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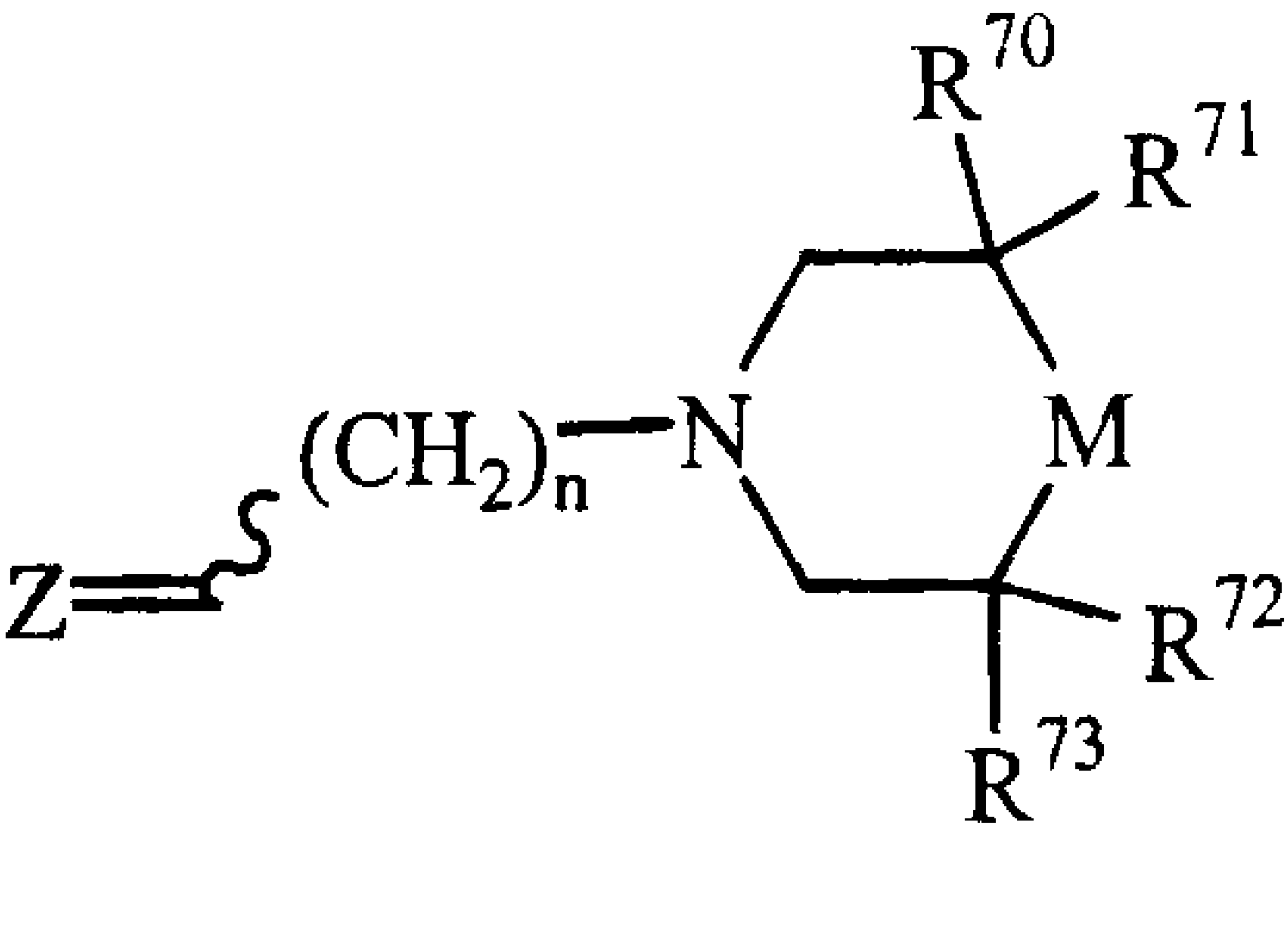
(54) Title: CHEMOKINE RECEPTOR ANTAGONISTS AND METHODS OF USE THEREFOR



(57) Abrégé/Abstract:
Disclosed are novel compounds and a method of treating a disease associated with aberrant leukocyte recruitment and/or activation. The method comprises administering to a subject in need an effective amount of a compound represented by: formula (1) or physiologically acceptable salt thereof.

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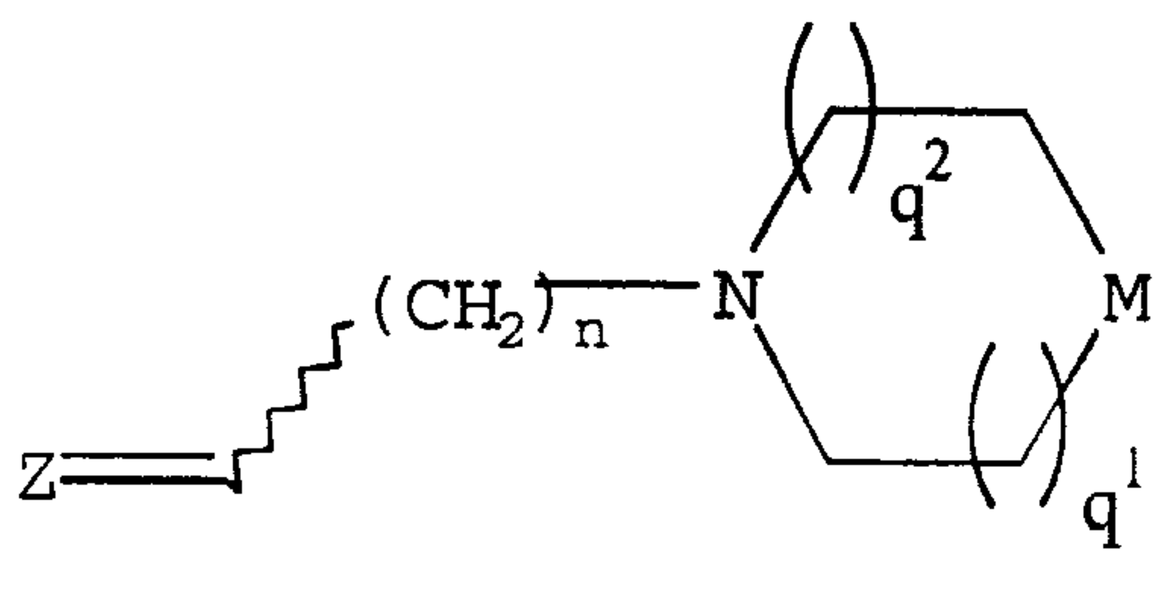
(54) Title: CHEMOKINE RECEPTOR ANTAGONISTS AND METHODS OF USE THEREOF



(1)

(57) Abstract: Disclosed are novel compounds and a method of treating a disease associated with aberrant leukocyte recruitment and/or activation. The method comprises administering to a subject in need an effective amount of a compound represented by: formula (1) or physiologically acceptable salt thereof.

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THIS IS VOLUME __1___ OF __2___

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CHEMOKINE RECEPTOR ANTAGONISTS AND METHODS OF USE THEREFOR

BACKGROUND OF THE INVENTION

Chemoattractant cytokines or chemokines are a family of proinflammatory mediators that promote 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)).

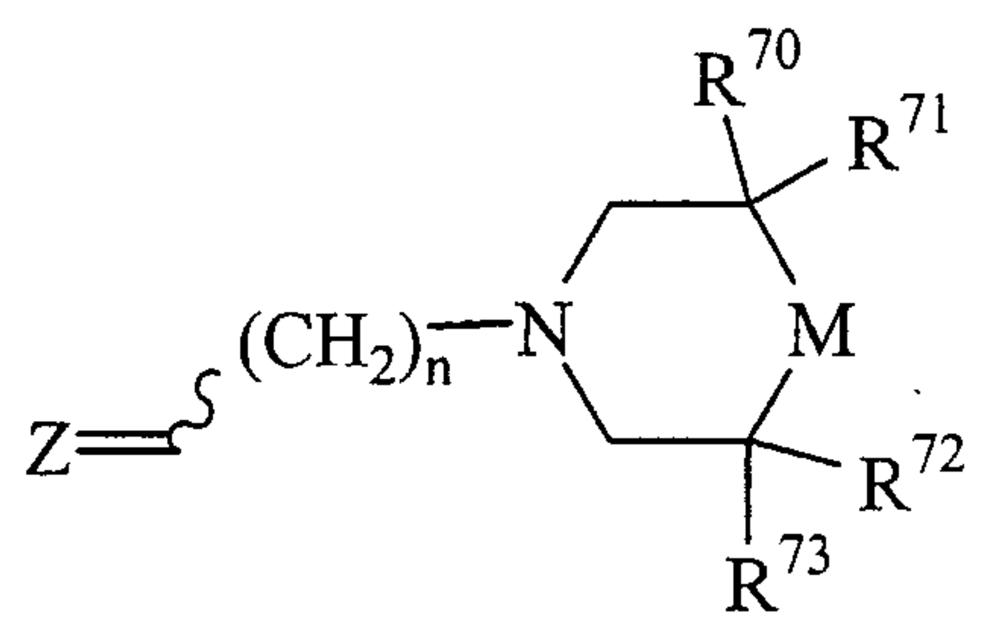
The C-X-C chemokines include a number of potent chemoattractants and activators of neutrophils, such as interleukin 8 (IL-8), PF4 and neutrophil-activating peptide-2 (NAP-2). The C-C chemokines include RANTES (Regulated on Activation, Normal T Expressed and Secreted), the macrophage inflammatory proteins 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.

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 MIP-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.

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 C5a. 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

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, a method of treating a disease associated with aberrant leukocyte recruitment and/or activation is disclosed as well as a method of treating a disease mediated by chemokine receptor function. The method comprises administering 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. In one aspect, the compound has the formula:



or a physiologically acceptable salt thereof, wherein Z, n, M, R^{70}, R^{71}, R^{72} and R^{73} are as described herein.

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 and methods for their preparation.

BRIEF DESCRIPTION OF THE DRAWINGS

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 (III) 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 (III) 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.

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

Figure 8A is a schematic showing the preparation of 4-(4-chlorophenyl)-4-fluoropiperidine.

Figure 8B is a schematic showing the preparation of 4-4-azido-4-(4-chlorophenyl)piperidine.

Figure 8C is a schematic showing the preparation of 4-(4-chlorophenyl)-4-methylpiperidine.

Figure 9A is a schematic showing the preparation of compounds represented by Structural Formulas (I), (VIII) and (VIII) wherein R^1 is an amine.

Figure 9B is a schematic showing the preparation of compounds represented by Structural Formulas (I), (VIII) and (VIII) wherein R^1 is an alkylamine.

Figure 9C is a schematic showing the preparation of 2-(4-chlorophenyl)-1-(*N*-

methyl)ethylamine.

Figure 9D is a schematic showing the preparation of 3-(4-chlorophenyl)-3-chloro-1-hydroxypropane.

Figure 9E is a schematic showing the preparation of 3-(4-chlorophenyl)-1-*N*-methylaminopropane.

Figure 10A is a schematic showing the preparation of 3-(4-chlorophenyl)-3-hydroxyl-3-methyl-1-*N*-methylaminopropane.

Figure 10B is a schematic showing the preparation of 1-(4-chlorobenzoyl)-1,3-propylenediamine.

Figure 10C is a schematic showing three procedures for the preparation of compounds represented by Structural Formulas (I),(VII), (VIII), (IX) and (XI) wherein Z is represented by Structural Formula (III) and wherein Ring A or Ring B in Z is substituted with R^{40}. In Figure 10C, R^{40} is represented by $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, u is one, t is zero.

Figure 10D is a schematic showing the preparation of 4-(4-chlorophenyl)-4-pyridine.

Figures 11A-11T show the structures of exemplary compounds of the present invention.

Figure 12 is a schematic showing preparation of compounds of formula (VI-c).

Figure 13 is a schematic showing preparation of compounds of formula (VI-e).

Figure 14 is a schematic showing a procedure for the preparation of Examples 434 and 435.

Figure 15 is a schematic showing a procedure for the preparation of Examples 436-438.

Figure 16 is a schematic showing a procedure for the preparation of compounds of formula (I-f).

Figure 17 is a schematic showing a procedure for the preparation of Examples 441 and 442.

Figure 18 is a schematic showing a procedure for the preparation of Example 443.

Figure 19 is a schematic showing a procedure for the preparation of Examples 315, 455, 338 and 446.

Figures 20-28 show the structures of exemplary compounds of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to small molecule compounds which are modulators of chemokine receptor function. In a preferred embodiment, the small molecule compounds are antagonists of chemokine receptor function. 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.

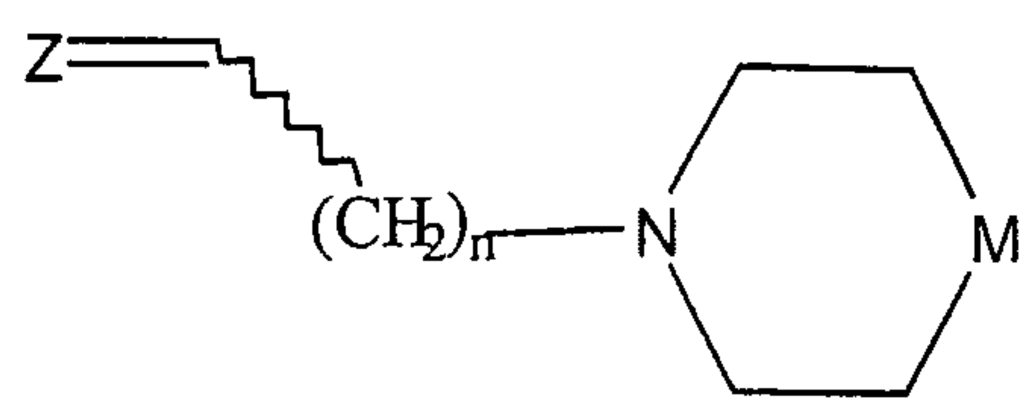
The invention further relates to a method of treatment, including prophylactic and therapeutic treatments, of a disease associated with aberrant leukocyte recruitment and/or activation or mediated by chemokines or chemokine receptor function, including chronic inflammatory disorders characterized by 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, restenosis, 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. Other diseases associated with aberrant leukocyte recruitment and/or activation which can be treated (including prophylactic treatments) with the methods 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. The method comprises administering to the subject in need of treatment an effective amount of a 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, sites of inflammation.

The invention further relates to methods of antagonizing a chemokine receptor, such as CCR1, in a mammal comprising administering to the mammal a compound as described herein.

According to the method, 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.

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, the method and 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.

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



(I)

and physiologically acceptable salts thereof.

Z is a cycloalkyl or non-aromatic heterocyclic ring group fused to one, two or more aromatic rings, wherein each ring in Z is independently substituted or unsubstituted.

n is an integer, such as an integer from one to four. Preferably, n is one, two or three. More preferably n is two. In alternative embodiments, other aliphatic or aromatic spacer groups (L) can be employed for $(CH_2)_n$.

M is $>NR^2$ or $>CR^1R^2$. M is preferably $>C(OH)R^2$.

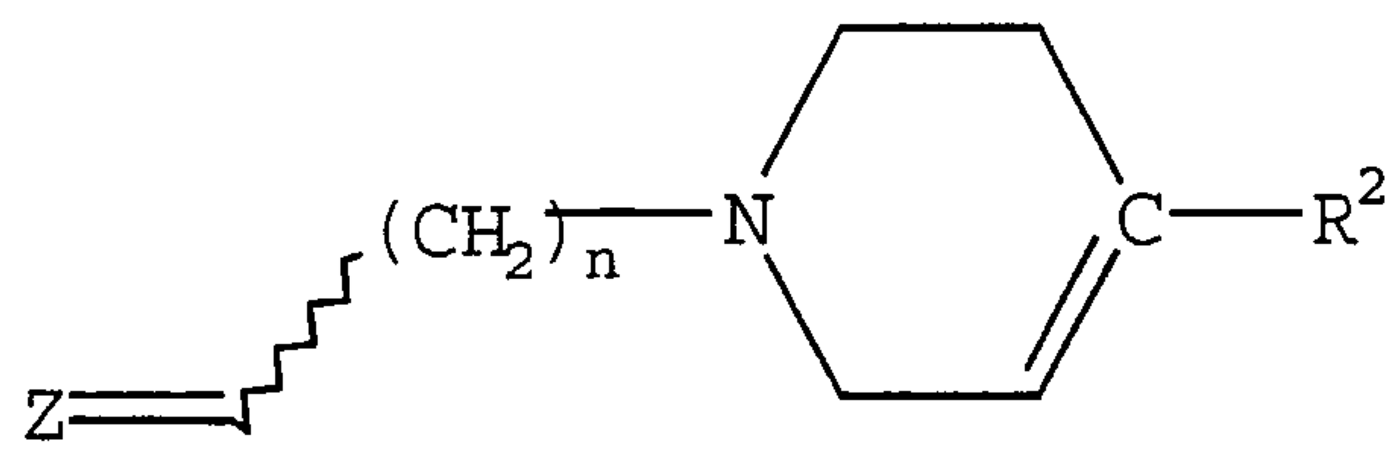
R^1 is -H, -OH, $-N_3$, a halogen, an aliphatic group, a substituted aliphatic group, an aminoalkyl group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -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 -H, -OH, a halogen, 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, a substituted non-aromatic heterocyclic group, -O-(substituted or unsubstituted aromatic group), -O-(substituted or unsubstituted aliphatic group) or -C(O)-(substituted or unsubstituted aromatic group) or -C(O)-(substituted or unsubstituted aliphatic group). R^2 is preferably an aromatic group or a substituted aromatic 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.

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 carbocyclic or heterocyclic ring.

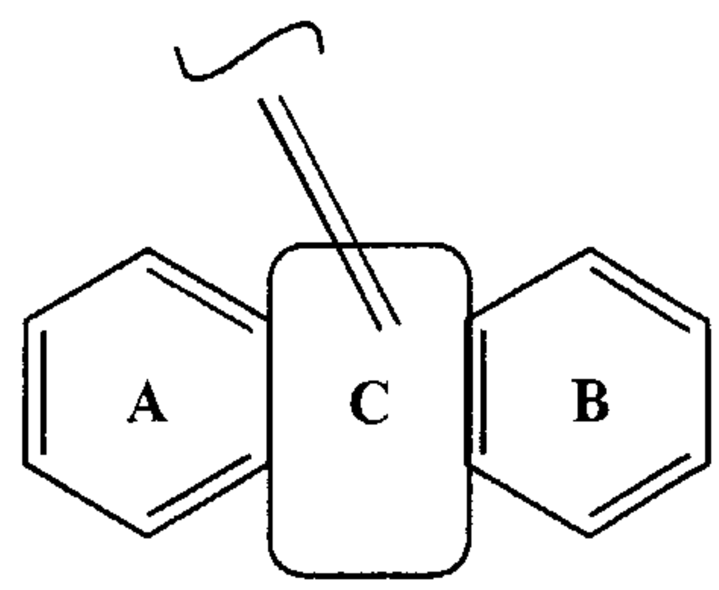
In embodiments where M is $>CR^1R^2$ and R^1 is a covalent bond between the carbon atom at M and an adjacent carbon atom in the ring which contains M, the antagonist of chemokine function can be represented by Structural Formula (Ia).



(Ia)

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

In one embodiment, Z is a tricyclic ring system comprising two carbocyclic aromatic groups fused to a five, six, seven or eight membered cycloalkyl group or to a non-aromatic heterocyclic ring. In one example, Z is represented by Structural Formula (II):



(II)

The phenyl rings in Structural Formula (II), labeled with an "A" and "B", are referred to herein as "Ring A" and "Ring B", respectively. The central ring, labeled with a "C", is referred to as "Ring C" and can be, for example, a five, six, seven or eight membered non-aromatic carbocyclic ring (e.g., a cycloheptane or cyclooctane ring) or a non-aromatic heterocyclic ring. When Ring C is a non-aromatic heterocyclic ring, it can contain one or two heteroatoms such as nitrogen, sulfur or oxygen. In particular embodiments, Ring c is When Z is represented by Structural Formula (II), the tricyclic ring system can be connected to the remainder of the molecule by a covalent double bond between a carbon atom in Ring C and the carbon atom which, as depicted in Structural Formula (I), is bonded to Z.

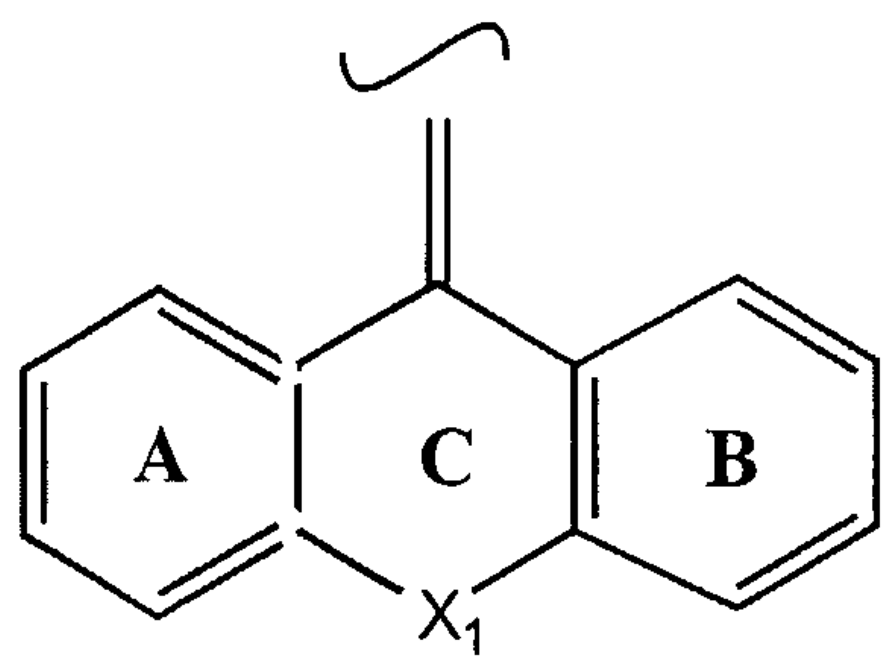
Ring A and/or Ring B in Structural Formula (II) can be unsubstituted. Alternatively, Ring A and/or Ring B can have one or more substituents. Suitable substituents are as described hereinbelow. In one example, Ring A or Ring B is substituted with $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$.

u is zero or one.

t is an integer, such as an integer from zero to three, and the methylene group $-(CH_2)_t-$ can be substituted, as described herein for aliphatic groups, or unsubstituted.

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

Ring C optionally contains one or more substituents, as described hereinbelow. Examples of suitable tricyclic ring systems, Z, are provided by Structural Formula (III):



(III)

Ring A and Ring B in Structural Formula (III) are as described for Structural

Formula (II).

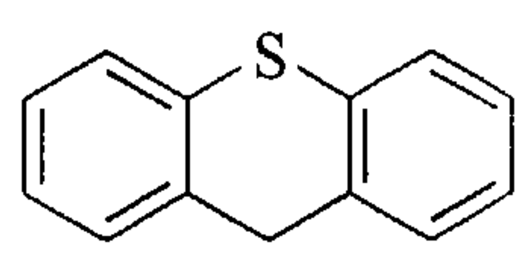
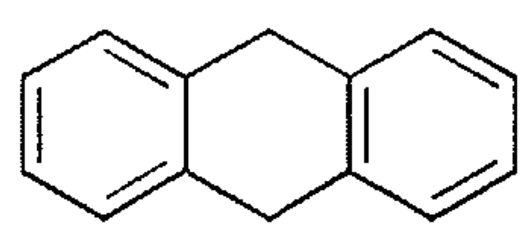
X_1 is a bond, -O-, -S-, -CH_2-, -CH_2-CH_2-, -CH_2-S-, -S-CH_2-,-O-CH_2-, -CH_2-O-, -NR_c-CH_2-, -CH_2-NR_c-, -SO-CH_2-, -CH_2-SO-, -$S(O)_2$-CH_2-, -CH_2-$S(O)_2$-, -CH=CH-, -NR_c-CO- or -CO-NR_c-. Preferably X_1 is -CH_2-O-, -CH_2-CH_2-, -CH_2-S- , -NR_c-CO- or -CO-NR_c-.

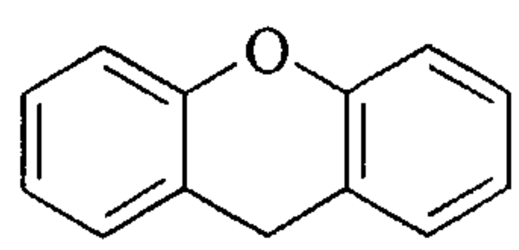
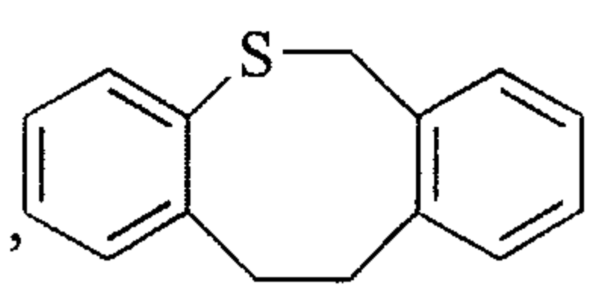
R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group.

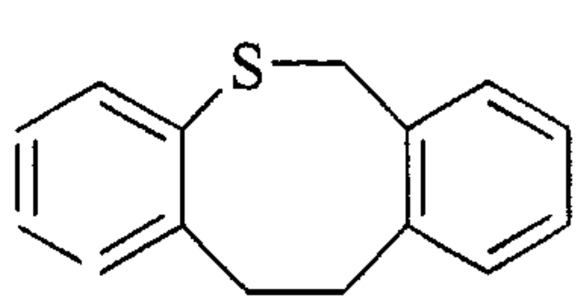
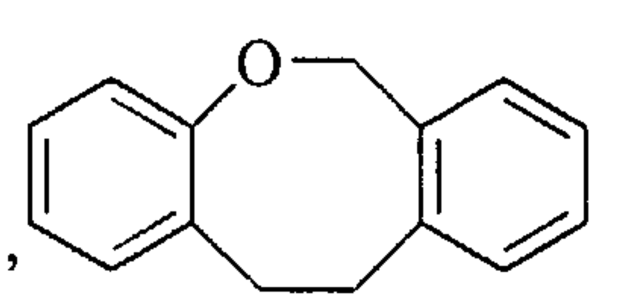
In one example, R_c is -$(CH_2)_s$-$COOR^{30}$, -$(CH_2)_s$-C(O)-$NR^{31}R^{32}$ or -$(CH_2)_s$-NHC(O)-O-R^{30}, wherein s is an integer, such as an integer from one to three;

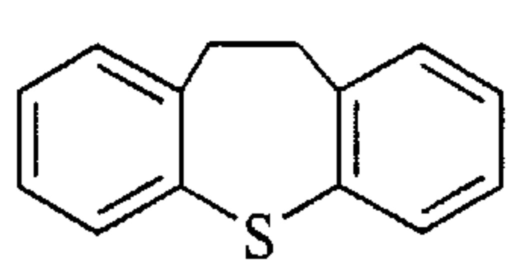
R^{30}, R^{31} and R^{32} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group. Alternatively, R^{31} and R^{32}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

Other examples of suitable tricyclic ring systems for Z include benzodiazepines, benzooxazepines, benzooxazines, phenothiazines and groups represented by the following structural formulas:

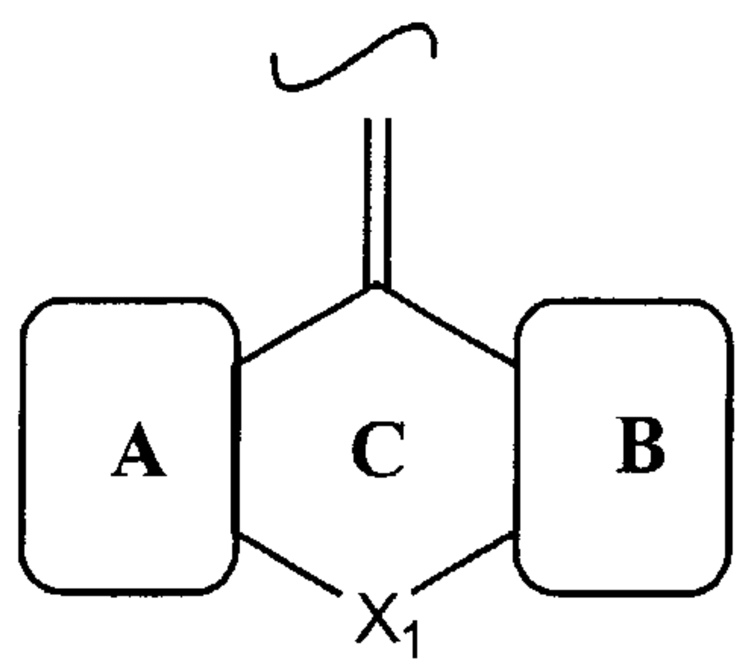
 ,  ,

 ,  ,

 ,  ,

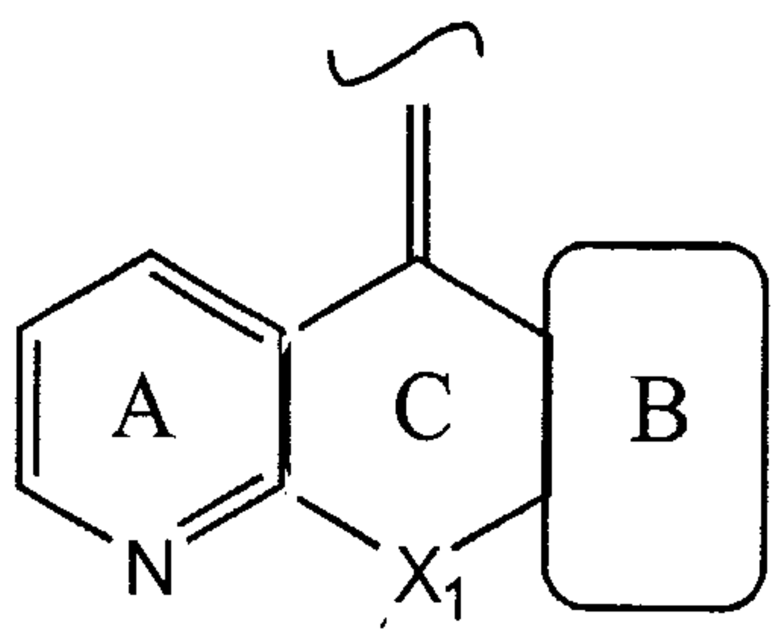
 .

In other embodiments, Z is a tricyclic ring system comprising two aromatic groups fused to a seven or eight membered cycloalkyl group or to a non-aromatic heterocyclic ring, wherein at least one of the aromatic groups is a heteroaryl group. In one example, Z is represented by Structural Formula (IV):


(IV)

Ring A in Structural Formula (IV) can be a substituted or unsubstituted heteroaryl group. Ring B in Structural Formula (IV) can be a substituted or unsubstituted aromatic group, e.g., a heteroaryl group or carbocyclic aryl group. Suitable substituents are as described hereinbelow. In one example, Ring A and/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 $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$ as described above. u, t, R^{20}, R^{21}, and R^{22} are as described above. X_1 and R_c can be as described above for Structural Formula (III).

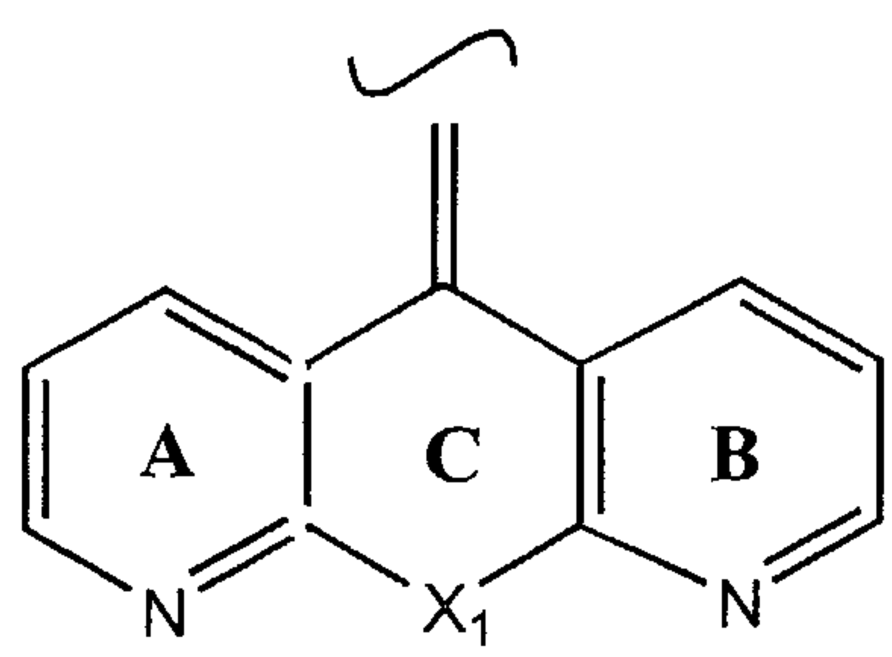
In another embodiment of the present invention Z is represented by Structural Formula (IV), wherein Ring A is a pyridyl group and Ring B is an aromatic or heteroaromatic group. In one example, Z is represented by Structural Formula (IVa):



(IVa).

In this embodiment Ring A and Ring B are independently substituted or unsubstituted, and Ring B is preferably a phenyl group. X_1 and R_c can be as described above for Structural Formula (III).

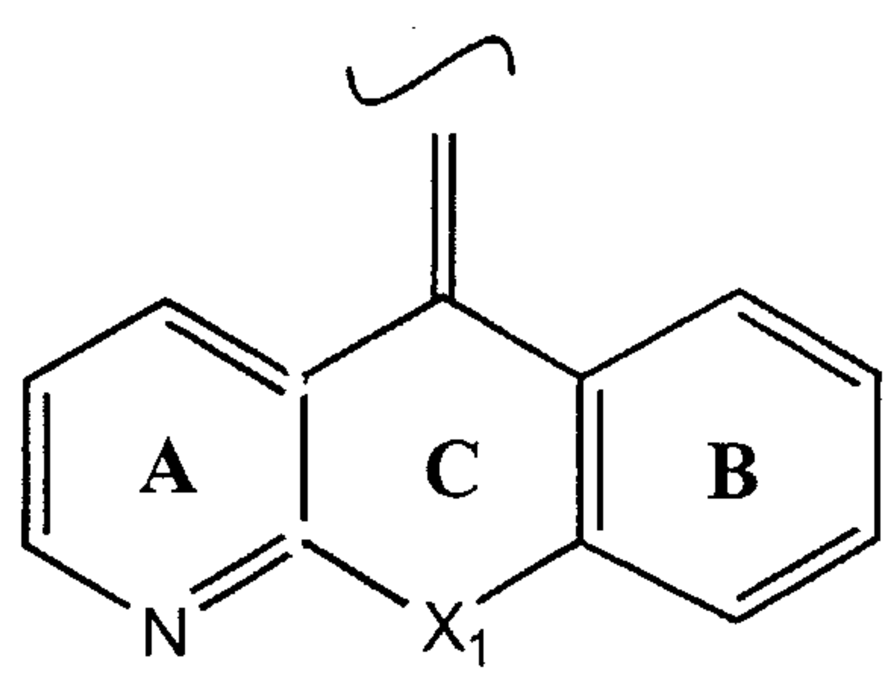
In another embodiment, both Ring A and Ring B are pyridyl groups, and Z is represented by Structural Formula (IVb):



(IVb)

Ring A and Ring B can be independently substituted or unsubstituted as described above in Structural Formula (II), and X_1 can be as described above for Structural Formula (III).

