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(54) **2-PHENOXY- AND 2-PHENYLSULFOMAMIDE DERIVATIVES WITH CCR3 ANTAGONISTIC ACTIVITY FOR THE TREATMENT OF ASTHMA AND OTHER INFLAMMATORY OR IMMUNOLOGICAL DISORDERS**

2-PHENOXY- UND 2-PHENYLSULFANYL-BENZENESULFONAMID DERIVATE MIT CCR3 ANTAGONISTISCHER AKTIVITÄT ZUR BEHANDLUNG VON ASTHMA UND ANDEREN ENTZÜNDLICHEN ODER IMMUNOLOGISCHEN ERKRANKUNGEN

DERIVES DE 2-PHENOXY- ET 2-PHENYLSULFONAMIDE A ACTIVITE ANTAGONISTE DE CCR3 POUR LE TRAITEMENT DE L'ASTHME ET D'AUTRES TROUBLES INFLAMMATOIRES OU IMMUNOLOGIQUES

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WO-A-03/022277

Description

TECHNICAL FIELD

[0001] The present invention relates to a benzenesulfonamide derivative, which is useful as an active ingredient of pharmaceutical preparations. The benzenesulfonamide derivatives of the present invention have CCR3 (CC type chemokine receptor 3) antagonistic activity, and can be used for the prophylaxis and treatment of diseases associated with CCR3 activity, in particular for the treatment of asthma, atopic dermatitis, allergic rhinitis and other inflammatory/immunological disorders.

BACKGROUND ART

[0002] Chemokines are chemotactic cytokines of which major functions are migration of inflammatory cells that express relevant chemokine receptors on their surfaces to sites of inflammation, and activation of inflammatory cells. There are two classes of chemokines, C--X--C (.alpha.) and C--C (i), depending on whether the first two cysteines are separated by a single amino acid (C--X--C) or are adjacent (C--C).

[0003] Eotaxin, one of the C-C family of chemokines, is an 8.4 kDa (74 amino acid) polypeptide and binds solely to the receptor CCR3 with high affinity. *In vitro* and *in vivo*, eotaxin causes chemotaxis of inflammatory cells expressing CCR3 [Elsner J., Hochstetter R., Kimming D. and Kapp A.: Human eotaxin represents a potent activator of the respiratory burst of human eosinophils. Eur. J. Immunol., 26: 1919-1925, 1996].

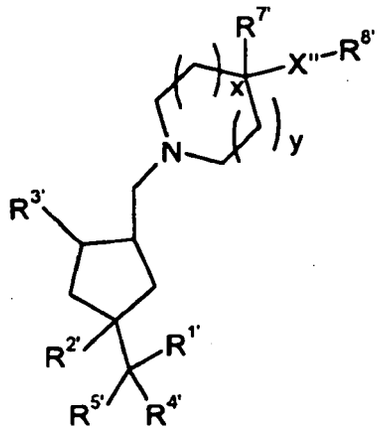
[0004] The chemokine receptor CCR3 is a G protein-coupled, seven transmembrane domain receptor (GPCR) which binds to known ligands, in addition to eotaxin, including eotaxin-2 (CCL24), RANTES (CCL5), MCP-3 (CCL7) and MCP-4 (CCL13). CCR3 is expressed on inflammatory cells relevant to the chronic asthma pathology. Such inflammatory cells include Eosinophils [Sabroe I., Conroy D.M., Gerard N.P., Li Y., Collins P.D., Post T.W., Jose P.J., Williams T.J., Gerard C.J., Ponath P.D. J. Immunol. 161: 6139-6147, 1998], basophils [Uguccioni M., Mackay C.R., Ochensberger B., Loetscher P., Rhis S., LaRosa G.J., Rao P., Ponath P.D., Baggiolini M., Dahinden C.A. J. Clin. Invest. 100: 1137-1143, 1997], Th2 cells [Sallusto F., Mackay C.R., Lanzavecchia A. Science. 277: 2005-2007, 1997], alveolar macrophages [Park I.W., Koziel H., Hatch W., Li X., Du B., Groopman J.E. Am. J. Respir. Cell Mol. Biol. 20:864-71, 1999] and mast cells [Oliveira S.H. and Lukacs N.W. Inflamm. Res. 50: 168-174. 2001]. It was also reported that BEAS-2B, an epithelial cell line, stimulated with TNF-a and IFN-γ, expressed CCR3 [Stellato C., Brummet M.E., Plitt J.R., Shahabuddin S., Baroody F.M., Liu M., Ponath P.D., and Beck L.A. J. Immunol., 166: 1457-1461, 2001].

[0005] In animal models, eotaxin-knockout mice showed decreased eosinophilia after antigen challenge [Rothenberg M.E., MacLean J.A., Pearlman E., Luster A.D. and Leder P. J. Exp. Med., 185: 785-790, 1997]. In IL5-/eotaxin- double knock-out mice, there is no eosinophilia or AHR in response to antigen challenge [Foster P.S., Mould A.W., Yang M., Mackenzie J., Mattes J., Hogan S.P., Mahalingam S., Mckenzie A.N.J., Rothenberg M.E., Young I.G., Matthaei K.I. and Webb D.C. Immunol. Rev., 179, 173-181, 2001]. Clinically, mRNA and protein expression of eotaxin and CCR3 are observed in the lung tissues of atopic asthmatics and are associated with AHR, reduced FEV_1 and lung eosinophilia [Ying S., Robin D.S., Meng Q., Rottman J., Kennedy R., Ringler D.J., Mackay C.R., Daugherty B.L., Springer M.S., Durham S.R., Williams T.J. and Kay A.B.: Enhanced expression of eotaxin and CCR3 mRNA and protein in atopic asthma. Association with airway hyperresponsiveness and predominant colocalization of eotaxin mRNA to bronchial epithelial and endothelial cells. Eur. J. Immunol., 27, 3507-3516, 1997; Lamkhioued Renzi P.M., AbiYounes S., GarciaZepada E.A., Allakhverdi Z., Ghaffar O., Rothenberg M.D., Luster A.D. and Hamid Q.: Increased expressions of eotaxin in bronchoalveolar lavage and airways of asthmatics contributes to the chemotaxis of eosinophils to the site of inflammation. J.Immunol., 159: 4593-4601, 1997; Jahnz-Royk K., Plusa T. and Mierzejewska J.: Eotaxin in serum of patients with asthma or chronic obstructive pulmonary disease: relationship with eosinophil cationic protein and lung function. Mediators of Inflammation, 9: 175-179, 2000]. In addition, in allergic rhinitis, CCR3-expressing Th2 lymphocytes co-localize with eosinophils in nasal polyps in close proximity to eotaxin-expressing cells [Gerber B.O., Zanni M.P., Uguccioni M., Loetscher M., Mackay C.R., Pichler W.J., Yawalkar N., Baggiolini M. and Moser B.: Functional expression of the eotaxin receptor CCR3 in T lymphocytes co-localizing with eosinophils. CURRENT BIOLOGY 7: 836-843, 1997]. Moreover, viral infections (RSV, influenza virus) which are known risk factors in asthma, result in increased eotaxin expression in lung tissue which is correlated with tissue eosinophilia [Matsukura S., Kokubo F., Kubo H., Tomita T., Tokunaga H., Kadokura M., Yamamoto T., Kuroiwa Y., Ohno T., Suzaki H. and Adachi M.: Expression of RANTES by normal airway epithelial cells after influenza virus A infection. Am. J. Respir. Cell and Mol. Biol., 18: 255-264, 1998; Saito T., Deskin R.W., Casola A., Haeberle H., Olszewska B., Ernest P.B., Alam R., Ogra P.L. and Garofalo R.: Selective regulation of chemokine production in human epithelial cells. J. Infec. Dis., 175: 497-504, 1997]. Thus the binding of CCR3 and related chemokine including eotaxin has been implicated as being important mediators of inflammatory and immunoregulatory disorders and diseases, including asthma, rhinitis, and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis, Grave's disease, and atherosclerosis.

[0006] It is also implicated that binding of CCR3 and related chemokine is an important factor of virus infections including HIV [(Marone G, de Paulis A, Florio G, Petraroli A, Rossi F, Triggiani M.: Int Arch Allergy Immunol 2001 Jun;125(2)/89-95), (Li Y et al.,: Blood 2001 Jun 1; 97(11):3484-90), and (Marone G, Florio G, Petraroli A, Triggiani M, de Paulis A: Trends Immunol 2001 May;22 (5):229-32)], lung granuloma (Ruth JH, Lukacs NW, Warmington KS, Polak TJ, Burdick M, Kunkel SL, Strieter RM, Chensue SW:J Immunol 1998 Oct 15;161 (8):4276-82), and Alzheimer's diseases (Xia MQ, Qin SX, Wu LJ, Mackay CR, and Hyman BT: Am J Pathol 1998 Jul;153 (1):31-37).

[0007] Therefore, CCR3 is an important target and antagonism of CCR3 is likely to be effective in the treatment of such inflammatory and immunoregulatory disorders and diseases.

[0008] WO 2000/76514 and WO 2000/76513 disclose cyclopentyl modulators of chemokine receptors including CCR3 activity represented by the general formula:



wherein

[0009] X", x, y, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ $R^{5'}$, $R^{6'}$ $R^{7'}$ and $R^{8'}$ are defined in the application.

[0010] Other applications also disclose CCR3 modulators. However, none of the reference and other reference discloses simple benzenesulfonamide derivatives having CCR3 antagonistic activity.

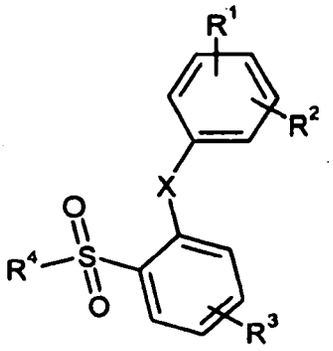
[0011] WO03/022277 discloses arylsulfonamide derivatives and their use in CCR3 antagonists.

[0012] The development of a compound having effective CCR3 antagonistic activity can be used for the prophylaxis and treatment of diseases associated with CCR3 activity has been desired.

SUMMARY OF THE INVENTION

[0013] As the result of extensive studies on chemical modification of benzenesulfonamide derivatives, the present inventors have found that the compounds of the structure related to the present invention have unexpectedly excellent CCR3 antagonistic activity. The present invention has been accomplished based on these findings.

[0014] The invention is to provide novel benzenesulfonamide derivatives of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:



(I)

wherein

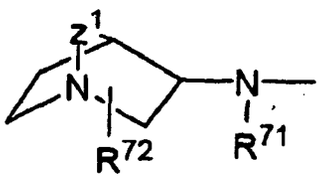
X represents O or S;

R^1 represents hydrogen, halogen, hydroxy, nitro, cyano, C_{1-6} alkoxy carbonyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} alkanoyl, phenyl, C_{1-6} alkyl optionally substituted by mono-, di- or tri- halogen, or C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen;

R^2 represents hydrogen, halogen, hydroxy, nitro, cyano, C_{1-6} alkoxy carbonyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} alkanoyl, phenyl, C_{1-6} alkyl optionally substituted by mono-, di- or tri- halogen or C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen;

R^3 represents hydrogen, halogen, hydroxy, nitro, cyano, amino, carboxy, tetrazolyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, C_{1-6} alkyl optionally substituted by mono-, di- or tri- halogen or hydroxy;

R^4 represents



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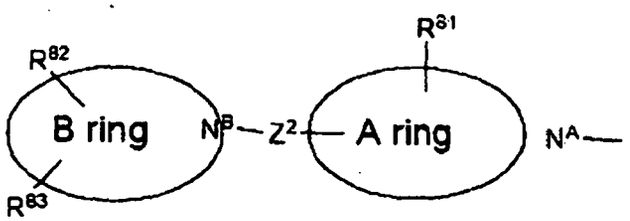


[0015] Wherein:

R^{71} represents hydrogen, or C_{1-6} alkyl optionally substituted by amino, hydroxy, carboxy, pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl, are optionally substituted by mono- or di- oxo;

R^{72} represents hydrogen, carboxy, C_{1-6} alkanoyl, amino, (C_{1-6}alkyl)amino, di(C_{1-6} alkyl) amino, N-(C_{1-6}alkyl)amino carbonyl, C_{1-6} alkyl optionally substituted by hydroxy, carboxy, or mono-, di- or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen, pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di-oxo;

Z^1 represents -$[CH_2]_p$-, wherein p represents an integer 1 or 2;

R^{81} represents hydrogen, C_{1-6} alkoxycarbonyl, or C_{1-6} alkyl substituted by pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;

R^{82} represents hydrogen, hydroxy, carboxy or C_{1-6} alkyl substituted by hydroxy, amino, or carboxy,

R^{83} represents hydrogen, hydroxy, carboxy, or C_{1-6} alkyl substituted by hydroxy, amino, or carboxy,

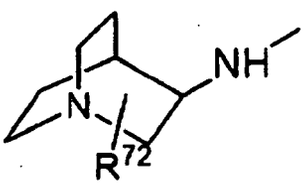
with the proviso that when R^{81} is hydrogen, R^{82} or R^{83} is other than hydrogen;

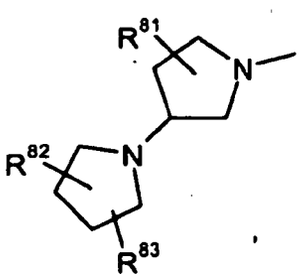
Z^2 represents -$[CH_2]_q$-, wherein q represents an integer selected from 0 to 3;

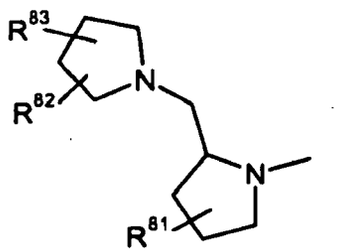
A ring represents a 3 to 8 membered saturated heterocyclic ring, in which the nitrogen atom N^A is the only hetero atom;

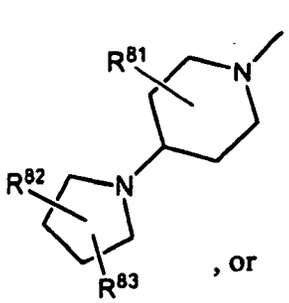
B ring represents a 3 to 8 membered saturated heterocyclic ring, in which the nitrogen atom N^B is the only hetero atom.

[0016] In certain embodiments, the benzenesulfonamide derivative of the formula (I), R^4 represents









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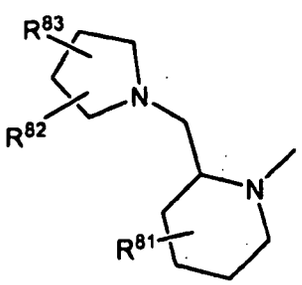


wherein:

R^{72} represents hydrogen, carboxy, C_{1-6} alkanoyl, amino, (C_{1-6}alkyl)amino, di(C_{1-6}alkyl)amino, N-(C_{1-6}alkyl)amino carbonyl, C_{1-6} alkyl optionally substituted by hydroxy, carboxy, or mono-, di- or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen, pyrrolidinyl or piperidinyl wherein said pyrrolidinyl and piperidinyl are

optionally substituted by mono- or di- oxo;

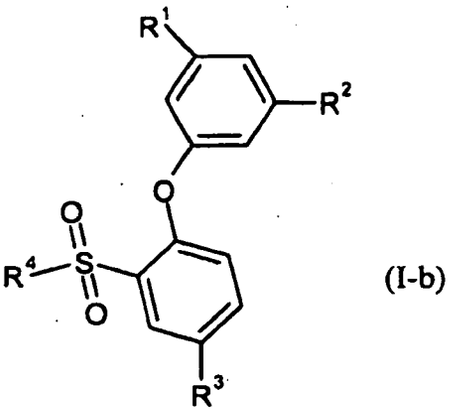
R^{81} represents hydrogen, methoxycarbonyl or C_{1-6} alkyl substituted by 2-oxo-pyrrolidin-1-yl, 2,5- dioxo pyrrolidin-1-yl, 2-oxo-piperidin-1-yl, 2-oxo-piperidin-3-yl, 4-oxo-piperidin-1-yl, 2-oxo-piperidin-6-yl, 2,5-dioxo-piperidin-1-yl, 2,6-dioxo-piperidin-1-yl, or 2,6-dioxo-piperidin-3-yl;

R^{82} represents hydrogen, hydroxy or C_{1-6} alkyl substituted by hydroxy;

R^{83} represents hydrogen, hydroxy or carboxy; and

with the proviso that when R^{82} and R^{83} are hydrogen at the same time, R^{81} is other than hydrogen, or when R^{81} and R^{83} are hydrogen at the same time, R^{82} is other than hydrogen.

[0017] In yet another embodiment, the derivative is of the formula (I-b), its tautomeric or stereoisomeric form, or a salt thereof:



(I-b)

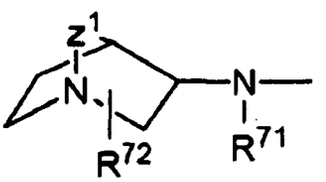
wherein:

R^1 represents fluoro, chloro, bromo, iodo, or nitro;

R^2 represents fluoro, chloro, bromo, iodo, or nitro;

R^3 represents acetyl, cyano, or tetrazolyl;

R^4 represents



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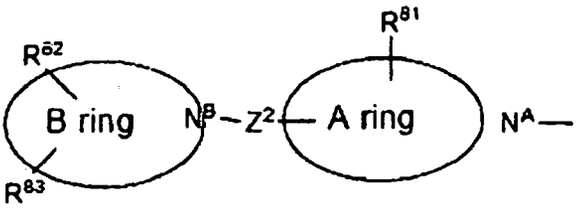


wherein:

R^{71} represents hydrogen, or C_{1-6} alkyl optionally substituted by amino, hydroxy, carboxy, pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;

R^{72} represents hydrogen, carboxy, C_{1-6} alkanoyl, amino, (C_{1-6}alkyl)amino, di(C_{1-6}alkyl)amino, N-(C_{1-6}alkyl)amino carbonyl, C_{1-6} alkyl optionally substituted by hydroxy, carboxy, or mono-, di- or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen, pyrrolidinyl or piperidinyl, herein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or dioxo;

Z^1 represents $-[CH_2]_p-$, wherein p represents an integer 1 or 2;

R^{81} represents hydrogen, C_{1-6} alkoxycarbonyl, or C_{1-6} alkyl substituted by pyrrolidinyl, or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;

R^{82} represents hydrogen, hydroxy, carboxy or C_{1-6} alkyl substituted by hydroxy, amino, or carboxy,

R^{83} represents hydrogen, hydroxy, carboxy, or C_{1-6} alkyl substituted by hydroxy, amino, or carboxy,

with the proviso that when R^{81} is hydrogen, R^{82} or R^{83} is other than hydrogen;

Z^2 represents $-[CH_2]_q-$,

wherein

q represents an integer selected from 0 to 3;

A ring represents a 3 to 8 membered saturated heterocyclic ring, in which the nitrogen atom N^A is the only hetero atom;

B ring represents a 3 to 8 membered saturated heterocyclic ring, in which the nitrogen atom N^B is the only hetero atom; and

E ring represents a 5 to 8 membered saturated heterocyclic ring, in which the nitrogen atom N^E is the only hetero atom.

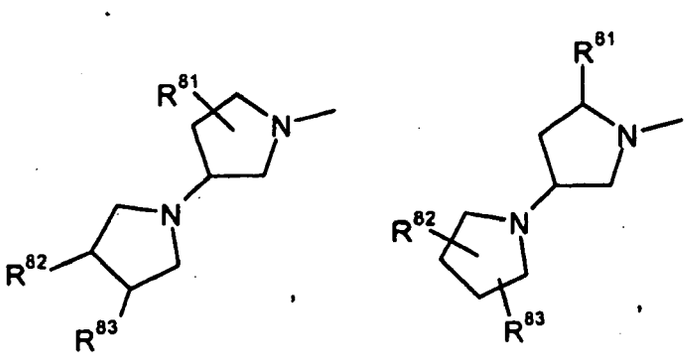
[0018] In yet one embodiment, in the benzenesulfonamide derivative of formula (I-b)

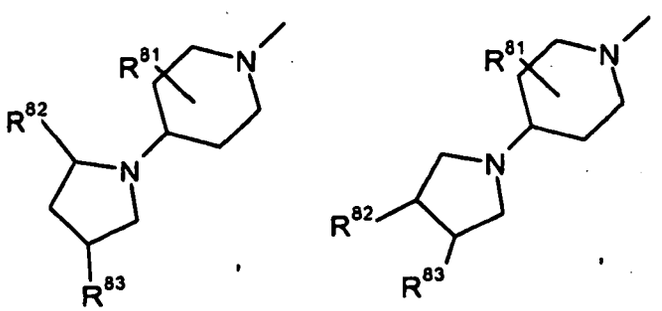
R^1 represents fluoro, chloro or bromo;

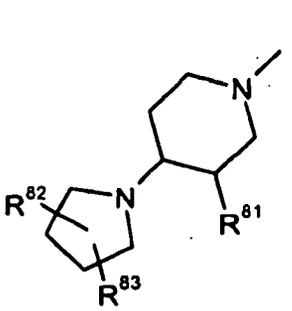
R^2 represents fluoro, chloro or bromo;

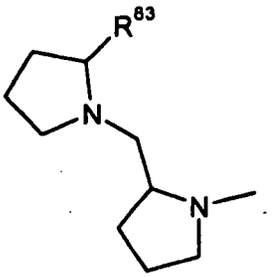
R^3 represents cyano;

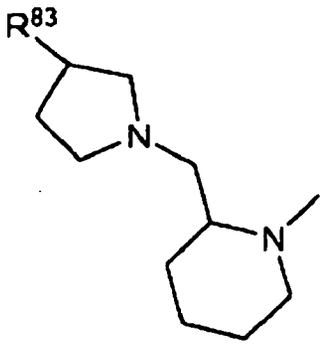
R^4 represents











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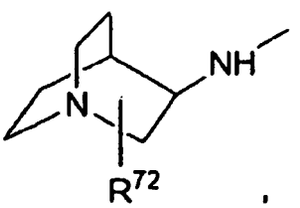


wherein:

R^{72} represents hydrogen, carboxy, C_{1-6} alkanoyl, amino, (C_{1-6}alkyl)amino, di(C_{1-6}alkyl)amino, N-(C_{1-6}alkyl)amino carbonyl, C_{1-6} alkyl optionally substituted by hydroxy, carboxy, or mono-, di- or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen, pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;

R^{81} represents hydrogen, methoxycarbonyl or C_{1-6} alkyl substituted by 2-oxo-pyrrolidin-1-yl, 2,5- dioxo pyrrolidin-1-yl, 2-oxo-piperidin-1-yl, 2-oxo-piperidin-3-yl, 4-oxo-piperidin-1-yl, 2-oxo-piperidin-6-yl, 2,5-dioxo-piperidin-1-yl, 2,6-dioxo-piperidin-1-yl, or 2,6-dioxo-piperidin-3-yl;

R^{82} represents hydrogen, hydroxy or hydroxy substituted C_{1-6} alkyl;

R^{83} represents hydrogen, hydroxy or carboxy; and

with the proviso that when R^{82} and R^{83} are hydrogen at the same time, R^{81} is other than hydrogen, or when R^{81} and R^{83} are hydrogen at the same time, R^{82} is other than hydrogen.

[0019] In specific embodiments, the benzenesulfonamide derivative is selected from the group consisting of:

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)-5-cyano-2-(3,5-dichloro-phenoxy)-benzenesulfonamide;

(S)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)-5-cyano-2-(3,5-dichloro-phenoxy)-benzenesulfonamide;

4-(3,5-Dichloro-phenoxy)-3-{4-[(2S)-(1-hydroxy-1-methyl-ethyl)-pyrrolidin-1-yl]-piperidine-1-sulfonyl}-benzonitrile;

4-(3,5-Dichloro-phenoxy)-3-[3-(2,5-dioxo-pyrrolidin-1-ylmethyl)-4-pyrrolidin-1-yl-piperidine-1-sulfonyl]-benzonitrile;

4-(3,5-Dichloro-phenoxy)-3-{4-[(2S)-hydroxymethyl-pyrrolidin-1-yl]-piperidine-1-sulfonyl}-benzonitrile;

4-(3,5-Dichloro-phenoxy)-3-{(2S)-[(2S)-hydroxymethyl-pyrrolidin-1-ylmethyl]-pyrrolidine-1-sulfonyl}-benzonitrile;

N-(1-aza-bicyclo[2.2.2]oct-3-yl)-2-(3,5-dichloro-phenylsulfanyl)-5-nitrobenzenesulfonamide;

4-(3,5-dichlorophenoxy)-3-(4-((3S,4S)-3,4-dihydroxypyrrolidin-1-yl)piperidin-1-ylsulfonyl)benzonitrile;

(3'S,5'S)-methyl-1'-(5-cyano-2-(3,5-dichlorophenoxy)phenylsulfonyl)-1,3'-bipyrrolidine-5'-carboxylate;

3-(4-((35,45)-3-(tert-butyldimethylsilyloxy)-4-hydroxypyrrolidin-1-yl)piperidin-1-ylsulfonyl)-4-(3,5-dichlorophenoxy)benzonitrile;

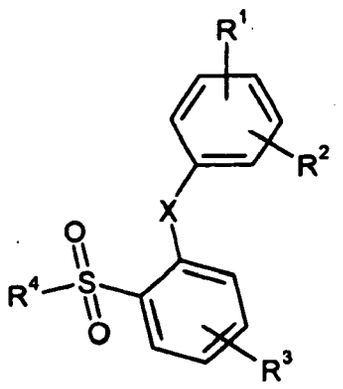
4-(3,5-dichlorophenoxy)-3-((3S,3'S,4S)-3,4-dihydroxy-1,3'-bipyrrolidin-1'-ylsulfonyl)benzonitrile;

(S)-1-(1-(5-cyano-2-(3,5-dichlorophenoxy)phenylsulfonyl)piperidin-4-yl)pyrrolidine-2-carboxylic acid;

4-(3,5-dichlorophenoxy)-3-(2-((3-hydroxypyrrolidin-1-yl)methyl)piperidin-1-ylsulfonyl)benzonitrile; and

(R)-5-cyano-2-(3,5-dichlorophenoxy)-N-(2-(2,5-dioxopyrrolidin-1-yl)ethyl)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)benzenesulfonamide.

[0020] The invention also relates to novel benzenesulfonamide derivatives shown by the following formula (I), its tautomeric and stereoisomeric form, and the salts thereof.



(I)

wherein

X represents O or S;

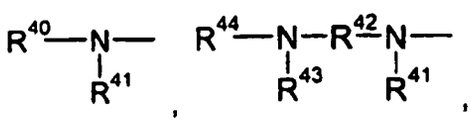
R^1 represents hydrogen, halogen, hydroxy, nitro, cyano, C_{1-6} alkoxy carbonyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} alkanoyl, phenyl, C_{1-6} alkyl optionally substituted by mono-, di- or tri- halogen, or C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen;

R^2 represents hydrogen, halogen, hydroxy, nitro, cyano, C_{1-6} alkoxy carbonyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} alkanoyl, phenyl, C_{1-6} alkyl optionally substituted by mono-, di- or tri- halogen or C_{1-6} alkoxy

optionally substituted by mono-, di- or tri- halogen;

R^3 represents hydrogen, halogen, hydroxy, nitro, cyano, amino, carboxy, tetrazolyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, C_{1-6} alkyl optionally substituted by mono-, di- or tri- halogen or hydroxy;

R^4 represents



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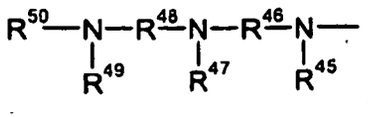

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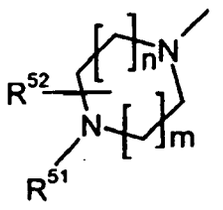

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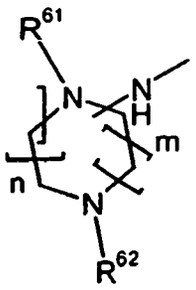

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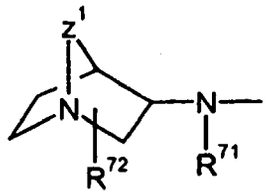

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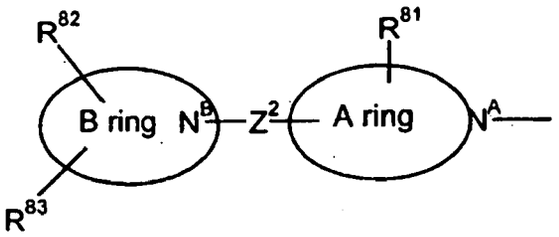

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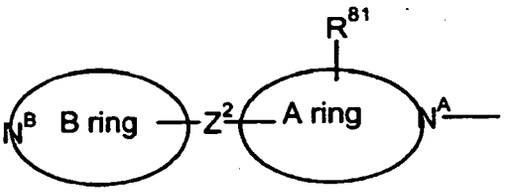

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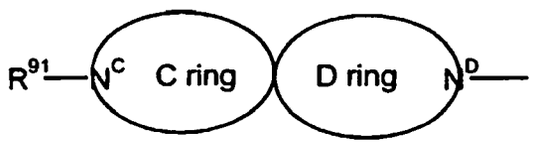

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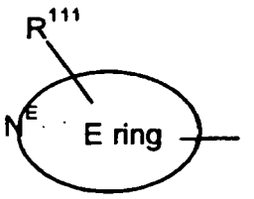


wherein

R^{40}	represents C_{1-6} alkyl substituted by pyrrolidinyl or piperidinyl wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo, 7-oxa-bicyclo[4.1.0]hept-3-yl optionally having 1 or 2 substituents selected from the group consisting of amino, (C_{1-6} alkyl)amino and di(C_{1-6} alkyl)amino, or a 5 to 8 membered saturated heterocyclic ring containing 1 or 2 heteroatoms selected from the group consisting of N and O and optionally having from 1 to 3 substituents selected from the group consisting of hydroxy, amino, oxo and C_{1-6} alkyl;
R^{41}	represents hydrogen, C_{1-6} alkyl optionally substituted by amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, or 2,5- dioxo pyrrolidin-1-yl or a C_{5-8} cycloalkyl optionally substituted by hydroxy, or
R^{40} and R^{41}	may form, together with adjacent N atom, a 5 to 8 membered saturated heterocyclic ring optionally interrupted by O;
R^{42}	represents C_{1-6} alkylene optionally substituted by hydroxy or carboxy, or a C_{5-8} cycloalkyl substituted by at least one hydroxy and moreover optionally 1 or 2 substituents selected from the group consisting of hydroxy, amino, oxo and C_{1-6} alkyl, or
R^{41} and R^{42}	may form, together with adjacent N atom, a 5 to 8 membered saturated heterocyclic ring optionally interrupted by NO or O, wherein said 5 to 8 membered saturated heterocyclic ring is substituted by mono- or di- oxo, with the proviso that when R^{41} is hydrogen, C_{1-6} alkyl optionally substituted by amino, C_{1-6} alkylamino, or di(C_{1-6} alkyl)amino, R^{42} is hydroxy substituted C_{1-6} alkylene or carboxy substituted C_{1-6} alkylene;
R^{43}	represents hydrogen, or C_{1-6} alkyl optionally substituted by hydroxy or carboxy;
R^{44}	represents hydrogen, or C_{1-6} alkyl optionally substituted by hydroxy or carboxy, with the proviso that when R^{41} and R^{42} form, together with adjacent N atom, a 5 to 8 membered saturated heterocyclic ring, R^{44} represents hydroxy substituted C_{1-6} alkyl or carboxy substituted C_{1-6} alkyl;
R^{45}, R^{47}, R^{49} and R^{50}	independently represent hydrogen or C_{1-6} alkyl;
R^{46} and R^{48}	independently represent C_{1-6} alkylene optionally substituted hydroxy or carboxy;
n	represents an integer selected from 1 to 3;
m	represents an integer selected from 0 to 3;
R^{51}	represents hydrogen, C_{1-6} alkyl, or a 3 to 8 membered saturated ring optionally interrupted by NH or O;
R^{52}	represents hydrogen, C_{1-6} alkoxy carbonyl, or C_{1-6} alkyl substituted by carboxy, amino, (C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, N-(C_{1-6} alkylsulfonyl)amino, N-(C_{1-6} alkanoyl)amino, C_{1-6} alkoxycarbonyl, tetrazolyl, triazolyl, indolinyl, isoindolinyl, indolyl, isoindolyl, pyrrolidinyl option-

ally substituted by mono- or di- oxo, or piperidinyl optionally substituted by mono- or di- oxo, with the proviso that when R^{51} and R^{52} are hydrogen at the same time, R^3 is tetrazolyl or C_{1-6} alkanoyl, or when R^{51} is hydrogen or C_{1-6} alkyl, R^{52} is other than hydrogen;

R^{61} and R^{62}	independently represent hydrogen or C_{1-6} alkyl optionally substituted by hydroxy, carboxy, phenyl or mono-, di- or tri halogen;
R^{71}	represents hydrogen, or C_{1-6} alkyl optionally substituted by amino, hydroxy, carboxy, pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;
R^{72}	represents hydrogen, carboxy, C_{1-6} alkanoyl, amino, (C_{1-6}alkyl)amino, di-(C_{1-6}alkyl)amino, N-(C_{1-6}alkyl)amino carbonyl, C_{1-6} alkyl optionally substituted by hydroxy, carboxy, or mono-, di- or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen, pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;
Z^1	represents -$[CH_2]_p$-, wherein p represents an integer 1 or 2;
R^{81}	represents hydrogen, C_{1-6} alkoxycarbonyl, or C_{1-6} alkyl substituted by Pyrrolidinyl, or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;
R^{82}	represents hydrogen, hydroxy, carboxy or C_{1-6} alkyl substituted by hydroxy, amino, or carboxy,
R^{83}	represents hydrogen, hydroxy, carboxy, or C_{1-6} alkyl substituted by hydroxy, amino, or carboxy, with the proviso that when R^{81} is hydrogen, R^{82} or R^{83} is other than hydrogen;
Z^2	represents -$[CH_2]_q$-, wherein q represents an integer selected from 0 to 3;
R^{91}	represents hydrogen or C 1-6 alkyl optionally substituted by phenyl;
R^{111}	represents hydrogen, carboxy, C1-6 alkoxy carbonyl, C1-6 alkanoyl, N-(C_{1-6}-$_6$alkyl) aminocarbonyl, C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen, or C_{1-6} alkyl optionally substituted by hydroxy, mono-, di- or tri- halogen, amino, (C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, N-(C_{1-6} alkylsulfonyl)amino, N-(C_{1-6} alkanoyl)amino, C_{1-6} alkoxycarbonyl, tetrazolyl, triazolyl, indolinyl, isoindolinyl, indolyl, isoindolyl, pyrrolidinyl or piperidinyl wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;
A	ring represents a 3 to 8 membered saturated heterocyclic ring, in which the nitrogen atom N^A is the only hetero atom;
B	ring represents a 3 to 8 membered saturated heterocyclic ring, in which the nitrogen atom N^B is the only hetero atom;
C ring and D ring	together form a 7 to 15 membered diazabicyclic ring; and
E	ring represents a 5 to 8 membered saturated heterocyclic ring, in which the nitrogen atom N^E is the only hetero atom.

