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(54) **CHEMOKINE RECEPTOR ANTAGONISTS AND METHODS OF USE THEREFOR**

CHEMOKIN REZEPTOR ANTAGONISTEN UND VERWNDUNG

ANTAGONISTES DU RECEPTEUR DE CHEMOKINE ET LEURS PROCEDES D'UTILISATION

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(Cont. next page)

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Description

RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. Serial No. 09/148,823, filed September 4, 1998, which is a continuation-in-part of U.S. Serial No. 09/010,320, filed January 21, 1998, now abandoned.

BACKGROUND OF THE INVENTION

[0002] Chemoattractant cytokines or chemokines are a family of proinflammatory mediators that promoce recruitment and activation of multiple lineages of leukocytes and lymphocytes. They can be released by many kinds of tissue cells after activation. Continuous release of chemokines at sites of inflammation mediates the ongoing migration of effector cells in chronic inflammation. The chemokines characterized to date are related in primary structure. They share four conserved cysteines, which form disulfide bonds. Based upon this conserved cysteine motif, the family is divided into two main branches, designated as the C-X-C chemokines (α-chemokines), and the C-C chemokines (β-chemokines), in which the first two conserved cysteines are separated by an intervening residue, or adjacent respectively (Baggiolini, M. and Dahinden, C. A., *Immunology Today*, *15*:127-133 (1994)).

[0003] The C-X-C chemokines include a number of potent chemoattractants and activators of neutrophils, such as interleukin 8 (IL-8), PF4 and neutrophil-activating peptide-2 (NAP-2). The C-C chemokines include RANTES (Regulated on Activation, Normal T Expressed and Secreted), the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β), eotaxin and human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2, MCP-3), which have been characterized as chemoattractants and activators of monocytes or lymphocytes but do not appear to be chemoattractants for neutrophils. Chemokines, such as RANTES and MIP-1α, have been implicated in a wide range of human acute and chronic inflammatory diseases including respiratory diseases, such as asthma and allergic disorders.

[0004] The chemokine receptors are members of a superfamily of G protein-coupled receptors (GPCR) which share structural features that reflect a common mechanism of action of signal transduction (Gerard, C. and Gerard, N.P., *Annu Rev. Immunol., 12*:775-808 (1994); Gerard, C. and Gerard, N. P., *Curr. Opin. Immunol., 6*:140-145 (1994)). Conserved features include seven hydrophobic domains spanning the plasma membrane, which are connected by hydrophilic extracellular and intracellular loops. The majority of the primary sequence homology occurs in the hydrophobic transmembrane regions with the hydrophilic regions being more diverse. The first receptor for the C-C chemokines that was cloned and expressed binds the chemokines MIP-1α and RANTES. Accordingly, this MIP-1α/RANTES receptor was designated C-C chemokine receptor 1 (also referred to as CCR-1; Neote, K., *et al*., Cell, *72*:415-425 (1993); Horuk, R. *et al*., WO 94/11504, May *26*, 1994; Gao, J.-I. *et al*., *J. Exp. Med*., *177*:1421-1427 (1993)). Three receptors have been characterized which bind and/or signal in response to RANTES: CCR3 mediates binding and signaling of chemokines including eotaxin, RANTES, and MCP-3 (Ponath et al., *J. Exp. Med*., *183*:2437 (1996)), CCR4 binds chemokines including RANTES, MIP-1α, and MCP-1 (Power, et al., *J. Biol. Chem*., *270*:19495 (1995)), and CCR5 binds chemokines including MIP-1α, RANTES, and MLP-1β (Samson, *et al*., *Biochem. 35*: 3362-3367 (1996)). RANTES is a chemotactic chemokine for a variety of cell types, including monocytes, eosinophils, and a subset of T-cells. The responses of these different cells may not all be mediated by the same receptor, and it is possible that the receptors CCR1, CCR4 and CCR5 will show some selectivity in receptor distribution and function between leukocyte types, as has already been shown for CCR3 (Ponath *et al*.). In particular, the ability of RANTES to induce the directed migration of monocytes and a memory population of circulating T-cells (Schall, T. et al., *Nature, 347*:669-71 (1990)) suggests this chemokine and its receptor (s) may play a critical role in chronic inflammatory diseases, since these diseases are characterized by destructive infiltrates of T cells and monocytes.

[0005] Many existing drugs have been developed as antagonists of the receptors for biogenic amines, for example, as antagonists of the dopamine and histamine receptors. No successful antagonists have yet been developed to the receptors for the larger proteins such as chemokines and csa. Small molecule antagonists of the interaction between C-C chemokine receptors and their ligands, including RANTES and MIP-1α, would provide compounds useful for inhibiting harmful inflammatory processes "triggered" by receptor ligand interaction, as well as valuable tools for the investigation of receptor-ligand interactions.

SUMMARY OF THE INVENTION

[0006] It has now been found that a class of small organic molecules are antagonists of chemokine receptor function and can inhibit leukocyte activation and/or recruitment. An antagonist of chemokine receptor function is a molecule which can inhibit the binding and/or activation of one or more chemokines, including C-C chemokines such as RANTES, MIP-1α, MCP-2, MCP-3 and MCP-4 to one or more chemokine receptors on leukocytes and/or other cell types'. As a consequence, processes and cellular responses mediated by chemokine receptors can be inhibited with these small organic molecules. Based on this discovery, the molecules can be used in the treatment of a disease associated with aberrant leukocyte recruitment and/or activation and also in the treatment of a disease mediated by chemokine receptor function. The claimed compounds can be administered to a subject in need an effective amount of a compound or small organic molecule which is an antagonist of chemokine receptor function. Compounds or small organic molecules which have been identified as antagonists of chemokine receptor function are discussed in detail hereinbelow, and can be used for the manufacture of a medicament for treating or for preventing a disease associated with aberrant leukocyte recruitment and/or activation. The invention also relates to the disclosed compounds and small organic molecules for use in treating or preventing a disease associated with aberrant leukocyte recruitment and/or activation. The invention also includes pharmaceutical compositions comprising one or more of the compounds or small organic molecules which have been identified herein as antagonists of chemokine function and a suitable pharmaceutical carrier. The invention further relates to novel compounds which can be used to treat an individual with a disease associated with aberrant leukocyte recruitment and/or activation.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007]

Figure 1 is a schematic showing the preparation of the compounds represented by Structural Formula (I).

Figure 2 is a schematic showing the preparation of the compounds represented by Compound (VI-b).

Figure 3 is a schematic showing the preparation of the compounds represented by Structural Formula (I)

Figure 4 is a schematic showing the preparation of the compounds represented by Structural Formula (I), wherein Z is represented by Structural Formula (II) and wherein Ring A and/or Ring B in Z is substituted with R^{40}.

Figure 5 is a schematic showing the preparation of the compounds represented by Structural Formula (I), wherein Z is represented by Structural Formula (II) and wherein Ring A and/or Ring B in Z is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$.

Figures 6A-6Z show the structures of exemplary compounds of the present invention as well as other compounds which fall outside the present invention.

Figure 7 shows the preparation of compounds represented by Structural Formula (I) where in Z is represented by Structural Formulas (II) and wherein Ring A or Ring B in Z is substituted with R^{40}.

DETAILED DESCRIPTION OF THE INVENTION

[0008] The present invention relates to small molecule compounds which are modulators of chemokine receptor function. The compounds of the invention are suitable for use in the treatment of the human or animal body by therapy. In a preferred embodiment, the small molecule compounds are antagonists of chemokine receptor function.

[0009] Accordingly, processes or cellular responses mediated by the binding of a chemokine to a receptor can be inhibited (reduced or prevented, in whole or in part), including leukocyte migration, integrin activation, transient increases in the concentration of intracellular free calcium $[Ca^{++}]_i$, and/or granule release of proinflammatory mediators.

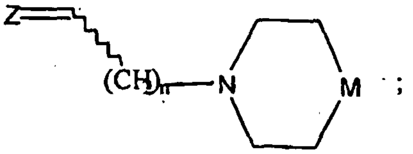
[0010] The invention further relates to the use of the claimed compounds in the manufacture of a medicament for treating, including prophylactically and therapeutically treatments, a disease associated with aberrant leukocyte recruitment and/or activation or mediated by chemokines or chemokine receptor function, including chronic inflammatory disorders characterized by the presence of RANTES, MIP-1α, MCP-2, MCP-3 and/or MCP-4 responsive T cells, monocytes and/or eosinophils, including but not limited to diseases such as arthritis (e.g., rheumatoid arthritis), atherosclerosis, arteriosclerosis, ischemia/reperfusion injury, diabetes mellitus (e.g., type 1 diabetes mellitus), psoriasis, multiple sclerosis, inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, rejection of transplanted organs and tissues (i.e., acute allograft rejection, chronic allograft rejection), graft versus host disease, as well as allergies and asthma. The compounds of the invention are particularly useful in the manufacture of medicaments for treating arthritis or multiple sclerosis. Other diseases associated with aberrant leukocyte recruitment and/or activation which can be treated (including prophylactic treatments) with the compounds disclosed herein are inflammatory diseases associated with Human Immunodeficiency Virus (HIV) infection, e.g., AIDS associated encephalitis, AIDS related maculopapular skin eruption, AIDS related interstitial pneumonia, AIDS related enteropathy, AIDS related periportal hepatic inflammation and AIDS related glomerulo nephritis. An effective amount of a claimed compound (i.e., one or more compounds) which inhibits chemokine receptor function, inhibits the binding of a chemokine to leukocytes and/or other cell types; and/or which inhibits leukocyte migration to, and/or activation at, can be administered at to a subject is need of treatment at sites of inflammation.

[0011] The invention further relates to use of the claimed compounds in the manufacture of a medicament for antagonizing a chemokine receptor, such as CCR1. Such medicaments can be administered to a mammal as described herein.

[0012] By administering such a medicament, chemokine-mediated chemotaxis and/or activation of pro-inflammatory cells bearing receptors for chemokines can be inhibited. As used herein, "pro-inflammatory cells" includes but is not limited to leukocytes, since chemokine receptors can be expressed on other cell types, such as neurons and epithelial cells.

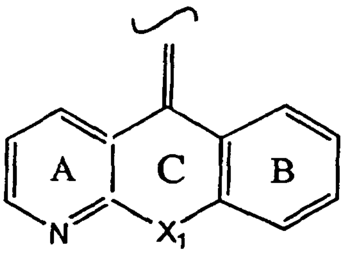
[0013] While not wishing to be bound by any particular theory or mechanism, it is believed that compounds of the invention are antagonists of the chemokine receptor CCR1, and that therapeutic benefits derived from the method of the invention are the result of antagonism of CCR1 function. Thus, compounds of the invention can be used to treat a medical condition involving cells which express CCR1 on their surface and which respond to signals transduced through CCR1, as well as the specific conditions recited above.

[0014] In one embodiment, the antagonist of chemokine receptor function is represented by Structural Formula (I):



and physiologically acceptable salts thereof.

[0015] Z is



(II)

wherein:

X_1 is -S-, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $S-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-NR_c-CH_2-$, $-CH_2-NR_c-$, $-SO-CH_2-$, $-CH_2-SO-$, $-S(O)_2-CH_2-$, $-CH_2-S(O)_2-$, -CH=CH-, $-NR_c-CO-$ or $-CO-NR_c-$;

R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group;

Ring A and Ring B are independently substituted or unsubstituted; said substituted aliphatic group comprises one or more substituents selected from the group consisting of an electron withdrawing group, halo, azido, -COOH, -OH, $-CONR^{24}R^{25}$, $-NR^{24}R^{25}$, $-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, $-S(O)_2NH_2$, guanidino, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$, -Q-H, -Q-(aliphatic group), -Q-(substituted aliphatic group), -Q-(aryl), -Q-(aromatic group), -Q-(substituted aromatic group), $-Q-(CH_2)_p-$(substituted or unsubstituted aromatic group), -Q-(non-aromatic heterocyclic group), $-Q-(CH_2)_p-$(non-aromatic heterocyclic group), aliphatic group and substituted aliphatic group; said substituted non-aromatic heterocyclic group comprises one or more substituents selected from the group consisting of an electron withdrawing group, halo, azido, -CN, -COOH, -OH, $-CONR^{24}R^{25}$, $-NR^{24}R^{25}$, $-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, $-S(O)_2NH_2$, guanidino, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$, -Q-H, -Q-(aliphatic group), -Q-(substituted aliphatic group), -Q-(aryl), -Q-(aromatic group), -Q-(substituted aromatic group), $-Q-(CH_2)_p-$(substituted or unsubstituted aromatic group), -Q-(non-aromatic heterocyclic group), $-Q-(CH_2)_p-$(non-aromatic heterocyclic group), aliphatic group, substituted aliphatic group, =O, =S, =NH, =N(aliphatic), =N(aromatic) and =N(substituted aromatic);

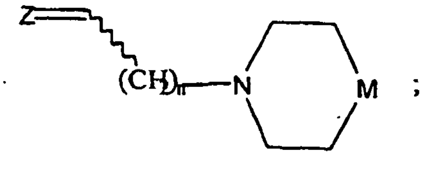
R^{20}, R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -NHC(O)-O-(aliphatic group), -NHC(O)-O-(aromatic group) or -NHC(O)-O-(non-aromatic heterocyclic group); or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

t is an integer from zero to three;
u is zero or one;
p is one to five;
Q is -O-, -S-, -S(O)-, $-S(O)_2-$, $-OS(O)_2-$, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, $-S(O)_2NH-$, $-NHS(O)_2-$, $-N(R^{23})-$, $-C(NR^{23})NHNH-$, $-NHNHC(NR^{23})-$, $-NR^{24}C(O)-$ or $-NR^{24}S(O)_2-$;
R^{23} is -H, an aliphatic group, a benzyl group, an aryl group or non-aromatic heterocyclic group;
R^{24} and R^{25} are independently -H, -OH, an aliphatic group, a substituted aliphatic group, a benzyl group, an aryl group or non-aromatic heterocyclic group;
said aliphatic group is a saturated or unsaturated C_1-C_{20} hydrocarbon;
said electron withdrawing group is alkylamino, alkylsulfonyl, carboxamido, carboxylic alkyl ester, -CH=NH or $-NO_2$;
the heterocycle of said non-aromatic heterocyclic group is a 5 to 8 membered non-aromatic ring that contains one or more heteroatoms selected from the group consisting of O, N, and S; and
said aromatic group is selected from the group consisting of a C_6 aromatic carbocycle, a C_5 - C_6 aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of O, S and N, and a C_6 aromatic carbocycle or a C_5 - C_6 aromatic heterocycle that is fused to one or more other rings.
n is an integer from one to four. Preferably, n is one; two or three. More preferably n is two.
M is $>CR^1R^2$. M is preferably $>C(OH)R^2$.
R^1 is -H, -OH, an aliphatic group, -O- (aliphatic group), -O- (substituted aliphatic group), -SH, -S- (aliphatic group), -S- (substituted aliphatic group), -OC(O)-(substituted aliphatic group), -C(O)O- (aliphatic group), -C(O)O- (substituted aliphatic group), -COOH, -CN, $-CO-NR^3R^4$, $-NR^3R^4$; or R^1 can be a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M. R^1 is preferably -H or -OH.
R^2 is -OH, an acyl group, substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group. R^2 is preferably an aromatic group or a substituted aromatic group. Preferably R^2 is an aromatic group substituted with halogen, for example a 4-chlorophenyl group.
R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group. The term acyl group represents an aliphatic carbonyl, aromatic carbonyl, aliphatic sulfonyl or aromatic sulfonyl.

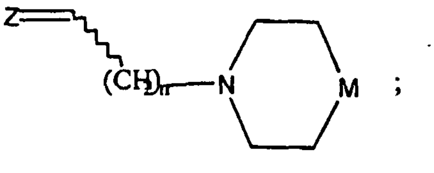
[0016] In some embodiments, R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, can alternatively form a substituted or unsubstituted non-aromatic heterocyclic ring.

[0017] In some embodiments the methylene group, $-(CH_2)_t-$, can be substituted or unsubstituted. In embodiments where M is $>CR^1R^2$ and R^1 is a covalent bond between the carbon atom at M and an adjacent carbon atom in the ring which contains M, the antagonist of chemokine function can be represented by Structural Formula (Ia).



Z, n and R^2 are as described in Structural Formula (I).

[0018] According to a different embodiment of the invention there is provided a compound of formula:

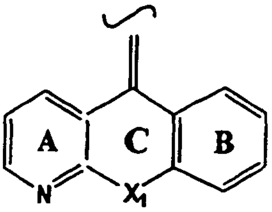


or physiologically acceptable salt thereof, wherein:

n is an integer from one to four;
M is $>CR^1R^2$
R^1 is -H, -OH, an aliphatic group, -O-(alipharic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$;
R^2 is -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group;
R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or
R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

said acyl group is an aliphatic carbonyl, aromatic carbonyl, aliphatic sulfonyl or aromatic sulfonyl;

Z is:



wherein:

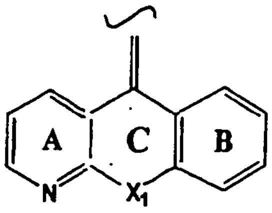
X_1 is -S-, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-NR_c-CH_2-$, $-CH_2-NR_c-$, $-SO-CH_2-$, $-CH_2-SO-$, $-S(O)_2-CH_2-$, $-CH_2-S(O)_2-$, -CH=CH-, $-NR_c-CO-$ or $-CO-NR_c-$;
R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group;

Ring A and Ring B are independently substituted or unsubstituted;
said substituted aliphatic group comprises one or more substituents selected from the group consiting of an electron withdrawing group, halo, -COOH, -OH, $-CONR^{24}R^{25}$, $-NR^{24}R^{25}$, $-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, $-S(O)_2NH_2$, guamdino, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, -Q-H, -Q-(aliphatic group), -Q-(substituted aliphatic group), -Q-(aryl), $-Q-(CH_2)_p-$(substituted or unsubstituted aromatic group), -Q-(non-aromatic heterocyclic group), $-Q-(CH_2)_p-$(non-aromatic heterocyclic group), oxo, epoxy, non-aromatic heterocycle, benzyl, substituted benzyl, aromatic group and substituted aromatic group;
said substituted benzyl group, substituted aromatic group, and Ring A or Ring B when substituted comprise one or more substitutents selected from the group consisting of an electron withdrawing group, halo, -CN, -COOH, -OH, $-CONR^{24}R^{25}$, $-NR^{24}R^{25}$, $-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, $-S(O)_2NH_2$, guanidino, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, -Q-H, -Q-(aliphatic group), -Q-(substituted aliphatic group), -Q-(aryl), $-Q-(CH_2)_p-$(substituted or unsubstituted aromatic group), -Q-(non-aromatic heterocyclic group), $-Q-(CH_2)_p-$(non-aromatic heterocyclic group), aliphatic group and substituted aliphatic group;
said substituted non-aromatic heterocyclic group comprises one or more substitutents selected from the group consisting of an electron withdrawing group, halo, -CN, -COOH, -OH, $-CONR^{24}R^{25}$, $-NR^{24}R^{25}$, $-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, $-S(O)_2NH_2$, guanidino, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, -Q-H, -Q-(aliphatic group), -Q-(substituted aliphatic group), -Q-(aryl), $-Q-(CH_2)_p-$(substituted or unsubstituted aromatic group), -Q-(non-aromatic heterocyclic group), $-Q-(CH_2)_p-$(non-aromatic heterocyclic group), aliphatic group, substituted aliphatic group, =O, =S, =NH, =N(aliphatic), =N(aromatic) and =N(substituted aromatic);
R^{20}, R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, -NHC(O)-O-(aliphatic group), -NHC(O)-O-(aromatic group) or -NHC(O)-O-(non-aromatic heterocyclic group); or
R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;
t is an integer from zero to three;

u is zero or one;
p is one to five;
Q is -O-, -S-, -S(O)-, -S(O)$_2$-, -OS(O)$_2$-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)$_2$NH-, -NHS(O)$_2$-, -N(R^{23})-, -CNR^{23})NHNH-, -NHNHC(NR^{23})-;
R^{23} is -H, an aliphatic group, a benzyl group, an aryl group or non-aromatic heterocyclic group;
said aliphatic group is a saturated or unsaturated C_1-C_{20}hydrocarbon;
said electron withdrawing group is alkylimino, alkylsulfonyl, carboxamido, carboxylic alkyl ester, -CH=NH or -NO$_2$;
the heterocycle of said non-aromatic heterocyclic group is a 5 to 8 membered non-aromatic ring that contains one or more heteroatoms selected from the group consisting of O, N, and S; and
said aromatic group is selected from the group consisting of a C_6 aromatic carbocycle, a C_5 - C_6 aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of O, S and N, and a C_6 aromatic carbocycle or a C_5 - C_6 aromatic heterocycle that is fused to one or more other rings.

[0019] In this embodiment, compounds are preferred wherein:

R^1 is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group) or -O-C(O)-(substituted aliphatic group);
R^2 is an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group;
Z is:



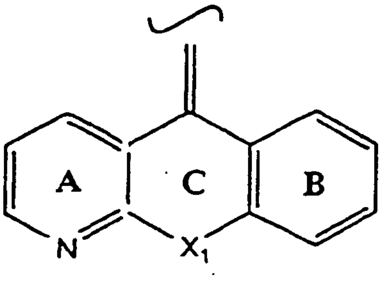
wherein:

X$_1$ is -CH$_2$-CH$_2$-, -CH$_2$-S-, -CH$_2$-O-, -CH$_2$-NR$_c$-, -CH$_2$-SO-, -CH$_2$-S(O)$_2$-, -CH=CH- or -CO-NR$_c$- ; wherein:

R$_c$ is an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted. It is preferred that R^1 is -OH and R^2 is a substituted or unsubstituted aromatic group. Preferably R^2 is 4-chlorophenyl.

[0020] As discussed above, in all embodiments of the present invention Z is represented by Structural Formula (II):



(II)

[0021] The phenyl rings in Structural Formula (II), labelled with an "A" and "B", are referred to herein as "Ring A" and "Ring B", respectively. The central ring, labelled with a "C", is referred to as "Ring C".

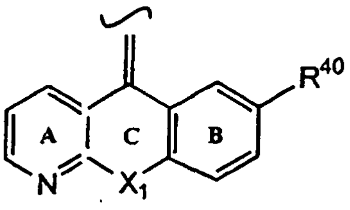
[0022] Ring A and/or Ring B in Structural Formula (II) can be unsubstituted. Alternatively, Ring A and/or Ring B can have one or more substituents. Suitable substituents are as described hereinbelow. In one example, Ring A or Ring B is substituted with -(O)$_u$-(CH$_2$)$_t$-C(O)OR^{20}, -(O)$_u$-(CH$_2$)$_t$-OC(O)R^{20}, -(O)$_u$-(CH$_2$)$_t$-C(O)-NR^{21}R^{22} or -(O)$_u$-(CH$_2$)$_t$-NHC(O)O-R^{20}.

[0023] Ring C optionally contains one or more substituents, as described hereinbelow.

[0024] Preferably Ring B is substituted with -OH, halo, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, -(O)$_u$-(CH$_2$)$_t$-C(O)OR^{20}, -(O)$_u$-(CH$_2$)$_t$-OC(O)R^{20}, -(O)$_u$-(CH$_2$)$_t$-C(O)-NR^{21}R^{22} or -(O)$_u$-(CH$_2$)$_t$-NHC(O)O-R^{20}; wherein:

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or
R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;
u is zero or one; and
t is an integer from zero to three.

[0025] In a preferred embodiment, Ring B in Structural Formula (II) is substituted para to the carbon atom of Ring B which is bonded to X$_1$ of Ring C, and Z is represented by Structural Formula (III):



(III)

wherein:

R^{40} is -OH, halogen, aliphatic group, substituted aliphatic group, -NR^{24}R^{25}, Q-(aliphatic group), Q-(substituted aliphatic group), -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, -(O)$_u$-(CH$_2$)$_t$-C(O)OR^{20}, -(O)$_u$-(CH$_2$)$_t$-OC(O)R^{20}, -(O)$_u$-(CH$_2$)$_t$-C(O)-NR^{21}R^{22} or -(O)$_u$-(CH$_2$)$_t$-NHC(O)OR^{20};
R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

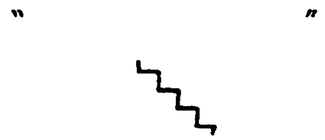
R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;
Q is $-NR^{24}C(O)-$ or $-NR^{24}S(O)_2-$;
R^{24} and R^{25} are independently -H, -OH, an aliphatic group or a substituted aliphatic group;
u is zero or one; and
t is an integer from zero to 3.

[0026] X_1 can be as described above in Structural Formula (II). Preferably X_1 is $-CH_2-O-$, $-CH_2-CH_2-$ or $-CH_2-S-$.

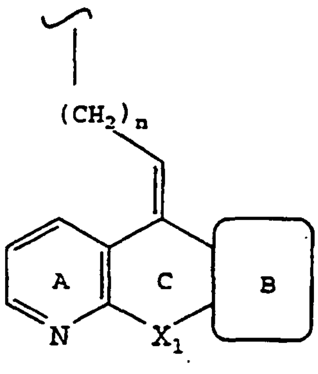
[0027] Preferably R^{40} is an aliphatic group, substituted aliphatic group, -O- (aliphatic group) or -O- (substituted aliphatic group). More preferably R^{40} is an -O-alkyl, such as $-O-CH_3$, $-O-C_2H_5$, $-O-C_3H_7$ or $-O-C_4H_9$. More preferably R^{40} is $-O-CH_3$.

[0028] Another embodiment of the present invention includes novel compounds employed in these methods.

[0029] The compounds disclosed herein can be obtained as E- and Z-configurational isomers. It is expressly pointed out that the invention includes compounds of the E-configuration and the Z-configuration around the double bond connecting Ring C of Z to the remainder of the molecule, and a method of treating a subject with compounds of the E-configuration, the Z-configuration, and mixtures thereof. Accordingly, in the structural formulas presented herein, the symbol:



is used to represent both the E-configuration and the Z-configuration. Preferably Ring A and the alkylene chain bonded to Ring C are in the cis configuration. For example, the compounds can have the configuration of:



[0030] It is understood that one configuration can have greater activity than another. The desired configuration can be determined by screening for activity, employing the methods described herein.

[0031] Additionally, certain compounds of the invention may be obtained as different sterioisomers (e.g., diastereomers and enantiomers). It is pointed out that the invention includes all isomeric forms and racemic mixtures of the disclosed compounds and a method of treating a subject with both pure isomers and mixtures thereof, including racemic mixtures. Again, it is understood that one sterioisomer may be more active than another. The desired isomer can be determined by screening.

[0032] Also included in the present invention are physiologically acceptable salts of the compounds represented by Structural Formula (I) above Salts of compounds containing an amine or other basic group can be obtained, for example, by reacting with a suitable organic or inorganic acid, such as hydrogen chloride, hydrogen bromide, acetic acid, citric acid, perchloric acid and the like. Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like. Salts of compounds containing a carboxylic acid or other acidic functional group can be prepared by reacting with a suitable base, for example, a hydroxide base. Salts of acidic functional groups contain a countercation such as sodium, potassium, ammonium, calcium and the like.

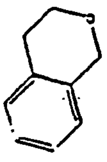
[0033] As used herein, aliphatic groups include straight chained, branched or cyclic C_1-C_{20} hydrocarbons which are completely saturated or which contain one or more units of unsaturation. For example, suitable aliphatic groups include substituted or unsubstituted linear, branched or cyclic C_1-C_{20} alkyl, alkenyl or alkynyl groups.

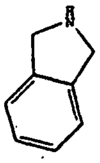
[0034] Aromatic groups include carbocyclic aromatic groups such as phenyl, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl, and heterocyclic aromatic or heteroaryl groups such as N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 5-tetrazolyl, 2-oxazolyl, 4-oxazolyl and 5-oxazolyl. Where these rings are fused, for example, to Ring C, the stated point of attachment can be either of the two fused bonds.

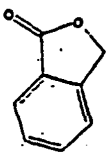
[0035] Aromatic groups also include fused polycyclic aromatic ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other rings. Examples include tetrahydronaphthyl, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 3-indolyl, 2-benzothiazolyl, 2-benzooxazolyl, 2-benzimidazolyl, 2-quinolinyl, 3-quinolinyl, 1-isoquinolinyl, 3-quinolinyl, 1-isoindolyl, 3-isoindolyl, acridinyl, 3-benzisoxazolyl, and the like.

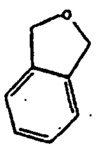
[0036] Also included within the scope of the term "aromatic group", as it is used herein, is a group in which one or more carbocyclic aromatic rings and/or heteroaryl rings are fused to a cycloalkyl or non-aromatic heterocyclic ring, for example, benzocyclopentane, benzocyclohexane.

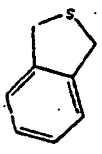
[0037] Non-aromatic heterocyclic rings are non-aromatic carbocyclic rings which include one or more heteroatoms such as nitrogen, oxygen or sulfur in the ring. The ring can be five, six, seven or eight-membered and/or fused to another ring, such as a cycloalkyl on aromatic ring. Examples include 3-1H-benzimidazol-2-one, 3-1-alkylbenzimidazol-2-one, 3-1-methyl-benzimidazol-2-one, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahyrothiophenyl, 3-tetrahyrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorphblino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 4-thiazolidinyl, diazolonyl, N-substituted diazolonyl, 1-phthalimidyl, 1-3-alkyl-phthalimidyl, beazoxane, benzopyrolidine, benzopiperidine, benzoxolane, benzothiolane, benzothiane,

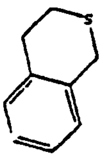


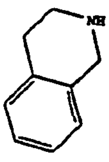


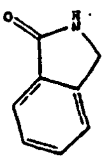


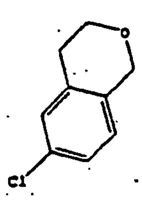


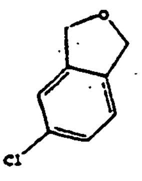


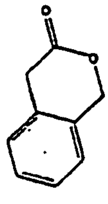


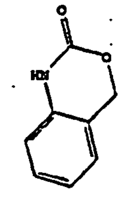


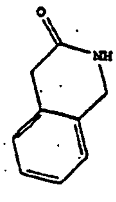


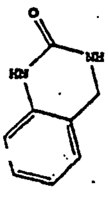


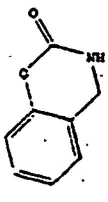




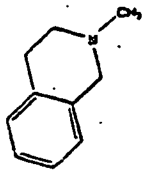








and



[0038] Suitable substituents on an aliphatic group, aromatic group (carbocyclic and heteroaryl), non-aromatic heterocyclic ring or benzyl group include, for example, an electron withdrawing group, a halogen, azido, -CN, -COOH, -OH, $-CONR^{24}R^{25}$, $-NR^{24}R^{25}$, $-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, $-S(O)_2NH_2$, guanidino, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$, -Q-H, -Q-(aliphatic group), -Q-(substituted aliphatic group), -Q-(aryl), -Q-(aromatic group), -Q-(substituted aromatic group), $-Q-(CH_2)_p-$(substituted or unsubstituted aromatic group) (p is an integer from 1-5), -Q-(non-aromatic heterocyclic group) or $-Q-(CH_2)_p-$(non-aromatic heterocyclic group).

[0039] A substituted non-aromatic heterocyclic ring, benzyl group or aromatic group can also have an aliphatic or substituted aliphatic group, as a substituent. A substituted aliphatic group can also have an oxo group, epoxy group, non-aromatic heterocyclic ring, benzyl group, substituted benzyl group, aromatic group or substituted aromatic group as a substituent. A substituted non-aromatic heterocyclic ring can also have =O, =S, =NH or =N(aliphatic, aromatic or substituted aromatic group) as a substituent. A substituted aliphatic, substituted aromatic, substituted non-aromatic heterocyclic ring or substituted benzyl group can have more than one substituent.

[0040] Acyl groups include substituted and unsubstituted aliphatic carbonyl, aromatic carbonyl, aliphatic sulfonyl and aromatic sulfonyl. Suitable electron withdrawing groups include, for example, alkylimines, alkylsulfonyl, carboxamido, carboxylic alkyl esters, -CH=NH, -CN, $-NO_2$ and halogens.

[0041] In the structural formulas depicted herein, the single or double bond by which a chemical group or moiety is connected to the remainder of the molecule or compound is indicated by the following symbol:

"  "

For example, the corresponding symbol in Structural Formulas (II) and (III) indicates the double bond by which the central ring of the tricyclic ring system is connected to the remainder of the molecule represented by Structural Formula (I).

[0042] A "subject" is preferably a bird or mammal, such as a human, but can also be an animal in need of veterinary treatment, e.g., domestic animals (e.g., dogs,' cats, and the like), farm animals (e.g., cows, sheep, fowl, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

[0043] An "effective amount" of a compound is an amount which results in the inhibition of one or more processes mediated by the binding of a chemokine to a receptor in a subject with a disease associated with aberrant leukocyte recruitment and/or activation. Examples of such processes include leukocyte migration, integrin activation, transient increases in the concentration of intracellular free calcium $[Ca^{2+}]_i$ and granule release of proinflammatory mediators. Alternatively, an "effective amount" of a compound.is a quantity sufficient to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in the prevention of or a decrease in the symptoms associated with a disease associated with aberrant leukocyte recruitment and/or activation.

[0044] The amount of compound administered to the individual will depend on the type and severity of the disease and on the characteristics of the individual, such as general health, age, sex, body weight and tolerance to drugs. It will also depend on the degree, severity and type of disease. The skilled artisan will be able to determine appropriate dosages depending on these and other factors.

[0045] Typically, an effective amount of the compound can range from about 0.1 mg per day to about 100 mg per day for an adult. Preferably, the dosage ranges from about 1 mg per day to about 100 mg per day. An antagonist of chemokine receptor function can also be administered in combination with one or more additional therapeutic agents, e.g. theophylline, β-adrenergic bronchodilators, corticosteroids, antihistamines, antiallergic agents, immunosuppressive agents (e.g., cyclosporin A, FK-506, prednisone, methylprednisolone) and the like.

[0046] The compound can be administered by any suitable route, including, for example, orally in capsules, suspensions or tablets or by parenteral administration. Pareriteral administration can include, for example, systemic administration, such as by intramuscular, intravenous, subcutaneous, or intraperitoneal injection. The compound can also be administered orally (e.g., dietary), transdermally, topically, by inhalation (e.g., intrabronchial, intranasal, oral inhalation or intranasal drops), or rectally, depending on the disease or condition to be treated. Oral or parenteral administration are preferred modes of administration.

[0047] The compound can be administered to the individual in conjunction with an acceptable pharmaceutical or physiological carrier as part of a pharmaceutical composition for treatment of HIV infection, inflammatory disease, or the other diseases discussed above.

[0048] Formulation of a compound to be administered will vary according to the route of administration selected (e.g., solution, emulsion, capsule). Suitable carriers may contain inert ingredients which do not interact with the compound. Standard pharmaceutical formulation techniques can be employed, such as those described in Remington's Pharmaceutical Sciences, Mack Publishirig Company, Easton, PA. Suitable carriers for parenteral administration include, for example, sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like. Methods for encapsulating compositions (such as in a coating of hard gelatin or cyclodextran) are known in the art (Baker, *et al.*, "Controlled Release of Biological Active Agents", John Wiley and Sons, 1986).