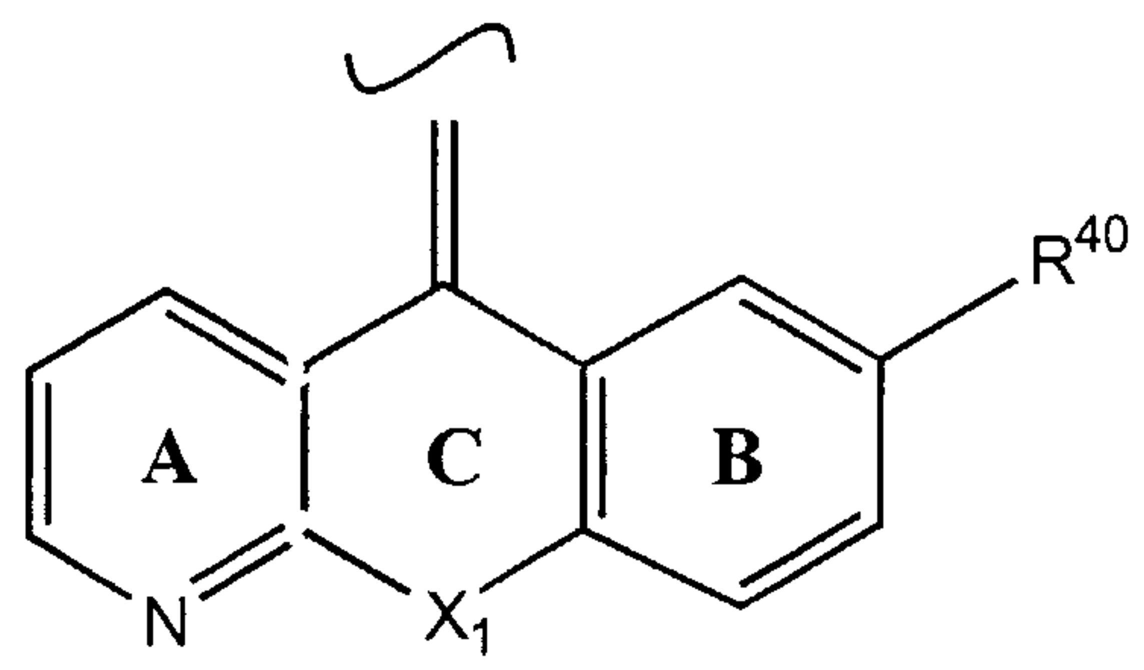
In preferred embodiments, Z is represented by Structural Formula (V):



(V)

Ring A and Ring B can be independently substituted or unsubstituted as described above in Structural Formula (II), and X_1 can be as described above for Structural Formula (III).

In particularly preferred embodiments, Ring B in Structural Formula (V) 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 (VI):



(VI)

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

R^{40} is a substituent as described herein for aromatic groups. In one embodiment, R^{40} is -OH, -COOH, a halogen, $-NO_2$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, $-NR^{24}R^{25}$, $-CONR^{24}R^{25}$, $-C(=NR^{60})NR^{21}R^{22}$, -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 $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$. Q, R^{20}, R^{21}, R^{22}, R^{24}, R^{25}, R^{60}, u and t are as described herein.

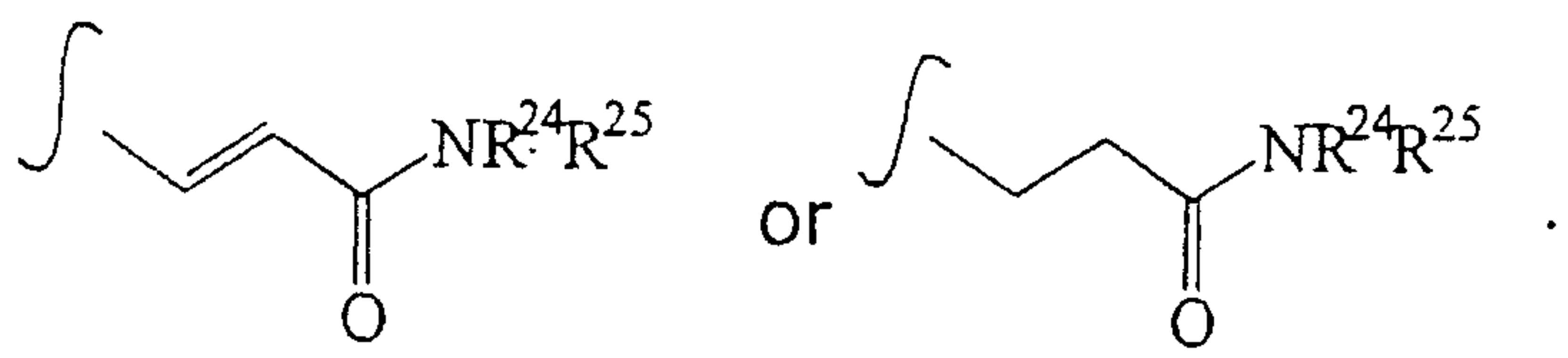
Preferably R^{40} is an aliphatic group, substituted aliphatic group, -O-(aliphatic group) or -O-(substituted aliphatic group). In certain embodiments, R^{40} is an -O-alkyl, such as $-O-CH_3$, $-O-C_2H_5$, $-O-C_3H_7$ or $-O-C_4H_9$.

In another embodiment, R^{40} can be represented by $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, wherein u is one, t is zero, and R^{21} and R^{22} are as described herein. In this embodiment, R^{21} and R^{22} can each independently be -H, a substituted or unsubstituted aliphatic group, a substituted or unsubstituted aromatic group, or R^{21} and R^{22} taken together with the nitrogen atom to which they are bonded form a substituted or unsubstituted nonaromatic heterocyclic ring (e.g., pyrrolidine, piperidine, morpholine).

In another embodiment, R^{40} can be represented by $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, wherein u is zero, t is one to about three, and R^{21} and R^{22} are as described herein.

In another embodiment, R^{40} can be represented by $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, wherein both u and t are zero, and R^{21} and R^{22} are as described herein.

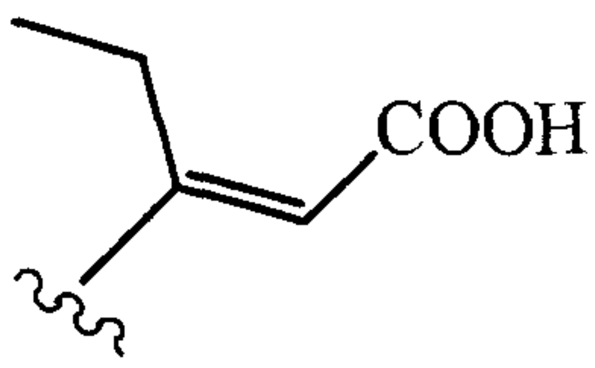
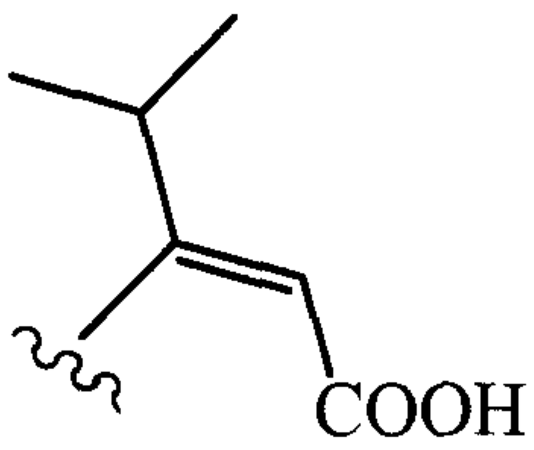
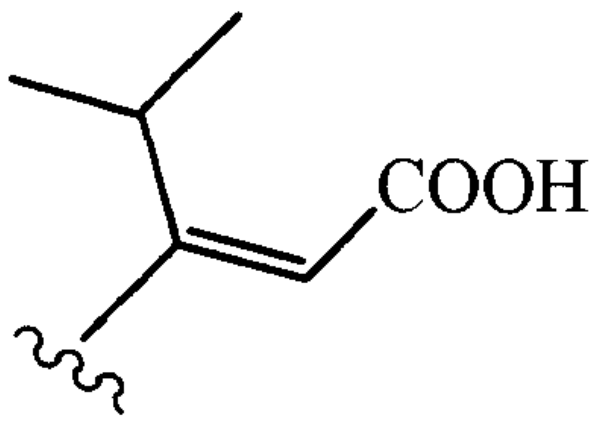
In another embodiment, R^{40} is an aliphatic group (e.g., methyl, ethyl, propyl) that is substituted with $-NR^{24}R^{25}$ or $-CONR^{24}R^{25}$, wherein R^{24} and R^{25} are as described herein. For example, R^{40} can be represented by

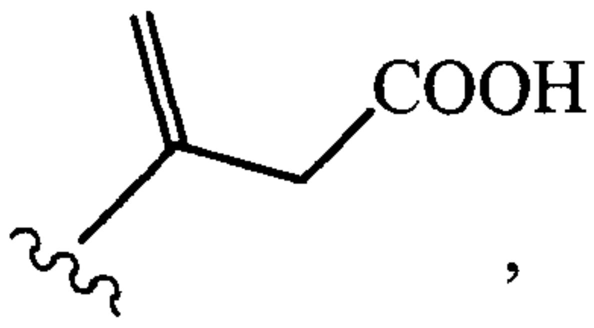
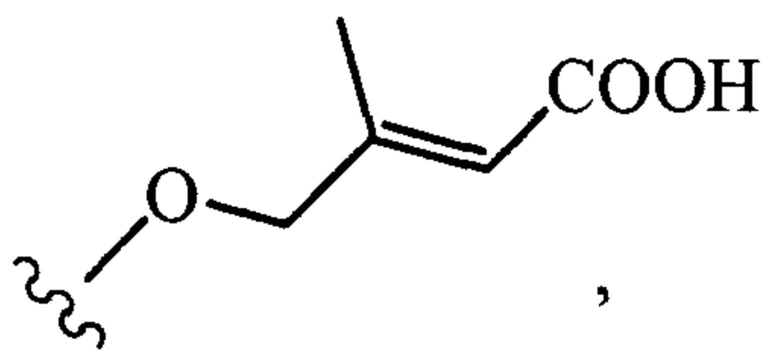
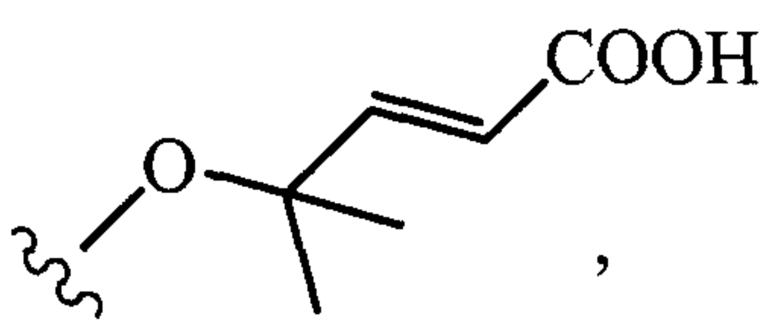


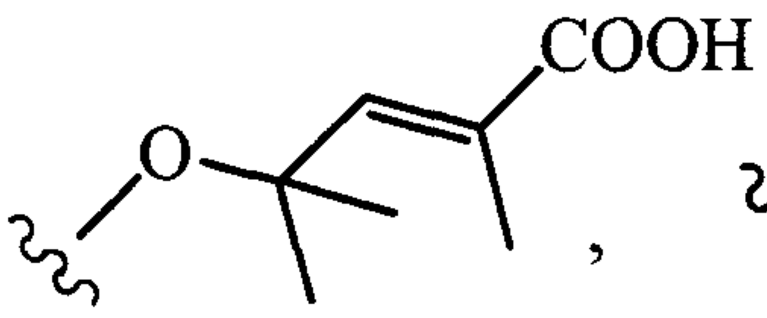
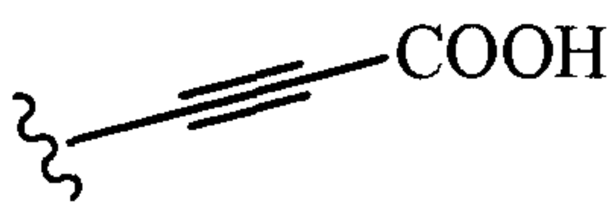
In another embodiment, R^{40} is $-O-C(O)-NR^{21}R^{26}$, wherein R^{21} is as described herein, R^{26} can be -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -C(O)-O-(substituted or unsubstituted aliphatic group), -C(O)-O-(substituted or unsubstituted aromatic group), $-S(O)_2$-(substituted or unsubstituted aliphatic group), $-S(O)_2$-(substituted or unsubstituted aromatic group) or R^{21} and R^{26}, taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

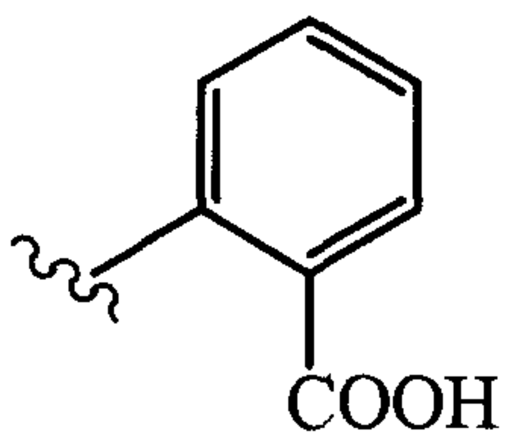
In additional embodiments, R^{40} can be $-S(O)_2-NR^{21}R^{22}$ or $-N-C(O)-NR^{21}R^{22}$, wherein R^{21} and R^{22} are as described herein.

In another embodiment, R^{40} is:

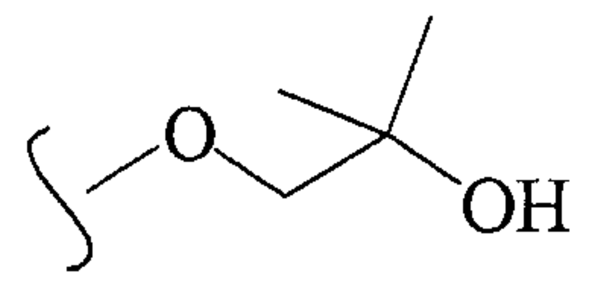
 ,  , 

 ,  ,  ,

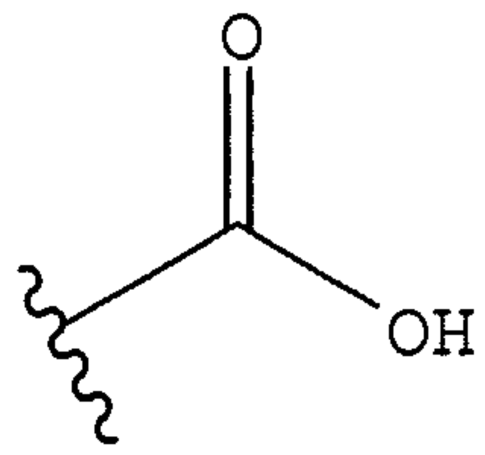
 ,  ,  or

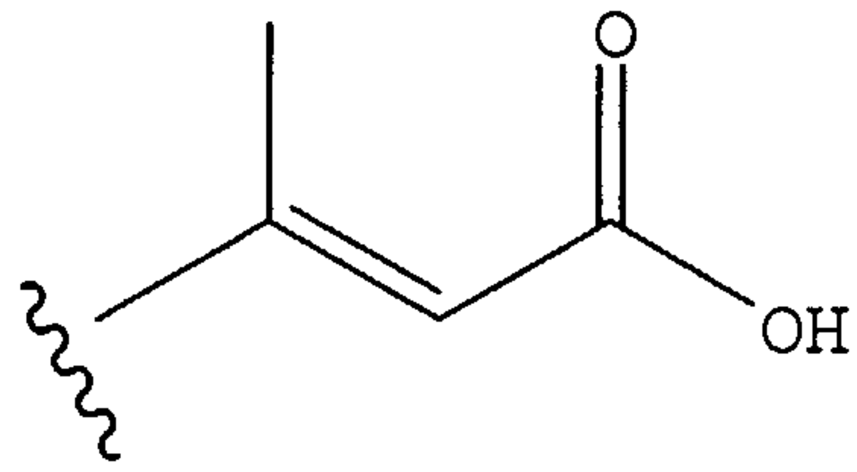
 .

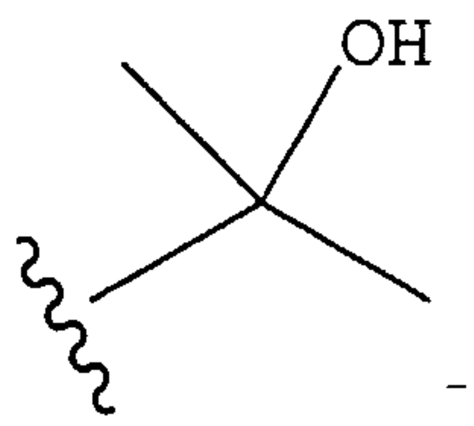
In a preferred embodiment, the chemokine receptor antagonist can be represented by Structural Formula I wherein n is three, M is $C(OH)R^2$, R^2 is a phenyl group of a halophenyl group (e.g., 4-chlorophenyl) and Z is represented by Structural Formula (VI) wherein X_1 is $-CH_2$-O-. In one example of this embodiment, R^{40} can be -O-(substituted aliphatic group), such as

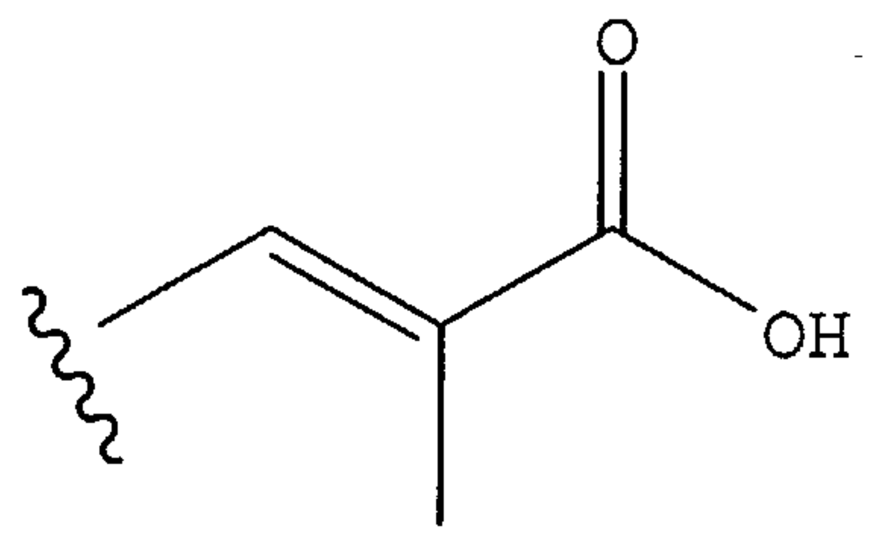
.

In particularly preferred embodiments, R^{40} is

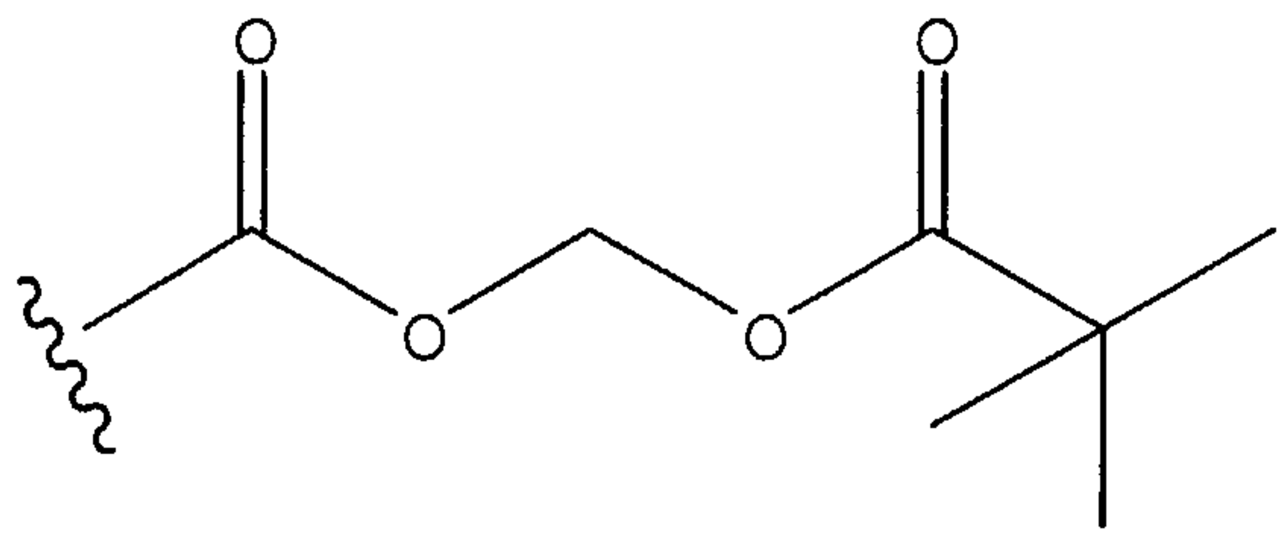
,

,

,



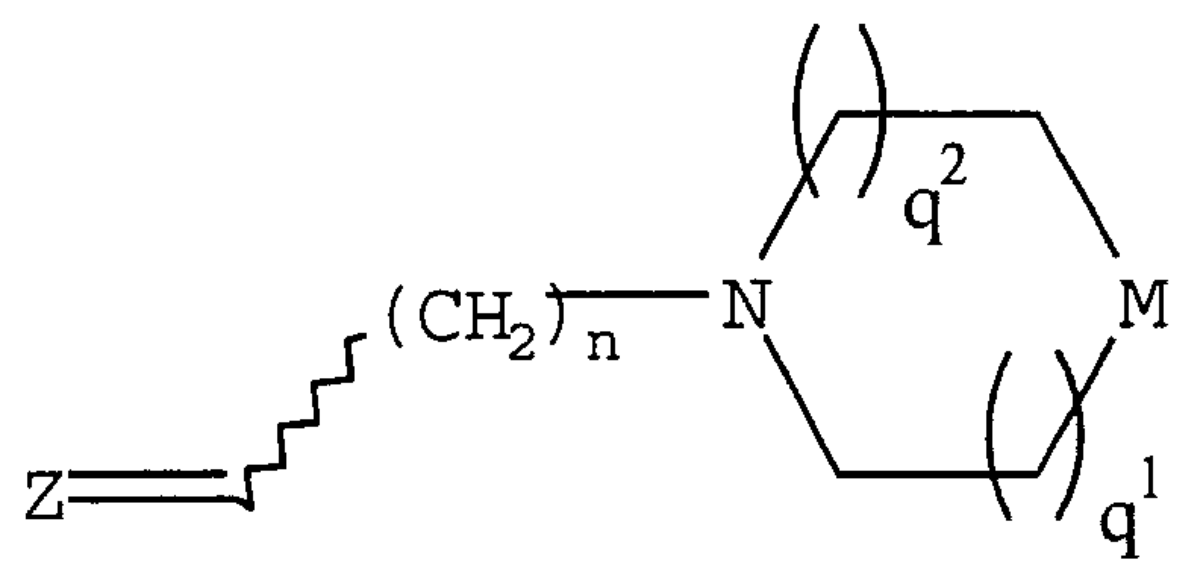
or

.

In other preferred embodiments, R^{40} is a substituted aliphatic group, a substituted aromatic group, -O-substituted aliphatic group or -O-substituted aromatic group. Preferably the aliphatic or aromatic moiety of the substituted aliphatic group, substituted aromatic group, -O-substituted aliphatic group or -O-substituted aromatic group bears a substituent selected from the group consisting of -OH, -COOR

-Q-aliphatic group or -Q-aromatic group substituent. Q is as described herein. Preferably, Q is -C(O)O-. For example, R^{40} can be a linear, branched or cyclic aliphatic group that contains 1 to 6 carbon atoms, such as a C_1-C_6 alkyl group, a C_2-C_6 alkenyl, C_2-C_6 alkynyl, that is substituted with -OH, -COOH, -C(O)O-(C_1-C_6 aliphatic) or -C(O)O-(aromatic).

In another embodiment, the antagonist of chemokine activity can be represented by Structural Formula (VII):



(VII)

and physiologically acceptable salts thereof.

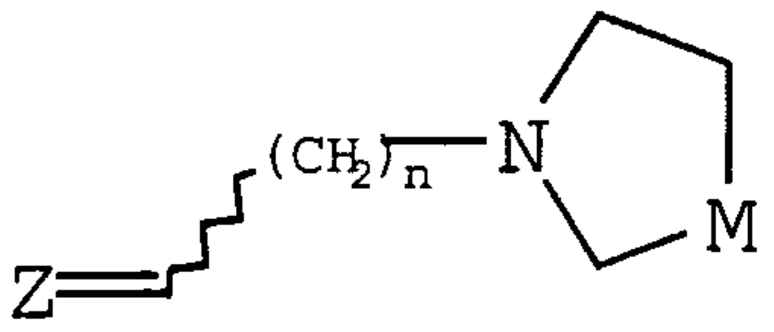
n is as described in Structural Formula (I). Z is as described herein, preferably as described in Structural Formula (V) or (VI).

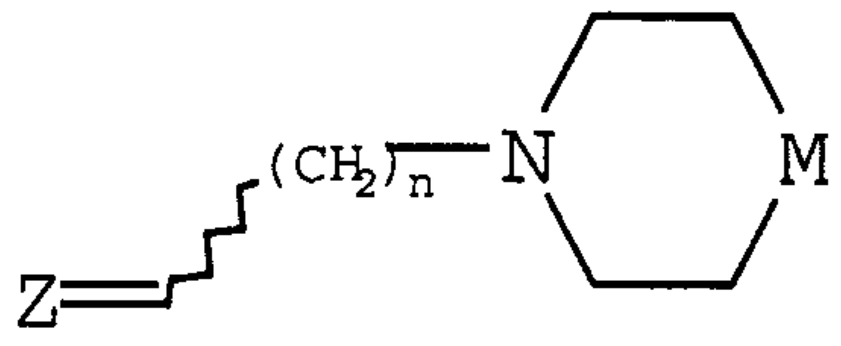
M is $>NR^2$, $>CR^1R^2$, $-O-CR^1R^2-O-$ or $-CH_2-CR^1R^2-O-$.

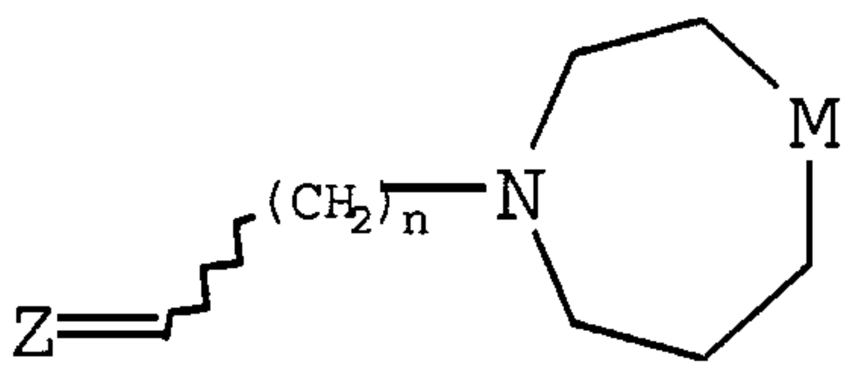
R^1 and R^2 are as described in Structural Formula (I).

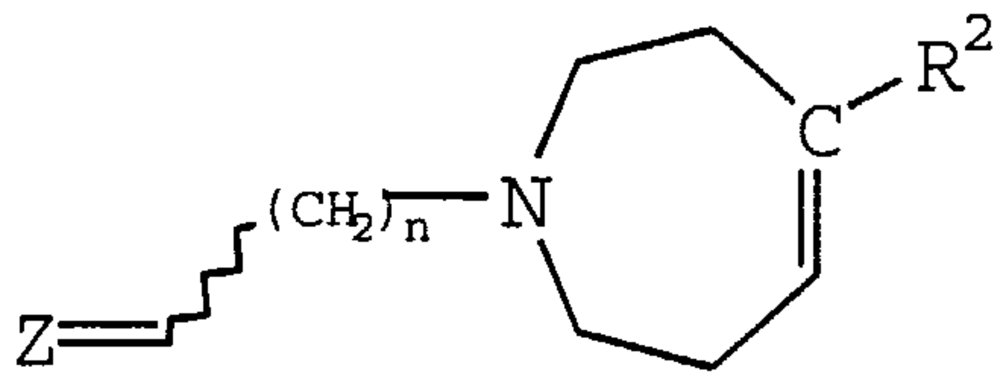
q^1 is an integer, such as an integer from zero to about three, and q^2 is an integer from zero to about one. The ring containing M can be substituted or unsubstituted.

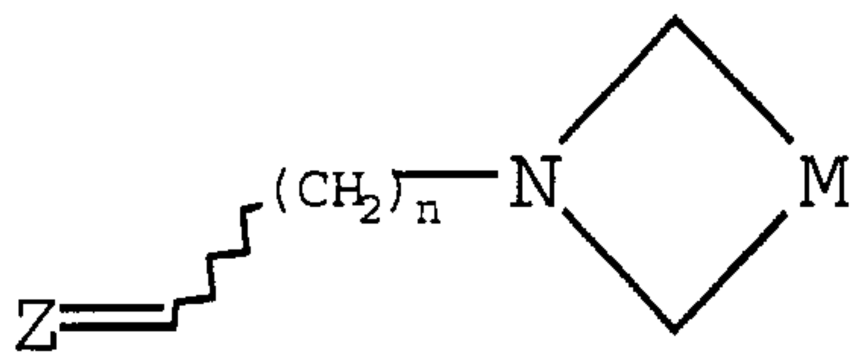
Thus, the antagonist of chemokine function can be represent by, for example, Structural Formulas (VIIa)-(VIIk):

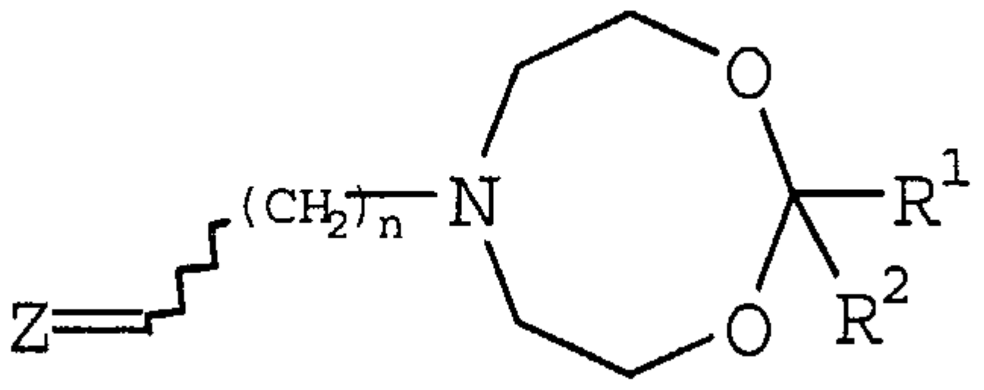

(VIIa)

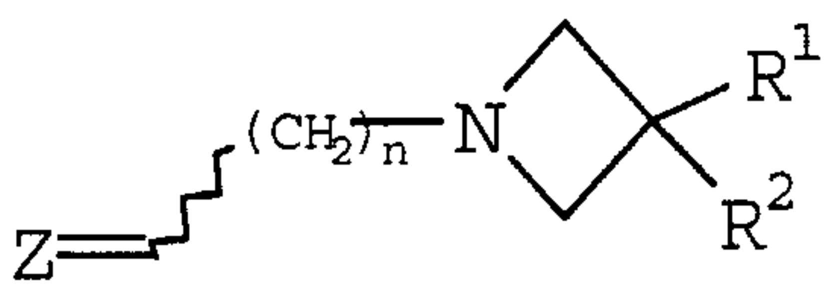

(VIIb)

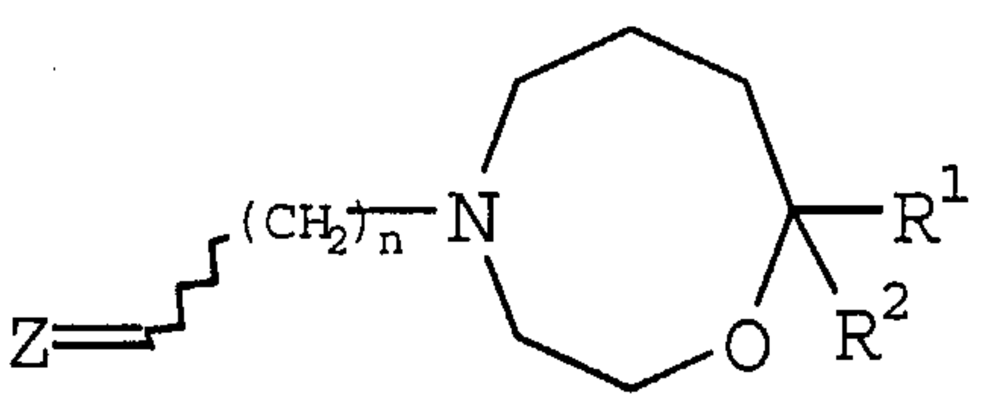

(VIIc)

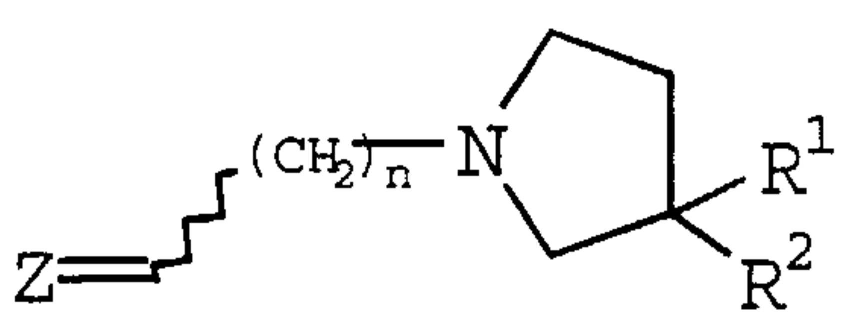

(VIId)

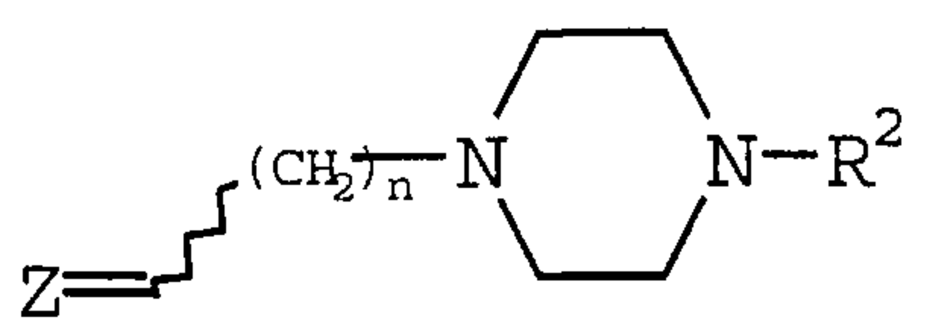

(VIIe)


(VIIf)

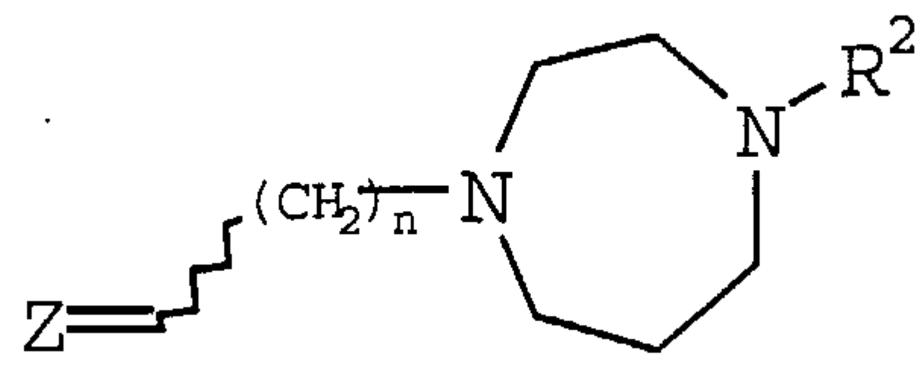

(VIIg)


(VIIh)


(VIIi)



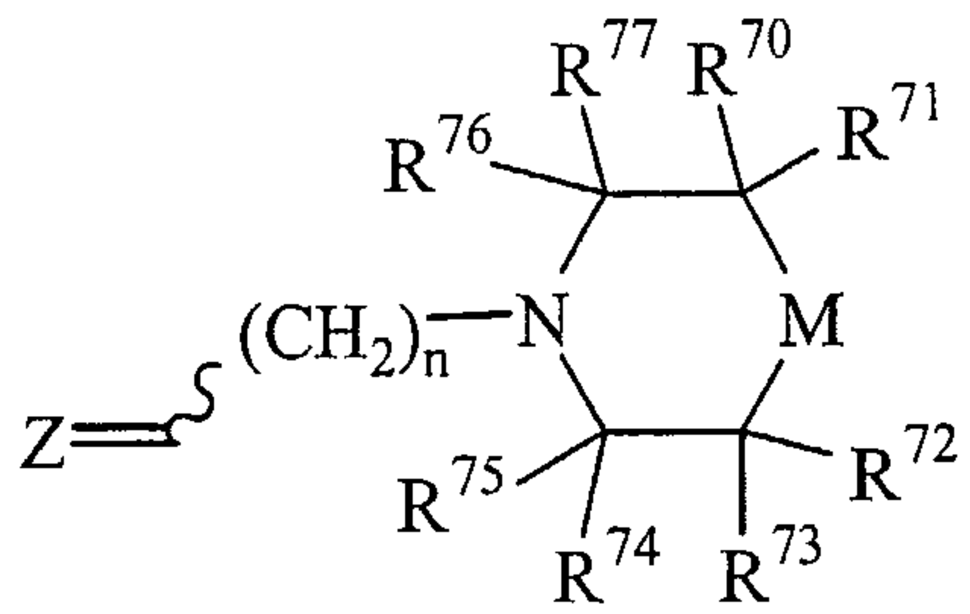
(VIIj)



(VIIk)

and physiologically acceptable salts thereof, wherein Z, n and M are as described in Structural Formula (VII), and the ring which contains M is substituted or unsubstituted. The ring containing M can have one or more suitable substituents which are the same or different. Suitable substituents for the ring which contains M and other nonaromatic heterocyclic rings are as described herein. For example, the ring containing M can be substituted with a methyl, ethyl, propyl, butyl or oxo group.