[0021] Further this invention is to provide a use of the benzenesulfonamide derivative shown in the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof in the preparation of a medicament for treating or preventing a CCR3 related disorder or disease.

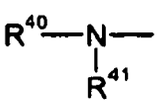
[0022] The compounds of the present invention surprisingly show excellent CCR3 antagonistic activity. They are, therefore suitable for the production of medicament or medical composition, which may be useful to treat CCR3 related diseases. More specifically, since the compounds of the present invention antagonize CCR3, they are useful for the preparation of a medicament for treatment and prophylaxis of diseases as follows; asthma, rhinitis, and allergic diseases, and autoimmune pathologies such as rheumatoid arthritis, Grave's disease, and atherosclerosis. Therefore, CCR3 is an important target and antagonism of CCR3 is likely to be effective in the treatment and prophylaxis of such inflammatory

and immunoregulatory disorders and diseases.

[0023] The compounds of the present invention are also useful for the preparation of a medicament for treatment and prophylaxis of diseases like virus infections including HIV, lung granuloma, and Alzheimer's diseases, since the diseases also relate to CCR3.

[0024] The invention also relates to compounds of formula (I) wherein:

R^4 represents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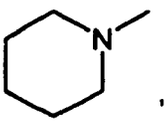
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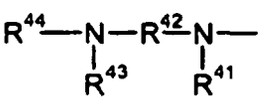
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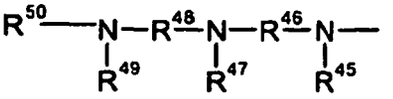
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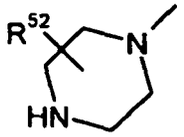
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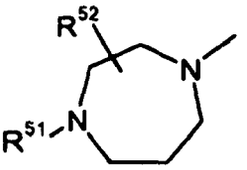
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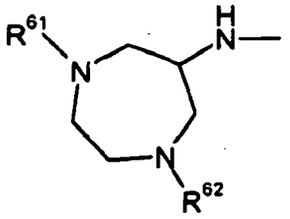
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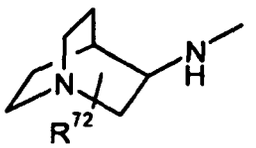
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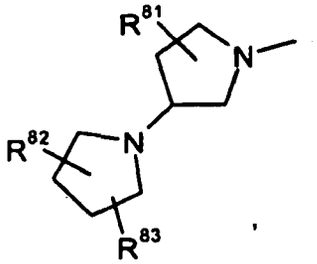
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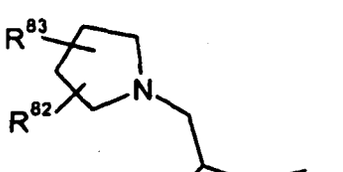
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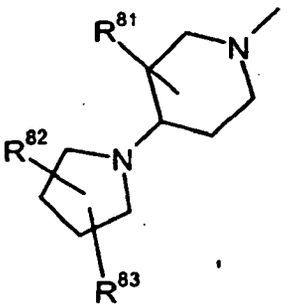

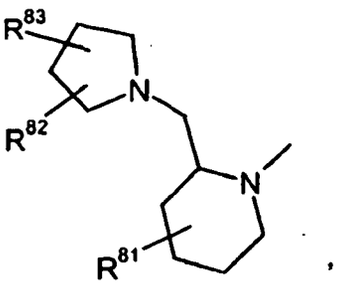

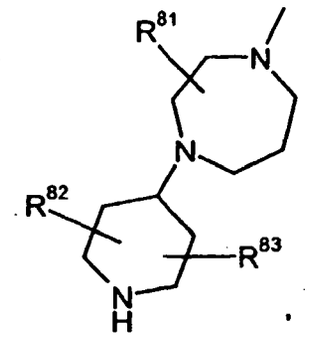

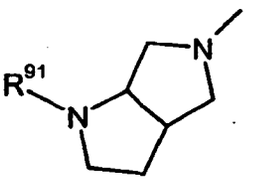

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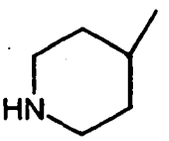


wherein

R^{40}	represents C_{1-6} alkyl having substituent selected from the group consisting of 2-oxo pyrrolidin-1-yl, 2,5-dioxo pyrrolidin-1-yl, 2-oxo-piperidin-1-yl, 2-oxo-piperidin-3-yl, 4-oxo-piperidin-1-yl, 2-oxo-piperidin-6-yl, 2,5-dioxo-piperidin-1-yl, 2,6-dioxo-piperidin-1-yl, and 2,6-dioxo-piperidin-3-yl, piperidin-1-yl, -2-yl, -3-yl or -4-yl (wherein said piperidin is optionally substituted by mono- or di- oxo), hexahydroazepin-1-yl,-2-yl, -3-yl or -4-yl (wherein said hexahydroazepin is optionally substituted by mono- or di- oxo), and 7-oxa-bicyclo[4.1.0]hept-3-yl optionally substituted by amino;
R^{41}	represents hydrogen, cyclopentyl or C_{1-6} alkyl optionally substituted by amino, C_{1-6} alkyl amino, di-(C_{1-6} alkyl)amino, or 2,5- dioxo pyrrolidin-1-yl,
R^{42}	represents C_{1-4} alkylene substituted by carboxy or cyclohexyl substituted by mono- or di- hydroxy,
R^{41} and R^{42}	may form, together with adjacent N atom, a 5 or 6 membered saturated heterocyclic ring; with the proviso that when R^{41} is hydrogen, C_{1-6} alkyl optionally substituted by amino, C_{1-6} alkylamino, or di(C_{1-6} alkyl)amino, R^{42} is hydroxy substituted C_{1-6} alkylene or carboxy substituted C_{1-6} alkylene;
R^{43}	represents hydrogen or C_{1-6} alkyl optionally substituted by hydroxy,

R^{44} represents C_{1-6} alkyl optionally substituted by hydroxy or carboxy,

[0025] With the proviso that when R^{41} and R^{42} form, together with adjacent N atom, a 5 or 6 membered saturated heterocyclic ring, R^{44} is hydroxy substituted C_{1-6} alkyl or carboxy substituted C_{1-6} alkyl;

R^{45}, R^{47}, R^{49} and R^{50} independently represent hydrogen, methyl or ethyl;

R^{46} and R^{48} independently represent C_{1-6} alkylene optionally substituted hydroxy or carboxy;

R^{51} represents hydrogen, cyclopentyl, ethyl or methyl;

R^{52} represents methoxycarbonyl or C_{1-6}alkyl substituted by carboxy, amino, methoxy-carbonyl, methanesulfonylamino, acetamido, indolyl, tetrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, pyrrolidin-1-yl, 2-oxo-pyrrolidin-1-yl, 2,5- dioxo pyrrolidin-1-yl, 2-oxo-piperidin-1-yl, 2-oxo-piperidin-3-yl, 4-oxo-piperidin-1-yl, 2-oxo-piperidin-6-yl, 2,5-dioxo-piperidin-1-yl, 2,6-dioxo-piperidin-1-yl, or 2,6-dioxo-piperidin-3-yl;

R^{61} and R^{62} independently represent benzyl or phenethyl;

R^{72} represents hydrogen, carboxy, C_{1-6} alkanoyl, amino, (C_{1-6}alkyl)amino, di-(C_{1-6}alkyl)amino, N-(C_{1-6}alkyl)amino carbonyl, C_{1-6} alkyl optionally substituted by hydroxy, carboxy, or mono-, di- or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen, pyrrolidinyl or piperidinyl wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;

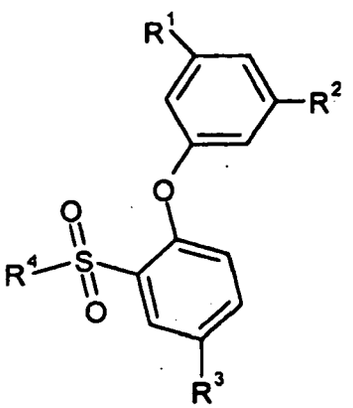
R^{81} represents hydrogen, methoxycarbonyl or C_{1-6} alkyl substituted by 2-oxo-pyrrolidin-1-yl, 2,5-dioxo pyrrolidin-1-yl, 2-oxo-piperidin-1-yl, 2-oxo-piperidin-3-yl, 4-oxo-piperidin-1-yl, 2-oxo-piperidin-6-yl, 2,5-dioxo-piperidin-1-yl, 2,6-dioxo-piperidin-1-yl, or 2,6-dioxo-piperidin-3-yl;

R^{82} represents hydrogen, hydroxy or C_{1-6} alkyl substituted by hydroxy;

R^{83} represents hydrogen, hydroxy or carboxy;
with the proviso that when R^{82} and R^{83} are hydrogen at the same time, R^{81} is other than hydrogen, or when R^{81} and R^{83} are hydrogen at the same time, R^{82} is other than hydrogen;

R^{91} represents benzyl or phenethyl.

[0026] The invention also relates to compounds of formula (I-b)



(I-b)

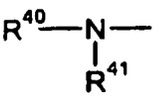
wherein

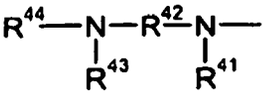
R^1 represent fluoro, chloro, bromo, iodo; or nitro;

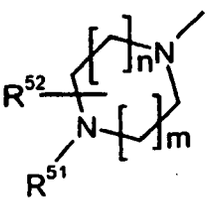
R^2 represents fluoro, chloro, bromo, iodo, or nitro;

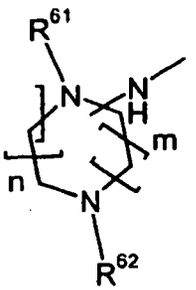
R^3 represents acetyl, cyano, or tetrazolyl;

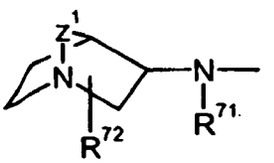
R^4 represents

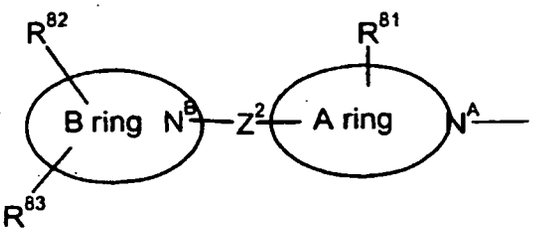


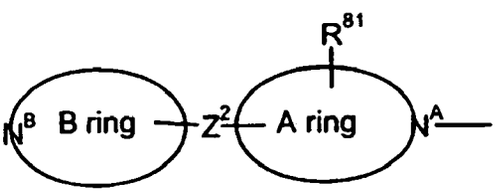


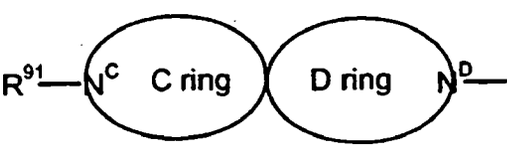












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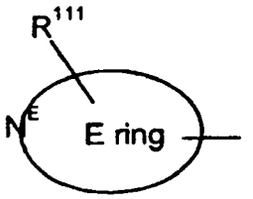


wherein

R^{40}	represents C_{1-6} alkyl substituted by pyrrolidinyl or piperidinyl wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo, 7-oxa-bicyclo[4.1.0]hept-3-yl optionally having 1 or 2 substituents selected from the group consisting of amino, (C_{1-6} alkyl)amino and di(C_{1-6} alkyl)amino, or a 5 to 8 membered saturated heterocyclic ring containing 1 or 2 heteroatoms selected from the group consisting of N and O and optionally having from 1 to 3 substituents selected from the group consisting of hydroxy, amino, oxo and C_{1-6} alkyl;
R^{41}	represents hydrogen, C_{1-6} alkyl optionally substituted by amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, or 2,5- dioxo pyrrolidin-1-yl or a C_{5-8} cycloalkyl optionally substituted by hydroxy,
	or
R^{40} and R^{41}	may form, together with adjacent N atom, a 5 to 8 membered saturated heterocyclic ring optionally interrupted by O;
R^{42}	represents C_{1-6} alkylene optionally substituted by hydroxy or carboxy, or a C_{5-8} cycloalkyl substituted by at least one hydroxy and moreover optionally 1 or 2 substituents selected from the group consisting of hydroxy, amino, oxo and C_{1-6} alkyl,
	or
R^{41} and R^{42}	may form, together with adjacent N atom, a 5 to 8 membered saturated heterocyclic ring optionally interrupted by NH or O, wherein said 5 to 8 membered saturated heterocyclic ring is substituted by mono- or di- oxo;
	with the proviso that when R^{41} is hydrogen, C_{1-6} alkyl optionally substituted by amino, C_{1-6} alkylamino, or di(C_{1-6} alkyl)amino, R^{42} is hydroxy substituted C_{1-6} alkylene or carboxy substituted C_{1-6} alkylene;
R^{43}	represents hydrogen, or C_{1-6} alkyl optionally substituted by hydroxy or carboxy;
R^{44}	represents C_{1-6} alkyl optionally substituted by hydroxy or carboxy,
	with the proviso that when R^{41} and R^{42} form, together with adjacent N atom, 5 to 8 membered saturated heterocyclic ring substituted by mono- or di- oxo, R^{44} represents hydroxy substituted C_{1-6} alkyl or carboxy substituted C_{1-6} alkyl;
R^{45}, R^{47}, R^{49} and R^{50}	independently represent hydrogen or C_{1-6} alkyl;
R^{46} and R^{48}	independently represent C_{1-6} alkylene optionally substituted hydroxy or carboxy;
n	represents an integer selected from 1 to 3;
m	represents an integer selected from 0 to 3;
R^{51}	represents hydrogen, C_{1-6} alkyl, or a 3 to 8 membered saturated ring optionally interrupted by NH or O;
R^{52}	represents hydrogen, C_{1-6} alkoxy carbonyl, or C_{1-6} alkyl substituted by amino, (C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, N-(C_{1-6} alkylsulfonyl)amino, N-(C_{1-6} alkanoyl)-amino, C_{1-6} alkoxycarbonyl, tetrazolyl, triazolyl, indolinyl, isoindolinyl, indolyl, isoindolyl, pyrrolidinyl or piperidinyl wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo,

with the proviso that when R^{51} and R^{52} are hydrogen at the same time, R^3 is tetrazolyl or C_{1-6} alkanoyl, or when R^{51} is hydrogen or C_{1-6} alkyl, R^{52} is other than hydrogen;

R^{61} and R^{62} independently represent hydrogen or C_{1-6} alkyl optionally substituted by hydroxy, carboxy, phenyl or mono-, di- or tri halogen;

R^{71} represents hydrogen, or C_{1-6} alkyl optionally substituted by amino, hydroxy, carboxy, pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;

R^{72} represents hydrogen, carboxy, C_{1-6} alkanoyl, amino, (C_{1-6}alkyl)amino, di-(C_{1-6}alkyl)amino, N-(C_{1-6}alkyl)amino

carbonyl, C_{1-6} alkyl optionally substituted by hydroxy, carboxy, or mono-, di- or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen, pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;

Z^1 represents $-[CH_2]_p-$, wherein p represents an integer 1 or 2;

R^{81} represents hydrogen, C_{1-6} alkoxycarbonyl, or C_{1-6} alkyl substituted by pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;

R^{82} represents hydrogen, hydroxy, carboxy or C_{1-6} alkyl substituted by hydroxy, amino, or carboxy,

R^{83} represents hydrogen, hydroxy, carboxy, or C_{1-6} alkyl substituted by hydroxy, amino, or carboxy,

with the proviso that when R^{81} is hydrogen, R^{82} or R^{83} is other than hydrogen;

Z^2	represents $-[CH_2]_q-$, wherein q represents an integer selected from 0 to 3;
R^{91}	represents hydrogen or C_{1-6} alkyl optionally substituted by phenyl;
R^{111}	represents hydrogen, carboxy, C_{1-6} alkoxy carbonyl, C_{1-6} alkanoyl, N-(C_{1-6} alkyl) aminocarbonyl, C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen, or C_{1-6} alkyl optionally substituted by hydroxy, mono-, di- or tri- halogen, amino, (C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, N-(C_{1-6} alkyl-sulfonyl)amino, N-(C_{1-6} alkanoyl)amino, C_{1-6} alkoxycarbonyl, tetrazolyl, triazolyl, indolinyl, isoindolinyl, indolyl, isoindolyl, pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;
A ring	represents a 3 to 8 membered saturated heterocyclic ring, in which the nitrogen atom N^A is the only hetero atom;
B ring	represents a 3 to 8 membered saturated heterocyclic ring, in which the nitrogen atom N^B is the only hetero atom;
C ring and D ring	together form a 7 to 12 membered diazabicyclic ring; and
E ring	represents a 5 to 8 membered saturated heterocyclic ring, in which the nitrogen atom N^E is the only hetero atom.

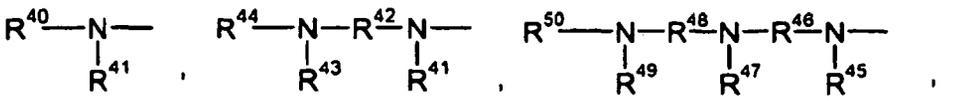
[0027] The invention also relates to compounds of formula (I-b) wherein:

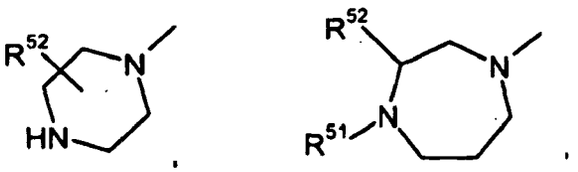
R^1 represents fluoro, chloro or bromo;

R^2 represents fluoro, chloro or bromo;

R^3 represents cyano;

R^4 represents





gegebenenfalls eine oder zwei nicht direkt benachbarte Methylengruppen durch Sauerstoff und/oder Schwefel ersetzt sind,
für jeweils gegebenenfalls einfach bis dreifach durch Halogen, Cyano, Nitro, C_1-C_6-Alkyl, C_1-C_6-Alkoxy,

C_1-C_6-Halogenalkyl, C_1-C_6-Halogenalkoxy, C_1-C_6-Alkylthio, C_1-C_6-Alkylsulfinyl oder C_1-C_6-Alkylsulfonyl substituiertes Phenyl, Phenyl-C_1-C_2-alkyl oder Phenyl-C_2-Alkenyl,
für gegebenenfalls einfach bis zweifach durch Halogen oder C_1-C_6-Alkyl substituiertes 5-oder 6-gliedriges Hetaryl mit ein oder zwei Heteroatomen aus der Reihe Sauerstoff, Schwefel und Stickstoff,

R^2 steht bevorzugt für jeweils gegebenenfalls einfach bis dreifach durch Halogen substituiertes C_1-C_{20}-Alkyl, C_2-C_{20}-Alkenyl, C_1-C_6-Alkoxy-C_2-C_6-alkyl oder Poly-C_1-C_6-alkoxy-C_2-C_6-alkyl,
für gegebenenfalls einfach bis zweifach durch Halogen, C_1-C_6-Alkyl oder C_1-C_6-Alkoxy substituiertes C_3-C_8-Cycloalkyl oder
für jeweils gegebenenfalls einfach bis dreifach durch Halogen, Cyano, Nitro, C_1-C_6-Alkyl, C_1-C_6-Alkoxy, C_1-C_6-Halogenalkyl oder C_1-C_6-Halogenalkoxy substituiertes Phenyl oder Benzyl,

R^3 steht bevorzugt für gegebenenfalls einfach bis mehrfach durch Halogen substituiertes C_1-C_8-Alkyl oder für jeweils gegebenenfalls einfach bis zweifach durch Halogen, C_1-C_6-Alkyl, C_1-C_6-Alkoxy, C_1-C_4-Halogenalkyl, C_1-C_4-Halogenalkoxy, Cyano oder Nitro substituiertes Phenyl oder Benzyl,

R^4 und R^5 stehen unabhängig voneinander bevorzugt für jeweils gegebenenfalls einfach bis dreifach durch Halogen substituiertes C_1-C_8-Alkyl, C_1-C_8-Alkoxy, C_1-C_8-Alkylamino, Di-(C_1-C_8-alkyl)amino, C_1-C_8-Alkylthio oder C_2-C_8-Alkenylthio oder für jeweils gegebenenfalls einfach bis dreifach durch Halogen, Nitro, Cyano, C_1-C_4-Alkoxy, C_1-C_4-Halogenalkoxy, C_1-C_4-Alkylthio, C_1-C_4-Halogenalkylthio, C_1-C_4-Alkyl oder C_1-C_4-Halogenalkyl substituiertes Phenyl, Phenoxy oder Phenylthio,

R^6 und R^7 stehen unabhängig voneinander bevorzugt für Wasserstoff, für jeweils gegebenenfalls einfach bis dreifach durch Halogen substituiertes C_1-C_8-Alkyl, C_3-C_8-Cycloalkyl, C_1-C_8-Alkoxy, C_3-C_8-Alkenyl oder C_1-C_8-Alkoxy-C_2-C_8-alkyl, für jeweils gegebenenfalls einfach bis dreifach durch Halogen, C_1-C_8-Alkyl, C_1-C_8-Halogenalkyl oder C_1-C_8-Alkoxy substituiertes Phenyl oder Benzyl oder zusammen für einen gegebenenfalls einfach bis zweifach durch C_1-C_4-Alkyl substituierten C_3-C_6-Alkylenrest, in welchem gegebenenfalls eine Methylengruppe durch Sauerstoff oder Schwefel ersetzt ist,

R^{13} steht bevorzugt für jeweils gegebenenfalls einfach bis dreifach durch Halogen, substituiertes C_1-C_6-Alkyl, C_3-C_6-Alkenyl, C_3-C_6-Alkinyl oder C_1-C_4-Alkoxy-C_2-C_4-alkyl oder für gegebenenfalls einfach bis zweifach durch Halogen, C_1-C_2-Alkyl oder C_1-C_2-Alkoxy substituiertes C_3-C_6-Cycloalkyl, in welchem gegebenenfalls eine oder zwei nicht direkt benachbarte Methylengruppen durch Sauerstoff ersetzt sind,

$R^{13'}$ steht bevorzugt für Wasserstoff, C_1-C_6-Alkyl oder C_3-C_6-Alkenyl, dann steht

A bevorzugt für Wasserstoff, für jeweils gegebenenfalls einfach bis dreifach durch Halogen substituiertes C_1-C_8-Alkyl, C_2-C_8-Alkenyl, C_1-C_6-Alkoxy-C_1-C_4-alkyl oder C_1-C_6-Alkylthio-C_1-C_4-alkyl, für gegebenenfalls einfach bis dreifach durch Halogen, C_1-C_6-Alkyl oder C_1-C_6-Alkoxy substituiertes C_3-C_8-Cycloalkyl,

B bevorzugt für Wasserstoff, C_1-C_6-Alkyl oder C_1-C_4-Alkoxy-C_1-C_2-alkyl oder

D bevorzugt für Wasserstoff, für jeweils gegebenenfalls einfach bis dreifach durch Halogen substituiertes C_1-C_8-Alkyl, C_1-C_8-Alkenyl, C_1-C_6-Alkoxy-C_2-C_4-alkyl oder C_1-C_6-Alkylthio-C_2-C_4-alkyl, für gegebenenfalls einfach bis dreifach durch Halogen, C_1-C_4-Alkyl, C_1-C_4-Alkoxy oder C_1-C_2-Hatogenalkyl substituiertes C_3-C_8-Cycloalkyl,

A und D gemeinsam bevorzugt für eine C_3-C_6-Alkandiyl- oder C_3-C_6-Alkendiylgruppe, in welchen jeweils gegebenenfalls eine Methylengruppe durch Sauerstoff oder Schwefel ersetzt ist und welche jeweils gegebenenfalls einfach bis zweifach substituiert sind durch Halogen, Hydroxy, C_1-C_4-Alkyl oder C_1-C_4-Alkoxy, oder durch eine weitere, einen ankondensierten Ring bildende C_3-C_6-Alkandiyl-, C_3-C_6-Alkendiyl- oder C_4-C_6-Alkandiendiylgruppe.

[0028] In den als bevorzugt genannten Restedefinitionen steht Halogen für Fluor, Chlor, Brom und Iod, insbesondere für Fluor, Chlor und Brom.

