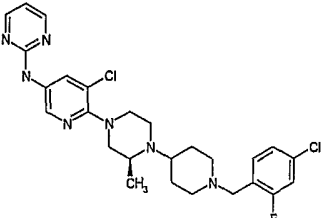
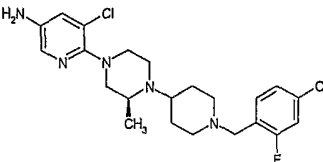
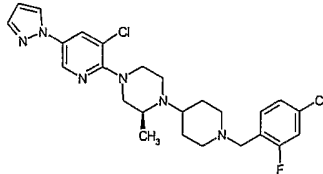
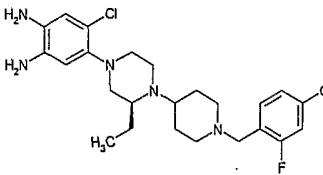
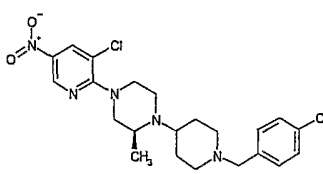
180	
181	
182	
183	
184	
185	

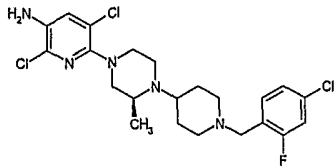
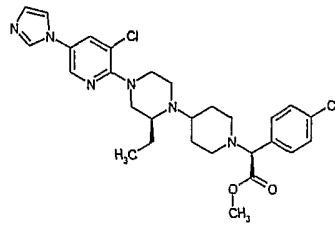
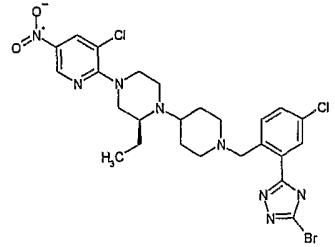
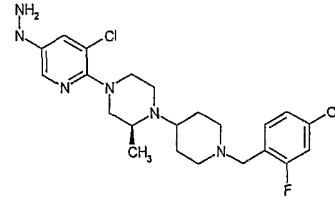
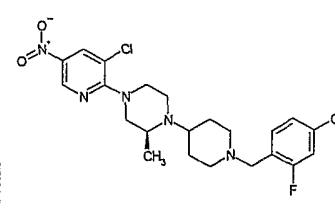
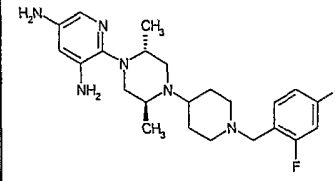
186	
187	
188	
189	
190	
191	

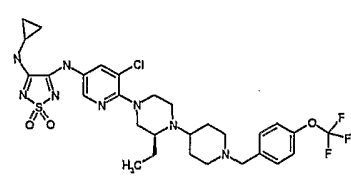
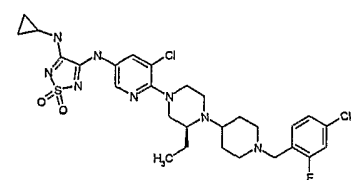
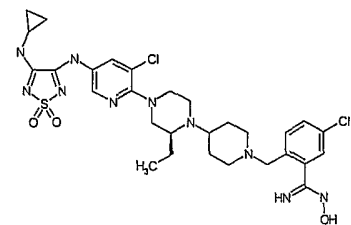
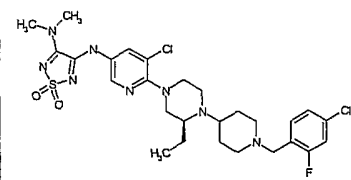
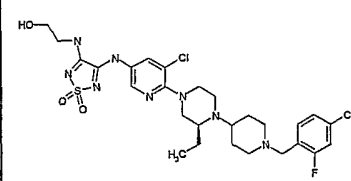
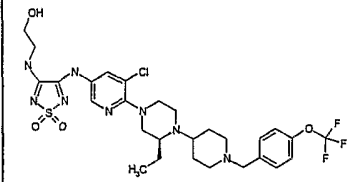
192	 <chem>CCN(C)C(=O)Nc1ccc(Cl)c(c1)CN2CCN(CC2)CN3CCCCN3Cc4ccc(Cl)cc4</chem>
193	 <chem>CCN(C)C(=O)Nc1cc(Cl)c(c2cc(Cl)cc2n1)CN2CCN(CC2)CN3CCCCN3Cc4ccc(Cl)cc4</chem>
194	 <chem>C1CCCCC1C(=O)Nc1cc(Cl)c(c2cc(Cl)cc2n1)CN2CCN(CC2)CN3CCCCN3Cc4ccc(Cl)cc4</chem>
195	 <chem>C1CCCCC1C(=O)Nc1cc(Cl)c(c2cc(Cl)cc2n1)CN2CCN(CC2)CN3CCCCN3Cc4cc(F)ccc4Cl</chem>
196	 <chem>C1CCCCC1C(=O)Nc1cc(Cl)c(c2cc(Cl)cc2n1)CN2CCN(CC2)CN3CCCCN3Cc4ccc(Cl)cc4</chem>
197	 <chem>FC(F)(F)C(=O)Nc1cc(Cl)c(c2cc(Cl)cc2n1)CN2CCN(CC2)CN3CCCCN3Cc4cc(F)ccc4Cl</chem>