When the ring containing M is substituted, the compound can be represented by Sturctural Formula (VIIl):



(VIIl)

or physiologically acceptable salt thereof.

R^{70}, R^{71}, R^{72}, R^{73}, R^{74}, R^{75}, R^{76} and R^{77} are independently -H, -OH, $-N_3$, a halogen, an aliphatic group, a substituted aliphatic group, an aminoalkyl 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), -COOH, -CN, $-CO-NR^3R^4$, $-NR^3R^4$, an acyl group, a substituted acyl group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group, -O-(substituted or unsubstituted aromatic group), or any two of R^{70}, R^{71}, R^{72}, R^{73}, R^{74}, R^{75}, R^{76} and R^{77} taken together with the atoms to which they are bonded form a three to eight membered ring.

n is as described in Structural Formula (I). Z is as described herein, preferably as described in Structural Formula (V) or (VI). M is as described in Structural Formula (VII). Preferably, M is $>NR^2$ or $>CR^1R^2$.

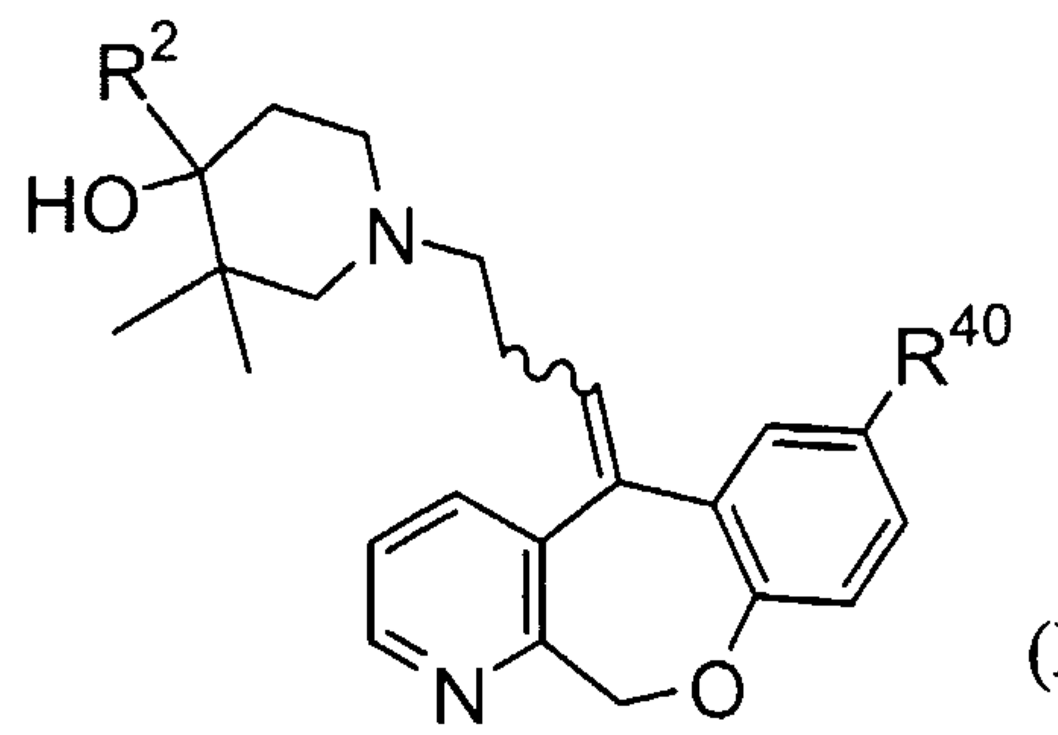
In certain embodiments R^{74}, R^{75}, R^{76} and R^{77} are -H. In other embodiments, R^{74}, R^{75}, R^{76} and R^{77} are -H, and at least one of R^{70}, R^{71}, R^{72} and R^{73} is an aliphatic group or a substituted aliphatic group. Preferred aliphatic groups at R^{70}, R^{71}, R^{72}, R^{73}, R^{74}, R^{75}, R^{76} and R^{77} are C_1-C_6 alkyl, preferred substitued aliphatic groups are are C_1-C_6 alkyl substituted with -OH, $-(O)_u-(CH_2)_t-C(O)OR_{20}$ or -O-(aliphatic group) wherein t is zero to three, u is zero or one, and R^{20} is C_1-C_6 alkyl. In more particular embodiments, the compound has the formula of Structural Formula VIII wherein R^{70}, R^{73}, R^{74}, R^{75}, R^{76} and R^{77} are -H, and at least one of R^{71} and R^{72} is $-CH_3$.

In a preferred embodiment, the chemokine receptor antagonist is represented by Structural Formula VIII wherein n is two; M is $>C(OH)R^2$; R^2 is a halophenyl group (*e.g.*, 4-chlorophenyl);

R^{72}, R^{73}, R^{74}, R^{75}, R^{76} and R^{77} are -H and R^{70} and R^{71} are independently C_1-C_6 alkyl or substituted C_1-C_6 alkyl; or R^{70}, R^{71}, R^{74}, R^{75}, R^{76} and R^{77} are -H and R^{72} and R^{73} are independently C_1-C_6 alkyl or substituted C_1-C_6 alkyl; and

Z is represented by Structural Formula (VI) wherein X_1 is $-CH_2-O-$.

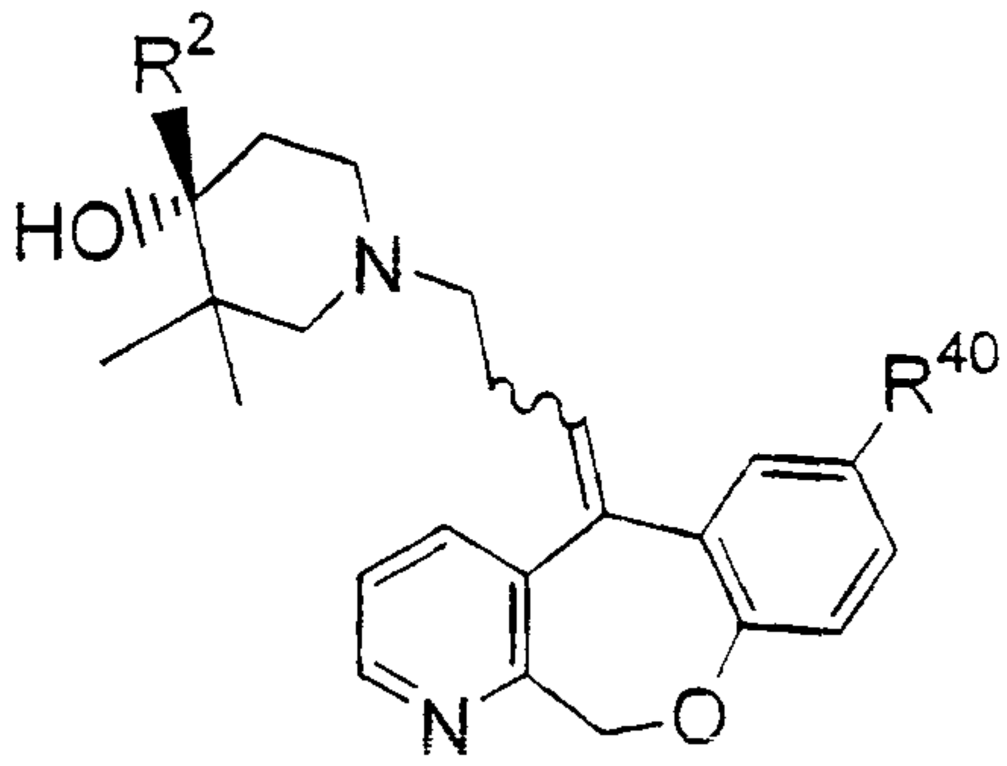
When R^{72} and R^{73} are each $-CH_3$, the compounds of this preferred embodiment can have the formula:



(XII)

or a physiologically acceptable salt thereof, wherein R^2 is 4-halophenyl. Preferably R^2 is selected from the group consisting of 4-chlorophenyl, 4-bromophenyl and 4-fluorophenyl. Preferred groups at R^{40} are as described herein. Particularly preferred at R^{40} are aliphatic groups (*e.g.*, C_1-C_6 alkyl) and substituted aliphatic groups.

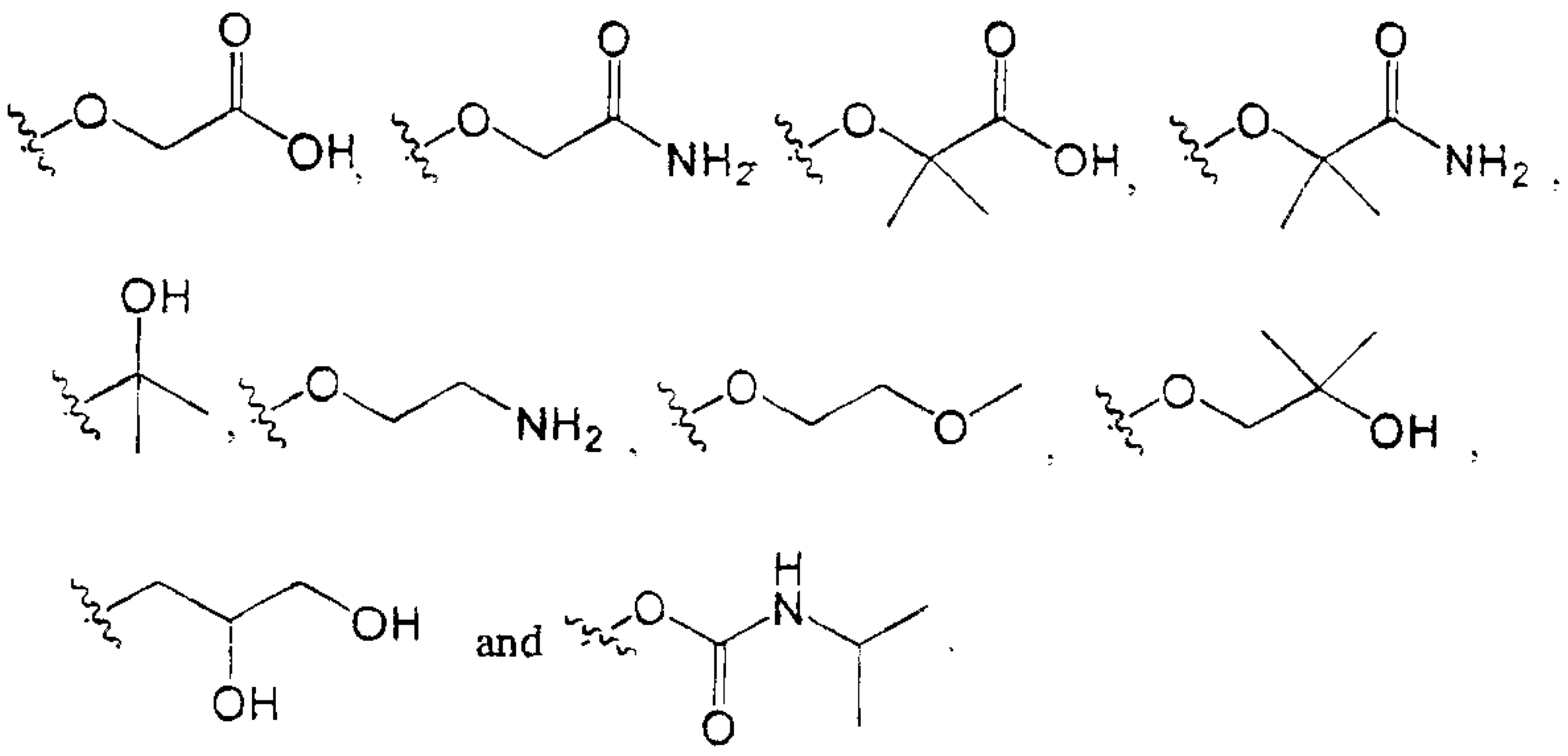
In a particularly preferred embodiment, the compound is the (*S*)-enantiomer of the compound of Formula (XII) and has the structure:



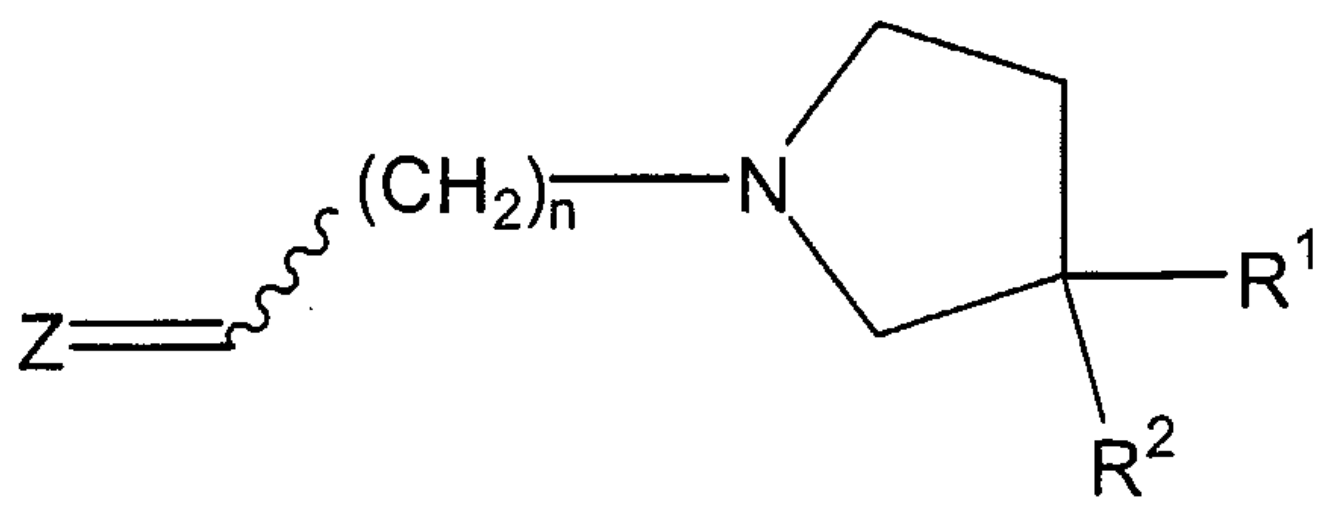
(XIII)

or a physiologically acceptable salt thereof, wherein R^2 is 4-halophenyl.

Particularly preferred compounds of the invention have the structure of Formula XIII wherein R^2 is 4-chlorophenyl and R^{40} is selected from the group consisting of:

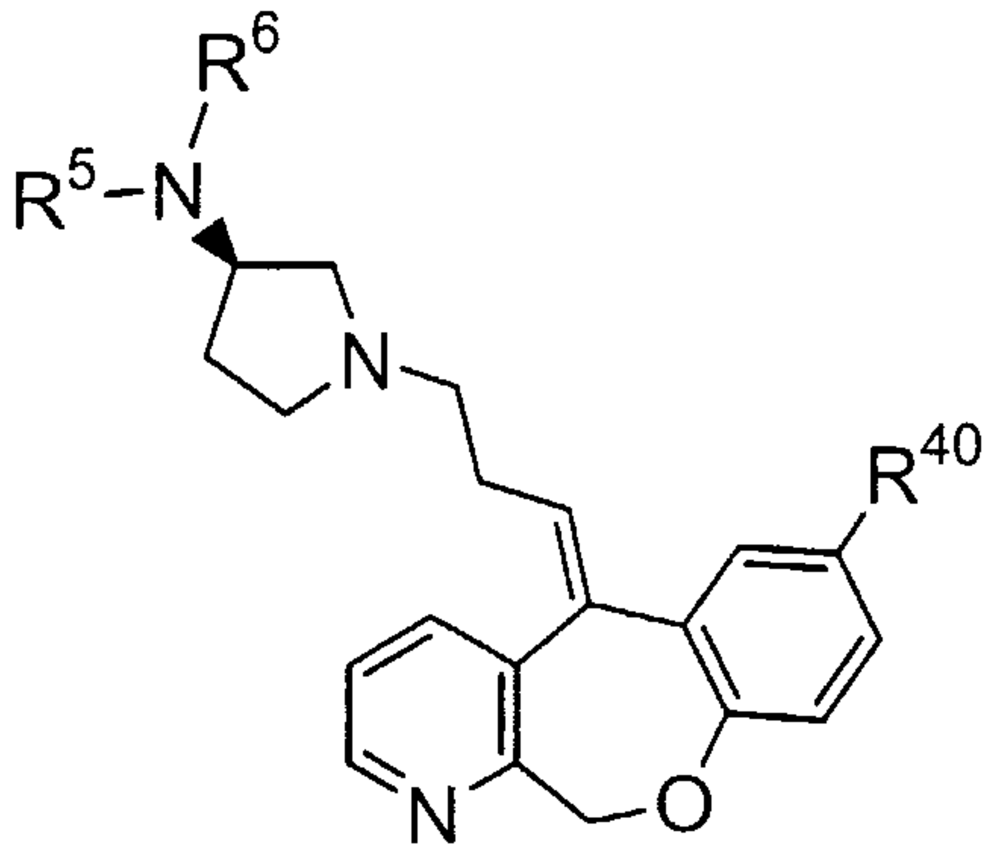


In another embodiment, the compound is represented by Structural Formula VIIi:



or a physiologically acceptable salt thereof, wherein n, R^1 and R^2 are as described in Structural Formula (I), and Z is as described in Structural Formula (V) or (VI).

In a certain embodiments, Z is represented by Structural Formula (VI) wherein X_1 is $-CH_2-O-$; n is two, R^1 is -H and R^2 is $-NR^5R^6$. Preferably, compounds of these embodiments have the structure:



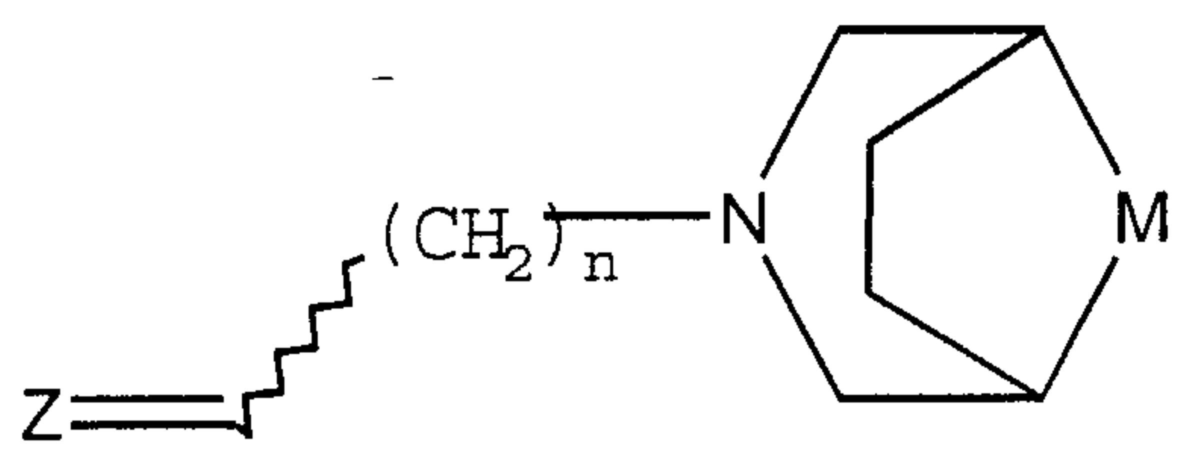
or a physiologically acceptable salt thereof, wherein R^5 and R^6 are as described in Structural Formula I, and preferred groups at R^{40} are as described herein.

In particular embodiments, R^5 is aliphatic group (*e.g.*, C_1-C_6 alkyl) or substituted aliphatic group, and R^6 is benzyl or substituted benzyl; 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. In more particular embodiments, R^5 is C_1-C_6 alkyl and R^6 is halo-substituted benzyl. In a preferred embodiment, R^5 is ethyl and R^6 is chloro-substituted benzyl (*e.g.*, 4-chlorobenzyl).

The nitrogen atom in the ring containing M can be a tertiary nitrogen as depicted in Structural Formula (IV), or the nitrogen atom can be quaternized with a suitable substituent, such as a C_1 to about C_6 or a C_1 to about C_3 substituted or unsubstituted aliphatic group. Compounds which comprise a quaternary nitrogen atom can also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like.

The antagonist of chemokine function can be represented by Structural Formula (VII) wherein the heterocyclic ring containing M is substituted with a suitable bivalent group which is bonded to two atoms that are in the ring, thereby forming a bicyclic moiety. Suitable bivalent groups include, for example, substituted or unsubstituted bivalent aliphatic groups, such as a C_1-C_6 alkylene group.

The antagonist of chemokine receptor function can comprise a variety of bicyclic moieties. In one embodiment, the antagonist of chemokine receptor function can be represented by Structural Formula (VIII):

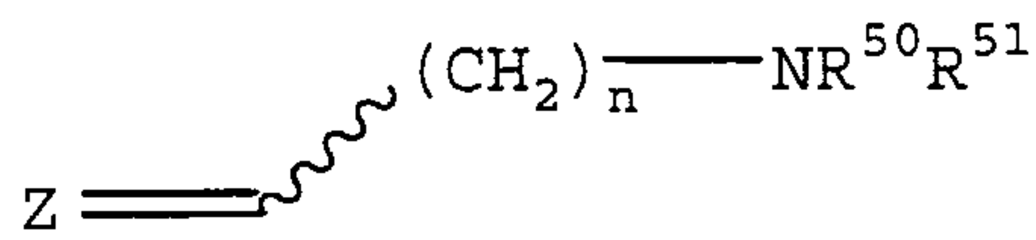


(VIII)

and physiologically acceptable salts thereof.

M is $>NR^2$, $>CR^1R^2$, $-O-CR^1R^2-O-$ or $-CH_2-CR^1R^2-O-$. Preferably, M is $>NR^2$ or $>CR^1R^2$. R^1 and R^2 are as described in Structural Formula (I), and n and Z are as described in structural Formula (VII).

In another embodiment, the antagonist of chemokine receptor function is represented by Structural Formula (IX):



(IX)

and physiologically acceptable salts thereof.

Z is as described herein, preferably as described in Structural Formula (V) or (VI).

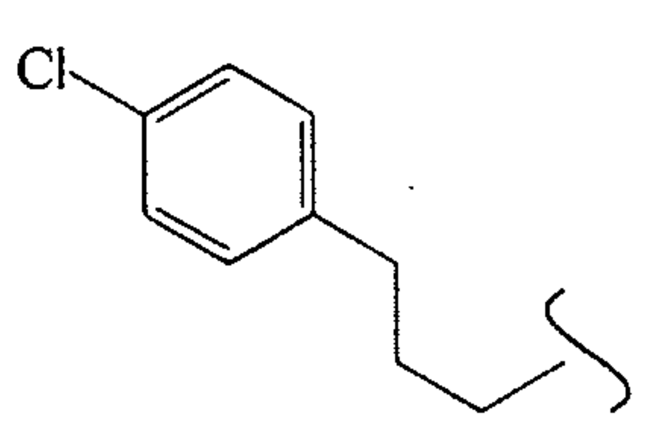
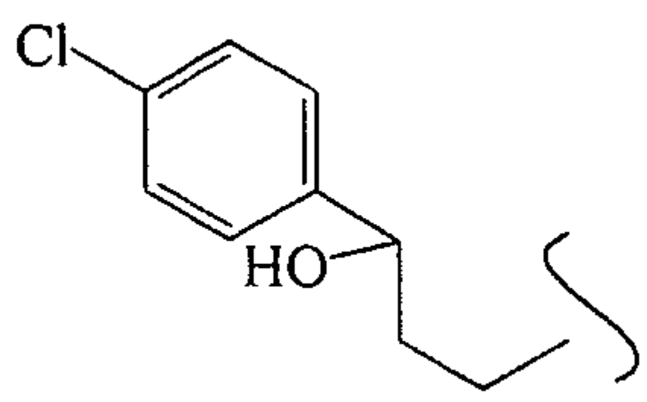
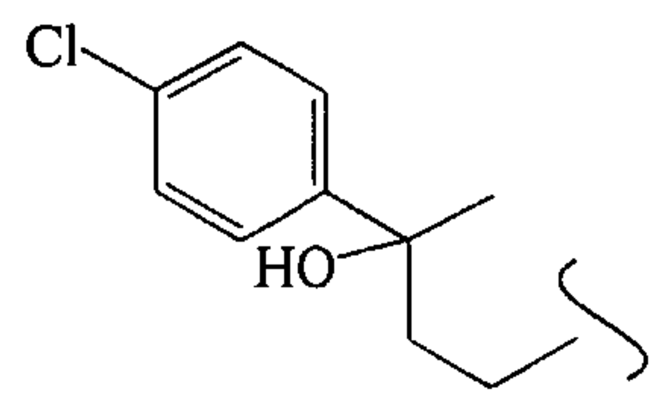
n is an integer, such as an integer from one to about four. Preferably, n is one, two or three. More preferably n is two. In alternative embodiments, other aliphatic or aromatic spacer groups (L) can be employed for $(CH_2)_n$.

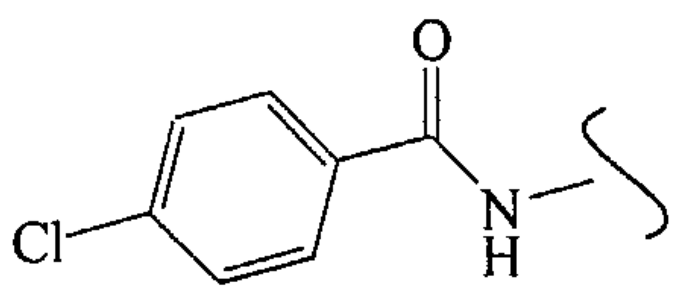
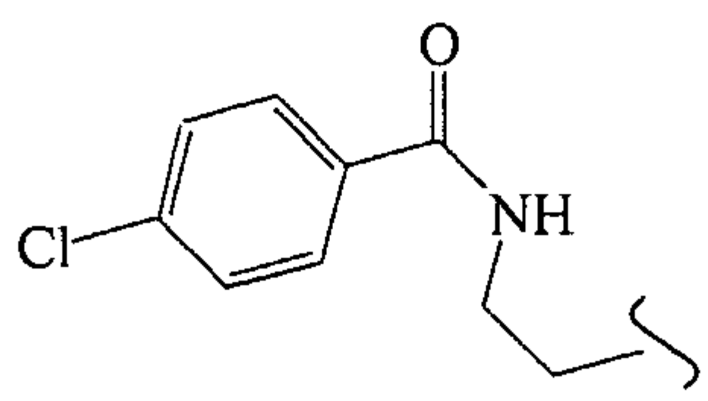
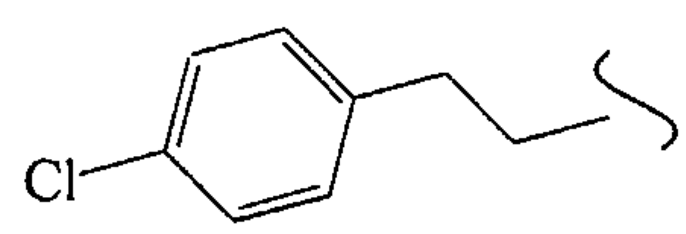
R^{50} and R^{51} are each independently -H, an aliphatic group, a substituted aliphatic group, an aminoalkyl group, $-NR^3R^4$, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group or a covalent bond between the nitrogen atom an adjacent carbon atom.

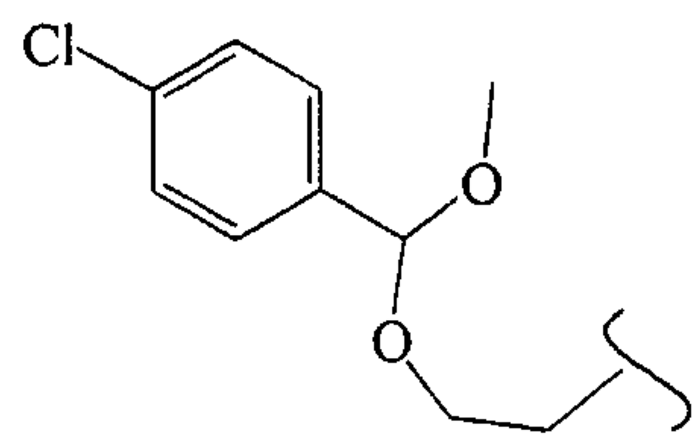
R^3 and R^4 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group.

R^3 and R^4 taken together with the atom to which they are bonded, can alternatively form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

In a preferred embodiment R^{50} is a substituted aliphatic group, such as a substituted C_1 to about C_{12} alkyl group, and R^{51} is -H or a substituted or unsubstituted aliphatic group. More preferably, R^{50} is a substituted linear or branched C_2 to about C_7 aliphatic group wherein one or more carbon atoms can be replaced by a heteroatom, such as nitrogen, oxygen or sulfur, and R^{51} is -H or a linear or branched C_1 to about C_6 or a C_1 to about C_3 aliphatic group wherein one or more carbon atoms can be replaced by a heteroatom. R^{50} and R^{51} can be substituted with one or more suitable substituents, as described herein, preferably an aromatic group (e.g., phenyl, 4-halophenyl). For example, R^{50} can be selected from the group consisting of:

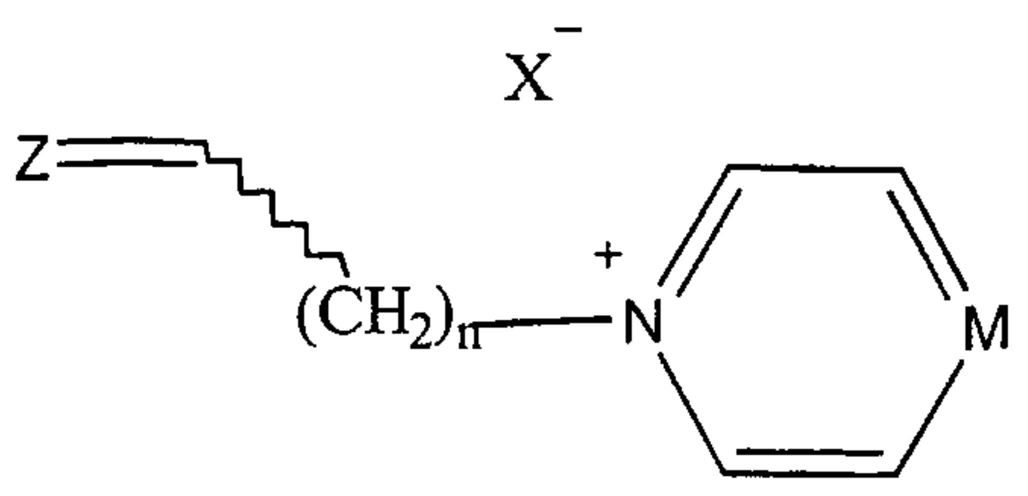
 ,  ,  ,

 ,  ,  and

 .