[0049] The activity of compounds of the present invention can be assessed using suitable assays, such as receptor binding assays and chemotaxis assays. For example, as described in the Exemplification Section, small molecule antagonists of RANTES and MIP-1α binding have been identified utilizing THP-1 cells which bind RANTES and chemotax in response to RANTES and MIP-1α as a model for leukocyte chemotaxis. Specifically, a high through-put receptor binding assay, which monitors ^{125}I-RANTES and ^{125}I-MIP-1α binding to THP-1 cell membranes, was used to identify small molecule antagonists which block binding of RANTES and MIP-1α.

[0050] Compounds of the present invention can also be identified by virtue of their ability to inhibit the activation steps triggered by binding of a chemokine to its receptor, such as chemotaxis, integrin activation and granule mediator release. They can also be identified by virtue of their ability to block RANTES and MIP-1α mediated HL-60, T-cell, peripheral blood mononuclear cell, and eosinophil chemotactic response.

[0051] The compounds disclosed herein can be prepared according to schemes differing slightly from those shown in Figures 1 to 5 and 7. The schemes are described in greater detail below.

[0052] Although Figures 1 to 5 and 7 show the preparation of compounds in which

[0053] Rings A and B are both phenyl rings (which are outside the scope of the invention), analogous compounds with a pyridyl group for Ring A and a phenyl group for Ring B (compounds according to the invention) can be prepared by using starting materials with a nitrogen atom in the appropriate the position in Ring A. These starting materials can be prepared according to methods disclosed in JP 61/152673, U.S. Patent 5089496, WO 89/10369, WO 92/20681 and WO 93/02081.

[0054] Figure 1 shows the preparation of compounds represented by Structural Formula (i). This differs from Structural Formula (I) in that Ring A lacks a nitrogen atom (i.e. Ring A is phenyl, rather than pyridyl). L^1 is PPh_3Cl, PPh_3Br, PPh_3I or $(EtO)_2P(O)$, L^2 is a suitable leaving group such as halogen, p-toluene sulfonate, mesylate, alkoxy, and phenoxy; Pg is a suitable protecting group such as tetrahydropyranyl; and the other symbols are as defined above.

[0055] In Step 1 of Figure 1, a Wittig reaction is carried out in a solvent such as ether, or tetrahydrofuran (THF) in the presence of a base such as sodium hydride, n-butyl lithium or lithium diisopropylamide (LDA) at 0°C up to the reflux temperature for the solvent used for 5 minutes to 72 h. Compounds represented by Formula ii in Figure 1 can be prepared by methods disclosed in JP 61/152673, U.S. Patent 5089496, WO 89/10369, WO 92/20681 and WO 93/02081.

[0056] In Step 2 of Figure 1, deprotection is carried out with an acid in a solvent such as methanol at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h. Alternatively, a compound of represented by Formula v in Figure 1 can be prepared directly from step 1 without isolating an intermediate.

[0057] The reaction mixture obtained after the work up of the reaction described in step 1 can be dissolved in the solvent and reacted with the acid. In Step 3 of Figure 1, the hydroxy group can be converted to a leaving group by known methods. Compounds represented by Formula vi in Figure 1 can be prepared by methods disclosed in J. Med. Chem., 1992 (35) 2074-2084 and JP 61/152673.

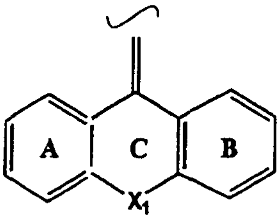
[0058] In Step 4 of Figure 1, an alkylation reaction is carried out in a solvent such as acetone, methyl ethyl ketone, ethyl acetate, toluene, tetrahydrofuran (THF) or dimethylformamide (DMF) in the presence of a base such as potassium carbonate or sodium hydride and a catalyst such as an alkali metal iodide at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

[0059] Figure 2 shows the preparation of compounds represented by Compound (vi-b). In Step 1 of Figure 2, a Grignard reaction may be carried out in a solvent such as ether, or tetrahydrofuran (THF) at 0°C up to the reflux temperature for the solvent used for 5 minuets to 72 h. Compound vii is available commercially.

[0060] In Step 2 of Figure 2, bromination may be carried out with brominate agents such as hydrobromic acid, bromotrimethylsilane or boron tribromide-methyl sulfide complex in a solvent such as acetic acid, dichloromethane or dichloroethane at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

[0061] Figure 3 shows the preparation of compounds represented by Structural Formula, (i). In Figure 3, a reductive amination may be carried out with reducing regents such as sodium cyanoborohydride, sodium acetoxyborohydride or sodium borohydride in a solvent such as methanol, ethanol, tetrahydrofuran (THF), dichloromethane or dichloroethane at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

[0062] Figure 4 shows the preparation of compounds represented by Structural Formula (i), where in Z is represented by Structural Formula:



(X)

wherein Ring A and/or Ring B in Z is substituted with R^{40}. In Figure 4, the alkylation reaction can be carried out in a solvent such as acetone, methyl ethyl ketone, ethyl acetate, toluene; tetrahydrofuran (THF) or dimethylformamide (DMF) in the presence of a base such as potassium carbonate or sodium hydride and a catalyst such as an alkali metal iodide at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

[0063] Figure 5 is a schematic showing the preparation of the compounds represented by Structural Formula (i), wherein Z is represented by Structural Formula (X) above and wherein Ring A and/or Ring B in Z is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$. In Figure 5, the hydrolysis reaction may be carried out in a mixture of aqueous alkali metal hydroxide solution and a solvent such as methanol, ethanol, tetrahydrofuran (THF) or dioxan at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h. The acylation reaction can be carried out using dicyclohexylcarbodiimide (DCC) or (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (DEC) in a solvent such as tetrahydrofuran (THF), dimethylformamide (DMF) or methylene chloride in the presence of a base such as pyridine or triethylamine (when necessary) at temperatures of 0 to 100°C for 5 minutes to 72 h.

[0064] Figure 7 shows the preparation of compounds represented by Structural Formula (i), wherein Z is represented by Structural Formula (X) and wherein Ring A or Ring B in Z is substituted with R^{40}. L4 is a suitable leaving group such as halogen or trifluoromethylsulfonate.

[0065] In Figure 7, a palladium coupling reaction such as Stille coupling, Suzuki coupling, Heck reaction, or carboxylation using carbon monoxide may be carried out using a palladium catalyst such as tetrakis(triphenylphosphine)palladium, bis(triphenylphosphine)palladium chloride, and palladium acetate in a solvent such as tetrahydrofuran (THF), 1,4-dioxane, toluene, dimethylformamide (DMF), or dimethylsufoxide (DMSO) in the presence of additive (when necessary) such as triphenylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, triethylamine, sodium bicarbonate, tetraethylammonium chloride, or lithium chloride at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

[0066] Compounds according to the invention, represented by Structural Formula (I), wherein Z is represented by Structural Formulas (II) or (III), X is $-CO-NR_c-$ and R_c is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$, can be prepared by suitable modification of the scheme shown in Figure 1-5 and 7. One modification utilizes the starting material shown in Figure 1, wherein X is -CO-NH-. The amide is then alkylated with $L^3-(CH_2)_s-COOR^{30}$, wherein L^3 is a suitable leaving group, using the alkylation procedures described above. The remainder of the synthesis is as described in Figures 1 - 5 and 7.

[0067] The invention is illustrated by the following examples which are not intended to be limiting in any way.

Example 1 - Membrane Preparations for Chemokine Binding and Binding Assays

[0068] Membranes were prepared from THP-1 cells (ATCC #TIB202). Cells were harvested by centrifugation, washed twice with PBS (phosphate-buffered saline)., and the cell pellets were frozen at -70 to -85°C. The frozen pellet was thawed in ice-cold lysis buffer consisting of 5 mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethane-sulfonic acid) pH 7.5, 2 mM EDTA (ethylenediaminetetraacetic acid), 5 μg/ml each aprotinin, leupeptin, and chymostatin (protease inhibitors), and 100 μg/ml PMSF (phenyl methane sulfonyl fluoride - also a protease inhibitor), at a concentration of 1 to 5 x 10^7 cells/ml. This procedure results in cell lysis. The suspension was mixed well to resuspend all of the frozen cell pellet. Nuclei and cell debris were removed by centrifugation of 400 x g for 10 minutes at 4°C. The supernatant was transferred to a fresh tube and the membrane fragments were collected by centrifugation at 25,000 x g for 30 minutes at 4°C. The supernatant was aspirated and the pellet was resuspended in freezing buffer consisting of 10 mM HEPES pH 7.5, 300 mM sucrose, 1 μg/ml each aprotinin, leupeptin, and chymostatin, and 10 μg/ml PMSF (approximately 0.1 ml per each 10^8 cells). All clumps were resolved using a minihomogenizer, and the total protein concentration was determined using a protein assay kit (Bio-Rad, Hercules, CA, cat #500-0002). The membrane solution was then aliquoted and frozen at -70 to -85°C until needed.

[0069] Binding Assays utilized the.membranes described above. Membrane protein (2 to 20 μg total membrane protein) was incubated with 0.1 to 0.2 nM ^{125}I-labeled RANTES or MIP-1α with or without unlabeled competitor (RANTES or MIP-1α) or various concentrations of compounds. The binding reactions were performed in 60 to 100 μl of a binding buffer consisting of 10 mM HEPES pH 7.2, 1 mM $CaCl_2$, 5 mM $MgCl_2$, and 0.5% BSA (bovine serum albumin), for 60 min at room temperature. The binding reactions were terminated by harvesting the membranes by rapid filtration through glass fiber filters (GF/B or GF/C, Packard) which were presoaked in 0.3% polyethyleneimine. The filters were rinsed with approximately 600 μl of binding buffer containing 0.5 M NaCl, dried, and the amount of bound radioactivity was determined by scintillation counting in a Topcount beta-plate counter.

[0070] The activities of test compounds are reported in the Table below as IC_{50} values or the inhibitor concentration required for 50% inhibition of specific binding in receptor binding assays using ^{125}I-RANTES or ^{125}I-MIP-1α as ligand and THP-1 cell membranes. Specific binding is defined as the total binding minus the non-specific binding; non-specific binding is the amount of cpm still detected in the presence of excess unlabeled Rantes or MIP-1α.

Table

BIOLOGICAL DATA

Example	IC_{50} (μM)
Reference Example 1	<1
Reference Example 2	<1
2	<1
3	<1

Table continued

BIOLOGICAL DATA

Example	IC_{50} (μM)
4	<1
5	<1
6	<1
7	<1
10	<1
11	<1
12	<1
13	<1
14	<1
15	<10
17	<1
18	<1
19	<10
20	<10
21	<10
22	<1
23	<1
24	<1000
25	<1
26	<10
27	<1
29	<10
30	<10
31	<1
32	<1
33	<1
37	<1000
39	<1
40	>10
42	<1
43	<1
61	<1
64	<1
67	<1
68	<1
78	<1
80	<1
81	<1
82	<1
83	<1
84	<1
85	<1
88	<1
89	<1
90	>10
91	<1
92	<10
93	<1
94	<1

Table continued

BIOLOGICAL DATA

Example	IC_{50} (μM)
95	<10
96	>10
97	<10
98	<10
99	<1000
100	<10
101	<1
102	<1
103	<1
104	<1
105	<1
108	<1
109	<1
110	<1
111	<10
112	<1
113	<1
114	<10
121	<1
122	<1
123	<1
124	<1
126	<1
129	<1
130	<1
131	<1
132	<10
133	<1000
134	<1
135	<1
136	>10
138	<1
139	<1
140	<10
142	<1
144	<1
193	<10

Reference Example 1 -4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-ethoxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

[0071] To a solution of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-hydroxydibenz[b,eloxepin-11-ylidene)propyl]piperidin-4-ol (Example 32) (200mg) in DMF (5ml) were added sodium hydride (60% in oil, 25mg), ethyl iodide (0.052ml) and the mixture was stirred at room temperature for 1 hour. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:1) to give the titled compound (170mg).
^{1}H-NMR ($CDCl_3$) δ: 1.37(3H,t), 1.60-1.65(2H,m), 1.95-2.08(3H,m), 2.28-75(8H,m), 3.96(2H,q), 5.15(2H,brs), 6.02(1H, t), 6.68(2H,brs), 6.82(1H,brs), 7.19-7.42(8H,m).
MS m/z: 490(M+1)

Reference Example 2 -4-(4-Chlorophenyl)-1-[3-(6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-methoxypiperidine

[0072] To a solution of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-methoxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (Example 2)(404mg) in DMF (5ml) were added sodium hydride (60% in oil, 50mg), methyl iodide (0.07ml) and the mixture was stirred at room temperature for 1 hour. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:1) to give the titled compound (100mg).
^{1}H-NMR ($CDCl_3$) δ: 1.90-2.04 (4H,m), 2.34-2.62(8H,m), 2.93(3H,s), 5.25(2H,brs), 6.04(1H,t), 6.75-6.91(3H,m), 7.09-7.37 (9H,m).
MS m/z: 460 (M+1)

Example 2 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-hydroxy [1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

Step 1

[0073] To a solution of the product of example 3, step 1 (4.3g) in dichloroethane (100ml) was added boron tribromide-methyl sulfide complex (19.3g) and the mixture was heated to reflux for 3 hour. Water and ethyl acetate were added to the reaction mixture and neutralized with dilute NaOH solution. The organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:2) to give 5-(3-bromopropylidene)-5,11-dihydro-7-hydroxy [1]benzoxepino[2,3-b]pyridine (3.2g).
^{1}H-NMR ($CDCl_3$) δ: 2.72(2H,q), 3.45(2H,t), 5.28(2H,brs), 6.03(1H,t), 6.66-6.80(3H,m), 7.26(1H,dd), 7.58(1H,dd), 8.51 (1H,dd).

Step 2

[0074] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 5-(3-bromopropylidene)-5,11-dihydro-7-methoxy [1]benzoxepino[2,3-b]pyridine with the product of step 1.
^{1}H-NMR (DMSO-d_6) δ: 1.46-1.51(2H,m), 1.74-1.85(2H,m), 2.29-2.51(8H,m), 5.15(2H,brs), 6.07(1H,t), 6.61-6.70(3H,m), 7.33-7.48(5H,m), 7.73(1H,dd), 8.47(1H,dd), 9.06(1H,s).
MS m/z: 463(M+1)

Example 3 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

Step 1

[0075] To a solution of 5,11-dihydro-7-methoxy [1]benzoxepino[2,3-b]pyridin-5-one (5.0g) in THF (50ml) was added 1.1M cyclopropylmagnesium bromide THF solution (25ml) at 0°C. The reaction mixture was warmed to room temperature, and stirred for 30 minutes. Aqueous ammonium chloride and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was filtered and washed with ethyl acetate-hexane (1:2) to give 5-cyclopropyl-5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ol (5.0g).

Step 2

[0076] To a solution of the product of step 1 (4.3g) in acetic acid (30ml) was added 48% aqueous HBr (25ml) at 10°C. The reaction mixture was warmed to room temperature, and stirred for 12 hours. Water and ethyl acetate were added to the reaction mixture and neutralized with dilute NaOH solution. The organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:4) to give 5-(3-bromopropylidene)-5,11-dihydro-7-methoxy [1]benzoxepino[2,3-b]pyridine (5.6g).
^{1}H-NMR ($CDCl_3$) δ: 2.74(2H,q), 3.46(2H,t), 3.78(3H,s), 5.25(2H,brs), 6.07(1H,t), 6.72-6.82(3H,m), 7.21-7.42(5H,m), 7.56(1H,dd), 8.45(1H,dd).

Step 3

[0077] To a solution the product of step 2 (1.1g) in DMF (15ml) were added 4-(4-chlorophenyl)-4-hydroxypiperidine (0.81g) and potassium carbonate (0.53g) and the mixture was stirred at room temperature for 3 hours. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with methylene chloride-methanol (10:1) to give the titled compound as major regioisomer (0.86g) and minor one (0.05g).
Major isomer
^{1}H-NMR ($CDCl_3$) δ: 1.64-1.69(2H,m), 1.91-2.08(3H,m), 2.34-2.69(8H,m), 3.77(3H,s), 5.25(2H,brs), 6.07(1H,t), 6.72-6.82 (3H,m), 7.21-7.42(5H,m), 7.56(1H,dd), 8.45(1H,dd). MS m/z: 477(M+1)
Minor isomer
^{1}H-NMR ($CDCl_3$) δ: 1.65-1.79(3H,m), 2.01-2.13(2H,m), 2.35-2.76(8H,m), 3.76(3H,s), 5.22(2H,brs), 5.95(1H,t), 6.72-6.80 (2H,m), 7.06(1H,d), 7.16(1H,dd), 7.28(2H,d), 7.42(2H,d), 7.66(1H,dd), 8.39(1H,dd).
MS m/z: 477(M+1)

Example 4 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethoxy [1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0078] The titled compound was prepared by following the procedure of reference example 1, but replacing 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-hydroxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol with 4-(4-chlorophenyl)-1-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol (example 44).
^{1}H-NMR ($CDCl_3$) δ: 1.38(3H,t), 1.67-1.72(3H,m), 2.05-2.16(2H,m), 2.40-2.80(8H,m), 3.99(2H,q), 5.26(2H,brs), 6.05(1H, t), 6.71-6.82(3H,m), 7.23-7.43(5H,m), 7.57(1H,dd), 8.47 (1H,dd).
MS m/z: 491(M+1)

Example 5 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-isopropoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0079] The titled compound was prepared by following the procedure of example 4, but replacing ethyl iodide with isopropyl bromide.
^{1}H-NMR ($CDCl_3$) δ: 1.30(6H,d), 1.60-1.70(3H,m), 1.99-2.09(2H,m), 2.33-2.69(8H,m), 4.37-4.48(1H,m), 5.26(2H,brs), 6.06(1H,t), 6.73-6.82(3H,m), 7.21-7.43(5H,m), 7.55(1H,dd), 8.47(1H,dd).
MS m/z: 505(M+1)

Example 6 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethoxycarbonylmethyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidin-4-ol

[0080] The titled compound was prepared by following the procedure of example 4, but replacing ethyl iodide with ethyl bromoacetate.
^{1}H-NMR ($CDCl_3$) δ: 1.28(3H,t), 1.63-1.63(2H,m), 1.97-2.02(3H,m), 2.33-2.68(8H,m), 4.24(2H,q), 4.55(2H,s), 5.26(2H, brs), 6.06(1H,t), 6.73-6.88(3H,m), 7.21-7.42(5H,m), 7.55(1H,dd), 8.44(1H,dd).
MS m/z: 549(M+1)

Example 7 -4-(4-Chlorophenyl)-1-[3-(7-cyanomethyloxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl] piperidin-4-ol

[0081] The titled compound was prepared by following the procedure of example 4, but replacing ethyl iodide with bromoacetonitrile.
^{1}H-NMR ($CDCl_3$) d: 1.62-1.67(2H,m), 1.94-2.06(2H,m), 2.21(1H,brs), 2.34-2.66(8H,m), 4.70(2H,s), 5.26(2H,brs), 6.10 (1H,t), 6.80(2H,brs), 6.92(1H,brs), 7.22-7.41(5H,m), 7.56(1H,dd), 8.44(1H,dd).
MS m/z: 502(M+1)

Example 8 -1-[3-(7-(2-Acetoxyethyl)oxy-5,11-dihydro [1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl) piperidin-4-ol

[0082] The titled compound was prepared by following the procedure of example 4, but replacing ethyl iodide with 2-bromoethyl acetate.

^{1}H-NMR ($CDCl_3$) δ: 1.65-1.72(3H,m), 1.97-2.09(5H,m), 2.37-2.70(8H,m), 4.11-4.14(2H,m), 4.37-4.41(2H,m), 5.25(2H, brs), 6.07(1H,t), 6.75-6.84(3H,m), 7.23-7.43(5H,m), 7.56(1H,dd), 8.47(1H,dd).
MS m/z: 549(M+1)

Example 9 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-hydroxyethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl] piperidin-4-ol

[0083] To a solution of 1-[3-(7-(2-acetoxyethyl)oxy-5,11-dihydro [1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol (Example 8) (140mg) in ethanol (5ml) were added 15% sodiun hydroxide aqueous solution (2ml) and the mixture was heated to reflux for 1 hour.

[0084] Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate.

[0085] The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with methylene chloride-methanol (10:1) to give the titled compound (120mg).
^{1}H-NMR ($CDCl_3$) δ: 1.64-1.69(2H,m), 1.98-2.10(3H,m), 2.36-2.79(8H,m), 3.89-3.94(2H,m), 3.99-4.04(2H,m), 5.24(2H, brs), 6.04(1H,t), 6.71-6.84(3H,m), 7.23-7.41(5H,m), 7.54(1H,dd), 8.43 (1H,dd).
MS m/z: 507(M+1)

Example 10 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-morpholinoethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidin-4-ol

[0086] The titled compound was prepared by following the procedure of example 4, but replacing ethyl iodide with 4-(2-chloroethyl)morpholine hydrochloride.
^{1}H-NMR ($CDCl_3$) δ: 1.62-1.67(2H,m), 1.95-2.08(2H,m), 2.20-2.67(13H,m), 2.74(2H,t), 3.67-3.71(4H,m), 4.04(2H,t), 5.23 (2H,brs), 6.05(1H,t), 6.73-6.82(3H,m), 7.20-7.41(5H,m), 7.53(1H,dd), 8.42(1H,dd).
MS m/z: 576(M+1)

Example 11 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro [1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

Step 1

[0087] 5-(3-Bromopropylidene)-5,11-dihydro [1]benzoxepino[2,3-b]pyridine was prepared by following the procedure of example 3, step 1 and 2, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 5,11-dihydro [1]benzoxepino[2,3-b]pyridin-5-one.
^{1}H-NMR ($CDCl_3$) δ: 2.71(2H,q), 3.46(2H,t), 5.33(2H,brs), 6.04(1H,t), 7.01-7.17(3H,m), 7.29(1H,dd), 7.56(1H,dd), 8.53 (1H,dd).

Step 2

[0088] The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-5,11-dihydro-7-methoxy [1]benzoxepino[2,3-b]pyridine with the product of step 1.
^{1}H-NMR ($CDCl_3$) δ: 1.66-1.71(2H,m), 2.00-2.20(3H,m), 2.36-2.69(8H,m), 5.34(2H,brs), 6.10(1H,t), 6.83-6.96(3H,m), 7.17-7.44(6H,m), 7.60(1H,dd), 8.46(1H,dd).
MS m/z: 447(M+1)

Example 12 -1-[3-(8-Bromo-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

[0089] 8-Bromo-5-(3-bromopropylidene)-5,11-dihydro[1]benzoxepino[2,3-b]pyridine was prepared by following the procedure of example 3, step 1 and 2, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 8-bromo-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-one.
^{1}H-NMR ($CDCl_3$) δ: 2.75(2H,q), 3.50(2H,t), 5.38(2H,brs), 6.08(1H,t), 6.85-6.98(2H,m), 7.18-7.35(3H,m), 7.59(1H,dd), 8.54(1H,dd).

Step 2

[0090] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 5-(3-bromopropylidene)-5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridine with the product of step 1.
^{1}H-NMR ($CDCl_3$) δ: 1.64-1.69(2H,m), 1.90-2.07(3H,m), 2.30-2.67(8H,m), 5.30(2H,brs), 6.08(1H,t), 7.00-7.07(2H,m), 7.13(1H,d), 7.25-7.42(5H,m), 7.56(1H,dd), 8.47(1H,dd).
MS m/z: 525, 527(M+1)

Example 13 -4-(4-Chlorophenyl)-1-[3-(10,11-dihydro-10-oxo-5H-pyrido[2,3-c][2]benzazepin-5-ylidene)propyl]piperidin-4-ol

Step 1

[0091] 5-(3-Bromopropylidene)-10,11-dihydro-10-oxo-5H-pyrido[2,3-c][2]benzazepine was prepared by following the procedure of example 3, step 1 and 2, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 10,11-dihydro-5H-pyrido[2,3-c][2]benzazepin-5,10-dione.
^{1}H-NMR ($CDCl_3$) δ: 2.75-2.90(2H,m), 3.45 (2H,t), 5.92(1H,t), 7.04-7.70(5H,m), 8.10(1H,dd), 8.48(1H,dd), 10.00(1H,brs).

Step 2

[0092] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 5- (3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with the product of step 1.
^{1}H-NMR ($CDCl_3$) δ: 1.64-1.69(3H,m), 2.00-2.12(2H,m), 2.35-2.70(8H,m), 5.82(1H,t), 7.08(1H,dd), 7.23-7.62(8H,m), 8.04 (1H,dd), 8.32(1H,dd), 8.76(1H,brs).
MS m/z: 460(M+1)

Example 14 -4-(4-Chlorophenyl)-1-[3-(10,11-dihydro-11-methyl-10-oxo-5H-pyrido[2,3-c][2]benzazepin-5-ylidene)propyl]piperidin-4-ol

[0093] The titled compound was prepared by following the procedure of reference example 2, but replacing of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-methoxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol with 5-(3-bromopropylidene)-10,11-dihydro-10-oxo-5H-pyrido[2,3-c][2]benzazepine.
^{1}H-NMR ($CDCl_3$) δ: 1.64-1.70 (3H,m), 2.00-2.10(2H,m), 2.41-2.69(8H,m), 3.62(3H.s), 5.82(1H,t), 7.07(1H,dd), 7.25-7.54 (8H,m), 7.91(1H,dd), 8.34(1H,dd).
MS m/z: 474(M+1)

Example 15 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)ethyl]piperidin-4-ol

Step 1

[0094] To a solution of methyltriphenylphosphonium bromide (2.2g) in THF (20ml) was added 1.6M n-butyl lithium hexane solution (2.9ml) at 0°C for 30 minutes. To the reaction mixture cooled to 0°C was added 5,11-dihydro-7-methoxy [1]benzoxepino[2,3-b]pyridin-5-one (1.0g) dropwise as THF solution (5ml), and the mixture was warmed to room temperature, and stirred for 3 hours. Aqueous ammonium chloride and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluding with ethyl acetate-hexane (1:4) to give 5,11-dihydro-7-methoxy-5-methylenepyrido[2,3-c][1]benzoxepine (0.14g).

Step 2

[0095] To a solution of DMF (0.54ml) was added phosphorus oxychloride (0.41ml) at 0°C for 10 minutes. To the reaction mixture was added the product of step 1 (210mg) in carbontetrachloride (5ml) and the mixture was heated to reflux for 5 hours. Aqueous sodium bicarbonate and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:4) to give 3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)acetaldehyde (130mg).
^{1}H-NMR ($CDCl_3$) δ: 3.77(0.7x3H,s),3.79(0.3x3H, s), 5.31(2H,s), 6.46(0.7x1H,d), 6.52(0.3x1H,d), 6.78-7.40(4H,m), 7.68

(0.3x1H,dd), 7.78(0.7x1H,dd), 8.55(0.7x1H,dd), 8.64(0.3x1H,dd), 9.62(0.3x1H,d), 9.79(0.7x1H,d).

Step 3

[0096] The titled compound was prepared by following the procedure of example 16, step 2, but replacing of 3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propanaldehyde with product of step 2.
^{1}H-NMR ($CDCl_3$) δ: 1.64-1.82(2H,m), 1.92-2.22(3H,m), 2.43-2.58(2H,m), 2.79-3.45(6H,m), 3.68(0.3x3H,s), 3.70(0.7x3H,s), 5.24(2H,brs), 6.18(0.7x1H,t), 6.21(0.3x1H,t), 6.72-7.42(8H,m), 7.78(0.3x1H,dd), 7.85(0.7x1H,dd), 8.42(0.7x1H,dd), 8.46(0.3x1H,dd).
MS m/z: 463(M+1).

Example 16 -4-(4-Chlorophenyl)-1-[4-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)butyl]piperidin-4-ol

Step 1

[0097] 3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propenaldehyde was prepared by following the procedure of example 15, step 2, but replacing 5,11-dihydro-7-methoxy-5-methylene[1]benzoxepino[2,3-b]pyridine with 5,11-dihydro-7-methoxy-5-(propyl-1-ene) [1]benzoxepino[2,3-b]pyridine (by-product of example 3, step 3).
^{1}H-NMR ($CDCl_3$) δ: 3.78(0.3x3H,s), 3.80(0.7x3H,s), 5.32(2H,brs), 6.34-6.39(1H,m), 6.72-7.38 (6H,m), 7.58(0.7x1H,dd), 7.77(0.3x1H,dd), 8.49(0.3x1H,dd), 8.60(0.7x1H,dd), 9.51(0.7x1H,d), 9.54(0.3x1H,d).

Step 2

[0098] To a solution of the product of step 1 (90mg) in dichloromethane (6ml) were added sodium triacetoxyborohydride (170mg), 4-(4-chlorophenyl)-4-hydroxypiperidine (70mg) and acetic acid (0.02ml) and the mixture stirred at room temperature for 24 hour. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with dichloromethane-methanol (95:5) to give 4-(4-chlorophenyl)-1-[4-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)buten-2-yl]piperidin-4-ol (110mg).
^{1}H-NMR ($CDCl_3$) δ: 1.68-1.73(2H,m), 2.04-2.16(2H,m), 2.43-2.72(3H,m), 2.77-2.81(2H,m), 3.08-3.13(2H,m), 3.73 (0.3x3H,s), 3.77(0.7x3H,s), 5.20(2H,brs), 5.98-6.05(1H,m), 6.23-7.43(10H,m), 7.58(0.7x1H,dd), 7.65(0.3x1H,dd), 8.37 (0.3x1H,dd), 8.45(0.7x1H,dd).
MS m/z: 489(M+1).

Step 3

[0099] To a solution of the product of step 2 (8mg) in ethanol (2ml) were added 10% Pd-C (2mg) was stirred under hydrogen (under a balloon) at room temperature for 1 hour. The mixture was filtered through the celite and distilled off under reduced pressure to give the titled compound (6mg).
^{1}H-NMR ($CDCl_3$) δ: 1.68-3.00(15H,m), 3.77(3H,s), 5.18-5.35(2H,m), 5.94(0.4H,t, *E* isomer), 6.06(0.6H,t, *Z* isomer), 6.65-6.88(3H,m), 7.05-7.73(6H,m), 8.30-8.56(1H,m).
MS m/z: 491(M+1)

Example 17 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-phenyl-4-ol

[0100] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-phenyl-4-hydroxypiperidine.
^{1}H-NMR ($CDCl_3$) d: 1.68-1.73(2H,m), 2.02-2.15(3H,m), 2.38-2.72(8H,m), 3.77(3H,s), 5.26(2H,brs), 6.08(1H,t), 6.72-6.83 (3H,m), 7.21-7.36(4H,m), 7.46-7.49(2H,m), 7.58(1H,dd), 8.46(1H,dd)
MS m/z: 443 (M+1).

Example 18 -4-(4-Bromophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0101] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-bromophenyl)-4-hydroxypiperidine.

^{1}H-NMR ($CDCl_3$) δ: 1.65-1.69(2H,m), 2.00-2.10(3H,m), 2.37-2.71(8H,m), 3.76(3H,s), 5.24(2H,brs), 6.05(1H,t), 6.70-6.82 (3H,m), 7.24(1H,dd), 7.38 (2H,d), 7.44(2H,s), 7.52(1H,dd), 8.44(1H,dd).
MS m/z: 521,523 (M+1).

Example 19 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0102] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-hydroxypiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.43-1.60(2H,m), 1.80-1.98 (2H,m), 2.00-2.18(3H,m), 2.34-2.48 (4H,m), 2.63-2.76(2H,m), 3.64-3.73 (1H,m), 3.70(3H,s), 5.35(2H,brs), 6.06(1H,t), 6.74-6.84(3H,m), 7.25(1H,dd), 7.60(1H,dd), 8.50(1H,dd).
MS m/z: 367 (M+1).

Example 20 -4-Benzyl-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0103] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-benzyl-4-hydroxypiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.42-1.57(3H,m), 1.62-1.75(2H,m), 2.22-2.70(8H,m), 2.79(2H,s), 3.80(3H,s), 5.25(2H,brs), 6.08(1H, t), 6.73-6.84(3H,m), 7.18-7.24(6H,m), 7.57(1H,dd), 8.50(1H,dd).
MS m/z: 457 (M+1).

Example 21 -4-Cyano-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-phenylpiperidine

[0104] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-cyano-4-phenylpiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.97-2.06(4H,m), 2.37-2.60(6H,m), 2.85-2.90(2H,m), 3.79(3H,s), 5.27(2H,brs), 6.08(1H,t), 6.72-6.84 (3H,m), 7.24-7.58(7H,m), 8.49(1H,dd).
MS m/z: 452 (M+1).

Example 22 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-phenylpiperidine

[0105] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-phenylpiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.73-1.79(4H,m), 1.96-2.03(2H,m), 2.37-2.52(5H,m), 2.86-2.94(2H,m), 3.77(3H,s), 5.26(2H,brs). 6.08(1H,t), 6.72-6.83(3H,m), 7.17-7.31(6H,m), 7.56 (1H,dd), 8.49(1H,dd).
MS m/z 426 (M+1).

Example 23 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

[0106] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)piperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.68-1.74(4H,m), 1.96-2.03(2H,m), 2.36-2.48(5H,m),2.89-2.94(2H,m), 3.77(3H,s), 5.27(2H,brs), 6.07(1H,t), 6.73-6.83(3H,m), 7.10-7.27(5H,m), 7.57(1H,dd), 8.48(1H,dd).
MS m/z: 461 (M+1).

Example 24 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-piperidinopiperidine

[0107] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-piperidinopiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.40-2.00(12H,m), 2.15-2.60(9H,m), 2.80-2.92(2H,m), 3.80(3H,s), 5.28(2H,brs), 6.05(1H,t), 6.75-6.86(3H,m), 7.30(1H,dd), 7.55(1H,dd), 8.46(1H,dd).
MS m/z 434 (M+1).

Example 25 -1-[3-(5,11-Dihydro-7-methoxy [1] benzoxepino [2,3-b]pyridin-5-ylidene)propyl]-4-(2-keto-1-benzimidazolinyl)piperidine

[0108] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(2-keto-1-benzimidazolinyl)piperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.75-1.79(2H,m), 2.03-2.15(2H,m), 2.38-2.52(6H,m), 2.93-2.98 (2H,m), 3.78(3H,s), 4.30-4.38(1H,

m), 5.30(2H,brs), 6.10(1H,t), 6.73-6.84(3H,m), 7.01-7.03(3H,m), 7.21-7.28(2H,m), 7.59(1H,dd), 8.48(1H,dd).
MS m/z: 483 (M+1).

Example 26 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-keto-3-methyl-1-benzimidazolinyl)piperidine

[0109] The titled compound was prepared by following the procedure of reference example 2, but replacing of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-methoxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol with 1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-keto-1-benzimidazolinyl)piperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.72-1.76(2H,m), 2.09-2.14(2H,m), 2.23-2.54(6H,m), 2.91-2.96 (2H,m), 3.38(3H,s), 3.77(3H,s), 4.30-4.37(1H,m), 5.27(2H,brs), 6.08(1H,t), 6.71-6.83(3H,m), 6.93-7.06(3H,m), 7.23-7.60(2H,m), 8.08(1H,dd), 8.48(1H, dd).
MS m/z: 497 (M+1).

Example 27 -8-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-1-phenyl-1,3,8-triazaspiro [4,5]decan-4-one

[0110] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one.
^{1}H-NMR ($CDCl_3$) δ: 1.65-1.70(2H,m), 2.36-2.41(2H,m), 2.53-2.79(8H,m), 3.76(3H, s), 4.70(2H,s), 5.25(2H,brs), 6.10 (1H,t), 6.71-6.88(6H,m), 7.21-7.27(3H,m), 7.58-7.61(2H,m), 8.48(1H,dd).
MS m/z: 497 (M+1).