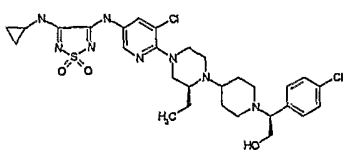
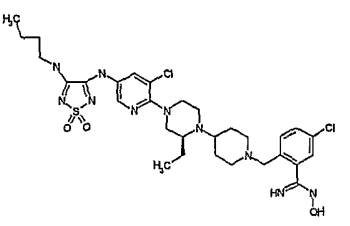
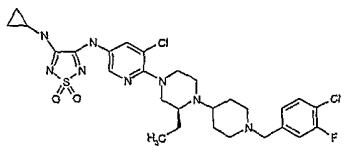
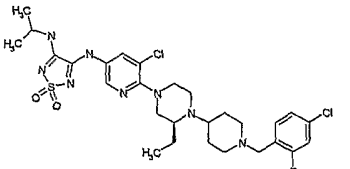
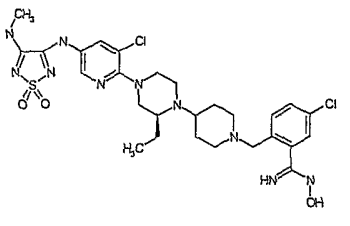
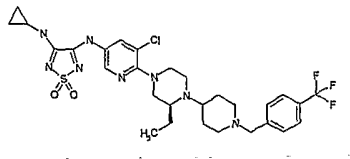
198	
199	
200	
201	
202	
203	

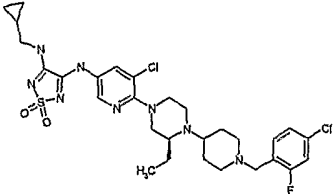
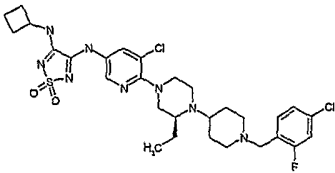
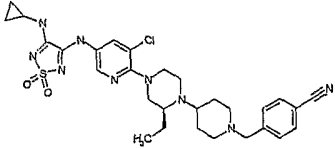
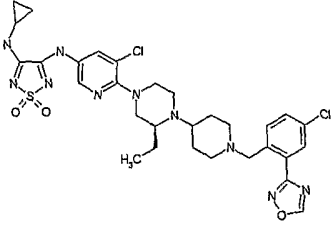
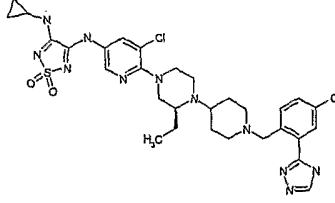
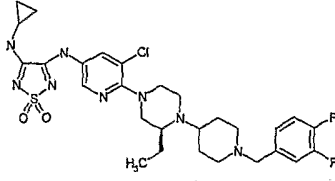
216	
217	
218	
219	
220	
221	