The activity of chemokine receptor antagonists represented by Structural Formula IX can be affected by the character of the nitrogen atom to which R^{50} and R^{51} are bonded. It is believed that compounds in which said nitrogen atom is basic can have potent chemokine receptor antagonist activity. It is known that the basicity of a nitrogen atom can be decreased when the nitrogen atom is bonded to a carbonyl group, sulfonyl group or a sulfinyl group. Therefore, it is preferred that neither R^{50} nor R^{51} comprise a carbonyl group, sulfonyl group or sulfinyl group that is directly bonded to the nitrogen atom.

In another aspect, the antagonist of chemokine receptor function is represented by Structural Formula (X):



(X)

and physiologically acceptable salts thereof.

Z is a cycloalkyl or non-aromatic heterocyclic ring group fused to one, two or more aromatic rings, wherein each ring in Z is independently substituted or unsubstituted. Preferably, Z is as described in Structural Formula (VI).

n is an integer, such as an integer from one to about four. Preferably, n is one, two or three. More preferably n is two. In alternative embodiments, other aliphatic or aromatic spacer groups (L) can be employed for $(CH_2)_n$.

M is $>NR^2$ or $>CR^2$.

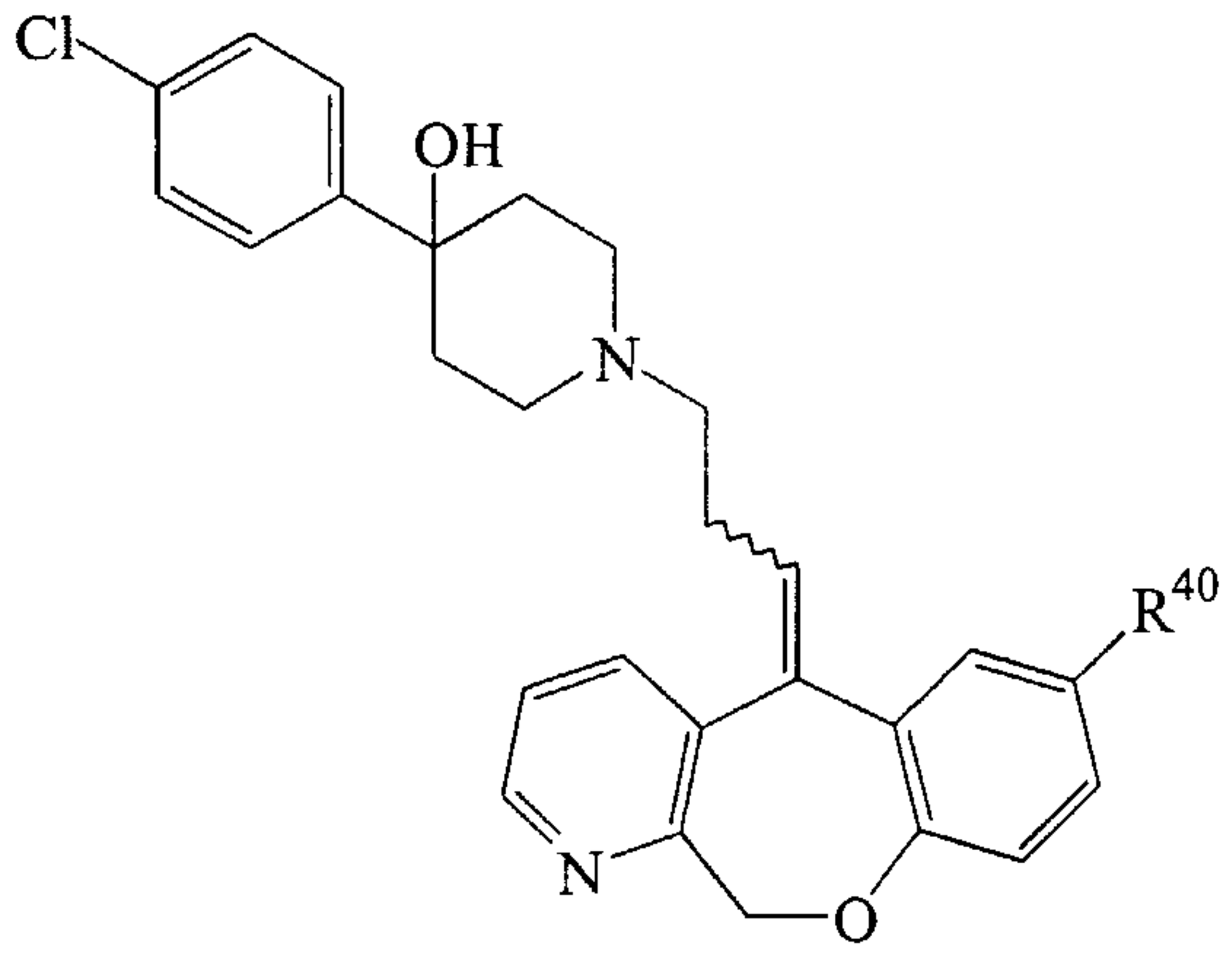
R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group, -O-(substituted or unsubstituted aromatic group) or -O-(substituted or unsubstituted aliphatic group). R^2 is preferably an aromatic group or a substituted aromatic group.

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.

R^5 and R^6 taken together with the atom to which they are bonded, can alternatively form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

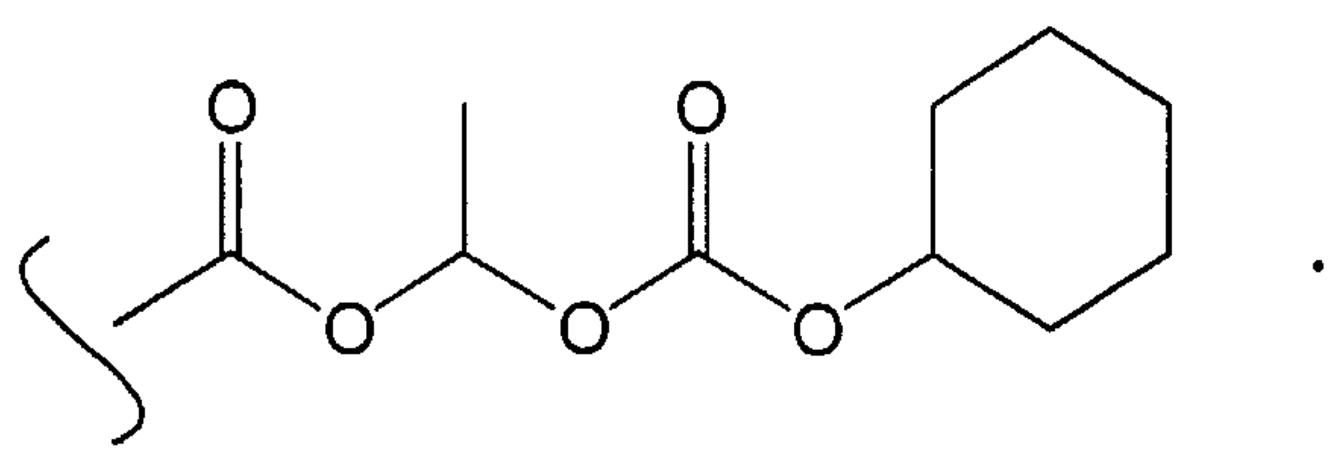
X^- is a physiologically acceptable anion. Preferably, X^- is Cl^- or Br^-.

The chemokine receptor antagonist described herein can be prepared and administered as active compounds or as prodrugs. Generally, prodrugs are analogues of pharmaceutical agents which can undergo chemical conversion by metabolic processes to become fully active. For example, A prodrug of the invention can be prepared by selecting appropriate groups for R^{40}. In one embodiment, a prodrug can be represented by Structural Formula (XI):



(XI)

wherein, R^{40} is Q-substituted aliphatic group, and the aliphatic group is substituted with $-(O)_u-(CH_2)_t-C(O)OR^{20}$, wherein Q is -C(O)O-, u is one, t is zero and R^{20} is a cyclic aliphatic group. For example, when the substituted aliphatic group is a substituted ethyl group, R^{40} can be represented by:



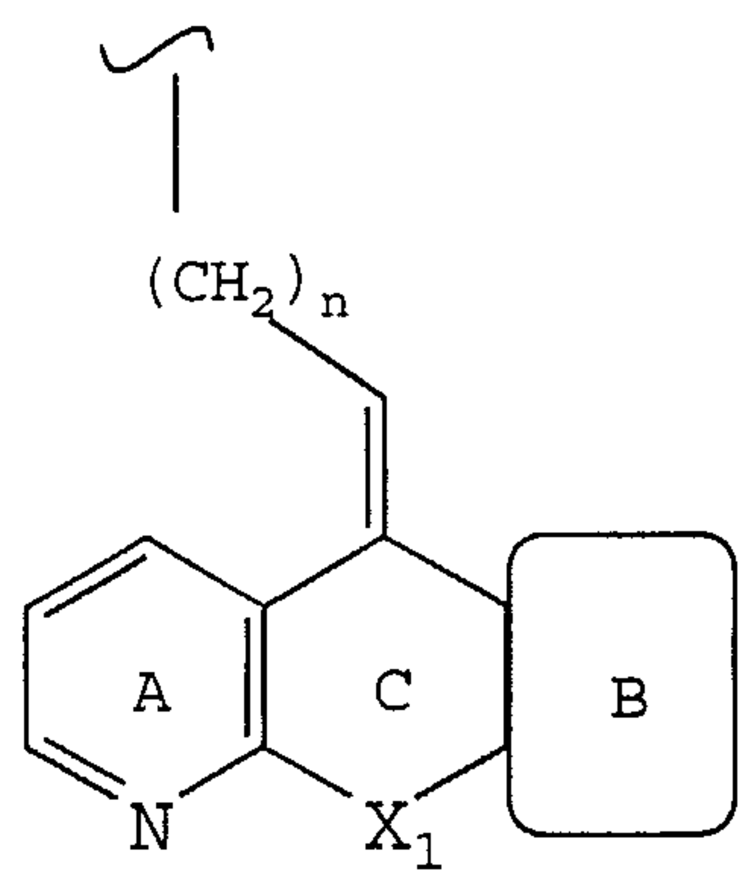
Such a prodrug can be converted to an active chemokine receptor antagonist represented by Structural Formula XI, wherein R^{40} is -COOH.

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

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:



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.

Additionally, certain compounds of the invention may be obtained as different stereoisomers (e.g., diastereomers and enantiomers). The compounds of the invention can be prepared as racemates or as substantially pure stereoisomers. The stereoisomers of the invention (e.g., (*S*)- and (*R*)-enantiomers) can be prepared using any suitable method. For example, the enantiomers can be resolved from the racemate using chiral chromatography or recrystallization. Preferably, the stereoisomers (e.g., (*S*)- and/or (*R*)-enantiomers) are prepared by stereospecific synthesis as described herein.

The optical configuration of the stereoisomers of the invention are assigned using the (*R*),(*S*) method of Cahn-Ingold-Prelog. (See, J. March, "Advanced Organic Chemistry," 4th Edition, Wiley Interscience, New York, pp.109-111 (1992).)

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. Sterioisomers can be separated and isolated using any suitable method, such as chromatography. Again, it is understood that one sterioisomer may be more active than another. The desired isomer determined by screening.

Also included in the present invention are physiologically acceptable salts of the compounds represented by Structural Formulas (I) through (XIII). 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. (See, for example, Berge S.M. *et al.*, "Pharmaceutical Salts," *J. Pharma. Sci.*, 66:1 (1977).)

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. Preferred aliphatic groups are C_1 to about C_{10} hydrocarbons.

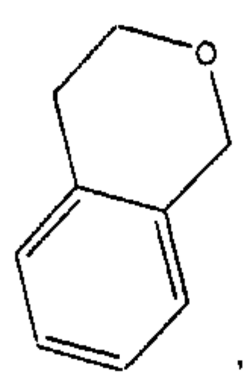
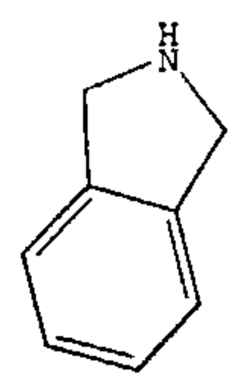
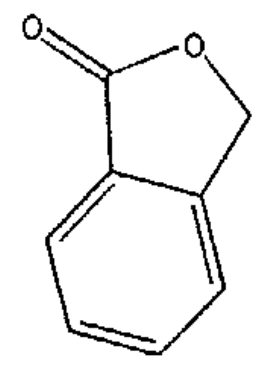
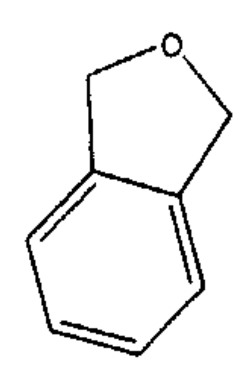
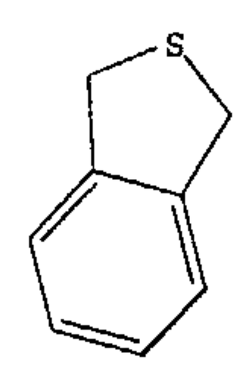
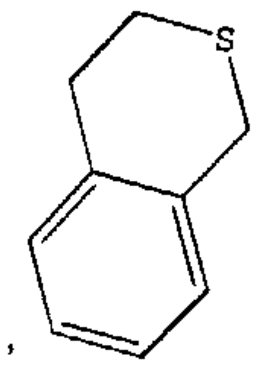
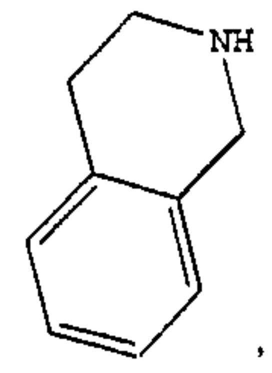
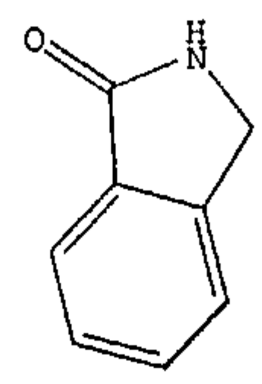
More preferred are C_1 to about C_6 or C_1 to about C_3 hydrocarbons. One or more carbon atoms in an aliphatic group can be replaced with a heteroatom, such as nitrogen, oxygen or sulfur. For example, suitable aliphatic groups include substituted or unsubstituted linear, branched or cyclic C_1-C_{20} alkyl, alkenyl or alkynyl groups.

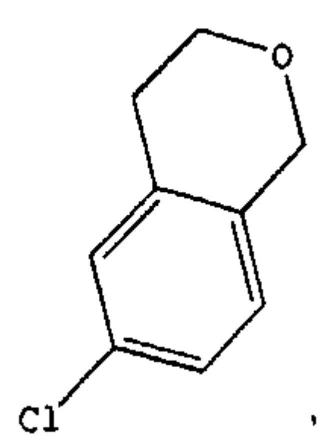
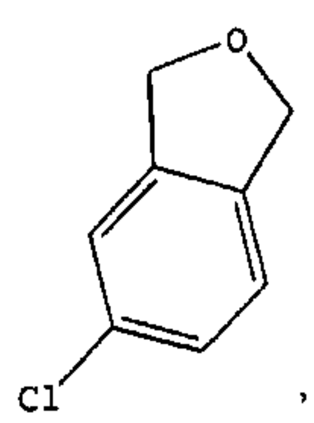
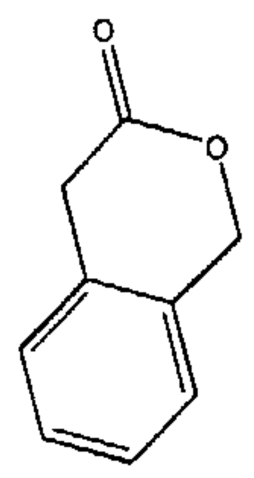
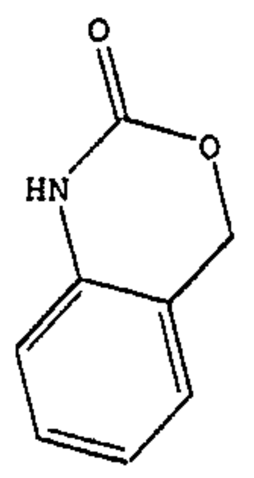
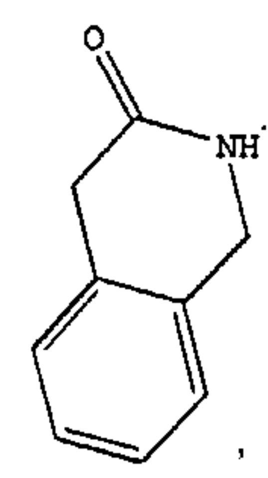
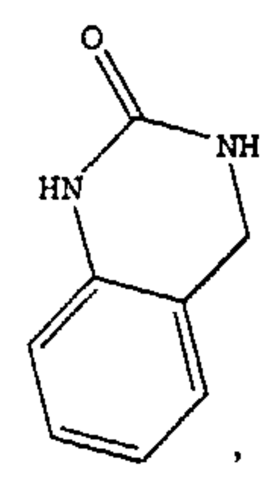
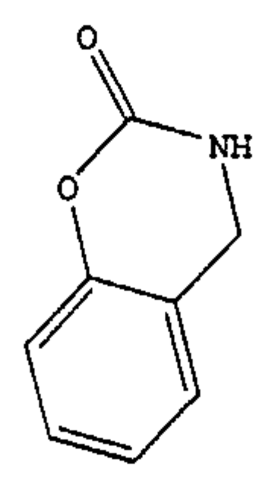
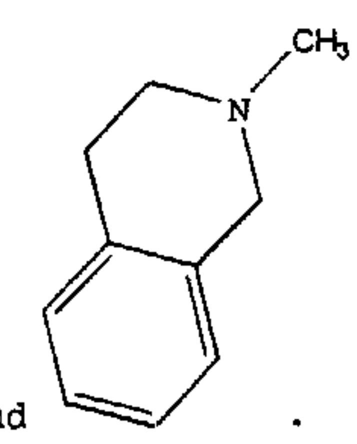
An aminoalkyl group is an alkyl group substituted with $-NR^{24}R^{25}$, R^{24} and R^{25} are as described herein. Preferably the alkyl moiety comprises one to about twelve, more preferably one to about six carbon atoms. The alkyl moiety of an aminoalkyl group can be unsubstituted or substituted as described herein for aliphatic groups. Examples of suitable aminoalkyl groups include aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, dimethylaminoethyl, diethylaminomethyl, methylaminohexyl, aminoethylenyl and the like.

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.

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-quinolinyl, 3-quinolinyl, 2-benzothiazolyl, 2-benzooxazolyl, 2-benzimidazolyl, 1-isoquinolinyl, 3-quinolinyl, 1-isoindolyl, 3-isoindolyl, acridinyl, 3-benzisoxazolyl, and the like. 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.

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 1,3-dioxolan-2-yl, 3-1H-benzimidazol-2-one, 3-1-alkyl-benzimidazol-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-thiomorpholino, 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, benzoxane, benzopyrolidine, benzopiperidine, benzoxolane, benzothiolane, benzothiane, tetrahydrofuran-2-one-3-yl, 2,5-dihydro-5-oxo-4H-1,2,4-thiadiazol-3-yl, 2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl,

, , , , , , , ,

, , , , , ,  and .

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 (chloride, bromide, fluoride, iodide), 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,

$-S(O)_2NH_2$, guanidino, ureido, oxalo, amidino, $-C(=NR^{60})NR^{21}R^{22}$,$=NR^{60}$, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$, -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).

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) and wherein R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

R^{60} is a -H, -OH, $-NH_2$, an aromatic group or a substituted aromatic group..

t is an integer from zero to about three, and the methylene group, $-(CH_2)_t-$, can be substituted, as described herein for aliphatic groups, or unsubstituted.

u is zero or one.

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, non-aromatic heterocyclic group or R^{24} and R^{25} taken together with the nitrogen atom to which they are bonded can form a substituted or unsubstituted non-aromatic heterocyclic ring.

A substituted non-aromatic heterocyclic ring, benzyl group or aromatic group can also have an aromatic group, an aliphatic or substituted aliphatic group, as a substituent. When a non-aromatic ring (carbocyclic or heterocyclic) or an aromatic ring (carbocyclic aromatic or heteroaryl) is substituted with another ring, the two rings can be fused. 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, which can be the same or different.

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. 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), (III) and (IV) 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).

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).

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.

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. 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), hormones (*e.g.*, adrenocorticotropic hormone (ACTH)), cytokines (*e.g.*, interferons (*e.g.*, IFNβ-1a, IFNβ-1b)) and the like.

The compound can be administered by any suitable route, including, for example, orally in capsules, suspensions or tablets or by parenteral administration. Parenteral 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.

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. 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 Publishing 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).

The quantity of active ingredient (one or more compounds of the invention) in the composition can range from about 0.1% to about 99.9% by weight. Preferably the quantity of active ingredient is about 10% to about 90%, or about 20% to about 80% by weight. A unit dose preparation can contain from 1 mg to about 1000 mg active ingredient, preferably about 10 mg to about 100 mg active ingredient. The composition can, if desired, also contain other compatible therapeutic agents, such as theophylline, β-adrenergic bronchodilators, corticosteroids, antihistamines, antiallergic agents, immunosuppressive agents (*e.g.*, cyclosporin A, FK-506, prednisone, methylprednisolone), hormones (*e.g.*, adrenocorticotropic hormone (ACTH)), cytokines (*e.g.*, interferons (*e.g.*, IFNβ-1a, IFNβ-1b)) and the like.

In one embodiment, the pharmaceutical composition comprises the (*S*)-enantiomer of a compound of the invention (*e.g.*, a compound of Structural Formula (XIII)) and a physiologically acceptable carrier or excipient. For example, in one embodiment, the composition comprises *(S)*-4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene]-propyl}-3,3-dimethyl-piperidin-4-ol and a physiologically acceptable carrier or excipient. In certain embodiments, the pharmaceutical composition comprises the (*S*)-enantiomer of a compound of the invention (*e.g.*, a compound of Structural Formula (XIII)) and is substantially free of the corresponding (*R*)-enantiomer (contains at least about 98% or at least about 99% enantiomeric excess of (*S*)-

enantiomer). In another embodiments, the composition comprises the (*S*)-enantiomer of a compound of the invention (e.g., a compound of Structural Formula (XII)), the corresponding (R)-enantiomer and a physiologically acceptable carrier or excipient. In a more particular embodiment, the composition comprises a racemic compound of Structural Formula (XII), for example, racemic-4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene]-propyl}-3,3-dimethyl-piperidin-4-ol In other embodiments, the ratio (*S*)-enantiomer:(*R*)-enantiomer (w/w) in the compositions is at least about 2:1 or about 5:1 or about 10:1 or about 20:1 or about 50:1.

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. 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.

The compounds disclosed herein can be prepared accordingly to the schemes shown in Figures 1 - 5 and 7. The schemes are described in greater detail below.

Figure 1 shows the preparation of compounds represented by Structural Formula (I). 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.

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.

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. 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.

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.

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.

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.

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.

Figure 4 shows the preparation of compounds represented by Structural Formula (I), where in Z is represented by Structural Formulas (III) and 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.

Figure 5 is a schematic showing the preparation of the compounds represented by Structural Formula (I), wherein Z is represented by Structural Formulas (III) 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 dioxane 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.

Figure 7 shows the preparation of compounds represented by Structural Formula (I), wherein Z is represented by Structural Formulas (III) and wherein Ring A or Ring B in Z is substituted with R^{40}. L^4 is a suitable leaving group such as halogen or trifluoromethylsulfonate. 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.

Figure 10C shows three procedures for the preparation of compounds represented by Structural Formulas (I),(VII), (VIII) and (IX), wherein Z is represented by Structural Formula (III) and wherein Ring A or Ring B in Z is substituted with $R^{40.}$ In Figure 10C, R^{40} is represented by $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, u is one, t is zero. In Figure 10C a compound containing a phenol can be reacted with a carbonate equivalent, such as a carbamoyl chloride (method A), an isocyanate (method B) or an acylimidazole (method C), in the presence of a base such as sodium hydroxide, potassium carbonate or sodium carbonate in a solvent such as dimethylformamide or tetrahydrofuran, at a temperature from 0°C to reflux temperature for a period of about 5 minutes to about 72 hours.

Compounds represented by Structural Formula (I), wherein Z is represented by Structural Formulas (III) or (IV), 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.

Figure 12 shows the preparation of compounds of formula (VI-c). The Friedel-Crafts acylation can be carried out using an acid chloride in the presence of a Lewis acid, such as aluminum trichloride or titanium tetrachloride, in a solvent such as dichloromethane, dichloroethane, nitrobenzene or carbon disulfide. The acylation reaction can be run at a temperature of about room temperature up to the reflux temperature of the chosen solvent, and for a period of about 5 minutes to about 72 hours.

Figure 13 shows the preparation of compounds of formula (VI-e). In Step 1 of Figure 13, a chlorosulfonylation can be carried out using chlorosulfonic acid in a solvent, such as dichloromethane, or in the absence of a solvent at a temperature of about 0°C to about 60°C for a period of about 5 minutes to about 72 hours. In Step 2 of Figure 12, a coupling reaction can be carried out using an amine in the presence of a base, such as triethylamine, in a solvent such as dichloromethane, acetone, ethanol, THF or DMF. The reaction can be carried out at a temperature of about room temperature up to the reflux temperature of the selected solvent, and for a period of about 5 minutes to about 72 hours.

Although Figures 1 - 5, 7, 12 and 13 show the preparation of compounds in which Rings A and B are phenyl rings, analogous compounds with heteroaryl groups for Rings A and B can be prepared by using starting materials with heteroaryl groups in the corresponding positions. 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.

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

EXEMPLIFICATION

Example 1: 4-(4-Chlorophenyl)-1-[3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)propyl]piperidin-4-ol

To a solution of 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (200mg) in DMF (10ml) were added 4-(4- chlorophenyl)-4-hydroxypiperidine (230mg), potassium carbonate (360mg), and potassium iodide (50mg). The mixture was stirred at 70°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. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:1) to give the titled compound (250mg). ^{1}H-NMR ($CDCl_3$) d: 1.65-2.11(5H,m), 2.32-3.10(8H,m), 3.22-3.67(4H,m), 5.87(1H,t), 7.03-7.44(12H,m). MS m/z: 444(M+1).

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

The titled compound was prepared by following the procedure of Example 1, but replacing 5-(3- bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-6,11-dihydrodibenz[b,e] oxepine. ^{1}H-NMR ($CDCl_3$) d: 1.61-2.16(5H,m), 2.37-2.80(8H,m), 5.22(2H,brs), 5.70(0.6x1H,t), 6.03(0.4x1H,t), 6.73-6.90(2H,m), 7.09-7.45(10H,m). MS m/z: 446(M+1)

Example 3: Membrane Preparations for Chemokine Binding and Binding Assays

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, 1μg/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.

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.

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	IC50 (μM)	Example	IC50 (μM)	Example	IC50 (μM)	Example	IC50 (μM)
1	<1	38	<1	63	<10	114	<1
2	<1	39	<10	64	<1	117	<1
8	<1	40	<1	65	<1	118	<1
12	<1	41	<1	66	<1000	120	<1
17	<10	42	<1	67	<1	122	<1
18	<1	43	<10	68	<10	123	<1
19	<1	44	<1	69	<1	128	<1
21	<1	45	<1	71	<1	130	<1
22	<1	46	<1	72	<10	131	<1
23	<1	47	<1	73	<10	132	<1
24	<10	48	<1	74	<1000	133	<1
25	<1	49	<1	75	<10	134	<1
26	<1	51	<1	76	<10	135	<1
27	<1	52	<1	77	<1	138	<1
28	<1	53	<1	78	<1	139	<1
29	<1	54	<1	79	<1	140	>10
30	<1	55	<1	83	<1000	141	<1
31	<1	56	<1	85	<1	142	<10
32	<1	57	<10	86	>10	143	<1
33	<1	59	<1	89	>10	144	<1
34	<1	60	<1	90	<1	145	10
35	<1	61	<10	91	<1	146	>10
36	<1	62	<10	111	<1		

Table

Example	IC50 (μM)	Example	IC50 (μM)	Example	IC50 (μM)	Example	IC50 (μM)
147	<10	180	<1	212	<1	282	<1
148	<10	181	<1	215	<1	283	<1
149	<1000	182	<1	216	<1	284	<1
150	<10	183	<1	218	<1	285	<1
151	<1	184	<10	242	<1	286	<1
152	<1	185	<1000	248	10	287	<1
153	<1	186	<1	249	<1	288	<1
154	<1	187	<1	262	<1	289	<1
155	<1	188	>10	263	<1	290	<1
158	<1	190	>10	264	<1	291	<1
159	<1	191	>10	265	<1	292	<1
160	<1	192	>10	266	<1	306	<1
161	<10	193	<1	267	<1	422	<1
162	<1	194	<1	268	<1	423	<1
163	<1	195	<10	269	<1	424	<1
166	<10	197	<1	270	<1	425	<1
167	>1	198	<1	271	<1	426	<1
168	1	199	<1	272	<1	427	<1
172	<1	200	<1	273	<1	428	<1
173	<1	201	<1	277	<1	429	<1
174	<1	203	<1	278	<1	430	<1
175	<1	204	<1	279	<1	431	<1
176	<1	205	<1	280	<1	432	<1
178	<1	211	<1	281	<1		

Table

Example	IC50 (μM)	Example	IC50 (μM)	Example	IC50 (μM)	Example	IC50 (μM)
456	<1	479	<1	502	<1	525	<20
457	<1	480	<1	503	<1	526	<1
458	<10	481	<1	504	<1	527	<1
459	<10	482	<1	505	<1	528	<10
460	<1	483-1	<1	506	<1	529	<20
		483-2	<10				
461	<10	484	<1	507	<1	530	<20
462	<10	485	<1	508	<1	531	<1
463	<10	486	<1	509	<1	532	<2
464	<1	487	<1	510	<1	533	<10
465	<1	488	<1	511	<1	534	<1
466	<50	489	<10	512	<1	535	<10
467	<1	490	<1	513	<1	536	<1
468	<1	491	<1	514	<1	537	<1
469	<1	492	<10	515	<1	538	<10
470	<1	493	<10	516	<1	539	<10
471	<1	494	<1	517	<1	540	<10
472	<1	495	<1	518	<1	541	<10
473	<1	496	<10	519	<1	542	<10
474	<1	497	<10	520	<1	543	<10
475	<1	498	<10	521	<1	544	<10
476	<1	499	<10	522	<1	545	<10
477	<10	500	<10	523	<1	546	<1
478	<10	501	<10	524	<1	547	<1

Table

Example	IC50 (µM)	Example	IC50 (µM)	Example	IC50 (µM)	Example	IC50 (µM)
548	<10	554	<1	560	<10	566	<20
549	<1	555	<1	561	<10	567	<1
550	<1	556	<1	562	<10	568	<1
551	<1	557	<1	563	<10	569	<1
552	<1	558	<10	564	<10	570	<10
553	<1	559	<1	565	<10	571	<10

Example 8: 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-dibenz[b,e]thiepin-11-ylidene)propyl]piperidin-4-ol

Step 1

11-(3-Bromopropylidene)-6,11-dihydrodibenz[b,e]thiepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one with 6,11-dihydrodibenz[b,e]thiepin-11-one.

^{1}H-NMR ($CDCl_3$) δ: 2.50-2.64(2H,m), 3.36-3.47(3H,m), 4.99(1H,d), 5.94(1H,t), 6.98-7.31(8H,m).

Step 2

The titled compound was prepared by following the procedure of example 45, 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: 1.65-1.80(3H,m), 1.95-2.70(10H,m), 3.35(1H,d), 4.98(1H,d), 5.96(1H,t), 7.09-7.43(12H,m).

MS m/z: 462(M+1)

Example 12: 1-[3-(5-Benzyl-6,11-dihydro-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

To a solution 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol hydrochloride (Example 39)(300mg) in DMF (5ml) were added sodium hydride (60% in oil, 200mg), benzyl bromide (0.15ml) 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 to give the titled compound (180mg).

^{1}H-NMR ($CDCl_3$) δ: 1.62-1.67(2H,m), 1.99-2.20(3H,m), 2.33-2.65(8H,m), 5.10(1H,d), 5.75(1H,d), 5.94(1H,t), 7.11-7.42(16H,m), 7.91(1H,dd).

MS m/z: 549(M+1)

Example 17: 1-[3-(5-Carboxymethyl-6,11-dihydro-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-5-ethoxycarbonylmethyl-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol (Example 18)(1.0g) was solved in 1M hydrogen chloride in diethyl ether and stirred at room temperature for 24 hours. Aqueous sodium hydroxide and ethyl acetate were added to the reaction mixture, the aqueous layer was separated and neutralized with dilute hydrochloric acid. The precipitation was filtered to give the titled compound (250mg).

^{1}H-NMR (DMSO-d_6) δ: 1.44-1.61(2H,m), 2.07-2.17(1H,m), 2.35-3.01(9H,m), 4.28(1H,d), 4.59(1H,d), 5.83(1H,t), 7.18-7.71(12H,m).

MS m/z: 517(M+1)

Example 18: 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-5-ethoxycarbonymetyl-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-5-ethoxycarbonymetyl-6-oxo-5H-dibenz[b,e]azepine.

^{1}H-NMR ($CDCl_3$) δ: 1.30(3H,t), 1.64-1.69(2H,m), 1.97-2.10(3H,m), 2.38-2.71(8H,m), 4.27(2H,q), 4.32(1H,d), 4.84(1H,d), 5.88(1H,t), 7.16-7.45(11H,m), 7.88(1H,dd).
MS m/z: 545(M+1)

Example 19: 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-5-methyl-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H- dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-5-methyl-6-oxo-5H-dibenz[b,e]azepin.
^{1}H-NMR ($CDCl_3$) δ: 1.58-2.06(5H,m), 2.39-2.75(8H,m), 3.53(3H,s), 5.84(1H,t), 7.10-7.44(11H,m), 7.85-7.89(1H,m). MS m/z: 473(M+1).

Example 21: 4-(4-Chlorophenyl)-1-[3-(5H-dibenzo[a,d]cycloheptene-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 5-(3-bromopropylidene)-5H-dibenzo[a,d]cycloheptene.
^{1}H-NMR ($CDCl_3$) δ: 1.58-1.63(2H,m), 2.00-2.05(2H,m), 2.26-2.46(6H,m), 2.62-2.66 (2H,m), 5.55(1H,t), 6.85(2H,s), 7.24-7.40(12H,m).
MS m/z: 442 (M+1).