Example 28 -4-Anilino-4-carbamyl-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

[0111] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-anilino-4-carbamylpiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.85-1.90(2H,m), 2.03-2.08(2H,m), 2.19-2.46(6H,m), 2.62-2.67(2H,m), 3.75(3H,s), 3.97(1H,brs), 5.27(2H,brs), 5.53-(1H,brs), 6.03(1H,t), 6.60(2H,d), 6.70-6.85(4H,m), 7.12-7.25(4H,m), 7.53(1H,dd), 8.46(1H,dd).
MS m/z 485 (M+1).

Example 29 -4-(3-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0112] The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(3-chlorophenyl)-4-hydroxypiperidine. ^{1}H-NMR ($CDCl_3$) δ: 1.61-1.75(2H,m), 1.98(1H,brs), 1.99(2H,dt), 2.25(3H,s), 2.30-2.76(8H,m), 3.73(3H,s), 5.22(2H,brs), 5.95(0.1H,t, E isomer), 6.04(0.9H,t, Z isomer), 6.71-6.89(3H,m), 6.95(1H,dd), 7.15-7.20(0.3H,m, E isomer),7.21-7.35(2.7H,m, Z isomer), 7.53(0.9H,dd, Z isomer), 7.65(0.1H,dd, E isomer), 8.35(0.1H,dd, E isomer), 8.45(0.9H,dd, Z isomer).
MS m/z: 477(M+1)

Example 30 -4-(2-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0113] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(2-chlorophenyl)-4-hydroxypiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.98-2.08(2H,m), 2.24(2H,dt), 2.38-2.78(9H,m), 3.77(3H,s), 5.27(2H,brs), 6.08(1H,t), 6.82-6.75(3H, m), 7.28-7.19(3H,m), 7.33(1H,dd), 7.49(1H,dd), 7.58(1H,dd), 8.40(0.1H,dd, Z isomer), 8.47(0.9H,dd, E isomer).
MS m/z: 477(M+1)

Example 31 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-fluorophenyl)piperidin-4-ol

[0114] The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-fluorophenyl)-4-hydroxypiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.58-1.72(2H,m), 2.04(2H,dt), 2.22-2.78(9H,m), 3.75(3H,s), 5.26(2H,brs), 6.09(1H,t), 6.70-6.88(3H, m), 7.00(2H,dd), 7.23(1H,dd), 7.42(2H,dd), 7.56(1H,dd), 8.41(1H,dd).

MS m/z: 461(M+1)

Example 32 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(p-tolyl)piperidin-4-ol

[0115] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(p-tolyl)-4-hydroxypiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.65-1.78(2H,m), 2.02(2H,dt), 2.31(3H,s), 2.24-2.75(9H,m), 3.75(3H,s), 5.25(2H,brs), 6.07(1H,t), 6.72-6.84(3H,m), 7.13(2H,d), 7.23(1H,dd), 7.34(1H,d), 7.56(1H,dd), 8.43(1H,dd).
MS m/z: 457(M+1)

Example 33 -4-(3,4-Dichlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino [2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0116] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(3,4-dichlorophenyl)-4-hydroxypiperidine.
^{1}HNMR ($CDCl_3$) δ: 1.58-1.72(2H,m), 1.84(1H,brs), 2.02(2H,td), 2.32-2.72 (8H,m), 3.76(3H,s), 5.27(2H,brs), 5.95(0.1H, t, *E* isomer), 6.07(0.9H,t, Z isomer), 6.72-6.85 (3H,M), 7.12-7.20(0.2H,m, *E* isomer), 7.21-7.32(0.18H,m, Z isomer), 7.32-7.45(1H,m), 7.52-7.56(2H,m), 8.37-(0.9H,dd, *E* siomer), 8.45(0.1H,dd, *Z* isomer).
MS m/z: 512(M+1)

Example 37 -4-(5-Chloropyridin-2-yl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0117] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(5-chloropyridin-2-yl)-4-hydroxypiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.77-1.82 (2H,m), 2.36-2.94(11H,m), 3.77(3H,brs), 5.26(2H,brs), 6.07(1H,t), 6.76-6.84(3H,m), 7.26 (1H,dd), 7.57(1H,dd), 8.49-7.48(1H,d), 8.42-8.53(3H,m).
MS m/z: 478(M+1)

Example 39 -4-(5-Chloro-2-keto-1-benzimidazolinyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

[0118] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(5-chloro-2-keto-1-benzimidazolinyl)piperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.68-1.72(2H,m), 2.03-2.60(8H,m), 2.90-3.02(2H,m), 3.78(3H,s), 4.32-4.21(1H,m), 5.29(2H,brs), 5.95(0.1H,t, E siomer), 6.08(0.9H,t, Z isomer), 6.70-6.92(3H,m), 7.02(1H,dd), 7.08-7.20(1H,m), 7.26(1H,dd), 7.58(0.9H, dd, Z isomer), 7.70(0.1H,dd, E isomer), 8.42(0.1H,dd, E isomer), 8.48(0.9H,dd, Z isomer), 10.5(1H,s). (NH is not observed in the spectrum)
MS m/z: 517(M+1)

Example 40 - 4-(p-Chloroanilino)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

[0119] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(p-chloroanilino)piperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.20-1.54(2H,m), 1.85-2.20(4H,m), 2.24-2.60(4H,m), 2.73(2H,m), 3.18(1H,m), 3.77(3H,s), 5.27(2H, brs), 6.06(1H,t), 6.47(2H,m), 6.68-6.90(3H,m), 7.07(2H,m), 7.24(1H,dd), 7.57(1H,m), 8.48(1Hdd). NH signal was not observed.
MS m/z: 476(M+1)

Example 42 -1'-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]spiro[isobenzofuran-1(3H), 4'-piperidine]

[0120] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with spiro[isobenzofuran-1(3H),4'-piperidine].
^{1}H-NMR ($CDCl_3$) δ: 1.62-1.82(2H,m), 1.92(2H,dt), 2.25-2.85(8H,m), 3.76(3H,s), 5.03(2H,s), 5.30(2H,brs), 6.11(1H,t), 6.68-6.90(3H,m), 7.02-7.34(5H,m), 7.58(1H,dd), 8.48(1H,dd).
MS m/z: 455(M+1)

Example 43 -5-Chloro-1'-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]spiro[isobenzofuran-1(3H),4'-piperidine]

[0121] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 5-chlorospiro[isobenzofuran-1(3H),4'-piperidine].
1H-NMR ($CDCl_3$) δ: 1.69-1.74(2H,m), 1.81-1.93(2H,m), 2.30-2.44(4H,m), 2.52-2.63(2H,m), 2.71-2.75(2H,m), 3.79(3H, s), 5.00(2H,s), 5.28(2H,brs), 6.09(1H,t), 6.73-6.84(3H,m), 7.03(1H,d), 7.17-7.28(3H,m), 7.58(1H,dd), 8.49(1H,dd).
MS m/z: 489(M+1)

Example 61 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro[1]benzothiepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0122] The titled compound was prepared by following the procedure of example 3, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 5,11-dihydro[1]benzothiepino[2,3-b]pyridin-5-one.
1H-NMR ($CDCl_3$) δ: 1.66-1.78(3H,m), 2.04-2.65(10H,m), 3.66(1H,brd), 5.05(1H,brd), 6.03(1H,t), 7.04-7.46(10H,m), 8.44 (1H,dd).
MS m/z: 463(M+1)

Example 64 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-8-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0123] The titled compound was prepared by following the procedure of example 3, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 5, 11-dihydro-8-methoxy[1]benzoxepino[2,3-b]pyridin-5-one.
1H-NMR ($CDCl_3$) δ: 1.66-1.70(3H,m), 1.98-2.09(2H,m), 2.34-2.70(8H,m), 3.75(3H,s), 5.32(2H,brs), 6.02(1H,t), 6.39(1H, d), 6.51(1H,dd), 7.19-7.44(6H,m), 7.57(1H,dd), 8.49(1H,dd).
MS m/z: 477(M+1)

Example 65 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0124] The titled compound was prepared by following the procedure of example 3, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 5,11-dihydro-7-methyl[1]benzoxepino[2,3-b]pyridin-5-one.
1H-NMR ($CDCl_3$) δ: 1.50(1H,brs), 1.66-1.70 (2H,m), 1.98-2.10(2H,m), 2.28(3H,s), 2.34-2.42(4H,m), 2.52-2.57(2H,m), 2.66-2.70(2H,m), 5.30(2H,brs), 6.08(1H,t), 6.76(1H,d), 6.97(1H,dd), 7.09(1H,d), 7.24-7.44(5H,m), 7.57 (1H, dd), 8.49 (1H,dd).
MS m/z: 461(M+1)

Example 67 -1-[3-(7-Chloro-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

[0125] The titled compound was prepared by following the procedure of example 3, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 7-chloro-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-one
1H-NMR ($CDCl_3$) δ: 1.66-1.71(3H,m), 2.00-2.10(2H,m), 2.36-2.44(4H,m), 2.52-2.57(2H,m), 2.66-2.70(2H,m), 5.32(2H, brs), 6.13(1H,t), 6.78(1H,d), 7.11(1H,dd), 7.26-7.44(5H,m), 7.58(1H,dd), 8.51(1H,dd).
MS m/z: 481(M+1)

Example 68 -1-[3-(7-Carboxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

[0126] A mixture of the product of example 117 (500 mg), potassium acetate (330 mg), palladium(II) diacetate (10 mg), 1,1'-bis(diphenylphosphino)ferrocene (93 mg), in dimethylsulfoxide (10 ml) was purged with carbon monoxide for 5 minutes and stirred under a carbon monoxide balloon at 60°C for 3 hours. Water was added to the reaction mixture, the precipitation was filtered. The solid were dissolved with ethyl acetate and dilute sodium hydroxide solution. The aqueous layer was separated and neutralized with dilute hydrochloric acid. The precipitation was filtered to give the titled compound (250 mg).
1H-NMR (DMSO-d_6) δ: 1.45-1.55(2H,m), 1.75-1.85(2H,m), 2.36-2.62(8H,m), 5.42(2H,brs), 6.21(1H,t), 6.90(1H,d), 7.40-7.52(5H,m), 7.75(1H,dd), 7.83(1H,dd), 7.95(1H,d), 8.56(1H,dd).
MS m/z: 491(M+1)

Example 78 -4-(4-Chlorophenyl)-1-[3-(5,-11-dihydro-7-propoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0127] The titled compound was prepared by following the procedure of example 4, but replacing ethyl iodide with propyl iodide.
1H-NMR ($CDCl_3$) δ: 1.03(3H,t), 1.65-1.70(2H,m), 1.78(2H,q), 1.98-2.09(3H,m), 2.37-2.45(4H,m), 2.51-2.56(2H,m), 2.66-2.70(2H,m), 3.88(2H,t), 5.26(2H,brs), 6.08(1H,t), 6.72-6.84(3H,m), 7.23-7.43(5H,m), 7.58(1H,dd), 8.43(1H,dd).
MS m/z: 505(M+1)

Example 80 -4-(4-Chlorophenyl)-1-[3-(7-cyclopropylmethyloxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidin-4-ol

[0128] The titled compound was prepared by following the procedure of example 4, but replacing ethyl iodide with cyclopropylmethyl bromide.
^{1}H-NMR ($CDCl_3$) δ: 0.31-0.37(2H,m), 0.60-0.67(2H,m), 1.21-1.28(1H,m), 1.66-1.72(3H,m), 2.01-2.11(2H,m), 2.37-2.71 (8H,m), 3.77(2H,d), 5.27(2H,brs), 6.08(1H,t), 6.73-6.86(3H,m), 7.23-7.44(5H,m), 7.58(1H,dd), 8.47(1H,dd).
MS m/z: 517(M+1)

Example 81 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-dimetylaminoethyl) oxy) [1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0129] The titled compound was prepared by following the procedure of example 4, but replacing ethyl iodide with 2-(dimethylamino)ethyl chloride hydrochloride.
^{1}H-NMR ($CDCl_3$) δ: 1.71-1.76(2H,m), 2.12-2.21(2H,m), 2.38(6H,s), 2.40-2.79(11H,m), 4.07(2H,t), 5.28(2H,brs), 6.07 (1H,t), 6.74-6.86(3H,m), 7.27-7.46(5H,m), 7.59(1H,dd), 8.49(1H,dd).
MS m/z: 534(M+1)

Example 82 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(tetrazol-5-yl)methyloxy) [1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidin-4-ol

Step 1

[0130] 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-triphenylmethyltetrazol-5-yl)methyloxy)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol was prepared by following the procedure of example 4, but replacing ethyl iodide with (2-triphenylmethyltetrazol-5-yl)methyl chloride.
^{1}H-NMR ($CDCl_3$) δ: 1.64-1.70(3H,m), 2.02-2.15(2H,m), 2.35-2.71(8H,m),5.29(2H,brs), 5.33(2H,s), 6.03(1H,t), 6.77(1H, d), 6.83(1H,dd), 6.96(1H,d), 7.04-7.08(6H,m), 7.23-7.45(14H,m), 7.54(1H,dd), 8.50(1H,dd).

Step 2

[0131] A solution of the product of step 1 (530 mg) in acetone (2.5 ml), acetic acid (2.5 ml) and water (2.5 ml) was stirred at 55°C for 30 minutes. The reaction mixture was distilled off under reduced pressure. The residue was washed with methanol to give the titled compound (280 mg).
^{1}H-NMR(DMSO-d_6) δ: 1.69-1.74(2H,m), 1.99-2.09(2H,m), 2.95-3.14(8H,m), 5.18(2H,brs), 5.20(2H,s), 6.14(1H,t), 6.76 (1H,d), 6.93(1H,dd), 7.04(1H,d), 7.39-7.48(5H,m), 7.78(1H,dd), 8.52(1H,dd).
MS m/z: 545(M+1)

Example 83 -1-[3-(7-Carboxymethyloxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl) piperidin-4-ol

[0132] To a solution of product of example 6 (3.0 g) in methanol (50 ml) was added 1N sodium hydroxide solution (8 ml) and the mixture stirred at room temperature for 1 hour. The reaction mixture was distilled off under reduced pressure. The residue was dissolved with water and neutralized with 1N hydrochloric acid. The precipitation was filtered and washed with water to give the titled compound (2.6 g).
^{1}H-NMR (DMSO-d_6) δ: 1.48-1.53 (2H,m), 1.76-1.88(2H,m), 2.32-2.60(8H,m), 4.60(2H,s), 5.18(2H,brs), 6.16(1H,t), 6.72-6.84(3H,m), 7.34-7.48(5H,m), 7.73(1H,dd), 8.50(1H,dd).
MS m/z: 521(M+1)

Example 84 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-dimethylaminocarbonylmethyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0133] To a solution of product of example 83 (420 mg) in dimethylformamide (17 ml) were added 1-hydroxybenzotriazol hydrate (250 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (310 mg), dimethylamine hydrochloride (270 mg) and triethylamine (0.45 ml), and the mixture stirred at room temperature for 12 hours. Water and chloroform were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure to give the titled compound (380 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.67-1.71(2H,m), 1.95-2.11(3H,m), 2.37-2.71(8H,m), 2.97(3H,s), 3.08(3H,s), 4.64-(2H,s), 5.27(2H, brs), 6.09(1H,t), 6.74-6.82(2H,m), 6.93(1H,d), 7.24-7.44(5H,m), 7.58(1H,dd), 8.47(1H,dd).
MS m/z: 548(M+1)

Example 85 -4-(4-Chlorophenyl)-1-(3-(5,11-dihydro-7-morpholinocarbonylmethyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0134] The titled compound was prepared by following the procedure of example 84, but replacing dimethylamine hydrochloride with morpholine.
^{1}H-NMR ($CDCl_3$) δ: 1.67-1.71(2H,m), 1.87(1H,brs), 2.00-2.11(2H,m), 2.38-2.71(8H,m), 3.61-3.68(8H,m), 4.65(2H,s), 5.27(2H,brs), 6.09(1H,t), 6.74-6.83(2H,m), 6.90(1H,d), 7.25-7.44(5H,m), 7.58(1H,dd), 8.48(1H,dd).
MS m/z: 590(M+1)

Example 88 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-ethoxycarbonyl-1-methylethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0135] The titled compound was prepared by following the procedure of example 4, but replacing ethyl iodide with ethyl 2-bromoisobutylate.
^{1}H-NMR ($CDCl_3$) δ: 1.27(3H,t), 1.56(6H.s), 1.63-1.71(3H,m), 2.01-2.10(2H,m), 2.35-2.70(8H,m), 4.24(2H,q), 5.28(2H, brs), 6.05(1H,t), 6.67-6.75(2H,m), 6.87(1H,d), 7.24-7.44(5H,m), 7.56(1H,dd), 8.49(1H,dd).
MS m/z: 577(M+1)

Example 89 -1-[3-(7-(1-Carboxy-1-methylethyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

[0136] The titled compound was prepared by following the procedure of example 83, but replacing product of example 48 with product of example 88.
^{1}H-NMR (DMSO-d_6) δ: 1.45-1.52(8H,m), 1.79-1.85(2H,m), 2.28-2.53(8H,m), 5.19(2H,brs), 6.07(1H,t), 6.69-6.73(2H,m), 6.85(1H,d), 7.33-7.47(5H,m), 7.71(1H,dd), 8.48(1H,dd).
MS m/z: 549(M+1)

Example 90 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-methoxyphenyl)piperidin-4-ol

[0137] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-methoxyphenyl)-4-hydroxypiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.62-1.75(2H,m), 2.08(2H,dt), 2.41-2.76(9H,m), 3.77(3H,s), 3.78(3H,s), 5.26(2H,brs), 6.06(1H,t), 6.75-6.871(5H,m), 7.23(1H,dd), 7.38(2H,d), 7.57(1H,dd), 8.45(1H,dd).
MS m/z: 473 (M+1)

Example 91 -4-(4-Cyanophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0138] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-cyanophenyl)-4-hydroxypiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.58-1.70(2H,m), 2.03(2H,t), 2.31-2.64(7H,m), 2.65-2.78(2H,m), 3.75(3H,s), 5.26(2H,brs), 5.95 (0.1H,t, E isomer), 6.05(0.9H,t, Z isomer), 6.70-6.80(3H,m), 7.22(1H,dd), 7.54-7.68(5H,m), 8.31(0.1H,dd, E iosmer), 8.39(0.9H,dd, Z isomer).
MS m/z:468(M+1)

Example 92 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-hydroxyphenyl)piperidin-4-ol

[0139] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-hydroxyphenyl)-4-hydroxypiperidine.
^{1}HNMR ($CDCl_3$) δ: 1.76-1.88(2H,m), 2.08-2.22(2H,m), 2.45-2.95(9H,m), 3.76(3H,s), 5.28(2H,brs), 5.95(0.3H,t, E isomer), 6.04(0.7H,t, Z iosmer), 6.69-6.72(3H,m), 6.90(2H,d), 7.20-7.30(3H,m), 7.56(0.7H,dd, Z isomer), 7.67(0.3H,dd, E isomer), 8.46(0.7H,dd, Z isomer), 8.47(0.3H,dd, E isomer). OH signal was not observed.
MS m/z: 473 (M+1)

Example 93 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-fluoro-3-methylphenyl) piperidin-4-ol

[0140] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-fluoro-3-methylphenyl)-4-hydroxypiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.62-1.75(2H,m), 2.05(1H,brs), 2.09(2H,dt), 2.25(3H,s), 2.30-2.76(8H,m), 3.76(3H,s), 5.26(2H, brs), 5.96(0.1H,t, E isomer), 6.07(0.9H,t, Z isomer), 6.75-6.89(3H,m), 6.93(1H,t), 7.11-7.20(0.3H,m, E isomer), 7.21-7.35 (0.24H,m, Z isomer), 7.56(0.9H,dd, E isomer), 7.67(0.1H, dd, E isomer), 8.38(0.1H,dd, E isomer), 8.45(0.9H,dd, Z isomer).
MS m/z: 475(M+1)

Example 94 -4-(3,4-difluorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0141] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(3,4-difluorophenyl)-4-hydroxypiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.58-1.72(2H,m), 1.96(2H,dt), 2.33-2.71(8H,m), 3.73(3H,s), 5.23(2H,brs), 5.94(0.1H,t, E isomer), 6.04(0.9H,t, Z isomer), 8.38-8.36(0.9H,m, Z isomer), 6.68-6.79(3H,m), 6.98-7.38(4H,m), 7.50-7.62(0.9H,m, Z isomer), 7.63-7.68(0.1H,m, E isomer), 8.29-8.32(0.1H,m, E isomer), 8.32-8.44(0.9H,m, Z isomer). OH signal was not observed.
MS m/z: 479 (M+1)

Example 95 -4-(4-Chloro-3-trifuluoromethylphenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0142] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chloro-3-trifluoromethylphenyl)-4-hydroxypiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.62-1.74(2H,m), 2.10(2H,dt), 2.35-2.80(8H,m), 2.42(1H, brs), 3.76(3H,s), 5.26(2H,brs), 6.07(0.9H, t, Z isomer), 6.03(0.1H,t, E isomer), 6.82-6.71(3H,m), 7.24(1H,dd), 7.43(1H,d), 7.56(1.8H,dd, Z isomer), 7.65(0.2,H,dd, E isomer) 7.83(1H,d), 8.36(0.1H,dd, E isomer), 8.44(0.9H,dd, Z iosmer),
MS m/z: 545(M+1)

Example 96 -4-(3,5-dichlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0143] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(3,5-dichlorophenyl)-4-hydroxypiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.58-2.22(5H,m), 2.38-2.77(8H,m), 3.76(3H,s), 5.26(2H,brs), 5.92(0.1H,t, E isomer), 6.07(0.9H,t, Z isomer), 6.83-6.71(3H,m), 7.19-7.42(4H,m), 7.56(0.9H,dd, Z isomer), 7.68(0.1H,dd, E isomer), 8.38(0.1H,dd, E isomer), 8.45(0.9H,dd, Z isomer).
MS m/z: 512(M+1)

Example 97 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-pyridyl)piperidin-4-ol

[0144] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(2-pyridyl)-4-hydroxypiperidine
^{1}H-NMR ($CDCl_3$) δ: 1.54-1.65(2H,m), 2.06(2H,dt), 2.07(1H,brs), 2.35-2.62(7H,m), 2.73-2.87(2H,m), 3.78(3H,s), 5.28 (2H, brs), 6.08(1H,t), 6.72-6.85(3H,m), 7.14-7.29(2H,m), 7.57(1H,d), 7.70(1H,dd), 8.48(2H,dd).
MS m/z: 444(M+1)

Example 98 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(3-pyridyl)piperidin-4-ol

[0145] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(3-pyridyl)-4-hydroxypiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.65-1.78(2H,m), 2.08(2H,dt), 2.37-2.88(7H,m), 2.63-2.79(2H,m), 3.78(3H,s), 5.28(2H, brs), 6.02 (0.1H,t, E isomer), 6.07(0.9H,t, Z isomer), 6.70-6.84(3H,m), 7.22-7.32(3H,m), 7.56(1H,dd), 7.77(1H,dd), 8.46(0.9H,d), 8.57(0.1H,dd, E isomer), 8.73(1H,dd).
MS m/z: 444(M+1)

Example 99 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-pyridyl)piperidin-4-ol

[0146] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-pyridyl)-4-hydroxypiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.58-1.72(2H,m), 2.03(2H,dt), 2.34-2.89(8H,m), 2.96(1H,brs), 3.76(3H,s), 5.25(2H, brs), 6.06(1H, t), 6.72-6.83(3H,m), 7.24(1H,dd), 7.37(2H,dd), 7.56(1H,dd), 8.45(1H,dd), 8.48(2H,dd).
MS m/z: 444(M+1)

Example 100 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-trifluoromethylphenyl) piperidin-4-ol

[0147] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-trifluoromethylphenyl)-4-hydroxypiperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.64-1.75(2H,m), 2.01(1H, brs), 2.16(2H,dt), 2.38-2.86(8H,m), 3.76(3H,s), 5.26(2H,brs), 6.04(1H, t), 6.72-6.84(3H,m), 7.23(1H,dd), 7.56(5H,m), 8.42(1H,dd).
MS m/z: 511(M+1)

Example 101 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

[0148] The titled compound was prepared by following the procedure of example 2, step 2, but replacing 4- (4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)piperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.62-1.92(4H,m), 1.94-2.18(2H,m), 2.28-2.64(5H,m), 2.99(2H,m), 5.25(2H,brs), 6.00(1H,t), 6.60-6.82(3H,m), 7.02-7.36(5H,m), 7.50(1H,dd), 8.47(1H,dd). OH signal was not observed.
MS m/z: 447(M+1)

Example 102 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

[0149] The titled compound was prepared by following the procedure of example 4, but replacing the product of example 44 with the product of example 151.
^{1}H-NMR ($CDCl_3$) δ: 1.40(3H,t), 1.52-2.14(6H,m), 2.30-2.57(5H,m), 2.94(2H,m), 4.00(2H,q), 5.28(2H,brs), 6.07(1H,t), 6.68-6.86(3H,m), 7.05-7.36(5H,m), 7.58(1H,m), 8.49(1H,m).
MS m/z: 475(M+1)

Example 103 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethoxycarbonylmethyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

[0150] The titled compound was prepared by following the procedure of example 6, but replacing the product of example 1 with the product of example 101.
^{1}H-NMR ($CDCl_3$) δ: 1.29(3H,t), 1.56-1.85(4H,m), 1.99(2H,dt), 2.28-2.55(5H,m), 2.91(2H,m), 4.27(2H,q), 4.58(2H,s), 5.28(2H,brs), 6.09(1H,t), 6.68-6.95(3H,m), 7.07-7.32(5H,m), 7.58(1H,dd), 8.49(1H,dd).
MS m/z: 533(M+1)

Example 104 -1-[3-(7-(Carboxymethyloxy-5,11-dihydro[1]benzoxepinol[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidine

[0151] The titled compound was prepared by following the procedure of example 83, but replacing the product of example 6 with the product of example 103.
^{1}H-NMR (CD_3OD) δ: 1.82-2.17(4H,m), 2.69(2H,m), 2.86(1H,m), 3.07(2H,m), 3.30(2H,m), 3.57(2H,m), 4.57(2H,s), 5.21

(2H,brs), 6.10(1H,t), 6.70-7.04 (3H,m), 7.16-7.38(4H,m), 7.44(1H,m), 7.77(1H,m), 8.47(1H,m). COOH signal was not observed.
MS m/z: 505(M+1)

Example 105 -4-(4-Chlorophenyl)-1- [3-(5,11-dihydro-7-dimethylaminocarbonylmethyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

[0152] The titled compound was prepared by following the procedure of example 84, but replacing the product of example 83 with the product of example 104.
^{1}H-NMR ($CDCl_3$) δ: 1.58-1.92(4H,m), 2.04(2H,m), 2.30-2.68(5H,m), 2.93(2H,m), 2.98(3H,s), 3.08(3H,s), 4.65(2H,s), 5.28(2H,brs), 6.07(1H,t), 6.70-6.98(3H,m), 7.08-7.36(5H,m), 7.60(1H,m), 8.50(1H,m).
MS m/z: 532(M+1)

Example 106 -1-[3-(7-(2-Acetoxyethyl)oxy-5,11-dihydro [1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

[0153] The titled compound was prepared by following the procedure of example 8, but replacing the product of example 2 with the product of example 101.
^{1}H-NMR ($CDCl_3$) δ: 1.55-1.88(4H,m), 1.90-2.32(2H,m), 2.10(3H,s), 2.28-2.60(5H,m), 2.82-3.02(2H,m), 4.14(2H,dd), 4.41(2H,dd), 5.29(2H,brs), 6.08(1H,t), 6.72-6.90(3H,m), 7.18-7.34(5H,m), 7.57(1H,m), 8.50(1H,m).
MS m/z: 533(M+1)

Example 107 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-hydroxyethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

[0154] The titled compound was prepared by following the procedure of example 9, but replacing the product of example 8 with the product of example 106.
^{1}H-NMR (CD_3OD) δ: 1.66-1.98(4H,m), 2.40-2.73(5H,m), 2.82-2.94(2H,m), 3.22(2H,m), 3.84(2H,dd), 4.01(2H,dd), 5.23 (2H,brs), 6.13(1H,t), 6.64-6.98(3H,m), 7.13-7.34(4H,m), 7.45(1H,m), 7.77(1H,m), 8.47(1H,m). OH signal was not observed.
MS m/z: 491(M+1)

Example 108 -4-(4-Chlorophenyl) -1- [3-(5, 11-dihydro-7-(1-ethoxycarbonyl-1-methylethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

[0155] The titled compound was prepared by following the procedure of example 88, but replacing the product of example 2 with the product of example 101.
^{1}H-NMR ($CDCl_3$) δ: 1.28(3H,t), 1.56(6H,s), 1.56-1.85(4H,m), 1.97(2H,dt), 2.28-2.55(5H,m), 2.93(2H,m), 4.24(2H,q), 5.28(2H,brs), 6.04(1H,t), 6.62-6.95(3H,m), 7.07-7.32(5H,m), 7.57(1H,dd), 8.50(1H,dd).
MS m/z: 561(M+1)

Example 109 -1-[3-(7-(1-Carboxy-1-methylethyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidine

[0156] The titled compound was prepared by following the procedure of example 83, but replacing the product of example 48 with the product of example 108.
^{1}H-NMR (CD_3OD) δ: 1.50(6H,s), 1.82-2.18(4H,m), 2.70(2H,m), 2.87(1H,m), 3.12(2H,m), 3.30 (2H,m), 3.60(2H,m), 5.25 (2H,brs), 6.07(1H,t), 6.67-7.04(3H,m), 7.16-7.38(4H,m), 7.58(1H,m), 7.96(1H,m), 8.52(1H,m). COOH signal was not observed.
MS m/z: 533 (M+1)

Example 110 -1-[3-(8-Bromo-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidine

[0157] The titled compound was prepared by following the procedure of example 23, but replacing the product of example 3, step 2 with the product of example 12, step 1.
^{1}H-NMR ($CDCl_3$) δ: 1.50-1.86(4H,m), 1.98(2H,m), 2.26-2.60(5H,m), 2.88(2H,m), 5.30(2H,brs), 6.09(1H,t), 6.96-7.36(8H,m), 7.57(1H,dd), 8.51(1H,dd).
MS m/z: 509, 511(M+1)

Example 111 -1-[3-(8-Carboxy-5,11-dihydro [1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidine

[0158] To a solution of 1-[3-(8-Bromo-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl) piperidine (Example 111) (130 mg) in THF(1.0 ml) was added 1.6M *n*-butyllithium hexane solution (0.17 ml) at -78°C. After stirring 10 minutes at the same temperature, CO_2 (dry-ice) was added to the mixture. After being warmed to ambient temperature, the mixture was stirred for 30 minutes at the same temperature. The mixture was concentrated *in vacuo*. The resulting oil was purified by silica gel chromatography eluted with dichloromethane -methanol (5:1) to give the titled compound (50mg)
^{1}H-NMR (CD_3OD) δ: 1.55-1.95(4H,m), 2.17(2H,dt), 2.32-2.78(5H,m), 3.00(2H,m), 5.30(2H,brs), 6.19(1H,t), 7.08-7.54 (8H,m), 7.76(1H,dd), 8.45(1H,dd) COOH signal was not observed .
MS m/z: 475(M+1)

Example 112 -1-[3-(7-Bromo-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

[0159] The titled compound was prepared by following the procedure of example 3, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 8-bromo-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-one.
1H-NMR ($CDCl_3$) δ: 1.60-1.71(3H,m), 1.98-2.09(2H,m), 2.34-2.69(8H,m), 5.32(2H,brs), 6.13(1H,t), 6.73(1H,d), 7.22-7.44 (7H,m), 7.57(1H,dd), 8.52(1H,dd).
MS m/z: 525, 527(M+1)

Example 113 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0160] The titled compound was prepared by following the procedure of example 3, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 5,11-dihydro-7-ethyl[1]benzoxepino[2,3-b]pyridin-5-one.
1H-NMR ($CDCl_3$) δ: 1.23(3H,t), 1.52(1H,brs), 1.66-1.71(2H,m), 1.98-2.06(2H,m), 2.35-2.70(11H,m), 5.31(2H,brs), 6.09 (1H,t), 6.79(1H,d), 7.01(1H,dd), 7.11(1H,d), 7.25-7.44(5H,m), 7.58(1H,dd), 8.49(1H,dd).
MS m/z: 475(M+1)

Example 114 -4-(4-Chlorophenyl)-1-[3-(5, 11-dihydro-8-vinyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0161] The titled compound was prepared by following the procedure of example 3, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 5,11-dihydro-8-vinyl[1]benzoxepino[2,3-b]pyridin-5-one.
1H-NMR ($CDCl_3$) δ: 1.66-1.71(3H,m), 2.00-2.10(2H,m), 2.36-2.70(8H,m), 5.22(2H,d), 5.34(2H,brs), 5.70(1H,d), 6.11 (1H,t), 6.61(1H,dd), 6.89(1H,d), 6.99(1H,dd), 7.24-7.44(6H,m), 7.58(1H,dd), 8.49(1H,dd).
MS m/z: 473(M+1)

Example 115 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-8-ethyl [1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0162] A mixture of the product of example 114 (100 mg) and Pd-C (20 mg) in ethanol(2 ml) stirred under a hydrogen balloon at room temperature for 1 hour. The mixture was filtered through the celite and distilled off under reduced pressure. The residue was purified by preparative thin layer chromatography eluting with chloroform-methanol (15:1) to give the titled compound (50 mg).
1H-NMR ($CDCl_3$) δ: 1.22(3H,t), 1.55-1.77(3H,m), 2.00-2.13(2H,m), 2.33-2.74(10H,m), 5.32(2H,brs), 6.07(1H,t), 6.70 (1H,d), 6.78(1H,dd), 7.19-7.44(6H,m), 7.57(1H,dd), 8.49(1H,dd).
MS m/z: 475(M+1)

Example 116 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-9-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0163] The titled compound was prepared by following the procedure of example 3, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 5,11-dihydro-9-methoxy[1]benzoxepino[2,3-b]pyridin-5-one. 1H-MMR ($CDCl_3$) δ: 1.65-1.70(2H,m), 1.95-2.06(2H,m), 2.15(1H,brs), 2.37-2.67(8H,m), 3.83(3H,s), 5.43(2H,brs), 6.09(1H,t), 6.79-6.91(3H,m), 7.22-7.43(5H,m), 7.57(1H,dd), 8.44(1H,dd).

MS m/z: 477(M+1)

Example 117 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-trifluoromethanesulfonyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0164] To a solution of product of example 2 (1.0 g) in pyridine (10 ml) was added trifluoromethanesulfonic acid anhydride (0.55 ml) at 0°C, and the mixture was stirred at room temperature for 1 hour. Water and diethyl ether were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (10:1) to give the titled compound (1.1 g).
1H-NMR ($CDCl_3$) δ: 1.56(1H,brs), 1.66-1.71(2H,m), 1.97-2.09(2H,m), 2.35-2.69(8H,m), 5.35(2H,brs) 6.15(1H,t), 6.88 (1H,d), 7.05(1H,dd), 7.21-7.44(6H,m), 7.60(1H,dd), 8.54(1H,dd).
MS m/z: 595(M+1)

Example 118 -1-[3-(7-Allyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

[0165] A mixture of the product of example 117 (240 mg), allyltributyltin (0.19 ml), dichlorobis(triphenylphosphine) palladium(II) (30 mg) and lithium chloride (76 mg) in dimethylformamide (3 ml) was heated under argon at 120°C for 2 hours. Aqueous ammonium fluoride solution and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel chromatography eluting with chloroform-methanol (10:1) to give the titled compound (180 mg).
1H-NMR (CDCl3) δ: 1.62-1.72(.3H,m), 2.03-2.11(2H,m), 2.39-2.73(8H,m), 3.31(2H,d), 5.04-5.11(2H,m), 5.29(2H,brs), 5.87-6.02(1H,m), 6.06(1H,t), 6.77(1H,d), 6.99(1H,dd), 7.10(1H,d), 7.23-7.43(5H,m), 7.57(1H,dd), 8.40(1H,dd).