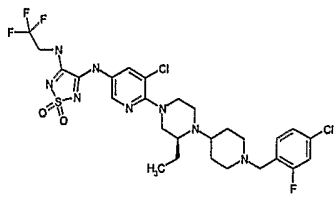
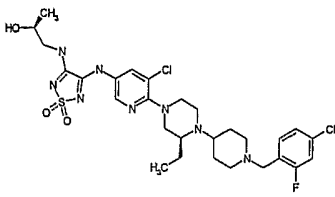
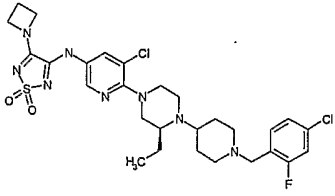
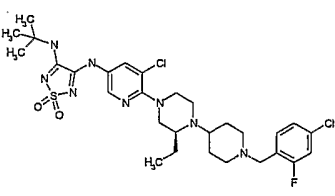
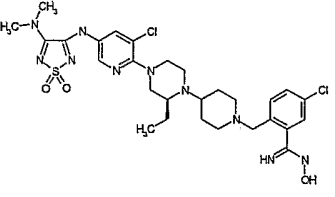
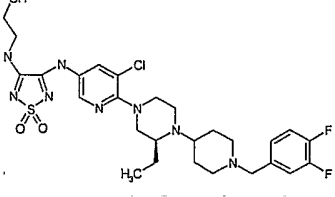
222	
223	
224	
225	
226	
227	

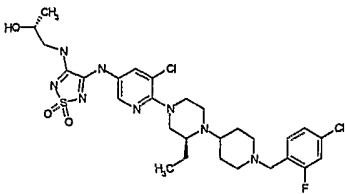
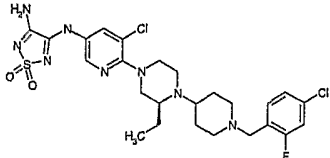
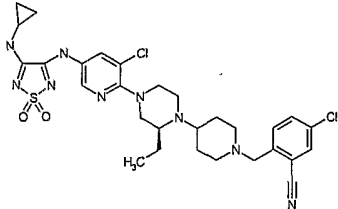
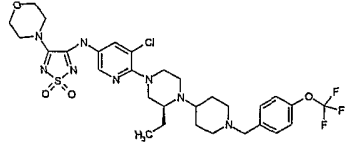
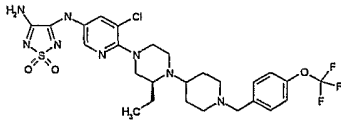
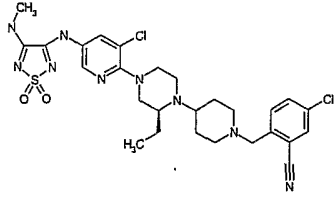
228	
229	
230	
231	
232	
233	

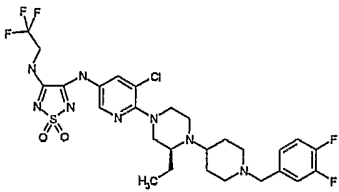
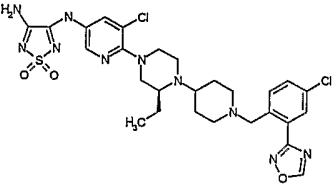
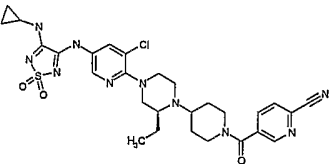
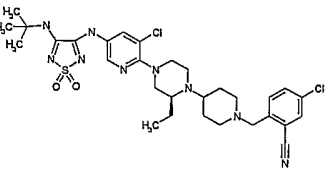
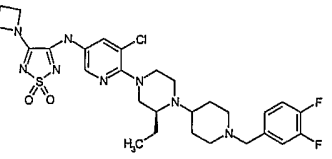
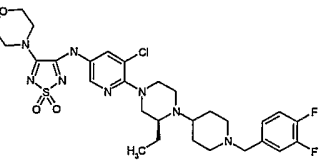
234	
235	
236	
237	
238	
239	