[0029] Wenn

G besonders bevorzugt für Wasserstoff (a) steht, dann steht

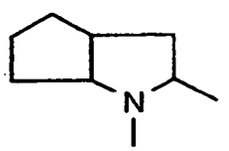
A besonders bevorzugt für Wasserstoff oder C_1-C_6-Alkyl,

B besonders bevorzugt für Wasserstoff oder C_1-C_4-Alkyl,

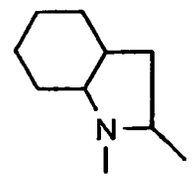
D besonders bevorzugt für jeweils gegebenenfalls einfach bis dreifach durch Fluor oder Chlor substituiertes C_1-C_6-Alkyl, C_3-C_6-Alkenyl, C_1-C_4-Alkoxy- C_2-C_3-alkyl oder C_1-C_4-Alkylthio-C_2-C_3-alkyl, für gegebenenfalls einfach bis zweifach durch Fluor, Chlor, C_1-C_2-Alkyl, C_1-C_2-Alkoxy oder Trifluormethyl substituiertes C_3-C_6-Cycloalkyl,

A und D gemeinsam besonders bevorzugt für eine C_3-C_5-Alkandiylgruppe, worin gegebenenfalls eine Methylengruppe durch Sauerstoff oder Schwefel ersetzt ist und welche gegebenenfalls einfach bis zweifach durch C_1-C_2-Alkyl oder C_1-C_2-Alkoxy substituiert ist,

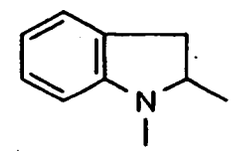
oder A und D stehen gemeinsam mit den Atomen, an die sie gebunden sind, für eine der Gruppen AD-1 bis AD-10



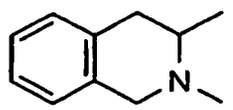
AD-1



AD-2



AD-3



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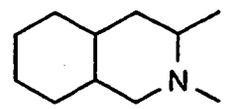
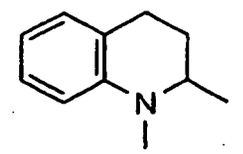
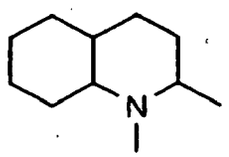


AD-5



AD-6



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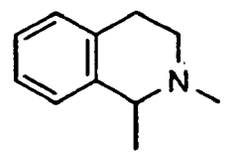

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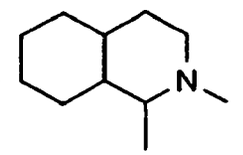

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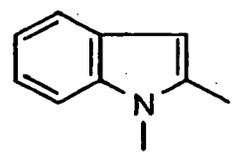


AD-10

und wenn

G besonders bevorzugt für eine der Gruppen

[0030] The present invention also relates to the following compounds:

3-(1-Benzyl-hexahydro-pyrrolo[3,4-b]pyrrole-5-sulfonyl)-4-(3,5-dichloro-phenoxy)-benzonitrile;

N-{4-[5-Cyano-2-(3,5-dichloro-phenoxy)-benzenesulfonyl]-piperazin-2-ylmethyl}-methanesulfonamide;

N-{4-[5-Cyano-2-(3,5-dichloro-phenoxy)-benzenesulfonyl]-piperazin-2-ylmethyl}-acetamide;

N-{1-[5-Cyano-2-(3,5-dichloro-phenoxy)-benzenesulfonyl]-piperazin-2-ylmethyl}-methanesulfonamide;

N-{1-[5-Cyano-2-(3,5-dichloro-phenoxy)-benzenesulfonyl]-piperazin-2-ylmethyl}-acetamide;

4-(3,5-Dichloro-phenoxy)-3-[(3R)-(2-hydroxy-ethylamino)-pyrrolidine-1-sulfonyl]-benzonitrile;

3-(2-Aminomethyl-piperazine-1-sulfonyl)-4-(3,5-dichloro-phenoxy)-benzonitrile dihydrochloride;

1-[5-Cyano-2-(3,5-dichloro-phenoxy)-benzenesulfonyl]-[1,4]diazepane-2-carboxylic acid methyl ester;

4-(3,5-Dichloro-phenoxy)-3-[3(S)-(1H-indol-3-ylmethyl)-piperazine-1-sulfonyl]-benzonitrile;

4-(3,5-Dichloro-phenoxy)-3-[2(S)-(1H-indol-3-ylmethyl)-piperazine-1-sulfonyl]-benzonitrile;

4-{3,5-Dichloro-phenoxy)-3-[2-(2,5-dioxo-pyrrolidin-1-ylmethyl)-piperazine-1-sulfonyl]-benzonitrile;

N-{1-[5-Cyano-2-(3,5-dichloro-phenoxy)-benzenesulfonyl]-[1,4]diazepan-2-ylmethyl}-methanesulfonamide;

1-[4-(3,5-Dichloro-phenoxy)-3-(piperazine-1-sulfonyl)-phenyl]-ethanone;

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)-5-cyano-2-(3,5-dichloro-phenoxy)-benzenesulfonamide;

(S)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)-5-cyano-2-(3,5-dichloro-phenoxy)-benzenesulfonamide;

4-(3,5-Dichloro-phenoxy)-3-{4-[(2S)-(1-hydroxy-1-methyl-ethyl)-pyrrolidin-1-yl]-piperidine-1-sulfonyl}-benzonitrile;

4-(3,5-Dichloro-phenoxy)-3-(3-tetrazol-2-ylmethyl-piperazine-1-sulfonyl)-benzonitrile;

4-(3,5-Dichloro-phenoxy)-3-(3-[1,2,4]triazol-1-ylmethyl-piperazine-1-sulfonyl)-benzonitrile;

4-(3,5-Dichloro-phenoxy)-3-(2-[1,2,4]triazol-1-ylmethyl-piperazine-1-sulfonyl)-benzonitrile;

5-Cyano-2-(3,5-dichloro-phenoxy)-N-(2-dimethylamino-ethyl)-N-[2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl]-benzenesulfonamide;

4-(3,5-Dichloro-phenoxy)-3-[3-(2,5-dioxo-pyrrolidin-1-ylmethyl)-piperazine-1-sulfonyl]-benzonitrile;

4-(3,5-Dichloro-phenoxy)-3-[3-(2,5-dioxo-pyrrolidin-1-ylmethyl)-4-pyrrolidin-1-yl-piperidine-1-sulfonyl]-benzonitrile;

4-(3,5-Dichloro-phenoxy)-3-{4-[(2S)-hydroxymethyl-pyrrolidin-1-yl]-piperidine-1-sulfonyl}-benzonitrile;

4-(3,5-Dichloro-phenoxy)-3-{(2S)-[(2S)-hydroxymethyl-pyrrolidin-1-ylmethyl]-pyrrolidine-1-sulfonyl}-benzonitrile;and

4-(3,5-Dichloro-phenoxy)-3-(piperidine-4-sulfonyl)-benzonitrile,

and their tautomeric and stereoisomeric form, and physiologically acceptable salts thereof.

[0031] Alkyl per se and "alk" and "alkyl" in alkylene, alkenyl, alkynyl, alkoxy, alkanoyl, alkylamino, alkylaminocarbonyl, alkylaminosulphonyl, alkylsulphonylamino, alkoxycarbonyl, alkoxycarbonylamino and alkanoylamino represent a linear or branched alkyl radical having generally 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3 carbon atoms, representing illustratively and preferably methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl.

[0032] Alkoxy illustratively and preferably represents methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

[0033] Alkylamino illustratively and preferably represents an alkylamino radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexyl-amino, N,N-dimethylamino, N,N-diethylamino, N-ethyl-N-methylamino, N-methyl-N-n-propylamino, N-isopropyl-N-n-propylamino, N-t-butyl-N-methylamino, N-ethyl-N-n-pentylamino and N-n-hexyl-N-methylamino.

[0034] Cycloalkyl per se and in cycloalkylamino and in cycloalkylcarbonyl represents a cycloalkyl group having generally 3 to 8 and preferably 5 to 7 carbon atoms, illustratively and preferably representing cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0035] Heterocyclyl per se and in heterocyclic represents a mono- or polycyclic, preferably mono- or bicyclic, nonaromatic heterocyclic radical having generally 4 to 10 and preferably 5 to 8 ring atoms and up to 3 and preferably up to 2 hetero atoms and/or hetero groups selected from the group consisting of N, O, S, SO and SO_2. The heterocyclyl radicals can be saturated or partially unsaturated. Preference is given to 5-to 8-membered monocyclic saturated heterocyclyl radicals having up to two hetero atoms selected from the group consisting of O, N and S.

EMBODIMENT OF THE INVENTION

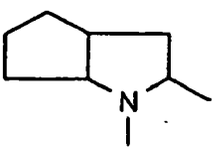
[0036] The compound of the formula (I) of the present invention can be, but not limited to be, prepared by combining various conventional methods. In some embodiments, one or more of the substituents, such as amino group, carboxyl group, and hydroxyl group of the compounds used as starting materials or intermediates are advantageously protected by a protecting group known to those skilled in the art. Examples of the protecting groups are described in "Protective Groups in Organic Synthesis (3rd Edition)" by Greene and Wuts.

[0037] The compound represented by the general formula (I-i), (I-ii) and (I-iii) can be, but not limited to be, prepared by using the Method [A], [B] and [C] below respectively.

[0038] Wenn

G	ganz besonders bevorzugt für Wasserstoff (a) steht, dann steht
A	ganz besonders bevorzugt für Wasserstoff, Methyl oder Ethyl,
B	ganz besonders bevorzugt für Wasserstoff,
D	ganz besonders bevorzugt für Methyl, Ethyl, n-Propyl, iso-Propyl, n-Butyl, sek-Butyl, iso-Butyl, Cyclopropyl, Cyclopentyl oder Cyclohexyl,
A und D	gemeinsam ganz besonders bevorzugt für eine C_3-C_4-Alkandiylgruppe, worin jeweils gegebenenfalls eine Methylengruppe durch Sauerstoff oder Schwefel ersetzt ist und welche gegebenenfalls einfach bis zweifach durch Methyl substituiert ist

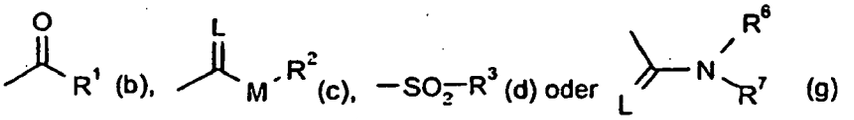
oder A und D gemeinsam mit den Atomen, an die sie gebunden sind, für die folgende Gruppe:



AD-1

und wenn

G ganz besonders bevorzugt für eine der Gruppen



steht, in welchen
L für Sauerstoff steht und
M für Sauerstoff oder Schwefel steht,

R^1 steht ganz besonders bevorzugt für jeweils gegebenenfalls einfach bis dreifach durch Fluor oder Chlor substituiertes C_1-C_6-Alkyl, C_2-C_6-Alkenyl, C_1-C_2-Alkoxy-C_1-C_2-alkyl, C_1-C_2-Alkylthio-C_1-C_2-alkyl oder Poly-C_1-C_2-alkoxy-C_1-C_2-alkyl oder für jeweils gegebenenfalls einfach durch Fluor, Chlor, Methyl, Ethyl oder Methoxy substituiertes Cyclopropyl, Cyclopentyl oder Cyclohexyl,
für gegebenenfalls einfach durch Fluor, Chlor, Brom, Cyano, Nitro, Methyl, Ethyl, n-Propyl, i-Propyl, Methoxy, Ethoxy, Methylthio, Ethylthio, Methylsulfinyl, Ethylsulfinyl, Methylsulfonyl, Ethylsulfonyl, Trifluormethyl oder Trifluormethoxy substituiertes Phenyl,
für jeweils gegebenenfalls einfach durch Chlor, Brom oder Methyl substituiertes Furanyl, Thienyl oder Pyridyl,

R^2 steht ganz besonders bevorzugt für C_1-C_8-Alkyl, C_2-C_6-Alkenyl oder C_1-C_3-Alkoxy-C_2-C_3-alkyl, Cyclopentyl oder Cyclohexyl,
oder für jeweils gegebenenfalls einfach durch Fluor, Chlor, Brom, Cyano, Nitro, Methyl, Methoxy, Trifluormethyl oder Trifluormethoxy substituiertes Phenyl oder Benzyl,

R^3 steht ganz besonders bevorzugt für gegebenenfalls einfach bis dreifach durch Fluor oder Chlor substituiertes C_1-C_4-Alkyl oder für jeweils gegebenenfalls einfach durch Fluor, Chlor, Brom, C_1-C_4-Alkyl, C_1-C_4-Alkoxy, Trifluormethyl, Trifluormethoxy, Cyano oder Nitro substituiertes Phenyl oder Benzyl,

R^6 steht ganz besonders bevorzugt für Wasserstoff, für C_1-C_4-Alkyl, C_3-C_6-Cycloalkyl oder Allyl, für jeweils gegebenenfalls einfach durch Fluor, Chlor, Brom, Methyl, Methoxy oder Trifluormethyl substituiertes Phenyl,

R^7 steht ganz besonders bevorzugt für Methyl, Ethyl, n-Propyl, iso-Propyl oder Allyl,

R^6 und R^7 stehen gemeinsam ganz besonders bevorzugt für einen C_5-C_6-Alkylenrest, in welchem gegebenenfalls eine Methylengruppe durch Sauerstoff ersetzt ist, dann steht

A ganz besonders bevorzugt für Wasserstoff, Methyl, Ethyl, n-Propyl, iso-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, Trifluormethyl, Cyclopropyl, Cyclopentyl oder Cyclohexyl,

B ganz besonders bevorzugt für Wasserstoff, Methyl oder Ethyl,

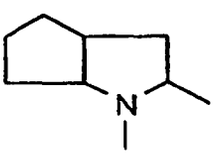
D ganz besonders bevorzugt für Wasserstoff oder

D auch ganz besonders bevorzugt für Methyl, Ethyl, n-Propyl, iso-Propyl, n-Butyl, sek.-Butyl, iso-Butyl, Cyclopropyl, Cyclopentyl oder Cyclohexyl, mit der Maßgabe, dass dann

A nur für Wasserstoff, Methyl oder Ethyl steht,

A und D gemeinsam ganz besonders bevorzugt für eine C_3-C_4-Alkandiylgruppe, worin jeweils gegebenenfalls eine Methylengruppe durch Sauerstoff oder Schwefel ersetzt ist und welche gegebenenfalls einfach bis zweifach durch Methyl substituiert ist oder

A und D gemeinsam mit den Atomen, an die sie gebunden sind, für die folgende Gruppe:



AD-1

[0039] Wenn

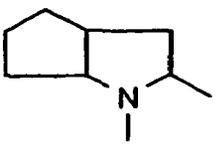
G hervorgehoben für Wasserstoff (a) steht, dann steht

A hervorgehoben für Wasserstoff, Methyl oder Ethyl,

B hervorgehoben für Wasserstoff,

D hervorgehoben für Methyl, Ethyl oder Cyclopropyl, Cyclopentyl,

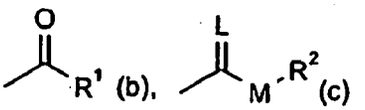
A und D gemeinsam hervorsehoben mit den Atomen, an die sie gebunden sind, für die folgende Gruppe:



AD-1

und wenn

G hervorgehoben für eine der Gruppen



oder $-SO_2-R^3$ (d) steht,
in welchen
L für Sauerstoff steht und
M für Sauerstoff steht,

R^1 steht hervorgehoben für C_1-C_6-Alkyl oder C_1-C_2-Alkoxy-C_1-C_2-alkyl,

R^2 steht hervorgehoben für C_1-C_8-Alkyl,

R^3 steht hervorgehoben für C_1-C_4-Alkyl, dann steht

A hervorgehoben für Wasserstoff, Methyl, Ethyl, n-Propyl, iso-Propyl oder iso-Butyl,

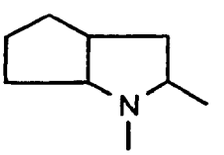
B hervorgehoben für Wasserstoff, Methyl oder Ethyl,

D hervorgehoben für Wasserstoff, oder

D auch hervorgehoben für Methyl, Ethyl oder Cyclopropyl, mit der Maßgabe, dass dann

A nur für Wasserstoff, Methyl oder Ethyl steht,

A und D gemeinsam hervorgehoben mit den Atomen, an die sie gebunden sind, für die folgende Gruppe steht:



AD-1

[0040] Die oben aufgeführten allgemeinen oder in Vorzugsbereichen aufgeführten Restedefinitionen bzw. Erläuter-

ungen können untereinander, also auch zwischen den jeweiligen Bereichen und Vorzugsbereichen beliebig kombiniert werden. Sie gelten für die Endprodukte sowie für die Vor- und Zwischenprodukte entsprechend.

[0041] Erfindungsgemäß bevorzugt werden die Verbindungen der Formel (I), in welchen eine Kombination der vorstehend als bevorzugt (vorzugsweise) aufgeführten Bedeutungen vorliegt.

[0042] Erfindungsgemäß besonders bevorzugt werden die Verbindungen der Formel (I), in welchen eine Kombination der vorstehend als besonders bevorzugt aufgeführten Bedeutungen vorliegt.

[0043] Erfindungsgemäß ganz besonders bevorzugt werden die Verbindungen der Fermel (I), in welchen eine Kombination der vorstehend als ganz besonders bevorzugt aufgeführten Bedeutungen vorliegt.

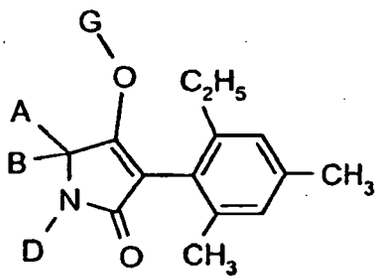
[0044] Erfindungsgemäß hervorgehoben werden die Verbindungen der Formel (I), in welchen eine Kombination der vorstehend als hervorgehoben aufgeführten Bedeutungen vorliegt.

[0045] Gesättigte oder ungesättigte Kohlenwasserstoffreste wie Alkyl, Alkandiyl oder Alkenyl können, auch in Verbindung mit Heteroatomen, wie z.B. in Alkoxy, soweit möglich, jeweils geradkettig oder verzweigt sein.

[0046] Gegebenenfalls substituierte Reste können einfach oder mehrfach substituiert sein, wobei bei Mehrfachsubstitutionen die Substituenten gleich oder verschieden sein können.

[0047] Im Einzelnen seien außer den bei den Herstellungsbeispielen genannten Verbindungen die folgenden Verbindungen der Formel (I-b) und (I-c) genannt:

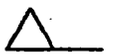
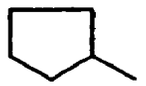
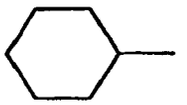
Tabelle 1

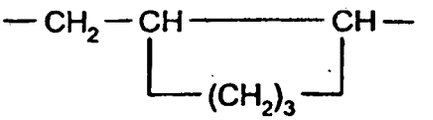


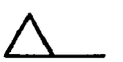
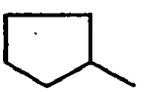
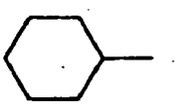
G=t-C_4H_9-CH_2-S-CO

A	B	D
CH_3	H	H
C_2H_5	H	H
C_3H_7	H	H
i-C_3H_7	H	H
C_4H_9	H	H
i-C_4H_9	H	H
s-C_4H_9	H	H
t-C_4H_9	H	H
CH_3	CH_3	H
C_2H_5	CH_3	H
C_3H_7	CH_3	H
i-C_3H_7	CH_3	H
C_4H_9	CH_3	H
i-C_4H_9	CH_3	H
s-C_4H_9	CH_3	H
t-C_4H_9	CH_3	H
C_2H_5	C_2H_5	H

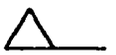
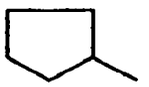
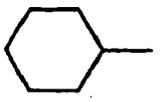
(continued)

A	B	D
	CH_3	H
	CH_3	H
	CH_3	H

A	D	B
$-(CH_2)_3-$		H
$-(CH_2)_4-$		H
$-CH_2-CHCH_3-CH_2-$		H
$-CH_2-CH_2-CHCH_3-$		H
$-CH_2-CHCH_3-CHCH_3-$		H
$-CH_2-S-(CH_2)_2-$		H
		H
H	CH_3	H
H	C_2H_5	H
H	C_3H_7	H

A	D	B
H	$i\text{-}C_3H_7$	H
H		H
H		H
H		H
CH_3	CH_3	H
CH_3	C_2H_5	H
CH_3	C_3H_7	H
CH_3	$i\text{-}C_3H_7$	H

(continued)

A	B	D
CH_3		H
CH_3		H
CH_3		H
C_2H_5	CH_3	H
C_2H_5	C_2H_5	H
A, B und D wie in Tabelle 1		

[0048] Typical salts of the compound shown by the formula (I) include salts prepared by reaction of the compounds of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively.

[0049] Acids to form acid addition salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

[0050] Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tris(hydroxymethyl)aminomethane, and the like. Examples of inorganic bases include, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

[0051] The compounds described herein or a salts thereof, depending on its substituents, may be modified to form lower alkylesters or known other esters; and/or hydrates or other solvates. Those esters, hydrates, and solvates are included in the description.

[0052] The compound of the present invention may be administered in oral forms, such as, without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions. They may also be administered in parenteral forms, such as, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, and the like forms, well-known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well known to those of ordinary skilled in the art.

[0053] The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including, without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

[0054] The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

[0055] Yet another embodiment of the present invention is pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations of the invention are prepared by combining a therapeutically effective amount of the compounds of the invention together with one or more pharmaceutically acceptable excipients therefore. In making the compositions of the present invention, the active ingredient may be mixed with a diluent, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper, or other container. The carrier may serve as a diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle,

or can be in the form of tablets, pills powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

[0056] For oral administration, the active ingredient may be combined with an oral, and non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, sodium carbonate, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, methyl cellulose, and the like; together with, optionally, disintegrating agents, such as, without limitation, maize, starch, methyl cellulose, agar bentonite, xanthan gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, acacia, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

[0057] In powder forms, the carrier may be a finely divided solid which is in admixture with the finely divided active ingredient. The active ingredient may be mixed with a carrier having binding properties in suitable proportions and compacted in the shape and size desired to produce tablets. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel composition of the present invention. Suitable solid carriers are magnesium carboxymethyl cellulose, low melting waxes, and cocoa butter.

[0058] Sterile liquid formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

[0059] The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in suitable oil.

[0060] The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

[0061] Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01mg /kg/day to about 100 mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10 mg/kg/day. In the case of parenteral administration, it has generally proven advantageous to administer quantities of about 0.001 to 100 mg /kg/day, preferably from 0.01 mg/kg/day to 1 mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

EXAMPLES

[0062] Some of the examples below disclose subject matter falling outside the scope of the claims and are disclosed herein as reference examples. For example, Examples 1-2 to 1-10, 1-12, 1-15 to 1-17, 1-19 to 1-31, 1-36, 1-37, 1-39 to 1-43, 1-47 and 2-1 are reference

examples.

[0063] The present invention will be described in detail below in the form of examples, but they should by no means be construed as defining the metes and bounds of the present invention.

[0064] In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight.
^{1}H NMR spectra were recorded using either Bruker DRX-300 (300MHz for ^{1}H) spectrometer in $CDCl_3$. Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard at zero ppm. Coupling constant (J) are given in hertz and the abbreviations s, d, t, q, m, and br refer to singlet, doublet, triplet, quartet,multiplet, and broad, respectively. Mass spectroscopy data were recorded on a FINNIGAN MAT 95. TLC was performed on a precoated silica gel plate (Merck silica gel 60 F-254). Silica gel (WAKO-gel C-200 (75-150 μm))was used for all column chromatography separations. Z in the table 1 represents decomposition.

[0065] All chemicals were reagent grade and were purchased from Sigma-Aldrich, Wako pure chemical industries, Ltd., Tokyo kasei kogyo Co., Ltd., Nacalai tesque, Inc., Watanabe Chemical Ind. Ltd., Maybridge plc, Lancaster Synthesis Ltd., Merck KgaA, Kanto Chemical Co.,Ltd.

[0066] The effects of the present compounds were examined by the following assays and pharmacological tests.

[Determination of IC50 values of compounds in receptor binding assay]

(1) cell

[0067] Human CCR3-transformed K562 cells were used. The cloned CCR3 cDNA was constructed with pcDNA3 vector and transfected into a K562 cell line. The human CCR3-transformed K562 cells were maintained in RPMI-1640 (Cat.#22400-089, Life Technologies) supplemented with 10% FCS (Cat.#A-1115-L, Hyclone), 55 μM 2-mercaptoethanol (Cat.#21985-023, Life Technologies), 1 mM sodium pyruvate (Cat.#11360-070, Life Technologies), 100 units/ml of penicillin G and 100 μg/ml of streptomycin (Cat.# 15140-122, Life Technologies), and 0.4 mg/ml of Geneticin (Cat.#10131-035, Life Technologies)(hereinafter called "culture medium"). Before the receptor binding assay, cells were pretreated with 5 mM sodium butyrate (Cat.#193-01522, Wako)-containing the culture medium (2 x 10^5 cells/ml) for 20-24 hours to increase the expression of CCR3.

(2) Receptor binding assay

[0068] Butyrate-pretreated cells, suspended in binding buffer (25 mM HEPES pH 7.6, 1 mM $CaCl_2$, 5 mM $MgCl_2$, 0.5% BSA, 0.1% NaN_3) at a cell density of 2 x 10^6 cells/ml, were added into 60 μl/well in the 96-well round bottom polypropylene plate (Cat.#3365, Costar). Compounds, diluted with the binding buffer (4-times higher concentration of the final concentration), were added into 30 μl/well in the polypropylene plate. [^{125}I]-labeled human eotaxin (Cat.#IM290, Amersham Pharmacia Biotech), diluted with the binding buffer at the concentration of 0.4 nM (final concentration; 0.1 nM), was added into 30 μl/well in the polypropylene plate. Total 120 μl/well of binding reaction mixture (60 μl/well of cell suspension, 30 μl/well of compound solution, and 30 μl/well of [^{125}I]-labeled eotaxin) were incubated in the polypropylene plate for 1 hour at room temperature after the incubation, 100 μl/well of the reaction mixture was transferred to a filtration plate (Cat.#MAFB-N0B, Millipore), and washed with the washing buffer (25 mM HEPES pH 7.6, 1 mM $CaCl_2$, 5 mM $MgCl_2$, 0.5% BSA, 0.1% NaN_3, 0.5 M NaCl) twice. The 96-well filtration plate was pretreated with 100 μl/well of 0.5% polyethylenimine (Cat.#P-3143, Sigma) for 2-4 hours at room temperature and washed with the washing buffer twice before use. The non-specific binding was determined by parallel incubation in the presence of 500 nM of non-labeled eotaxin (Cat.#23209, Genzyme Techne). The radioactivities remained on the filter were measured by liquid scintillation counter (TopCount™, Packard) after an addition of 45 μl/well of scintillant (Microscint20, Cat.#6013621, Packard). The inhibition percent at each concentration of compound was calculated, and IC50 values were determined from the inhibition curve.

[Determination of IC50 values of compounds in calcium mobilization assay]

(1) cell

[0069] Human CCR3-transformed K562 cells were used. The human CCR3-transformed K562 cells were maintained in RPMI-1640 supplemented with 10% FCS, 55 μM 2-mercaptoethanol (Cat.#21985-023, Life Technologies), 1 mM sodium pyruvate, 100 units/ml of penicillin G and 100 μg/ml of streptomycin, and 0.4 mg/ml of Geneticin. Before the calcium mobilization assay, cells were pretreated with 5 mM sodium butyrate -containing the culture medium (2 x 10^5 cells/ml) for 20-24 hours to increase the expression of CCR3.

(2) Calcium mobilization assay

[0070] Butyrate-pretreated cells were loaded with Fluo-3AM (Cat.#F-1242, Molecular Probes) in loading buffer (Hanks' solution Cat.#05906 Nissui, 20 mM HEPES pH 7.6, 0.1% BSA, 1 mM probenecid Cat.#P-8761 Sigma, 1 μM Fluo-3AM, 0.01% pluronic F-127 Cat.#P-6866 Molecular Probes) at a cell density of 1 x 10^7 cells /ml. Then, cells were washed with calcium assay buffer (Hanks' solution Cat.#05906 Nissui, 20 mM HEPES pH 7.6, 0.1% BSA, 1 mM Probenecid Cat.#P-8761 Sigma). The cell suspension (3.3 x 10^6 cells/ml) was added into 60 μl/well in the 96-well clear bottom black plate (Cat.#3904, Costar). Compounds, diluted (5-times concentration of the final concentration) with the calcium assay buffer, were added into 20 μl/well in the plate 10 minutes before assay. Human recombinant eotaxin, diluted with the calcium assay buffer at the concentration of 50 nM (final concentration;10nM), was added into in a polypropylene plate (Cat.#3365, Costar). Mobilization of cytoplasmic calcium was measured by FDSS-6000 or FDSS-3000(Hamamatsu Photonics) over 60 sec after the stimulation with 10 nM eotaxin. The inhibition percent at the each concentration of compound was calculated, and IC50 values were determined from the inhibition curve.

[Determination of IC50 values of compounds in chemotaxis assay]

(1) cell

[0071] Human CCR3-transformed L1.2 cells were used. Human CCR3-expressing L1.2 stable transformant was established by electroporation, referring to the methods described in J. Exp. Med. 183:2437-2448, 1996. The human CCR3-transformed L1.2 cells were maintained in RPMI-1640 supplemented with 10% FCS, 100 units/ml of penicillin G and 100 μg/ml of streptomycin, and 0.4 mg/ml of Geneticin. One day before the chemotaxis assay, cells were pretreated with 5 mM sodium butyrate -containing culture medium (5 x 10^5 cells/ml) for 20-24 hours to increase the expression of CCR3.

(2) Chemotaxis assay

[0072] Butyrate-pretreated cells were suspended in chemotaxis buffer (Hanks' solution Cat.#05906 Nissui, 20 mM HEPES pH 7.6, 0.1% human serum albumin Cat.#A-1887 Sigma) at a cell density of 1.1 x 10^7 cells /ml. A mixture of 90 μl of cell suspension and 10 μl of compound solution diluted with chemotaxis buffer (10-times concentration of the final concentration) were preincubated for 10 minutes at 37˚C. The mixture of cells and compounds was added into the upper chamber of the 24-well chemotaxis chamber (Transwell™, Cat.#3421, Costar, pore size;5 μm). 0.5 ml of 10 nM of human recombinant eotaxin(Cat.#23209, Genzyme Techne) solution, diluted with chemotaxis buffer, was added into the lower chamber of the chemotaxis plate. Then, chemotaxis was performed in CO_2 incubator at 37˚C for 4 hours. After 4hrs incubation, migrated cells were counted using FACScan (Becton Dickinson). The inhibition percent at the each concentration of compound was calculated, and IC50 values were determined from the inhibition curve.

[Selectivity test]

[0073] Selectivity test was done in calcium mobilization assay and in receptor binding assay by using CCR1, CCR2, CCR4, CCR5, CCR7, CCR8, CXCR1 and PAR-1 (peptidase activate receptor) stable transformants. Methods for the test are the same as that of CCR3. Only the difference is that different stable transformants were used for these selectivity tests.

[Determination of IC50 values of compounds in chemotaxis assay with the use of human eosinophils]

[0074] Human eosinophils were purified from peripheral blood. Twenty five ml of heparinized blood was layered on 15 ml of Mono-Poly Resolving Medium (#16-980-49DN, ICN Biomedicals Co. Ltd, Japan) in 50 ml tube (#2335-050, Iwaki, Japan) gently and then centrifuged at 400G, for 20 min, at room temperature. After centrifugation, red blood cells were removed by hypotonic lysis. The polymorphonuclear leukocyte pellet was incubated with anti-human CD16 Microbeads (#130-045-701, Milteynyi Biotec GmbH, Germany) for 30 min at 4˚C. After washing the cells, magnetically labeled neutrophils were then depleted by applying the cell suspension to BS columns (#130-041-304, Milteynyi Biotec GmbH, Germany) attached to VarioMACS (#130-090-282, Milteynyi Biotec GmbH, Germany).

[0075] Chemotaxis assay with the use of the obtained eosinophils was done by the same protocols as that using CCR3 stable transformants, L1.2 cells.

[Primate Chronic Asthma Model: Protocol]

[0076] *Materials and Methods:* The animals used in this study were wild caught, adult male cynomolgus monkeys (*Macaca fascicularis*) weighing 4.0 to 9.0 kg (Charles River BRF, Inc.). All animals studied demonstrated a naturally occurring respiratory sensitivity to inhaled *Ascaris suum* extract. Animals were housed individually in environmentally controlled rooms in open mesh cages and provided food twice daily and water *ad libitum*. Each animal was fasted for approximately 12 hours prior to the day of study. For each study the animals were anesthetized with ketamine hydrochloride (7 mg/kg, i.m.; Ketaset, Fort Dodge, IA) and xylazine (1.2 mg/kg, i.m.; Bayer Corp., Elkart, IN), incubated with a cuffed endotracheal tube (5.0 mm ID; Mallinckrodt Critical Care, Glen Falls, NY) and seated in a specially designed support chair. Ketamine (5 mg/kg, i.m.) was used to supplement anesthesia as needed.

[0077] *Study Protocol:* Airway responsiveness (AR) to inhaled methachroline followed by bronchoalveolar lavage (BAL) to assess airway cellular composition (ACC) were determined 3 days before (day 0) and 3 days after (day 10) three alternate-day (days 3,5,7) inhalations of *Ascgris suum* extract. Animals were rested 6 to 8 weeks between studies to allow airway responsiveness and inflammation to return to baseline (pre-antigen) levels. Treatment studies were bracketed by vehicle control studies to assure that no changes in sensitivity to antigen occurred over time.

[0078] The test compounds dissolved in Ethanol:PEG400:Water (10:50:40 v/v) were administered under light anes-

thetisia.

[0079] *Aerosol Delivery System and Inhalation Challenges:* Aerosol inhalation challenges were administered by intermittent positive pressure breathing with a Bird Mark 7A respirator and micronebulizer (model 8158). Each challenge consisted of 30 breaths (maximum inspiratory pressure=20 cmH_2O). *Ascaris suum* extract (Greer Laboratories, Lenoir, NC) was diluted with PBS to a final threshold concentration previously determined for each animal and administered as an aerosol (particle size <2μm). Methacholine (Sigma Chemical Co, St. Louis, Missouri) was dissolved in PBS at a concentration of 100 mg/ml and serial dilutions of 30, 10, 3, 1, 0.3 and 0.1 mg/ml were subsequently prepared for nebulization.