Example 22: 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-methoxycarbonyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-6,11-dihydro-2-methoxy-carbonyldibenz[b,e]oxepine.
^{1}H-NMR ($CDCl_3$) δ: 1.65-1.70(2H,m), 2.01-2.13(3H,m), 2.41-2.80(7H,m), 3.85(3H, s), 5.40(2H,brs), 5.73(0.6x1H,t), 6.09(0.4x1H,t), 6.76(0.6x1H,d), 6.82(0.4x1H,d),

7.21-7.43(8H,m), 7.73(1H,dd), 7.87(0.6x1H,d), 7.97(0.4x1H,d).
MS m/z: 504 (M+1).

Example 23: 1-[3-(2-Butoxycarbonyl-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-2-butoxy-6,11-dihydrodibenz[b,e]oxepine.
^{1}H-NMR ($CDCl_3$) δ: 0.96(3H,t), 1.53(2H,q), 1.70-1.77(3H,m), 2.02-2.14(3H,m), 2.39-2.78(5H,m), 4.27(2H,t), 5.27(2H,brs), 5.75(0.8x1H,t), 6.10(0.2x1H,t), 6.78(1H,d), 7.27-7.43(8H,m), 7.76(1H,dd), 7.89(0.8x1H,d), 7.98(0.2x1H,d).
MS m/z: 546 (M+1).

Example 24: 1-[3-(2-Carboxyl-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

To a solution of 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-methoxycarbonyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (Example 22)(100mg) in ethanol (3ml) were added 15% sodiun hydroxide aqueous solution (0.6ml) and the mixture was heated to reflux for 12 hours. The solvent was distilled off under reduced pressure. Water and ethyl acetate were added to the reaction mixture, the aqueous layer was separated and neutralized with dilute hydrochloric acid. The precipitation was filtered to give the titled compound (80mg).
^{1}H-NMR (CD_3OD) δ: 1.73-1.79(2H,m), 2.14-2.19(2H,m), 2.80-2.93(3H,m), 3.02-3.11 (3H,m), 3.24-3.29(2H,m), 5.25(2H,brs), 5.61(0.7x1H,t), 6.05(0.3x1H,t), 6.72(1H,d),7.22-7.40(8H,m), 7.52-7.65(1H,m), 7.75(0.7x1H,d), 7.80(0.3x1H,d).
MS m/z: 490 (M+1).

Example 25: 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-dimethylaminocarbonyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-2-dimethylaminocarbonyl-6,11-dihydrodibenz[b,e]oxepine.

^{1}H-NMR ($CDCl_3$) δ: 1.62-1.67(2H,m), 2.00-2.12(2H,m), 2.37-2.47(8H,m), 2.89(6H, s), 5.25(2H,brs), 5.68(0.7x1H,t), 6.03 (0.3x1H,t), 6.71(0.3x1H,d), 6.78(0.7x1H,d), 7.13-7.40 (10H,m).

MS m/z: 517 (M+1).

Example 26: 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-hydroxymethyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

To a solution of (4-chlorophenyl)-1-[3-(6,11-dihydromethoxycarbonyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (110mg) in THF (8ml) were added lithium aluminum hydride (1.0M, 0.42ml) dropwise at 0 °C, and the mixture was stirred at room temperature for 1 hour. Aqueous sodium hydroxide (1M) was added to the reaction mixture to stir for 30 minutes, then ethyl acetate and brine was 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. The residue was purified by silica gel chromatography eluting with dichloromethane-methanol (10:1) to give the titled compound (90mg).

^{1}H-NMR ($CDCl_3$) δ: 1.61-1.66(2H,m), 1.98-2.03(2H,m), 2.39-2.48(3H,m), 2.57-2.79 (6H,m), 4.52(2H,s), 5.20(2H,brs), 5.66(0.8x1H,t), 6.01(0.2x1H,t), 6.67(0.2x1H,d), 6.79(0.8x1H,d), 7.06(1H,dd), 7.15-7.37(9H,m).

MS m/z: 476 (M+1).

Example 27: 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-(1-hydroxy-1-methyl)ethyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

To a solution of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-methoxycarbonyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (60mg) in THF

(6ml) were added methylmagnesium chloride (3.0M, 0.16ml) dropwise at 0 °C, and the mixture was stirred at room temperature for 2 hour, the reaction mixture was quenched by saturated ammonium aqueous, then ethyl acetate and water was 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. The residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (95:5) to give the titled compound (20mg).
^{1}H-NMR ($CDCl_3$) δ: 1.54(0.7x6H,s), 1.62(0.3x6H,s), 1.63-1.70(2H,m), 2.03-2.10(3H,m), 2.38-2.49 (3H,m), 2.62-2.82(4H,m), 5.17(2H,brs), 5.68(0.7x1H,t), 6.05(0.3x1H,t), 6.75(0.3x1H,d), 6.83(0.7x1H,d), 7.18-7.43(10H,m).
MS m/z: 504 (M+1).

Example 28: 4-(4-Chlorophenyl)-1-[3-(2-cyano-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-2-cyano-6,11-dihydrodibenz[b,e]oxepine.
^{1}H-NMR ($CDCl_3$) δ: 1.67-1.72(2H,m), 2.02-2.13(2H,m), 2.37-2.77 (8H,m), 5.35 (2H,brs), 5.75(0.7x1H,t), 6.07(0.3x1H,t), 6.78(0.3x1H,d), 6.82(0.7x1H,d), 7.25-7.51(10H,m).
MS m/z: 471 (M+1).

Example 29: 1-[3-(2-Aminomethyl-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

To a solution of 4-(4-chlorophenyl)-1-[3-(2-cyano-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (380mg) in EtOH (20ml) were added Raney* nickel (50% slurry in water, 60 mg), and the mixture was hydrogenated at 15 psi for 2 hours. The mixture was filtered through the celite* and distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with dichloromethane-methanol-aqueous ammonium

*Trade-mark

(95:5:1) to give the titled compound (130mg).
^{1}H-NMR ($CDCl_3$) δ: 1.76-1.94(3H,m), 2.18-2.34(2H,m), 2.85-3.10(8H,m), 3.88(2H,s), 5.30(2H,brs), 5.59(1H,t), 6.78(1H,d), 7.13-7.40(10H,m).
MS m/z: 475 (M+1).

Example 30: 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-nitrodibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-6,11-dihydro-2-nitorodibenz[b,e]oxepine.
^{1}H-NMR ($CDCl_3$) δ: 1.62-1.67(2H,m), 1.80-2.12(3H,m), 2.28-2.78(8H,m), 5.05(0.3x2H,brs), 5.40(0.7x2H,brs), 5.90(0.7x1H,t), 6.17(0.3x1H,t), 6.82(0.3x1H,d), 6.92(0.7x1H), 7.28-7.41(8H,m), 7.82(1H,dd), 8.15(0.7x1H,d), 8.22(0.3x1H,d).
MS m/z: 491 (M+1).

Example 31: 1-[3-(2-Amino-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

To a solution of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-nitrodibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (120mg) in EtOH (15ml) were added tin (II) chloride (190mg), and the mixture was heated to reflux for 1 hour. The solvent was distilled off under reduced pressure. To the residue was added ethyl acetate and sodium aqueous to neutralize. 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 the titled compound (70mg).
^{1}H-NMR (DMSO-d_6) δ: 1.54-1.60(2H,m), 1.85-2.00(2H,m), 2.30-2.80(8H,m), 3.88(2H,s).5.07(2H,brs), 5.66(1H,t), 6.41-6.46(2H,m), 6.59(1H,d), 7.24-7.49(8H,m).
MS m/z: 461 (M+1).

Example 32: 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-hydroxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

Step 1

11-(3-Bromopropylidene)-6,11-dihydro-2-hydroxydibenz[b,e]oxepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one with 6,11-dihydro-2-hydroxydibenz[b,e]oxepin-11-one.

^{1}H-NMR ($CDCl_3$) δ: 2.69(2H,q), 3.39 (2H,t), 5.20(2H,brs), 5.92(1H,t), 6.50-6.81(4H,m), 7.17-7.37(4H,m).

Step 2

The titled compound was prepared by following the procedure of example 45, 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: 1.60-1.75(3H,m), 1.95-2.10(2H,m), 2.35-2.80(8H,m), 5.10(2H,brs), 5.93(1H,t), 6.56(2H,brs), 6.71(1H,brs), 7.11-7.35(8H,m).

MS m/z: 462(M+1)

Example 33: 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-methoxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

Step 1

11-(3-Bromopropylidene)-6,11-dihydro-2-methoxydibenz[b,e]oxepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one with 6,11-dihydro-2-methoxydibenz[b,e]oxepin-11-one.

^{1}H-NMR ($CDCl_3$) δ: 2.74(2H,q), 3.43 (2H,t), 3.77(3H,s), 5.10(2H,brs), 6.02(1H,t), 6.70-6.83(3H,m), 7.21-7.38(4H,m).

Step 2

The titled compound was prepared by following the procedure of example 45, 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: 1.59-1.65(2H,m), 1.95-2.66(11H,m), 3.75(3H,s), 5.10(2H,brs), 6.03(1H,t), 6.69(2H,brs), 6.82(1H,brs), 7.20-7.40(8H,m).

MS m/z: 476(M+1)

Example 34: 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-ethoxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

To a solution of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-hydroxydibenz[b,e]oxepin-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)

Example 35: 1-[3-(3-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

3-Bromo-11-(3-bromopropylidene)-6,11-dihydrodibenz[b,e]oxepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one with 3-bromo-6,11-dihydrodibenz[b,e]oxepin-11-one.

^{1}H-NMR ($CDCl_3$) δ: 2.74(2H,q), 3.43 (2H,t), 3.77(3H,s), 5.10(2H,brs), 6.02(1H,t), 6.70-6.83(3H,m), 7.21-7.38(4H,m).

Step 2

The titled compound was prepared by following the procedure of example 45, 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: 1.63-1.70(3H,m), 1.96-2.10(2H,m), 2.32-2.69(8H,m), 5.20(2H,brs), 6.00(1H,t), 6.92-7.00(2H,m), 7.11-7.14(1H,m), 7.24-7.42(8H,m).
MS m/z: 524, 526(M+1)

Example 36: 4-(4-Chlorophenyl)-1-[3-(6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-methoxypiperidine

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)(400mg) 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 37: 4-Acetoxy-4-(4-chlorophenyl)-1-[3-(6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]piperidine

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)(200mg) in dichloromethane (5ml) were added acetyl chloride (0.06ml), triethylamine (0.19ml) and the mixture was stirred at room temperature for 1 hour. 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 the titled compound (190mg).

^{1}H-NMR ($CDCl_3$) δ: 1.98-2.85(12H,m), 2.02(3H,s), 2.93(3H,s), 5.23(2H,brs), 6.01(1H,t), 6.73-6.90(3H,m), 7.11-7.40(9H,m).

MS m/z: 488(M+1)

Example 38: 1-[3-(8-Bromo-4,10-dihydrothieno[3,2-c][1]benzoxepin-10-ylidene)propyl]piperidin-4-(4-chlorophenyl)-4-ol

Step 1

8-Bromo-10-(3-bromopropylidene)-4,10-dihydrothieno[3,2-c][1]benzoxepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one with 4,10-dihydrothieno[3,2-c][1]benzoxepin-10-one.

^{1}H-NMR ($CDCl_3$) δ: 2.84(2H,q), 3.45(2H,t), 5.10(2H,s), 6.11(1H,t), 6.65(1H,d), 7.03-7.08(2H,m), 7.38-7.43(2H,m).

Step 2

The titled compound was prepared by following the procedure of example 45, 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: 1.66-1.75(3H,m), 2.03-2.16(2H,m), 2.40-2.86(8H,m), 5.09(0.7x2H,s),5.14(0.3x2H,s), 5.90(0.3x1H,t), 6.10(0.7x1H,t), 6.64(0.7x1H,d), 6.75(0.3x1H,d), 6.90(0.3x1H,d), 7.03-7.09(2H,m), 7.21-7.45(6H,m).

MS m/z: 532(M+1)

Example 39: 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol

Step 1

11-(3-Bromopropylidene)-6,11-dihydro-6-oxo-5H-dibenz[b,e]azepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one with 6,11-dihydro-6-5H-dibenz[b,e]azepin-6,11-dione.

^{1}H-NMR ($CDCl_3$) δ: 2.70-2.92(2H,m), 3.45 (2H,t), 5.92(1H,t), 7.08-7.58(7H,m), 8.05(1H,dd), 9.00(1H,brs).

Step 2

The titled compound was prepared by following the procedure of example 45, 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: 1.61-1.66(2H,m), 1.97-2.20(3H,m), 2.35-2.68(8H,m), 5.80(1H,t), 7.03-7.53(11H,m), 8.02(1H,dd), 9.27(1H,brs). MS m/z: 459(M+1)

Example 40: 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-5-ethyl-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 12, but replacing benzyl bromide with ethyl iodide.

^{1}H-NMR ($CDCl_3$) δ: 1.19-1.28(3H,m), 1.63-1.69(2H,m), 1.99-2.16(3H,m), 2.37-2.70(8H,m), 3.77-3.85(1H,m), 4.40-4.48(1H,m), 5.85(1H,t), 7.12-7.45(11H,m), 7.85(1H,dd).

MS m/z: 487(M+1)

Example 41: 1-[3-(5-n-Butyl-6,11-dihydro-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

The titled compound was prepared by following the procedure of example 12, but replacing benzyl bromide with n-butyl iodide.

^{1}H-NMR ($CDCl_3$) δ: 0.90-0.98(3H,m), 1.25-2.20(9H,m), 2.40-2.87(8H,m), 3.62-3.72(1H,m), 4.52-4.64(1H,m), 5.85(1H,t), 7.16-7.45(11H,m), 7.88(1H,dd).

MS m/z: 515(M+1)

Example 42: 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-5-(3-hydroxypropyl)-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol

To a solution 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol hydrochloride (Example 39)(500mg) in DMF (8ml) were added sodium hydride (60% in oil, 200mg), 2-(3-bromopropoxy)tetrahydro-2H-pyran (0.5ml) and the mixture was stirred at room temperature for 6 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 solved in 1M hydrogen chloride in diehyl ether and stirred at room temperature for 1 hour. 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 to give the titled compound (250mg).

^{1}H-NMR ($CDCl_3$) δ: 1.25-2.87(15H,m), 3.51-3.56(2H,m), 3.76-3.82(1H,m), 4.81-4.87(1H,m), 5.86(1H,t), 7.16-7.45(11H,m), 7.82(1H,dd).

MS m/z: 517(M+1)

Example 43: 1-[3-(5-tert-Butoxycarbonymethyl-6,11-dihydro-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

The titled compound was prepared by following the procedure of example 12, but replacing benzyl bromide with tert-butyl bromoacetate.

^{1}H-NMR ($CDCl_3$) δ: 1.50(9H,s), 1.65-1.70(2H,m), 1.95-2.10(3H,m), 2.42-2.75(8H,m), 4.24(1H,d), 4.75(1H,d), 5.88(1H,t), 7.16-7.46(11H,m), 7.90(1H,dd).

MS m/z: 573(M+1)

Example 44: 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-hydroxy [1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

Step 1

To a solution of the product of example 45, 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

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 (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 45: 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

Step 1

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

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

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

1H-NMR ($CDCl_3$) d: 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 46: 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethoxy [1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 34, 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 47: 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-isopropoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, 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 48: 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-

ethoxycarbonylmethyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with ethyl bromoacetate.

^{1}H-NMR ($CDCl_3$) δ: 1.28(3H,t), 1.63-1.68(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 49: 4-(4-Chlorophenyl)-1-[3-(7-cyanomethyloxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with bromoacetonitrile.

^{1}H-NMR ($CDCl_3$) δ: 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 50: 1-[3-(7-(2-Acetoxyethyl)oxy-5,11-dihydro [1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, 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 51: 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-hydroxyethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

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 50)(140mg) in ethanol (5ml) were added 15% sodiun hydroxide aqueous solution (2ml) and the mixture was heated to reflux 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 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 52: 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-morpholinoethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, 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 53: 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro [1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

Step 1

5-(3-Bromopropylidene)-5,11-dihydro [1]benzoxepino[2,3-b]pyridine was prepared by following the procedure of example 45, 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

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 54: 1-[3-(8-Bromo-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

8-Bromo-5-(3-bromopropylidene)-5,11-dihydro[1]benzoxepino[2,3-b]pyridine was prepared by following the procedure of example 45, 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

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: 1.64-1.69(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 55: 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

5-(3-Bromopropylidene)-10,11-dihydro-10-oxo-5H-pyrido[2,3-c][2]benzazepine was prepared by following the procedure of example 45, 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

The titled compound was prepared by following the procedure of example 45, 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 56: 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

The titled compound was prepared by following the procedure of example 36, 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 57: 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)ethyl]piperidin-4-ol

Step 1

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 eluting with ethyl acetate-hexane (1:4) to give 5,11-dihydro-7-methoxy-5-methylenepyrido[2,3-c][1]benzoxepine (0.14g).

Step 2

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

The titled compound was prepared by following the procedure of example 58, 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 58: 4-(4-Chlorophenyl)-1-[4-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)butyl]piperidin-4-ol

Step 1

3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propenaldehyde was prepared by following the procedure of example 57, 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 45, 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

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

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 59: 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-phenyl-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-phenyl-4-hydroxypiperidine.

^{1}H-NMR ($CDCl_3$) δ: 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 60: 4-(4-Bromophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, 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 61: 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, 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 62: 4-Benzyl-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, 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 63: 4-Cyano-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-phenylpiperidine

The titled compound was prepared by following the procedure of example 45, 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 64: 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-phenylpiperidine

The titled compound was prepared by following the procedure of example 45, 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 65: 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 45, 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 66: 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-piperidinopiperidine

The titled compound was prepared by following the procedure of example 45, 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 67: 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-keto-1-benzimidazolinyl)piperidine

The titled compound was prepared by following the procedure of example 45, 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 68: 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-keto-3-methyl-1-benzimidazolinyl)piperidine

The titled compound was prepared by following the procedure of example 36, 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 69: 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

The titled compound was prepared by following the procedure of example 45, 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 70: 4-Anilino-4-carbamyl-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-anilino-4-carbamylpiperidine.

^{1}H-NMR ($CDCl_3$) d: 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 71: 1-(4-Chlorophenyl)-4-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperazine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 1-(4-chlorophenyl)piperazine.

^{1}H-NMR ($CDCl_3$) δ: 2.36-2.53(8H,m), 3.07-3.09(4H,m), 3.76(3H,s), 5.26(2H,brs), 6.08(1H,t), 6.72-6.81(5H,m), 7.16-7.28(3H,m), 7.56(1H,dd), 8.49(1H,dd).
MS m/z: 462 (M+1).

Example 72: 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-pyrimidyl)piperazine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 1-(2-pyrimidyl)piperazine.

^{1}H-NMR ($CDCl_3$) δ: 2.37-2.53(8H,m), 3.74-3.83(7H,m), 5.27(2H, brs), 6.08(1H,t),

6.45(1H,t), 6.72-6.83(3H,m), 7.25(1H,dd), 7.56(1H,dd), 8.27(2H,d), 8.49(1H,dd).
MS m/z: 430 (M+1).

Example 73: 1-Cyclohexyl-4-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperazine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 1-cyclohexylpiperazine.

^{1}H-NMR ($CDCl_3$) δ: 1.12-1.27(6H,m), 1.74-1.86(6H,m), 2.18-2.52 (11H,m), 3.76(3H,s), 5.26(2H,brs), 6.04(1H,t), 6.74-6.81(3H,m), 7.23 (1H,dd), 7.55(1H,dd), 8.48(1H,dd).
MS m/z: 434 (M+1).

Example 74: 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-furoyl)piperazine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 1-(2-furoyl)piperazine.

^{1}H-NMR ($CDCl_3$) δ: 2.34-2.48(8H,m), 3.71-3.74(7H,s), 5.24(2H,brs), 6.05(1H,t), 6.42(1H,dd), 6.70-6.80(3H,m), 6.93(1H,d), 7.23(1H,dd), 7.42(1H,d), 7.53(1H,dd), 8.46(1H,dd).
MS m/z: 446 (M+1).

Example 75:
4-(3-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

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 76:

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

The titled compound was prepared by following the procedure of example 45, 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 77:

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

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 78:

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

(p-tolyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, 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 79: 4-(3,4-Dichlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(3,4-dichlorophenyl)-4-hydroxypiperidine.

^{1}HNMR ($CDCl_3$) d: 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 83:

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

The titled compound was prepared by following the procedure of example 45, 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 85:

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

The titled compound was prepared by following the procedure of example 45, 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 86:

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

The titled compound was prepared by following the procedure of example 45, 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 89:

1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(p-tosyl)piperazine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 1-(p-tosyl)piperazine.
^{1}H-NMR ($CDCl_3$) δ: 2.20-2.54(11H,m), 2.82-3.10(4H,m), 3.73(3H,s), 5.16(2H,brs), 6.00(1H,t), 6.66-6.85(3H,m), 7.21(1H,dd), 7.31(2H,m), 7.51(1H,dd), 7.61(2H,m), 8.45(1H,dd).
MS m/z: 506(M+1)

Example 90:
1'-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]spiro[isobenzofuran-1(3H),4'-piperidine]
The titled compound was prepared by following the procedure of example 45, 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 91:
5-Chloro-1'-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]spiro[isobenzofuran-1(3H),4'-piperidine]
The titled compound was prepared by following the procedure of example 45, 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 111:

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

The titled compound was prepared by following the procedure of example 45, 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 ($CDCl_3$) d: 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 114:

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

The titled compound was prepared by following the procedure of example 45, 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 ($CDCl_3$) d: 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 115:

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

The titled compound was prepared by following the procedure of example 45, 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 117:
1-[3-(7-Chloro-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, 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 118:
1-[3-(7-Carboxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

A mixture of the product of example 169 (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 120:

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

To a solution of product of Example 290 (3.7g) in methanol (74ml), acetic acid (6ml), and water (37ml) were added sodium periodate (1.7g) in water (15ml) at 0°C, and the mixture was stirred at room temperature for 1 hour. To the reaction mixture were added amidosulfuric acid (1.2g) and sodium chlorite (0.89g) in water (10ml), and the mixture was stirred at room temperature for 15 minutes. The reaction mixture was distilled off under reduced pressure into half volume. The residue was neutralized with 1N sodium hydroxide. The precipitation was filtered and washed with water to give the titled compound (2.6g).

^{1}H-NMR (DMSO-d_6) δ: 1.45-1.50(2H,m), 1.73-1.82(2H,m), 2.24-2.50(8H,m), 3.50(2H,s), 4.84(1H,brs), 5.24(2H,brs), 6.13(1H,t), 6.74(1H,d), 7.06(1H,dd), 7.21(1H,d), 7.33-7.48(5H,m), 7.74(1H,dd), 8.50(1H,dd).

Example 122:

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

The titled compound was prepared by following the procedure of example 134, but replacing the product of example 133 with the product of example 120.

^{1}H-NMR ($CDCl_3$) δ: 1.65-1.70(2H,m), 1.95-2.06(2H,m), 2.31-2.66(9H,m), 2.93(3H,s), 3.00(3H,s), 3.61(2H,s), 5.29(2H,brs), 6.09(1H,t), 6.78(1H,d), 7.00(1H,dd), 7.20-7.43(6H,m), 7.56(1H,dd), 8.42(1H,dd).

MS m/z: 532(M+1)

Example 123:

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

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 288.

^{1}H-NMR (DMSO-d_6) δ: 1.44-1.49(2H,m), 1.70-1.82(2H,m), 2.22-2.48(10H,m), 2.75(2H,t), 4.82(1H,brs), 5.23(2H,brs), 6.14(1H,t), 6.71(1H,d), 7.04(1H,dd), 7.17(1H,d), 7.33-7.48(5H,m), 7.72(1H,dd), 8.49(1H,dd).

MS m/z: 519(M+1)

Example 128:

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

The titled compound was prepared by following the procedure of example 46, 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 130:

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

The titled compound was prepared by following the procedure of example 46, 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 131:

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

The titled compound was prepared by following the procedure of example 46, 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 132:

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

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 46, 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

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 133:

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

To a solution of product of example 48 (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 134: 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-dimethylaminocarbonylmethyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of product of example 133 (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 135:

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

The titled compound was prepared by following the procedure of example 134, 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 138: 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

The titled compound was prepared by following the procedure of example 46, 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 139:

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

The titled compound was prepared by following the procedure of example 133, but replacing product of example 48 with product of example 138.

^{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 140:

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

(4-methoxyphenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, 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 141:

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

The titled compound was prepared by following the procedure of example 45, 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 142:

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

The titled compound was prepared by following the procedure of example 45, 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 143:

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

The titled compound was prepared by following the procedure of example 45, 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 144:

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

The titled compound was prepared by following the procedure of example 45, 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 145:

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

The titled compound was prepared by following the procedure of example 45, 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(0.2H,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 146:

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

The titled compound was prepared by following the procedure of example 45, 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 147:

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

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with

4-(2-pyridyl)-4-hydroxypiperidine

^{1}H-NMR ($CDCl_3$) d: 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 148:
1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(3-pyridyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, 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 149:
1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-pyridyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, 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 150:

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

The titled compound was prepared by following the procedure of example 45, 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 151:

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

The titled compound was prepared by following the procedure of example 44, 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 152:

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

The titled compound was prepared by following the procedure of example 46, 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 153:

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

The titled compound was prepared by following the procedure of example 48, but replacing the product of example 44 with the product of example 151.

^{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 154:

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

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 153.

^{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 155:

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

The titled compound was prepared by following the procedure of example 134, but replacing the product of example 133 with the product of example 154.

^{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 156:

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

The titled compound was prepared by following the procedure of example 50, but replacing the product of example 44 with the product of example 151.

^{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 157:

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

The titled compound was prepared by following the procedure of example 51, but replacing the product of example 50 with the product of example 156.

^{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 158:

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

The titled compound was prepared by following the procedure of example 138, but replacing the product of example 44 with the product of example 151.

^{1}H-NMR ($CDCl_3$) d: 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 159: 1-[3-(7-(1-Carboxy-1-methylethyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidine

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 158.

^{1}H-NMR (CD_3OD) d: 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 160:

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

The titled compound was prepared by following the procedure of example 65, but replacing the product of example 45, step 2 with the product of example 54, step 1.

^{1}H-NMR ($CDCl_3$) d: 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 161:

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

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 160) (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

^{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 162:

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

The titled compound was prepared by following the procedure of example 45, 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 163: 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, 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 ($CDCl_3$) d: 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 164: 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-8-vinyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, 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 ($CDCl_3$) d: 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 165:

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

A mixture of the product of example 164 (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 166:

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

The titled compound was prepared by following the procedure of example 45, 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-NMR ($CDCl_3$) 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 167:

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

The titled compound was prepared by following the procedure of example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 5,11- dihydro[1]benzoxepino[4,3-c]pyridin-5-one.

1H-NMR ($CDCl_3$) δ: 1.67-1.71(2H,m), 1.97-2.08(2H,m), 2.16(1H,s), 2.40-2.69(8H,m), 5.16(2H,brs), 6.14(1H,t), 6.80(1H,dd), 6.91-6.97(1H,m), 7.13-7.19(1H,m), 7.26-7.44(6H,m), 7.50-8.54(2H,m).

MS m/z: 447(M+1)

Example 168:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro[1]benzoxepino[4,3-d]pyrimidin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 5,11- dihydro[1]benzoxepino[4,3-d]pyrimidin-5-one.

1H-NMR ($CDCl_3$) δ: 1.68-1.72(2H,m), 1.90(1H,brs), 2.06-2.19(2H,m), 2.41-2.78(8H,m), 5.20(2H,s), 6.12(1H,t), 7.14-7.45(8H,m), 8.72(1H,s), 8.97(1H,s).

MS m/z: 448(M+1)

Example 169:

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

To a solution of product of example 44 (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 170:

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

A mixture of the product of example 169 (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 171:

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

A mixture of the product of example 169 (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 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 172:

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

The product of example 171 (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 173:

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

The titled compound was prepared by following the procedure of example 46, 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 174:

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

The titled compound was prepared by following the procedure of example 46, 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 175:

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

The titled compound was prepared by following the procedure of example 46, 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 176:

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

The titled compound was prepared by following the procedure of example 134, but replacing the product of example 133 with the product of example 139.

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 177:

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

The titled compound was prepared by following the procedure of example 46, 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 178:

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

The titled compound was prepared by following the procedure of example 133, but replacing product of example 48 with product of example 177.

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 179:

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

The titled compound was prepared by following the procedure of example 46, 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 180:

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

The titled compound was prepared by following the procedure of example 133, but replacing product of example 48 with product of example 179.

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 181:

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

The titled compound was prepared by following the procedure of example 134, 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 182:

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

The titled compound was prepared by following the procedure of example 134, 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 183:

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

-hydroxyphenyl)piperidine

The titled compound was prepared by following the procedure of example 45, 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 184:

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

The titled compound was prepared by following the procedure of example 45, 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 185:

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

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(7-chloro-1,2-benzisoxazol-3-yl) piperidine. This tetrahydropyridine 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 186:
4-(7-Chloroindol-3-yl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-
ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 45, 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 187:
4-Azido-4-(4-chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

Step 1 4-azido-4-(4-chlorophenyl)piperidine (15): Fig. 8b

To a cold (0°C) solution of **1** (3.0 g, 14 mmol) in anhydrous dioxane (15 mL) under an inert atmosphere was added NaN_3 (1.0 g, 15.4 mmol) followed by the slow dropwise addition of and BF_3●OEt (4.4 mL, 35 mmol). The reaction was stirred at 0°C for 3 hrs and was quenched at 0°C by the slow careful addition of saturated aqueous $NaHCO_3$ to basicity. The organic layer was separated and dried over Na_2SO_4. The reaction mixture was purified via silica gel flash chromatography eluting a 2 g 1:3 mixture of azidopiperidine **2** and olefin **3** with 2% $MeOH/CH_2Cl_2$. The mixture was taken directly on to the next reaction.

Step 2

The titled compound was prepared by then following the procedure of example 45, step 3, with the above reaction mixture (thereby replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-azido-4-(4-chlorophenyl)piperidine)), but limiting the amount of bromide to 0.25 equivalents.

^{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 188:

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

The titled compound was prepared by following the procedure of example 45, 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 189:

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

The titled compound was prepared by following the procedure of example 133, but replacing product of example 48 with product of example 188.

^{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 190:
1-(2-Chlorophenylsulfonyl)-4-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperazine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 1-(2-chlorophenylsulfonyl)piperazine.

^{1}H-NMR ($CDCl_3$) δ: 2.20-2.58(8H,m), 3.12-3.38(4H,m), 3.76(3H,s), 5.22(2H,brs), 6.03(1H,t), 6.64-6.90(3H,m), 7.23(1H,dd), 7.32-7.60(4H,m), 8.01(1H,dd), 8.48(1H,dd).
MS m/z: 526(M+1)

Example 191:
1-(3-Chlorophenylsulfonyl)-4-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperazine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 1-(3-chlorophenylsulfonyl)piperazine.

^{1}H-NMR ($CDCl_3$) δ: 2.20-2.60(8H,m), 2.82-3.12(4H,m), 3.76(3H,s), 5.18(2H,brs), 6.00(1H,t), 6.64-6.90(3H,m), 7.23(1H,dd), 7.42-7.78(5H,m), 8.48(1H,dd).
MS m/z: 526(M+1)

Example 192:
1-(4-Chlorophenylsulfonyl)-4-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperazine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 1-(4-chlorophenylsulfonyl)piperazine.

^{1}H-NMR ($CDCl_3$) δ: 2.20-2.56(8H,m), 2.82-3.10(4H,m), 3.76(3H,s), 5.18(2H,brs), 5.99(1H,t), 6.62-6.92(3H,m), 7.23(1H,dd), 7.42-7.78(5H,m), 8.48(1H,dd).
MS m/z: 526(M+1)

Example 193:
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-1,2,3,6-tetrahydropyridine

The titled compound was prepared by following the procedure of example 44, step 2, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine.

^{1}H-NMR ($CDCl_3$) d: 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 194:
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-1,2,3,6-tetrahydropyridine

The titled compound was prepared by following the procedure of example 45, 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 195:
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.

The titled compound was prepared by following the procedure of example 45, 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 196:

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

The titled compound was prepared by following the procedure of example 44, step 2, but replacing4-(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 197:

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]

The titled compound was prepared by following the procedure of example 175, but replacing the product of example 44 with the product of example 196.

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: 531(M+1)

Example 198:

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

The titled compound was prepared by following the procedure of example 134, but replacing the product of example 133 with the product of example 118.

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 199:

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

To a solution of product of example 138 (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 200:

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

To a solution of product of example 48 (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), 1.66-1.71(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 203:

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

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with 2-ethoxyethyl bromide.

^{1}H-NMR ($CDCl_3$) δ: 1.24(3H,t), 1.66-1.75(3H,m), 2.00-2.11(2H,m), 2.36-2.71(8H,m), 3.59(2H,q), 3.71-.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: 535(M+1)

Example 205:

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

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with glycidol.

^{1}H-NMR ($CDCl_3$) δ: 1.66-1.75(2H,m), 2.00-2.11(2H,m), 2.36-2.71(8H,m), 3.62-3.76(2H,m), 3.94-4.02(4H,m), 4.21(2H,brs), 5.27(2H,brs), 6.09(1H,t), 6.76-6.86(3H,m), 7.23-7.44(5H,m), 7.57(1H,dd), 8.48(1H,dd).

MS m/z: 537(M+1)

Example 211:

1-[3-(7-(1-Carbamoyl-1-methyl)ethyloxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 176, but replacing dimethylamine hydrochloride with ammonium hydroxide.

^{1}H-NMR ($CDCl_3$) δ: 1.50(6H,s), 1.67-1.72(2H,m), 1.96-2.09(3H,m), 2.36-2.70(8H,m), 5.30(2H,brs), 5.70(1H,brs), 6.05(1H,t), 6.75-6.90(4H,m), 7.25-7.44(5H,m), 7.58(1H,dd), 8.49(1H,dd).

MS m/z: 548(M+1)

Example 212:

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

The titled compound was prepared by following the procedure of example 176, but replacing dimethylamine hydrochloride with methylamine.

^{1}H-NMR ($CDCl_3$) δ: 1.47(6H,s), 1.67-1.72(2H,m), 1.96-2.09(2H,m), 2.20(1H,brs), 2.36-2.70(8H,m), 2.87(3H,d), 5.29(2H,brs), 6.04(1H,t), 6.72-6.86(4H,m), 7.27-7.44(5H,m), 7.58(1H,dd), 8.47(1H,dd).

MS m/z: 562(M+1)

Example 215:

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

The titled compound was prepared by following the procedure of example 134, but replacing the product of example 133 with the product of example 172.