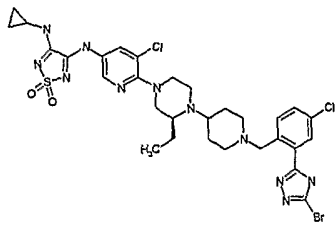
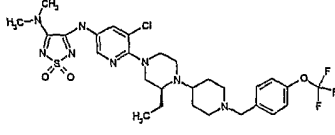
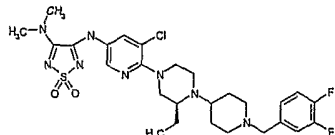
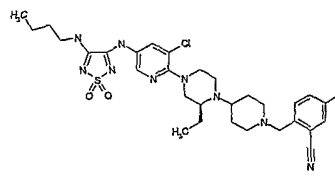
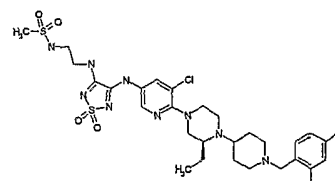
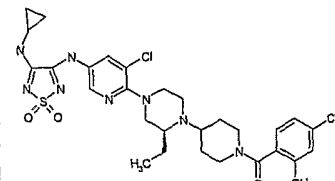
240	
241	
242	
243	
244	
245	

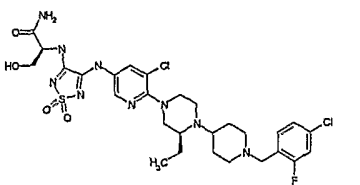
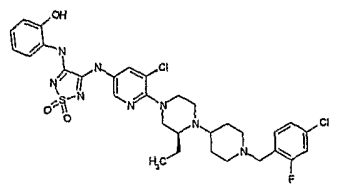
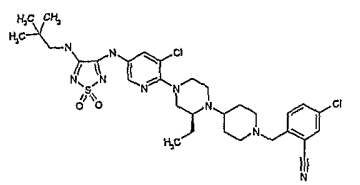
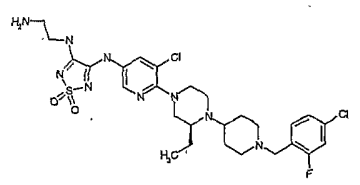
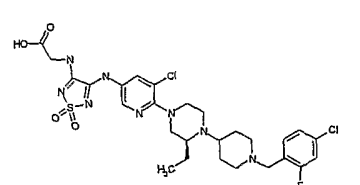
246	
247	
248	
249	
250	
251	

252	
253	
254	
255	
256	
257	

258	
259	
260	
261	
262	
263	

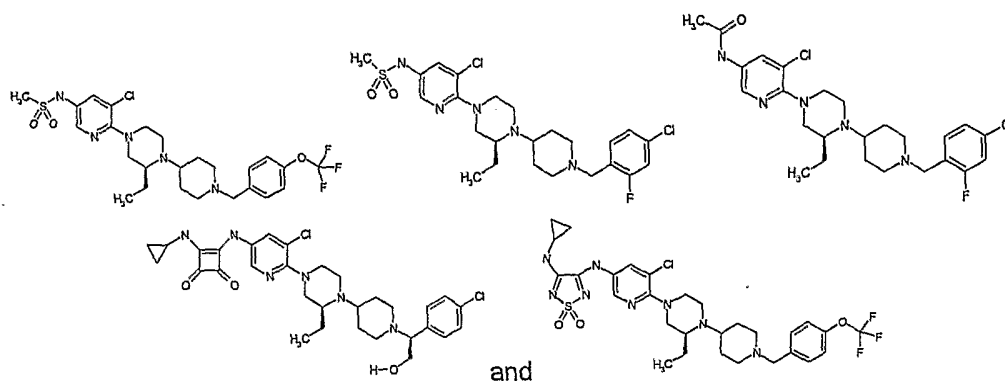
264	
265	
266	
267	
268	
269	

270	
271	
272	
273	
274	
275	

276	
277	
278	
279	
280	

or a pharmaceutically acceptable salt, solvate or ester thereof.

45. The compound according to 44, selected from the group consisting of:



or pharmaceutically acceptable salts, solvates or esters thereof.