[0080] *Measurement of Respiratory System Resistance (Rrs):* The animal was connected to a Harvard Ventilator (Harvard Apparatus, S. Natick, MA) via the endotracheal tube and ventilated at a rate between 30-35 breaths per minute. Airflow was measured by a Fleisch (Hans Rudolph) pneumotachograph and thoracic pressure was measured by a validyne pressure transducer (as the difference between the pressure at the distal end of the endotracheal tube and room pressure). The pneumotachograph and validyne were connected to a pre-amplifier and then into an MI^2 respiratory analyzer (Malvern, PA). Using the primary signals of flow and pressure the analyzer computed airway resistance and compliance (as well as a number of other respiratory parameters).

[0081] *Methacholine Dose Response Determinations:* To assess airway responsiveness to inhaled methacholine, cumulative dose response curves were constructed by administering increasing concentrations of methacholine until increases in Rrs of between 100 and 200% were obtained. A vehicle control challenge was performed prior to the first dose of methacholine. Changes in Rrs were measured continuously over a 10 minute period post aerosol challenge. Aerosol challenges were separated by 5 to 10 minutes or until Rrs returned to baseline values.

[0082] *Determination of PC_{100} Values:* The resistance obtained with PBS was set as zero. The percentage increase in resistance above zero at each dose of methacholine was entered into the computer and the program used an algorithm to determine the exact methacholine concentration which caused an increase in resistance of 100% above baseline (PC_{100}). Differences (day 10-day 0) in PC_{100} values were calculated as logs (base 10) to normalize the data and account for the large variation in absolute values for the PC_{100} between animals.

[0083] *Bronchoalveolar Lavage:* Following methacholine dose response determinations each monkey was placed in the supine position and a fiberoptic bronchoscope (Olympus Optical, model 3C-10, Lake Success, NY) was guided past the carina and wedged into a fifth to seventh generation bronchus. A total of 15 ml of bicarbonate buffered saline (pH 7.4) was infused and gently aspirated through a channel in the bronchoscope. Collected samples were immediately centrifuged at 2000 rpm for 10 minutes at 4˚C. The resulting pellets were resuspended in Ca++ and Mg++ free Hank's balanced salt solution. To avoid possible effects of the BAL procedure on lung cellular composition, BAL was performed on alternating right and left lungs. Total white cells per milliliter of BAL fluid was obtained using a Coulter counter (Coulter Corp., Miami, FL). BAL cell composition was determined by counting a minimum of 200 cells from a Wright's stained cytospin slide preparation.

[0084] *Blood Samples:* Blood samples were collected prior to and 30minutes, 1hr and 2hr after the first dose of the test compounds (morning of day 2), immediately before each subsequent dose, and 30 minutes, 1hr and 2hr after the final dose (evening of day 9). Blood was collected from the femoral vein into EDTA, centrifuged at 1500 rpm for 15minutes at 4˚C and the plasma stored at -70˚C until assayed for the test compounds.

[0085] *Statistical Analysis:* All data were evaluated statistically with the use of students t-test where a p value <0.05 was considered statistically significant.

[0086] Results of receptor binding assay (RBA), Ca^{2+} mobilization assay (Ca^{2+}) are shown in Examples and tables of the Examples below. The data corresponds to the compounds as yielded by solid phase synthesis and thus to levels of purity of about 40 to 90%. For practical reasons, the compounds are grouped in three classes of activity as follows:

$$IC_{50} = A \ \ 100nM < B \ \ 500\ nM < C$$

The compounds of the present invention also show more than 100-fold selectivity against CCR1, CCR5, CCR7, CCR8 and CXCR1 in receptor binding assays.

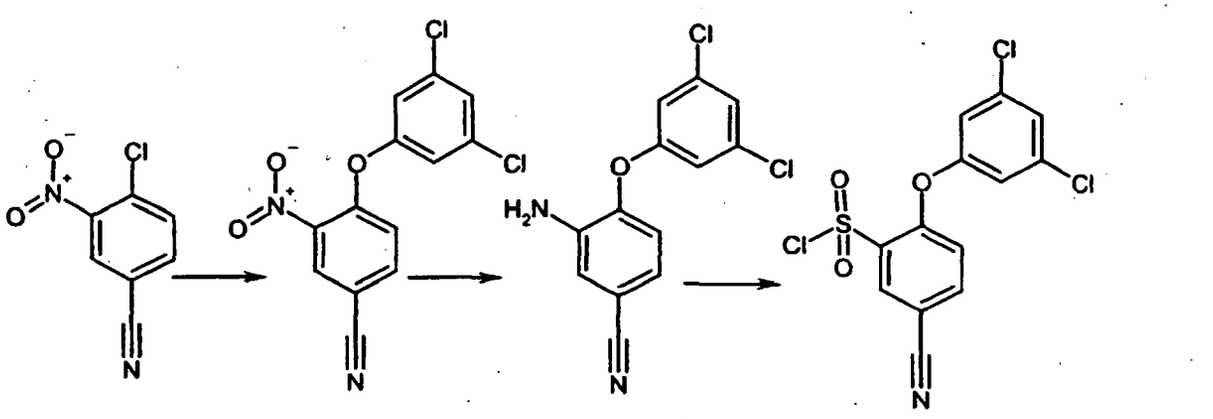
[0087] The compounds of the present invention show dose-dependent inhibitory effect on eotaxin-induced chemotaxis of human eosinophils and strong activity in vivo assays.

Procedure for starting compound

[Starting compound A]

5-cyano-2-(3,5-dichlorophenoxy)phenylsulfonylchloride

[0088]



(1) To a mixture of 4-chloro-3-nitro-benzonitrile (24.0 g, 131 mmol) and 3,5-dichloro-phenol (32.0 g, 197 mmol) in dry THF (150 ml) was added NaH (6.84 g, 171 mmol) in portions and the mixture was refluxed for 1 hour. After cooled to room temperature, the solvent was evaporated, and 100 ml of ice water and 20 ml of 4N NaOH aq. were added to the residue. The precipitate was collected by filtration, washed with 0.5 N NaOH aq. and water, dried in vacuo to give the 5-cyano-2-(3,5-dichlorophenoxy)nitrobenzene (40.0 g, 98.4%) as slight yellow solid.

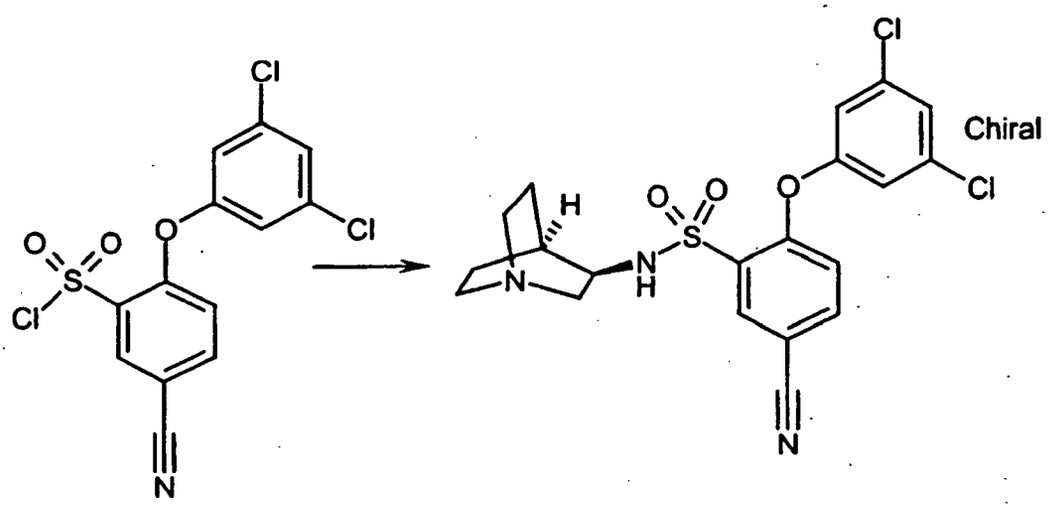
(2) The mixture of 5-cyano-2-(3,5-dichlorophenoxy) nitrobenzene (4.08 g, 13.20 mmol) and Tin(II) chloride dihydrate (17.87 g, 79.20 mmol) in EtOAc (200 mL) was heated to reflux for 2 hours. After cooled to room temperature, the reaction mixture was poured into sat. $NaHCO_3$ aq.. The mixture was extracted with EtOAc. The extract was washed with brine, and dried over $MgSO_4$. The solvent was evaporated in vacuo to give 5-cyano-2-(3,5-dichlorophenoxy)aniline (3.53 g, 95.8 %).

(3) 5-cyano-2-(3,5-dichlorophenoxy)aniline (3.53 g, 12.65 mmol) was dissolved in the mixture of conc. HCl aq. (6.33 ml) and HOAc (2.53 ml). The solution was cooled to 0˚C and sodium nitrite (0.96 g, 13.9 mmol) in water (1.27 ml) was added dropwise with stirring. After 30 minutes, the reaction mixture was added dropwise to the suspended mixture of CuCl (0.63 g, 6.32 mmol) in saturated solution of SO_2 in HOAc (25.3 ml) at 5˚C. The reaction mixture was stirred for 30 minutes at 10˚C, and poured into water. The resulting mixture was extracted with EtOAc. The extract was washed with sat. $NaHCO_3$ aq., brine, and dried over $MgSO_4$. The solvent was evaporated in vacuo to give 5-cyano-2-(3,5-dichlorophenoxy) phenylsulfonylchloride as a brown powder (4.45 g, 97%): HPLC-MS (ESI): Calcd for $C_{13}H_6Cl_3NO_3S$ $[M+H]^+$ 362, found: 362.

Example 1-1

***N*-(R)(+)-(1-aza-bicyclo[2.2.2]oct-3-yl)-5-cyano-2-(3,5-dichloro-phenoxy)-benzenesulfonamide**

[0089]



[0090] To a suspension of (R)-(+)-3-aminoquinuclidine 2HCl (2.87 g, 14.4 mmol) in dry CH_2Cl_2(25 ml) was added Et_3N (5.88 ml, 42.0 mmol). The mixture was stirred for 2 hours at room temperature followed by the addition of the solution of 5-cyano-2-(3,5-dichlorophenoxy)phenylsulfonylchloride (90%, 4.83 g, 12 mmol) in dry CH_2Cl_2 (10 ml) dropwise. After stirred for 5 hours at room temperature, CH_2Cl_2 (160 mL) was added and the mixture was washed with water, sat. Na_2CO_3 aq., brine and dried over $MgSO_4$. The solvent was evaporated, and the product was recrystallized from the mixture of EtOAc and hexane to give *N*-(R)-(+)-(1-aza-bicyclo[2.2.2]oct-3-yl)-5-cyano-2-(3,5-dichloro-phenoxy)-benzenesulfonamide (4.30g, 79.2%) as white solid.

[0091] ^{1}H NMR(300 MHz, CDCl3): 1.46-1.59 (2H,m), 1.68-1.72 (1H, m), 1.86-1.88 (2H,m), 2.69-2.99(6H, m), 3.20-3.28 (1H,m), 3.46-3.51(1H, m), 7.00 (1H, d, J = 8.67 Hz), 7.04 (2H, s), 7.32 (1H, t, J = 1.7 Hz), 7.79 (1H, dd, J = 8.64, 2.07 Hz),8.31 (1H,d, J = 2.07 Hz); HPLC-MS (ESI): Calcd for $C_{20}H_{19}C_{12}N_3O_3S$ $[M+H]^+$ 452, found: 452.

Molecular weight: 452.36

Melting point: 215-220˚C (decomp.)

Activity grade CCR3: A

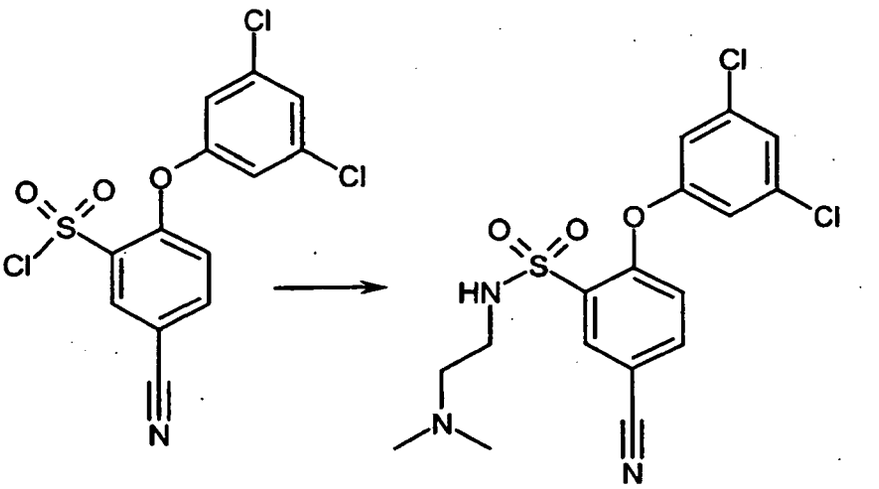
Activity grade IC_{50}: A

Example 1-2

5-cyano-2{3,5-dichloro-phenoxy)-*N*-(2-dimethylamino-ethyl)-*N*-[2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl]-benzenesulfonamide

(1) 5-cyano-2-(3,5-dichloro-phenoxy)-*N*-(2-dimethylamino-ethyl)-benzenesulfonamide

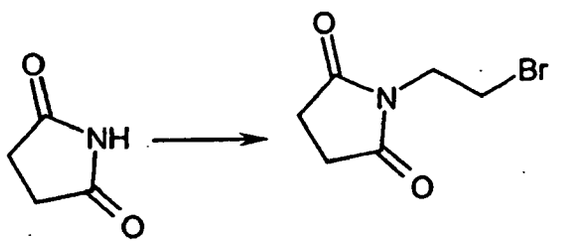
[0092]



[0093] To a solution of N^1, N^1-dimethyl-ethane-1, 2-diamine (74.0 mg, 0.84 mmol) and Et_3N in dry CH_2Cl_2 (3 ml) was added the solution of 5-cyano-2-(3,5-dichlorophenoxy)phenylsulfonylchloride (90%, 282 mg, 0.7 mmol) in dry CH_2Cl_2 (6 ml) dropwise. The resulting solution was stirred at room temperature for 1 hour. CH_2Cl_2 (60 ml) was added and the mixture was washed with water, brine, and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by column chromatography (CH_2Cl_2/CH_3OH = 10:1) to give 5-cyano-2-(3,5-dichloro-phenoxy)-*N*-(2-dimethylamino-ethyl)-benzenesulfonamide as white solid (220 mg, 75.9%): HPLC-MS (ESI): Calcd for $C_{19}H_{21}Cl_2N_3O_4S$ $[M + H]^+$ 414, Found: 414

(2) 1-(2-bromo-ethyl)-pyrrolidine-2, 5-dione

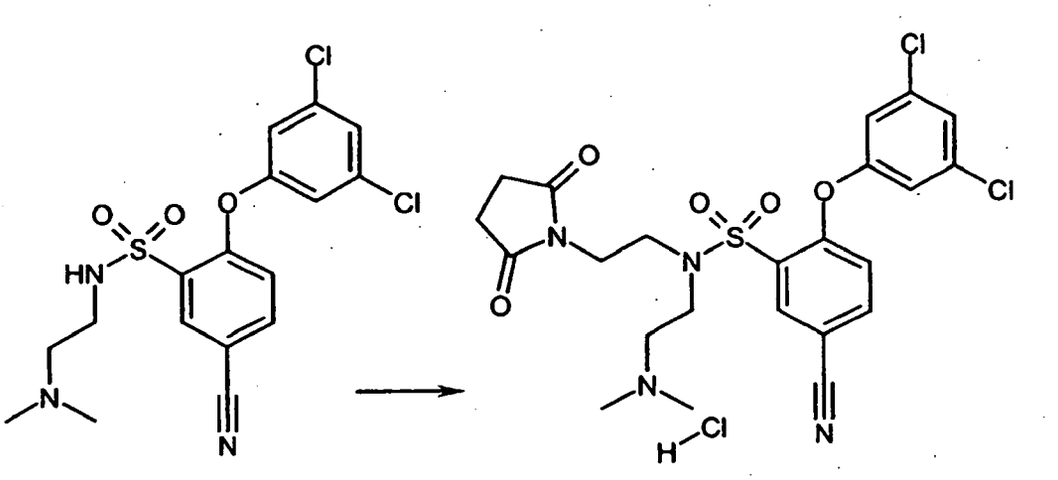
[0094]



[0095] To a mixture of dihydro-furan-2, 5-dione (396 mg, 4.00 mmol) and 1,2-dibromo-ethane (1.50 g, 8.00 mmol) in CH_3CN (20 ml) was added K_2CO_3 (829 mg, 6.00 mmol) at room temperature. The mixture was stirred at reflux overnight and the solvent was evaporated. The mixture was diluted with EtOAc (150 mL), washed with water, sat. Na_2CO_3aq., brine, and dried over $MgSO_4$. The solvent was evaporated to give 1-(2-bromo-ethyl)-pyrrolidine-2, 5-dione that was used for next step without further purification (580 mg, 70.4%).

(3)5-cyano-2-(3,5-dichloro-phenoxy)-*N*-(2-dimethylamino-ethyl)-*N*-[2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl]-benzenesulfonamide

[0096]



[0097] To a solution of 5-cyano-2-(3,5-dichloro-phenoxy)-*N*-(2-dimethylamino-ethyl)-benzene-sulfonamide (41.4 mg, 0.1 mmol) in dry DMF (2 ml) was added 1-(2-bromo-ethyl)-pyrrolidine-2, 5-dione (30.9 mg, 0.15 mmol) and NaH (60%, 6.00 mg, 0.15 mmol). The mixture was stirred for 8 hours at 90°C. After cooled to room temperature, the solvent was evaporated. The mixture was diluted with EtOAc (60 ml), washed with brine,and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by preparative TLC (CH_2Cl_2/CH_3OH = 20/1) to give 5-cyano-2- (3,5-dichloro-phenoxy)- *N*-(2-dimethylaminoethyl)- *N*-[2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl]-benzenesulfonamide (44 mg, 81.6%) and the free base was converted into HCl salt by 4N HCl in dioxane.
^{1}H NMR(300 MHz, CDCl3): δ 2.76 (4H,s), 2.85 (6H, s), 3.56 (4H,br,s), 3.74-3.80(2H, m), 3.94 (2H,br,s), 7.01 (1H, d, J = 8.64 Hz), 7.09 (2H, s), 7.33 (1H, s), 7.81 (1H, d, J = 8.64 Hz),8.21 (1H,s); HPLC-MS (ESI): Calcd for $C_{23}H_{24}Cl_2N_4O_5S.HCl$ $[M+H]^+$ 539, found: 539.

Molecular weight: 575.90

Melting point:

Activity grade CCR3: A

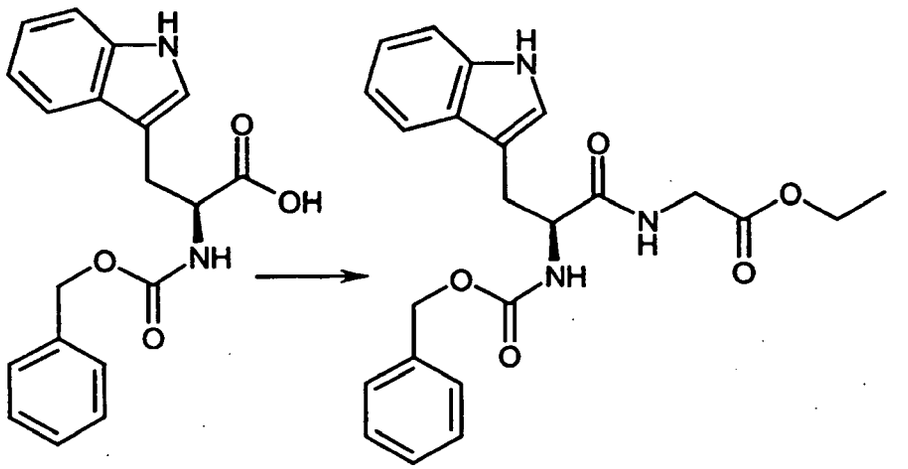
Activity grade IC_{50}: A

Example 1-3

4-(3,5-dichloro-phenoxy)-3-[(3*S*)-(1*H*-indol-3-ylmethyl)-piperazine-1-sulfonyl]-benzonitrile

(1) [(2*S*)-benzyloxycarbonylamino-3-(1*H*-indol-3-yl)-propionylamino]-acetic acid ethyl ester

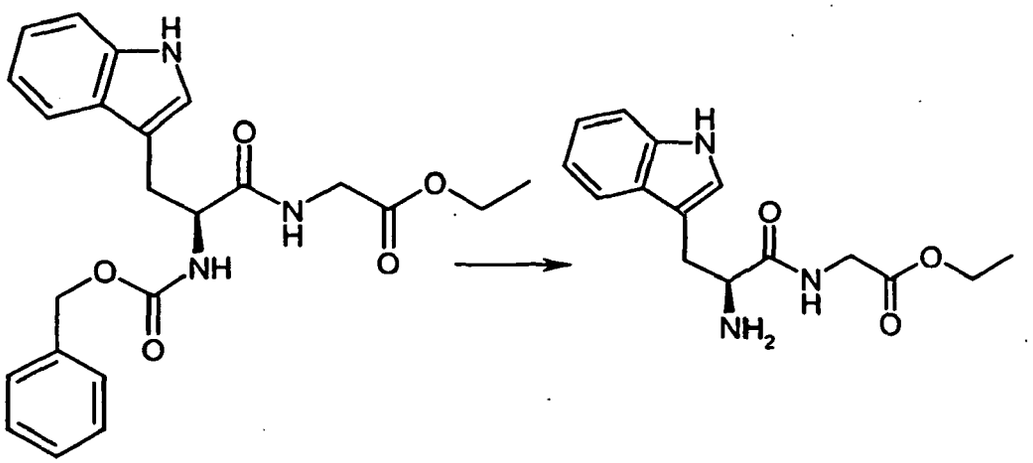
[0098]



[0099] To a mixture of (2*S*)-benzyloxycarbonylamino-3-(1*H*-indol-3-yl)-propionic acid (4.16 g, 12.3 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrogen chloride (2.83 g, 14.8 mmol), 1-hydroxybenzotriazole (1.99 g, 14.8 mmol) and Et_3N (5.14 ml, 36.9 mmol) in dry THF (20 ml) was added amino-acetic acid ethyl ester hydrogen chloride (1.72 g, 12.3 mmol) portionwise. The reaction mixture was stirred for 3 days at room temperature. The organic solvent was evaporated in vacuo, and the residue was diluted with EtOAc. The organic layer was washed with 0.5N HCl, saturated $NaHCO_3$aq., brine, and dried over $MgSO_4$. The organic layer was concentrated to give [(2*S*)-benzyloxycarbonylamino-3-(1*H*-indol-3-yl)-propionylamino]-acetic acid ethyl ester (5.10 g, 97.9%) as yellow sticky oil: HPLC-MS (ESI): Calcd for $C_{23}H_{25}N_3O_5[M+H]^+$ 424, found: 424.

(2) [(2*S*)-amino-3-(1*H*-indol-3-yl)-propionylamino]-acetic acid ethyl ester

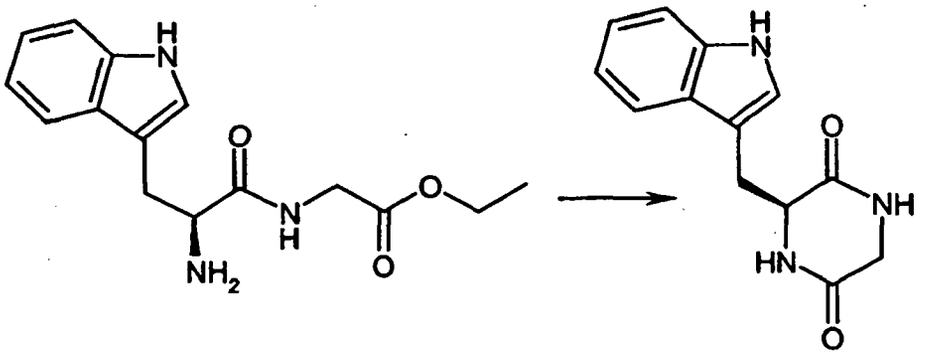
[0100]



[0101] To a suspension of 10% Pd/C (0.50 g) in dry MeOH (70 ml) was added a solution of [(2*S*)-benzyloxycarbonylamino-3-(1*H*-indol-3-yl)-propionylamino]-acetic acid ethyl ester (5.10 g, 17.6 mmol) in dry MeOH (30 ml). The reaction mixture was stirred under 1 atm of H_2 in hydrogenator for 1 day at room temperature. After removing all article with celite pad, the filtrate was concentrated in vacuo to give [(2*S*)-amino-3-(1*H*-indol-3-yl)-propionylamino]-acetic acid ethyl ester (3.26 g, 91.6%) as an oil: HPLC-MS (ESI): Calcd for $C_{15}H_{19}N_3O_3[M+H]^+$ 290, found: 290.

(3) (3*S*)-(1*H*-indol-3-ylmethyl)-piperazine-2,5-dione

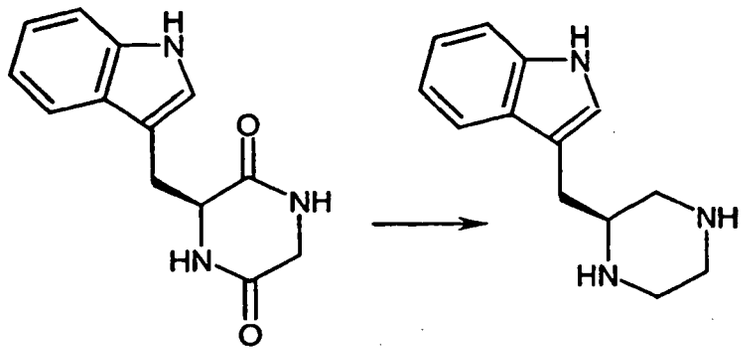
[0102]



[0103] The solution of [(2*S*)-amino-3-(1*H*-indol-3-yl)-propionylamino]-acetic acid ethyl ester (3.25 g, 11.2 mmol) and Et_3N in dry MeOH was heated to reflux overnight. The resulting white precipitate was collected and dried to give (3*S*)-(1*H*-indol-3-ylmethyl)-piperazine-2,5-dione (1.80 g, 65.9%): HPLC-MS (ESI): Calcd for $C_{13}H_{13}N_3O_2[M+H]^+$ 244, found: 244.

(4) 3-(piperazin-(2*S*)-ylmethyl)-1*H*-indole

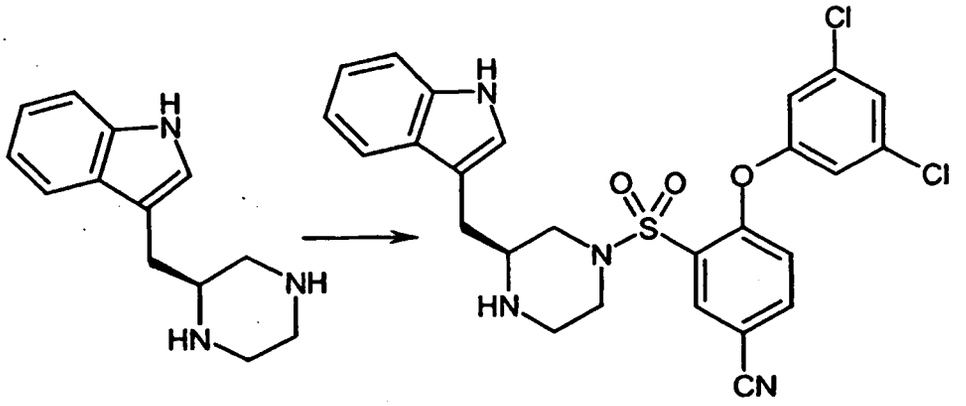
[0104]



[0105] To a suspension of lithium aluminum hydride (0.19 g, 5.08 mmol) in dry THF (10 ml) was added the solution (3*S*)-(1*H*-indol-3-ylmethyl)-piperazine-2,5-dione (0.30 g, 1.23 mmol) in THF (10 ml) dropwise. The reaction mixture was stirred at 75°C overnight, cooled to room temperature. 0.19 ml of water, 0.19 mL of 4N NaOH aq., and 0.58 ml of water were successively added to the mixture at 0°C. The resulting white precipitate was filtered off with celite pad, and the filtrate was concentrated in vacuo to give 3-(piperazin-(2*S*)-ylmethyl)-1*H*-indole (0.26 g, quant.) as a yellow oil: HPLC-MS (ESI): Calcd for $C_{13}H_{17}N_3[M+H]^+$ 216, found: 216.

(5) 4-(3,5-dichloro-phenoxy)-3[(3*S*)-(1*H*-indol-3-ylmethyl)-piperazine-1-sulfonyl]-benzonitrile

[0106]



[0107] To a solution of 3-(piperazin-(2*S*)-ylmethyl)-1*H*-indole (33.0 mg, 0.15 mmol) and di-isopropyl-ethyl amine (0.08 mL, 0.46 mmol) in dry THF (2 mL) was added 5-cyano-2-(3,5-dichloro-phenoxy)-benzene-sulfonyl chloride (50.0 mg, 0.14 mmol) in portions. The reaction mixture was stirred for 2 hours at room temperature. The solvent was evaporated in vacuo. The residue was purified by preparative TLC (CH_2Cl_2/MeOH=10/1) twice to give 4-(3,5-dichloro-phenoxy)-3-[(3*S*)-(1*H*-indol-3-ylmethyl)-piperazine-1-sulfonyl]-benzonitrile (6.20 mg, 7.5%) as a white solid.

[0108] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56-3.07 (7H, m), 3.71-3.75 (1H, d, *J* = 10.9 Hz), 3.83-3.86 (1H, d, *J* = 11.1 Hz), 6.98 (2H, d, *J* = 1.7 Hz), 7.04-7.05 (1H, d, *J* = 2.3 Hz), 7.10-7.15 (1H, t, *J* = 7.0 Hz), 7.20-7.25 (1H, t, *J* = 7.0 Hz), 7.28-7.29 (1H, t, *J* = 1.9 Hz), 7.37-7.40 (1H, d, *J* = 7.9 Hz), 7.55-7.58 (1H, d, *J* = 7.5 Hz), 7.75-7.78 (1H, dd, *J* = 2.1, 8.7 Hz), 8.09 (1H, br), 8.28-8.29 (1H, d, *J* = 2.1 Hz); HPLC-MS (ESI): Calcd for $C_{26}H_{22}C_{12}N_4O_3S[M+H]^+$ 541, found: 541.