Example 119 -1-[3-(7-(2-t-Butoxycarboxy)ethenyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

[0166] A mixture of the product of example 117 (1.7 g), t-butyl acrylate (0.85 ml), triethylamine (2.5 ml), 1,1'-bis (diphenylphosphino)ferrocene (250 mg) and palladium(II) diacetate (33 mg) in dimethylformamide (3 ml) was heated under argon at 90°C for 24 hours. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate The solvent was distilled off under reduced pressure, and the residue was purified.by silica gel chromatography eluting with ethyl acetate-methanol (30:1) to give the titled compound (780 mg).
1H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.63-1.71(3H,m), 1.98-2.10(2H,m), 2.35-2.72(8H,m), 5.35(2H,brs), 6.15(1H,t), 6.26(1H, d), 6.83(1H,d), 7.22-7.44(7H,m), 7.53(1H,d), 7.58(1H,dd), 8.52(1H,dd).

Example 120 -1-[3-(7-(2-Carboxy)ethenyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

[0167] The product of example 119 (330 mg) was dissolved with 4N hydrochloric acid 1,4-dioxane solution (4 ml), and stirred at room temperature for 1 hour. The solvent was distilled off under reduced pressure. Water was added to the residue, and neutralized with sodium hydroxide solution. The precipitation was filtered to give the titled compound (190 mg).
1H-NMR (DMSO-d_6) δ: 1.45-1.52(2H,m), 1.72-1.84(2H,m), 2.25-2.58(8H,m), 5.25(2H,brs), 6.28(1H,t), 6.43(1H,d), 6.82 (1H,d), 7.34-7.60(8H,m), 7.75(1H,dd), 8.52(1H,dd).

Example 121 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-propargyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0168] The titled compound was prepared by following the procedure of example 4, but replacing ethyl iodide with propargyl chloride.
1H-NMR ($CDCl_3$) δ: 1.66-1.71(2H,m), 1.79(1H,brs), 1.99-2.10(2H,m), 2.35-2.71-(9H,m), 4.66(2H,d), 5.28(2H,brs), 6.10 (1H,t), 6.80-6.93(3H,m), 7.24-7.46(5H,m), 7.59(1H,dd), 8.48(1H,dd).
MS m/z: 501(M+1)

Example 122 -4-(4-Chlorophenyl)-1-[3-(7-cyclopentoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0169] The titled compound was prepared by following the procedure of example 4, but replacing ethyl iodide with cyclopentyl bromide.
1H-NMR ($CDCl_3$) δ: 1.54-2.18(13H,m), 2.41-2.72(8H,m), 4.66-4.73(1H,m), 5.27(2H,brs), 6.08(1H,t). 6.70-6.87(3H,m), 7.23-7.44(5H,m), 7.58(1H,dd), 8.49(1H,dd).
MS m/z: 531(M+1)

Example 123 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-methoxyethyl)oxy)[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidin-4-ol

[0170] The titled compound was prepared by following the procedure of example 4, but replacing ethyl iodide with 2-methoxyethyl chloride.
1H-NMR ($CDCl_3$) δ: 1.66-1.75(3H,m), 2.00-2.11(2H,m), 2.36-2.71(8H,m), 3.45(3H,s), 3.71-3.75(2H,m), 4.07-4.11(2H, m), 5.27(2H,brs), 6.09(1H,t), 6.75-6.91(3H,m), 7.23-7.44(5H,m), 7.57(1H,dd), 8.48(1H,dd).
MS m/z: 521(M+1)

Example 124 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-dimethyaminocarbonyl-1-methylethyl)oxy[1]benzoxepino [2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0171] The titled compound was prepared by following the procedure of example 84, but replacing the product of example 83 with the product of example 89.
1H-NMR ($CDCl_3$) δ: 1.59(6H,s), 1.67-1.72(2H,m), 1.99-2.09(2H,m), 2.36-2.70(9H,m), 2.96(3H,s), 3.21(3H,s), 5.25(2H, brs), 6.02(1H,t), 6.60-6.77(3H,m), 7.24-7.44(5H,m), 7.58(1H,dd), 8.44(1H,dd).
MS m/z: 576(M+1)

Example 125 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-ethoxycarbonylethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0172] The titled compound was prepared by following the procedure of example 4, but replacing ethyl iodide with ethyl 2-bromopropionate.
1H-NMR ($CDCl_3$) δ: 1.25(3H,t), 1.59(3H,d), 1.65-1.70(2H,m), 1.98-2.08(2H,m), 2.35-2.68(8H,m), 2.80(1H,brs), 4.21(2H, q), 4.68(1H,q), 5.24(2H,brs), 6.07(1H,t), 6.68-6.79(2H,m), 6.88(1H,d), 7.22-7.44(5H,m), 7.56(1H,dd), 8.40(1H,dd).

Example 126 -1-[3-(7-(1-Carboxyethyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

[0173] The titled compound was prepared by following the procedure of example 83, but replacing product of example 48 with product of example 125.
1H-NMR (DMSO-d_6) δ: 1.46(3H,d), 1.58-1.63(2H,m), 1.98-2.06(2H,m), 2.41-2.45(2H,m), 2.72-2.86(6H,m), 4.74(1H,q), 5.18(2H,brs), 6.11(1H,t), 6.73(2H,s), 6.84(1H,s), 7.36-7.47(5H,m), 7.73(1H,dd), 8.50(1H,dd).
MS m/z: 535(M+1)

Example 127 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-ethoxycarbonyl)cyclobutoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0174] The titled compound was prepared by following the procedure of example 4, but replacing ethyl iodide with ethyl 2-bromocyclobutanecarboxylate.
1H-NMR ($CDCl_3$) δ: 1.19(3H,t), 1.67-1.71(2H, m), 1.92-2.11(5H,m), 2.33-2.77(12H,m), 4.21(2H,q), 5.25(2H,brs), 6.05 (1H,t), 6.47(1H,dd), 6.70(1H,d), 6.73(1H,d), 7.23-7.44(5H,m), 7.55(1H,dd), 8.44(1H,dd).

Example 128 -1-[3-(7-(1-Carboxy)cyclbutoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

[0175] The titled compound was prepared by following the procedure of example 83, but replacing product of example 6 with product of example 127.
1H-NMR (DMSO-d_6) δ: 1.60-1.65(2H,m), 1.86-2.08(4H,m), 2.24-2.90(12H,m), 5.17 (2H,brs), 6.05(1H,t), 6.50(1H,dd),

6.66(1H,d), 6.73(1H,d), 7.37-7.48(5H,m), 7.74(1H,dd), 8.51(1H,dd).
MS m/z: 561(M+1)

Example 129 -1-[3-(7-Carbamoylmethyloxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

[0176] The titled compound was prepared by following the procedure of example 84, but replacing dimethylamine hydrochloride with ammonium hydroxide.
1H-NMR ($CDCl_3$) δ: 1.66-1.71(2H,m), 1.98-2.09(2H,m), 2.21(1H,brs), 2.38-2.70(8H,m), 4.45(2H,s), 5.28(2H,brs), 6.09 (1H,t), 6.11(1H,brs), 6.58(1H,brs), 6.74-6.85(3H,m), 7.24-7.44(5H,m), 7.58(1H,dd), 8.47(1H,dd).
MS m/z: 520(M+1)

Example 130 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methylaminocarbonylmethyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0177] The titled compound was prepared by following the procedure of example 84, but replacing dimethylamine hydrochloride with methylamine.
1H-NMR ($CDCl_3$) δ: 1.67-1.72(2H,m), 1.99-2.10(2H,m), 2.36-2.70(9H,m), 2.89(3H,d), 4.45(2H,s), 5.28(2H,brs), 6.08 (1H,t), 6.66(1H,brs), 6.73-6.84(3H,m), 7.25-7.45(5H,m), 7.58(1H,dd), 8.47(1H,dd).
MS m/z: 534(M+1)

Example 131 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl] -4-(4-hydroxyphenyl)piperidine

[0178] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-hydroxyphenyl)piperidine.
1H-NMR (CDCL3) δ: 1.52-1.88(4H,m), 2.01(2H,dt), 2.28-2.60(5H,m), 2.93(2H,m), 3.79(3H,s), 5.28(2H,brs), 6.08(1H,t), 6.68-6.88(3H,m), 7.05-7.36(5H,m), 7.58(1H,dd), 8.50(1H,dd).
MS m/z: 461(M+1)

Example 132 -1-[3- (5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl] 4-(2-hydroxyphenyl)piperidine

[0179] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(2-hydroxyphenyl)piperidine.
^{1}H-NMR ($CDCl_3$) δ: 1.78-1.92(4H,m), 2.12-2.25(2H,m), 2.32-2.70(4H,m), 2.80-2.97(1H,m), 3.01-3.15(2H,m), 3.77(3H, s), 3.78.(1H,brs), 5.28(2H,brs), 6.03(1H,t), 6.74-6.86(4H,m), 7.05(1H,dd), 7.11(1H,dd), 7.23-7.28(2H,m), 7.56(1H,dd), 8.48(1H,dd) OH signal was not observed.
MS m/z: 443(M+1)

Example 133 -4-(7-Chloro-1,2-benzisoxazol-3-yl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine

[0180] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(7-chloro-1,2-benzisoxazol-3-yl) piperidine. This piperidine was prepared by the same method described in *J. Med. Chem. 28*:761-769 (1985).
^{1}H-NMR ($CDCl_3$) δ: 1.94-2.20 (6H,m), 2.30-2.60(4H,m), 2.86-3.14(3H,m), 3.79(3H,s), 5.29(2H,brs), 6.10(1H,t), 6.70-6.88(3H,m), 7.22(1H,t), 7.27(1H,dd), 7.50(1H,dd), 7.57-7.68(2H,m), 8.49(1H,dd).

Example 134 -4-(7-Chloroindol-3-yl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

[0181] The titled compound was prepared by following the procedure of example 3, step 3, but replacing. 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(7-chloroindol-3-yl)piperidine. This piperidine was prepared by the same method described in *J. Med. Chem. 36*:4006-4014 (1993) and following hydrogenation described in Example 58, step 3.
^{1}H-NMR($CDCl_3$) δ: 1.66-1.88(2H,m), 1.92-2.22(4H,m), 2.32-2.63(4H,m), 2.78(1H,m), 2.97(2H,m), 3.79(3H,s), 5.29(2H, brs), 6.09(1H,t), 6.70-6.87(3H,m), 6.97-7.07(2H,m), 7.12-7.30(2H,m), 7.52(1H,m), 7.59(1H,dd), 8.45(1H,brs), 8.50(1H, dd).

Example 135 -4-Azido-4-(4-chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl] piperidine

[0182] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-azido-4-(4-chlorophenyl) piperidine.
^{1}H-NMR ($CDCL_3$) δ: 1.88(2H,m), 2.55-2.85(4H,m), 3.00-3.30(6H,m). 3.75(3H,s), 5.19(2H,brs), 5.97(1H,t), 6.68-6.65 (3H,m), 7.20-7.46(5H,m), 7.63(1H,dd), 8.35(1H,dd).
MS m/z: 477(M+1-N_2+H_2)

Example 136 -Methyl 1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-phenylpiperidin-4-carboxylate

[0183] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with methyl 4-phenylpiperidin-4-carboxylate.
^{1}H-NMR ($CDCl_3$) δ: 1.82-2.15 (4H,m), 2.28-2.60(6H,m), 2.78-2.82(2H,m), 3.62(3H,s), 3.68(3H,s), 5.26(2H,brs), 5.95 (0.1H,t, E isomer), 6.05(0.9H,t, Z isomer), 6.82-6.70(3H,m), 7.33-7.22(6H,m), 7.65(0.1H,dd, Z isomer), 7.55(0.9H,dd, Z isomer), 8.39(0.1H, dd, E isomer), 8.48(0.9H,dd, Z isomer).
MS m/z: 485(M+1)

Example 137 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-phenylpiperidin-4-carboxylic acid

[0184] The titled compound was prepared by following the procedure of example 83, but replacing product of example 6 with product of example 136.
^{1}H-NMR (CD_3OD) δ: 2.16-2.23(2H,m), 2.69-2.91(4H,m), 3.00-3.16(2H,m), 3.37-3.25(2H,m), 3.68-3.73(2H,m), 3.76(3H, s), 5.34(2H,brs), 6.24(1H,t), 6.70-7.04(3H,m), 7.26-7.55(5H,m), 7.79-7.89(1H,m), 8.21-8.34(1H,m), 8.56-8.62(0.1H,m), 8.63-8.77(0.9H,m),
MS m/z: 471(M+1)

Example 138 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-1,2,3,6-tetrahydropyridine

[0185] The titled compound was prepared by following the procedure of example 2, step 2, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine.
^{1}H-NMR ($CDCl_3$) δ: 2.37-2.72(8H,m), 3.07(2H,m), 5.25(2H,brs), 6.00(1H,m), 6.07(1H,t), 6.60-6.78(3H,m), 7.18-7.47(5H, m), 7.56(1H,dd), 8.50(1H,dd), OH signal was not observed.
MS m/z: 445(M+1)

Example 139 -4-(4-Chlorophenyl)-1-[3-(5, 11-dihydro-7-methoxy [1] benzoxepino [2,3-b]pyridin-5-ylidene)propyl]-1,2,3,6-tetrahydropyridine

[0186] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4- (4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine.
^{1}H-NMR ($CDCl_3$) δ: 2.37-2.72(8H,m), 3.06(2H,m), 3.78(3H,s), 5.27(2H,brs), 5.99(1H,m), 6.10(1H,t), 6.72-6.90(3H,m), 7.20-7.44(5H,m), 7.60(1H,dd), 8.50(1H,dd).
MS m/z: 459(M+1)

Example 140 -4-(7-Chloroindol-3-yl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-1,2,3,6-tetrahydropyridine.

[0187] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(7-chloroindol-3-yl)-1,2,3,6-tetrahydropyridine. This piperidine was prepared by the.same method described in *J. Med. Chem. 36*:4006-4014 (1993).
^{1}H-NMR ($CDCl_3$) δ: 2.37-2.76(8H,m), 3.14(2H,m), 3.78(3H,s), 5.29(2H,brs), 6.02-6.23(2H,m), 6.67-6.90(3H,m), 7.05 (1H,dd), 7.12-7.33(3H,m), 7.60(1H,dd), 7.77(1H,m), 8.50(1H,dd), 9.06(1H,br s).

Example 141 -5-Chloro-1'-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]spiro[isobenzofuran-1(3H),4'-piperidine]

[0188] The titled compound was prepared by following the procedure of example 2, step 2, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 5-chlorospiro[isobenzofuran-1(3H),4'-piperidine].
1H-NMR ($CDCl_3$) δ: 1.66-1.71(2H,m), 1.79-1.91(2H,m), 2.26-2.73(8H,m), 4.99(2H,s), 5.22(2H,brs), 6.07(1H,t), 6.63-6.70 (2H,m), 6.76(1H,d), 7.06(1H,d), 7.19-7.32(3H,m), 7.60(1H,dd), 8.47(1H,dd), 8.63(1H,s).
MS m/z: 475(M+1)

Example 142 -5-Chloro-1'-[3-(5,11-dihydro-7-(2-methoxyethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]spiro [isobenzofuran-1(3H),4'-piperidine]

[0189] The titled compound was prepared by following the procedure of example 123, but replacing the product of example 2 with the product of example 141.
1H-NMR ($CDCl_3$) δ: 1.69-1.74(2H,m), 1.83-1.94(2H,m), 2.31-2.76(8H,m), 3.45(3H,s), 3.72-3.75(2H,m), 4.08-4.11(2H, m), 5.00(2H,s), 5.28(2H,brs), 6.09(1H,t), 6.74-6.82(2H,m), 6.89(1H,d), 7.04(1H,d), 7.17-7.28(3H,m), 7.57(1H,dd), 8.49 (1H,dd).
MS m/z: (M+1)

Example 143 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-dimethylaminocarbonyl[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidin-4-ol

[0190] The titled compound was prepared by following the procedure of example 84, but replacing the product of example 83 with the product of example 68.
1H-NMR ($CDCl_3$) δ: 1.65-1.70(2H,m), 1.99-2.09(3H,m), 2.32-2.69(8H,m), 2.17(3H,s), 5.35(2H,brs), 6.15(1H,t), 6.82(1H, d), 7.19(1H,dd), 7.28-7.46(6H,m), 7.58(1H,dd), 8.49(1H,dd).

Example 144 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1,1-dimethyl-2-hydroxyethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0191] To a solution of product of example 88 (500 mg) in methanol (5 ml) was added sodium borohydride (330 mg), and the mixture was heated to reflux for 1 hour. The mixture was distilled off under reduced pressure. Water and ethyl acetate were added to the residue, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel chromatography eluting with chloroform-methanol (10:1) to give the titled compound (440 mg).
1H-NMR ($CDCl_3$) δ: 1.26 (6H, s), 1.66-1.70(2H, m), 1.79(1H.brs), 2.00-2.08(2H,m), 2.37-2.70(9H,m), 3.58(2H,s), 5.30 (2H,brs), 6.05(1H,t), 6.75-6.84(2H,m), 6.91(1H,d), 7.26-7.44(5H,m), 7.58(1H,dd), 8.49(1H,dd).
MS m/z: 535(M+1)

Example 145 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2,2-dimethyl-2-hydroxyethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

[0192] To a solution of product of example 6 (500 mg) in tetrahydrofuran (5 ml) was added 0.95M methylmagnesium bromide tetrahydrofuran solution (3.8 ml) at 0°C, and the mixture was stirred at room temperature for 20 minutes. Aqueous ammonium chloride solution and ethyl acetate were added to the mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel chromatography eluting with chloroform-methanol (10:1) to give the titled compound (360 mg).
1H-NMR ($CDCl_3$) δ: 1.34(6H,s), 1.58(1H,brs), 1.65-1.71(2H,m), 1.99-2.10(2H,m), 2.25(1H,brs), 2.36-2.71(8H,m), 3.77 (2H,s), 5.28(2H,brs), 6.09(1H,t), 6.74-6.86(3H,m), 7.24-7.44(5H,m), 7.57(1H,dd), 8.49(1H,dd).
MS m/z: 535(M+1)

Example 179 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidine)propyl]-4-(indol-3-yl)-piperidine

[0193] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(indol-3-yl)-piperidine. This piperidine was prepared by the same method described in *J. Med. Chem. 36*:4006-4014 (1993) and follow hydrogenation described in Example 58, step 3.
^{1}H-NMR($CDCl_3$) δ: 1.65-1.93(2H,m), 1.94-2.28(4H,m), 2.34-2.70(4H,m), 2.81(1H,m), 2.96(2H,m), 3.78(3H,s), 5.28(2H,

brs), 6.09(1H,t), 6.70-7.42(8H,m), 7.53-7..72 (2H,m), 8..28 (1H,brs), 8.49(1H,m).

Example 180 -1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidine)propyl]-4-(indol-3-yl)-1,2,3,6-tetrahydropyridine.

[0194] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(indol-3-yl)-1,2,3,6-tetrahydropyridine. This tetrahydropyridine was prepared by the same method described in *J. Med. Chem. 36*:4006-4014 (1993).
^{1}H-NMR (CDCl$_3$) δ: 2.35-2.77(8H,m), 3.06-3.26(2H,m), 3.78(3H,s), 5.29(2H,brs), 6.05-6.22(2H,m), 6.70'-6.88(3H,m), 7.07-7.38(5H,m), 7.60(1H,dd), 7.87(1H,m), 8.42(1H,brs), 8.50(1H,m).

Example 181 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(3-(ethoxycarbonyl)propyloxy[1]benzoxipino[2,3-b]pyridin-5-ylidine)propyl)piperidine

[0195] The titled compound was prepared by following the procedure of example 103, but replacing ethyl bromoacetate with ethyl 4-bromobutyrate.
^{1}H-NMR (CDCL$_3$) δ: 1.26(3H,t), 1.56-1.85(4H,m), 2.01(2H,dt), 2.09(2H,quint), 2.30-2.60(7H,m), 2.93(2H,m), 3.98(2H.t), 4,15(2H,q), 5.28(2H,brs), 6.07(1H,t), 6.68-6.86(3H,m), 7.07-7.33(5H,m),7.58(1H,dd), 8.50(1H,dd).
MS m/z: 561(M+1)

Example 182 -1-[3-(7-(3-Carboxypropyl)oxy-5,11-dihydro-[1]benzoxepino[2,3-b]pyridin-5-ylidine)propyl]-4-(4-chlorophenyl)-piperidine

[0196] The titled compound was prepared by following the procedure of example 83, but replacing the product of example 6 with the product of example 181.
^{1}H-NMR (CD$_3$OD) δ: 1.92-2.20(6H,m), 2.48(2H,t), 2.70-3.02(3H,m), 3.06-3.45(4H,m), 3.66(2H,m), 4.01(2H,t), 5.48(2H, brs), 6.36(1H,t), 6.85(2H,s), 7.00(1H,s), 7.20-7.40(4H,m), 8.11(1H,dd), 8.64(1H,d), 8.81(1H,d). COOH signal was not observed.
MS m/z: 533(M+1)

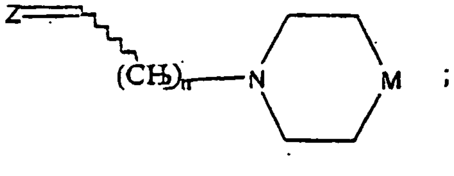
Example 183 -1'-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidine)propyl)-6-methylspiro[4H-3,1-benzoxazine-4,4'-piperidine]-2(1H)-one

[0197] The titled compound was prepared by following the procedure of example 3, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 6-methylspiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.
^{1}H-NMR (CDCl$_3$) δ: 1.99-2.06(2H,m), 2.29(3H,s), 2.32-2.69(10H,m), 3.77(3H,s), 5.27(2H,brs), 6.08(1H,t), 6.69-6.83(4H, m), 6.94(1H,s), 7.02(1H,d), 7.25(1H,dd), 7.55(1H,dd), 8.48(1H,dd), 8.56(1H,s).
MS m/z: 498(M+1)

[0198] Examples 34-36, 38, 41, 44-60, 62, 63, 66, 69-77, 79, 86, 87, 137, 138-140, 146-178, 181, 183-192 shown in Figure 6 can be prepared by the schemes similar to those set forth in Figures 1 - 5 and 7 and by the procedures described above.

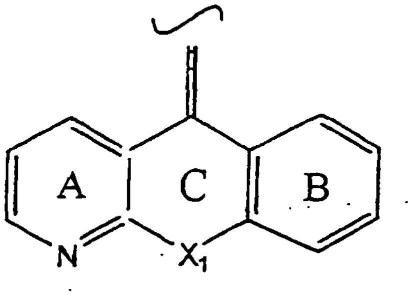
Claims

1. A compound of formula:



or physiologically acceptable salt thereof, wherein:

n is an integer from one to four;
M is $>CR^1R^2$;
R^1 is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$; or R^1 is a covalent bond between the ring atom M and an adjacent carbon atom in the ring which contains M;
R^2 is -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group;
R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or
R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic heterocyclic ring;
said acyl group is an aliphatic carbonyl, aromatic carbonyl, aliphatic sulfonyl or aromatic sulfonyl;
Z is:



wherein:

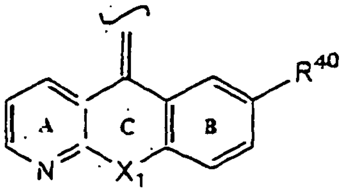
X_1 is -S-, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-NR_c-CH_2-$, $-CH_2-NR_c-$, $-SO-CH_2-$,$-CH_2-SO-$, $-S(O)_2-CH_2-$, $-CH_2-S(O)_2-$, -CH=CH-, $-NR_c-CO-$ or $-CO-NR_c-$;
R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; Ring A and Ring B are independently substituted or unsubstituted; said substituted aliphatic group comprises one or more substituents selected from the group consisting of an electron withdrawing group, halo, azido, -COOH,
-OH, $-CONR^{14}R^{25}$, $-NR^{24}R^{25}$, $-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, $-S(O)_2NH_2$, guanidino, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$, -Q-H, -Q-(aliphatic group), -Q-(substituted aliphatic group), -Q-(aryl), -Q-(aromatic group), -Q-(substituted aromatic group), $-Q-(CH_2)_p-$(substituted or unsubstituted aromatic group), -Q-(non-aromatic heterocyclic goup), $-Q-(CH_2)_p-$(non-aromatic heterocyclic group), oxo, epoxy, non-aromatic heterocycle, benzyl, substituted benzyl, aromatic group and substituted aromatic group;
said substituted benzyl group, substituted aromatic group, and Ring A or Ring B when substituted comprise one or more substitutents selected from the group consisting of an electron withdrawing group, halo, azido, -CN, -COOH, -OH, $-CONR^{24}R^{25}$, $-NR^{24}R^{25}$, $-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, $-S(O)_2NH_2$, guanidino, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$, -Q-H, -Q-(aliphatic group), -Q-(substituted aliphatic group), -Q-(aryl), -Q-(aromatic group), -Q-(substituted aromatic group), $-Q-(CH_2)_p-$(substituted or unsubstituted aromatic group), -Q-(non-aromatic heterocyclic group), $-Q-(CH_2)_p-$(non-aromatic heterocyclic group), aliphatic group and substituted aliphatic group; said substituted non-aromatic heterocyclic group comprises one or more substitutents selected from the group consisting of an electron withdrawing group, halo, azido, -CN, -COOH, -OH, $-CONR^{24}R^{25}$, $-NR^{24}R^{25}$, $-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, $-S(O)_2NH_2$, guanidino, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$, -Q-H, -Q-(aliphatic group), -Q-(substituted aliphatic group), -Q-(aryl), -Q-(aromatic group), -Q-(substituted aromatic group), $-Q-(CH_2)_p-$(substituted or unsubsdtuted aromatic group), -Q-(non-aromatic heterocyclic group), $-Q-(CH_2)_p-$(non-aromatic heterocyclic group), aliphatic group, substituted aliphatic group, =O, =S, =NH, =N(aliphatic), =N(aromatic) and =N(substituted aromatic);

R^{20}, R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -NHC(O)-O-(aliphatic group), -NHC(O)-O-(aromatic group) or -NHC(O)-O-(non-aromatic heterocyclic group); or
R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;
t is an integer from zero to three;
u is zero or one;
p is one to five;
Q is -O-, -S-, -S(O)-, $-S(O)_2-$, $-OS(O)_2-$, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, $-S(O)_2NH-$, $-NHS(O)_2-$, $-N(R^{23})-$, $-C(NR^{23})NHNH-$, $-NHNHC(NR^{23})-$, $-NR^{24}C(O)-$ or $-NR^{24}S(O)_2-$;
R^{23} is -H, an aliphatic group, a benzyl group, an aryl group or non-aromatic heterocyclic group;
R^{24} and R^{25} are independently -H, -OH, an aliphatic group, a substituted aliphatic group, a benzyl group, an aryl group or non-aromatic heterocyclic group;
said aliphatic group is a saturated or unsaturated C_1-C_{20} hydrocarbon;
said electron withdrawing group is alkylimino, alkylsulfonyl, carboxamido, carboxylic alkyl ester, -CH=NH or $-NO_2$;
the heterocycle of said non-aromatic heterocyclic group is a 5 to 8 membered non-aromatic ring that contains one or more heteroatoms selected from the group consisting of O, N, and S; and
said aromatic group is selected from the group consisting of a C_6 aromatic carbocycle, a C_5 - C_6 aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of O, S and N, and a C_6 aromatic carbocycle or a C_5 - C_6 aromatic heterocycle that is fused to one or more other rings.

2. A compound according to Claim 1, wherein Ring B is substituted with -OH, halo, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$; wherein:

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or
R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;
u is zero or one; and
t is an integer from zero to three.

3. A compound according to Claim 1, wherein Z:



wherein:

R^{40} is -OH, halogen, aliphatic group, substituted aliphatic group, $-NR^{24}R^{25}$, Q-(aliphatic group), Q-(substztuted aliphatic group), -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$;
R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or
R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;
Q is $-NR^{24}C(O)-$ or $-NR^{24}S(O)_2-$;

R^{24} and R^{25} are independently -H, -OH, an aliphatic group or a substituted aliphatic group;
u is zero or one; and
t is an integer from zero to 3.

4. A compound according to Claim 3, wherein R^{40} is $-O-CH_3$.

5. A compound according to any one of Claims 1 - 4, wherein R^1 is -OH.

6. A compound according to Claim 5, wherein n is two.

7. A compound according to one of Claims 1 - 6, wherein R^2 is a substituted or unsubstituted aromatic group.

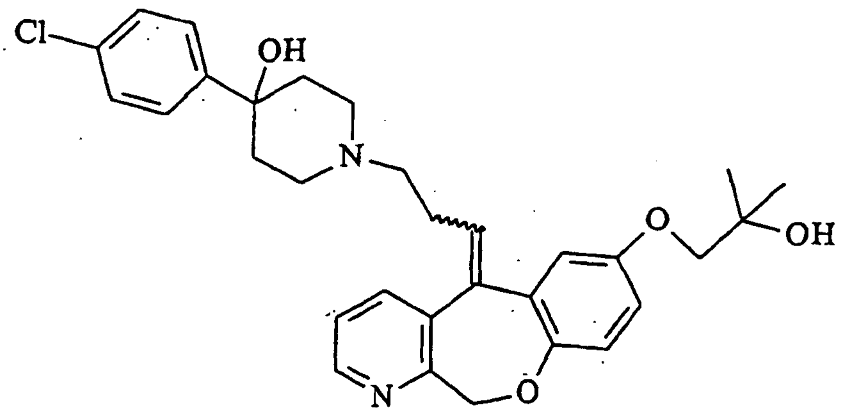
8. A compound according to any one of Claims 1 - 6, wherein R^2 is an aromatic group substituted with halogen.

9. A compound according to any one of Claims 1 - 6, wherein R^1 is a 4-chlorochenyl group.

10. A compound according to any one of Claims 1-9, wherein X_1 is $-CH_2-O-$.

11. A compound according to any one of Claims 1-9, wherein X_1 is $-CH_2-S$ or $-CH_2-CH_2-$.

12. A compound according to claim 1 which is selected from:



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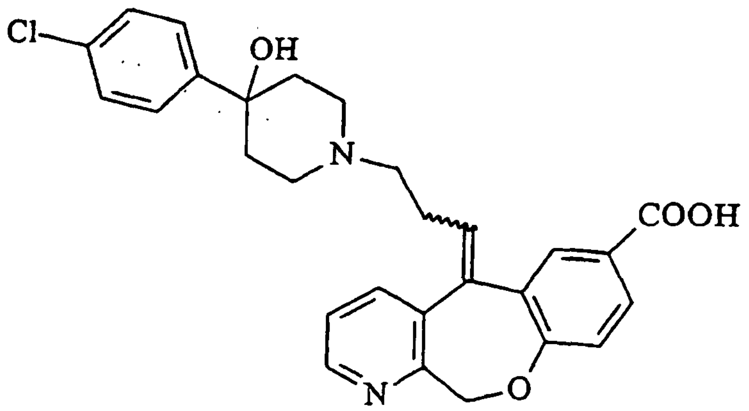

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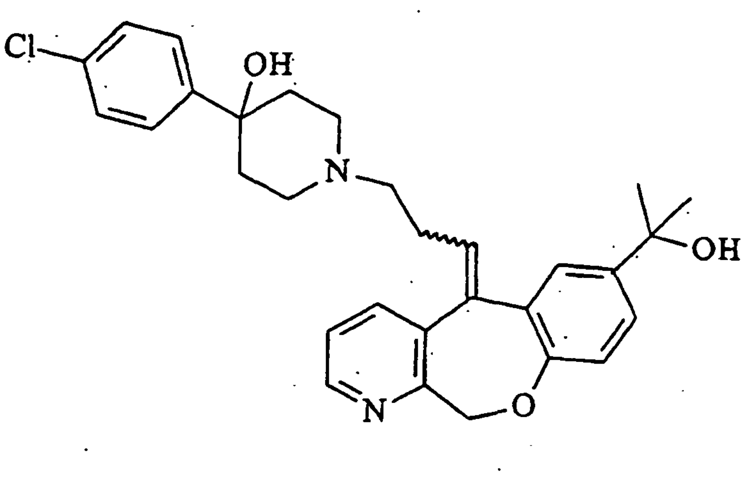
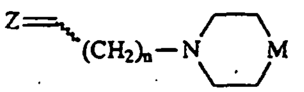


and physiologically acceptable salts thereof.