- 5 46. A compound according to Claim 1 in purified form.
47. A pharmaceutical composition comprising at least one compound of Claim 1 or 44, or a pharmaceutically acceptable salt, solvate or ester thereof, in combination with at least one pharmaceutically acceptable carrier.
48. The pharmaceutical composition of claim 47, further comprising at least
- 10 one additional agent, drug, medicament, antibody and/or inhibitor for treating a CXCR3 chemokine receptor mediated disease.
49. 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
- 15 Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof.
50. The method according to Claim 49, comprising administering to the patient (a) an effective amount of at least one compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one additional agent, drug, medicament,
- 20 antibody and/or inhibitor for treating a CXCR3 chemokine receptor mediated disease, in combination with a pharmaceutically acceptable carrier.
51. The method according to Claim 48 wherein the compound binds to a CXCR3 receptor.
52. The method according to Claim 48 comprising administering: (a) a
- 25 therapeutically effective amount of at least one compound according to Claim 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; steroids; PDE IV inhibitors, anti-TNF- α compounds, TNF-alpha-convertase inhibitors, cytokine inhibitors, MMP inhibitors, glucocorticoids, chemokine inhibitors, CB2-selective inhibitors, p38 inhibitors, biological response modifiers; anti-inflammatory agents and therapeutics.

5 53. The method according to Claim 49 wherein the disease is an inflammatory disease.

54. 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
10 to Claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

55. 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 Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof.

15 56. The method according to Claim 55, the method comprising administering to the patient a therapeutically effective amount of: (a) at least one compound according to Claim 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-
20 aminosalicylic acid, sulfapyridine, anti-TNF compounds, anti-IL-12 compounds, corticosteroids, glucocorticoids, T-cell receptor directed therapies, immunosuppressives, methotrexate, azathioprine, and 6-mercaptopurines.

57. A method of treating or preventing graft rejection in a patient in need of
25 such treatment comprising administering to the patient a therapeutically effective amount of at least one compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof.

58. The method according to Claim 57, the method comprising administering to the patient a therapeutically effective amount of: (a) at least
30 one compound according to Claim 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.

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 Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or
5 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 compounds, and CB2-selective inhibitors.

60. A method of treating multiple sclerosis in a patient in need of such
10 treatment the method comprising administering to the patient a therapeutically effective amount of: a) at least one compound according to Claim 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,
15 corticosteroids, β -methasone, β -interferon, glatiramer acetate, prednisone, etonercept, and infliximab.

61. 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 Claim 1, or a
20 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,
25 glucocorticoids, chemokine inhibitors, CB2-selective inhibitors, caspase (ICE) inhibitors and other classes of compounds indicated for the treatment of rheumatoid arthritis.

62. A method of treating psoriasis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective
30 amount of: a) at least one compound according to Claim 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.

63. 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 Claim 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.
64. 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, 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 Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof.
65. 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 Claim 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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/005266

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 C07D409/14 C07D401/14 C07D405/14 C07D211/58
C07D417/14 C07D413/14 A61K31/497 A61P31/00 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 A61P

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, PAJ, 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	WO 2004/113323 A (SCHERING AKTIENGESELLSCHAFT; LU, SHOU-FU; PHILLIPS, GARY; YE, BIN) 29 December 2004 (2004-12-29) page 1 - page 2 example 76 claims 18-21	1-65
A	----- DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MACHII, DAISUKE ET AL: "Preparation of 5-cyanopyrimidine derivatives as anti-inflammatory agents" XP002384407 retrieved from STN Database accession no. 2003:796691 abstract CAS RN: 611200-92-1, 611201-32-2 -/--	1-65

☒ Further documents are listed in the continuation of Box C.

☒ 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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

8 June 2006

Date of mailing of the international search report

28/06/2006

Name and mailing address of the ISA/

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

Authorized officer

Seitner, I

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/005266

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	-& WO 03/082855 A1 (KYOWA HAKKO KOGYO CO., LTD., JAPAN) 9 October 2003 (2003-10-09) page 70; example 108 page 74; example 148 page 87; examples 267,272,278 ----- WO 2005/003127 A (CELLTECH R & D LIMITED; OWEN, DAVID, ALAN; WATSON, ROBERT, JOHN; MEISS) 13 January 2005 (2005-01-13) pages 1-3 examples 20,39 claims 11,12 -----	1-65

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/005266

Box 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. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 50-65 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 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 all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers 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.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/005266

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2004113323	A	29-12-2004	AU 2004249698 A1	29-12-2004
			CA 2529161 A1	29-12-2004
			EP 1633737 A1	15-03-2006
WO 03082855	A1	09-10-2003	AU 2003220968 A1	13-10-2003
WO 2005003127	A	13-01-2005	NONE	