Molecular weight: 541.46

Melting point: 128-129˚C

Activity grade CCR3: A

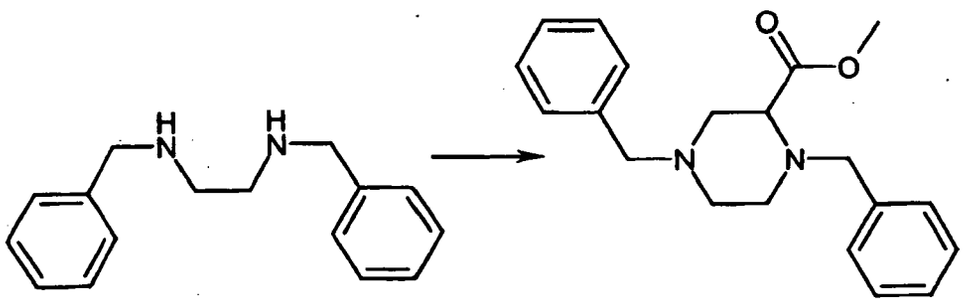
Activity grade IC_{50}: A

Example 1-4

4-(3,5-dichlorophenoxy)-3-{[2-(1H-1,2,4-triazol-1-ylmethyl)-1-piperazinyl]sulfonyl}benzonitrile hydrochloride

(1) 1,4-dibenzyl-piperazine-2-carboxylic acid methyl ester

[0109]

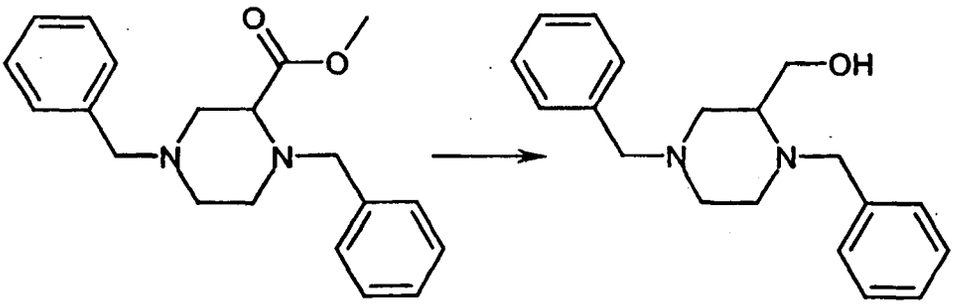


[0110] To the preheated solution (50˚C) of 2,3-dibromo-propionic acid methyl ester in toluene (40 ml) and Et_3N (5.80 ml, 41.6 mmol), was added *N,N'*-dibenzyl-ethane-1,2-diamine (4.90 ml, 20.8 mmol) dropwise. Resulting white slurry was heated to reflux to a clear solution and the solution was stirred at reflux overnight. After cooled to room temperature, the reaction mixture was extracted with 2N HCl (ca.500 ml) and the extract was neutralized with 4N NaOH. The aqueous

layer was extracted with EtOAc three times. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give 1,4-dibenzyl-piperazine-2-carboxylic acid methyl ester (5.73 g, 84.8%) as a colorless oil: HPLC-MS (ESI): Calcd for $C_{20}H_{24}N_2O_2[M+H]^+$ 325, found: 325.

(2) (1,4-dibenzyl-piperazin-2-yl)-methanol

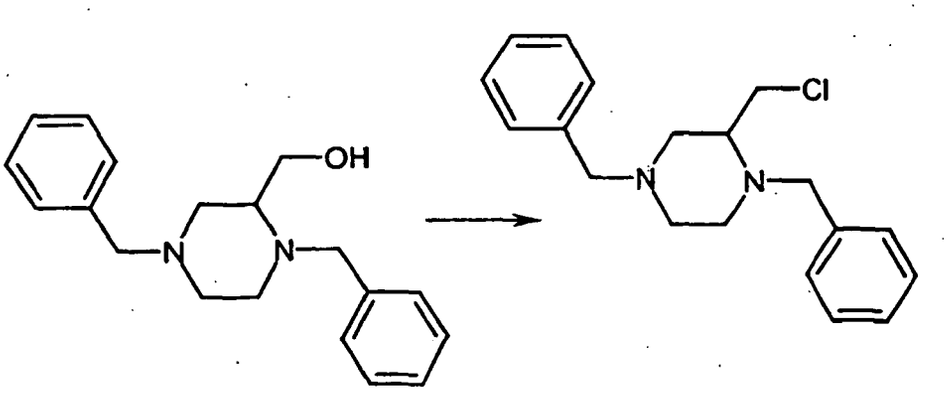
[0111]



[0112] To the suspension of lithium aluminum hydride (1.54 g, 40.6 mmol) was added 1,4-dibenzyl-piperazine-2-carboxylic acid methyl ester (3.00 g, 9.25 mmol) portionwise at room temperature. The reaction mixture was stirred at reflux for 3 hours. After cooled to 0˚C, 1.5 ml of water, 1.5 ml of 4N NaOH aq., and 4.5 ml of water was added successively. The mixture was stirred for 1 hour, and the white precipitate was filtered off with celite pad. The filtrate was concentrated in vacuo to give (1,4-dibenzyl-piperazin-2-yl)-methanol (2.74 g, quant.) as a yellow oil: HPLC-MS (ESI): Calcd for $C_{19}H_{24}N_2O[M+H]^+$ 297, found: 297.

(3) 1,4-dibenzyl-2-chloromethyl-piperazine

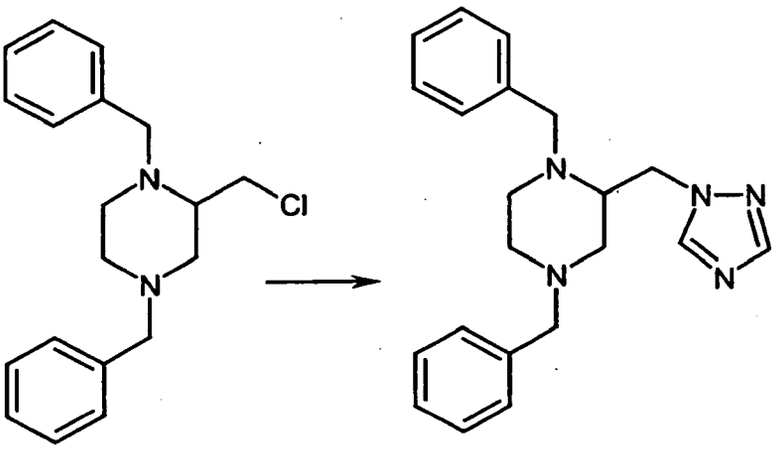
[0113]



[0114] To the solution of thionyl chloride (1.63 ml, 22.4 mmol) in CCl_4 (30 ml) was added the solution of (1,4-dibenzyl-piperazin-2-yl)-methanol (2.74 g, 9.25 mmol) in CCl_4 dropwise in 10 minutes. The produced suspension was stirred for 2 hours at 77˚C. After cooled to room temperature, 20 ml of ice water was added and the aqueous layer was separated from the organic solvent. The PH of aqueous layer was adjusted to 12 with 4N NaOH aq., and extracted with $CHCl_3$ three times. The combined organic layer was dried over $MgSO_4$, and concentrated to give brownish oil which was purified by column chromatpgraphy on silica gel (CH_2Cl_2/MeOH=30/1) to give 1,4-dibenzyl-2-chloromethyl-piperazine in crude form (3.08 g, 95%, ca. 90% purity from HPLC analysis). The compound was used for next reaction without further purification: HPLC-MS (ESI): Calcd for $C_{19}H_{23}ClN_2[M+H]^+$ 315, found: 315.

(4) 1,4-dibenzyl-2-(1H-1,2,4-triazol-1-ylmethyl)piperazine

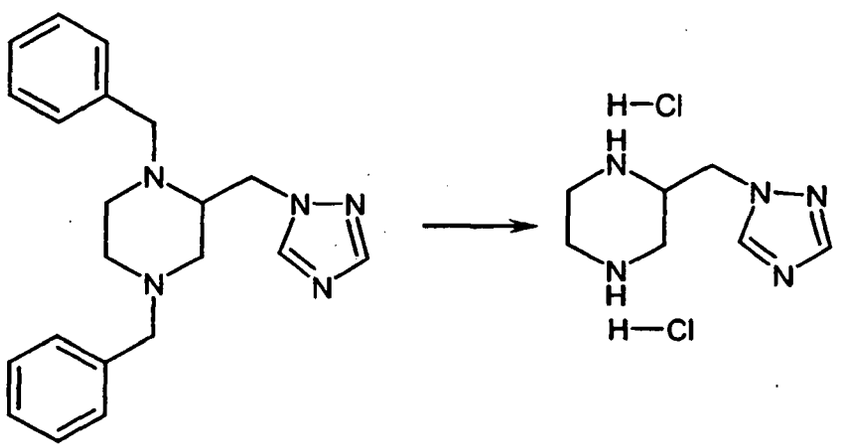
[0115]



[0116] To a solution of 1,2,4-triazole (48.3 mg, 0.70 mmol) in DMF (2 ml) was added NaH (18.3 mg, 0.76 mmol). After 10 minutes stirring, 1,4-dibenzyl-2-(chloromethyl)piperazine (200 mg, 0.64 mmol) and KI (156 mg, 0.70 mmol) were added to the mixture. The mixture was stirred at 60˚C overnight. The mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by column chromatography on NH-silica gel (Hex/AcOEt =1/4) to give 1,4-dibenzyl-2-(1H-1,2,4-triazol-1-ylmethyl)piperazine (220.0 mg, 99.7%): HPLC-MS (ESI): Calcd for $C_{21}H_{25}N_5$ $[M+H]^+$ 348, found: 348.

(5) 2-(1H-1,2,4-triazol-1-ylmethyl)piperazine dihydrochloride

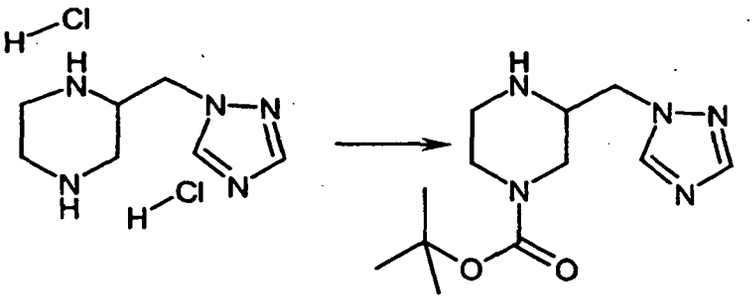
[0117]



[0118] To a solution of 1,4-dibenzyl-2-(1H-1,2,4-triazol-1-ylmethyl)piperazine (206 mg, 0.59 mmol) in MeOH (3.0 ml) was added a few drops of 4N HCl in 1,4-dioxane and 20% wet $Pd(OH)_2$ (100 mg). The mixture was stirred overnight under H_2 atomosphere with a balloon. The catalyst was filtered off through Celite pad and the filtrate was concentrated in vacuo to give 2-(1H-1,2,4-triazol-1-ylmethyl)piperazine dihydrochloride (122.9 mg, 86.3 %): HPLC-MS(ESI): Calcd for $C_7H_{13}N_5$ $[M+H]^+$ 168, found: 168.

(6) *tert*-butyl 3-(1H-1,2,4-triazol-1-ylmethyl)-1-piperazinecarboxylate

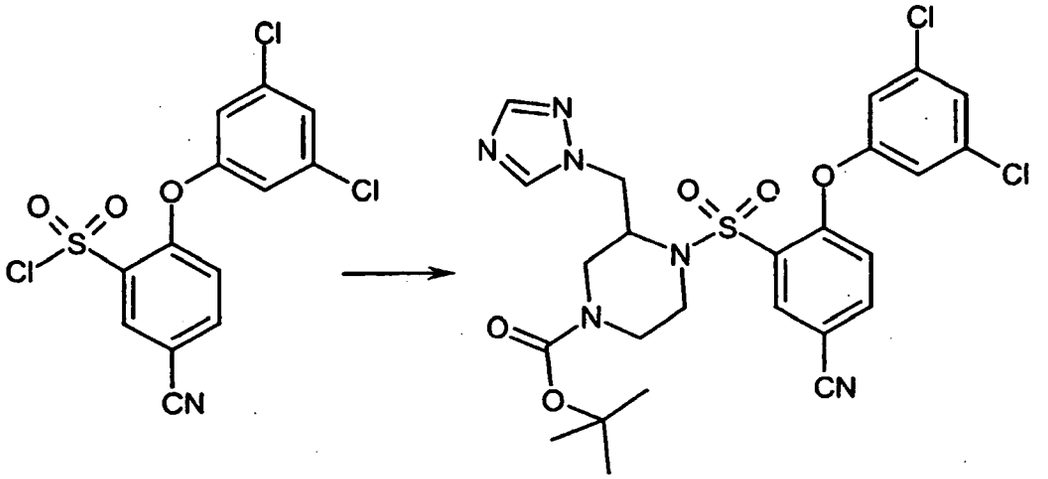
[0119]



[0120] To a suspention of 2-(1H-1,2,4-triazol-1-ylmethyl)piperazine dihydrochloride (104 mg, 0.39 mmol) and Et_3N (157.7 mg, 1.56 mmol) in CH_2Cl_2 (3 ml) was added [{[(*tert*-butoxycarbonyl) oxy]amino}(cyano)methyl]benzene (106.5 mg, 0.43 mmol). The mixture was stirred for 2 hours at room temperature. The solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (MeOH/$CHCl_3$ = 1/50 - 1/10) to give *tert*-butyl 3-(1H-1,2,4-triazol-1-ylmethyl)-1-piperazinecarboxylate (50.9 mg, 48.9%): HPLC-MS (ESI): Calcd for $C_{11}H_{20}N_6O_2$ $[M+H]^+$ 268, found: 268.

(7) *tert*-butyl 4-{[5-cyano-2-(3,5-dichlorophenoxy) phenyl]sulfonyl}-3-(1H-1,2,4-triazol-1-ylmethyl)-1-piperazinecarboxylate

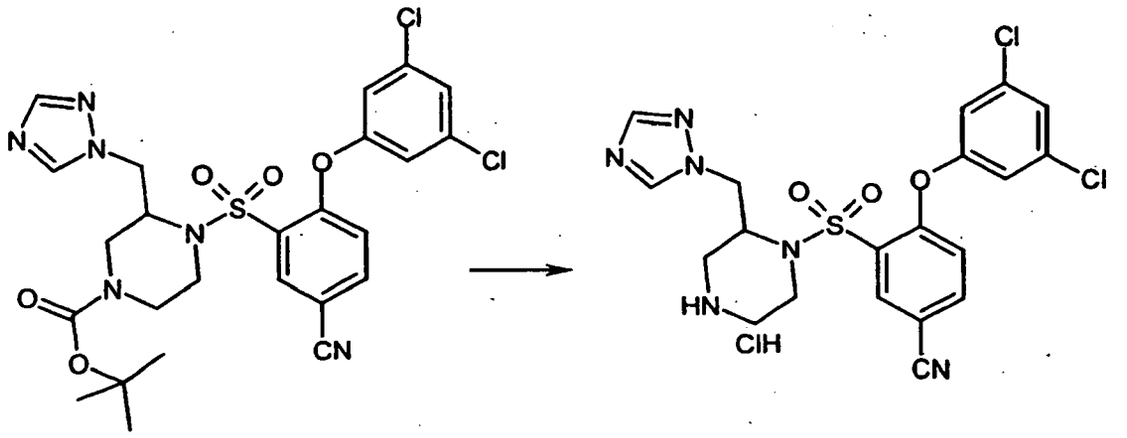
[0121]



[0122] To a solution of *tert*-butyl 3-(1H-1,2,4-triazol-1-ylmethyl)-1-piperazinecarboxylate (29.5 mg, 0.11 mmol) and di-isopropyl-ethyl amine (28.5 mg, 0.22 mmol) in THF (2 ml) was added 5-cyano-2-(3,5-dichlorophenoxy)benzenesulfonyl chloride (40.0 mg, 0.11 mmol). The mixture was stirred at 50˚C overnight. The solvent was removed and the residue was diluted with $CHCl_3$, washed with sat. $NaHCO_3$ aq. and brine. The organic layer was dried over $MgSO_4$. The solvent was evaporated in vacuo, and the resulting residue was purified by prep. TLC (MeOH/CHCl3 = 1/10) to give *tert*-butyl 4-{[5-cyano-2-(3,5-dichlorophenoxy)phenyl]sulfonyl}-3-(1H-1,2,4-triazol-1-yl methyl)-1-piperazinecarboxylate (42.5 mg, 64.9 %): HPLC-MS (ESI): Calcd for $C_{25}H_{26}Cl_2N_6O_5S$ $[M+H]^+$ 593, found:593.

(8) 4-(3,5-dichlorophenoxy)-3-{[2-(1H-1,2,4-triazol-1-ylmethyl)-1-piperazinyl]-sulfonyl}benzonitrile hydrochloride

[0123]



[0124] To a solution of *tert*-butyl 4-{[5-cyano-2-(3,5-dichlorophenoxy) phenyl]sulfonyl}-3-(1H-1,2,4-triazol-1-ylmethyl)-1-piperazinecarboxylate (37 mg, 0.06 mmol) in CH_2Cl_2 (1 ml) was added 4N HCl in 1,4-dioxane (1 ml). The mixture was stirred for 2 hours at room temperature. The solvent was evaporated in vacuo, the residue was triturated with Et_2O and the white solid was collected by filtration to give 4-(3,5-dichlorophenoxy)-3-{[2-(1H-1,2,4-triazol-1-ylmethyl)-1-piperazinyl]sulfonyl}benzonitrile hydrochloride (28.5 mg, 86.3 %).

[0125] ^{1}H NMR(500 MHz, DMSO-*d*6): 2.30-3.37 (1H,m), 3.71 (1H, t, J = 12.9 Hz), 4.01 (2H, d, J = 14.2 Hz), 4.56 (1H, dd, J = 14.2, 5.4 Hz), 4.60-4.63 (1H, m), 4.82 (1H, dd, J = 13.9, 9.5 Hz), 7.21 (1H, d, J = 8.5 Hz), 7.40 (2H, d, J = 1.6 Hz), 7.59 (1H, t, J = 3.5, 1.6 Hz), 7.68 (1H, s), 8.05 (1H, d, J =2.2 Hz), 8.07 (1H, s), 8.59 (1H, s), 9.51 (1H, br, s), 9.58 (1H, br, s); HPLC-MS (ESI): Calcd for $C_{25}H_{26}Cl_2N_6O_5S$ $[M+H]^+$ 494, found: 494.

Molecular weight: 529.84

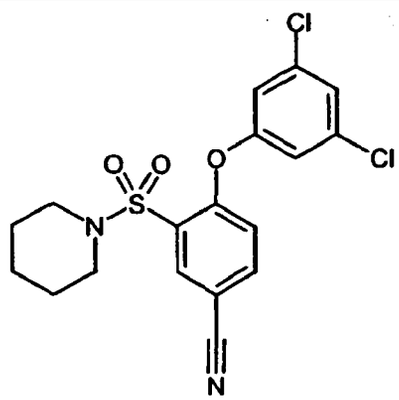
Melting point: 177 ˚C (decomp.);

Activity grade CCR3: A

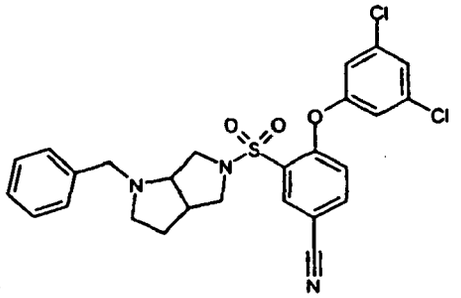
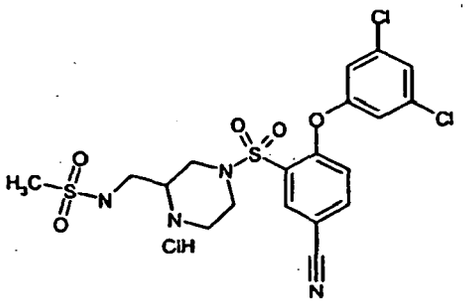
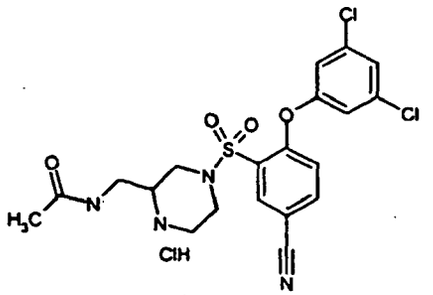
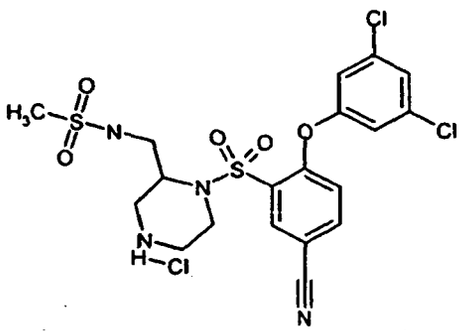
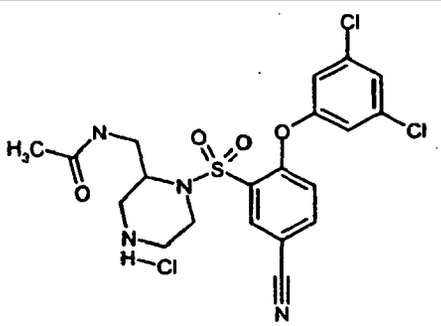
Activity grade IC_{50}: A

[0126] The compounds in Example 1-5 to -47 as shown in Table 1 were synthesized similar procedure as described in Example 1-1 to 1-4 above or conventional reactions.

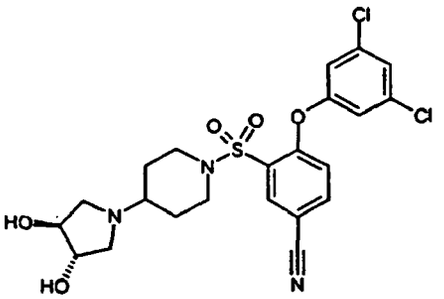
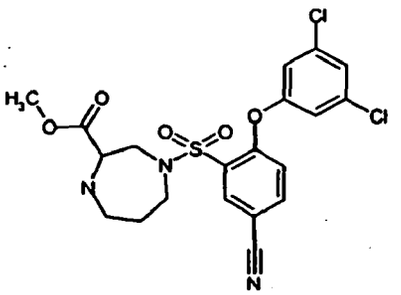
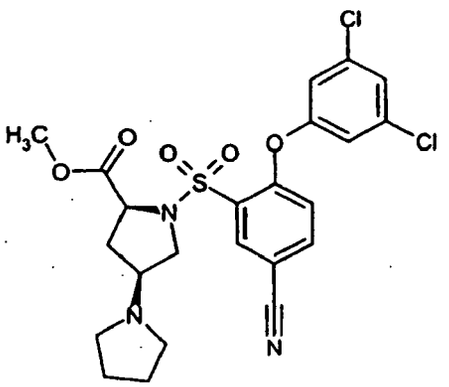
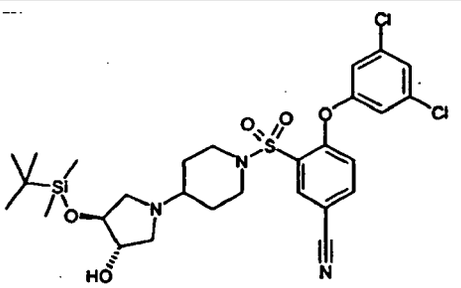
Table 1

Ex No	Structure	Mol weight	MASS	MP (˚C)	CCR3	IC50
1-5		411,31	411	171-172	C	C

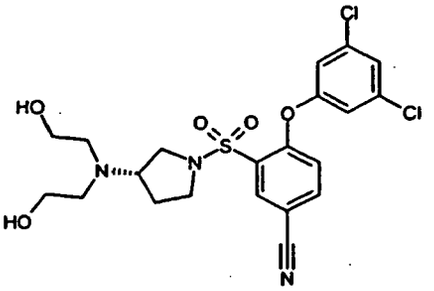
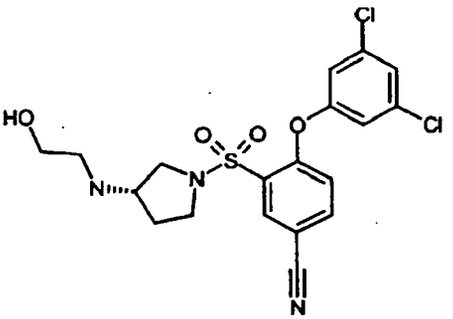
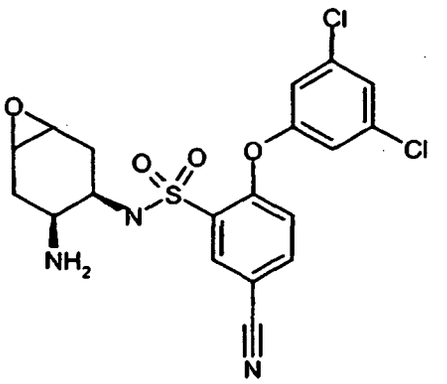
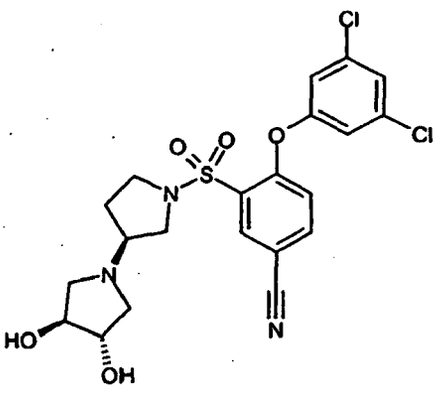
(continued)

Ex No	Structure	Mol weight	MASS	MP (˚C)	CCR3	IC50
1-6		528,46	528		A	A
1-7		555,89	519	296 Z	A	A
1-8		519,84	483	> 160 Z	A	A
1-9		555,89	519	270 Z	A	A
1-10		519,84	483	> 160 Z	A	A

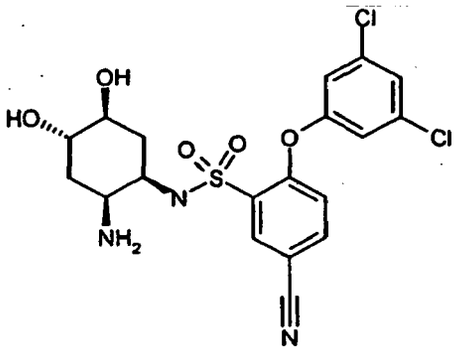
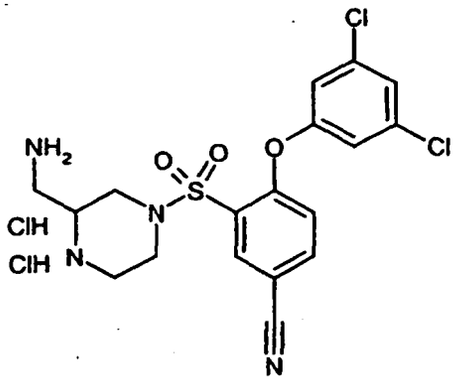
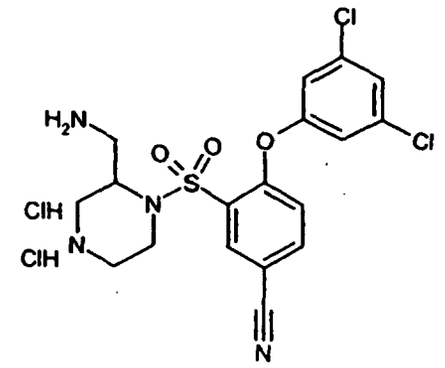
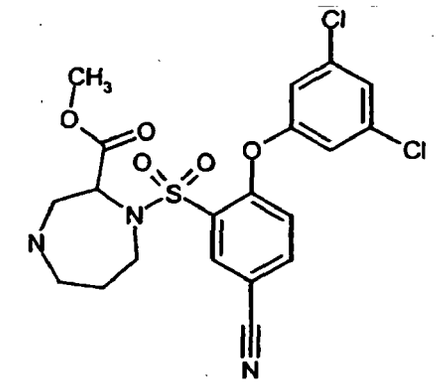
(continued)

Ex No	Structure	Mol weight	MASS	MP (˚C)	CCR3	IC50
1-11		512,421	512	137-139	B	A
1-12		484,36	484		B	B
1-13		524,43	524		B	A
1-14		626,68	626			B

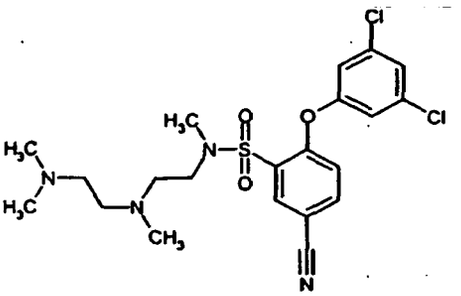
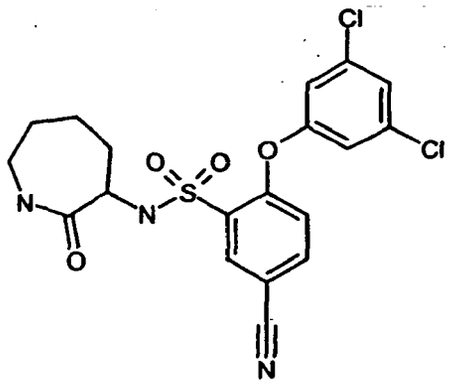
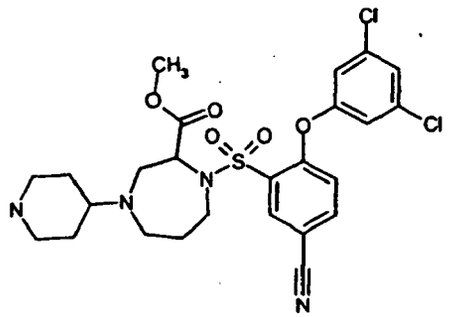
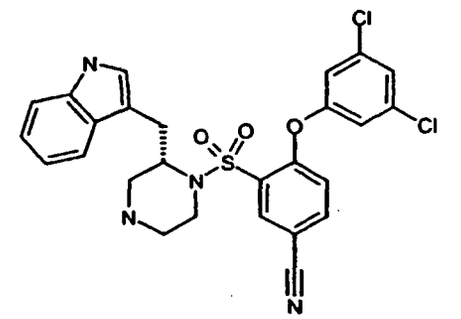
(continued)

Ex No	Structure	Mol weight	MASS	MP (˚C)	CCR3	IC50
1-15		500,4	500	153-154		B
1-16		456,35	456	155-156	A	A
1-17		454,33	454	165-182 Z		C
1-18		498,39	498			B

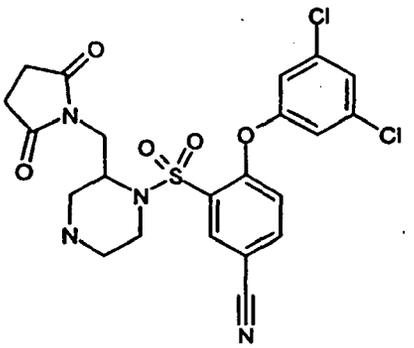
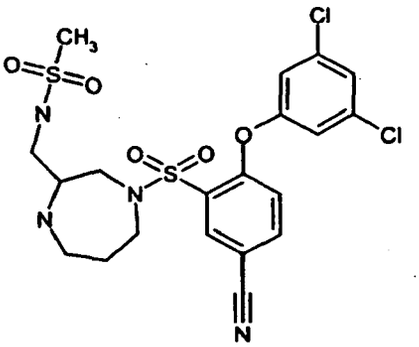
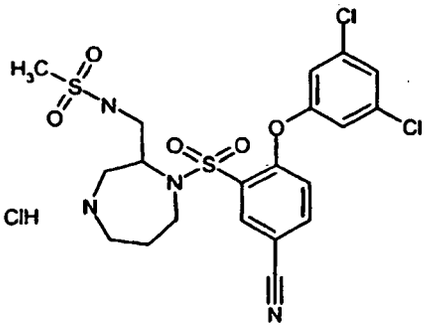
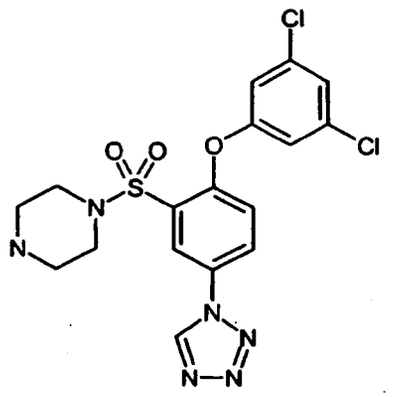
(continued)