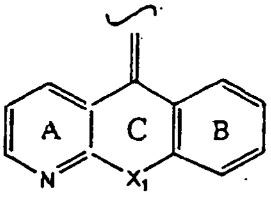
13. A compound of formula:



;

or physiologically acceptable salt thereof, wherein:

n is an integer from one to four,
M is >CR^1R^2;
R^1 is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O) -(substituted aliphatic group), -C(O) O-(aliphatic group), -C(O)O-(substituted alipatic group), -CN, -COOH, -CO-NR^3R^4 or -NR^3R^4;
R^2 is -OH, an acyl group, a substituted acyl group, -NR^5R^6, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group;
R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or
R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;
said acyl group is an aliphatic carbonyl, aromatic carbonyl, aliphatic sulfonyl or aromatic sulfonyl;
Z is:



(II)

wherein:

X_1 is -S-, -CH_2-, -CH_2-CH_2-, -CH_2-S-, -S-CH_2-, -O-CH_2-, -CH_2-O-, -NR_c-CH_2-, -CH_2-NR_c-, -SO-CH_2-, -CH_2-SO-, -$S(O)_2$-CH_2-, -CH_2-$S(O)_2$-, -CH=CH-, -NR_c-CO- or -CO-NR_c- ;

R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; Ring A and Ring B are independently substituted or unsubstituted; said substituted aliphatic group comprises one or more substituents selected from the group consisting of an electron withdrawing group, halo, -COOH, -OH, $-CONR^{24}R^{25}$, $-NR^{24}R^{25}$, $-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, $-S(O)_2NH_2$, guanidino, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, -Q-H, -Q-(alipharic group), -Q-(substituted aliphatic group), -Q-(aryl), $-Q-(CH_2)_p$-(substituted or unsubstituted aromatic group), -Q-(non-aromatic heterocyclic group), $-Q-(CH_2)_p$-(non-aromatic heterocyclic group), oxo, epoxy, non-aromatic heterocycle, benzyl, substituted benzyl, aromatic group and substituted aromatic group;

said substituted benzyl group, substituted aromatic group, and Ring A or Ring B when substituted comprise one or more substitutents selected from the group consisting of an electron withdrawing group, halo, -CN, -COOH, -OH, $-CONR^{24}R^{25}$, $-NR^{24}R^{25}$, $-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, $-S(O)_2NH_2$, guanidino, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, -Q-H, -Q-(aliphatic group), -Q-(substituted aliphatic group), -Q-(aryl), $-Q-(CH_2)_p$-(substituted or unsubstituted aromatic group), -Q-(non-aromatic heterocyclic group), $-Q-(CH_2)_p$-(non-aromatic heterocyclic group), aliphatic group and substituted aliphatic group;

said substituted non-aromatic heterocyclic group comprises one or more substitutents selected from the group consisting of an electron withdrawing group, halo, -CN, -COOH, -OH, $-CONR^{24}R^{25}$, $-NR^{24}R^{25}$, $-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, $-S(O)_2NH_2$, guanidino, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, -Q-H, -Q-(aliphatic group), -Q-(substituted aliphatic group), -Q-(aryl), $-Q-(CH_2)_p$-(substituted or unsubstituted aromatic group), -Q-(non-aromatic heterocyclic group), $-Q-(CH_2)_p$-(non-aromatic heterocyclic group), aliphatic group, substituted aliphatic group, =O, =S, =NH, =N(aliphatic), =N(aromatic) and =N(substituted aromatic);

R^{20}, R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, -NHC(O)-O-(aliphatic group), -NHC(O)-O-(aromatic group) or -NHC(O)-O-(non-aromatic heterocyclic group); or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

t is an integer from zero to three;

u is zero or one;

p is one to five;

Q is -O-, -S-, -S(O)-, $-S(O)_2-$, $-OS(O)_2-$, -C(O)-, -OC(O)-, -C(O)O-, - C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, - NH-C(O)-NH-, $-S(O)_2NH-$, $-NHS(O)_2-$, $-N(R^{23})-$, $-C(NR^{23})NHNH-$, $-NHNHC(NR^{23})-$;

R^{23} is -H, an aliphatic group, a benzyl group, an aryl group or non-aromatic heterocyclic group;

said aliphatic group is a saturated or unsaturated C_1-C_{20}hydrocarbon;

said electron withdrawing group is alkylimino, alkylsulfonyl, carboxamido, carboxylic alkyl ester, -CH=NH or $-NO_2$;

the heterocycle of said non-aromatic heterocyclic group is a 5 to 8 membered non-aromatic ring that contains one or more heteroatoms selected from the group consisting of O, N, and S; and

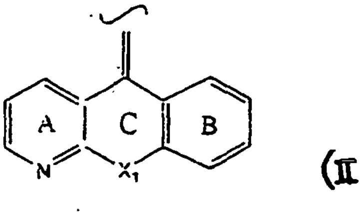
said aromatic group is selected from the group consisting of a C_6 aromatic carbocycle, a C_5 - C_6 aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of O, S and N, and a C_6 aromatic carbocycle or a C_5 - C_6 aromatic heterocycle that is fused to one or more other rings.

14. A compound according to Claim 13, wherein:

R^1 is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group) or -O-C(O)-(substituted aliphatic group);

R^2 is an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group;

Z is:



wherein:

X_1 is $-CH_2-CH_2-$, $-CH_2-S-$, $-CH_2-O-$, $-CH_2-NR_c-$, $-CH_2-SO-$, $-CH_2-S(O)_2-$, -CH=CH- or $-CO-NR_2-$; wherein: R_c is an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and
Ring A and Ring B are independently substituted or unsubstituted.

15. A compound according to Claim 14 or Claim 13, wherein R^1 is -OH and R^2 is a substituted or unsubstituted aromatic group.

16. The compound as defined in Claim 15, wherein R^2 is an aromatic group substituted with halogen.

17. The compound as defined in Claim 16, wherein R^2 is a 4-chlorophenyl group.

18. The compound as defined in any one of Claims 13 to 17, wherein X_1 is $-CH_2-O-$.

19. A compound as defined in any one of Claims 1 to 18 for use in the treatment of the human or animal body by therapy.

20. Use of a compound as defined in any one of Claims 1 to 11 in the manufacture of a medicament for antagonizing a chemokine receptor.

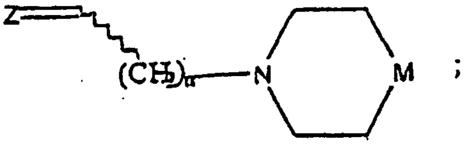
21. Use of a compound as defined in any one of Claims 1 to 18 in the manufacture of a medicament for treating a disease associated with aberrant leukocyte recruitment and/or activation.

22. Use according to Claim 21, wherein said disease associated with aberrant leukocyte recruitment and/or activation is arthritis, atherosclerosis, arteriosclerosis, ischemia/reperfusion injury, diabetes mellitus, psoriasis, multiple sclerosis, ulcerative colitis, Crohn's disease, rejection of a transplanted organ or tissue, graft versus host disease, allergy, asthma, AIDS associated encephalitis, AIDS related maculopapular skin eruption, AIDS related interstitial pneumonia, AIDS related enteropathy, AIDS related periportal hepatic inflammation or AIDS related glomerulonephritis.

23. Use according to Claim 22, wherein said disease associated with aberrant leukocyte recruitment and/or activation is arthritis or multiple sclerosis.

Patentansprüche

1. Verbindung der Formel:



oder ein physiologisch annehmbares Salz davon, worin:

n eine ganze Zahl von 1 bis 4 ist,

m >CR^1R^2 ist,

R^1 ist -H, -OH, eine aliphatische Gruppe, -O-(aliphatische Gruppe), -O-(substituierte aliphatische Gruppe), -SH, -S-(aliphatische Gruppe), -S-(substituierte aliphatische Gruppe), -OC(O)-(aliphatische Gruppe), -O-C(O)-(substituierte aliphatische Gruppe), -C(O)O-(aliphatische Gruppe), -C(O)O-(substituierte aliphatische Gruppe), -CN, -COOH, -CO-NR^3R^4 oder -NR^3R^4; oder

R^1 ist eine kovalente Bindung zwischen dem Ringatom M und einem benachbarten Kohlenstoffatom in dem Ring, der M enthält;

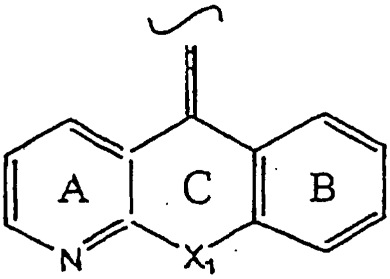
R^2 ist -OH, eine Acylgruppe, eine substituierte Acylgruppe, -NR^5R^6, eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, eine aromatische Gruppe, eine substituierte aromatische Gruppe, eine Benzylgruppe, eine substituierte Benzylgruppe, eine nicht-aromatische heterocyclische Gruppe oder eine substituierte nicht-aromatische heterocyclische Gruppe;

R^3, R^4, R^5 und R^6 sind unabhängig von einander -H, eine Acylgruppe, eine substituierte Acylgruppe, eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, eine aromatische Gruppe, eine substituierte aromatische Gruppe, eine Benzylgruppe, eine substituierte Benzylgruppe, eine nicht-aromatische heterocyclische Gruppe oder eine substituierte nicht-aromatische heterocyclische Gruppe, oder

R^1 und R^2, R^3 und R^4 oder R^5 und R^6 bilden zusammen mit dem Atom, an das sie gebunden sind, einen substituierten oder unsubstituierten nicht-aromatischen heterocyclischen Ring;

die Acylgruppe ist ein aliphatisches Carbonyl, aromatisches Carbonyl, aliphatisches Sulfonyl oder aromatisches Sulfonyl;

Z ist:



worin:

X_1 ist -S-, -CH_2-, -CH_2-CH_2-, -CH_2-S-, -S-CH_2-, -O-CH_2-, -CH_2-O-, -NR_c-CH_2-, -CH_2-NR_c-, -SO-CH_2-, -CH_2-SO-, -$S(O)_2$-CH_2-, -CH_2-$S(O)_2$-, -CH=CH-, -NR_c-CO- oder -CO-NR_c-;

R_c ist -H, eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, eine aromatische Gruppe, eine substituierte aromatische Gruppe, eine Benzylgruppe oder eine substituierte Benzylgruppe;

Ring A und Ring B sind unabhängig von einander substituiert oder unsubstituiert;

die substituierte aliphatische Gruppe umfasst einen oder mehrere Substituenten, ausgewählt aus der Gruppe bestehend aus einer Elektronen-abziehenden Gruppe, Halogen, Azido, -COOH, -OH, -$CONR^{24}R^{25}$, -$NR^{24}R^{15}$, -$OS(O)_2NR^{24}R^{25}$, -$S(O)_2NR^{24}R^{25}$, -SO_3H, -$S(O)_2NH_2$, Guanidino, -$(O)_u$-$(CH_2)_t$-$C(O)OR^{20}$, -$(O)_u$-$(CH_2)_t$-$OC(O)R^{20}$, -$(O)_u$-$(CH_2)_t$-C(O)-$NR^{21}R^{22}$, -$(O)_u$-$(CH_2)_t$-NHC(O)O-R^{20}, -Q-H, -Q-(aliphatische Gruppe), -Q-(substituierte aliphatische Gruppe), -Q-(Aryl), -Q-(aromatische Gruppe), -Q-(substituierte aromatische Gruppe), -Q-$(CH_2)_p$-(substituierte oder unsubstituierte aromatische Gruppe), -Q-(nicht-aromatische heterocyclische Gruppe), -Q-$(CH_2)_p$-(nicht-aromatische heterocyclische Gruppe), Oxo, Epoxy, nicht-aromatische heterocyclische Benzyl-, substituierte Benzyl-, aromatische Gruppe und substituierte aromatische Gruppe;

die substituierte Benzylgruppe, substituierte aromatische Gruppe und Ring A oder B, wenn sie substituiert sind, umfassen einen oder mehrere Substituenten, ausgewählt aus der Gruppe, bestehend aus einer Elektronen-abziehenden Gruppe, Halogen, Azido, -CN, -COOH, -OH, -$CONR^{24}R^{25}$, -$NR^{24}R^{15}$, -$OS(O)_2NR^{24}R^{25}$, -$S(O)_2NR^{24}R^{25}$, -SO_3H, -$S(O)_2NH_2$, Guanidino, -$(O)_u$-$(CH_2)_t$-$C(O)OR^{20}$, -$(O)_u$-$(CH_2)_t$-$OC(O)R^{20}$, -$(O)_u$-$(CH_2)_t$-C(O)-$NR^{21}R^{22}$, -$(O)_u$-$(CH_2)_t$-NHC(O)O-R^{20}, -Q-H, -Q-(aliphatische Gruppe), -Q-(substituierte aliphatische Gruppe), -Q-(Aryl), -Q-(aromatische Gruppe), -Q-(substituierte aromatische Gruppe), -Q-$(CH_2)_p$-(substituierte oder unsubstituierte aromatische Gruppe), -Q-(nicht-aromatische heterocyclische Gruppe), -Q-$(CH_2)_p$-(nicht-aromatische heterocyclische Gruppe), aliphatische Gruppe und substituierte aliphatische Gruppe;

die substituierte nicht-aromatische heterocyclische Gruppe umfasst einen oder mehrere Substituenten, ausgewählt aus der Gruppe bestehend aus einer Elektronen-abziehenden Gruppe, Halogen, Azido, -CN, -COOH, -OH, -CONR^{24}R^{25}, -NR^{24}R^{25}, -OS(O)$_2$NR^{24}R^{25}, -S(O)$_2$NR^{24}R^{25}, -SO$_3$H, -S(O)$_2$NH$_2$, Guanidino, -(O)$_u$-(CH$_2$)$_t$-C(O)OR^{20}, -(O)$_u$-(CH$_2$)$_t$-OC(O)R^{20}, -(O)$_u$-(CH$_2$)$_t$-C(O)-NR^{21}R^{22}, -(O)$_u$-(CH$_2$)$_t$-NHC(O)O-R^{20}, -Q-H, -Q-(aliphatische Gruppe), -Q-(substituierte aliphatische Gruppe), -Q-(Aryl), -Q-(aromatische Gruppe), -Q-(substituierte aromatische Gruppe), -Q-(CH$_2$)$_p$-(substituierte oder unsubstituierte aromatische Gruppe), -Q-(nicht-aromatische heterocyclische Gruppe), -Q-(CH$_2$)$_p$-(nicht-aromatische heterocyclische Gruppe), aliphatische Gruppe, substituierte aliphatische Gruppe, =O, =S, =NH, =N(aliphatische), =N(aromatische) und =N(substituierte aromatische);

R^{20}, R^{21} und R^{22} sind unabhängig von einander -H, eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, eine aromatische Gruppe, eine substituierte aromatische Gruppe, eine nicht-aromatische heterocyclische Gruppe, -NHC(O)-O-(aliphatische Gruppe) -NHC(O)-O-(aromatische Gruppe) oder NHC (O)-O-(nicht-aromatische heterocyclische Gruppe); oder

R^{21} und R^{22} bilden zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen nicht-aromatischen heterocyclischen Ring;

t ist eine ganze Zahl von 0 bis 3;

u ist 0 oder 1;

p ist 1 bis 5;

Q ist -O-, -S-, -S(O)-, -S(O)$_2$, -OS(O)$_2$-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)$_2$NH-, -NHS(O)$_2$-, -N(R^{23})-, -C(NR^{23})NHNH-, -NHNHC(NR^{23})-, -NR^{24}C(O)- oder -NR^{24}S(O)$_2$-;

R^{23} ist -H, eine aliphatische Gruppe, eine Benzylgruppe, eine Arylgruppe oder eine nicht-aromatische heterocyclische Gruppe;

R^{24} und R^{25} sind unabhängig von einander -H, -OH, eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, eine Benzylgruppe, eine Arylgruppe oder eine nicht-aromatische heterocyclische Gruppe,

die aliphatische Gruppe ist eine gesättigte oder ungesättigte C$_1$-C$_{20}$-Kohlenwasserstoffgruppe;

die Elektronen-abziehende Gruppe ist Alkylimino, Alkylsulfonyl, Carboxamido, Carboxylalkylester, -CH=NH oder -NO$_2$;

der Heterocyclus der nicht-aromatischen heterocyclischen Gruppe ist ein 5- bis 8-gliedriger nicht-aromatischer Ring, der eine oder mehrere Heteroatome enthält, ausgewählt aus der Gruppe bestehend aus O, N und S; und

die aromatische Gruppe ist ausgewählt aus der Gruppe bestehend aus einem C$_6$-aromatischen Carbocyclus, einem C$_5$-C$_6$-aromatischen Heterocyclus, der ein oder mehrere Heteroatome enthält, ausgewählt aus der Gruppe bestehend aus O, S und N, und einem C$_6$-aromatischen Carbocyclus oder einem C$_5$-C$_6$-aromatischen Heterocyclus, der mit einem oder mehreren anderen Ringen fusioniert ist.

2. Verbindung nach Anspruch 1, worin Ring B substituiert ist mit -OH, Halogen, einer -O-(aliphatischen Gruppe), -O-(substituierten aliphatischen Gruppe), -O-(aromatischen Gruppe), -O-(substituierten aromatischen Gruppe), einer Elektronen-abziehenden Gruppe, -(O)$_u$-(CH$_2$)$_t$-C(O)OR^{20}, -(O)$_u$-(CH$_2$)$_t$-OC(O)R^{20}, -(O)$_u$-(CH$_2$)$_t$-C(O)-NR^{21}R^{22}, -(O)$_u$-(CH$_2$)$_t$-NHC(O)O-R^{20}, worin sind

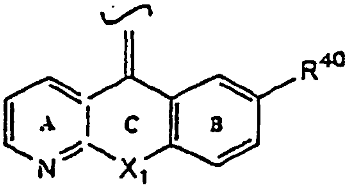
R^{20}, R^{21} oder R^{22} unabhängig von einander -H, eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, eine aromatische Gruppe, eine substituierte aromatische Gruppe oder eine nicht-aromatische heterocyclische Gruppe; oder

R^{21} und R^{22} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen nicht-aromatischen heterocyclischen Ring bilden;

u ist 0 oder 1; und

t ist eine ganze Zahl von 0 bis 3.

3. Verbindung nach Anspruch 1, worin Z ist:



worin:

R^{40} ist -OH, Halogen, eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, $-NR^{24}R^{25}$ eine Q-(aliphatische Gruppe), eine Q-(substituierte aliphatische Gruppe), eine -0-(aliphatische Gruppe), eine -0-(substituierte aliphatische Gruppe), eine -O-(aromatische Gruppe), eine -O-(substituierte aromatische Gruppe), eine Elektronen-abziehende Gruppe, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$;
R^{20} , R^{21} oder R^{22} unabhängig von einander -H, eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, eine aromatische Gruppe, eine substituierte aromatische Gruppe oder eine nicht-aromatische heterocyclische Gruppe; oder
R^{21} und R^{22} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen nicht-aromatischen heterocyclischen Ring bilden;
Q ist $-NR^{24}C(O)-$ oder $-NR^{24}S(O)_2-$;
R^{24} und R^{25} sind unabhängig von einander -H, -OH, ein aliphatische Gruppe oder eine substituierte aliphatische Gruppe;
u ist 0 oder 1; und
t ist eine ganze Zahl von 0 bis 3.

4. Verbindung nach Anspruch 3, worin R^{40} $-O-CH_3-$ ist.

5. Verbindung nach einem der Ansprüche 1 bis 4, worin R^1-OH ist.

6. Verbindung nach Anspruch 5, worin n 2 ist.

7. Verbindung nach einem der Ansprüche 1 bis 6, worin R^2 eine substituierte oder unsubstituierte aromatische Gruppe ist.

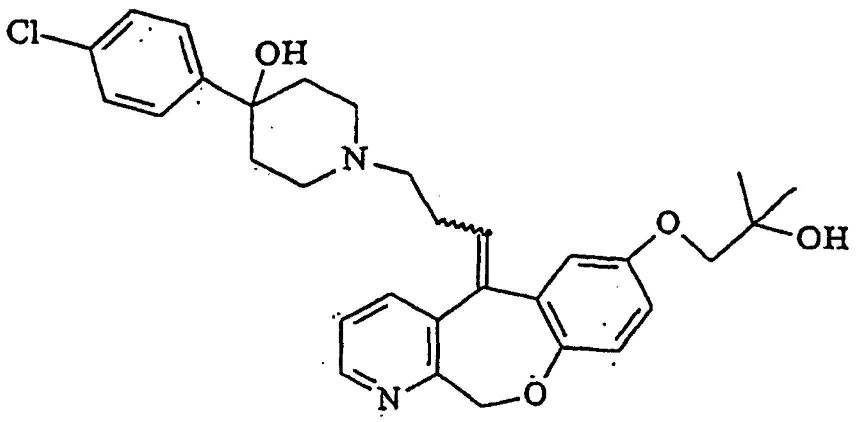
8. Verbindung nach einem der Ansprüche 1 bis 6, worin R^2 eine mit Halogen substituierte aromatische Gruppe ist.

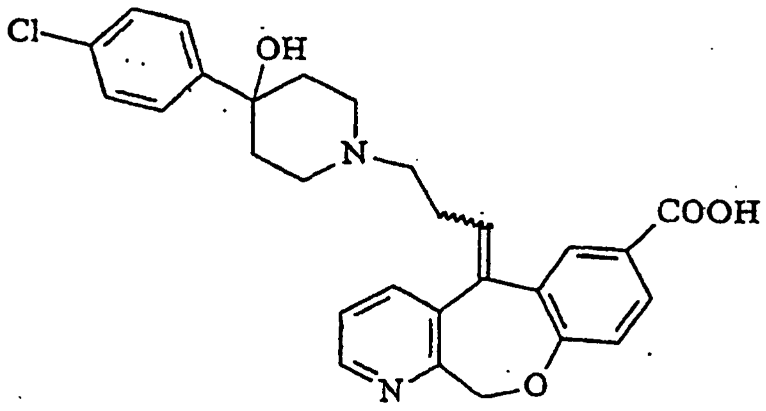
9. Verbindung nach einem der Ansprüche 1 bis 6, worin R^2 eine 4-Chlorphenylgruppe ist.

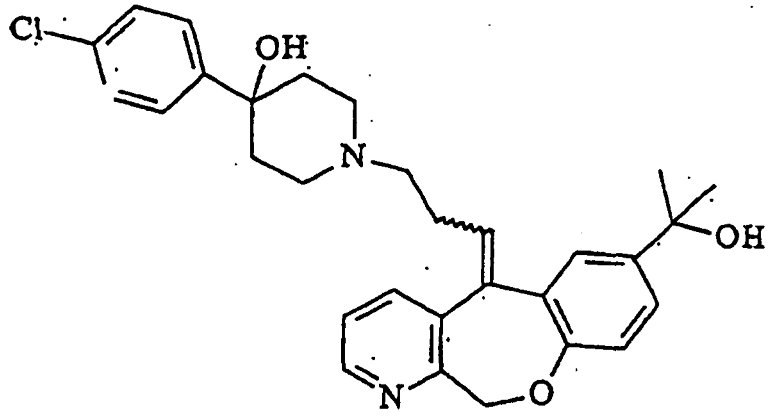
10. Verbindung nach einem der Ansprüche 1 bis 9, worin X_1 $-CH_2-O-$ ist.

11. Verbindung nach einem der Ansprüche 1 bis 9, worin X_1-CH_2-S- oder $-CH_2-CH_2-$ ist.

12. Verbindung nach Anspruch 1, ausgewählt aus:

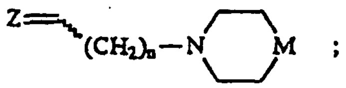






und physiologisch annehmbaren Salzen davon.

13. Verbindung der Formel:



oder ein physiologisch annehmbares Salz davon, worin:

n ist eine ganze Zahl von 1 bis 4;

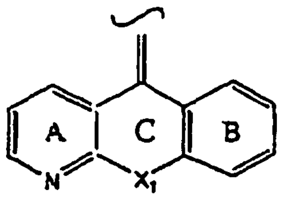
M ist > CR^1R^2;

R^1 ist -H, -OH, eine aliphatische Gruppe, -O-(aliphatische Gruppe), -O-(substituierte aliphatische Gruppe), -SH, -S-(aliphatische Gruppe), -S-(substituierte aliphatische Gruppe), -OC(O)-(aliphatische Gruppe), -O-C(O)-(substituierte aliphatische Gruppe), -C(O)O-(aliphatische Gruppe), -C(O)O-(substituierte aliphatische Gruppe), -CN, -COOH, -CO-NR^3R^4 oder -NR^3R^4;

R^2 ist -OH, eine Acylgruppe, eine substituierte Acylgruppe, -NR^5R^6, eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, eine aromatische Gruppe, eine substituierte aromatische Gruppe, eine Benzylgruppe, eine substituierte Benzylgruppe, eine nicht-aromatische heterocyclische Gruppe oder eine substituierte nicht-aromatische heterocyclische Gruppe;

R^3, R^4, R^5 und R^6 sind unabhängig von einander -H, eine Acylgruppe, eine substituierte Acylgruppe, eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, eine aromatische Gruppe, eine substituierte aromatische Gruppe, eine Benzylgruppe, eine substituierte Benzylgruppe, eine nicht-aromatische heterocyclische Gruppe oder eine substituierte nicht-aromatische heterocyclische Gruppe, oder

R^1 und R^2, R^3 und R^4 oder R^5 und R^6 bilden zusammen mit dem Atom, an das sie gebunden sind, einen substituierten oder unsubstituierten nicht-aromatischen carbocyclischen oder heterocyclischen Ring;
die Acylgruppe ist ein aliphatisches Carbonyl, aromatisches Carbonyl, aliphatisches Sulfonyl oder aromatisches Sulfonyl;
Z ist:



(II)

worin:

X_1 ist -S-, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-NR_c-CH_2-$, $-CH_2-NR_c-$, $-SO-CH_2-$, $-CH_2-SO-$, $-S(O)_2-CH_2-$, $-CH_2-S(O)_2-$, -CH=CH-, $-NR_c-CO-$ oder $-CO-NR_c-$;
R_c ist -H, eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, eine aromatische Gruppe, eine substituierte aromatische Gruppe, eine Benzylgruppe oder eine substituierte Benzylgruppe;
Ring A und Ring B sind unabhängig von einander substituiert oder unsubstituiert; die substituierte aliphatische Gruppe umfasst eine oder mehrere Substituenten, ausgewählt aus der Gruppe bestehend aus einer Elektronen-abziehenden Gruppe, Halogen, -COOH, -OH, $-CONR^{24}R^{25}$, $-NR^{24}R^{15}$, $-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, $-S(O)_2NH_2$, Guanidino, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-C(O)NR^{21}R^{22}$, -Q-H, Q-(aliphatische Gruppe), -Q-(substituierte aliphatische Gruppe), -Q-(Aryl), $-Q-(CH_2)_p-$(substituierte oder unsubstituierte aromatische Gruppe), -Q-(nicht-aromatische heterocyclische Gruppe), $-Q-(CH_2)_p-$(nicht-aromatische heterocyclische Gruppe), Oxo, Epoxy, nicht-aromatische heterocyclische, Benzyl-, substituierte Benzyl-, aromatische Gruppe und substituierte aromatische Gruppe;
die substituierte Benzylgruppe, substituierte aromatische Gruppe und Ring A oder B, wenn sie substituiert sind, umfassen einen oder mehrere Substituenten, ausgewählt aus der Gruppe, bestehend aus einer Elektronen-abziehenden Gruppe, Halogen, -CN, -COOH, -OH, $-CONR^{24}R^{25}$, $-NR^{24}R^{15}$, $-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, $-S(O)_2NH_2$, Guanidino, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, -Q-H, -Q-(aliphatische Gruppe), -Q-(substituierte aliphatische Gruppe), -Q-(Aryl), $-Q-(CH_2)_p-$(substituierte oder unsubstituierte aromatische Gruppe), -Q-(nicht-aromatische heterocyclische Gruppe), $-Q-(CH_2)_p-$(nicht-aromatische heterocyclische Gruppe), aliphatische Gruppe und substituierte aliphatische Gruppe;
die substituierte nicht-aromatische heterocyclische Gruppe umfasst einen oder mehrere Substituenten, ausgewählt aus der Gruppe bestehend aus einer Elektronen-abziehenden Gruppe, Halogen, -CN, -COOH, -OH, $-CONR^{24}R^{25}$, $-NR^{24}R^{25}$, $-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, $-S(O)_2NH_2$, Guanidino, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, -Q-H, -Q-(aliphatische Gruppe), -Q-(substituierte aliphatische Gruppe), -Q-(Aryl), $-Q-(CH_2)_p-$(substituierte oder unsubstituierte aromatische Gruppe), -Q-(nicht-aromatische heterocyclische Gruppe), $-Q-(CH_2)_p-$(nicht-aromatische heterocyclische Gruppe), aliphatische Gruppe, substituierte aliphatische Gruppe, =O, =S, =NH, =N(aliphatische), =N(aromatische) und =N(substituierte aromatische);
R^{20}, R^{21} und R^{22} sind unabhängig von einander -H, eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, eine aromatische Gruppe, eine substituierte aromatische Gruppe, -NHC(O)-O-(aliphatische Gruppe), -NHC(O)-O-(aromatische Gruppe), -NHC(O)-O-(nicht-aromatische heterocyclische Gruppe); oder
R^{21} und R^{22} bilden zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen nicht-aromatischen heterocyclischen Ring;
t ist eine ganze Zahl von 0 bis 3;
u ist 0 oder 1;
p ist 1 bis 5;
Q ist -O-, -S-, -S(O)-, $-S(O)_2$, $-OS(O)_2-$, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, $-S(O)_2NH-$, $-NHS(O)_2-$, $-N(R^{23})-$, $-C(NR^{23})NHNH-$, $-NHNHC(NR^{23})-$;
R^{23} ist -H, eine aliphatische Gruppe, eine Benzylgruppe, eine Arylgruppe oder eine nicht-aromatische heterocyclische Gruppe;
die aliphatische Gruppe ist ein gesättigter oder ungesättigter C_1-C_{20}-Kohlenstoff, Wasserstoff;

die Elektronen-abziehende Gruppe ist Alkylimino, Alkylsulfonyl, Carboxamido, Carboxylalkylester, -CH=NH oder $-NO_2$;

der Heterocyclus der nicht-aromatischen heterocyclischen Gruppe ist ein 5- bis 8-gliedriger nicht-aromatischer Ring, der eine oder mehrere Heteroatome enthält, ausgewählt aus der Gruppe bestehend aus O, N und S; und

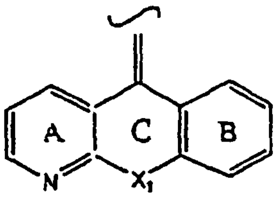
die aromatische Gruppe ist ausgewählt aus der Gruppe bestehend aus einem C_6-aromatischen Carbocyclus, einem C_5-C_6-aromatischen Heterocyclus, der ein oder mehrere Heteroatome enthält, ausgewählt aus der Gruppe bestehend aus O, S und N, und einem C_6-aromatischen Carbocyclus oder einem C_5-C_6-aromatischen Heterocyclus, der mit einem oder mehreren anderen Ringen fusioniert ist.

14. Verbindung nach Anspruch 13, worin:

R^1 ist -H, -OH, eine aliphatische Gruppe, -O-(aliphatische Gruppe), -O-(substituierte aliphatische Gruppe), -SH, -S-(aliphatische Gruppe), -S-(substituierte aliphatische Gruppe), -OC(O)-(aliphatische Gruppe) oder -O-C (O)-(substituierte aliphatische Gruppe);

R^2 ist eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, eine aromatische Gruppe, eine substituierte aromatische Gruppe, eine Benzylgruppe, eine substituierte Benzylgruppe, eine nicht-aromatische heterocyclische Gruppe oder eine substituierte nicht-aromatische heterocyclische Gruppe;

Z ist:



(II)

worin

X_1 ist $-CH_2-CH_2-$, $-CH_2-S-$, $-CH_2-O-$, $-CH_2-NR_c-$, $-CH_2-SO-$, $-CH_2-S(O)_2-$, -CH=CH-, oder $-CO-NR_c-$; worin

R_c ist eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, eine aromatische Gruppe, eine substituierte aromatische Gruppe, eine Benzylgruppe oder eine substituierte Benzylgruppe;

Ring A und Ring B sind unabhängig von einander substituiert oder unsubstituiert.

15. Verbindung nach Anspruch 14 oder Anspruch 13, worin R^1 -OH und R^3 eine substituierte oder eine unsubstituierte aromatische Gruppe ist.

16. Verbindung nach Anspruch 15, worin R^2 eine mit Halogen substituierte aromatische Gruppe ist.

17. Verbindung nach Anspruch 16, worin R^2 eine 4-Chlorphenylgruppe ist.

18. Verbindung nach einem der Ansprüche 13 bis 17, worin X_1 $-CH_2-O-$ ist.

19. Verbindung nach einem der Ansprüche 1 bis 18 zur Verwendung bei der therapeutischen Behandlung des menschlichen oder tierischen Körpers.

20. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 11 zur Herstellung eines Arzneimittels zur Antagonisierung eines Chemokin-Rezeptors.

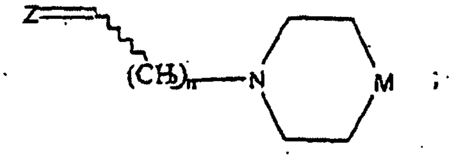
21. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 18 zur Herstellung eines Arzneimittels zur Behandlung einer mit einer aberrierenden Leukozytenverstärkung und/oder -aktivierung verbundenen Erkrankung.

22. Verwendung nach Anspruch 21, worin die mit einer aberrierenden Leukozytenverstärkung und/oder -aktivierung verbundene Erkrankung Arthritis, Atherosklerose, Arteriosklerose, Ischämie/Reperfusions-Schädigung, Diabetes Mellitus, Psoriasis, Multiple Sklerose, ulcerative Colitis, Crohn-Erkrankung, Abstoßung eines transplantierten Organs oder Gewebes, Transplantat-Wirt-Reaktion, Allergie, Asthma, AIDS-assoziierte Enzephalitis, AIDS-verbundene makulopapulöse Hauteruption, AIDS-verbundene interstitielle Pneumonie, AIDS-verbundeene Enteropathie, AIDS-verbundene periportale Leberentzündung oder AIDS-verbundene Glomerulonephritis ist.

23. Verwendung nach Anspruch 22, worin die mit aberrierender Leukozytenverstärkung und/oder -aktivierung verbundene Erkrankung Arthritis oder Multiple Sklerose ist.