^{1}H-NMR (CDCl3) δ: 1.63-1.71(3H,m), 1.98-2.10(2H,m), 2.35-2.72(8H,m), 3.07(3H,s), 3.17(3H,s), 5.36(2H,brs), 6.16(1H,t), 6.76(1H,d), 6.84(1H,d), 7.28-7.45(7H,m),

7.59-7.65(2H,m), 8.52(1H,dd).
MS m/z: 544(M+1)

Example 218:

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

The titled compound was prepared by following the procedure of example 181, but replacing the product of example 133 with the product of example 123. ^{1}H-NMR ($CDCl_3$) δ: 1.65-1.90(3H,m), 2.10-2.22(2H,m), 2.40-2.80(10H,m), 2.91(2H,t), 5.31-5.46(4H,m), 6.11(1H,t), 6.78(1H,d), 7.01(1H,dd), 7.16(1H,d), 7.28-7.46(5H,m), 7.57(1H,dd), 8.49(1H,dd).
MS m/z: 518(M+1)

Example 234: 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidine)propyl]-4-(indol-3-yl)-piperidine

The titled compound was prepared by following the procedure of example 45, 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($CDCl_3$) d: 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 235: 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.

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with

4-(indol-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 ($CDCl_3$) d: 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 236: 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(3-(ethoxycarbonyl)propyloxy[1]benzoxipino[2,3-b]pyridin-5-ylidine)propyl]piperidine

The titled compound was prepared by following the procedure of example 153, 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 237: 1-[3-(7-(3-Carboxypropyl)oxy-5,11-dihydro-[1]benzoxepino[2,3-b]pyridin-5-ylidine)propyl]-4-(4-chlorophenyl)-piperidine

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 236.

^{1}H-NMR (CD_3OD) 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 242:

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

The titled compound was prepared by following the procedure of example 200, but replacing the product of example 48 with the product of example 273.

[1]H-NMR ($CDCl_3$) δ: 1.58(6H,s), 1.65-1.70(3H,m), 1.93-2.21(2H,m), 2.28-2.73(8H,m), 5.32(2H,brs), 6.13(1H,t), 6.82(1H,d), 7.20-7.50(7H,m), 7.59(1H,dd), 8.50(1H,dd)
MS m/z: 505(M+1)

Example 243:
1-[3-(7-(1-Carboxy-1-methyl)ethyl-5, 11-dihydro[1]benzoxepino [2,3-b]pyridin-5-ylidene)propyl]-4(4-chlorophenyl)piperidin-4-ol

Step 1
To a solution of Example 363, step 2 (2.4 g) in toluene (30 ml) was added DIBAL (1 mol/L toluene solution, 9.2 ml) at -78°C, and the mixture stirred at 0°C for 1 hour, and at room temperature for 30 minutes. The reaction mixture was added saturated aqueous ammonium chloride. 1 N aqueous hydrochloric acid, saturated sodium chloride 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. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:4) to give 5-(3-bromopropylidene)-5, 11-dihydro-7-(1-hydroxy-1-methyl)ethyl[1]benzoxepino[2m30b]pyridine (2.0 g).
[1]H-NMR ($CDCl_3$) δ:1.45(H,s), 2.75(2H,q), 3.47(1H,t), 5.33(2H, brs), 6.04(1H,t), 6.87(1H, d), 7.09-7.14(2H, m), 7.30(1H, dd), 7.57(1H, dd), 8.53(1H, dd), 9.46(1H,s).

Step 2
5-(3-bromopropylidene)-7-(1-carboxy-1-methyl)ethyl-5, 11-dihydro[1]benzoxepino [2,3-b]pyridine was prepared by following the procedure of Example 382, step 2, but replacing the product of Example 382, step 1 with the product of step 1 above.

Step 3

The titled compound was prepared by following the procedure of example 44, step 2, but replacing the product of example 44, step 1 with the product of step 2.
^{1}H-NMR (DMSO-d6) δ: 1.46(6H, s), 1.63-1.84(2H, m), 2.17-2.37(4H, m), 2.37-2.53(4H, m), 3.20-3.43(2H, m), 4.83(1H, s), 5.23(2H, brs), 6.13(1H, t), 6.76(1H, d), 7.16(1H, dd), 7.25(1H, d), 7.35(2H, d), 7.42-7.48(3H, m), 7.76(1H, dd), 8.50(1H, dd). MS m/z:533(M+1)

Example 248: 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

The titled compound was prepared by following the procedure of example 45, 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)

Example 249: 5-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4,6-dioxazacane.
5-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4,6-diazacyclooctylamine
Step1

5-(3-(N,N'-Bis(2-hydroxyethyl)amino)propylidene)-5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridine was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with diethanolamine.
^{1}H-NMR (CD_3OD) δ: 2.46(2H,m), 2.84(4H,t), 2.98(2H,m), 3.67(4H,t), 3.75(3H,s), 5.20(2H,brs), 6.16(1H,t),
6.68-6.80(2H,m), 6.87(1H,d), 7.46(1H,dd), 7.81(1H,dd), 8.45(1H,dd).

Step2

To a mixture of product of step1 (78mg) and 4-chlorobenzaldehyde dimethyl acetal (0.1ml) in 1,2-dichloroethane (60ml) was added *p*-toluenesulfonic acid monohydrate (5mg) at room temperature, and the mixture was stirred at reflux for 12 hours. Dichloromethane and saturated aqueous sodium bicarbonate was added to the cooled 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 dichloromethane-methanol (20:1) to give the titled compound (40mg).

^{1}H-NMR ($CDCl_3$) δ: 2.35(2H,m), 2.64-2.94(6H, m), 3.52-3.68(2H, m), 3.78(3H,s), 3.72-3.90(2H,m), 5.27(2H,brs), 5.66(1H,s), 6.08(1H,t), 6.68-6.88(3H,m), 7.18-7.46(5H,m), 7.58(1H,dd), 8.50(1H,dd).

Example 252:

Step 1

To a cold (0°C) stirred solution of 4-oxohomopiperidine●HCl (0.6 g, 4.05 mmol), K_2CO_3 (0.615 g, 4.46 mmol) in anhydrous THF (10 mL) will be ethyl chloroformate (0.44 mL, 4.05 mmol) dropwise. The reaction was warmed to RT for 2 hrs then quenched with H_2O, extracted with EtOAc, and the organic layer dried over Na_2SO_4. Pure 1-ethylcarbonyl-4-oxohomopiperidine will be isolated via silica gel flash chromatography

Step 2

To a cold (0°C) stirred solution of 1-ethylcarbonyl-4-oxohomopiperidine (1.42 g, 6.07 mmol) in anhydrous THF (50 mL) under argon can be added dropwise 1.o mM 4-chlorophenylmagnesium bromide in diethyl ether (10 mL, 10mmol). The reaction can be warmed to RT for 2 hrs then quenched with saturated aqueous NH_4Cl 95 mL). The reaction mixture can then be extracted with EtOAc (2 X 50 mL), the organic layers combined and dried over Na_2SO_4. Pure 1-ethoxycarbonyl-4-(4-

chlorophenyl)-4-hydroxyhomopeperidine (2.1 g, 96%) can be isolated via silica gel flash chromatography eluting with 50% ETOAc/hexane.

4-(4-chlorophenyl)-4-hydroxyhomopiperidine can be prepared by reacting 1-ethoxycarbonyl-4-(4-chlorophenyl)-4-hydroxyhomopeperidine with a nucleophilic hydroxide equivalent such as LiOH in a solvent such as THF, methanol or ethanol. Removal of the solvent can afford 4-(4-chlorophenyl)-4-hydroxyhomopeperidine.

Step 4

The compound was prepared by following the procedure for Example 44, but replacing 4-(4-chlorophenyl)-4-hydroxypeperidine with 4-(4-chlorophenyl)-4-hydroxyhomopeperidine.

Examples 253 and 254:

Step 1

To a stirred solution of 4-oxohomopiperidine●HCl (1.2 g, 8.05 mmol), NaOH (0.68 g, 16.9 mmol) in t-BuOH/H_2O (1:1, 10 mL) was added *t*-butyldicarbonate (1.93 mL, 8.9 mmol) drop-wise. The reaction was stirred at RT overnight, extracted with EtOAc (2 X 10 mL) and the organic layer separated. The organic layer was dried over Na_2SO_4 and concentrated under vacuo. Pure 1-*t*-butoxycarbonyl-4-oxohomopiperidine (1.42 g, 84%) was isolated via silica gel flash chromatography eluting with 50% EtOAc/hexane. ^1H NMR $CDCl_3$ δ: 44 (9H, s), 1.72-1.84 (2H, m), 2.60-2.65 (4H, m), 3.55-3.61 (4H, m).

Step 2

To a cold (0°C) stirred solution of 1-*t*-butoxycarbonyl-4-oxohomopiperidine (1.42 g, 6.07 mmol) in anhydrous THF (50 mL) under argon was added dropwise 1.0 M 4-chlorophenylmagnesium bromide in diethyl ether (10 mL, 10 mmol). The reaction was warmed to RT for 2 hrs then quenched with sat'd aqueous NH_4Cl (5 mL). The reaction mixture was extracted with EtOAc (2 X 50 mL), the organic layers combined and dried over Na_2SO_4. Pure 1-*t*-butoxycarbonyl-4-(4-chlorophenyl)-4-hydroxyhomopiperidine (2.1 g, 96%) was isolated via silica gel flash chromatography eluting with 50% EtOAc/hexane. ^{1}H NMR $CDCl_3$ δ 1.43 (9H,s), 1.61-2.22 (6H, m), 3.21-3031 (2H, m), 3.48-3.82 (2H, m).

Step 3

To a stirred solution of 1-*t*-butoxycarbonyl-4-(4-chlorophenyl)-4-hydroxyhomopiperidine (2.1 g) at RT in CH_2Cl_2 (48 mL) was added TFA (2.0 mL). The reaction was stirred at RT for 2 hrs. Excess solvent and TFA was removed affording 2.0 g (92% yield) 1:1 mixture of 3-(4-chlorophenyl)-2,3-dehydrohomopiperidine and 3-(4-chlorophenyl)-3,4-dehydrohomopiperidine. ^{1}H NMR (MeOD, isomer A) δ 2.01-2.11 (2H, m, 4), 2.60-2.71 (2H, m, 5), 2.81-2.92 (2H, m, 4), 2.83-3.05 (2H, m, 5), 3.66-3.92 (4H, m, 5), 6.16-6.21 (1H, t, 5). ^{1}H NMR (MeOD, isomer B) 3.44-3.56 (2H, m, 4), 3.88-3.97 (2H, m, 4), 6.01-6.12 (1H, t, 4), 7.32-7.44 (1H, t, 4).

Step 4

The compounds can be prepared by following the procedure for Example 44 but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 3-(4-chlorophenyl)-3,4-dehydrohomopiperidine and 3-(4-chlorophenyl)-4,5-dehydrohomopiperidine.

Example 255:

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

The titled compound was prepared by following the procedure of example 44, step 2, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 1-(4-chlorophenyl)piperazinone.

^{1}H-NMR (DMSO-d_6) δ: 2.30-2.34(2H,m), 2,49-2.57(2H,m), 2.68(2H,t), 3.06(2H,s), 3.58(2H,t), 5,12(2H,brs), 6.06(2H,t), 6.57-6.69(3H,m), 7.35-7.71(5H,m), 7.72(1H,dd), 8.48(1H,dd).

Example 256:

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

The titled compound was prepared by following the procedure of example 44, step 2, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 1-(4-chlorophenyl)homopiperazdine.

^{1}H-NMR ($CDCl_3$) δ: 1.89(2H,brs), 2.27-2.35(2H,m), 2.51-2.70(6H,m), 3.37-3.53(4H,m), 5.23(2H,brs), 5.98(1H,t), 6.48-6.74(6H,m), 7.05-7.26(2H,m), 7.52(1H,dd), 8.45(1H,dd).

MS m/z: 462(M+1)

Example 260:

3-(4-Chlorophenyl)-8-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-8-azabicyclo[3.2.1]octan-3-ol

The titled compound was prepared by following the procedure of example 44, step 2, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol

^{1}H-NMR($CDCl_3$) δ:1.65-2.10(4H,m), 2.1-2.7(8H,m), 3.32(2H,bs), 3.78(3H,s), 5.24(2H,bs), 6.10(1H,dd),
6.70-6.90(3H,m), 7.15-7.31(3H,m), 7.45(bd,2H), 7.64(dd,1H)
8.46(dd,1H)

MS m/z: 503(M+1)

Example 261:

1'-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]spiro[5-chloro-1,3-benzodioxole-2,4'-piperidine]

The titled compound was prepared by following the procedure of example 44, step 2, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with spiro[5-chloro-1,3-benzodioxole-2,4'-piperidine] (*Journal of Medicinal Chemistry.* 1995, 38, 2009-2017).

^{1}H-NMR(DMSO-d_6) δ: 1.78-2.02(4H, m), 2.18-2.63(8H, m), 4.97-5.27(2H, brs), 6.06(1H, t), 6.58-6.67(3H, m),
6.79-6.87(2H, m), 6.99(1H, d), 7.42(1H, dd), 7.72(1H, dd), 8.49(1H, dd), 9.07(1H,

s).

Example 262:

1-[3-(7-(1-Carbamoyl-1-methyl)ethyloxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)-4-hydroxy-1-methylpiperidinium iodide

To a solution of the product of example 211 (330mg) and in acetonitrile (1.2ml) was added iodomethane (0.07ml), and the reaction mixture was stirred at room temperature for 2 hours. The precipitation was filtered and washed with acetonitrile to give the titled compound (250mg).

^{1}H-NMR (DMSO-d_6) δ: 1.39(6H,s), 1.65-1.85(2H,m), 2.20-2.64(4H,m), 3.09(3H,s), 3.30-3.65(6H,m), 5.20(2H,m), 5.61(1H,s), 6.01(1H,t), 6.75-6.92(3H,m), 7.27(1H,s), 7.38-7.64(6H,m), 7.83(1H,dd), 8.56(1H,dd)

MS m/z: 562[(M-I)+]

Example 263:

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

The titled compound was prepared by following the procedure of example 134, but replacing dimethylamine hydrochloride with diethylamine.

^{1}H-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 268:

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

The titled compound was prepared by following the procedure of example 198, but replacing dimethylamine hydrochloride with methylamine.

^{1}H-NMR (DMSO-d6) δ: 1.75-1.80(2H, m), 2.38-2.50(2H, m), 2.63-2.73(2H, m), 2.78(3H,d), 3.17-3.50(6H, m), 5.38(2H, brs), 6.36(1H, t), 6.87(1H, d), 7.41-7.50(4H, m), 7.55-7.99(4H, m), 8.48-8.50(1H, m), 8.61(1H, dd).

MS m/z: 504(M+1)

Example 269:

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

The titled compound was prepared by following the procedure of example 198, but replacing dimethylamine hydrochloride with ammonium hydroxide.

^{1}H-NMR ($CDCl_3$) δ: 1.67-1.79(2H,m), 2.01-2.10(2H,m), 2.17-2.71(8H,m), 5.38(2H,brs), 6.21(1H,t), 6.85(1H,d), 7.27-7.57(9H,m), 7.90(1H,dd), 8.50(1H,dd).

MS m/z: 490(M+1)

Example 270:

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

The titled compound was prepared by following the procedure of example 198, but replacing dimethylamine hydrochloride with diethylamine.

MS m/z: 546(M+1)

Example 273:

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

A mixture of the product of example 169 (15.0g), palladium(II) diacetate (170mg), 1,3-bis(diphenylphosphino)propane (310mg), and triethylamine (7.0ml) in methanol (100ml) and dimethylformamide (150ml) was purged with carbon monoxide for 5 minutes and stirred under a carbon monoxide balloon at 70°C for 8 hours. The reaction mixture was evaporated under reduced pressure. The residue was added water and extracted with ethyl acetate. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate : methanol = 10:1) to give the titled compound(13.1g).

^{1}H-NMR($CDCl_3$) δ: 1.45-1.80 (3H,m), 1.90-2.15 (2H,m), 2.28-2.48 (4H,m), 2.50-2.75 (4H,m), 3.89(3H,s), 5.25-5.50(2H,m), 6.20(1H,dd), 6.85(1H,d), 7.20-7.37(3H,m), 7.42(2H,d), 7.58(1H,d), 7.80(1H,dd), 8.01(1H,dd), 8.52(1H,dd)

MS m/z: 505(M+1)

Example 274:

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

To an ice-cooled solution of the product of example 273 (2.0g) in tetrahydrofuran (100ml) was added lithium aluminum hydride (300mg), and the reaction mixture was stirred at room temperature for 12 hours. After the reaction mixture was cooled to 0°C, water (0.3ml), 15% sodium hydroxide aqueous solution (0.3ml), and water (0.9ml) were added. The reaction mixture was filtered, and the filtrate was dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform: methanol : 28% ammonia in water = 100 : 5 : 1) to give the titled compound (1.6g).

^{1}H-NMR ($CDCl_3$) δ: 1.55-1.71(3H,m), 1.95-2.25(2H,m), 2.34-2.70(8H,m), 4.62(2H,s), 5.20-5.45(2H,brs), 6.13(1H,t), 6.84(1H,d), 7.16(1H,dd), 7.23-7.43(6H,m), 7.58(1H,dd), 8.51(1H,dd)

MS m/z: 477(M+1)

Example 275:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-propylamino)methyl

[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of the product of example 314 (300mg) and 1-propylamine (0.26ml) in tetrahydrofuran (6 ml) was added acetic acid (0.36ml), and the reaction mixture was stirred at 60°C for 30 minutes. Then the reaction mixture was added sodium triacetoxyborohydride (670mg) at 0°C , and stirred for 1.5 hours at room temperature. Sodium bicarbonate, water, and chloroform were added to the reaction mixture. The organic layer was extracted, and dried over potassium carbonate, and evaporated under reduced pressure. The residue was recrystallized with ethyl acetate to give titled compound (130mg).

^{1}H-NMR ($CDCl_3$) δ: 0.92(3H,t), 1.49-1.70(6H,m), 1.98(2H,m), 2.34-2.42(4H,m), 2.51-2.70(6H,m), 3.71(2H,s), 5.32(2H,brs), 6.12(1H,t), 6.81(1H,d), 7.11(1H,dd), 7.25-7.45(6H,m), 7.57(1H,dd), 8.49(1H,dd).

MS m/z: 518(M+1)

Example 276:

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

The titled compound was prepared by following the procedure of Example 275, but replacing 1-propylamine with 3-amino-1-propanol.

MS m/z:534(M+1)

Example 277:

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

The titled compound was prepared by following the procedure of example 275, but replacing 1-propylamine with piperidine.

MS m/z: 544(M+1)

Example 278:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(4-

morpholino)methyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol
The titled compound was prepared by following the procedure of example 275, but replacing 1-propylamine with morpholine.

MS m/z: 546(M+1)

Example 279:

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

The titled compound was prepared by following the procedure of Example 275, but replacing 1-propylamine with 4-aminobutyric acid.

^{1}H-NMR ($CDCl_3$) δ: 1.70-1.75(2H,m), 1.98(2H,m), 2.12-2.23(2H,m), 2.40-2.86(10H,m), 3.27(2H,t), 4.36(2H,s), 5.29(2H,brs), 6.07(1H,t), 6.80(1H,d), 7.04(1H,dd), 7.19(1H,d), 7.28-7.32(3H,m), 7.50(1H,t), 7.61(1H,dd), 8.51(1H,dd).

MS m/z: 544(M+1)

Example 280:

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

The titled compound was prepared by following the procedure of example 273, but replacing the product of example with the product of example 274.

^{1}H-NMR ($CDCl_3$) δ: 1.60-1.70(4H,m), 2.01-2.12(2H,m), 2.37-2.70(8H,m), 2.81(2H,t), 3.84(2H,t), 5.31(2H,brs), 6.09(1H,t), 6.81(1H,d), 7.03(1H,dd), 7.15(1H,d),
7.26-7.43(5H,m), 7.57(1H,dd), 8.49(1H,dd).

MS m/z: 491(M+1)

Example 281:

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

The titled compound was prepared by following the procedure of example 122, but replacing dimethylamine hydrochloride with ammonium hydroxide.
^{1}H-NMR ($CDCl_3$) δ: 1.65-1.70(2H,m), 1.98-2.06(2H,m), 2.27-2.70(9H,m), 3.46(2H,s), 5.30(2H,brs), 5.74(1H,brs), 6.04(1H,brs), 6.09(1H,t), 6.79(1H,d), 7.02(1H,dd), 7.18-7.41(6H,m), 7.54(1H,dd), 8.43(1H,dd).
MS m/z: 504(M+1)

Example 288:
4-(4-Chlorophenyl)-1-[3-(7-(2-ethoxycarboxy)ethyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol
The titled compound was prepared by following the procedure of example 165, but replacing the product of example 164 with the product of example 310.
^{1}H-NMR ($CDCl_3$) δ: 1.23(3H,t), 1.63-1.71(3H,m), 1.98-2.10(2H,m), 2.35-2.71(10H,m), 2.89(2H,t), 4.13(2H,q), 5.31(2H,brs), 6.08(1H,t), 6.78(1H,d), 7.00(1H,dd), 7.12(1H,d), 7.26-7.44(5H,m), 7.57(1H,dd), 8.49(1H,dd).
MS m/z: 548(M+1)

Example 289:
4-(4-Chlorophenyl)-1-[3-(7-(1-(3-hydroxy)propyl)-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol
The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 288.
^{1}H-NMR (DMSO-d_6) δ: 1.45-1.50(2H,m), 1.66-1.80(4H,m), 2.26-2.57(10H,m), 3.41(2H,q), 4.46(1H,t), 4.83(1H,s), 5.23(2H,brs), 6.14(1H,t), 6.71(1H,d), 7.01(1H,dd), 7.13(1H,d), 7.34-7.48(5H,m), 7.72(1H,dd), 8.49(1H,dd).
MS m/z: 505(M+1)

Example 290:

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

To a solution of product of example 170 (6.9g) in tetrahydrofuran (70ml) and water (14ml) were added N-methylmorpholine oxide(1.7g) and osmium tetraoxide at 0°C, and the mixture was stirred at room temperature for 3 hours. Ethyl acetate was added to the mixture, the aqueous layer was separated. Chloroform-isopropanol (4:1) was added to the aqueous layer, the organic layer was extracted, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure to give the titled compound (7.0g).

^{1}H-NMR ($CDCl_3$) δ: 1.65-1.73(2H,m), 1.95-2.10(2H,m), 2.30-2.75(13H,m), 3.45-3.50(1H,m), 3.60-3.65(1H,m), 3.83-3.90(1H,m), 5.28(2H,brs), 6.06(1H,t), 6.84(1H,d), 7.03(1H,dd), 7.15(1H,d), 7.26-7.43(5H,m), 7.57(1H,dd), 8.49(1H,dd).

MS m/z: 521(M+1)

Example 291:

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

The titled compound was prepared by following the procedure of example 170, but replacing allyltributyltin with phenyltributyltin.

^{1}H-NMR ($CDCl_3$) δ: 1.84-1.92(2H, m), 2.85-3.40(10H, m), 5.33(2H, brs), 6.05(1H,t), 6.95(1H, d), 7.30-7.58(12H, m), 7.63-7.66(1H, m), 8.56-8.58(1H, m)

MS m/z: 523(M+1)

Example 292:

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

The titled compound was prepared by following the procedure of example 170, but replacing allyltributyltin with ethyl (2-furyl)tributyltin.

^{1}H-NMR ($CDCl_3$) δ: 1.70-1.80(3H,m), 1.97-2.16(2H,m), 2.3-2.8(8H,m), 5.36(2H,m), 6.19(1H,t), 6.45(1H,dd), 6.55(1H,d), 6.87(1H,d), 7.20-7.50(7H,m), 7.60-7.65(2H,m), 8.52(1H,dd)

MS m/z: 513(M+1)

Example 293: 4-(4-Chlorophenyl)-1-[3-(7-ethoxycarbonylamino-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidine)propyl]piperidin-4-ol

A mixture of product of example 118 (490mg) and diphenylphosphonic azide (0.28ml) was stirred at 110°C for 30minutes. After the mixture was cooled, and triethylamine (0.14ml) and ethanol (5ml) were added, and the mixture was heated to reflux for 8 hours. The reaction mixture was diluted with ethyl acetate and filterd through Celite. The filtrate was washed with saturated aqueous sodium bicarbonate, and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (chloroform : methanol = 10 : 1) to give the titled compound (210mg).

1H-NMR ($CDCl_3$) δ 1.31(3H,t), 1.65-1.70(2H,m), 2.01-2.09(2H,m), 2.36-2.70(8H,m), 4.21(2H,q), 5.30(2H,brs), 6.13(1H,t), 6.46(1H,brs), 6.80(1H,d), 7.02(1H,dd), 7.28-7.50(6H,m), 7.57(1H,dd), 8.50(1H,dd).

MS m/z: 534(M+H)

Example 294:

1-[Bis(ethoxycarbonylmetyl)methoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with diethyl bromomalonate.

1
H-NMR ($CDCl_3$) δ: 1.30(3H,t), 1.66-1.71(2H,m), 1.98-2.09(2H,m), 2.35-2.69(9H,m), 4.30(2H,q), 5.14(1H,s), 5.26(2H,brs), 6.10(1H,t), 6.78(2H,d), 7.00(1H,t), 7.26-7.45(5H,m), 7.57(1H,dd), 8.43(1H,dd).

MS m/z: 621(M+1)

Example 295:

1-[1,1-Bis(ethoxycarbonylmetyl)ethyloxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with diethyl 2-bromo-2-methylmalonate.

^{1}H-NMR ($CDCl_3$) δ: 1.27(6H,t), 1.65-1.70(5H,m), 1.99-2.08(3H,m), 2.31-2.69(8H,m), 4.28(4H,q), 5.27(2H,brs), 6.06(1H,t), 6.72(1H,d), 6.80(1H,dd), 7.00(1H,d), 7.27-7.45(5H,m), 7.56(1H,dd), 8.46(1H,dd).

Example 296:

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

The titled compound was prepared by following the procedure of example 199, but replacing the product of example 138 with the product of example 294.

^{1}H-NMR ($CDCl_3$) δ: 1.70-1.75(2H,m), 2.10-2.80(11H,m), 3.90(4H,d), 4.36(1H,quint), 5.28(2H,brs), 6.13(1H,t), 6.71-6.87(2H,m), 7.00(1H,d), 7.29-7.45(5H,m), 7.58(1H,dd), 8.51(1H,dd).

MS m/z: 537(M+1)

Example 297:

1-[1,1-Bis(hydroxymetyl)ethyloxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

The titled compound was prepared by following the procedure of example 199, but replacing the product of example 138 with the product of example 295.

^{1}H-NMR ($CDCl_3$) δ: 1.09(3H,s), 1.66-1.71(2H,m), 1.90-2.10(3H,m), 2.37-2.75(8H,m), 3.72-3.82(4H,m), 5.29(2H,brs), 6.05(1H,t), 6.77(1H,d), 6.88(1H,dd), 7.03(1H,d), 7.26-7.43(5H,m), 7.56(1H,dd), 8.48(1H,dd).

MS m/z: 551(M+1)

Example 299:

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

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with ethyl 4-bromobutyrate.

^{1}H-NMR ($CDCl_3$) δ: 1.24(3H, t), 1.65-1.69(2H, m), 1.96-2.12(4H, m), 2.26-2.67(10H,m), 3.96(2H, t), 4.12(2H, q), 5.24(2H, brs), 6.08(1H, t), 6.70-6.83(3H, m), 7.21-7.59(6H,m), 8.39(1H, dd).

Example 300:

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

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 299.

^{1}H-NMR (DMSO-d6) δ: 1.41-1.95(2H, m), 1.41-1.95(4H, m), 2.20-2.72(10H, m), 3.95(2H,t), 5.18(2H, brs), 6.17(1H, t), 6.72-6.84(3H, m), 7.36-7.48(5H, m), 7.77(1H, dd), 8.50(1H, dd).

MS m/z: 549(M+1)

Example 301:

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

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with methyl 4-bromomethylbenzoate.

^{1}H-NMR ($CDCl_3$) δ: 1.66-1.70(2H, m), 1.93-2.09(3H, m), 2.37-2.70(8H, m), 3.91(3H,s), 5.09(2H, s), 5.27(2H, brs), 6.06(1H, t), 6.80-6.91(3H, m), 7.24-7.60(8H, m), 8.01-8.07(2H, m), 8.47(1H, dd).

Example 302:

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

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 301.

^{1}H-NMR (DMSO-d6) δ: 1.44-1.49(2H, m), 1.67-1.87(2H, m), 2.26-2.56(8H, m), 4.85(1H,brs), 5.15-5.25(4H, m), 6.17(1H, t), 6.72-6.95(3H, m), 7.30-7.75(8H, m), 7.92-7.99(2H, m), 8.48(1H, dd).

MS m/z: 597(M+1)

Example 303:

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

Step 1

1-[3-(7-((1-Benzoyloxymethyl)cyclopropyl) methoxy-5,11-dihydro [1]benzoxepino [2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol was prepared by following the procedure of example 46, but replacing ethyl iodide with (1-benzoyloxymethyl)cyclopropylmethyl methanesulfonate.

^{1}H-NMR ($CDCl_3$) δ: 0.70-0.81(4H, m), 1.65-1.70(3H, m), 1.98-2.07(2H, m), 2.35-2.70(8H,m), 3.91(2H, s), 4.39(2H, s), 5.25(2H, brs), 6.06(1H, t), 6.72-6.84(3H, m), 7.23-7.59(9H, m), 8.02-8.06(2H, m), 8.48(1H, dd).

Step 2

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of step 1.

^{1}H-NMR ($CDCl_3$) δ:0.62(4H,s), 1.67-1.72(2H,m), 1.96-2.06(2H,m), 2.34-2.69(8H,m), 3.39(1H,brs), 3.91(2H,s), 3.91(2H,s), 5.26(2H,brs, 6.09(1H,t), 6.72-6.86(3H,M), 7.27-7.60(6H,m), 8.48(1H,dd).

MS m/z: 547(M+1)

Example 305:

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

The titled compound was prepared by following the procedure of example 198, but replacing dimethylamine hydrochloride with 2-hydroxyehylamine.

^{1}H-NMR ($CDCl_3$) δ: 1.65-1.70(2H,m), 2.03-2.06(2H,m), 2.21(1H,d), 2.32-2.68(8H,m), 3.63(2H,dt), 3.83(2H,t), 5.37(2H,brs), 6.18(1H,t), 6.67(1H,brs), 7.25-7.54(7H,m), 7.86(1H,dd), 8,50(1H,dd).

MS m/z: 534(M+1)

Example 306:

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

To a solution of product of example 118 (1.1g) in dimethylformamide (15ml) were added sodium iodide(0.17g), potassium carbonate (0.38 g) and cyclohexyl 1-chloroethyl carbonate (*J. Antibiotics*, 1987, *40*, 81.) (0.57g) at room temperature. The mixture was stirred at 70°C 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 and the residue was purified by silica gel column chromatography (ethyl acetate : methanol = 100 : 3). The obtained oil was dissolved with ethyl acetate, and 4 N hydrochloric acid ethyl acetate solution (0.8ml) was added. The precipitation was filtered to give the titled compound (0.96g).

^{1}H-NMR (DMSO-d_6) δ: 1.22-1.47(6H,m), 1.58(3H,d), 1.63-1.81(6H,m), 2.38-3.30(10H,m), 4.07-4.59(1H,m), 5.80(2H,brs), 6.28(1H,t), 6.87(1H, q), 6.97(1H,d), 7.40-7.49(4H,m), 7.64(1H,dd), 7.79(1H,dd), 7.96(1H,d), 8.03(1H,dd), 8.65(1H,dd), 11.07(1H,brs).

MS m/z: 661[(M-2HCl)+1]

Example 307:

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

The titled compound was prepared by following the procedure of Example 307, but replacing cyclohexyl 1-chloroethyl carbonate with ethyl 1-chloroethyl carbonate.

MS m/z: 607(M+1)

Example 308:

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

Step 1

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(5-formylfuran-2-yl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol was prepared by following the procedure of example 170, but replacing allyltributyltin with (5-formylfuran-2-yl)tributyltin.

1H-NMR (CDC13) δ: 1.40-1.80(2H,m), 1.89-2.12(2H,m), 2.20-2.75(8H,m), 5.28(2H,brs), 6.16(1H,t), 6.69(1H,d), 6.84(1H,d), 7.22-7.55(8H,m), 7.76(1H,d), 8.42(1H,dd), 9.52(1H,s).

Step 2

The titled compound was prepared by following the procedure of example 199, but replacing the product of example 138 with the product of step 1.

MS m/z: 543(M+1)

Example 309:

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

The titled compound was prepared by following the procedure of Example 382, step 2, butreplacing the product of Example 382, step 1 with the product of example 307, step 1.

MS m/z: 557(M+1)

Example 310:

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

The titled compound was prepared by following the procedure of example 171, but replacing t-butyl acrylate with ethyl acrylate.

^{1}H-NMR ($CDCl_3$) δ: 1.33(3H,t), 1.63-1.71(3H,m), 1.98-2.10(2H,m), 2.35-2.72(8H,m), 4.25(2H,q), 5.36(2H,brs), 6.10(1H,t), 6.33(1H,d), 6.85(1H,d), 7.22-7.44(7H,m), 7.58-7.65(2H,m), 8.53(1H,dd).

Example 311:

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

The titled compound was prepared by following the procedure of example 200, but replacing ethylmagnesium bromide with methylmagnesium bromide.

^{1}H-NMR ($CDCl_3$) δ: 0.93(6H,t), 1.60-1.70(6H,m), 1.95-2.10(3H,m), 2.36-2.70(8H,m), 3.79(2H,s), 5.28(2H,brs), 6.09(1H,t), 6.77-6.86(3H,m), 7.24-7.43(5H,m), 7.57(1H,dd), 8.47(1H,dd).

MS m/z: 563(M+1)

Example 312:

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

The titled compound was prepared by following the procedure of example 200, but replacing the product of example 48 with the product of example 138.

^{1}H-NMR ($CDCl_3$) δ: 1.22(6H,s), 1.32(6H,s), 1.66-1.71(2H,m), 1.99-2.10(2H,m), 2.35-2.85(9H,m), 3.77(2H,s), 5.28(2H,brs), 6.04(1H,t), 6.74-6.89(3H,m), 7.26-7.43(5H,m), 7.57(1H,dd), 8.44(1H,dd).

MS m/z: 563(M+1)

Example 313:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-oxopropyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 146, but replacing ethyl iodide with chloracetone.

1H-NMR ($CDCl_3$) δ: 1.62-1.71(3H,m), 1.99-2.10(2H,m), 2.27(3H,s), 2.35-2.70(8H,m), 4.51(2H,s), 5.28(2H,brs), 6.08(1H,t), 6.70-6.84(3H,m), 7.25-7.32(3H,m), 7.41-7.44(2H,m), 7.58(1H,dd), 8.50(1H,dd).

MS m/z: 519(M+1)

Example 314:

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

To a solution of the product of example 274(1.0g) in methylene chloride(200ml) was added manganese(IV) oxide(3.0g), and the suspension was stirred at ambient temperature for 12 hours. The reaction mixture was diluted with ethyl acetate and filtered through Celite. The solvent was evaporated under reduced pressure to give the titled compound(930mg).