Ex No	Structure	Mol weight	MASS	MP (˚C)	CCR3	IC50
1-19		472,35	472			C
1-20		514,26	441	240-241		C
1-21		514,26	441	280-281	A	A
1-22		520,82	525 (484 plus CH3CN)	150 Z	A	A

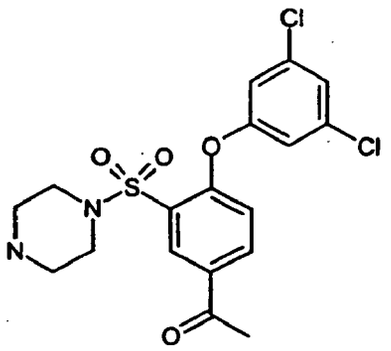
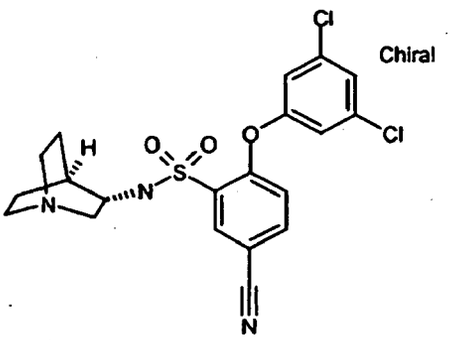
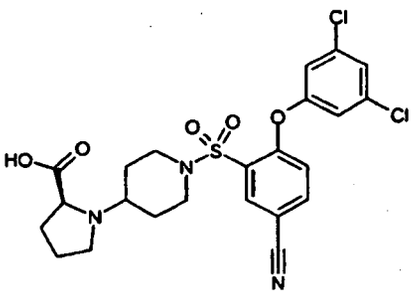
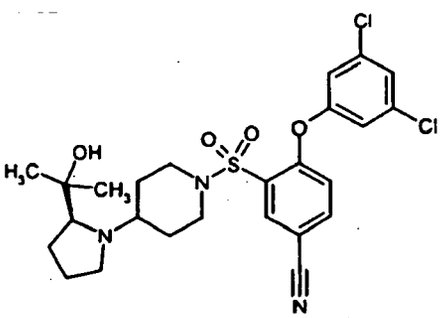
(continued)

Ex No	Structure	Mol weight	MASS	MP (˚C)	CCR3	IC50
1-23		485,44	485			B
1-24		454,34	454	172-173		B
1-25		567,5	567	>95 Z		B
1-26		541,46	541	116-117	A	A

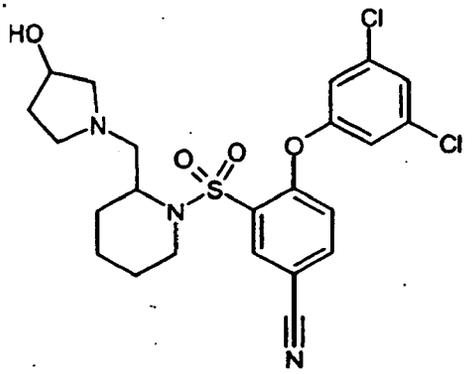
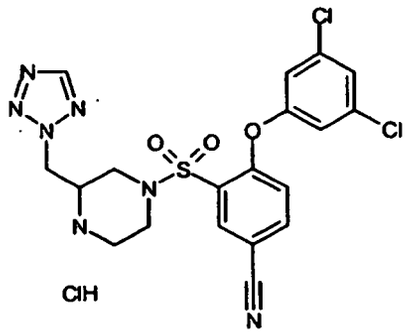
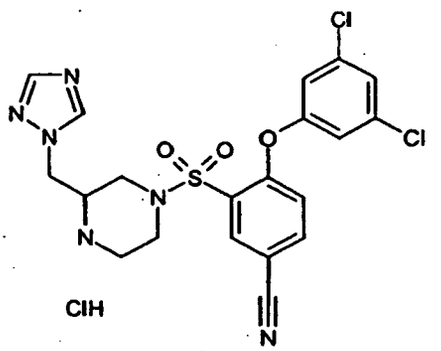
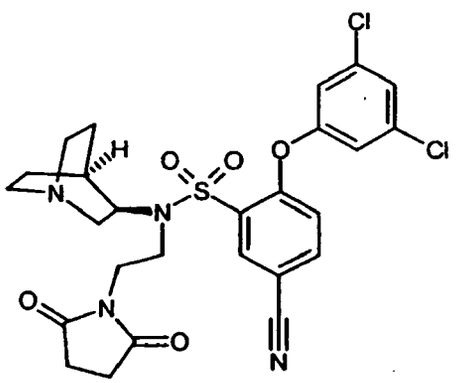
(continued)

Ex No	Structure	Mol weight	MASS	MP (˚C)	CCR3	IC50
1-27		523,4	523		A	A
1-28		533,46	533	127 Z	A	A
1-29		569,92	533	183-184	A	A
1-30		455,33	455	> 185 Z		C

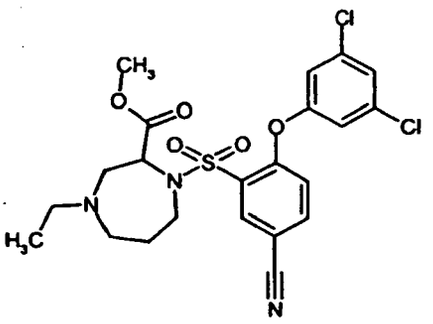
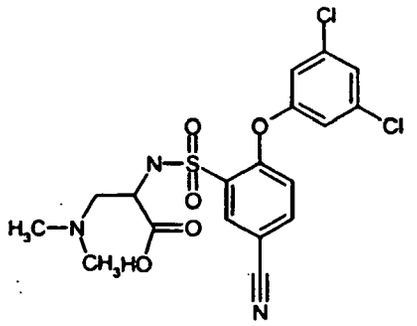
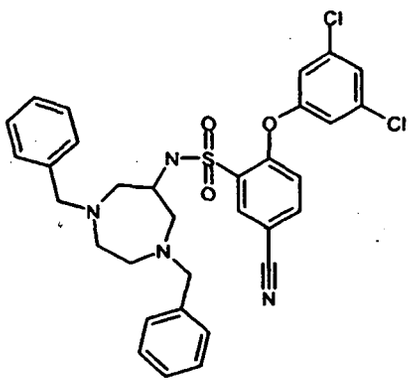
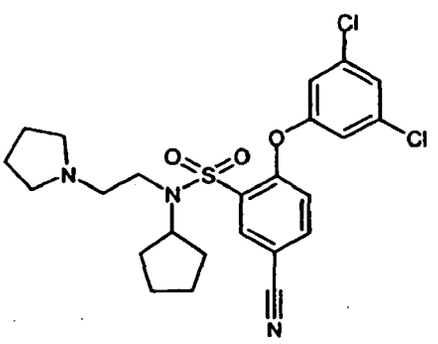
(continued)

Ex No	Structure	Mol weight	MASS	MP (˚C)	CCR3	IC50
1-31		429,33	429	169-170	A	A
1-32		452,36	452		A	A
1-33		524,43	524	224-225	A	B
1-34		538,5	538	103	A	A

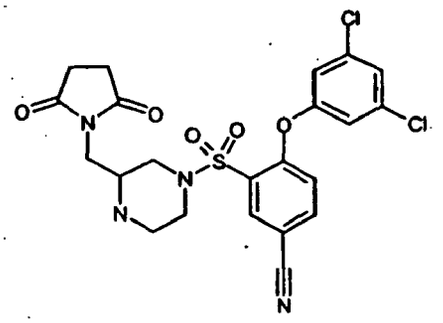
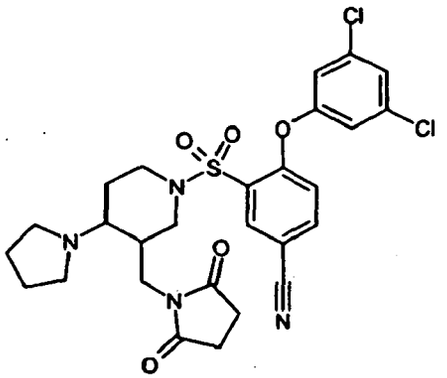
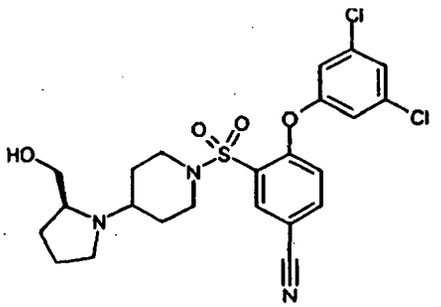
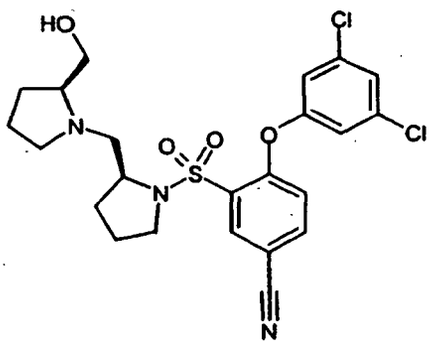
(continued)

Ex No	Structure	Mol weight	MASS	MP (˚C)	CCR3	IC50
1-35		510,44	509		B	A
1-36		530,82	494	178 Z	A	A
1-37		529,84	493	184-185 Z	A	A
1-38		577,49	577			C

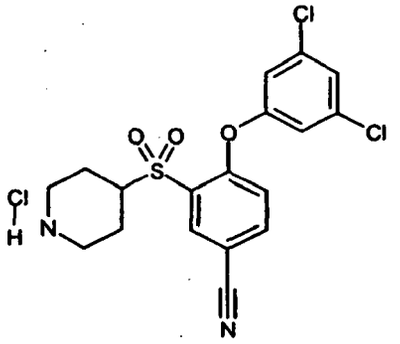
(continued)

Ex No	Structure	Mol weight	MASS	MP (˚C)	CCR3	IC50
1-39		512,42	512		B	A
1-40		458,32	458	190		C
1-41		621,59	621			C
1-42		508,47	508		B	A

(continued)

Ex No	Structure	Mol weight	MASS	MP (˚C)	CCR3	IC50
1-43		523,4	523	123-125	A	A
1-44		591,52	591	121	A	A
1-45		510,44	510	124	A	A
1-46		510,44	510	157	A	A

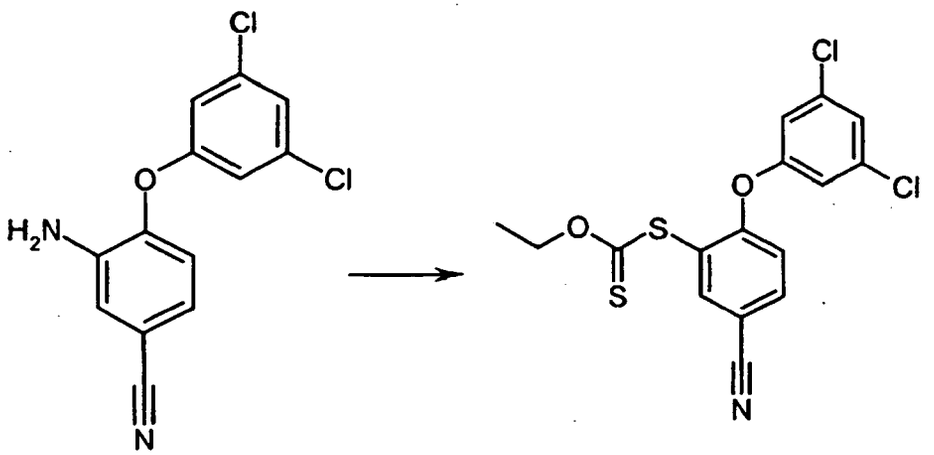
(continued)

Ex No	Structure	Mol weight	MASS	MP (˚C)	CCR3	IC50
1-47		447,77	411	220-226 Z	C	C
Z: Decomposed						

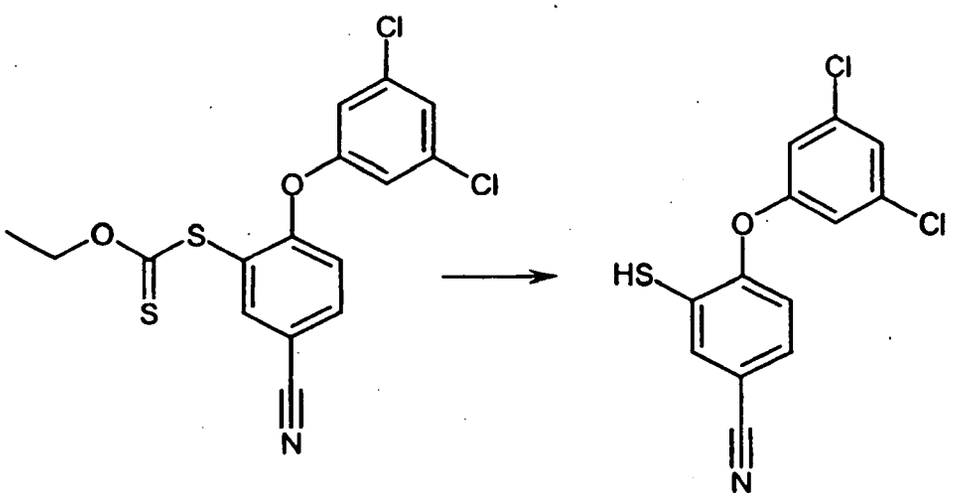
Example 2-1

4-(3,5-Dichloro-phenoxy)-3-(piperidine-4-sulfonyl)-benzonitrile

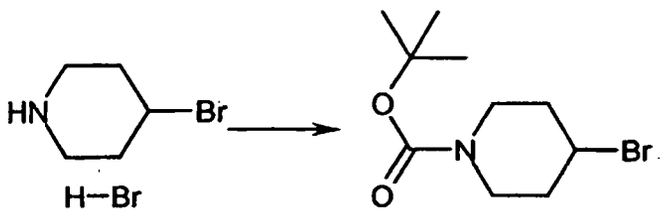
[0127]



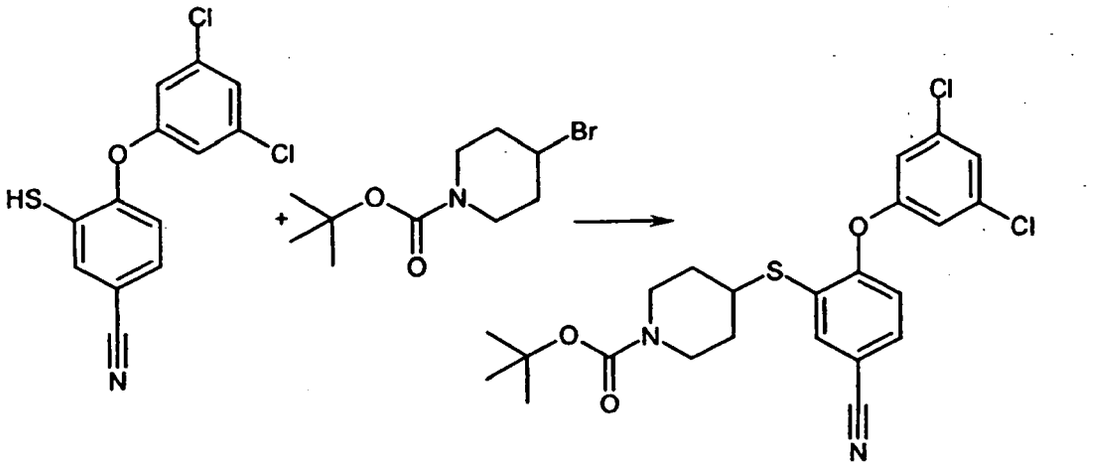
(1) To a solution of 3-amino-4-(3,5-dichloro-phenoxy)-benzonitrile (4.19 g, 15 mmol) in HCl aq [con. HCl (10 ml)+ water (25ml)] was added the solution of $NaNO_2$ (1.14 g, 16.5 mmol) in water (6 ml) dropwise with stirring below 4˚C. After addition, the PH of the solution was brought to 4 by addition of sodium acetate. After stirred at 0˚C for 20 minutes, the mixture was added to the hot solution (80˚C) of potassium O-ethyldithiocarbonate (4.81 g, 30 mmol) in water (45 ml) with stirring. The mixture was stirred at 80˚C for 0.5 hours. After cooled to room temperature, the solution was extracted with EtOAc, dried over $MgSO_4$. The solvent was evaporated to give dithiocarbonic acid *S*-[5-cyano-2-(3,5-dichloro-phenoxy)-phenyl] ester *O*-ethyl ester that was used for next reaction without further purification [5.50g, 66.8%(70% purity)].



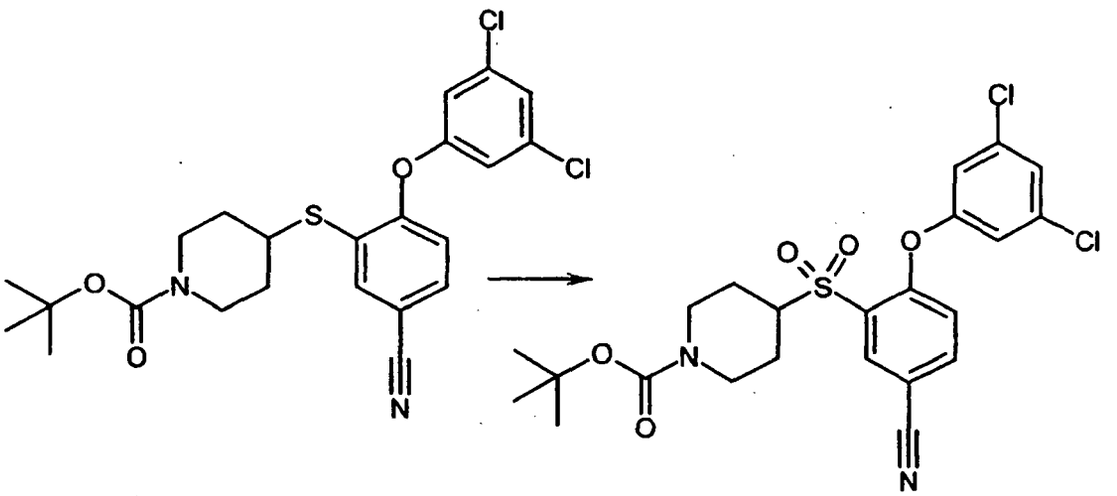
(2) The mixture of dithiocarbonic acid *S*-[5-cyano-2-(3,5-dichloro-phenoxy)-phenyl] ester *O*-ethyl ester [5.50g,10.2 mmol (70% purity)], KOH (3.37 g, 60.1 mmol) in ethanol (20 ml) was refluxed for 1 hour. After cooled to room temperature, the solvent was evaporated. 30 ml of ice water was added to the residue. The PH of the mixture was adjusted to 4 by addition of acetic acid. The mixture was extracted with EtOAc. The extract was washed with water, brine, dried over $MgSO_4$. The solvent was evaporated to give 4-(3,5-Dichloro-phenoxy)-3-mercapto-benzonitrile that was used for next reaction without purification [3.20 g, 75.5% (70% purity)].



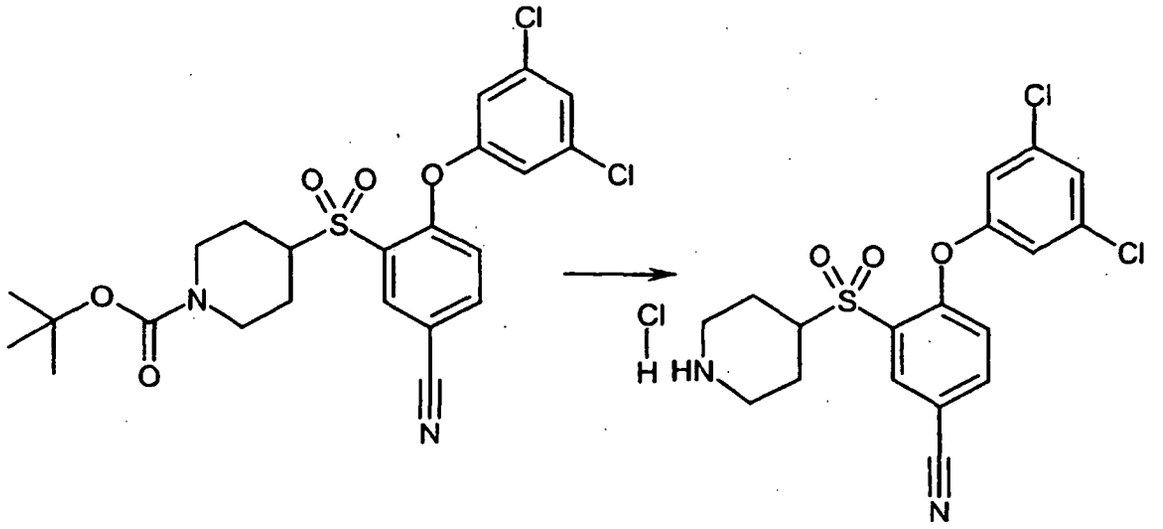
(3) To the suspension of 4-bromo-piperidine; hydrobromide (2.94 g, 12 mmol) in CH_2Cl_2 (30 ml) was added NEt_3 (3.04 g, 4.2 ml, 30 mmol) with stirring. Di-*tert*-butyl dicarbonate (3.14 g, 14.4 mmol) was added 10 min later. The mixture was stirred at room temperature for 3 hours, and diluted with CH_2Cl_2 (60 ml). The mixture was washed with 0.2 N HCl aq., 5% $NaHCO_3$ aq., brine, dried over $MgSO_4$. The solvent was evaporated to give 4-bromo-piperidine-1-carboxylic acid *tert*-butyl as colorless liquid that was used for the next step without further purification [2.60 g, 69.5%(70% purity)].



(4) The mixture of 4-(3,5-dichloro-phenoxy)-3-mercapto-benzonitrile ester [338 mg, 0.8 mmol, (70% purity)], 4-bromo-piperidine-1-carboxylic acid *tert*-butyl [362 mg, 0.96 mmol(70% purity)], and K_2CO_3 (552 mg, 4 mmol) in dry DMF(8 ml) was stirred at 95°C overnight. The solvent was evaporated, and the residue was diluted with EtOAc (100 ml). The mixture was washed with brine, and the organic layer was dried over $MgSO_4$. The solvent was evaporated to give 4-[5-cyano-2-(3,5-dichloro-phenoxy)-phenylsulfanyl]-piperidine-1-carboxylic acid *tert*-butyl ester that was used for the next reaction without any purification [360 mg, 56.3%(60% purity)].



(5) To a solution of 4-[5-cyano-2-(3,5-dichloro-phenoxy)-phenylsulfanyl]-piperidine-1-carboxylic acid *tert*-butyl ester [320 mg, 0.4 mmol (60 purity)] in the mixture of CCl_4 (6 ml) and CH_3CN (6 ml) was added the solution of $NaIO_4$ (599 mg, 2.80 mmol)and $RuCl_3$ (41.5 mg, 0.2 mmol)in water (12 ml). The mixture was stirred at room temperature for 4 hours, and the solvent was evaporated. The residue was diluted with EtOAc (100 ml). The mixture was washed with water, brine, and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by preparative TLC (EtOAC/Hexane = 1:1) to give 4-[5-cyano-2-(3,5-dichloro-phenoxy)-benzenesulfonyl]-piperidine-1-carboxylic acid *tert*-butyl ester (50.0 mg, 24.4%): HPLC-MS (ESI): Calcd for $C_{23}H_{24}Cl_2N_2O_5S$ $[M+H]^+$ 511, found: 511.

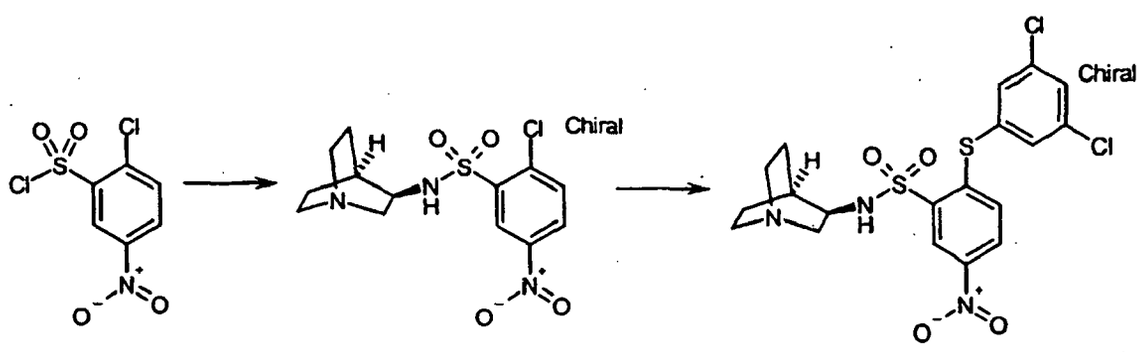


(6) To a solution in 4-[5-cyano-2-(3,5-dichloro-phenoxy)-benzenesulfonyl]-piperidine-1-carboxylic acid *tert*-butyl ester (30 mg, 0.06 mmol) in CH_2Cl_2 (1 ml) was added 4N HCl (in dioxane, 0.6 ml) and the mixture was stirred at room temperature for 1.5 hours. The produced white precipitate was collected by filtration and dried in vacuo to give 4-(3,5-Dichloro-phenoxy)-3-(piperidine-4-sulfonyl)-benzonitrile; hydrochloride (23 mg, 87.6%).
^{1}H NMR(300 MHz, DMSO-d6): 1.72-1.77 (2H, ddm, J = 13.4 Hz, J = 3.78 Hz), 2.03-2.09 (2H, ddm, J = 13.4 Hz, J = 3.78 Hz), 3.09 (2H, br, S), 3.18(2H, br, S), 4.94 (1H, q, J = 3.78 Hz), 7.54(1H, d, J = 9.03 Hz), 7.96 (2H, s), 8.07 (1H, s), 8.76 (1H, s), 8.46 (1H, s),8.83 (1H, br, S), 9.14 (1H, br, S); HPLC-MS (ESI): Calcd for $C_{18}H_{17}Cl_3N_2O_3S$ $[M+H]^+$ 411, found: 411.
Molecular weight: 447.77
Melting point: 220-226 ˚C (decomp.)
Activity grade CCR3: C
Activity grade IC_{50}: C

Example 3-1

***N*-(1-aza-bicyclo[2.2.2]oct-3-yl)-2-(3,5-dichloro-phenylsulfanyl)-5-nitro-benzenesulfonamide**

[0128]

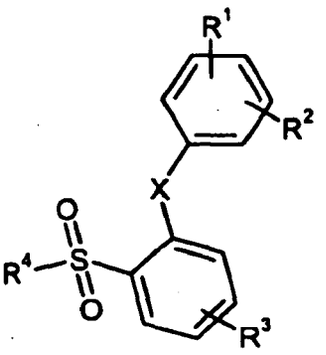


(1) To a suspension of 1-aza-bicyclo[2.2.2]oct-3-ylamine dihydrogen chloride (44.9 mg, 0.205 mmol) in THF was added NaH (60%, 41.0 mg, 1.03 mmol) portion wise, and the mixture was stirred for 30 minutes. The stirred mixture was then added to a solution of 2-chloro-5-nitro-benzenesulfonyl chloride (52.5 mg, 0.205 mmol) in THF drop wise at 0˚C . The resulting mixture was stirred at 0˚C for 2 hours.

(2) After removing an ice bath, NaH (60%, 9.80 mg, 0.246 mmol) was added to the mixture followed by the addition of 3,5-dichloro-benzenethiol (44.0 mg, 0.246 mmol). The mixture was stirred at room temperature for 2 hours, and concentrated in vacuo. The residue was diluted by EtOAc and washed with water, 1N NaOH, and brine. The organic layer was dried over $MgSO_4$, and concentrated in vacuo to give crude product. The crude compound was further purified by preparative TLC to give *N*-(1-aza-bicyclo[2.2.2]oct-3-yl)-2-(3,5-dichloro-phenylsulfanyl)-5-nitro-benzenesulfonamide (41.3 mg, 41.3%) as a white powder:
^1H NMR (300 MHz, $CDCl_3$) δ 1.48-1.59 (1H, m), 1.61-1.73 (1H, m), 1.75-1.83 (2H, m), 2.54-2.61 (1H, m), 2.64-2.82 (2H, m), 2.85-2.90 (2H, t, *J* = 7.5 Hz), 3.19-3.27 (1H, dd, *J* = 9.4, 14.1 Hz), 3.42-3.46 (1H, m), 7.13-7.16 (1H, d, *J* = 8.9 Hz), 7.39-7.40 (2H, d, *J* = 1.9 Hz), 7.52-7.53 (1H, t, *J* = 1.9 Hz), 8.18-8.22 (1H, dd, *J* = 2.6, 8.9 Hz), 8.87-8.88 (1H, d, *J* = 2.5 Hz); HPLC-MS (ESI): Calcd for $C_{19}H_{19}Cl_2N_3O_4S_2[M+H]^+$ 488, found: 488.
Molecular weight: 488.41
Melting point: 256˚C

Claims

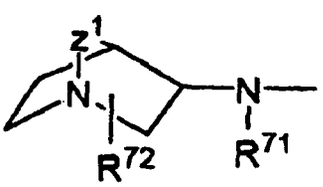
1. A benzenesulfonamide derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:



(I)

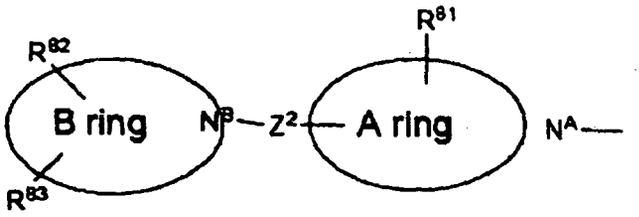
wherein

X represents O or S;
R^1 represents hydrogen, halogen, hydroxy, nitro, cyano, C_{1-6} alkoxy carbonyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} alkanoyl, phenyl, C_{1-6} alkyl optionally substituted by mono-, di- or tri- halogen, or C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen;
R^2 represents hydrogen, halogen, hydroxy, nitro, cyano, C_{1-6} alkoxy carbonyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} alkanoyl, phenyl, C_{1-6} alkyl optionally substituted by mono-, di- or tri- halogen or C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen;
R^3 represents hydrogen, halogen, hydroxy, nitro, cyano, amino, carboxy, tetrazolyl, C_{1-6} alkoxy, C_{1-6} alkoxy-carbonyl, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, C_{1-6} alkyl optionally substituted by mono-, di- or tri- halogen or hydroxy;
R^4 represents



,

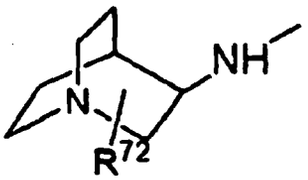
or

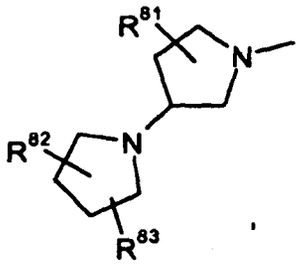


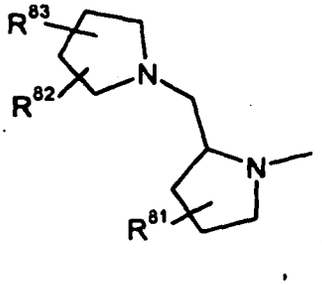
Wherein:

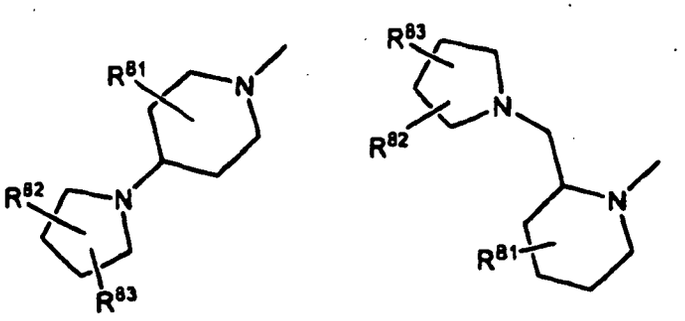
R^{71} represents hydrogen, or C_{1-6} alkyl optionally substituted by amino, hydroxy, carboxy, pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;
R^{72} represents hydrogen, carboxy, C_{1-6} alkanoyl, amino, (C_{1-6}alkyl)amino, di(C_{1-6} alkyl) amino, N-(C_{1-6}alkyl)amino carbonyl, C_{1-6} alkyl optionally substituted by hydroxy, carboxy, or mono-, di- or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen, pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;
Z^1 represents $-[CH_2]_p-$, wherein p represents an integer 1 or 2;
R^{81} represents hydrogen, C_{1-6} alkoxycarbonyl, or C_{1-6} alkyl substituted by pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;
R^{82} represents hydrogen, hydroxy, carboxy or C_{1-6} alkyl substituted by hydroxy, amino, or carboxy,
R^{83} represents hydrogen, hydroxy, carboxy, or C_{1-6} alkyl substituted by hydroxy, amino, or carboxy,
with the proviso that when R^{81} is hydrogen, R^{82} or R^{83} is other than hydrogen;
Z^2 represents $-[CH_2]_q-$, wherein q represents an integer selected from 0 to 3;
A ring represents a 3 to 8 membered saturated heterocyclic ring, in which the nitrogen atom N^A is the only hetero atom;
B ring represents a 3 to 8 membered saturated heterocyclic ring, in which the nitrogen atom N^B is the only hetero atom.