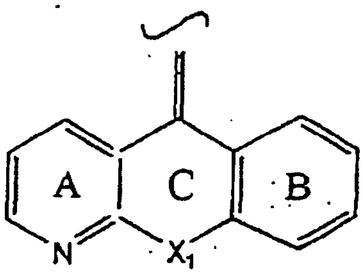
Revendications

1. Composé de formule :



ou ses sels physiologiquement acceptables,
où :

n est un entier de un à quatre;
M est >CR^{1}R^2;
R^1 est -H, -OH, un groupement aliphatique, -O-(groupement aliphatique), -O-(groupement aliphatique substitué), -SH, -S-(groupement aliphatique), -S-(groupement aliphatique substitué), -OC(O)-(groupement aliphatique), -O-C(O)-(groupement aliphatique substitué), -C(O)O-(groupement aliphatique), -C(O)O-(groupement aliphatique substitué), -CN, -COOH, -CO-NR^{3}R^4 or -NR^{3}R^4; ou bien R^1 est une liaison covalente entre l'atome de cycle M et un atome de carbone adjacent dans le cycle qui contient M;
R^2 est -OH, un groupement acyle, un groupement acyle substitué, -NR^{5}R^6, un groupement aliphatique, un groupement aliphatique substitué, un groupement aromatique, un groupement aromatique substitué, un groupement benzyle, un groupement benzyle substitué, un groupement hétérocyclique non aromatique, ou un groupement hétérocyclique non aromatique substitué;
R^3, R^4, R^5 et R^6 sont indépendamment -H, un groupement acyle, un groupement acyle substitué, un groupement aliphatique, un groupement aliphatique substitué, un groupement aromatique, un groupement aromatique substitué, un groupement benzyle, un groupement benzyle substitué, un groupement hétérocyclique non aromatique ou un groupement hétérocyclique non aromatique substitué; ou
R^1, R^2, R^3 et R^4 ou R^5 et R^6, pris conjointement avec l'atome auquel ils sont fixés, forment un cycle hétérocyclique non aromatique, substitué ou non substitué;
ledit groupement acyle est un carbonyle aliphatique, un carbonyle aromatique, un sulfonyle aliphatique ou un sulfonyle aromatique;
Z a la formule :



dans laquelle :

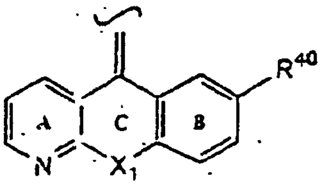
X$_1$ est -S-, -CH$_2$, -CH$_2$-CH$_2$-, -CH$_2$-S-, -S-CH$_2$-, -O-CH$_2$, -CH$_2$-O-, -NR$_c$-CH$_2$-, -CH$_2$-NR$_c$,- -SO-CH$_2$-, -CH$_2$-SO-, -S(O)$_2$-CH$_2$, -CH$_2$-S(O)$_2$, -CH=CH-, -NR$_c$CO- ou -CO-NR$_c$-;
R$_c$ est -H, un groupement aliphatique, un groupement aliphatique substitué, un groupement aromatique,

un groupement aromatique substitué, un groupement benzyle ou un groupement benzyle substitué;
le cycle A et le cycle B sont indépendamment substitués ou non substitués; ledit groupement aliphatique substitué comprend un ou plusieurs substituants choisis dans le groupe constitué d'un groupement électro-attracteur, halo, azido, -COOH, -OH, -CONR^{24}R^{25}, -NR^{24}R^{25}, -OS(O)$_2$NR^{24}R^{25}, -S(O)$_2$NR^{24}R^{25}, -SO$_3$H, -S(O)$_2$-NH$_2$, guanidino, -(O)$_u$-(CH$_2$)$_t$-C(O)OR^{20}, -(O)$_u$-(CH$_2$)$_t$-OC(O)R^{20}, -(O)$_u$-(CH$_2$)$_t$-C(O)-NR^{21}-R^{22}, -(O)$_u$-(CH$_2$)$_t$-NHC(O)OR^{20}, -Q-H, -Q-(groupement aliphatique), -Q-(groupement aliphatique substitué), -Q-(aryle), -Q-(groupement aromatique), -Q-(groupement aromatique substitué), -Q-(CH$_2$)$_p$-(groupement aromatique substitué ou non substitué), -Q-(groupement hétérocyclique non aromatique), -Q-(CH$_2$)$_p$-(groupement hétérocyclique non aromatique), oxo, époxy, hétérocycle non aromatique, benzyle, benzyle substitué, groupement aromatique et groupement aromatique substitué;
lesdits groupement benzyle substitué, groupement aromatique substitué et le cycle A et le cycle B, lorsqu'ils sont substitués, comprennent un ou plusieurs substituants choisis dans le groupe constitué d'un groupement électro-attracteur, halo, azido, -CN, -COOH, -OH, -CONR^{24}R^{25}, -NR^{24}R^{25}, -OS(O)$_2$NR^{24}R^{25}, -S(O)$_2$NR^{24}R^{25}, -SO$_3$H, -S(O)$_2$NH$_2$, guanidino,-(O)$_u$-(CH$_2$)$_t$-C(O)OR^{20}, -(O)$_u$(CH$_2$)$_t$-OC(O)R^{20}, -(O)$_u$-(CH$_2$)$_t$-C(O)-NR^{21}R^{22}, -(O)$_u$-(CH$_2$)$_t$-NHC(O)-O-R^{20}, -Q-H, -Q-(groupement aliphatique) -Q-(groupement aliphatique substitué), -Q-(aryle), -Q-(groupement aromatique), -Q-(groupement aromatique substitué), -Q-(CH$_2$)$_p$-(groupement aromatique substitué ou non substitué), -Q-(groupement hétérocyclique non aromatique), -Q-(CH$_2$)$_p$- (groupement hétérocyclique non aromatique) un groupement aliphatique et un groupement aliphatique substitué; ledit groupement hétérocyclique non aromatique substitué comprend un ou plusieurs substituants choisis dans le groupe constitué d'un groupement électro-attracteur, halo, azido, -CN, -COOH, -OH, -CONR^{24}R^{25}, -NR^{24}R^{25}, -OS(O)$_2$NR^{24}R^{25}, -S(O)$_2$NR^{24}R^{25}, -SO$_3$H, -S(O)$_2$NH$_2$, guanidino, -(O)u-(CH$_2$)$_t$-C(O)OR^{20},-(O)$_u$-(CH$_2$)$_t$-OC(O)R^{20}, -(O)$_u$-(CH$_2$)$_t$-C(O)-NR^{21}R^{22}, -(O)$_u$-(CH$_2$)$_t$-NHC(O)O-R^{20}, -Q-H, -Q-(groupement aliphatique), -Q-(groupement aliphatique substitué), -Q-(aryle), -Q-(groupement aromatique), -Q-(groupement aromatique substitué) -Q-(CH$_2$)$_p$-(groupement aromatique substitué ou non substitué), -Q-(groupement hétérocyclique non aromatique), -Q-(CH$_2$)$_p$-(groupement hétérocyclique non aromatique), un groupement aliphatique, un groupement aliphatique substitué, =O, =S, =NH, =N(aliphatique), =N(aromatique) et =N (aromatique substitué);
R^{20}, R^{21} et R^{22} sont indépendamment -H, un groupement aliphatique, un groupement aliphatique substitué, un groupement aromatique, un groupement aromatique substitué, un groupement hétérocyclique non aromatique, -NHC(O)-O- (groupement aliphatique) -NHC(O)-O-(groupement aromatique) ou -NHC(O)-O-(groupement hétérocyclique non aromatique); ou
R^{21} et R^{22}, pris conjointement avec l'atome d'azote auquel ils sont fixés, forment un cycle hétérocyclique non aromatique;
t est un entier de zéro à trois;
u vaut zéro ou un;
p vaut un à cinq;
Q est -O-, -S-, -S(O), -S(O)$_2$, -OS(O)$_2$, -C(O), -OC(O)-, -C(O)O-, C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)$_2$NH-, -NHS(O)$_2$-N(R^{23})-, -C(NR^{23})NHNH-, NH-NHC(NR^{23})-,
-NR^{24}C(O)- ou -NR^{24}S(O)$_2$;
R^{23} est -H, un groupement aliphatique, un groupement benzyle, un groupement aryle ou un groupement hétérocyclique non aromatique;
R^{24} et R^{25} sont indépendamment -H, -OH, un groupement aliphatique, un groupement aliphatique substitué, un groupement benzyle, un groupement aryle ou un groupement hétérocyclique non aromatique; ledit groupement aliphatique est un hydrocarbure en C$_1$ à C$_{20}$ saturé ou insaturé;
ledit groupement électro-attracteur est un alkylimino, un alkylsufonyle, un carboxamido, un ester d'alkyle carboxylique, -CH=NH ou -NO$_2$;
l'hétérocycle dudit groupement hétérocyclique non aromatique est un cycle non aromatique de 5 à 8 éléments qui contient un ou plusieurs hétéroatomes choisis dans le groupe constitué de O, N et S; et
ledit groupement aromatique est choisi dans le groupe constitué d'un carbocycle aromatique en C$_6$, d'un hétérocycle aromatique en C$_5$ à C$_6$ comprenant un ou plusieurs hétéroatomes choisis dans le groupe constitué de O,S et N et d'un carbocycle aromatique en C$_6$ ou d'un hétérocycle aromatique en C$_5$ à C$_6$ qui est fusionné avec un ou plusieurs autres cycles.

2. Composé selon la revendication 1 , dans lequel le cycle B est substitué par -OH, halo, -O-(groupement aliphatique), -O-(groupement aliphatique substitué),-O-(groupement aromatique), -O-(groupement aromatique substitué) un groupement électro-attracteur, -(O)$_u$-(CH$_2$)$_t$-C(O)OR^{20}, -(O)$_u$-(CH$_2$)$_t$-OC(O)R^{20}, -(O)$_u$-(CH$_2$)$_t$-C(O)-NR^{21}R^{22} ou -(O)$_u$-(CH$_2$)$_t$-NHC(O)O-R^{20}, où :

R^{20}, R^{21} ou R^{22} sont indépendamment -H, un groupement aliphatique, un groupement aliphatique substitué, un groupement aromatique, un groupement aromatique substitué ou un groupement hétérocyclique non aromatique; ou
R^{21} et R^{22}, pris conjointement avec l'atome d'azote auquel ils sont fixés, forment un cycle hétérocyclique non aromatique;
u vaut zéro ou un; et
t est un entier de zéro à trois.

3. Composé selon la revendication 1, dans lequel Z a pour formule :



dans laquelle :

R^{40} est -OH, un halogène, un groupement aliphatique, un groupement aliphatique substitué, $-NR^{24}R^{25}$, Q-(groupement aliphatique), Q-(groupement aliphatique substitué), -O-(groupement aliphatique), -O-(groupement aliphatique substitué), -O-(groupement aromatique), -O-(groupement aromatique substitué), un groupement électro-attracteur, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ ou $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$;
R^{20}, R^{21} ou R^{22} sont indépendamment -H, un groupement aliphatique, un groupement aliphatique substitué, un groupement aromatique, un groupement aromatique substitué ou un groupement hétérocyclique non aromatique; ou
R^{21} et R^{22}, pris conjointement avec l'atome d'azote auquel ils sont fixés, forment un cycle hétérocyclique non aromatique;
Q est $-NR^{24}C(O)-$ ou $-NR^{24}S(O)_2-$;
R^{24} et R^{25} sont indépendamment -H, -OH, un groupement aliphatique ou un groupement aliphatique substitué;
u vaut zéro ou un; et
t est un entier de zéro à trois.

4. Composé selon la revendication 3, dans lequel R^{40} est $-O-CH_3$.

5. Composé selon l'une quelconque des revendications 1 à 4, dans lequel R^1 est -OH.

6. Composé selon la revendication 5, dans lequel n vaut deux.

7. Composé selon l'une quelconque des revendications 1 à 6, dans lequel R^2 est un groupement aromatique substitué ou non substitué.

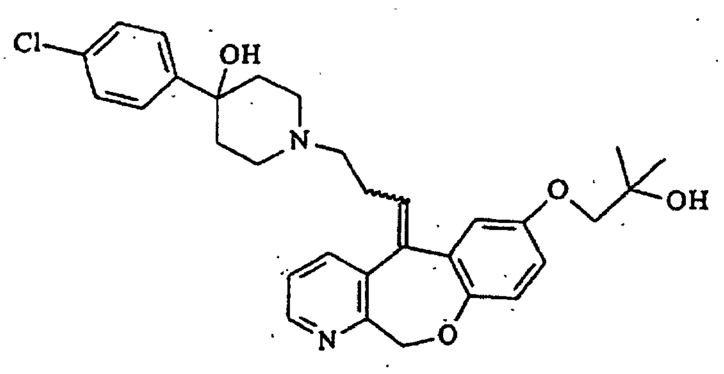
8. Composé selon l'une quelconque des revendications 1 à 6, dans lequel R^2 est un groupement aromatique substitué par un halogène.

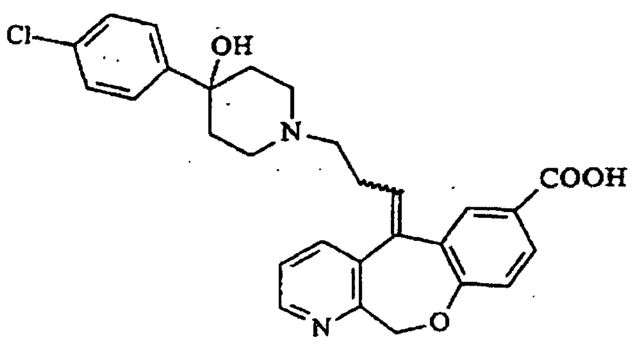
9. Composé selon l'une quelconque des revendications 1 à 6, dans lequel R^2 est un groupement 4-chlorophényle.

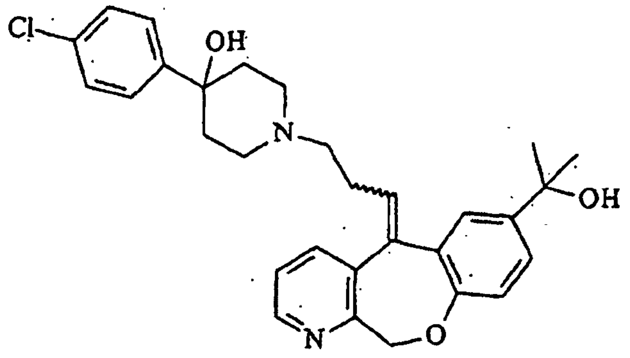
10. Composé selon l'une quelconque des revendications 1 à 9, dans lequel X_1 est $-CH_2-O-$.

11. Composé selon l'une quelconque des revendications 1 à 9, dans lequel X_1 est $-CH_2-S$ ou $-CH_2-CH_2-$.

12. Composé selon la revendication 1, qui est choisi parmi :

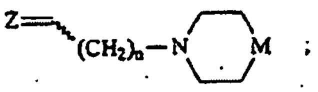






et leurs sels physiologiquement acceptables.

13. Composé de formule :



ou ses sels physiologiquement acceptables, dans lesquels :

n est un entier de un à quatre;
M est >CR^1R^2;
R^1 est -H, -OH, un groupement aliphatique, -0-(groupement aliphatique), -O-(groupement aliphatique substitué), -SH, -S-(groupement aliphatique), -S-(groupement aliphatique substitué), -OC(O)-(groupement aliphatique), -O-C(O)-(groupement aliphatique substitué), -C(O)O-(groupement aliphatique), -C(O)O-(groupement aliphati-

que substitué),-CN,-COOH,-CO-NR^{3}R^4 ou -NR^{3}R^4;

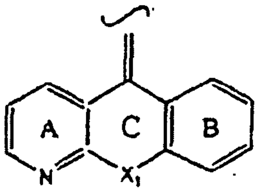
R^2 est -OH, un groupement acyle, un groupement acyle substitué, -NR^{5}R^6, un groupement aliphatique, un groupement aliphatique substitué, un groupement aromatique, un groupement aromatique substitué, un groupement benzyle, un groupement benzyle substitué, un groupement hétérocyclique non aromatique ou un groupement hétérocyclique non aromatique substitué;

R^3, R^4, R^5 et R^6 sont indépendamment -H, un groupement acyle, un groupement acyle substitué, un groupement aliphatique, un groupement aliphatique substitué, un groupement aromatique, un groupement aromatique substitué, un groupement benzyle, un groupement benzyle substitué, un groupement hétérocyclique non aromatique ou un groupement hétérocyclique non aromatique substitué; ou

R^1 et R^2, R^3 et R^4 ou R^5 et R^6, pris conjointement avec l'atome auquel ils sont fixés, forment un cycle hétérocyclique ou carbocyclique non aromatique substitué ou non substitué;

ledit groupement acyle est un carbonyle aliphatique, un carbonyle aromatique, un sulfonyle aliphatique ou un sulfonyle aromatique;

Z a pour formule :



(II)

dans laquelle :

X$_1$ est -S-, -CH$_2$, -CH$_2$CH$_2$-, -CH$_2$-S-, -S-CH$_2$, -O-CH$_2$-, -CH$_2$-O-, -NR$_c$-CH$_2$, -CH$_2$-NR$_c$-, -SO-CH$_2$-, -CH$_2$-SO-, -S(O)$_2$-CH$_2$-, -CH$_2$-S(O)$_2$-, -CH=CH-, -NR$_c$-CO- ou -CO-NR$_c$-;

R$_c$ est -H, un groupement aliphatique, un groupement aliphatique substitué, un groupement aromatique, un groupement aromatique substitué, un groupement benzyle ou un groupement benzyle substitué; le cycle A et le cycle B sont indépendamment substitués ou non substitués; ledit groupement aliphatique substitué comprend un ou plusieurs substituants choisis dans le groupe constitué d'un groupement électro-attracteur, halo, -COOH, -OH, -CONR^{24}R^{25}, -NR^{24}R^{25}, -OS(O)$_2$NR^{24}R^{25}, -S(O)$_2$NR^{24}R^{25}, -SO$_3$H, -S(O)$_2$NH$_2$, guanidino, -(O)$_u$-(CH$_2$)$_t$-C(O)OR^{30}, -(O)$_u$-(CH$_2$)$_t$-C(O)-NR^{21}R^{22}, -Q-H, -Q-(groupement aliphatique), -Q-(groupement aliphatique substitué), -Q-(aryle), -Q-(CH$_2$)$_p$-(groupement aromatique substitué ou non substitué), -Q-(groupement hétérocyclique non aromatique), -Q-(CH$_2$)$_p$-(groupement hétérocyclique non aromatique), oxo, époxy, hétérocycle non aromatique, benzyle, benzyle substitué, un groupement aromatique et un groupement aromatique substitué;

lesdits groupement benzyle substitué, groupement aromatique substitué et le cycle A et le cycle B lorsqu'ils sont substitués comprennent un ou plusieurs substituants choisis dans le groupe constitué d'un groupement électro-attracteur, halo, -CN, -COOH, -OH, -CONR^{24}R^{25}, -NR^{24}R^{25}, -OS(O)$_2$NR^{24}R^{25}, -S(O)$_2$NR^{24}R^{25}, -SO$_3$H, -S(O)$_2$NH$_2$, guanidino, -(O)$_u$-(CH$_2$)$_t$-C(O)OR^{20}, -(O)$_u$-(CH$_2$)$_t$-C(O)-NR^{21}R^{22}, -Q-H, -Q-(groupement aliphatique), -Q-(groupement aliphatique substitué), -Q-(aryle), -Q-(CH$_2$)$_p$-(groupement aromatique substitué ou non substitué), -Q-(groupement hétérocyclique non aromatique), -Q-(CH$_2$)$_p$-(groupement hétérocyclique non aromatique), groupement aliphatique et groupement aliphatique substitué;

ledit groupement hétérocyclique non aromatique substitué comprend un ou plusieurs substituants choisis dans le groupe constitué d'un groupement attracteur d'électrons, halo, -CN, -COOH, -OH, -CONR^{24}R^{25}, -NR^{24}R^{25}, -OS(O)$_2$NR^{24}R^{25}, -S(O)$_2$NR^{24}R^{25}, -SO$_3$H, -S(O)$_2$NH$_2$, guanidino, -(O)$_u$-(CH$_2$)$_t$-C(O)OR^{20}, -(O)$_u$-(CH$_2$)$_t$-C(O)-NR^{21}R^{22}, -Q-H, -Q-(groupement aliphatique), -Q-(groupement aliphatique substitué), -Q-(aryle), -Q-(CH$_2$)$_p$-(groupement aromatique substitué ou non substitué), -Q-(groupement hétérocyclique non aromatique), -Q-(CH$_2$)$_p$-(groupement hétérocylique non aromatique), groupement aliphatique, groupement aliphatique substitué, =O, =S, =NH, =N(aliphatique), =N(aromatique) et =N(aromatique substitué);

R^{20}, R^{21} et R^{22} sont indépendamment -H, un groupement aliphatique, un groupement aliphatique substitué, un groupement aromatique, un groupement aromatique substitué, -NHC(O)-O-(groupement aliphatique), -NHC(O)-O-(groupement aromatique) ou -NHC(O)-O-(groupement hétérocyclique non aromatique); ou

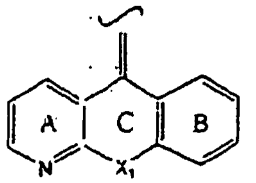
R^{21} et R^{22}, pris conjointement avec l'atome d'azote auquel ils sont fixés, forment un cycle hétérocyclique non aromatique;

t est un entier de zéro à trois;

u vaut zéro ou un;
p vaut un à cinq;
Q est -O-, -S-, -S(O)-, $-S(O)_2-$, $-OS(O)_2-$, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, NH-C(O)-NH-, $-S(O)_2NH-$, $-NHS(O)_2$, $-N(R^{23})-C(NR^{23})NHNH-$, $-NHNHC(NR^{23})-$;
R^{23} est -H, un groupement aliphatique, un groupement benzyle, un groupement aryle ou un groupement hétérocyclique non aromatique;
ledit groupement aliphatique est un hydrocarbure en C_1 à C_{20} saturé ou insaturé;
ledit groupement électro-attracteur est un alkylimino, un alkylsulfonyle, un carboxamido, un ester d'alkyle carboxylique, -CH=NH ou NO_2;
l'hétérocycle dudit groupement hétérocyclique non aromatique est un cycle non aromatique de 5 à 8 éléments qui contient un ou plusieurs hétéroatomes choisis dans le groupe constitué de O, N, et S; et
ledit groupement aromatique est choisi dans le groupe constitué d'un carbocycle aromatique en C_6, d'un hétérocycle aromatique en C_5 à C_6 comprenant un ou plusieurs hétéroatomes choisis dans le groupe constitué de O, S et N, et d'un carbocycle aromatique en C_6 ou d'un hétérocycle aromatique en C_5 à C_6 qui est fusionné avec un ou plusieurs autres cycles.

14. Composé selon la revendication 13, dans lequel :

R^1 est -H, -OH, un groupement aliphatique, -O-(groupement aliphatique), -O-(groupement aliphatique substitué), -SH, -S-(groupement aliphatique), -S-(groupement aliphatique substitué), -OC(O)-(groupement aliphatique) ou -O-C(O)-(groupement aliphatique substitué);
R^2 est un groupement aliphatique, un groupement aliphatique substitué, un groupement aromatique, un groupement aromatique substitué, un groupement benzyle, un groupement benzyle substitué, un groupement hétérocyclique non aromatique ou un groupement hétérocyclique non aromatique substitué;
Z a pour formule :



(II

dans laquelle :

X_1 est $-CH_2-CH_2-$, $-CH_2-S-$, $-CH_2-O$, $-CH_2-NR_c$, $-CH_2-SO-$, $CH_2-S(O)_2-$, -CH=CH- ou $-CO-NR_2-$; où
R_c est un groupement aliphatique, un groupement aliphatique substitué, un groupement aromatique, un groupement aromatique substitué, un groupement benzyle ou un groupement benzyle substitué; et
le cycle A et le cycle B sont indépendamment substitués ou non substitués.

15. Composé selon la revendication 14 ou 13, dans lequel R^1 est -OH et R^2 est un groupement aromatique substitué ou non substitué.

16. Composé selon la revendication 15, dans lequel R^2 est un groupement aromatique substitué par un halogène.

17. Composé selon la revendication 16, dans lequel R^2 est un groupement 4-chlorophényle.

18. Composé selon l'une quelconque des revendications 13 à 17, dans lequel X_1 est $-CH_2-O-$.

19. Composé selon l'une quelconque des revendications 1 à 18 destiné au traitement du corps humain ou du corps animal par thérapie.

20. Utilisation d'un composé selon l'une quelconque des revendications 1 à 11 dans la préparation d'un médicament pour antagoniser un récepteur de chémokine.

21. Utilisation selon l'une quelconque des revendications 1 à 18 dans la préparation d'un médicament destiné au traitement d'une maladie associée à un recrutement et/ou à une activation aberrants de leucocytes.

22. Utilisation selon la revendication 21, dans laquelle ladite maladie associée au recrutement et/ou à l'activation aberrants de leucocytes est l'arthrite, l'athérosclérose, l'artériosclérose, une lésion due à une ischémie ou à une reperfusion, le diabète sucré, le psoriasis, la sclérose en plaques, la colite ulcéreuse, la maladie de Crohn, le rejet d'un organe ou d'un tissu transplanté, les réactions d'un greffon contre l'hôte, l'allergie, l'asthme, l'encéphalite associée au SIDA, l'éruption cutanée maculopapuleuse associée au SIDA, la pneumonie interstitielle associée au SIDA, l'entéropathie associée au SIDA, l'inflammation hépatique périportale associée au SIDA ou la glomérulonéphrite associée au SIDA.

23. Utilisation selon la revendication 22, dans laquelle ladite maladie associée au recrutement et/ou à l'activation aberrants de leucocytes est l'arthrite ou la sclérose en plaques.

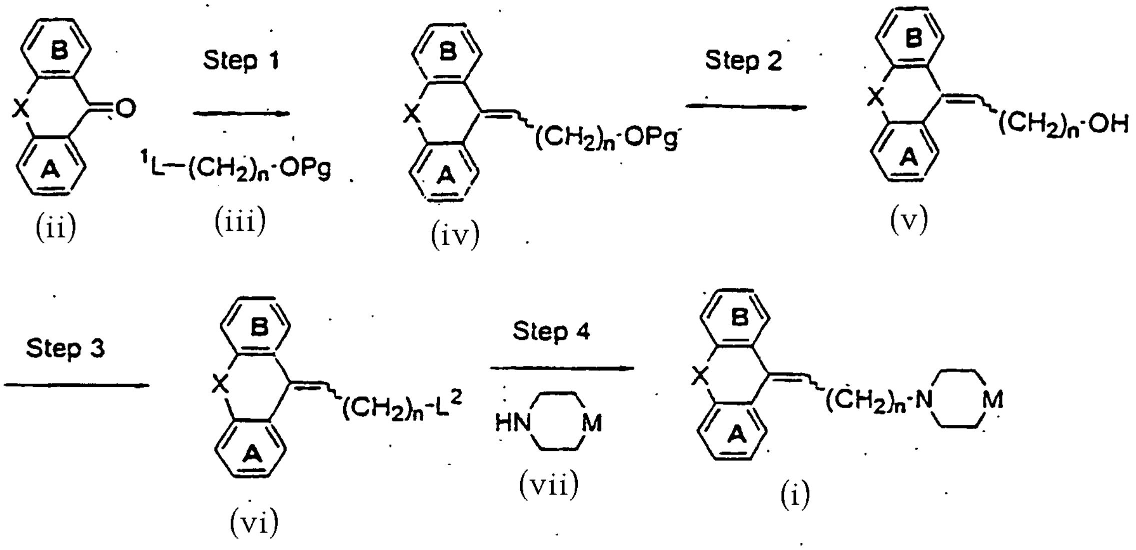
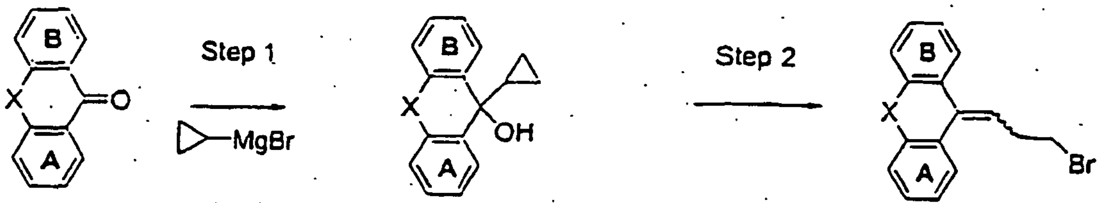

B
X
A
O
Step 1
¹L—(CH₂)ₙ-OPg
(ii)
(iii)
(CH₂)ₙ-OPg
(iv)
Step 2
(CH₂)ₙ-OH
(v)
Step 3
(CH₂)ₙ-L²
(vi)
Step 4
HN
M
(vii)
(CH₂)ₙ-N
M
(i)

Figure 1



(ii) (vii) (viii) (vi-b)

Figure 2

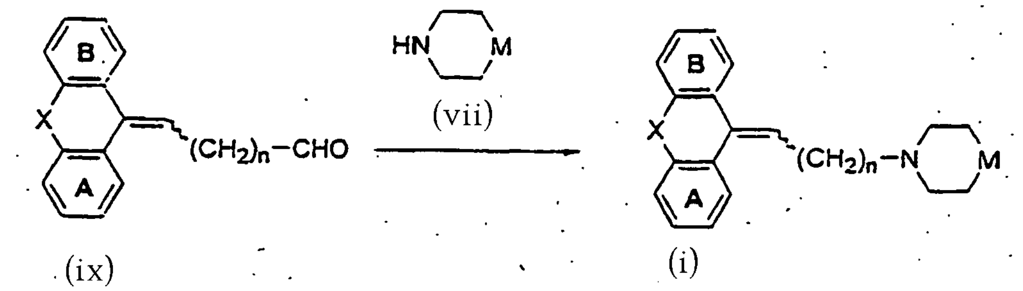
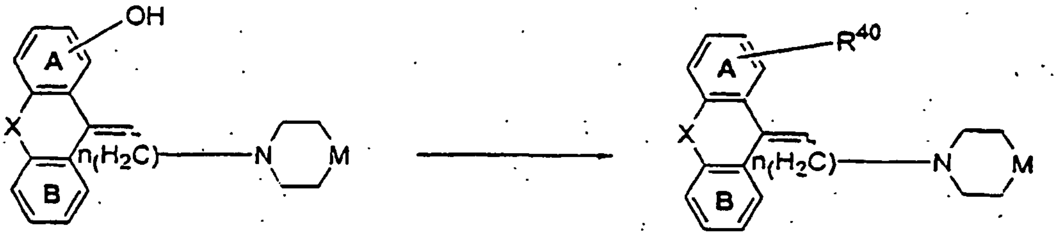


Figure 3



(i-a) (i-b)

Figure 4

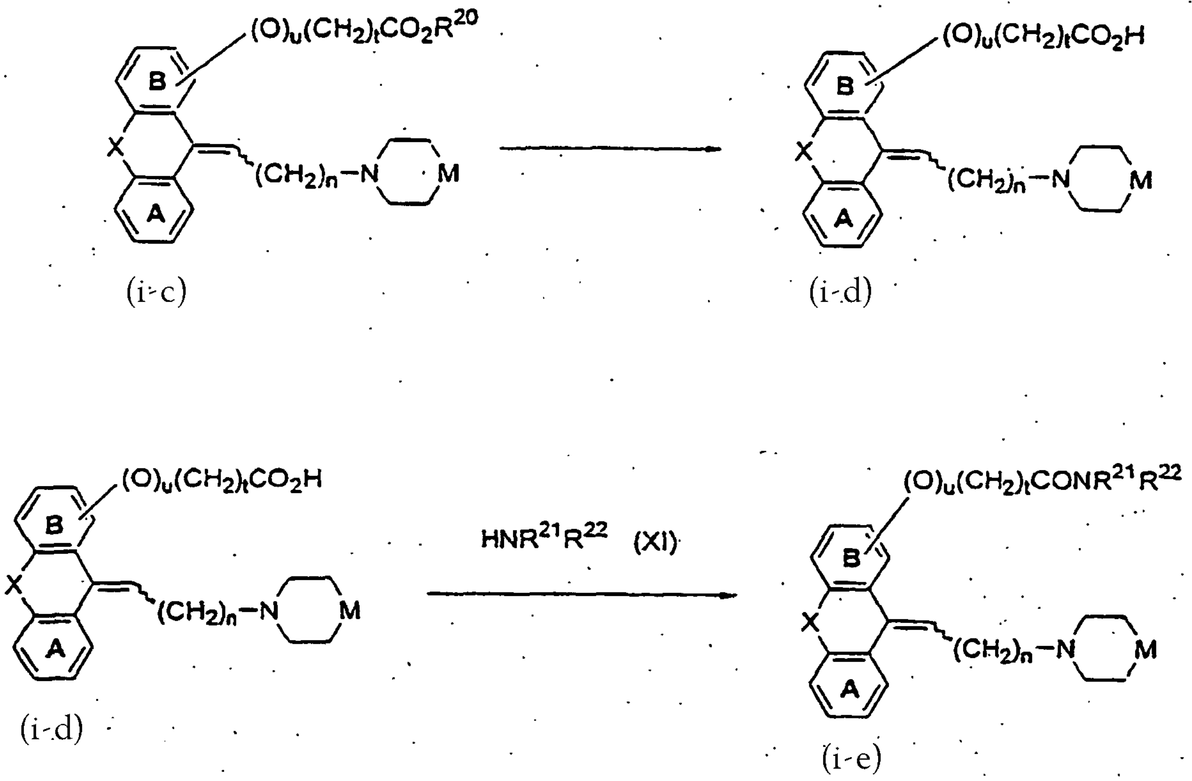
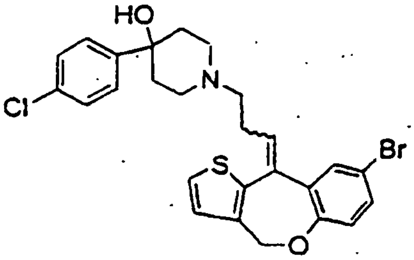
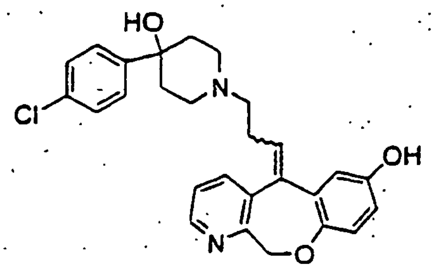

(O)u(CH2)tCO2R20
B
X
A
(CH2)n–N M
(i-c)
(O)u(CH2)tCO2H
B
X
A
(CH2)n–N M
(i-d)
(O)u(CH2)tCO2H
B
X
A
(CH2)n–N M
(i-d)
HNR21R22 (XI)
(O)u(CH2)tCONR21R22
B
X
A
(CH2)n–N M
(i-e)

Figure 5

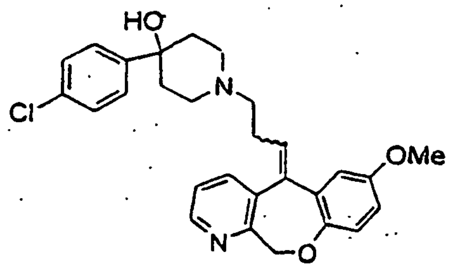


Reference Example 2

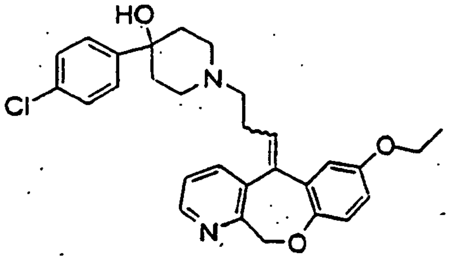
Figure 6A



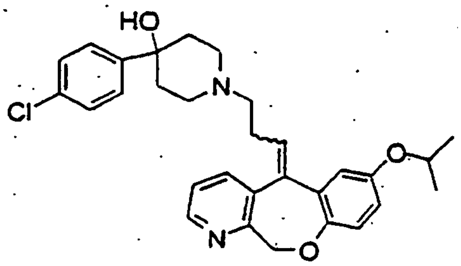
Example 2



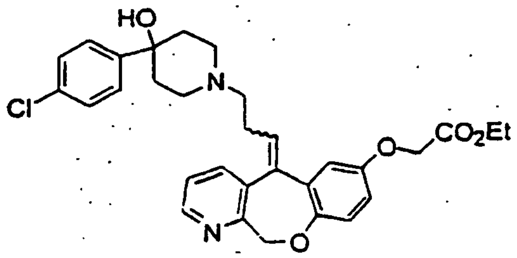
Example 3



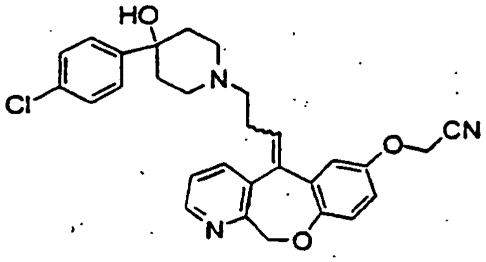
Example 4



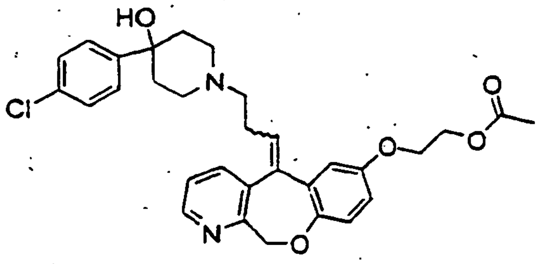
Example 5



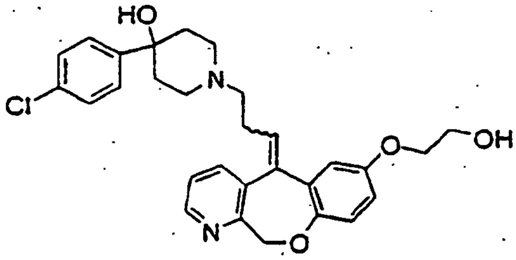
Example 6



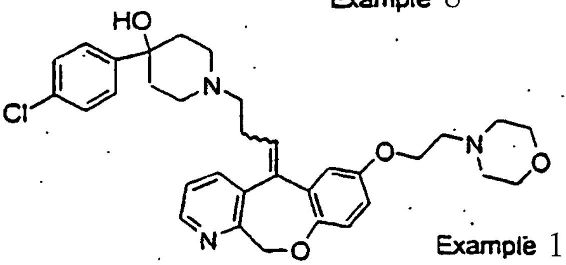
Example 7



Example 8

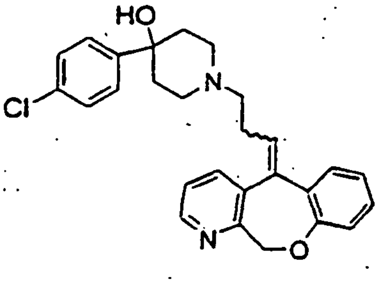


Example 9

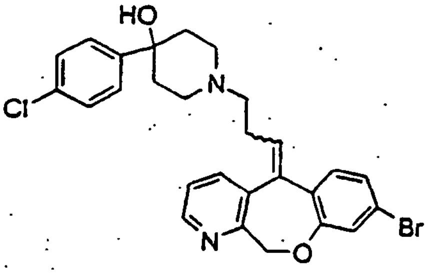


Example 10

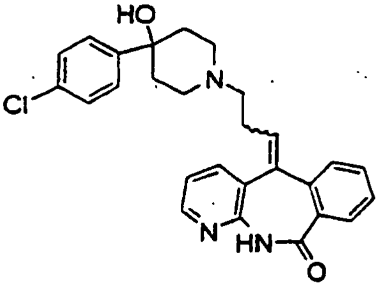
Figure 6B.