^{1}H-NMR ($CDCl_3$) δ: 1.71-1.80(3H,m), 1.98-2.09(2H,m), 2.35-2.43(4H,m), 2.53-2.69(4H,m), 5.30(2H,brs), 6.24(1H,t), 6.95(1H,d), 7.27-7.44(5H,m), 7.61(1H,dd), 7.67(1H,dd), 7.85(1H,d), 8.54(1H,dd), 9.88(1H,s).

Example 315:

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

Step 1

To a solution of example 53, step 1 (7.2g) in dichloromethane (70 ml) was added aluminum chloride (9.1 g) and acetyl chloride (3.2 ml), and the mixture stirred at 0°C for 10 minutes. The reaction mixture was poured into ice. The aqueous layer was extracted with ethyl acetate, and the organic layer was 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 (1:2) to give 7-acetyl-5-(3-bromopropylidene)-5,11-dihydro[1]benzoxepino[2,3-b]pyridine (7.9 g).
^{1}H-NMR ($CDCl_3$) δ:2.57(3H,s), 2.77(2H,m), 3.49(2H,t), 5.40(2H, brs), 6.16(1H,t),6.88(1H,d), 8.33(1H,dd), 7.58(1H,dd), 7.77(1H,dd), 7.96(1H,d), 8.56(1H,dd).

Step 2

The titled compound was prepared by following the procedure of example 44, step 2,but replacing the product of example 44, step 1 with the product of step 1.
^{1}H-NMR ($CDCl_3$) δ:1.52-1.79(2H,m), 1.93-2.11(2H,m), 2.27-2.49(4H,m), 2.49-2.60(5H,m), 2.60-2.73(2H,m), 5.40(2H,brs), 6.22(1H,t),6.87(1H,d), 7.29-7.34(3H,m), 7.42(2H,d), 7.59(1H,dd), 7.75(1H,dd), 7.96(1H,d), 8.53(1H,dd).
MS m/z: 489(M+1)

Example 316:

To a stirred solution of phenol containing the product of Example 44 (1.0 mmol) and K_2CO_3 (1.5 mmol) in THF (10 mL) at RT was added *N, N*-dimethylcarbamoylchloride (1.2 mmol). The reaction was stirred at reflux for 24 hrs. Excess solvent was removed and pure compound was isolated via silica gel chromatography eluting with 5% MeOH/CH_2Cl_2. MS m/z: (M+ 535)

Example 317:

To a stirred solution of phenol containing the product of Example 44 (1.0 mmol) and K_2CO_3 (1.5 mmol) in THF (10 mL) at RT was added morpholinocarbamoylchloride (1.2 mmol). The reaction was stirred at reflux for 24 hrs. Excess solvent was removed and pure compound was isolated via silica gel chromatography eluting with 5% MeOH/CH_2Cl_2. MS m/z: (M+ 577)

Example 318:

To a stirred solution of phenol containing the product of Example 44 (1.0 mmol) in DMF at RT was added NaH (1.5 mmol) followed by the addition of *N*-isopropylisocyanate (1.5 mmol). The reaction was heated to 60°C for 6 hrs. The reaction was quenched with 1.5 equivalents of H_2O and excess DMF was removed under reduced pressure. Residue was charged on a silica gel column and eluted off with 5% $MeOH/CH_2Cl_2$. MS m/z: (M+548)

Example 319:

To a stirred solution of phenol containing the product of Example 44 (1.0 mmol) and K_2CO_3 (1.5 mmol) in THF (10 mL) at RT was added *N*-methyl-*N*-phenylcarbamoylchloride (1.2 mmol). The reaction was stirred at reflux for 24 hrs. Excess solvent was removed and pure compound was isolated via silica gel chromatography eluting with 5% $MeOH/CH_2Cl_2$. MS m/z: (M+ 597)

Example 320:

To a stirred solution of phenol containing the product of Example 44 (1.0 mmol) in DMF at RT was added NaH (1.5 mmol) followed by the addition of *N*-phenylisocyanate(1.5 mmol). The reaction was heated to 60°C for 6 hrs. The reaction was quenched with 1.5 equivalents of H_2O and excess DMF was removed under reduced pressure. Residue was charged on a silica gel column and eluted off with 5% $MeOH/CH_2Cl_2$. MS m/z: (M+ 583)

Example 321:

To a stirred solution of phenol containing the product of Example 44 (1.0 mmol) in DMF at RT was added NaH (1.5 mmol) followed by the addition of *N*-(3-pyridyl)isocyanate(1.5 mmol). The reaction was heated to 60°C for 6 hrs. The reaction was quenched with 1.5 equivalents of H_2O and excess DMF was removed under reduced pressure. Residue was charged on a silica gel column and eluted off with 5% $MeOH/CH_2Cl_2$. MS m/z: (M+ 584)

Example 322:

To a stirred solution of phenol containing the product of Example 44 (1.0 mmol) and K_2CO_3 (1.5 mmol) in THF (10 mL) at RT was added pyrolidinylcarbamoylchloride
(1.2 mmol). The reaction was stirred at reflux for 24 hrs. Excess solvent was removed and pure compound was isolated via silica gel chromatography eluting with 5% $MeOH/CH_2Cl_2$. MS m/z: (M+ 560)

Example 323:

The compound was prepared by following the procedure for example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-4-cyanopiperidine. MS m/z: (M+ 486).

Example 324:

To a cold (0°C) stirred solution of Example 323 (0.50 g, 0.104 mmol) in anhydrous THF (5 mL) was added lithium aluminum hydride (8 mg, 0.21 mmol). The reaction was stirred at RT for 2 hrs. The reaction was then quenched by the careful addition of H_2O (0.21 mL), 15% aqueous KOH (0.21 mL), then H_2O (0.21 mL). The organic layer was separated and dried over Na_2SO_4. The compound was purified via silica gel flash chromatography eluting with 10% methanol/methylene chloride. MS m/z: (M+ 490).

Example 325:

The compound can be obtained by the reduction of the azido functionality of Example 187 with a reducing agent, such as triphenyl phoshine, lithium aluminum hydride, sodium borohydride, in a solvent such as tetrahydrofuran or diethyl ether in reaction temperature ranges from 0°C to reflux with a reaction time between 5 minutes and 72 hours.

Example 326:

The compound was prepared by following the procedure for example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-4-methylpiperidine provide in Example 329, steps 1-3. MS m/z: (M+ 475)

Example 328:

Step 1

N-benzyl-4-(4-chlorophenyl)-4-hydroxypiperidine: Fig. 8a

To a stirred solution of commercially available 4-(4-chlorophenyl)-4-hydroxypiperidine (10 g, 47 mmol., **1**) in anhydrous DMF (10 mL) was added benzyl bromide (5.6 mL, 47 mmol) and K_2CO_3 (7.4 g, 94 mmol.) and stirred at RT overnight. Excess solvent was removed under reduced pressure, brought up into CH_2Cl_2 (100 mL) washed with H_2O (2 X 50 mL). Organic layer separated, dried over Na_2SO_4 and charged on a silica gel flash column. Eluting off with 2% MeOH/CH_2Cl_2 10 g **2** (80% yield) was obtained as a viscous liquid. MS m/z: (M+ 303)

Step 2

N-benzyl-4-(4-chlorophenyl)-4-fluoropiperidine: Fig. 8a

To a cold (-78°C) solution of **2** (10 g, 33 mmol) in CH_2Cl_2 (20 mL) was slowly added DAST (diethylaminosulfur trifluoride, 5.3 mL, 39.8 mmol) under an inert atmosphere. The reaction was stirred at –78°C for an additional 45 min. The reaction was quenched at –78°C by the slow addition of enough saturated aqueous sodium bicarbonate solution to afford a pH >8. This reaction resulted a quantitative conversion of the starting material to a 1:1 mixture of fluoropiperidine **3** and 4-(4-chlorophenyl)tetrahydropyridine **4.** The mixture of **3** and **4** (3.5 g, mixture, ~35% yield) was purified via silica gel flash chromatography, eluting with 2% MeOH/CH_2Cl_2. This mixture proved to be inseparable by silica gel flash chromatography. In order to separate out the desired product, the mixture of **3** and **4** were subjected to osmium tetroxide oxidation.

To a stirred solution of the mixture of **3** and **4** (1.8 g) in acetone/H_2O (5:1, 10 mL) was added a catalytic amount of OsO_4 in isopropanol (2.5 mol %, 1 mL) and *N*-methylmorpholine-*N*-oxide (0.69 g, 6.56 mmol). The reaction was stirred at RT overnight. The reaction was then evaporated to dryness, brought up into CH_2Cl_2 and washed with NaHSO3. This reaction resulted in the dihydroxylation of the undesired **4** to **5** and the clean separation of the desired fluoropiperidine **3** (1.0 g, 55% yield) from the byproduct by silica gel flash chromatography eluting with 2% MeOH/CH_2Cl_2. MS m/z: (M+306)

Step 3

4-(4-chlorophenyl)-4-fluoropiperidine: Fig. 8a

To a cold (0°C) solution of **3** (1.07 g, 3.5 mmol) in 1,2-dichloroethane was added 1,1-chloroethylchloroformate (0.45 mL, 4.2 mmol). The reaction was then heated to reflux for 2 hrs. Excess solvent was removed and the residue was brought up into 5 mL methanol. The mixture was refluxed for 2 hrs and excess methanol was removed under reduced pressure. Precipitation of the hydrochloride salt of **6** by the addition of CH_2Cl_2/hexane (1:1) followed by filtration resulted in the quantitative isolation of the desired crystalline product **6** (80%, 0.70 g). MS m/z: (M+215)

Step 4

The compound was prepared by following the procedure for example 44, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-4-fluoropiperidine. MS m/z: (M+ 466).

Example 329:

Step 1

N-benzyl-4-methylpiperidine: Fig. 8c

To a cold (-78°C) stirred solution of 1.4 M methyllithium in THF (39 mL, 54 mmol) under an inert atmosphere was added *N*-benzyl-4-oxopiperidine (**1**, 5.1 g, 27 mmol). The reaction was stirred at –78°C for 2hrs. The reaction was quenched by the slow addition of saturated aqueous NH_4Cl, the organic layer was separated and dried over Na_2SO_4. Pure methylpiperidine (**2**) was isolated via silica gel flash chromatography eluting with 5% $MeOH/CH_2Cl_2$. MS m/z: (M+206)

Step 2

N-benzyl-4-(4-chlorophenyl)-4-methylpiperidine: Fig. 8c

To a flask containing chlorobenzene (10 mL, excess) and methylpiperidine (0.42 g, 2.06 mmol, **2**) was added aluminum trichloride (1.65 mL, 12.4 mmol). The reaction was heated to reflux for 24 hrs. Excess chlorobenzene was removed under reduced pressure and pure **3** was obtained via silica gel flash chromatography eluting with % EtOAc/hexane. MS m/z: (M+ 300)

Step 3

4-(4-chlorophenyl)-4-methylpiperidine: Fig. 8c

To a cold (0°C) solution of *N*-benzyl-4-(4-chlorophenyl)-4-methylpiperidine (**3**) (0.41 g, 1.4 mmol) in CH_2Cl_2 was 1.1 equivalent of 1-chloroethylchloroformate. The reaction was then heated to reflux for 2 hrs. Excess solvent was removed and the residue was brought up into methanol. The mixture was refluxed for 2 hrs and excess methanol was removed under reduced pressure. Precipitation of the hydrochloride salt **4** by the addition of CH_2Cl_2 followed by filtration resulted in the quantitative isolation of the desired crystalline product **4** (100%, 0.34 g). MS m/z: (M+ 210)

Step 4

The compound was prepared by following the procedure for example 44, step 2, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-4-methylpiperidine. MS m/z: (M+ 461)

Example 330:

The compound was prepared by following the procedure for example 199, but replacing the resultant compound of example 44 with the resultant compound of Example 329. MS m/z: (M+ 533)

Example 331:

Step 1

A mixture of epichlorohydrin (5.92 g, 64 mmol) and benzhydrylamine (11.7 g, 64 mmol) in MeOH (120 mL) was stirred under the protection of argon at room temperature for 48 hours. The mixture was then stirred at 50°C for 72 hours. The reaction mixture was then stirred at room temperature for 72 hours. The reaction mixture was concentrated in vacuo and partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (200 mL x 3), dried over $MgSO_4$ and concentrated in vacuo. Chromatographic purification on silica gel (CH_2Cl_2/MeOH = 95/5) provided 10.0 g (65%) of 1-benzhydril-3-hydroxyazetidine. m/z 240 (m+1)

Step 2

A mixture 1-benzhydril-3-hydroxyazetidine (2.6 g, 11 mmol) and palladium hydroxide on active carbon (0.26 g, w/w 20%) in EtOH (40 mL) was shaken in hydrogenation parr under 60 psi for 24 hours. The reaction mixture was filtered through celite and concentrated under vacuum. Concentration in vacuo provided 0.75 (95%) 3-hydroxyazetidine. ^{1}H NMR (250 MHz, CD3OD) 3.81-3.92 (2H, m), 4.14-4.25 (2H, m), 4.61-4.69 (1H, m).

Step 3

The compound 1-[3-(5,11-dihydro-7-(methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]azetidin-3-ol was prepared by following the procedure for example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 3-hydroxyazetidine. m/z 339 (m+1).

Step 4

To a mixture of morpholine N-oxide (0.028 g, 0.244 mmol), crushed molecular sieves (0.066 g) and $Pr_4N^+RO_4$ (0.01 g, 0.024 mmol) in CH_2Cl_2 was added the 1-[3-(5,11-dihydro-7-(methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]azetidin-3-ol (0.055 g, 0.16 mmol) under the protection of argon. The mixture was stirring over night at room temperature. The reaction mixture was filtered off through celite and concentrated under vacuum. Chromatographic purification on silica gel (CH_2Cl_2/MeOH = 95/5 to 9/1) provided 0.033 g 1-[3-(5,11-dihydro-7-(methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]azetidin-3-one (60%) of the desired product. m/z 337 (m+1)

Step 5

To a solution of 1-[3-(5,11-dihydro-7-(methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]azetidin-3-one (0.06 g, 0.18 mmol) in THF (8 mL) was added dropwise a solution of 4-chlorophenyl magnesium bromide in diethyl ether (1.0 M, 0.27 mL) under the the protection of argon at 0°C. The reaction was stirred at room temperature for 1.5 hours and quenched by the addition of saturated aqueous NH_4OH (4 mL). The aqueous layer was extracted with EtOAc (10 mL x 2), dried over MgSO4 and concentrated in vacuo. Chromatographic purification on silica gel (CH_2Cl_2/MeOH = 95/5) provided 0.048 g 3-(4-chlorophenyl)-1-[3-(5,11-dihydro-7-(methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]azetidine (51%) m/z 449 (m+1)

Example 332:

Step 1

tert-Butyl 3-(4-chlorobenzoyl)-1-(2-aminoethyl) carbamate: Fig. 10b

tert-Butyl *N*-(2-aminoethyl) carbamate (**1**, 0.50 g g, 3.12 mmol) was added to the mixture of 4-chlorobenzoic acid chloride (0.547 g, 3.12 mmol) and Et_3N (1.74 mL, 12.5 mmol) in CH_2Cl_2 (20 mL) under the protection of argon. Stirring at room temperature for 2 hours. The reaction mixture was diluted with H_2O (25 mL), extracted with CH_2Cl_2 (50 mL x 2), dried over $MgSO_4$ and concentrated in vacuo. Chromatographic purification on silica gel (CH_2Cl_2/MeOH = 95/5) to provide 0.86

g (**2**, 93%) of the desired product *tert*-Butyl 3-(4-chlorobenzoyl)-1-(2-aminoethyl) carbamate. MS m/z: (M+ 299).

Step 2

1-(4-chlorobenzoyl)-1,2-ethylenediamine: Fig. 10b

Trifluoroacetic acid (7.5 mL) was added to the solution of *tert*-Butyl 3-(4-chlorobenzoyl)-1-(2-aminoethyl)carbamate (**2**, 0.86 g, 2.89 mmol) in CH_2Cl_2 (35 mL) at 0°C. Stirring at room temperature for 30 minutes. Concentration in vacuo provided 0.88 g (95%) of the desired product 1-(4-chlorobenzoyl)-1,2-ethylenediamine (**3**). MS m/z: (M+ 199).

Step 3

The compound was prepared by following the procedure for example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 1-(4-chlorobenzoyl)-1,3-propylenediamine. MS m/z: (M+ 465).

Example 333:

Step 1

2-(4-Chlorophenyl)-1-bromoethylene: Fig. 9c

To a solution of $AlCl_3$ (1.96 g, 14.7 mmol) in anhydrous CH_2Cl_2 (50 mL), Borane-*tert*-butyl amine complex (2.57 g, 29.6 mmol) was added at 0°C under argon protection, stirred for 10 minutes and clear solution was formed. 4-Chlorophenacyl bromide (**1**, 1.11 g, 4.91 mmol) in CH_2Cl_2 (5 mL) was added to the resulted mixture at 0°C. The reaction was stirred for 1.5 hours and then quenched by the addition of 0.1 N HCl (25 mL). The mixture was extracted with EtOAc (80 mL x 3), dried over MgSO4 and concentrated in vacuo. Chromatographic purification on silica gel (Hexane/EtOAc = 9:1) provided 0.85 g (84%) of 2-(4-chlorophenyl)-1-bromoethylene (**2**). MS m/z: (M+ 219).

Step 2

2-(4-chlorophenyl)-1-(*N*-methyl)ethylamine: Fig. 9c

A mixture of 2-(4-chlorophenyl)-1-bromoethylene (**2**, 1.02 g, 4.62 mmol), EtOH (3 mL) and H_2NMe in H_2O (6 mL, 40% w/w) was heated at 135 0°C over night. The mixture was cooled down to room temperature. The mixture was extracted with Et_2O (5mL x 2), dried over $MgSO_4$ and concentrated in vacuo. Chromatographic purification on silica gel (CH_2Cl_2/MeOH/NH_4OH = 9/1/0.1) provided 0.61 g 2-(4-chlorophenyl)-1-(*N*-methyl)ethylamine (**3**, 79%). MS m/z: (M+ 170).

Step 3

The compound was prepared by following the procedure for example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 2-(4-chlorophenyl)-1-(*N*-methyl)ethylamine. MS m/z: (M+ 451).

Example 334:

Step 1

3-(4-chlorophenyl)-1-*N*-methylaminopropane: Fig. 9e

A mixture of 3-(4-chlorophenyl)-1-bromoropane (**1**, 0.70 g, 3.73 mmol), EtOH (3 mL) and H_2NMe in H_2O (6 mL, 40% w/w) was heated at 135 0°C overnight. The mixture was then cooled down to room temperature. The mixture was extracted with Et_2O (5 mL x 2), dried over $MgSO_4$ and concentrated in vacuo. Chromatographic purification on silica gel (CH_2Cl_2/MeOH/NH_4OH = 9/1/0.1) provided 0.5 g (76%) of 3-(4-chlorophenyl)-1-*N*-methylaminopropane (**2**). MS m/z: (M+ 189).

Step 2

The compound was prepared by following the procedure for example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 3-(4-chlorophenyl)-1-*N*-methylaminopropane. MS m/z: (M+ 450).

Example 335:

Step 1

3-(4-chlorophenyl)-3-chloro-1-hydroxypropane: Fig. 9d

To 3,4'-Dichloropropylphenone (0.52 g, 2.53 mmol) in anhydrous MeOH (10 mL) at 0°C under the protection of argon, $NaBH_4$ (0.23 g, 3.03 mmol) was added to the solution by several portions. The reaction was stirred under the same condition for 15 minutes. The mixture was warmed up to room temperature, stirred an additional 30 minutes, then concentration in vacuo. The residue was partitioned between EtOAc and H_2O. The aqueous layer was re-extracted with EtOAc (30 mL x 2), dried over $MgSO_4$ and concentrated in vacuo. Chromatographic purification on silica gel (Hexane/EtOAc = (1/1) provided 0.52 g (99%) of 3-(4-chlorophenyl)-3-chloro-1-hydroxypropane. MS m/z: (M+205).

Step 2

The compound was prepared by following the procedure for example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 3-(4-chlorophenyl)-3-chloro-1-hydroxypropane. MS m/z: (M+ 481).

Example 336:

Step 1

3-(4-chlorophenyl)-3-hydroxy-3-methyl-1-chloropropane: Fig. 10a

To 3,4'-Dichloropropylphenone (**1**, 1.10 g, 5.40 mmol) in anhydrous THF at 0°C under the protection of argon, was added MeMgBr (2.50 mL, 7.35 mmol) dropwise at 0°C. The reaction was stirred at room temperature for an additional hour. The reaction was quenched by adding saturated aqueous NH_4Cl. The reaction was then extracted with Et_2O (60 mL x 2), dried over $MgSO_4$ and concentrated in vacuo. Chromatographic purification on silica gel (Hexane/EtOAc = 10/1) provided 1.0 g (85%) of 3-(4-chlorophenyl)-3-hydroxy-3-methyl-1-bromoropane (**2**). MS m/z: (M+ 219).

Step 2

3-(4-chlorophenyl)-3-hydroxyl-3-methyl-1-*N*-methylaminopropane: Fig. 10a

A mixture of 3,3,3-(4-Chlorophenyl)-hydroxylmethyl-1-bromoropane (**2**, 1.04 g, 4.74 mmol), EtOH (5 mL) and H_2NMe in H_2O (10 mL, 40% w/w) was heated at 135 0°C for 3 hours. The mixture was cooled down to room temperature. The mixture was extracted with Et_2O (5mL x 2), dried over $MgSO_4$ and concentrated in vauco. Chromatographic purification on silica gel

(CH_2Cl_2/MeOH/NH_2OH = 9/1/0.1) provided 1.01 g 3-(4-chlorophenyl)-3-hydroxyl-3-methyl-1-*N*-methylaminopropane (**3**, 99%). MS m/z: (M+ 214).

Step 3

The compound was prepared by following the procedure for example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 3-(4-chlorophenyl)-3-hydroxyl-3-methyl-1-*N*-methylaminopropane. MS m/z: (M+ 480).

Example 345:

Using the procedure of Example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 1-azaxanthone, gives the desired compound.

Example 346:

Using the procedure of Example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 1-4-azafluorene, gives the desired compound.

Example 347:

Using the procedure of Example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 7-amino-1-azaxanthone, gives the desired compound.

Example 348:

Using the procedure of Example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 4,5-diazafluorene, gives the desired compound.

Example 349:

Using the procedure of Example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 1-aza-7-nitroxanthone, gives the desired compound.

Example 350:
3-(4-chlorophenyl)-1-[3-(5,11-dihydro-7-(methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]pyrrolidine

Step 1

A mixture of 1-benzyl-3-pyrrolidinone (10.0 g, 57 mmol), di-*tert*-butyl dicarbonate (13.7 g, 63 mmol) and palladium on active carbon (2.5 g, w/w 20%) in MeOH was shaken in a Parr hydrogenation vessel (50 psi H_2) for 48 hours. The reaction mixture was filtered through celite and concentrated in vacuo. Chromatographic purification on silica gel (Hexane/EtOAc = 1/1) provided 6.21 g 1-*t*-butoxycarbonyl-3-pyrrolidinone (59%). ^{1}H NMR (250 MHz, CDCl3) δ: 1.46 (9H, s), 2.57 (2H, t, J = 7.8 Hz), 3.71-3.75 (4H, m)

Step 2

To a stirred solution of 1-*t*-butoxycarbonyl-3-pyrrolidinone (0.57 g, 3.23 mmol) in THF (10 mL) was added 4-chlorophenyl magnesium bromide (1.0 M, 5.2 mL) under the protection of argon at 0°C. The reaction was stirred at room temperature for 1 hour then quenched by the addition of saturated aqueous NH_4OH (8 mL). The aqueous layer was extracted with EtOAc (50 mL x 2), dried over $MgSO_4$ and concentrated in vacuo. Chromatographic purification on silica gel (Hexane/EtOAc = 3/1) provided 0.57 g 1-*t*-butoxycarbonyl-3-(4-chlorophenyl)-3-hydroxypyrrolidine (60%). m/z 298 (m+1)

Step 3

To a stirred solution of 1-*t*-butoxycarbonyl-3-(4-chlorophenyl)-3-hydroxypyrrolidine (0.335 g, 1.28 mmol) in CH_2Cl_2 (8 mL) was added trifluoroacetic acid (2 mL) at 0°C slowly. The reaction was stirred at room temperature for 30 minutes and concentrated in vacuo. This provided 0.355 g 3-(4-chlorophenyl)-3-hydroxypyrrolidine (100%) the desired product. m/z 198 (m+1)

Step 4

The titled compound was prepared by following the procedure for example

44 but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 3-(4-chlorophenyl)-3-hydroxypyrrolidine. m/z 432 (m+1).

Example 351:

Step 1

4-(4-chlorophenyl)-4-pyridine: Fig 10d

To a solution of 4-bromopyridine (**1**, 1.94 g, mmol), 4-chlorophenylboronic acid (**2**, 1.56 g, mmol) and K_2CO_3 (2.76 g, 2.0 equiv) in ethanol/toluene (5mL/100mL) was added $Pd(PPh_3)_3$. The reaction was refluxed for 1 hr, cooled back down to RT and quenched with H_2O (15 mL). The reaction mixture was extracted with EtOAc and the organic layer was dried over Na_2SO_4. Pure 4-(4-chlorophenyl)-4-pyridine **2** (1.3g, 68% yield) was isolated after silica gel flash column purification eluting with 50% EtOAc/hexane. MS m/z: (M+191).

Step 2

T he titled compound was prepared by following the procedure for example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-4-pyridine. MS m/z: (M+456).

Example 352:

The compound was prepared by following the procedure for example 44, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-4-pyridine. MS m/z: (M+442).

Example 353:

5-(2-(N-(4-(4-Chlorophenyl)-4-hydroxycyclohexyl)-N-methyl)ethylidene)-5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridine

The compound was prepared by the procedure of Example 57, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-N-methyl-(4-chlorophenyl)-4-hydroxycyclohexylamin. The starting material can be prepared according to methods disclosed in Journal of Medicinal Chemistry, Vol. 15, No. 12, pp.1239-1243 (1972).

Example 354:

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

Step 1

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

was prepared by following the procedure of example 46, but replacing ethyl iodide with

ethyl 4-fluorobenzoate

^{1}H-NMR ($CDCl_3$) δ: 1.36(3H,t), 1.65-2.07(4H,m), 2.32-2.63(8H,m), 4.34(2H,q),5.33(2H,brs), 6.07(1H,t). 6.88-7.10(5H,m), 7.27-7.51(5H,m), 7.58(1H,dd), 7.97-8.00(2H,m), 8.49(1H, dd).

Step 2

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of step 1.

^{1}H-NMR (DMSO-d6) δ: 1.44-1.49(2H, m), 1.67-1.87(2H,m), 2.26-2.56(8H,m),4.85(1H,brs), 5.29(2H,brs), 6.17(1H,t), 6.88-7.09(5H,m), 7.33-7.48(5H,m), 7.75(1H,dd), 7.89-7.93(2H,m), 8.52(1H,dd).

MS m/z: 582(M)

Example 355:

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

To a solution of the product of example 313 (300mg) in ethanol (3,ml) was added hydroxylammonium chloride (80mg) at room temperature, and the mixture was stirred for 1 hour. The precipitation was filtered and washed with ethanol to give the titled compound (300mg).

^{1}H-NMR (DMSO-d6) δ: 1.75-1.80(2H,m). 2.23-2.42(2H,m), 2.53(3H,s)3.16-3.48(8H,m), 4.54(2H,s), 5.19(2H,brs), 5.57(1H,s), 6.14(1H,t), 6.76-6.98(3H,m),7.41-7.48(5H,m), 7.79(1H,dd), 8.53(1H,dd), 10.93(1H,s).

MS m/z: 515(M+1)

Example 356:

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

Step 1

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-ethoxycarbonyl-2-methylproyl)oxy)[1] benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol was prepared by following the procedure of example 46, but replacing ethyl iodide with ethyl 2-bromo-1,1-dimethyl propionate.

^{1}H-NMR ($CDCl_3$) δ: 1.31(6H,s), 1.67-1.72(2H,m), 1.96-2.15(2H,m), 2.39-2.78(8H,m), 3.69(3H,s), 3.93(2H,s), 5.27(2H, brs), 6.09(1H,t), 6.70-6.83(3H,m), 7.23-7.59(6H,m), 8.46(1H,dd).

Step 2

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of step 1.

^{1}H-NMR (DMSO-d6) δ: 1.46-1.50(2H,m), 1.74-1.85(2H,m), 2.22-2.38(8H,m),3.92(2H,s), 4.58(1H,brs), 5.19(2H,brs), 6.18(1H,t), 6.71-6.83(3H,m), 7.33-7.48(5H,m), 7.72(1H,dd), 8.49(1H,dd).

MS m/z: 514(M+1)

Example 357:

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

The titled compound was prepared by following the procedure of Example 354, but replacingthe product of example 313 with the product of example 315.
[1]H-NMR (DMSO-d6) δ: 1.39-1.54(2H,m), 1.64-1.86(2H,m), 2.13(3H,s), 2.19-2.36(4H,m), 2.36-2.52(4H,m), 4.83(1H,s), 5.28(2H,brs), 6.20(1H,t), 6.80(1H,d),7.35(2H,d), 7.43-7.49(4H,m), 7.58(1H,d), 7.76(1H,d), 8.51(1H,dd), 11.04(1H,s).
MS m/z: 504(M+1)

Example 358:
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-propionyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 315, but replacing acetyl chloride with propionyl chloride.
[1]H-NMR ($CDCl_3$) δ:1.22(3H,t), 1.63-1.77(2H,m), 1.97-2.13(2H,m), 2.25-2.48(4H,m), 2.48-2.60(2H,m). 2.60-2.73(2H,m), 2.96(2H,q), 5.41(2H,brs), 6.21 (1H,t),6.86(1H,d), 7.30-7.34(3H,m), 7.43(2H,d), 7.59(1H,d), 7.75(1H,dd), 7.97(1H,d),8.53(1H,d).
MS m/z: 503(M+1)

Example 359:
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-isobutyry[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 315, but replacing acetyl chloride with isobutyryl chloride.
1H-NMR ($CDCL_3$) δ: 1.21-1.33(2H,m), 1.76-2.00(2H,m), 2.46-3.47(8H, m), 3.53(1H,m), 5.47(2H,brs), 6.09(1H,t), 6.89(1H,d), 7.32-7.45(6H,m), 7.64(1H,d),7.79(1H,dd), 7.94(1H,d), 8.57(1H,d).
MS m/z: 517(M+1)

Example 360:

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

The titled compound was prepared by following the procedure of Example 315, but replacing acetyl chloride with cyclopropylacetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 0.98-1.05(2H,m), 1.20-1.24(2H,m), 1.58-1.70(2H,m), 1.99-2.09(2H,m), 2.34-2.55(4H,m), 2.58-2.68(5H,m), 5.40(2H,brs), 6.23(1H,t), 6.89(1H,d), 7.30-7.34(3H,m), 7.43(2H,d), 7.59(1H,dd), 7.86(1H,dd), 8.00(1H,d), 8.53(1H, dd).

MS m/z: 515(M+1)

Example 361:

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

Step 1

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(3-methoxycarbonylpropionyl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)piperidin-4-ol was prepared by following the procedure of Example 315, but replacing acetyl chloride with methyl succinyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.57-1.77(4H,m), 1.94-2.14(4H,m), 2.27-2.61(6H,m) 2.61-2.73(2H,m), 3.67(3H,s), 4.70(1H,t), 5.30(2H,brs), 6.11(1H,t), 6.83(1H,d), 7.14(1H,d), 7.29-7.32(4H,m), 7.42(2H,d), 7.58(1H,d), 8.50(1H,d).

Step 2

The titled compound was prepared by following the procedure of Example 133, but replacing the product of example 48 with the product of step 1.

^{1}H-NMR (DMSO-d6) δ: 1.37-1.57(2H,m), 1.63-1.86(2H,m), 2.13-2.37(4H,m), 2.45-2.63(4H,m), 3.17-3.28(4H, m), 4.85(1H,brs), 5.36(2H,brs), 6.30(1H, t), 6.91(1H, d),7.35(2H,d), 7.46-7.50(3H,m), 7.78-7.83(2H,m), 7.95(1H, d), 8.53(1H,dd).

MS m/z: 547(M+1)

Example 362:

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

The titled compound was prepared by flowing the procedure of example 242, but replacing methylmagnesium bromide with ethylmagnesium bromide.

^{1}H-NMR ($CDC1_3$) δ: 0.79(6H,t), 1.65-2.04(9H,m), 2.35-2.66(8H, m), 5.37(2H, brs),6.09(1H,t), 6.81(1H,d), 7.10(1H, dd), 7.26-7.51(6H, m), 7.59(1H, dd), 8.49(1H, dd).

MS m/z: 533(M+1)

Example 363:

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

Step 1

5-(3-bromopropylidene)-7-(1-hydroxy-1-methyl)ethyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridine was prepared by following the procedure of Example 200, but replacing the product of example 48 with the product of example 315,

step1.

^{1}H-NMR ($CDC1_3$) δ: 1.58(6H, s), 2.74(2H, q), 3.47(2H,t), 5.34(2H, brs), 6.09(1H, t), 6.82(1H, d), 7.25-7.31(2H, m), 7.45(1H, d), 7.57(1H, dd), 8.52(1H, dd).

Step 2

To a solution of the product of step 1 (3.8 g) in dichloromethane (40 ml) was added trimethylsilyl cyanide (4.1 ml) and boron trifluoride diethyl etherate (2.5 ml) at 0 ^{0}C, and the mixture stirred at room temperature for 10 minutes. The reaction mixture was poured into saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate, and the organic layer was 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 (1:3) to give 5-(3-

bromopropylidene)-7-(-1-cyano-1-methyl)ethyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridine (3.4 g).

^{1}H-NMR ($CDCl_3$) δ: 1.58(6H,s), 2.76(2H,m), 3.48(2H,t), 5.34(2H,brs), 6.09(1H,t),6.87(1H,d), 7.22(1H,dd), 7.32(1H,dd), 7.42(1H,d), 7.58(1H,dd), 8.55(1H,dd).

Step 3

The titled compound was prepared by following the procedure of example 44, step 2,but replacing the product of example 44, step 1 with the product of step 2.

^{1}H-NMR ($CDCl_3$) δ: 1.58(6H,s), 1.60-1.70(2H,m), 1.93-2.12(2H,m), 2.30-2.47(4H,m), 2.50-2.74(4H, m), 5.31(2H,brs, 6.15(1H,t), 6.86(1H, d), 7.19(1H,dd), 7.28-7.32(3H, m), 7.41-7.43(3H, m), 7.61(1H,d), 8.53(1H, dd).

MS m/z: 514(M+1)

Example 364:

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

The titled compound was prepared by following the procedure of example 44, step 2,but replacing the product of example 44, step 1 with 5-(3-bromopropylidene)-7-cyano-5,11-dihydro[1]benzoxepino[2,3-b]pyridine.