2. The benzenesulfonamide derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,
wherein R^4 represents







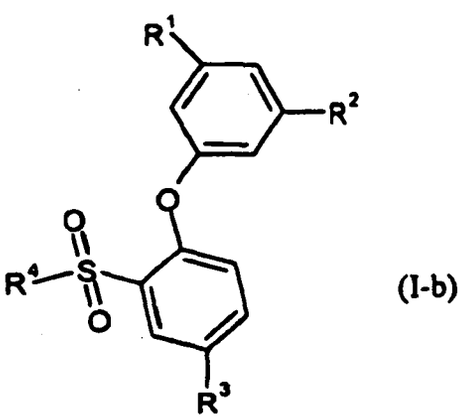


wherein:

R^{72} represents hydrogen, carboxy, C_{1-6} alkanoyl, amino, (C_{1-6}alkyl)amino, di(C_{1-6}alkyl)amino, N-(C_{1-6}alkyl)amino carbonyl, C_{1-6} alkyl optionally substituted by hydroxy, carboxy, or mono-, di- or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen, pyrrolidinyl or piperidinyl wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;
R^{81} represents hydrogen, methoxycarbonyl or C_{1-6} alkyl substituted by 2-oxo-pyrrolidin-1-yl, 2,5- dioxo pyrrolidin-1-yl, 2-oxo-piperidin-1-yl, 2-oxo-piperidin-3-yl, 4-oxo-piperidin-1-yl, 2-oxo-piperidin-6-yl, 2,5-dioxo-piperidin-1-yl, 2,6-dioxo-piperidin-1-yl, or 2,6-dioxo-piperidin-3-yl;
R^{82} represents hydrogen, hydroxy or C_{1-6} alkyl substituted by hydroxy;
R^{83} represents hydrogen, hydroxy or carboxy; and

with the proviso that when R^{82} and R^{83} are hydrogen at the same time, R^{81} is other than hydrogen, or when R^{81} and R^{83} are hydrogen at the same time, R^{82} is other than hydrogen.

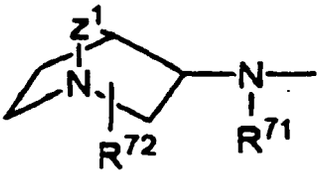
3. The benzenesulfonamide derivative of claim 1, wherein the derivative is of the formula (I-b), its tautomeric or stereoisomeric form, or a salt thereof:



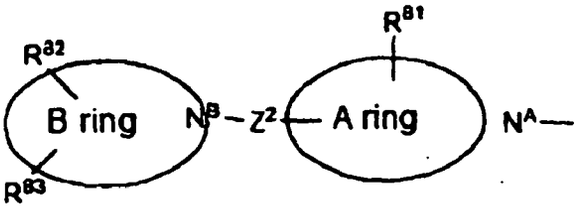
(I-b)

wherein:

R^1 represents fluoro, chloro, bromo, iodo, or nitro;
R^2 represents fluoro, chloro, bromo, iodo, or nitro;
R^3 represents acetyl, cyano, or tetrazolyl;
R^4 represents



or



wherein:

R^{71} represents hydrogen, or C_{1-6} alkyl optionally substituted by amino, hydroxy, carboxy, pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;
R^{72} represents hydrogen, carboxy, C_{1-6} alkanoyl, amino, (C_{1-6}alkyl)amino, di(C_{1-6}alkyl)amino, N-(C_{1-6}alkyl)amino carbonyl, C_{1-6} alkyl optionally substituted by hydroxy, carboxy, or mono-, di- or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen, pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;
Z^1 represents -$[CH_2]_p$-, wherein p represents an integer 1 or 2;
R^{81} represents hydrogen, C_{1-6} alkoxycarbonyl, or C_{1-6} alkyl substituted by pyrrolidinyl, or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;
R^{82} represents hydrogen, hydroxy, carboxy or C_{1-6} alkyl substituted by hydroxy, amino, or carboxy,
R^{83} represents hydrogen, hydroxy, carboxy, or C_{1-6} alkyl substituted by hydroxy, amino, or carboxy,

with the proviso that when R^{81} is hydrogen, R^{82} or R^{83} is other than hydrogen;

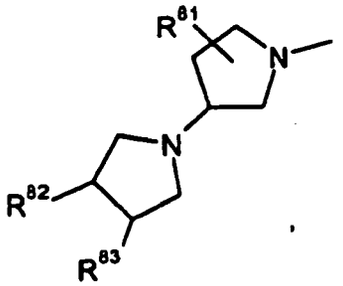
Z^2 represents -$[CH_2]_q$-,

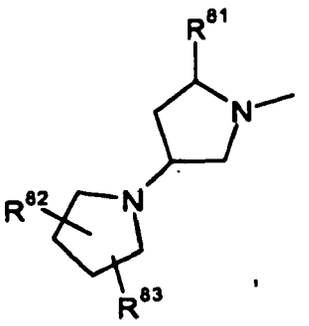
wherein

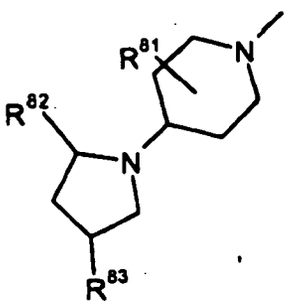
q represents an integer selected from 0 to 3;
A ring represents a 3 to 8 membered saturated heterocyclic ring, in which the nitrogen atom N^A is the only hetero atom;
B ring represents a 3 to 8 membered saturated heterocyclic ring, in which the nitrogen atom N^B is the only hetero atom;

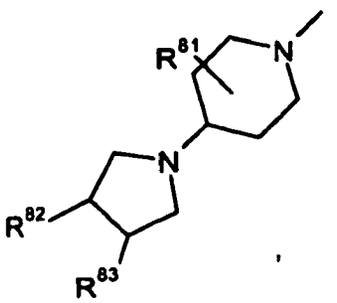
4. The benzenesulfonamide derivative of claim 3, its tautomeric or stereoisomeric form, or a salt wherein:

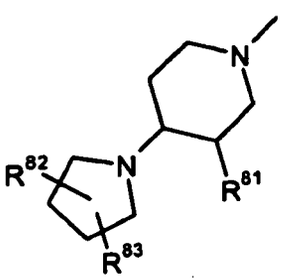
R^1 represents fluoro, chloro or bromo;
R^2 represents fluoro, chloro or bromo;
R^3 represents cyano;
R^4 represents

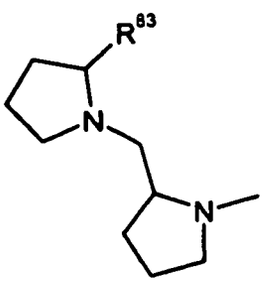

R81
N
N
R82
R83

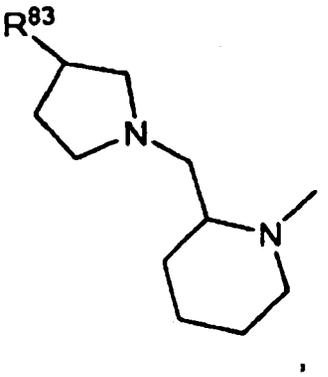

R81
N
N
R82
R83


R81
N
R82
N
R83

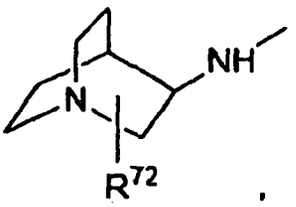

R81
N
N
R82
R83


N
R82
N
R81
R83


R83
N
N



or



wherein:

R^{72} represents hydrogen, carboxy, C_{1-6} alkanoyl, amino, (C_{1-6}alkyl)amino, di(C_{1-6}alkyl)amino, N-(C_{1-6}alkyl)amino carbonyl, C_{1-6} alkyl optionally substituted by hydroxy, carboxy, or mono-, di- or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen, pyrrolidinyl or piperidinyl, wherein said pyrrolidinyl and piperidinyl are optionally substituted by mono- or di- oxo;
R^{81} represents hydrogen, methoxycarbonyl or C_{1-6} alkyl substituted by 2-oxo-pyrrolidin-1-yl, 2,5- dioxo pyrrolidin-1-yl, 2-oxo-piperidin-1-yl, 2-oxo-piperidin-3-yl, 4-oxo-piperidin-1-yl, 2-oxo-piperidin-6-yl, 2,5-dioxo-piperidin-1-yl, 2,6-dioxo-piperidin-1-yl, or 2,6-dioxo-piperidin-3-yl;
R^{82} represents hydrogen, hydroxy or hydroxy substituted C_{1-6} alkyl;
R^{83} represents hydrogen, hydroxy or carboxy; and

with the proviso that when R^{82} and R^{83} are hydrogen at the same time, R^{81} is other than hydrogen, or when R^{81} and R^{83} are hydrogen at the same time, R^{82} is other than hydrogen.

5. The benzenesulfonamide derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 to 4, wherein said benzenesulfonamide derivative of the formula is selected from the group consisting of:

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)-5-cyano-2-(3,5-dichloro-phenoxy)-benzenesulfonamide;
(S)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)-5-cyano-2-(3,5-dichloro-phenoxy)-benzenesulfonamide;
4-(3,5-Dichloro-phenoxy)-3-{4-[(2S)-(1-hydroxy-1-methyl-ethyl)-pyrrolidin-1-yl]-pipendine-1-sulfonyl}-benzonitrile;
4-(3,5-Dichloro-phenoxy)-3-[3-(2,5-dioxo-pyrrolidin-1-ylmethyl)-4-pyrrolidin-1-yl-piperidine-1-sulfonyl]-benzonitrile;
4-(3,5-Dichloro-phenoxy)-3-{4-[(2S)-hydroxymethyl-pyrrolidin-1-yl]-piperidine-1-sulfonyl}-benzonitrile;
4-(3,5-Dichloro-phenoxy)-3-{(2S)-[(2S)-hydroxymethyl-pyrrolidin-1-ylmethyl]-pyrrolidine-1-sulfonyl}-benzonitrile;

N-(1-aza-bicyclo[2.2.2]oct-3-yl)-2-(3,5-dichloro-phenylsulfanyl)-5-nitrobenzenesulfonamide;
4-(3,5-dichlorophenoxy)-3-(4-((3S,4S)-3,4-dihydroxypyrrolidin-1-yl)piperidin-1-ylsulfonyl)benzonitrile;
(3'S,5'S)-methyl-1'-(5-cyano-2-(3,5-dichlorophenoxy)phenylsulfonyl)-1,3'-bipyrrolidine-5'-carboxylate;

3-(4-((3S,4S)-3-(tert-butyldimethylsilyloxy)-4-hydroxypyrrolidin-1-yl)piperidin-1-ylsulfonyl)-4-(3,5-dichlorophenoxy)benzonitrile;
4-(3,5-dichlorophenoxy)-3-((3S,3'S,4S)-3,4-dihydroxy-1,3'-bipyrrolidin-1'-ylsulfonyl)benzonitrile;
(S)-1-(1-(5-cyano-2-(3,5-dichlorophenoxy)phenylsulfonyl)piperidin-4-yl)pyrrolidine-2-carboxylic acid;
4-(3,5-dichlorophenoxy)-3-(2-((3-hydroxypyrrolidin-1-yl)methyl)piperidin-1-ylsulfonyl)benzonitrile; and
(R)-5-cyano-2-(3,5-dichlorophenoxy)-N-(2-(2,5-dioxopyrrolidin-1-yl)ethyl)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)benzenesulfonamide.

6. A medicament comprising the benzenesulfonamide derivative of the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

7. The medicament as claimed in claim 6, further comprising one or more pharmaceutically acceptable excipients.

8. The medicament as claimed in claim 6, wherein said benzenesulfonamide derivative of the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is a CCR3 antagonist.

9. The medicament as claimed in claim 6 suitable for the treatment and/or prophylaxis of an inflammatory disorder or disease.

10. The medicament as claimed in claim 9, wherein said inflammatory disorder or disease is selected from the group consisting of asthma, rhinitis, allergic diseases, and autoimmune pathologies.

11. The medicament as claimed in claim 6 suitable for the treatment or prevention of a disease selected from the group consisting of HIV, lung granuloma, and Alzheimer's diseases.

12. Use of the benzenesulfonamide derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 to 5 in the preparation of a medicament for treating or preventing a CCR3 related disorder or disease.

13. The use of claim 12, wherein said disorder or disease is an inflammatory or immunoregulatory disorder or disease.

14. The use of claim 12, wherein said disorder or disease is selected from the group consisting of asthma, rhinitis, allergic diseases, and autoimmune pathologies.

15. The use of claim 12, wherein said disorder or disease is selected from the group consisting of HIV, lung granuloma, and Alzheimer's diseases.

16. The use of claim 12, wherein said benzenesulfonamide derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is formulated with one or more pharmaceutically acceptable excipients.

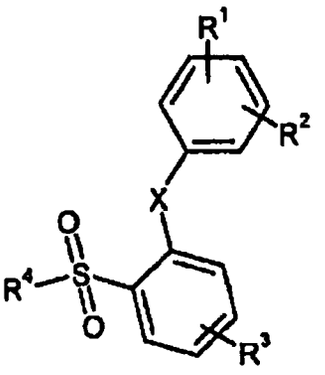
17. Use of at least one compound according to claim 1 in the preparation of a medicament for controlling an inflammatory or immunoregulatory disorder or disease, in which the amount of the compound in the medicament is a CCR3-antagonisticly effective amount.

18. The medicament of claim 7, wherein the excipient is an inert substance such as a carrier, a diluent, a flavoring agent, a sweetener, a lubricant, a solubilizer, a suspending agent, a binder, a tablet disintegrating agent or a encapsulating agent.

19. The use of claim 16, wherein the excipient is an inert substance such as a carrier, a diluent, a flavoring agent, a sweetener, a lubricant, a solubilizer, a suspending agent, a binder, a tablet disintegrating agent or a encapsulating agent.

Patentansprüche

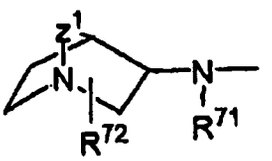
1. Benzolsulfonamid-Derivat der Formel (I), eine tautomere oder stereoisomere Form davon oder ein Salz davon:



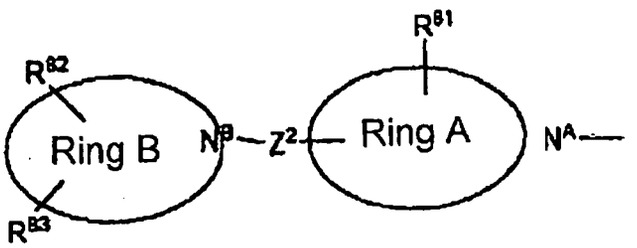
(I)

worin

X O oder S bedeutet,
R^1 Wasserstoff, Halogen, Hydroxy, Nitro, Cyano, C_{1-6}-Alkoxycarbonyl, Amino, C_{1-6}-Alkylamino, Di(C_{1-6}-alkyl)amino, C_{1-6}-Alkanoyl, Phenyl, C_{1-6}-Alkyl, welches gegebenenfalls substituiert ist mit Mono-, Di- oder Trihalogen, oder C_{1-6}-Alkoxy bedeutet, welches gegebenenfalls substituiert ist mit Mono-, Di- oder Trihalogen,
R^2 Wasserstoff, Halogen, Hydroxy, Nitro, Cyano, C_{1-6}-Alkoxycarbonyl, Amino, C_{1-6}-Alkylamino, Di(C_{1-6}-alkyl)amino, C_{1-6}-Alkanoyl, Phenyl, C_{1-6}-Alkyl, welches gegebenenfalls substituiert ist mit Mono-, Di- oder Trihalogen, oder C_{1-6}-Alkoxy bedeutet, welches gegebenenfalls substituiert ist mit Mono-, Di- oder Trihalogen,
R^3 Wasserstoff, Halogen, Hydroxy, Nitro, Cyano, Amino, Carboxy, Tetrazolyl, C_{1-6}-Alkoxy, C_{1-6}-Alkoxycarbonyl, C_{1-6}-Alkanoyl, C_{1-6}-Alkanoylamino, C_{1-6}-Alkyl bedeutet, welches gegebenenfalls substituiert ist mit Mono-, Di- oder Trihalogen oder Hydroxy,
R^4



oder



bedeutet, worin

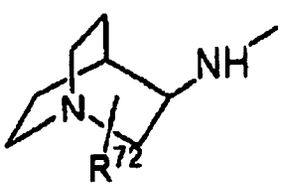
R^{71} Wasserstoff oder C_{1-6}-Alkyl bedeutet, welches gegebenenfalls substituiert ist mit Amino, Hydroxy, Carboxy, Pyrrolidinyl oder Piperidinyl, worin das Pyrrolidinyl und Piperidinyl gegebenenfalls substituiert sind mit Mono- oder Dioxo,
R^{72} Wasserstoff, Carboxy, C_{1-6}-Alkanoyl, Amino, (C_{1-6}-Alkyl)amino, Di-(C_{1-6}-alkyl)amino, N-(C_{1-6}-alkyl)amino-carbonyl, C_{1-6}-Alkyl, welches gegebenenfalls substituiert ist mit Hydroxy, Carboxy oder Mono-, Di- oder Trihalogen, C_{1-6}-Alkoxy bedeutet, welches gegebenenfalls substituiert ist mit Mono-, Di- oder Trihalogen, Pyrrolidinyl oder Piperidinyl, worin das Pyrrolidinyl und Piperidinyl gegebenenfalls substituiert sind mit Mono- oder Dioxo,
Z^1 -$[CH_2]_p$- bedeutet, worin p eine ganze Zahl 1 oder 2 bedeutet,
R^{81} Wasserstoff, C_{1-6}-Alkoxycarbonyl oder C_{1-6}-Alkyl bedeutet, welches substituiert ist mit Pyrrolidinyl oder Piperidinyl, worin das Pyrrolidinyl und Piperidinyl gegebenenfalls substituiert sind mit Mono- oder Dioxo,
R^{82} Wasserstoff, Hydroxy, Carboxy oder C_{1-6}-Alkyl bedeutet, welches substituiert ist mit Hydroxy, Amino oder Carboxy,
R^{83} Wasserstoff, Hydroxy, Carboxy oder C_{1-6}-Alkyl bedeutet, welches substituiert ist mit Hydroxy, Amino oder Carboxy,

mit der Maßgabe, dass R^{82} oder R^{83} nicht Wasserstoff ist, wenn R^{81} Wasserstoff ist,

Z^2 -$[CH_2]_q$- bedeutet, worin q eine ganze Zahl bedeutet, ausgewählt aus 0 bis 3,

Ring A einen 3- bis 8-gliedrigen gesättigten heterozyklischen Ring bedeutet, worin das Stickstoffatom N^A das einzige Heteroatom ist,
Ring B einen 3- bis 8-gliedrigen gesättigten heterozyklischen Ring bedeutet, worin das Stickstoffatom N^B das einzige Heteroatom ist.

2. Benzolsulfonamid-Derivat der Formel (I), eine tautomere oder stereoisomere Form davon oder ein Salz davon nach Anspruch 1,
worin R^4



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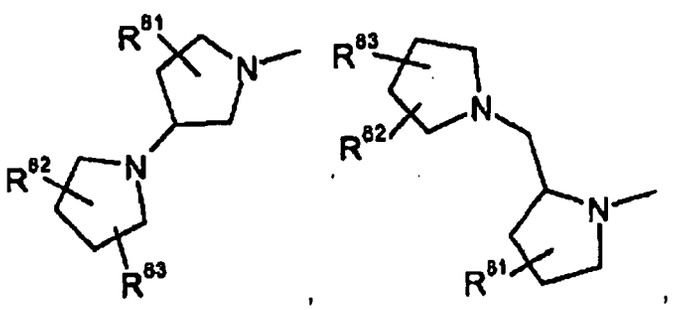

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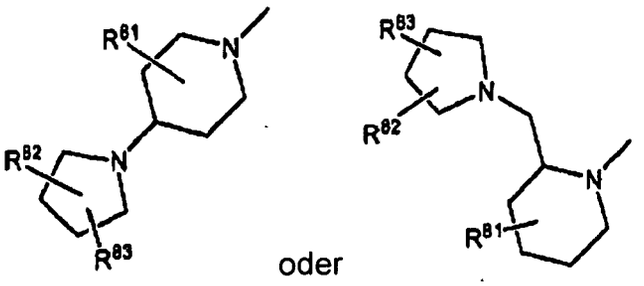
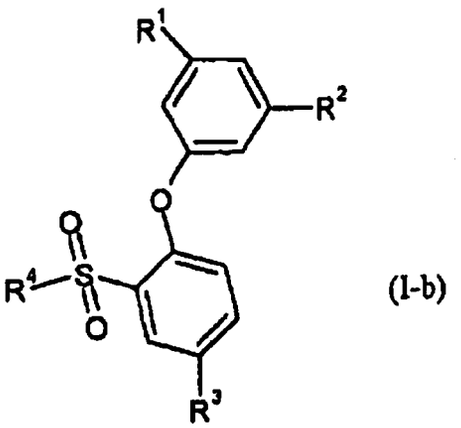


bedeutet, worin

R^{72} Wasserstoff, Carboxy, C_{1-6}-Alkanoyl, Amino, (C_{1-6}-Alkyl)amino, Di(C_{1-6}-alkyl)amino, N-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-Alkyl, welches gegebenenfalls substituiert ist mit Hydroxy, Carboxy oder Mono-, Di- oder Trihalogen, C_{1-6}-Alkoxy bedeutet, welches gegebenenfalls substituiert ist Mono-, Di- oder Trihalogen, Pyrrolidinyl oder Piperidinyl, worin das Pyrrolidinyl und Piperidinyl gegebenenfalls substituiert sind mit Mono- oder Dioxo,
R^{81} Wasserstoff, Methoxycarbonyl oder C_{1-6}-Alkyl bedeutet, welches substituiert ist mit 2-Oxopyrrolidin-1-yl, 2,5-Dioxopyrrolidin-1-yl, 2-Oxopiperidin-1-yl, 2-Oxopiperidin-3-yl, 4-Oxopiperidin-1-yl, 2-Oxopiperidin-6-yl, 2,5-Dioxopiperidin-1-yl, 2,6-Dioxopiperidin-1-yl oder 2,6-Dioxopiperidin-3-yl,
R^{82} Wasserstoff, Hydroxy oder C_{1-6}-Alkyl bedeutet, welches substituiert ist mit Hydroxy,
R^{83} Wasserstoff, Hydroxy oder Carboxy bedeutet, und

mit der Maßgabe, dass R^{81} kein Wasserstoff ist, wenn R^{82} und R^{83} gleichzeitig Wasserstoff sind, oder dass R^{82} kein Wasserstoff ist, wenn R^{81} und R^{83} gleichzeitig Wasserstoff sind.

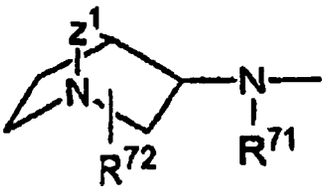
3. Benzolsulfonamid-Derivat nach Anspruch 1, worin das Derivat die Formel (1-b) aufweist, eine tautomere oder stereoisomere Form davon oder ein Salz davon:



(I-b)

worin

R^1 Fluor, Chlor, Brom, Iod oder Nitro bedeutet,
R^2 Fluor, Chlor, Brom, Iod oder Nitro bedeutet,
R^3 Acetyl, Cyano oder Tetrazolyl bedeutet,
R^4



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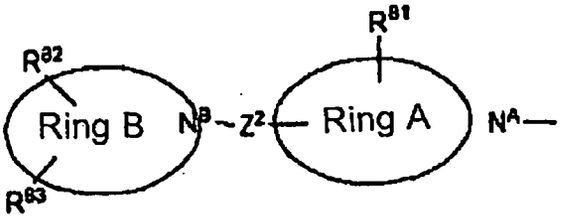


bedeutet,

worin

R^{71} Wasserstoff oder C_{1-6}-Alkyl bedeutet, welches gegebenenfalls substituiert ist mit Amino, Hydroxy, Carboxy, Pyrrolidinyl oder Piperidinyl, worin das Pyrrolidinyl und Piperidinyl gegebenenfalls substituiert sind mit Mono- oder Dioxo,
R^{72} Wasserstoff, Carboxy, C_{1-6}-Alkanoyl, Amino, (C_{1-6}-Alkyl)amino, Di-(C_{1-6}-alkyl)amino, N-(C_{1-6}-alkyl)amino-carbonyl, C_{1-6}-Alkyl, welches gegebenenfalls substituiert ist mit Hydroxy, Carboxy oder Mono-, Di- oder Trihalogen, C_{1-6}-Alkoxy bedeutet, welches gegebenenfalls substituiert ist mit Mono-, Di- oder Trihalogen, Pyrrolidinyl oder Piperidinyl, worin das Pyrrolidinyl und Piperidinyl gegebenenfalls substituiert sind mit Mono- oder Dioxo,
Z^1 -$[CH_2]_p$- bedeutet, worin p eine ganze Zahl 1 oder 2 bedeutet,
R^{81} Wasserstoff, C_{1-6}-Alkoxycarbonyl oder C_{1-6}-Alkyl bedeutet, welches substituiert ist mit Pyrrolidinyl oder Piperidinyl, worin das Pyrrolidinyl und Piperidinyl gegebenenfalls substituiert sind mit Mono- oder Dioxo,
R^{82} Wasserstoff, Hydroxy, Carboxy oder C_{1-6}-Alkyl bedeutet, welches substituiert ist mit Hydroxy, Amino oder Carboxy,
R^{83} Wasserstoff, Hydroxy, Carboxy oder C_{1-6}-Alkyl bedeutet, welches substituiert ist mit Hydroxy, Amino oder Carboxy,

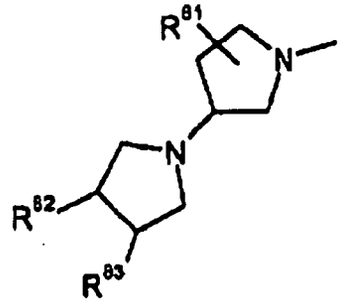
mit der Maßgabe, dass R^{82} oder R^{83} nicht Wasserstoff ist, wenn R^{81} Wasserstoff ist,

Z^2 -$[CH_2]_q$- bedeutet, worin q eine ganze Zahl bedeutet, ausgewählt aus 0 bis 3,

Ring A einen 3- bis 8-gliedrigen gesättigten heterozyklischen Ring bedeutet, worin das Stickstoffatom N^A das einzige Heteroatom ist,
Ring B einen 3- bis 8-gliedrigen gesättigten heterozyklischen Ring bedeutet, worin das Stickstoffatom N^B das einzige Heteroatom ist.

4. Benzolsulfonamid-Derivat nach Anspruch 3, eine tautomere oder stereoisomere Form davon oder ein Salz davon, worin

R^1 Fluor, Chlor oder Brom bedeutet,
R^2 Fluor, Chlor oder Brom bedeutet,
R^3 Cyano bedeutet,
R^4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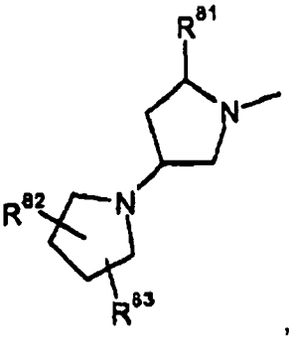
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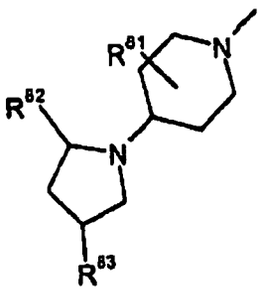
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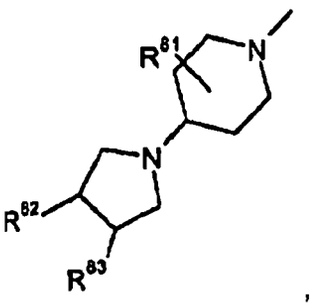
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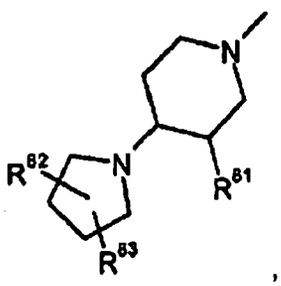
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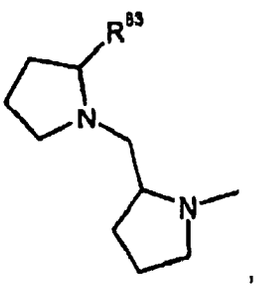
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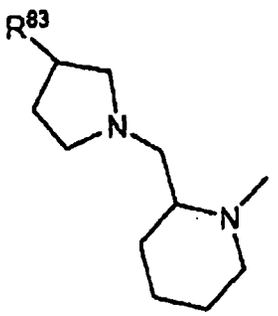

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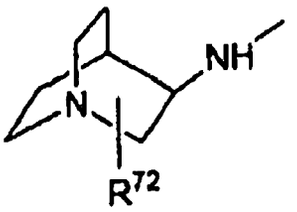


bedeutet, worin
R^{72} Wasserstoff, Carboxy, C_{1-6}-Alkanoyl, Amino, (C_{1-6}-Alkyl)amino, Di-(C_{1-6}-alkyl)amino, N-(C_{1-6}-alkyl)amino-carbonyl, C_{1-6}-Alkyl, welches gegebenenfalls substituiert ist mit Hydroxy, Carboxy oder Mono-, Di- oder Trihalogen, C_{1-6}-Alkoxy bedeutet, welches gegebenenfalls substituiert ist mit Mono-, Di- oder Trihalogen, Pyrrolidinyl oder Piperidinyl, worin das Pyrrolidinyl und Piperidinyl gegebenenfalls substituiert sind mit Mono- oder Dioxo,
R^{81} Wasserstoff, Methoxycarbonyl oder C_{1-6}-Alkyl bedeutet, welches substituiert ist mit 2-Oxopyrrolidin-1-yl, 2,5-Dioxopyrrolidin-1-yl, 2-Oxo-piperidin-1-yl, 2-Oxopiperidin-3-yl, 4-Oxopiperidin-1-yl, 2-Oxopiperidin-6-yl, 2,5-Dioxopiperidin-1-yl, 2,6-Dioxopiperidin-1-yl oder 2,6-Dioxo-piperidin-3-yl,
R^{82} Wasserstoff, Hydroxy oder C_{1-6}-Alkyl bedeutet, welches substituiert ist mit Hydroxy,
R^{83} Wasserstoff, Hydroxy oder Carboxy bedeutet, und

mit der Maßgabe, dass R^{81} kein Wasserstoff ist, wenn R^{82} und R^{83} gleichzeitig Wasserstoff sind, oder dass R^{82} kein Wasserstoff ist, wenn R^{81} und R^{83} gleichzeitig Wasserstoff sind.