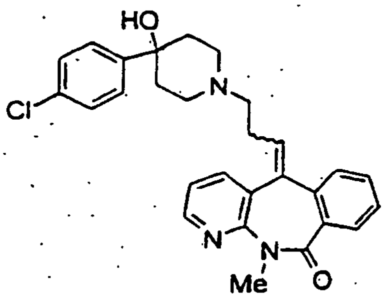
Example 11



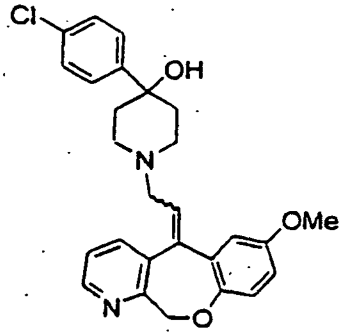
Example 12



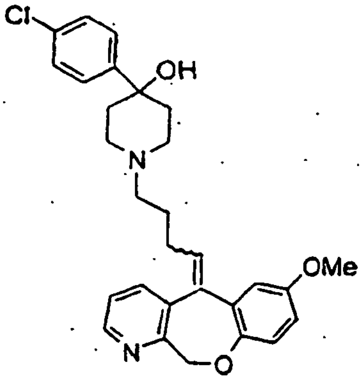
Example 13



Example 14

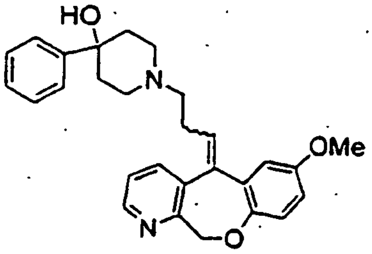


Example 15

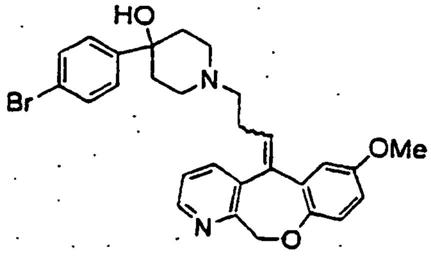


Example 16

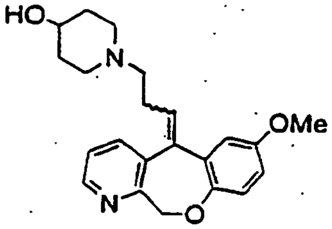
Figure 6C



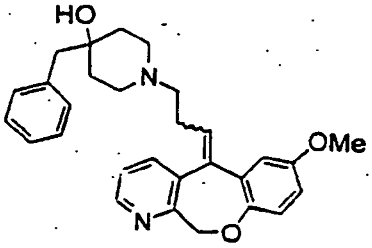
Example 17



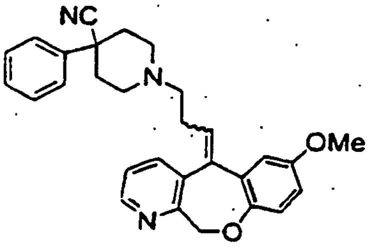
Example 18



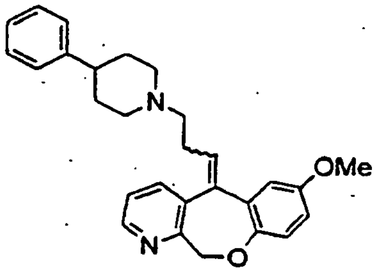
Example 19



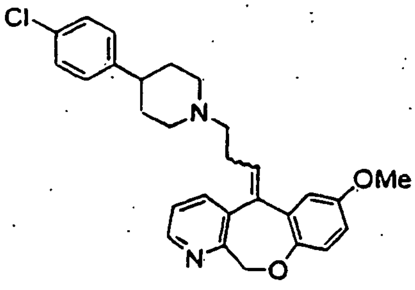
Example 20



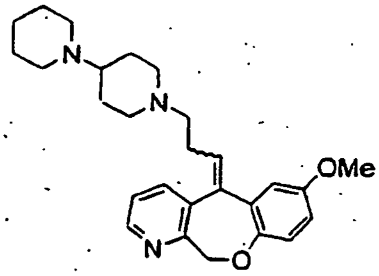
Example 21



Example 22

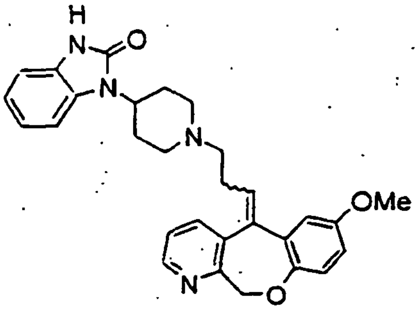


Example 23

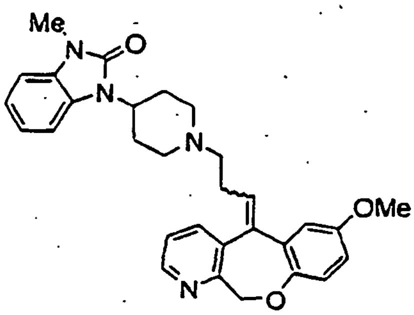


Example 24

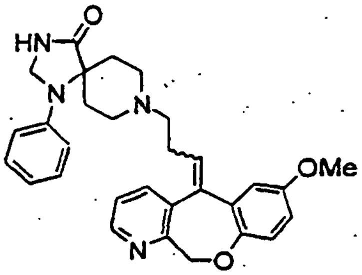
Figure 6D



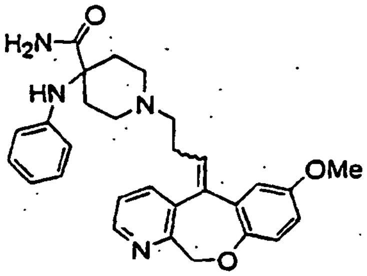
Example 25



Example 26

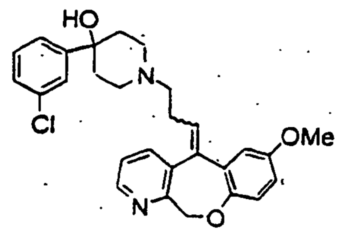


Example 27

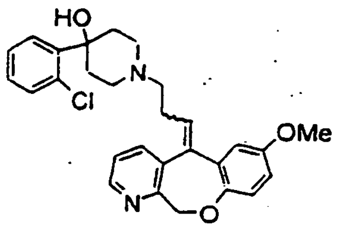


Example 28

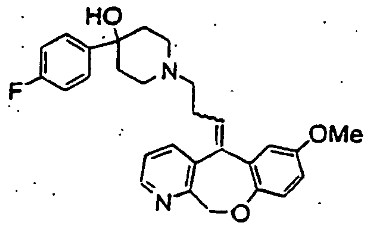
Figure 6E



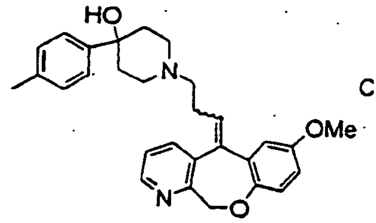
Example 29



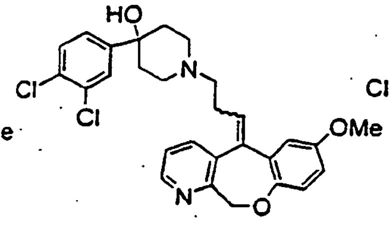
Example 30



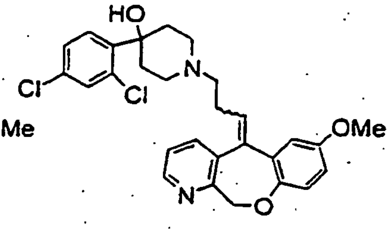
Example 31



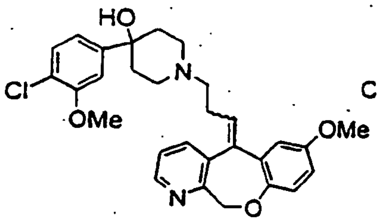
Example 32



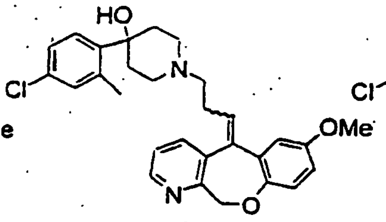
Example 33



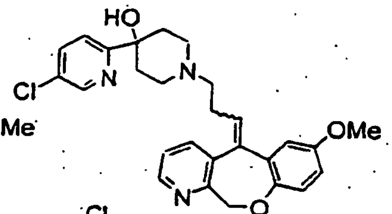
Example 34



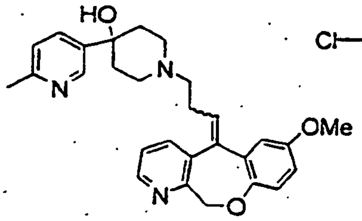
Example 35



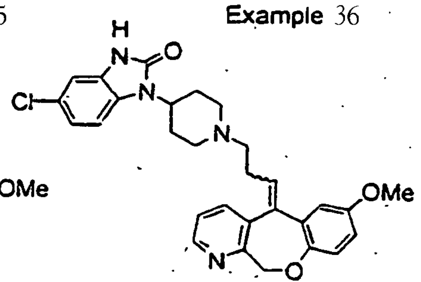
Example 36



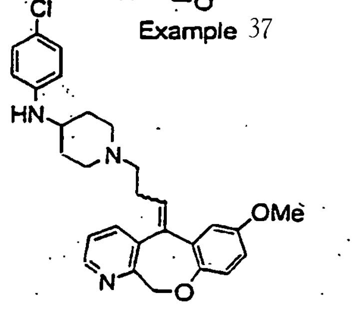
Example 37



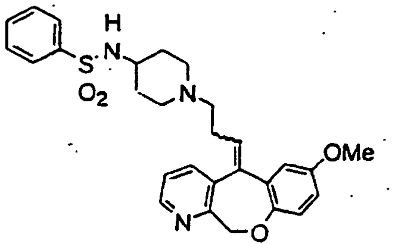
Example 38



Example 39

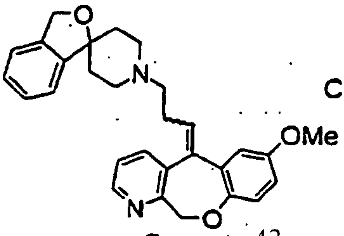


Example 40

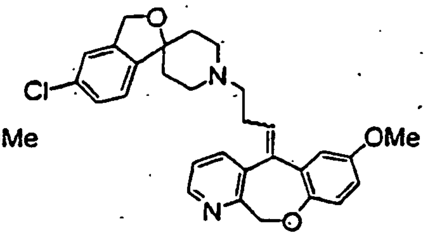


Example 41

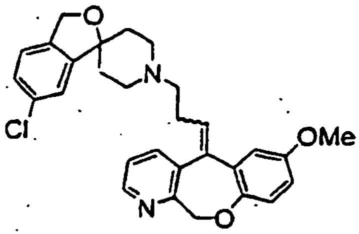
Figure 6F



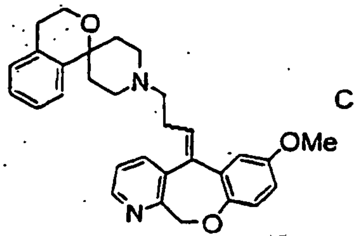
Example 42



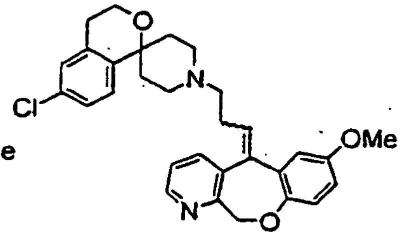
Example 43



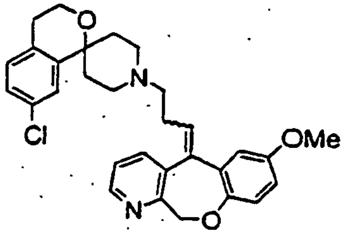
Example 44



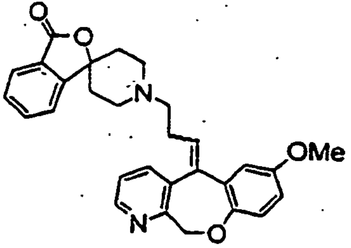
Example 45



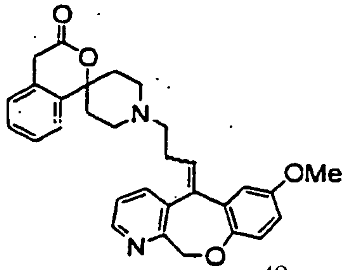
Example 46



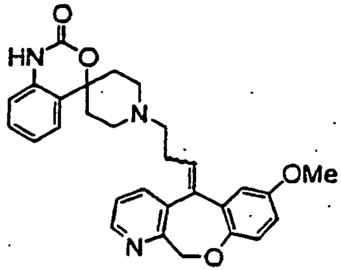
Example 47



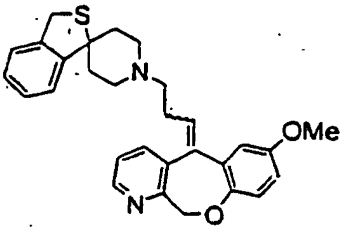
Example 48



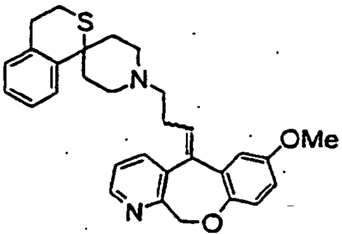
Example 49



Example 50

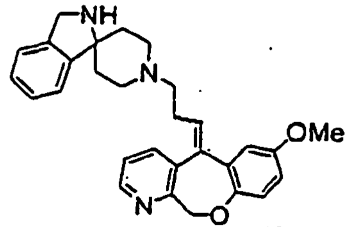


Example 51

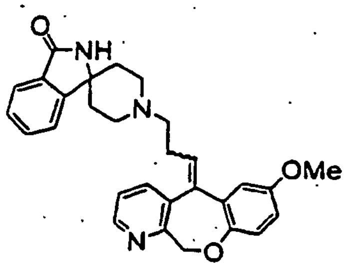


Example 52

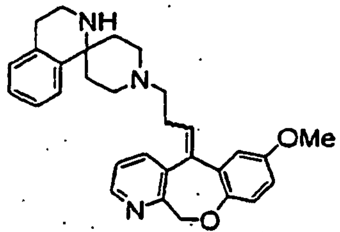
Figure 6G



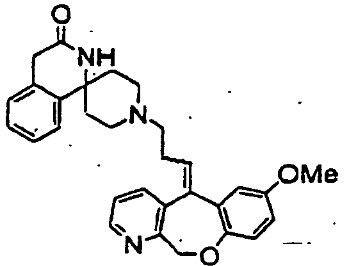
Example 53



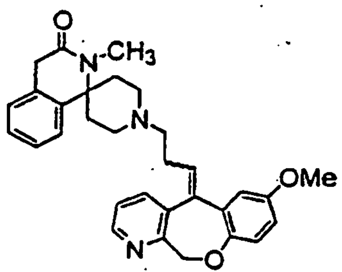
Example 54



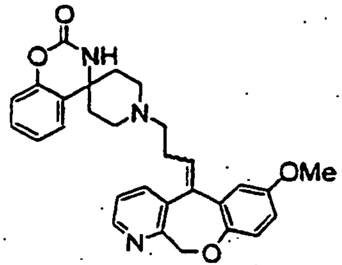
Example 55



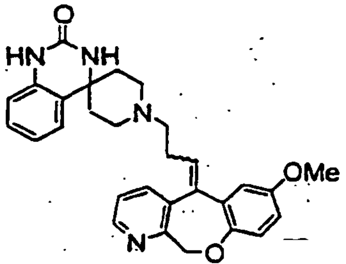
Example 56



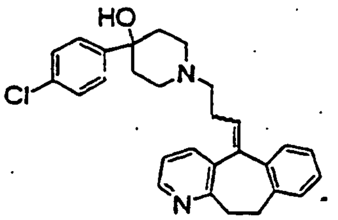
Example 57



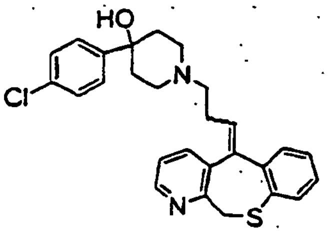
Example 58



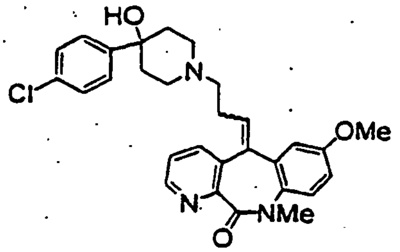
Example 59



Example 60

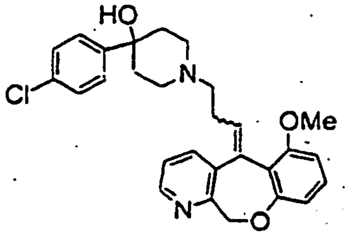


Example 61

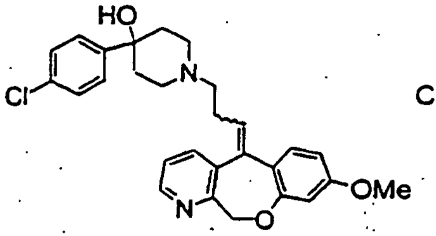


Example 62

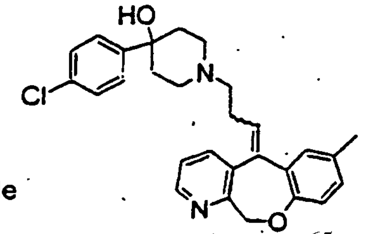
Figure 6H



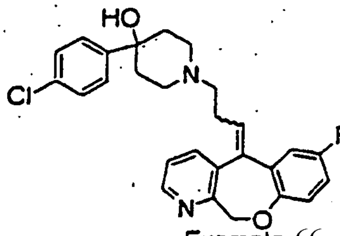
Example 63



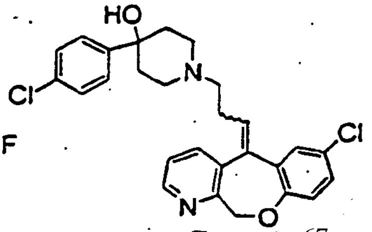
Example 64



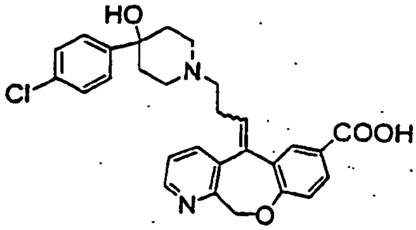
Example 65



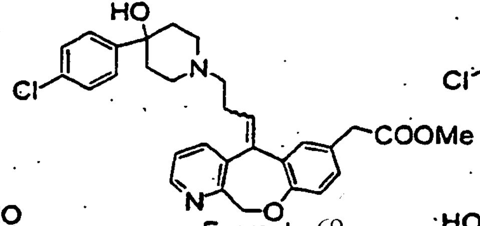
Example 66



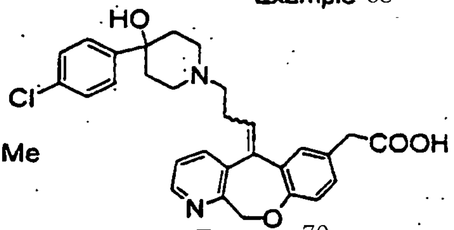
Example 67



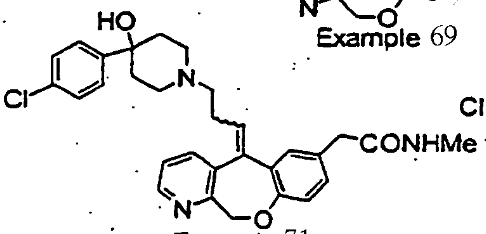
Example 68



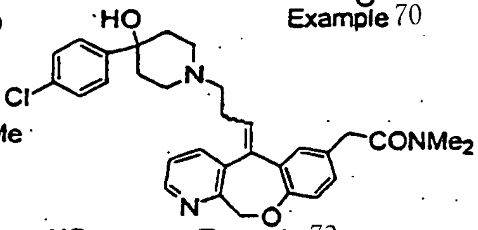
Example 69



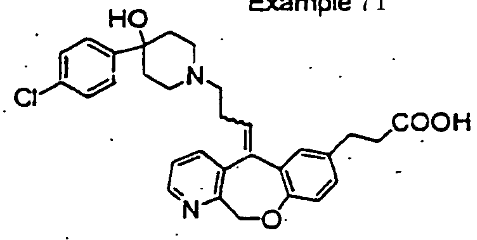
Example 70

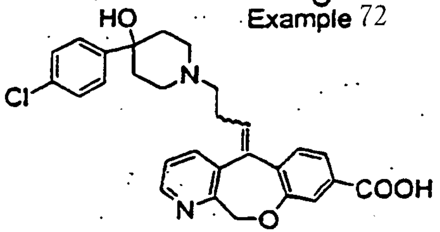


Example 71

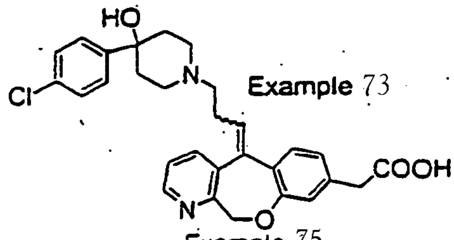


Example 72



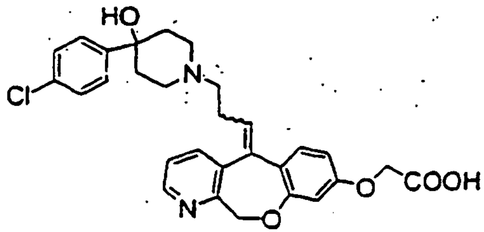


Example 74



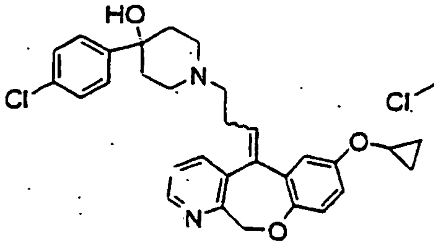
Example 73

Example 75

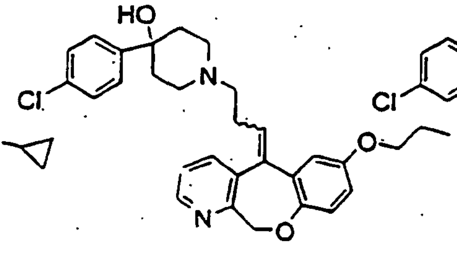


Example 76

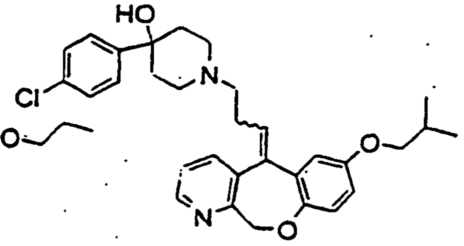
Figure 6I



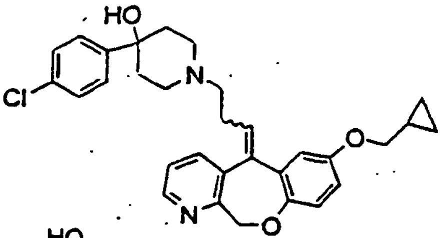
Example 77



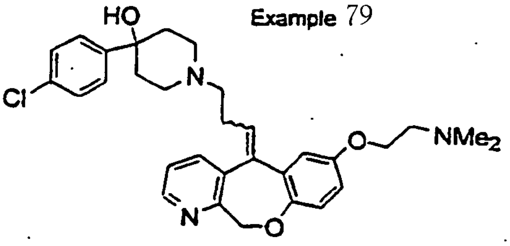
Example 78



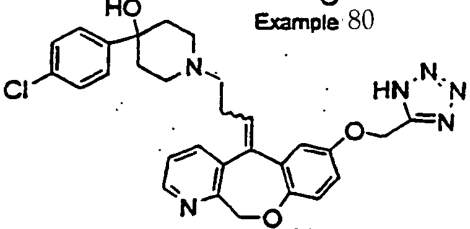
Example 79



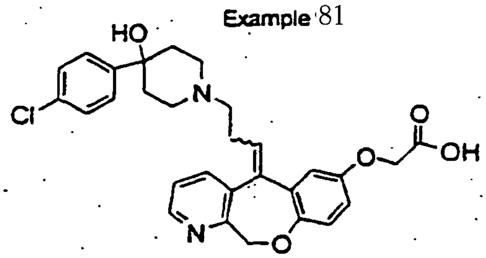
Example 80



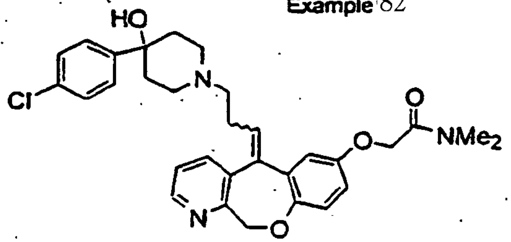
Example 81



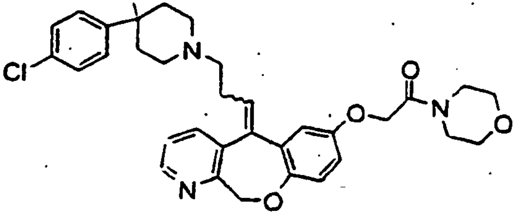
Example 82



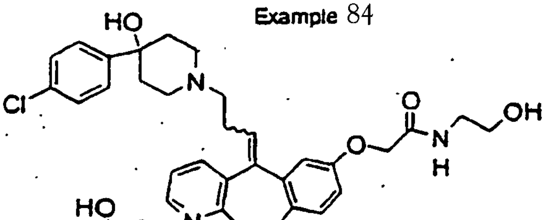
Example 83



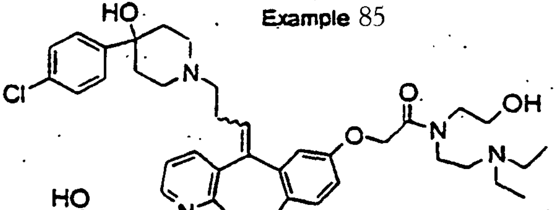
Example 84



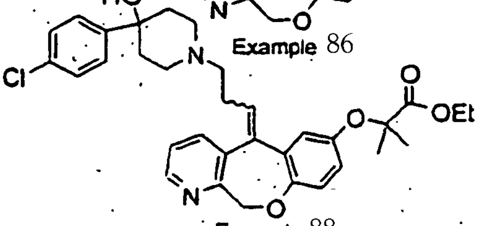
Example 85



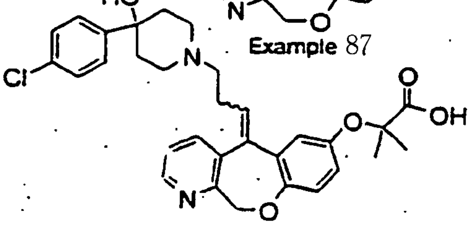
Example 86



Example 87

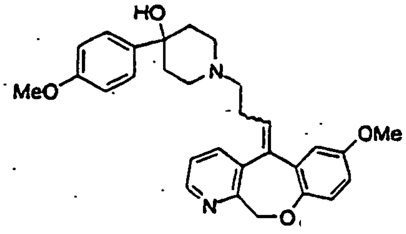


Example 88

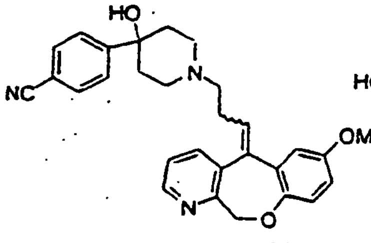


Example 89

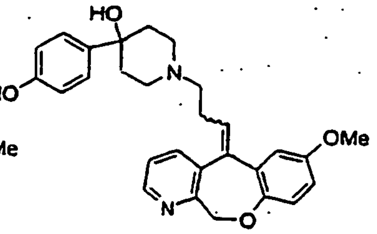
Figure 6J



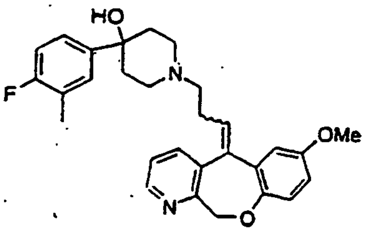
Example 90



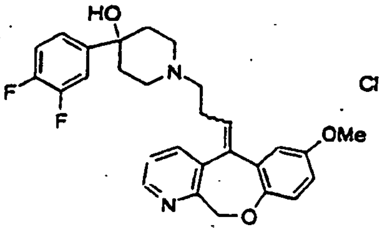
Example 91



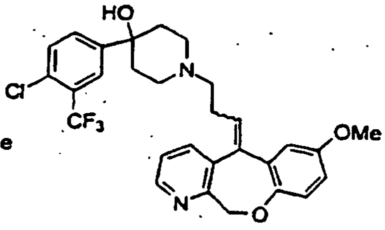
Example 92



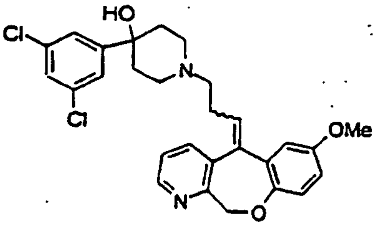
Example 93



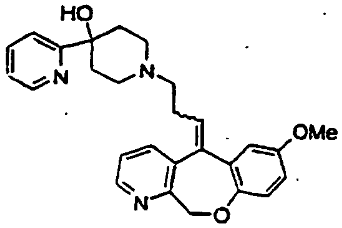
Example 94



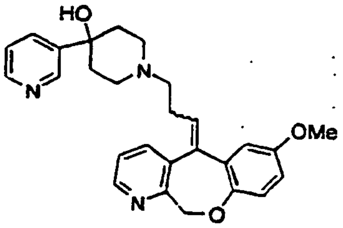
Example 95



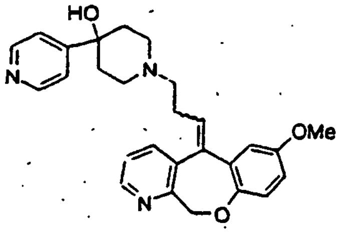
Example 96



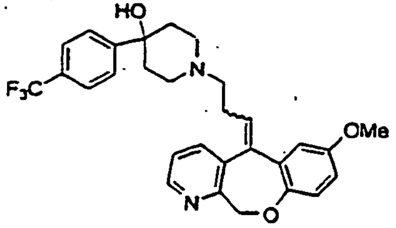
Example 97



Example 98

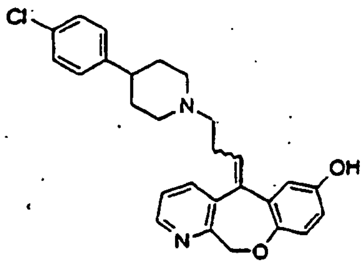


Example 99

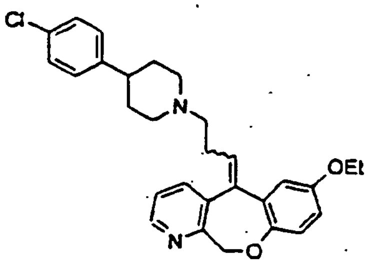


Example 100

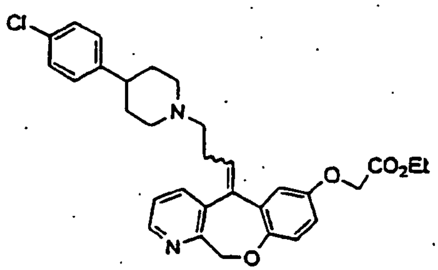
Figure 6K



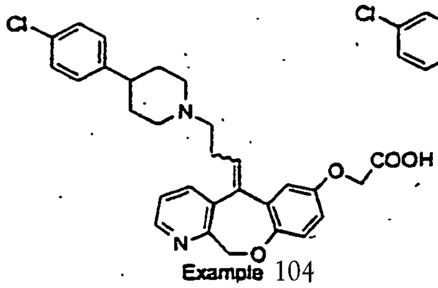
Example 101



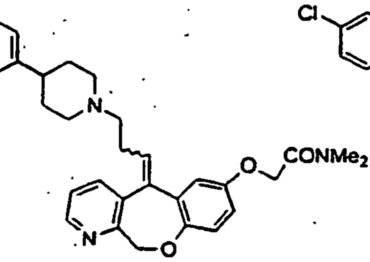