5. Benzolsulfonamid-Derivat, eine tautomere oder stereoisomere Form davon oder ein physiologisch annehmbares Salz davon nach einem der Ansprüche 1 bis 4, worin das Benzolsulfonamid-Derivat der Formel ausgewählt ist aus der Gruppe bestehend aus

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)-5-cyano-2-(3,5-dichlorphenoxy)benzolsulfonamid,
(S)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)-5-cyano-2-(3,5-dichlorphenoxy)benzolsulfonamid,
4-(3,5-Dichlorphenoxy)-3-{4-[(2S)-1-hydroxy-1-methylethyl)-pyrrolidin-1-yl]-piperidin-1-sulfonyl}-benzonitril,
4-(3,5-Dichlorphenoxy)-3-[3-(2,5-dioxopyrrolidin-1-ylmethyl)-4-pyrrolidin-1-yl-piperidin-1-sulfonyl]-benzonitril,
4-(3,5-Dichlorphenoxy)-3-{4-[(2S)-hydroxymethylpyrrolidin-1-yl]-piperidin-1-sulfonyl}-benzonitril,
4-(3,5-Dichlorphenoxy)-3-{(2S)-[(2S)-hydroxymethylpyrrolidin-1-ylmethyl]-pyrrolidin-1-sulfonyl}-benzonitril,
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)-2-(3,5-dichlorphenylsulfanyl)-5-nitro-benzolsulfonamid,
4-(3,5-Dichlorphenoxy)-3-(4-((3S, 4S)-3,4-dihydroxypyrrolidin-1-yl)piperidin-1-yl-sulfonyl)-benzonitril,
(3'S, 5'S)-Methyl-1'-(5-cyano-2-(3,5-dichlorphenoxy)phenylsulfonyl)-1,3'-bipyrrolidin-5'-carboxylat,

3-(4-((3S,4S)-3-(tert-butyldimethylsilyloxy)-4-hydroxypyrrolidin-1-yl)piperidin-1-yl-sulfonyl)-4-(3,5-dichlorphenoxy)benzonitril,
4-(3,5-Dichlorphenoxy)-3-((3S,3'S,4S)-3,4-dihydroxy-1,3'-bipyrrolidin-1'-ylsulfonyl)-benzonitril,
(S)-1-(1-(5-Cyano-2-(3,5-dichlorphenoxy)phenylsulfonyl)piperidin-4-yl)pyrrolidin-2-carbonsäure,
4-(3,5-Dichlorphenoxy)-3-(2-((3-hydroxypyrrolidin-1-yl)methyl)piperidin-1-ylsulfonyl)benzonitril und
(R)-5-Cyano-2-(3,5-dichlorphenoxy)-N-(2-(2,5-dioxopyrrolidin-1-yl)ethyl)-N-(1-aza-bicyclo[2.2.2]oct-3-yl)benzolsulfonamid.

6. Arzneimittel, welches das Benzolsulfonamid-Derivat der Formel (I), eine tautomere oder stereoisomere Form davon oder ein physiologisch annehmbares Salz davon nach Anspruch 1 als Wirkstoff enthält.

7. Arzneimittel nach Anspruch 6, welches weiter eine oder mehrere pharmazeutisch annehmbare Trägersubstanzen umfasst.

8. Arzneimittel nach Anspruch 6, worin das Benzolsulfonamid-Derivat der Formel (I), eine tautomere oder stereoisomere Form davon oder ein physiologisch annehmbares Salz davon ein CCR3-Antagonist ist.

9. Arzneimittel nach Anspruch 6, welches für die Behandlung und/oder Prophylaxe einer entzündlichen Störung oder Erkrankung geeignet ist.

10. Arzneimittel nach Anspruch 9, worin die entzündliche Störung oder Erkrankung ausgewählt ist aus der Gruppe

bestehend aus Asthma, Rhinitis, allergischen Erkrankungen und Autoimmunpathologien.

11. Arzneimittel nach Anspruch 6, das für die Behandlung oder Prävention einer Erkrankung geeignet ist, ausgewählt aus der Gruppe bestehend aus HIV, Lungengranulom und Alzheimer-Krankheit.

12. Verwendung des Benzolsulfonamid-Derivats, einer tautomeren oder stereoisomeren Form davon oder eines physiologisch annehmbaren Salzes davon nach einem der Ansprüche 1 bis 5 bei der Herstellung eines Arzneimittels für die Behandlung oder Prävention einer mit CCR3 in Verbindung stehenden Störung oder Erkrankung.

13. Verwendung nach Anspruch 12, worin die Störung oder Erkrankung eine entzündliche oder immunregulatorische Störung oder Erkrankung ist.

14. Verwendung nach Anspruch 12, worin die Störung oder Erkrankung ausgewählt wird aus der Gruppe bestehend aus Asthma, Rhinitis, allergischen Erkrankungen und Autoimmunpathologien.

15. Verwendung nach Anspruch 12, worin die Störung oder Erkrankung ausgewählt wird aus der Gruppe bestehend aus HIV, Lungengranulom und Alzheimer-Krankheit.

16. Verwendung nach Anspruch 12, worin das Benzolsulfonamid-Derivat, eine tautomere oder stereoisomere Form davon oder ein physiologisch annehmbares Salz davon mit einem oder mehreren pharmazeutisch annehmbaren Trägersubstanzen formuliert wird.

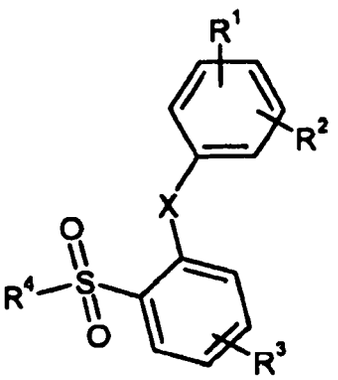
17. Verwendung von mindestens einer Verbindung nach Anspruch 1 bei der Herstellung eines Arzneimittels zum Kontrollieren bzw. Bekämpfen einer entzündlichen oder immunregulatorischen Störung oder Erkrankung, worin die Menge der Verbindung in dem Arzneimittel eine bezüglich CCR3 antagonistisch wirksame Menge ist.

18. Arzneimittel nach Anspruch 7, worin die Trägersubstanz eine inerte Substanz wie etwa ein Träger, ein Verdünnungsmittel, ein Aromastoff, ein Süßstoff, eine Gleitsubstanz, ein Lösungsvermittler, ein Suspensionmittel, ein Bindemittel, ein Tablettenaufschlußmittel oder ein Verkapselungsmittel ist.

19. Verwendung nach Anspruch 16, worin die Trägersubstanz eine inerte Substanz wie etwa ein Träger, ein Verdünnungsmittel, ein Aromastoff, ein Süßstoff, eine Gleitsubstanz, ein Lösungsvermittler, ein Suspensionmittel, ein Bindemittel, ein Tablettenaufschlußmittel oder ein Verkapselungsmittel ist.

Revendications

1. Dérivé de benzènesulfonamide de formule (I), sa forme tautomère ou stéréoisomère, ou un sel de celui-ci :

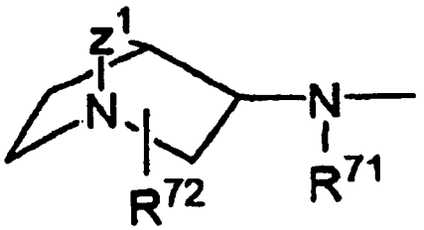


(I)

dans lequel :

X représente O ou S ;

R^1 représente l'hydrogène, un groupe halogène, hydroxy, nitro, cyano, alcoxycarbonyle en C_{1-6}, amino, alkylamino en C_{1-6}, dialkylamino en C_{1-6}, alcanoyle en C_{1-6}, phényle, alkyle en C_{1-6} éventuellement substitué par mono-, di-, ou tri-halogène, ou alcoxy en C_{1-6} éventuellement substitué par mono-, di-, ou tri-halogène ;
R^2 représente l'hydrogène, un groupe halogène, hydroxy, nitro, cyano, alcoxycarbonyle en C_{1-6}, amino, alkylamino en C_{1-6}, dialkylamino en C_{1-6}, alcanoyle en C_{1-6}, phényle, alkyle en C_{1-6} éventuellement substitué par mono-, di-, ou tri-halogène ou alcoxy en C_{1-6} éventuellement substitué par mono-, di- ou tri-halogène ;
R^3 représente l'hydrogène, un groupe halogène, hydroxy, nitro, cyano, amino, carboxy, tétrazolyle, alcoxy en C_{1-6}, alcoxycarbonyle en C_{1-6}, alcanoyle en C_{1-6}, alkanoylamino en C_{1-6}, alkyle en C_{1-6} éventuellement substitué par mono-, di-, ou tri-halogène ou hydroxy ;
R^4 représente



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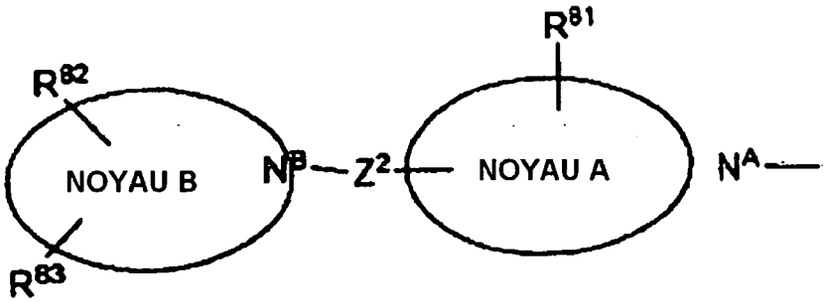
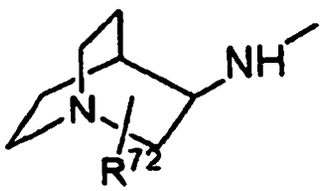


dans lequel :

R^{71} représente l'hydrogène, ou un groupe alkyle en C_{1-6} éventuellement substitué par amino, hydroxy, carboxy, pyrrolidinyle ou pipéridinyle, dans lequel lesdits groupes pyrrolidinyle et pipéridinyle sont éventuellement substitués par mono- ou di-oxo ;
R^{72} représente l'hydrogène, un groupe carboxy, alcanoyle en C_{1-6}, amino, alkylamino en C_{1-6}, dialkylamino en C_{1-6}, N-(alkyle en C_{1-6})aminocarbonyle, alkyle en C_{1-6} éventuellement substitué par hydroxy, carboxy, ou mono-, di- ou tri-halogène, alcoxy en C_{1-6} éventuellement substitué par mono-, di- ou tri-halogène, pyrrolidinyle ou pipéridinyle, dans lequel lesdits groupes pyrrolidinyle et pipéridinyle sont éventuellement substitués par mono- ou di-oxo ;
Z^1 représente $-(CH_2)_p-$, dans lequel p représente un nombre entier égal à 1 ou 2.
R^{81} représente l'hydrogène, un groupe alcoxycarbonyle en C_{1-6}, ou alkyle en C_{1-6} substitué par pyrrolidinyle ou pipéridinyle, dans lequel lesdits groupes pyrrolidinyle et pipéridinyle sont éventuellement substitués par mono ou di-oxo ;
R^{82} représente l'hydrogène, un groupe hydroxy, carboxy ou alkyle en C_{1-6} substitué par hydroxy, amino, ou carboxy,
R^{83} représente l'hydrogène, un groupe hydroxy, carboxy ou alkyle en C_{1-6} substitué par hydroxy, amino, ou

carboxy,
à condition que lorsque R^{81} est l'hydrogène, R^{82} ou R^{83} n'est pas l'hydrogène,
Z^2 représente $-(CH_2)_q-$, dans lequel q représente un nombre entier choisi de 0 à 3.
le noyau A représente un noyau hétérocyclique saturé de 3 à 8 chaînons, dans lequel l'atome d'azote N^A est le seul hétéroatome;
le noyau B représente un noyau hétérocyclique saturé de 3 à 8 chaînons, dans lequel l'atome d'azote N^B est le seul hétéroatome;

2. Dérivé de benzènesulfonamide de formule (I), sa forme tautomère ou stéréoisomère, ou un sel de celui-ci selon la revendication 1,
dans lequel R^4 représente



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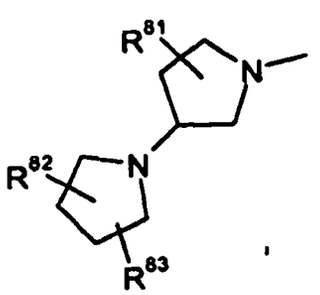

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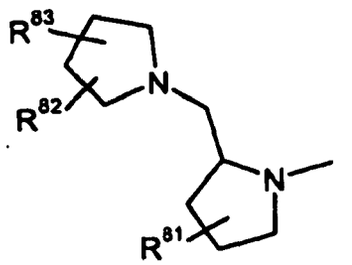

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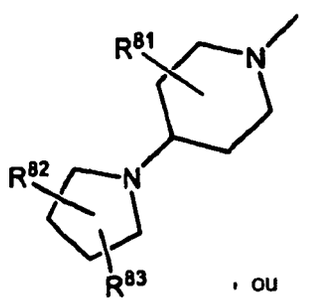

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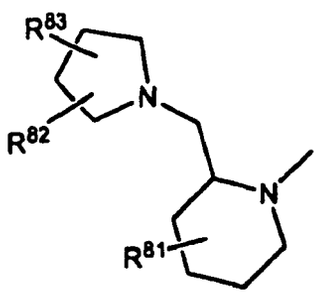
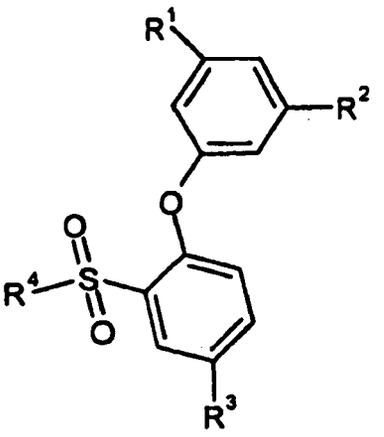


dans lequel :

R^{72} représente l'hydrogène, un groupe carboxy, alcanoyle en C_{1-6}, amino, alkylamino en C_{1-6}, dialkylamino en C_{1-6}, N-(alkyle en C_{1-6})aminocarbonyle, alkyle en C_{1-6} éventuellement substitué par hydroxy, carboxy, ou mono-, di- ou tri-halogène, alcoxy en C_{1-6} éventuellement substitué par mono-, di- ou tri-halogène, pyrrolidinyle ou

pipéridinyle, dans lequel lesdits groupes pyrrolidinyle et pipéridinyle sont éventuellement substitués par mono ou di-oxo ;
R^{81} représente l'hydrogène, un groupe méthoxycarbonyle ou alkyle en C_{1-6} substitué par 2-oxo-pyrrolidin-1-yl, 2,5-dioxo-pyrrolidin-1-yl, 2-oxo-pipéridin-1-yl, 2-oxo-pipéridin-3-yl, 4-oxo-pipéridin-1-yl, 2-oxo-pipéridin-6-yl, 2,5-dioxo-pipéridin-1-yl, 2,6-dioxo-pipéridin-1-yl, ou 2,6-dioxo-pipéridin-3-yl;
R^{82} représente l'hydrogène, un groupe hydroxy ou alkyle en C_{1-6} substitué par hydroxy ;
R^{83} représente l'hydrogène, un groupe hydroxy ou carboxy; et
à condition que lorsque R^{82} et R^{83} sont en même temps l'hydrogène, R^{81} n'est pas l'hydrogène, ou lorsque R^{81} et R^{83} sont en même temps l'hydrogène, R^{82} n'est pas l'hydrogène.

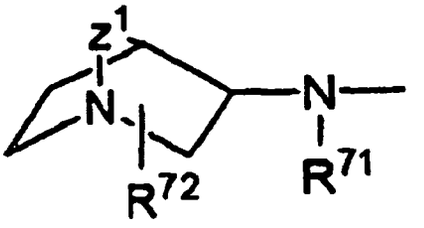
3. Dérivé de benzènesulfonamide selon la revendication 1, dans lequel le dérivé est de formule (I-b), sa forme tautomère ou stéréoisomère, ou un sel de celui-ci :



(I-b)

dans lequel :

R^1 représente un groupe fluor, chlore, brome, iode ou nitro ;
R^2 représente un groupe fluor, chlore, brome, iode ou nitro ;
R^3 représente un groupe acétyle, cyano, ou tétrazolyle ;
R^4 représente



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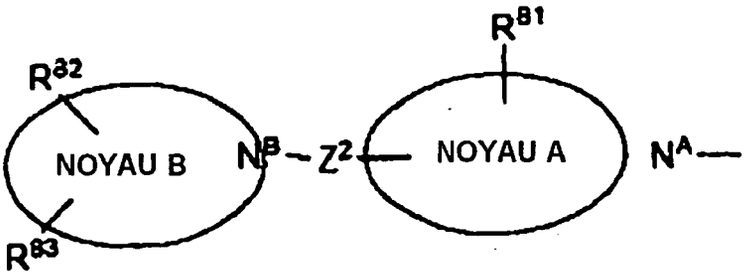


dans lequel :

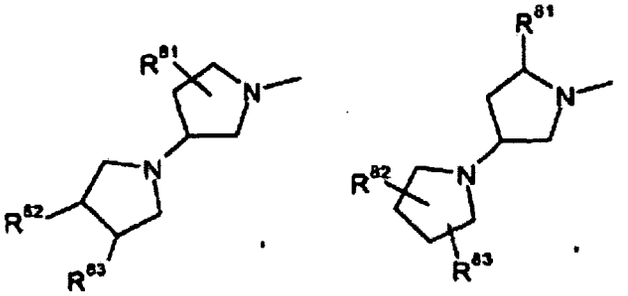
R^{71} représente l'hydrogène, ou un groupe alkyle en C_{1-6} éventuellement substitué par amino, hydroxy, carboxy, pyrrolidinyle ou pipéridinyle, dans lequel lesdits groupes pyrrolidinyle et pipéridinyle sont éventuellement substitués par mono- ou di-oxo ;
R^{72} représente l'hydrogène, un groupe carboxy, alcanoyle en C_{1-6}, amino, alkylamino en C_{1-6}, dialkylamino en C_{1-6}, N-(alkyle en C_{1-6})aminocarbonyle, alkyle en C_{1-6} éventuellement substitué par hydroxy, carboxy, ou mono-, di- ou tri-halogène, alcoxy en C_{1-6} éventuellement substitué par mono-, di- ou tri-halogène, pyrrolidinyle ou pipéridinyle, dans lequel lesdits groupes pyrrolidinyle et pipéridinyle sont éventuellement substitués par mono ou di-oxo ;
Z^1 représente $-(CH_2)_p-$, dans lequel p représente un nombre entier égal à 1 ou 2.
R^{81} représente l'hydrogène, un groupe alcoxycarbonyle en C_{1-6}, ou alkyle en C_{1-6} substitué par pyrrolidinyle ou pipéridinyle, dans lequel lesdits groupes pyrrolidinyle et pipéridinyle sont éventuellement substitués par mono ou di-oxo ;
R^{82} représente l'hydrogène, un groupe hydroxy, carboxy ou alkyle en C_{1-6} substitué par hydroxy, amino, ou carboxy,
R^{83} représente l'hydrogène, un groupe hydroxy, carboxy ou alkyle en C_{1-6} substitué par hydroxy, amino, ou carboxy, à condition que lorsque R^{81} est l'hydrogène, R^{82} ou R^{83} n'est pas l'hydrogène ;
Z^2 représente $-[CH_2]_q-$,

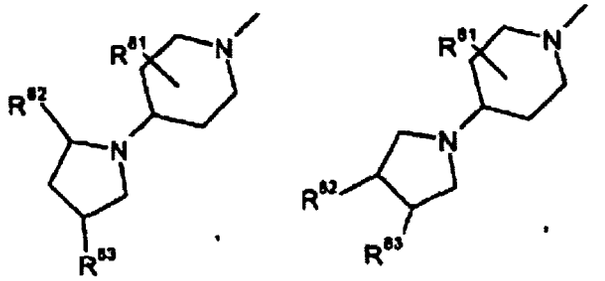
dans lequel

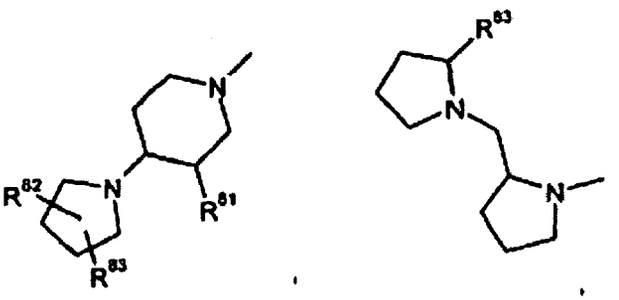
q représente un nombre entier choisi de 0 à 3;
le noyau A représente un noyau hétérocyclique saturé de 3 à 8 chaînons, dans lequel l'atome d'azote N^A est le seul hétéroatome ;
le noyau B représente un noyau hétérocyclique saturé de 3 à 8 chaînons, dans lequel l'atome d'azote N^B est le seul hétéroatome.

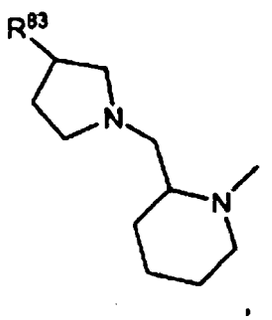
4. Dérivé de benzènesulfonamide selon la revendication 3, sa forme tautomère ou stéréoisomère, ou un sel de celui-ci : dans lequel :

R^1 représente un groupe fluor, chlore ou brome ;
R^2 représente un groupe fluor, chlore ou brome ;
R^3 représente un groupe cyano ;
R^4 représente

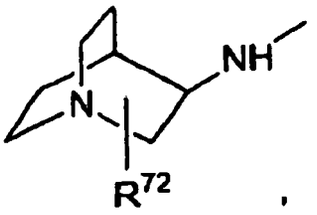








ou



dans lequel :

R^{72} représente l'hydrogène, un groupe carboxy, alcanoyle en C_{1-6}, amino, alkylamino en C_{1-6}, dialkylamino en C_{1-6}, N-(alkyle en C_{1-6})aminocarbonyle, alkyle en C_{1-6}, éventuellement substitué par hydroxy, carboxy, ou mono-, di- ou tri-halogène, alcoxy en C_{1-6} éventuellement substitué par mono-, di- ou tri-halogène, pyrrolidinyle ou pipéridinyle, dans lequel lesdits groupes pyrrolidinyle et pipéridinyle sont éventuellement substitués par mono ou di-oxo ;
R^{81} représente l'hydrogène, un groupe méthoxycarbonyle ou alkyle en C_{1-6} substitué par 2-oxo-pyrrolidin-1-yl, 2,5-dioxo-pyrrolidin-1-yl, 2-oxo-pipéridin-1-yl, 2-oxo-pipéridin-3-yl, 4-oxo-pipéridin-1-yl, 2-oxo-pipéridin-6-yl, 2,5-dioxo-pipéridin-1-yl, 2,6-dioxo-pipéridin-1-yl, ou 2,6-dioxo-pipéridin-3-yl;
R^{82} représente l'hydrogène, un groupe hydroxy, alkyle en C_{1-6} substitué par hydroxy ;
R^{83} représente l'hydrogène, un groupe hydroxy ou carboxy; et
à condition que lorsque R^{82} et R^{83} sont en même temps l'hydrogène, R^{81} n'est pas l'hydrogène, ou lorsque R^{81} et R^{83} sont en même temps l'hydrogène, R^{82} n'est pas l'hydrogène.

5. Dérivé de benzènesulfonamide, sa forme tautomère ou stéréoisomère, ou un sel physiologiquement acceptable de celui-ci selon les revendications 1 à 4, dans lequel le dérivé de benzènesulfonamide de la formule est choisi dans le groupe comprenant :

le (R)-N-(1-aza-bicyclo[2.2.2]oct-3-yl)-5-cyano-2-(3,5-di-chloro-phenoxy)benzènesulfonamide;
le (S)-N-(1-aza-bicyclo[2.2.2]oct-3-yl)-5-cyano-2-(3,5-di-chloro-phénoxy)benzènesulfonamide;
le 4-(3,5-dichloro-phénoxy)-3-{4-[(2S)-(1-hydroxy-1-méthyléthyl)-pyrrolidin-1-yl]-pipéridin-1-sulfonyl}-benzonitrile;
le 4-(3,5-dichloro-phénoxy)-3-[3-(2,5-dioxo-pyrrolidin-1-yl-méthyl)-4-pyrrolidin-1-yl-pipéridin-1-sulfonyl]-benzonitrile;
le 4-(3,5-dichloro-phenoxy)-3-{4-[(2S)-hydroxy-méthylpyrrolidin-1-yl]-pipéridin-1-sulfonyl}-benzonitrile ;
le 4-(3,5-Dichloro-phénoxy)-3-{(2S)-[(2S)-hydroxy-methyl-pyrrolidin-1-yl-méthyl]-pyrrolidine-1-sulfonyl}-benzonitrile;
le N-(1-aza-bicyclo[2.2.2]oct-3-yl)-2-(3,5-dichlorophénylsulfanyl)-5-nitro-benzènesulfonamide;
le 4-(3,5-dichlorophénoxy)-3-(4-((3S,4S)-3,4-dihydroxypyrrolidin-1-yl)pipéridin-1-yl-sulfonyl)benzonitrile;
le (3'S,5'S)-méthyl-1'-(5-cyano-2-(3,5-dichloro-phénoxy)-phénylsulfonyl)-1,3'-bipyrrolidine-5'carboxylate;
le 3-(4-((3S,4S)-3-(tert-butyldiméthylsilyloxy)-4-hydroxy-pyrrolidin-1-yl)pipéridin-1-yl-sulfonyl)-4-(3,5-dichloro-phénoxy)benzonitrile;
le 4-(3,5-dichlorophénoxy)-3-((3S,3'S,4S)-3,4-dihydroxy-1,3'-bipyrrolidin-1'-yl-sulfonyl)benzonitrile;
l'acide (S)-1-(1-(5-cyano-2-(3,5-dichlorophénoxy)-phénylsulfonyl)pipéridin-4-yl)pyrrolidine-2-carboxylique;
le 4-(3,5-dichlorophénoxy)-3-(2-((3-hydroxy-pyrrolidin-1-yl)-méthyl)pipéridin-1-yl-sulfonyl)benzo-nitrile; et
(R)-le 5-cyano-2-(3,5-dichlorophénoxy)-N-(2-(2,5-dioxopyrrolidin-1-yl)éthyl)-N-(1-aza-bicyclo[2.2.2]oct-3-yl)-benzenesulfonamide.

6. Médicament comprenant le dérivé de benzènesulfonamide de formule (I), sa forme tautomère ou stéréoisomère, ou un sel physiologiquement acceptable de celui-ci selon la revendication 1 en tant qu'ingrédient actif.

7. Médicament selon la revendication 6, comprenant en outre un ou plusieurs excipients pharmaceutiquement acceptables.

8. Médicament selon la revendication 6, dans lequel ledit dérivé de benzènesulfonamide de formule (I), sa forme tautomère ou stéréoisomère, ou un sel physiologiquement acceptable de celui-ci est un antagoniste de CCR3.

9. Médicament selon la revendication 6 adéquat pour le traitement et/ou la prophylaxie d'une maladie ou d'un trouble inflammatoire.

10. Médicament selon la revendication 9, dans lequel ledit trouble ou maladie inflammatoire est choisi dans le groupe comprenant l'asthme, la rhinite, les maladies allergiques et les pathologies auto-immunes.

11. Médicament selon la revendication 6 adéquat pour le traitement ou la prévention d'une maladie choisie dans le groupe comprenant le VIH, le granulome du poumon, et la maladie d'Alzheimer.

12. Utilisation du dérivé de benzènesulfonamide, de sa forme tautomère ou stéréoisomère, ou d'un sel physiologiquement acceptable de celui-ci selon les revendications 1 à 5 dans la préparation d'un médicament pour le traitement ou la prévention d'une maladie ou d'un trouble associé au CCR3.

13. Utilisation selon la revendication 12, dans laquelle ledit trouble ou ladite maladie est un trouble ou une maladie inflammatoire ou d'immunorégulation.

14. Utilisation selon la revendication 12, dans laquelle ledit trouble ou ladite maladie est choisi dans le groupe comprenant l'asthme, la rhinite, les maladies allergiques et les pathologies auto-immunes.

15. Utilisation selon la revendication 12, dans laquelle ledit trouble ou ladite maladie est choisi dans le groupe comprenant le VIH, le granulome du poumon, et la maladie d'Alzeihmer.

16. Utilisation selon la revendication 12, dans laquelle ledit dérivé de benzènesulfonamide, sa forme tautomère ou stéréoisomère, ou un sel physiologiquement acceptable de celui-ci est formulé avec un ou plusieurs excipients pharmaceutiquement acceptables.

17. Utilisation d'au moins un composé selon la revendication 1 dans la préparation d'un médicament pour contrôler une maladie ou un trouble inflammatoire ou d'immunorégulation, dans laquelle la quantité de composé dans le médicament est dans une quantité efficace pour une activité antagoniste de CCR3.

18. Médicament selon la revendication 7, dans lequel l'excipient est une substance inerte telle qu'un support, un diluant, un aromatisant, un édulcorant, un lubrifiant, un solubilisant, un agent de suspension, un liant, un agent de désintégration de comprimé ou un agent d'encapsulation.

19. Utilisation selon la revendication 16, dans laquelle l'excipient est une substance inerte telle qu'un support, un diluant, un aromatisant, un édulcorant, un lubrifiant, un solubilisant, un agent de suspension, un liant, un agent de désintégration de comprimé ou un agent d'encapsulation.

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