Example 102



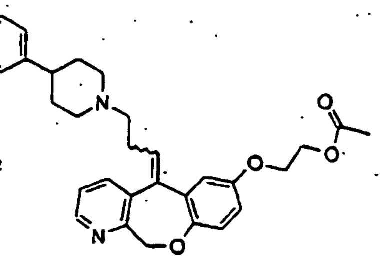
Example 103



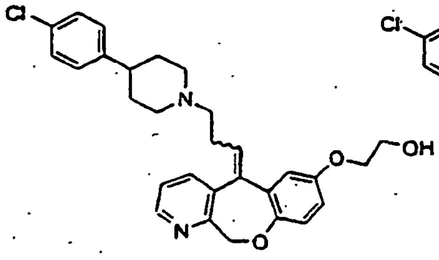
Example 104



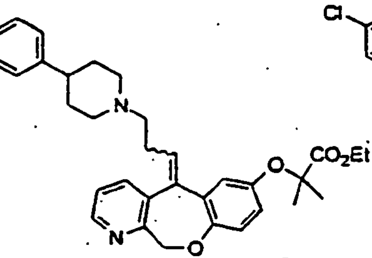
Example 105



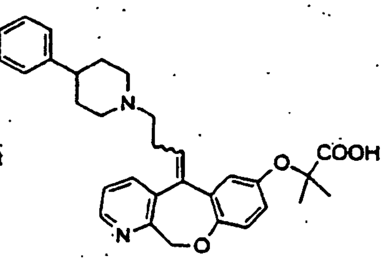
Example 106



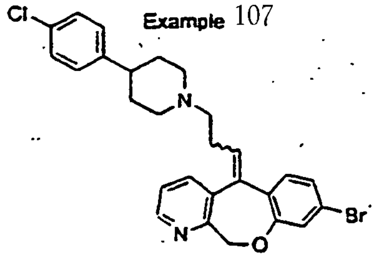
Example 107



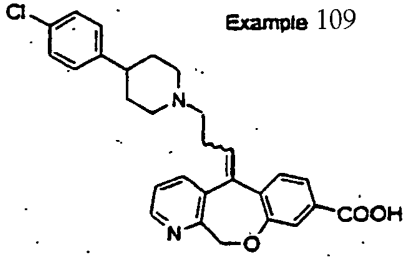
Example 108



Example 109

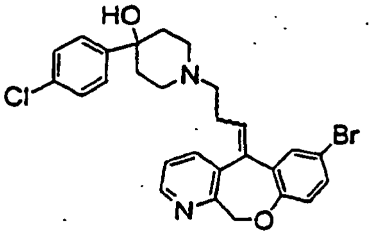


Example 110

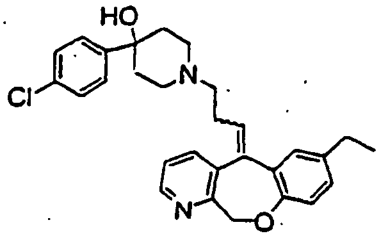


Example 111

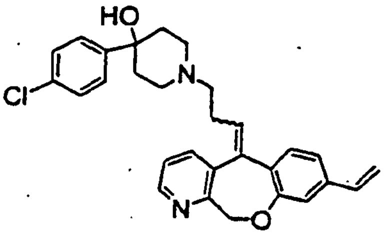
Figure 6L



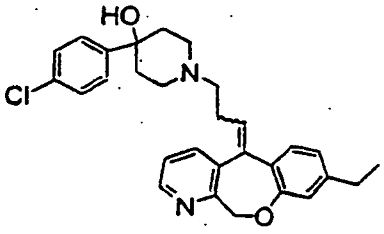
Example 112



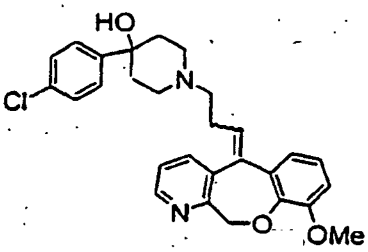
Example 113



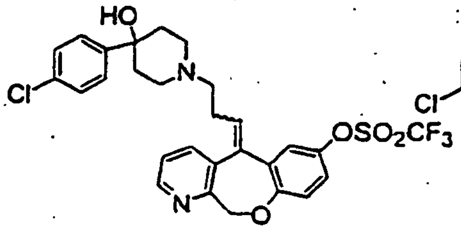
Example 114



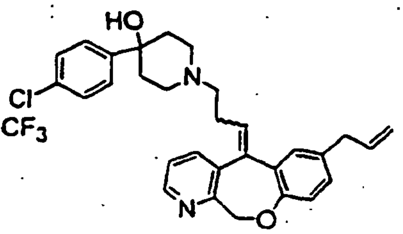
Example 115



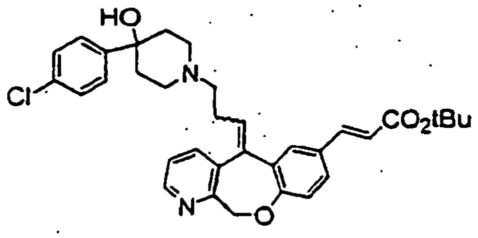
Example 116



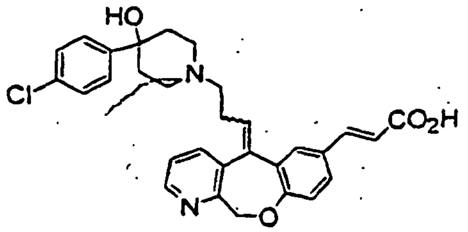
Example 117



Example 118

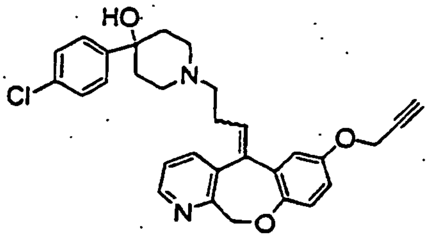


Example 119

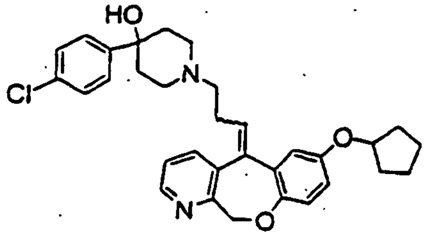


Example 120

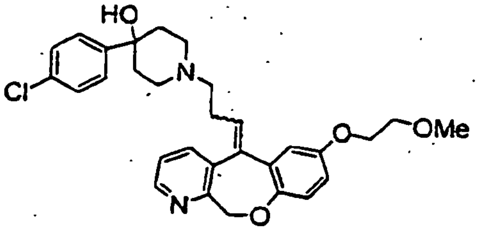
Figure 6M



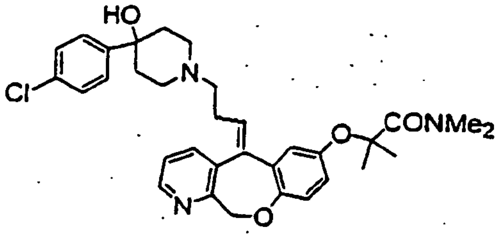
Example 121



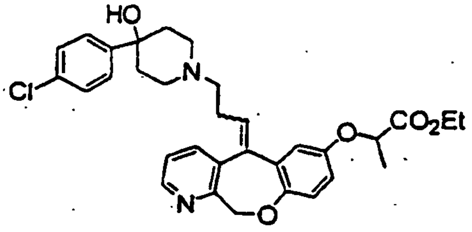
Example 122



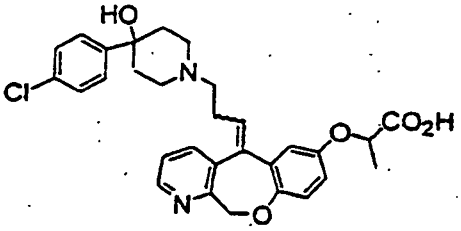
Example 123



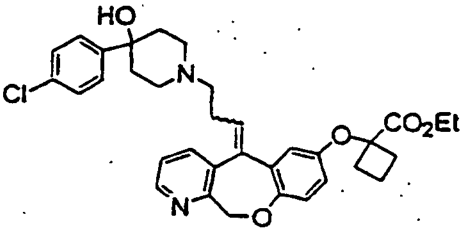
Example 124



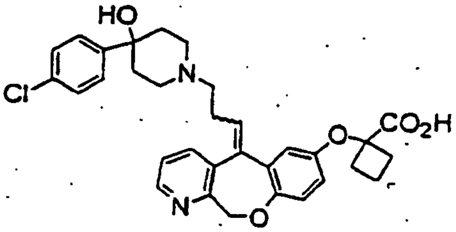
Example 125



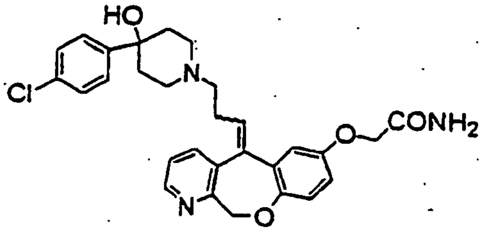
Example 126



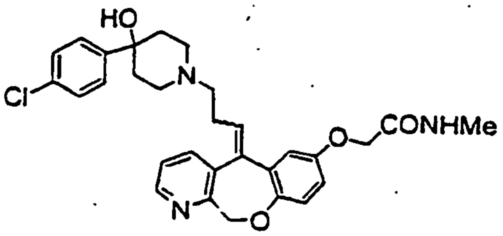
Example 127



Example 128

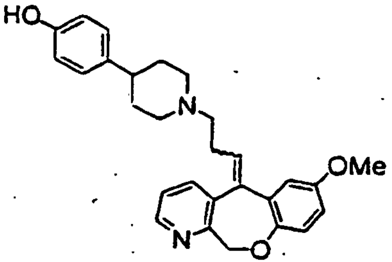


Example 129

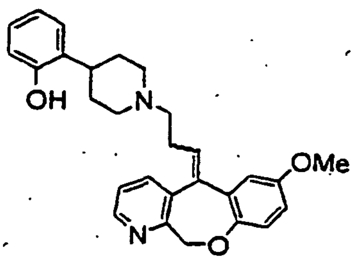


Example 130

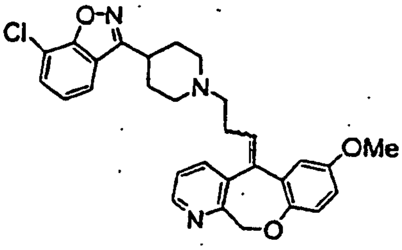
Figure 6N



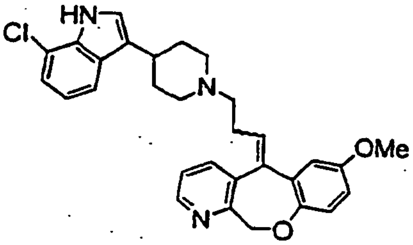
Example 131



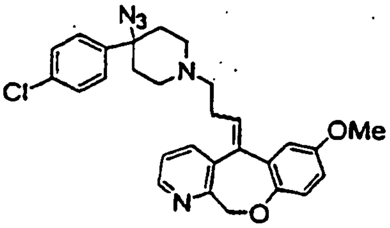
Example 132



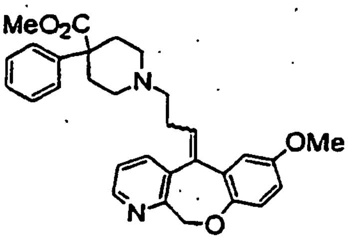
Example 133



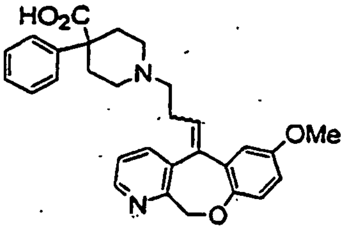
Example 134



Example 135

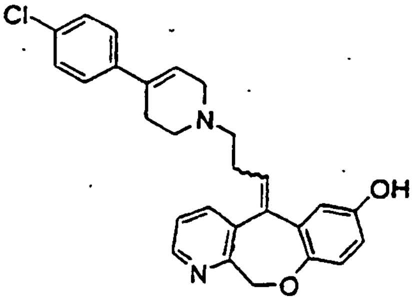


Example 136

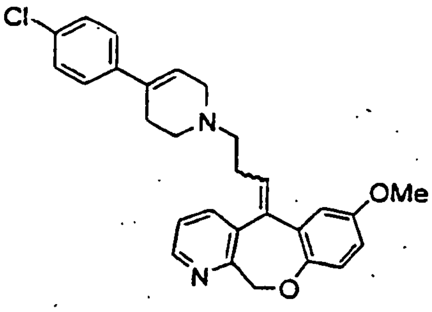


Example 137

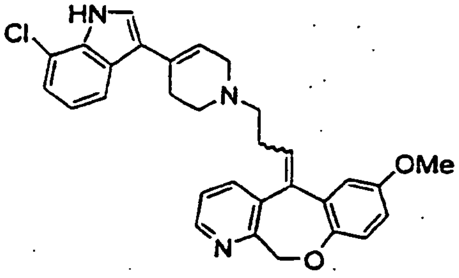
Figure 6O



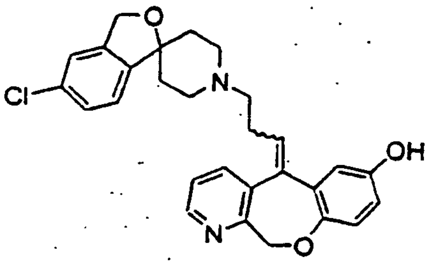
Example 138



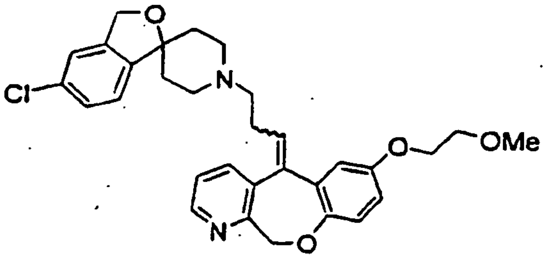
Example 139



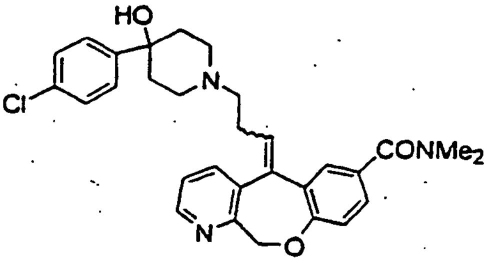
Example 140



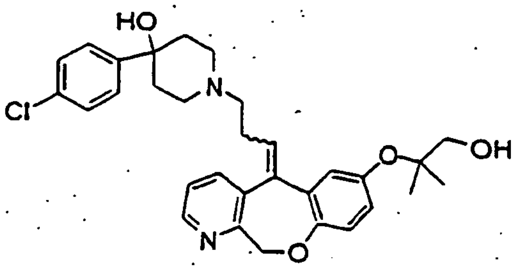
Example 141



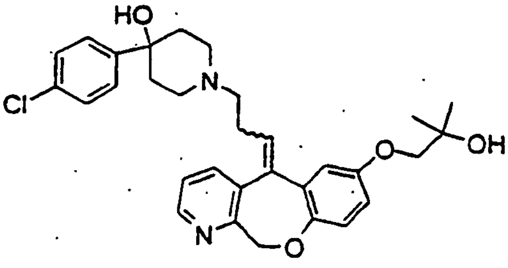
Example 142



Example 143

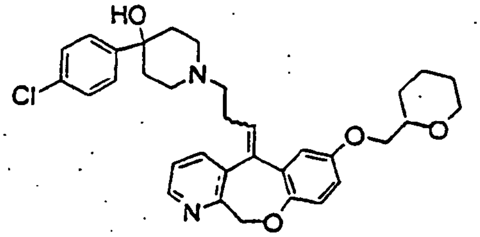


Example 144

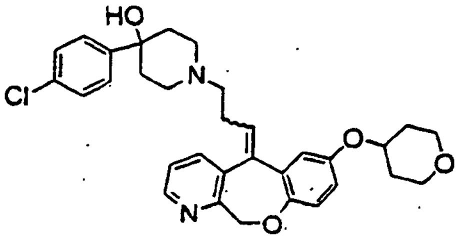


Example 145

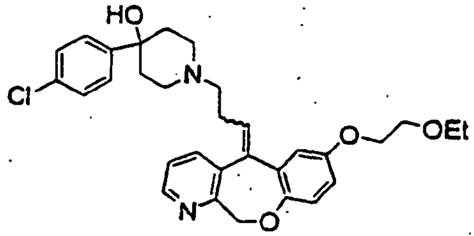
Figure 6P



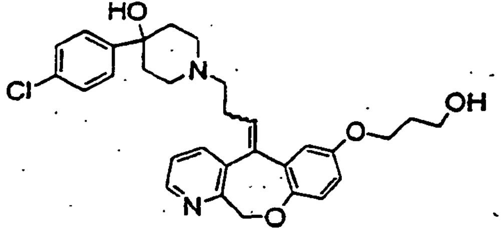
Example 146



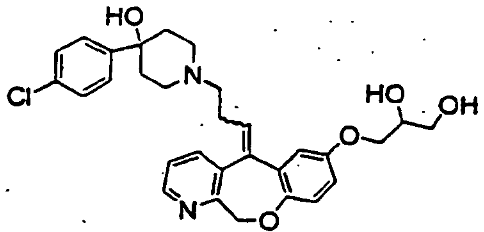
Example 147



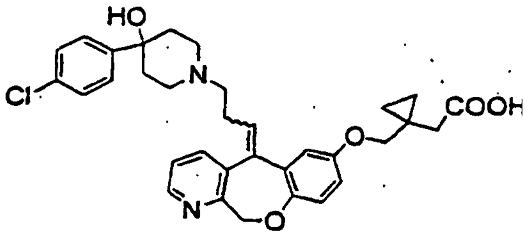
Example 148



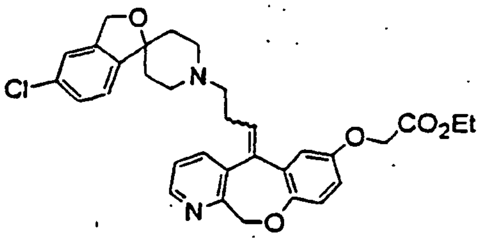
Example 149



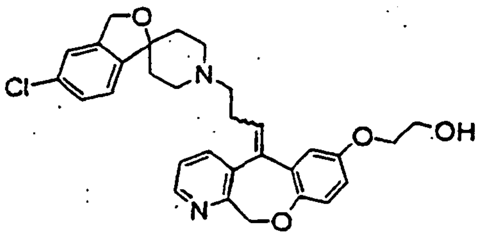
Example 150



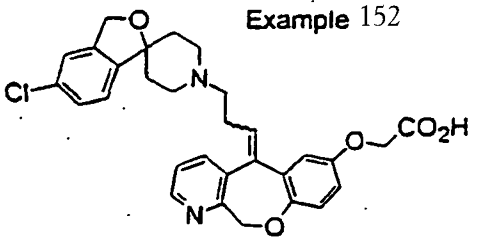
Example 151



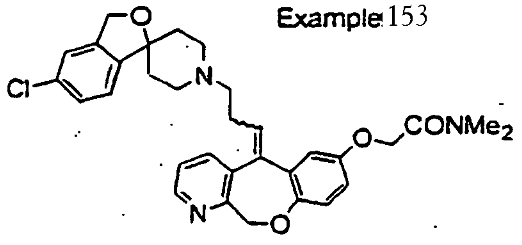
Example 152



Example 153

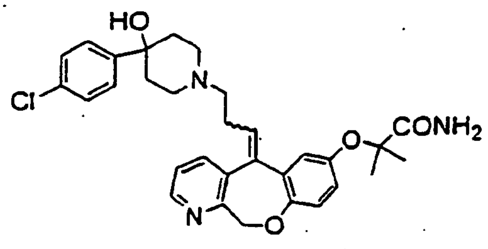


Example 154

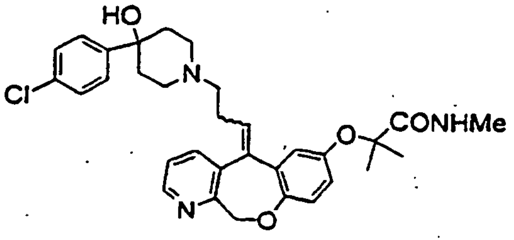


Example 155

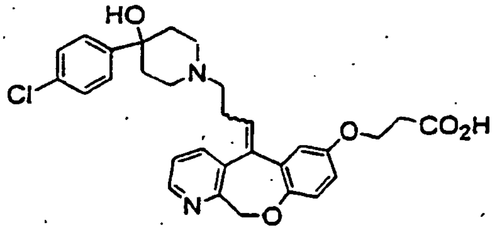
Figure 6Q



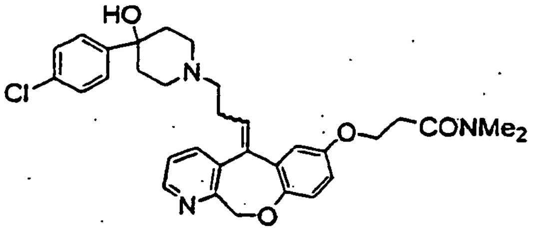
Example 156



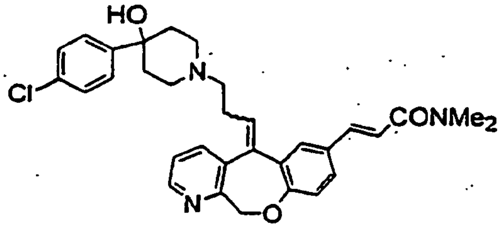
Example 157



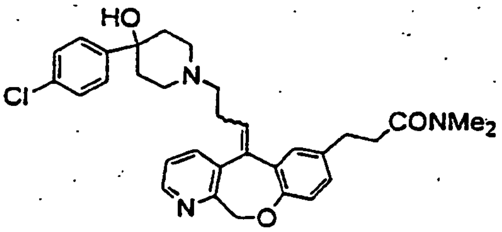
Example 158



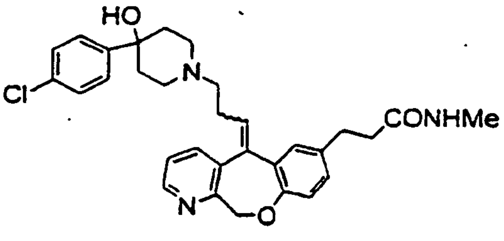
Example 159



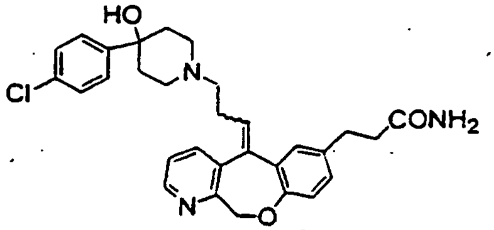
Example 160



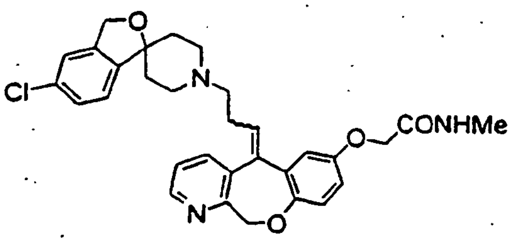
Example 161



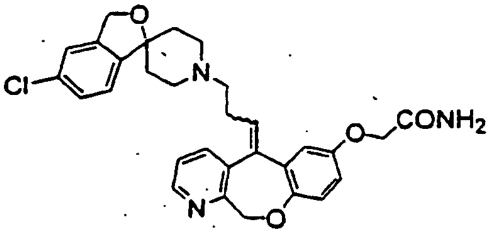
Example 162



Example 163

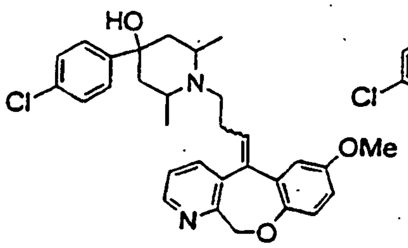


Example 164

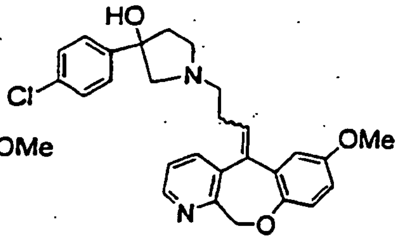


Example 165

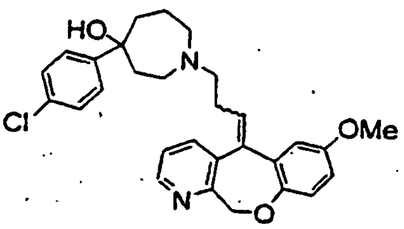
Figure 6R



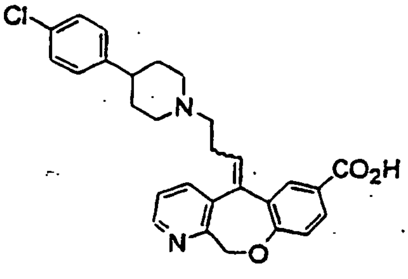
Example 166



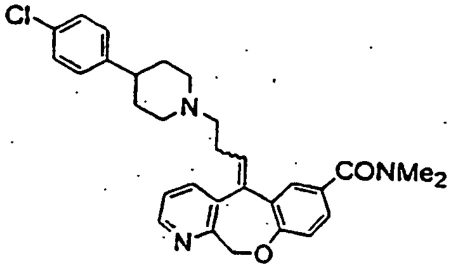
Example 167



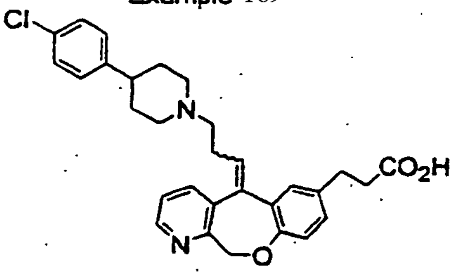
Example 168



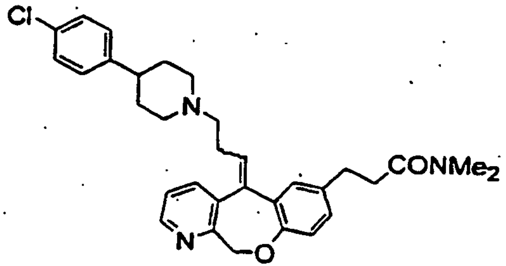
Example 169



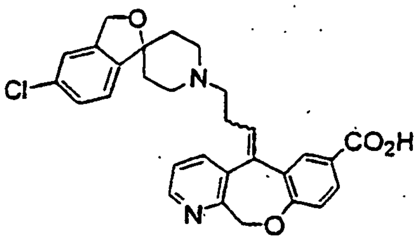
Example 170



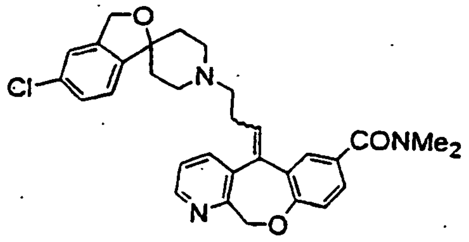
Example 171



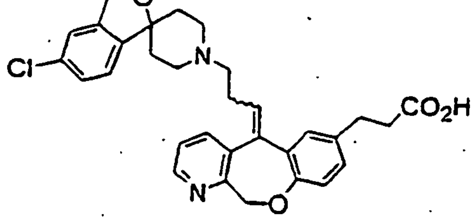
Example 172



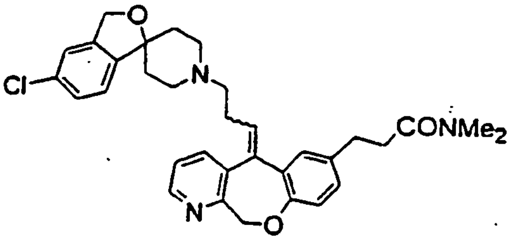
Example 173



Example 174

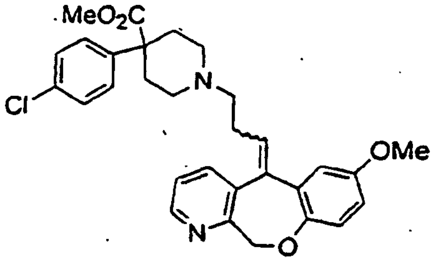


Example 175

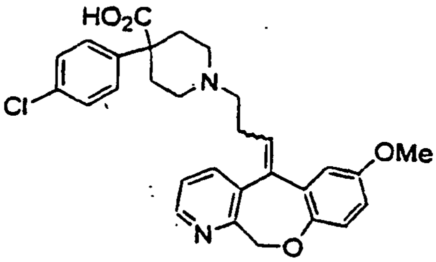


Example 176

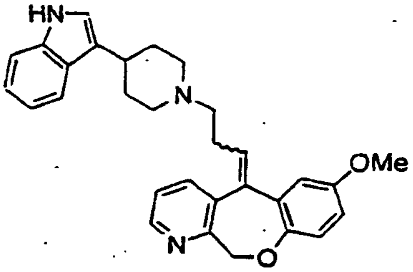
Figure 6S



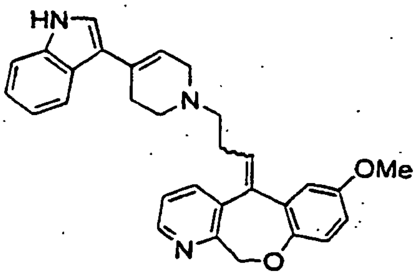
Example 177



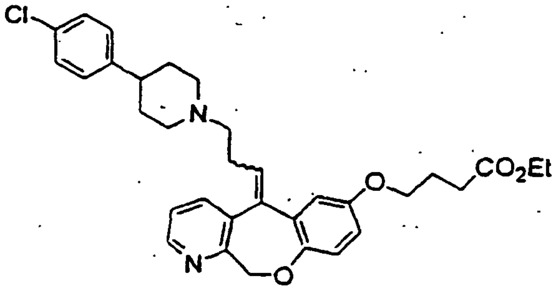
Example 178



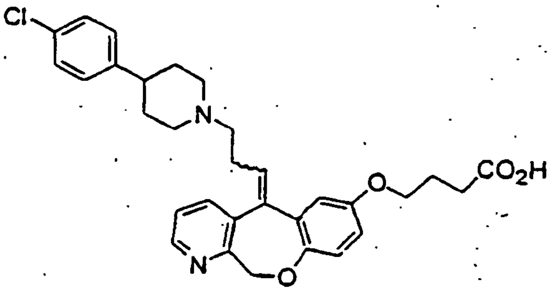
Example 179



Example 180

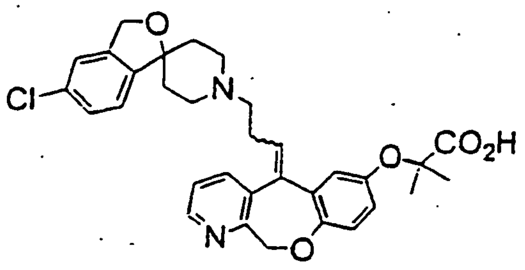


Example 181

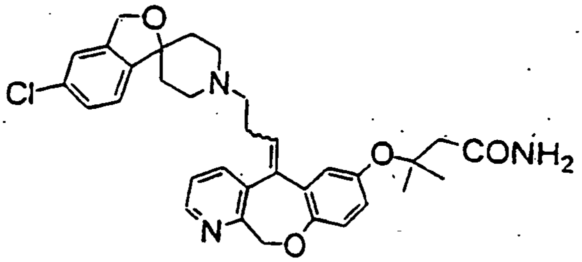


Example 182

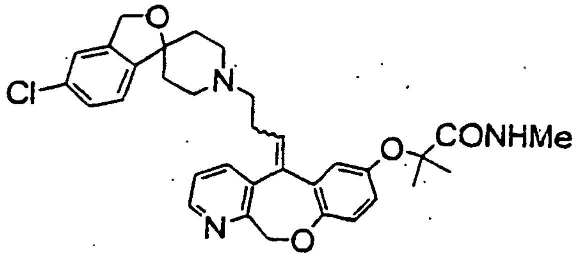
Figure 6T



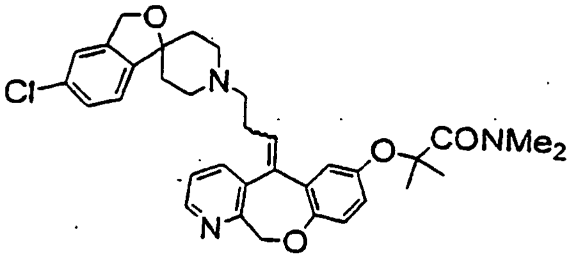
Example 183



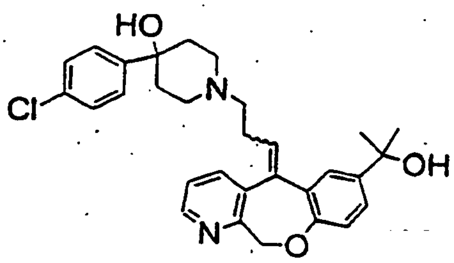
Example 184



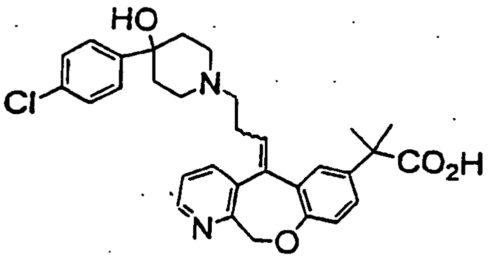
Example 185



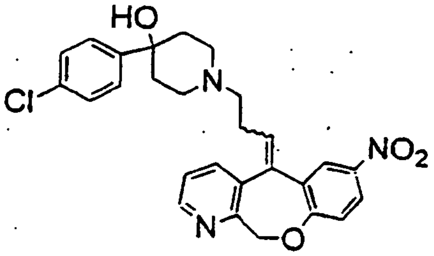
Example 186



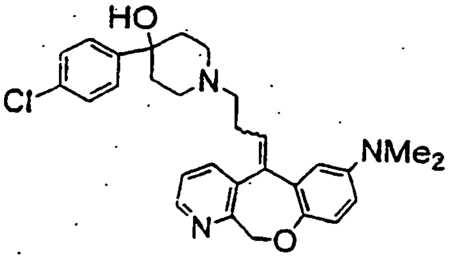
Example 187



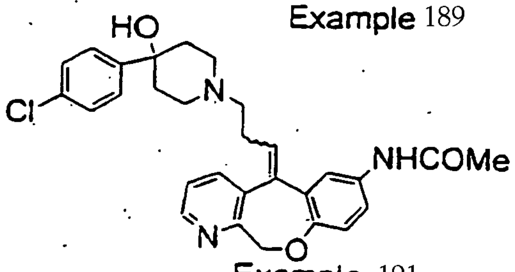
Example 188



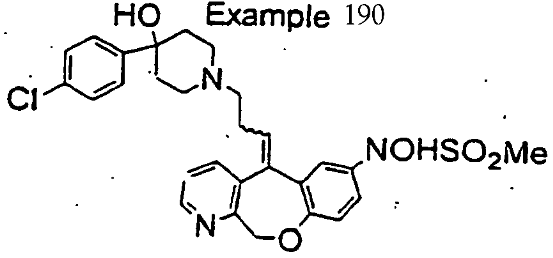
Example 189



Example 190

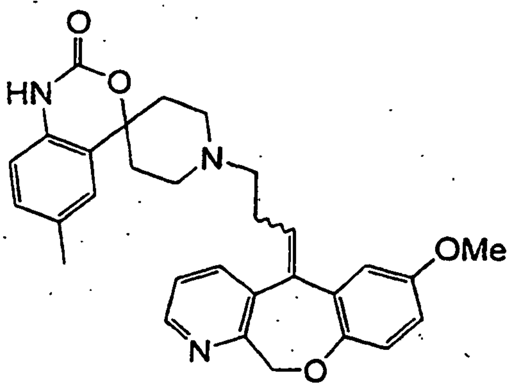


Example 191



Example 192

Figure 6U



Example 193

Figure 6V

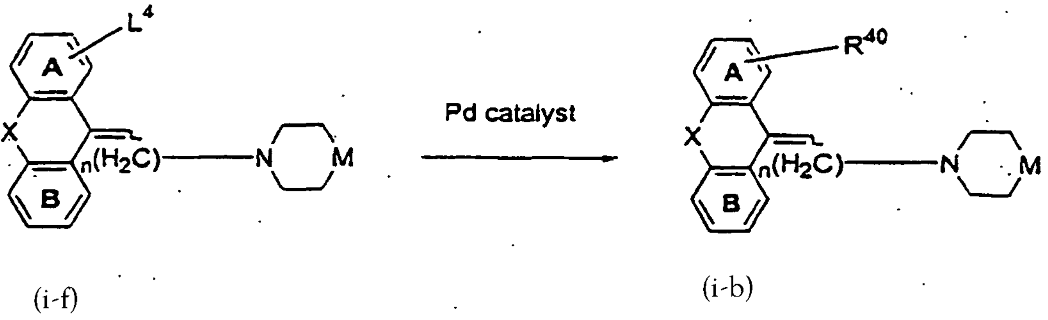


Figure 7