^{1}H-NMR ($CDCL_3$) δ: 1.62-1.75(2H, m), 1.98-2.09(2H, m), 2.36-2.69(8H, m), 5.36(2H,brs), 6.19(1H, t), 6.89(1H, d), 7.29-7.62(8H, m), 8.55(1H, d).

MS m/z: 472(M+1)

Example 365:

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

To a solution of the product of Example 364 (1.0g) in DMF (10ml) were added sodium azide (0.69g) and ammonium chloride (0.56g) and the mixture stirred at 100 ^{0}C for 36 hour. Water was added to the reaction mixture, and the precipitate was filtered and washed with ethanol to give the titled compound (800mg).

^{1}H-NMR (DMSO-d6) δ: 1.66-1.71(2H, m), 1.91-2.01(2H, m), 2.86-3.09(8H, m),5.33(2H, brs), 6.22(1H, t), 6.91(1H, d), 7.39-7.51(5H, m), 7.79-7.84(2H, m), 8.03(1H,d), 8.55(1H, dd).
MS m/z: 515(M+1)

Example 366:
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(hydroxyiminomethyl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 357, but replacing the product of example 315, step 2 with the product of example 314.
^{1}H-NMR (DMSO-d6) δ: 141-1.52(2H, m), 1.70-1.82(2H, m), 2.27-2.46(8H, m),4.83(1H, s), 5.37(2H, brs), 6.20(1H, t), 6.83(1H, d), 7.34-7.53(7H, m), 7.76(2H, dd),
MS m/z: 490(M+1)

Example 367:
1-(4-Chlorophenyl)-4-[3-(5,11-dihydro-7-(1-hydroxy-1-methyl)ethyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperazine

The titled compound was prepared by following the procedure of example 71, but replacing the product of example 45, step 2 with the product of Example 363, step 1.
^{1}H-NMR ($CDCl_3$) δ: 1.58(6H, s), 2.31-2.63(8H, m), 3.02-3.20(4H, m), 5.32(2H, brs),6.12(1H, t), 6.79-6.83(3H, m), 7.17-7.31(6H, m), 7.45(1H, d), 7.58(1H, dd), 8.51(1H,dd).
MS m/z: 490(M+1)

Example 368:
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-sulfamoyl[1]benzoxepino[2,3-b]pyridin-5-

ylidene)propyl]piperidin-4-ol

Step 1

To the product of example 53, step 1 (5.4g) was added chlorosulfonic acid (50ml) and the mixture stirred at 0^0C for 1 hour. The reaction mixture was poured to ice, and ethyl acetate was 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. To the residue were added THF (250ml) and ammonium hydroxide (30ml) and the mixture stirred at room temperature for 10 minutes. Ethyl acetate and water 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. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:1) to give 5-(3-bromopropylidene)-5,11-dihydro-7-sulfamoyl[1]benzoxepino[2,3-b]pyridine(5.0g).

^{1}H-NMR ($CDCl_3$) δ: 2.70-2.75(2H, m), 3.48(2H, t), 5.39-5.49(4H, m), 6.16(1H, t),6.88(1H,d), 7.25-7.34(2H,m), 7.53(1H, dd), 7.68(1H, dd), 7.93(1H, d), 8.53(1H, dd).

Step 2

The titled compound was prepared by following the procedure of example 44, step 2,but replacing the product of example 44, step 1 with the product of step 1.

^{1}H-NMR (DMSO-d6) δ: 1.65-1.70(3H, m), 1.98-2.07(2H, m), 2.35-2.64(8H, m),4.98(2H, brs), 5.39(2H, brs), 6.22(1H, t), 6.92(1H, d) 7.26-7.43(5H, m), 7.55-7.69(2H, m), 7.91(1H, d), 8.53(1H, dd).

MS m/z: 526(M+1)

Example 369:

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

Step 1

7-bromoacetyl-5-(3-bromopropylidene)-5, 11-dihydro[1]benzoxepino[2,3-b]pyridine

was prepared by following the procedure of example 315, step 1, but replacing acetyl chloride with bromoacetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 2.77(2H, m), 3.50(2H, m), 4.40(2H, s), 5.45(2H, brs), 6.17(1H, t),6.90(1H, d), 7.35(1h, dd), 7.60(1H, dd), 7.79(1H, dd), 8.01(1H, d), 8.57(1H, dd).

Step 2

To a solution of the product of step 1 (1.1 g) in ethanol (11 ml) was added thiourea (193mg) at room temperature, and the mixture stirred at 70^{0}C for 30 minutes. The reaction mixture was cooled to room temperature and poured into saturated aqueous sodiumbicarbonate. The aqueous layer was extracted with ethyl acetate, and the organic layer was 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 to give 7-(2-aminothiazol-4-yl)-5-(3-bromopropylidene)-5,11-dihydro[1]benzoxepino[2,3-b]pyridine (749 mg).

^{1}H-NMR ($CDCl_3$) δ: 2.74(2H, m), 3.47(2H, t), 5.02(2H, brs), 5.39(2H, brs), 6.16(1H, t),6.62(1H, s), 6.85(1H, d), 7.30(1H, dd), 7.54-7.57(2H, m), 7.77(1H, d), 8.53(1H, dd).

Step 3

The titled compound was prepared by following the procedure of example 44, step 2, but replacing the product of example 44, step 1 with the product of step 2.

^{1}H-NMR ($CDCl_3$) δ: 1.57-1.70(2H, m), 1.83-2.13(2H, m), 2.30-2.46(4H, m), 2.46-2.60(2H, m), 2.60-2.73(2H, M), 5.02(2H, s), 5.37(2H, brs), 6.20(1H, t), 6.61(1H, s),6.85(1H, d), 7.27-7.32(3H, m), 7.42(2H, d), 7.50-7.58(2H, m), 7.76(1H, d), 8.50(1H,
dd).

MS m/z: 545(M+1)

Example 370:

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

Step 1

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(3-methoxycarbony-1-hydroxy)propyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol was prepared by following the procedure of example 199, but replacing the product of example 138 with the product of Example 361, step 1.

^{1}H-NMR ($CDCl_3$) δ: 1.57-1.77(4H, m), 1.94-2.14(4H, m), 2.27-2.61(6H, m), 2.61-2.73(2H, m), 3.67(3H, s), 4.70(1H, t), 5.30(2H, brs), 6.11(1H, t), 6.83(1H, d), 7.14(1H,d), 7.29-7.32(4H, m), 7.42(2H,d), 7.58(1H, d), 8.50(1H, d).

Step 2

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product step 1.

^{1}H-NMR (DMSO-d6) δ: 1.44-1.63(2H, m), 1.69-1.90(2H, m), 2.17-2.29(2H, m), 2.29-2.82(6H, m), 3.24-3.53(4H, m), 4.49(1H, t), 5.03(1H, brs), 5.20(2H, brs), 6.13(1H, t),6.76(1H, d), 7.12(1H, dd), 7.27(1H, d), 7.37(2H, d), 7.43-7.48(3H, m), 7.76(1H, d),
8.32(1H, s), 8.51(1H, dd).

MS m/z: 549(M+1)

Example 371:

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

The titled compound was prepared by following the procedure of example 134, but replacing dimethylamine hydrochloride with 2-fluoroethylamine.

^{1}H-NMR ($CDCl_3$) δ: 1.62-1.71(3H, m), 1.98-2.10(2H, m), 2.36-2.71(8H, m), 3.63(1H, q), 3.73(1H, q), 4.46(1H, t), 4.49(2H, s), 4.63(1H, t), 5.29(2H, brs), 6.10(1H, t), 6.75-6.96(4H, m), 7.28-7.44(5H, m), 7.60(1H, dd), 8.51(1H, dd).

MS m/z: 566(M+1)

Example 372:

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

The titled compound was prepared by following the procedure of Example 368, but replacing ammonium hydroxide with methylamine.

^{1}H-NMR ($CDCl_3$) δ: 1.57-1.70(3H, m), 1.93-2.08(2H, m), 2.34-2.73(11H, m), 4.33(1H, q), 5.36(2H, brs), 6.21(1H, t), 6.91(1H, d), 7.29-7.45(6H, m), 7.58-7.65(2H, m), 7.83(1H, dd), 8.53(1H, dd).

MS m/z: 540(M+1)

Example 373:

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

The titled compound was prepared by following the procedure of Example 368, but replacing ammonium hydroxide with dimethylamine.

^{1}H-NMR ($CDCl_3$) δ: 1.55-1.75(3H, m), 1.96-2.07(2H, m), 2.35-2.67(8H, m), 2.71(6H, s), 5.51(2H, brs), 6.19(1H, t), 6.92(1H, d), 7.29-7.73(8H, m), 8.55(1H, dd).

MS m/z: 554(M+1)

Example 374:

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

Step 1

4-(4-Chlorophenyl-1-[3-(5,11-dihydro-7-(1-ethoxycarboxy-2-hydroxyethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol was prepared by following the procedure of example 199, but replacing the product of example 138 with the product of example 294.

^{1}H-NMR ($CDCl_3$) δ: 1.65-1.70(2H, m), 2.01-2.11(2H, m), 2.35-2.70(8H, m), 3.76(3H, s), 3.97-4.08(2H, m), 4.71(1H, t), 5.25(1H, brs) 6.02(1H, t) 6.70-6.91(3H, m), 7.23-7.56(6H, m), 8.44(1H, dd).

Step 2

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of Step 1.

^{1}H-NMR (DMSO-d6) δ: 1.51-1.56(2H, m), 1.86-1.94(2H, m), 2.33-2.67(8H, m), 3.65-3.82(2H, m), 4.58(1H, t), 5.17(2H, brs), 6.10(1H, t), 6.71-6.89(3H, m), 7.34-7.47(5H, m), 7.72(1H, dd), 8.48(1H, dd).

MS m/z: 551(M+1)

Example 375:

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

To a solution of the product of example 314 (800 mg) in acetic acid (20 ml) were added urea (2 g) and trimethylsilyl chloride (0.24 ml) at room temperature, and the mixture stirred for 2 hours. Sodium borohydride was added to the reaction mixture at room temperature, and the mixture was stirred for 1 hour. The solvent was distilled off under reduced pressure, and, chloroform, 2-propanol and water were added. The organic layer was extracted, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with chloroform-methanol-ammonium hydroxide (100:10:1) to give the titled compound (250 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.62-2.04(5H, m), 2.35-2.69(8H, m), 4.26(2H, d), 4.40(2H, s), 4.48(1H, t), 5.32(2H, brs), 6.12(1H, t), 6.80(1H, d), 7.07(1H, dd), 7.23-7.58(7H, m), 8.49(1H, dd).

MS m/z: 519(M+1)

Example 376:

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

The titled compound was prepared by following the procedure of example 44, step 2, but replacing the product of example 44, step 1 with 5-(3-bromopropylidene)-5,11-dihydro-7-methylthio[1]benzoxepino[2,3-b]pyridine.
^{1}H-NMR ($CDCl_3$) δ: 1.53-1.70(3H, m), 1.98-2.16(2H, m), 2.17(3H, s), 2.34-2.70(8H, m), 5.32(2H, brs), 6.12(1H, t), 6.81(1H, d), 7.11-7.44(7H, m), 7.57(1H, dd), 8.50(1H, dd).
MS m/z: 493(M+1)

Example 377:
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-furanon-3-yl)oxy[1]benzoxepino[2,3]b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with 3-bromotetrahydro-2-franon.
^{1}H-NMR ($CDCl_3$) δ:1.65-1.70(2H, m), 1.97-2.13(2H, m), 2.25-2.73(10H, m), 4.25-4.53(2H, m), 4.82(1H, t), 5.27(2H, brs), 6.09(1H, t), 6.73-6.91(2H, m), 7.03(1H, d), 7.22-7.59(6H, m), 8.43(1H, dd).
MS m/z: 547(M+1)

Example 378:
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(N-methoxycarbonylmethylsulfamoyl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 368, but replacing ammonium hydroxide with glycine methyl ester hydrochloride.
^{1}H-NMR ($CDCl_3$) δ: 1.66-1.74(3H, m), 1.97-2.15(2H, m), 2.37-2.80(8H, m), 3.63(3H, s), 3.78(2H, s) 5.40(2H, brs), 6.22(1H, t), 6.92(1H, d), 7.28-7.45(5H, m), 7.62(2H, dd), 7.83(1H, d), 8.53(1H, dd).
MS m/z: 598(M+1)

Example 379:

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

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of Example 378. ^{1}H-NMR (DMSO-d6) δ: 1.60-1.65(2H, m), 2.16-2.25(2H, m), 2.43-3.03(8H, m), 3.45(2H, s), 5.33(2H, brs), 6.39(1H, t), 6.94(1H, d), 7.41-7.57(6H, m), 7.83(1H, dd), 8.00(1H, d), 8.54(1H, dd).

Example 380:

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

The titled compound was prepared by following the procedure of example 249, step 2, but replacing the product of example 249, step 1 with the product of Example 370, step 1.

^{1}H-NMR ($CDCl_3$) δ: 1.45-1.78(4H, m), 1.93-2.12(2H, m), 2.30-2.50(4H, m), 2.50-2.78(6H, m), 5.33(2H, brs), 5.46(1H, t), 6.12(1H, t), 6.86(1H, d), 7.09(1H, dd), 7.27-7.32(4H, m), 7.42(2H, d), 7.58(1H, dd), 8.51(1H, dd).

MS m/z: 531(M+1)

Example 381:

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

To a solution of the produce of example 293 (3.7g) in ethanol (130ml) was added 5N sodium hydroxide solution (100ml) and the mixture stirred at 90°C for 1 hour. The reaction mixture was distilled off under reduced pressure. The residue was dissolved with water and neutralized with 1N hydrochloric acid. Ethyl acetate was added to the mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate to give the titled compound (3.0g).

^{1}H-NMR ($CDCl_3$) δ: 1.62-1.72(2H, m), 1.96-2.08(2H, m), 2.27-2.72(8H, m), 3.48(2H, brs), 5.23(2H, brs), 6.01(1H, t), 6.49-6.73(3H, m), 7.18-7.59(6H, m), 8.49(1H, dd).

MS m/z: 462(M+1)

Example 382:

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

Step 1

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-formylphenyl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol was prepared by following the similar procedure of example 170, but replacing allyltributyltin with 2-formylphenylboronic acid.

^{1}H-NMR ($CDCl_3$) δ: 1.65-1.91(3H, m), 1.99-2.04(2H, m), 2.37-2.65(8H, m), 5.39(2H, brs), 6.15(1H, t), 6.95(1H, d), 7.19-7.65(10H, m), 7.97-8.05(2H, m), 8.52(1H, dd), 10.03(1H, s).

Step 2

To a solution of the product of step 1 (270mg) in acetic acid (2.2 ml) and water (0.5ml) were added amidosulfuric acid (67mg) and sodium chlorite (68mg) in water (0.1ml), and the mixture was stirred at room temperature for 15 minutes. The reaction mixture was distilled off under reduced pressure into half volume. The residue was neutralized with 1N sodium hydroxide. The precipitation was filtered and washed with water to give the titled compound (80mg).

^{1}H-NMR (DMSO-d6) δ: 1.41-1.57(2H, m), 1.74-1.92(2H, m), 2.21-2.58(8H, m), 5.32(2H, brs), 6.20(1H, t), 6.82(1H, d), 7.15(1H, dd), 7.31-7.78(11H, m), 8.52(1H, dd).

MS m/z: 567(M+1)

Example 383:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(N-(2,2,2-trifluoroethyl)sulfamoyl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-

4-ol

The titled compound was prepared by following the procedure of Example 368, but replacing ammonium hydroxide with 2,2,2-trifluoroethylamine hydrochloride.

^{1}H-NMR ($CDCl_3$) δ: 1.64-1.77(2H, m), 1.97-2.18(2H, m), 2.35-2.80(8H, m), 3.63(2H, q), 5.41(2H, brs), 6.21(1H, t), 6.91(1H, d), 7.22-7.65(7H, m), 7.84(1H, d), 8.57(1H, dd).

MS m/z: 608(M+1)

Example 384:

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

The titled compound was prepared by following the procedure of Example 44, step 2, but replacing the product of Example 44, step 1 with 5-(3-bromopropylidene)-5,11-dihydro-7-metylsulfonyl[1]benzoxepino[2,3-b]pyridine.

^{1}H-NMR ($CDCl_3$) δ: 1.54-1.71(3H, m), 1.99-2.08(2H, m), 2.34-2.68(8H, m), 3.04(3H, s), 5.43(2H, brs), 6.24(1H, t), 6.97(1H, d), 7.22-7.70(7H, m), 7.89(1H, d), 8.55(1H, dd).

MS m/z: 525(M+1)

Example 385:

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

Step 1

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

The titled compound was prepared by following the procedure of Example 293, but replacing ethanol with phenol.

^{1}H-NMR ($CDCl_3$) δ: 1.62-1.68(2H, m), 1.96-2.08(2H, m), 2.35-2.65(8H, m), 5.28(2H, brs), 6.10(1H, t), 6.78(1H, m), 7.08-7.40(6H, m), 7.52(1H, dd), 7.62(1H, s), 8.44(1H, dd).

MS m/z: 582(M+1)

Step 2

To a solution of the product of Step 1 (300mg) in DMF (3ml) was added ammonium hydroxide (1.5ml) and the mixture was stirred at room temperature for 2 hours. Ethyl acetate and water 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. The residue was purified by silica gel chromatography eluting with (chloroform : methanol = 10 : 1) to give the titled compound (140mg).

^{1}H-NMR (DMSO-d6) δ: 1.45-1.50(2H, m), 1.72-1.88(2H, m), 2.28-2.51(8H, m), 4.82(1H, s), 5.19(1H, brs), 5.74(2H, brs), 6.09(1H, t), 6.69(1H, d), 7.12(1H, dd), 7.32-7.48(6H, m), 7.74(1H, dd), 8.37(1H, s), 8.50(1H, dd).

MS m/z: 505(M+1)

Example 386:

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

The titled compound was prepared by following the procedure of Example 385, step 2, but replacing ammonium hydroxide with morpholine.

^{1}H-NMR ($CDCl_3$) δ: 1.62-1.67(2H, m), 1.95-2.16(2H, m), 2.28-2.64(8H, m), 3.41(4H, t), 3.69(4H, t), 5.26(2H, brs), 6.08(1H, t), 6.69-6.76(2H, m), 6.98(1H, dd), 7.21-7.51(7H, m), 8.42(1H, dd).

MS m/z: 575(M+1)

Example 387:

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

The titled compound was prepared by following the procedure of Example 385, step 2, but replacing ammonium hydroxide with beta-alanine ethyl ester hydrochloride.

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.39(3H, t), 1.62-1.66(2H, m), 1.92-2.01(2H, m), 2.21-2.62(10H, m), 3.47-3.50(2H, m), 4.08(2H, q), 5.22(2H, brs), 5.98-6.03(2H, m), 6.68-6.92(2H, m), 7.15-7.42(7H, m), 7.62(1H, s), 8.36(1H, dd).

MS m/z: 605(M+1)

Example 388:

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

Step 1

4-(4-Chlorophenyl)-1-[3-(7-(E)-(2-ethoxycarboxy-1-methyl)ethenyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol was prepared by following the procedure of Example 411, but replacing ethyl cyanoformate with ethyl (trimethylsilyl)acetate.

^{1}H-NMR ($CDCl_3$) δ: 1.30(3H, t), 1.67-1.72(3H, m), 1.98-2.05(2H, m), 2.42-2.67(11H, m), 4.23(2H, q), 5.36(2H, brs), 6.14-6.19(2H, m), 6.85(1H, d), 7.20-7.61(8H, m), 8.52(1H, dd).

Step 2

The titled compound was prepared by following the procedure of Example 133, but replacing the product of Example 48 with the product of step 1.

^{1}H-NMR (DMSO-d6) δ: 1.50-1.55(2H, m), 1.87-1.99(2H, m), 2.34-2.61(11H, m), 5.29(2H, brs), 6.12(1H, s), 6.31(1H, t), 6.83(1H, d), 7.35-7.49(7H, m), 7.76(1H, dd), 8.52(1H, dd).

MS m/z: 530(M+1)

Example 389:

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

The titled compound was prepared by following the procedure of Example 361, but replacing methyl succinyl chloride with methyl oxalyl chloride.
^{1}H-NMR (DMSO-d6) δ: 1.66-1.86(2H, m), 2.08-2.34(2H, m), 2.46-2.77(2H, m), 3.00-3.68(6H, m), 5.10(2H, brs), 5.53(1H, s), 6.15(1H, t), 6.89(1H, d), 7.34-7.49(5H, m), 7.68(1H, dd), 7.75(1H, dd), 7.87(1H, d), 8.53(1H, dd).
MS m/z: 519(M+1)

Example 390:
1-[3-(7-(3-(2-Carboxy)ethyl)ureido-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of Example 133, but replacing the product of Example 48 with the product of Example 387.
^{1}H-NMR (DMSO-d6) δ: 1.45-1.55(2H, m), 1.72-1.85(2H, m), 2.32-2.49(10H, m), 3.29(2H, q), 4.88(1H, s), 5.19(2H, brs), 6.06-6.14(2H, m), 6.69(1H, d), 7.07(1H, dd), 7.33-7.48(6H, m), 7.73(1H, dd), 8.43(1H, s), 8.49(1H, dd).
MS m/z: 577(M+1)

Example 391:
1-[3-(7-(3-(2-Hydroxy)ethyl)ureido-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of Example 385, step 2, but replacing ammonium hydroxide with 2-aminoethanol.
^{1}H-NMR (DMSO-d6) δ: 1.45-1.51(2H, m), 1.72-1.84(2H, m), 2.24-2.51(8H, m), 3.11-3.46(4H, m), 4.71(1H, t), 4.83(1H, s), 5.19(2H, brs), 6.08(1H, t), 6.69(1H, d), 7.08(1H, dd), 7.33-7.48(6H, m), 7.73(1H, dd), 8.41(1H, s), 8.50(1H, dd).
MS m/z: 549(M+1)

Example 392:
1-[3-(5,11-Dihydro-7-(1-hydroxy-1-methyl)ethyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-keto-1-imidazolinyl)piperidine

The titled compound was prepared by following the procedure of Example 67, but replacing the product of Example 45, step 2 with the product of Example 363, step 1.

^{1}H-NMR ($CDCl_3$) δ: 1.59(6H, s), 1.71-1.87(2H, m), 2.01-2.18(2H, m), 2.28-2.61(6H, m), 2.86-3.00(2H, m), 4.32(1H, m), 5.36(2H, brs), 6.15(1H, t), 6.84(1H, d), 7.02-7.07(3H, m), 7.24-7.31(3H, m), 7.47(1H, d), 7.60(1H, dd), 8.51(1H, dd), 8.97(1H, s).

MS m/z: 511(M+1)

Example 393:

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

To a solution of sodium hydride (60% in oil, 100 mg) in THF (6 ml) were added triethyl 2-phosphonopropionate (0.3 ml) and the product of Example 314 (300 mg) at 0°C, and the mixture was stirred at room temperature for 30 minutes. Water and ethyl acetate were added to the reaction mixture. The organic layer was extracted, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with chloroform-methanol (30:1) to give the titled compound (310 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.34(3H, t), 1.58-1.71(3H, m), 1.98-2.15(5H, m), 2.37-2.70(8H, m), 2.27(2H, q), 5.37(2H, brs), 6.14(1H, t), 6.86(1H, d), 7.25-7.44(7H, m) 7.58-7.63(2H, m), 8.52(1H, dd).

MS m/z: 559(M+1)

Example 394:

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

The titled compound was prepared by following the procedure of Example 133, but replacing the product of Example 48 with the product of step 1.

^{1}H-NMR (DMSO-d6) δ: 1.62-1.67(2H, m), 1.91-2.05(5H, m), 2.50-2.94(8H, m), 5.28(2H, brs), 6.23(1H, t), 6.87(1H, d), 7.34-7.55(8H, m), 7.79(1H, dd), 8.54(1H, dd).

MS m/z: 531(M+1)

Example 395:

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

Step 1

4-(4-Chlorophenyl)-1-[3-(7-(5-ethoxycarbonyl-1-pentyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol was prepared by following the procedure of Example 46, but replacing ethyl iodide with ethyl 6-bromohexanoate.

^{1}H-NMR ($CDCl_3$) δ: 1.21(3H, t), 1.42-1.79(8H, m), 1.98-2.03(2H, m), 2.26-2.67(10H, m), 3.87(2H, t), 4.16(2H, q), 5.23(2H, brs), 6.09(1H, t), 6.67-6.81(3H, m), 7.21-7.63(6H, m), 8.16(1H, dd).

Step 2

The titled compound was prepared by following the procedure of Example 133, but replacing the product of Example 48 with the product of step 1.

^{1}H-NMR (DMSO-d6) δ: 1.41-1.95(10H, m), 2.20-2.72(10H, m), 3.92(2H, t), 5.18(2H, brs), 6.17(1H, t), 6.72-6.84(3H, m), 7.36-7.48(5H, m), 7.77(1H, dd), 8.50(1H, dd).

MS m/z: 577(M+1)

Example 396:

1-[3-(7-(1-(2-Carboxy)ethyl)aminocarbonyl-1-methyl)ethyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

4-(4-Chlorophenyl)-1-[3-(7-(1-(2-ethoxycarbonyl)ethyl)aminocarbonyl-1-methyl)ethyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol was prepared by following the procedure of Example 176, but replacing dimethylamine hydrochloride with beta-alanine ethyl ester hydrochloride.

^{1}H-NMR ($CDCl_3$) δ: 1.42(3H, s), 1.62-1.67(2H, m), 1.95-2.10(3H, m), 2.35-2.59(10H, m), 3.51-3.53(2H, m), 4.00(2H, q), 5.23(2H, brs), 6.00(1H, t), 6.68-6.81(3H, m), 7.24-7.56(6H, m), 8.39(1H, dd).

Step 2

The title compound was prepared by following the procedure of Example 133, but replacing the product of Example 48 with the product of step 1.

^{1}H-NMR (DMSO-d6) δ: 1.37(6H, s), 1.41-1.52(2H, m), 1.79-1.87(2H, m), 2.28-2.41(10H, m), 3.33(2H, q), 5.21(2H, brs), 6.12(1H, t), 6.70-6.87(3H, m), 7.34-7.48(5H, m), 7.74(1H, dd), 8.08(1H, t), 8.50(1H, dd).

MS m/z: 620(M+1)

Example 397:

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

To a solution of the product of Example 314 (590 mg) in ethanol (6 ml) were added 2,4-thiazolinedione (440 mg) and piperidine (0.36 ml), and the mixture was heated to reflux for 3 hours. The solvent was distilled off under reduced pressure, and, chloroform, 2-propanol and water were added. The organic layer was extracted, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with chloroform-methanol (5:1) to give the titled compound (510 mg).

^{1}H-NMR (DMSO-d6) δ: 1.61-1.66(2H, m), 1.97-2.12(2H, m), 2.79-2.99(8H, m), 5.21(2H, brs), 6.25(1H, t), 6.90(1H, d), 7.34-7.52(7H, m), 7.81(1H, dd), 8.54(1H, dd).

MS m/z: 574(M+1)

Example 398:

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

The titled compound was prepared by following the procedure of Example 402, but replacing trifluoromethanesulfonic acid anhydride with methanesulfony chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.64-1.69(2H, m), 1.89-2.05(2H, m), 2.24-2.77(8H, m), 2.95(3H, s), 5.29(2H, brs), 6.10(1H, t), 6.84(1H, d), 7.06(1H, dd), 7.18-7.40(6H, m), 7.56(1H, dd), 8.42(1H, dd).

MS m/z: 540(M+1)

Example 399:

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

The titled compound was prepared by following the procedure of Example 320, but replacing compound of Example 44, step 2 with compound of Example 368, step 2.

^{1}H-NMR (DMSO-db) δ: 1.65-1.69(2H, m), 1.95-2.05(2H, m), 2.89-3.06(8H, m), 5.31(2H, brs), 6.14(1H, t), 6.74-6.85(2H, m), 7.08-7.12(2H, m), 7.37-7.64(8H, m), 7.80-7.84(2H, m), 8.44(1H, s), 8.54(1H, dd).

MS m/z: 645(M+1)

Example 400:

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

The titled compound was prepared by following the procedure of Example 399, but replacing phenyl isocyanate with cyclohexyl isocyanate.

^{1}H-NMR (DMSO-d6) δ: 1.07-1.81(14H, m), 2.23-2.58(8H, m), 3.22-3.35(1H, m), 4.91(1H, s), 5.38(2H, brs), 6.17-6.29(2H, m), 6.96(1H, d), 7.34-7.51(5H, m), 7.62-7.84(3H, m), 8.53(1H, dd).

MS m/z: 651(M+1)

Example 401:

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

The titled compound was prepared by following the procedure of Example 399, but replacing phenyl isocyanate with propyl isocyanate.

^{1}H-NMR (DMSIO-d6) δ: 0.74(3H, t), 1.25-1.53(4H, m), 1.81-1.91(2H, m), 2.33-2.59(10H, m), 2.89(2H, q), 4.92(1H, s), 5.35(2H, brs), 6.20(1H, t), 6.44(1H, brs), 6.96(1H, d), 7.34-7.51(5H, m), 7.64(1H, dd), 7.78-7.85(2H, m), 8.54(1H, dd).

MS m/z: 611(M+1)

Example 402:

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

The title compound was prepared by following the procedure of Example 169, but replacing the product of Example 44, step 2 with the product of Example 381.

^{1}H-NMR (DMSO-d6) δ: 1.75-1.80(2H, m), 2.02-2.07(2H, m), 2.49-2.54(2H, m), 3.10-3.40(6H, m), 5.15(2H, brs), 5.52(1H, s), 5.97(1H, t), 6.58(1H, d), 6.80(1H, dd), 6.96(1H, d), 7.43-7.47(5H, m), 7.78(1H, dd), 8.51(1H, dd).

MS m/z: 593(M+1)

Example 403:

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

Step 1

To a solution of the product of Example 361, step 1 (820 mg) in TFA (8.0 ml) was added triethyl silane (0.92 ml) at 0°C, and the mixture stirred at room temperature for 4 hour. The solvent was distilled off under reduced pressure. The residue was poured into saturated aqueous sodium bicarbonate, and the aqueous layer was extracted with ethyl acetate. The organic layer was 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 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(3-methoxycarbonyl)propyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol (636 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.93(2H, m), 2.34(2H, t), 2.59(2H, t), 2.74(2H, q), 3.47(2H, t), 3.67(3H, s), 5.33(2H, brs), 6.05(1H, t), 6.78(1H, d), 7.00(1H, dd), 7.09(1H, d), 7.29(1H, dd), 7.57(1H, dd), 8.52(1H, dd).

Step 2

The titled compound was prepared by following the procedure of Example 133, but replacing the product of Example 48 with the product of step 1.

^{1}H-NMR (DMSO-d6) δ: 1.37-1.57(2H, m), 1.63-1.87(4H, m), 2.10-2.36(6H, m), 2.36-2.61(6H, m), 4.83(1H, brs), 5.24(2H, brs), 6.14(1H, t), 6.72(1H, d), 7.00(1H, dd), 7.12(1H, d), 7.35(2H, d), 7.41-7.48(3H, m), 7.73(1H, dd), 8.49(1H, dd).

MS m/z: 533(M+1)

Example 404:

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

The titled compound was prepared by following the procedure of Example 399, but replacing phenyl isocyanate with benzoyl chloride.

MS m/z: 630(M+1)

Example 405:

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

To a solution of the product of Example 407 (1.7 g) in DMF (20 ml) was added 2-ethylhexyl chloroformate (0.62 ml) and the mixture was stirred at 0°C for 1 hour. Chloroform and water were added to the reaction mixture. The organic layer was extracted, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with chloroform-methanol (30:1) and dissolved in xylene (50 ml). The solution was heated to reflux for 4 hours. The solvent was distilled off under reduced pressure. The residue was reslurried with ethanol to the titled compound (490 mg).

^{1}H-NMR (DMSO-d6) δ: 1.60-1.65(2H, m), 1.91-1.99(2H, m), 2.41-2.52(2H, m), 2.70-2,89(6H, m), 4.90(2H, s), 5.19(2H, brs), 6.16(1H, t), 6.75-7.05(3H, m), 7.37-7.48(5H, m), 7.75(1H, dd), 8.52(1H, dd).

MS m/z: 561(M+1)

Example 406:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 405, but replacing the product of Example 407 with the product of Example 408.

^{1}H-NMR (DMSO-d6) δ: 1.58-1.63(2H, m), 1.87-1.96(2H, m), 2.40-2.51(2H, m), 2.63-2.85(6H, m), 5.14(2H, brs), 6.23(1H, t), 6.92(1H, d), 7.36-7.62(6H, m), 7.77-7.81(2H, m), 8.54(1H, dd).

MS m/z: 531(M+1)

Example 407:

4-(4-Chlorophenyl)-1-[3-(7-hydroxyamidinomethoxy-5,11-

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

The titled compound was prepared by following the procedure of Example 355, but replacing the product of Example 313 with the product of Example 49. ^{1}H-NMR (DMSO-d6) δ:1.45-1.50(2H, m), 1.70-1.82(2H, m), 2.27-2.51(8H, m), 4.37(2H, s), 4.83(1H, s), 5.20(1H, brs), 5.57(2H, brs), 6.17(1H, t), 6.72-6.94(3H, m), 7.33-7.48(5H, m), 7.72(1H, dd), 8.49(1H, dd), 9.26(1H, s).
MS m/z: 535(M+1)

Example 408:
4-(4-Chlorophenyl)-1-[3-(7-hydroxyamidino-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 355, but replacing the product of Example 313 with the product of Example 364. ^{1}H-NMR (DMSO-d6) δ: 1.45-1.50(2H, m), 1.73-1.81(2H, m), 2.28-2.51(8H, m), 4.83(1H, s), 5.79(2H, brs), 6.25(1H, t), 6.81(1H, d), 7.33-7.49(6H, m), 7.63-7.76(2H, m), 8.51(1H, dd), 9.48(1H, s).
MS m/z: 505(M+1)

Example 409:
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl)methyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of the product of Example 407 (700 mg) in THF (20 ml) were added pyridine (0.21 ml) and thionyl chloride (0.1 ml) at 0°C, and the mixture was stirred at 0°C for 1 hour and the mixture was stirred at room temperature for 30 minutes. Water, chloroform and 2-propanol were added to the reaction mixture. The organic layer was extracted and the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with chloroform-methanol (5:1) to give the titled compound (170 mg).
MS m/z: 581(M+1)

Example 410:
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2,5-dihydro-5-oxo-4H-1,2,4-thiadiazol-3-yl)methyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of the product of Example 407 (700 mg) in THF (20 ml) was added thiocarbonyldiimidazole (280 mg) and the mixture was stirred at room temperature for 30 minutes. Water and ethyl acetate were added to the reaction mixture. The organic layer was extracted, and the solvent was distilled off under reduced pressure. To the residue were added THF (50 ml) and boron trifluoride diethyl etherate (0.8 ml), and the mixture was stirred at room temperature for 1 hour. Chloroform, 2-propanol and water were added to the reaction mixture. The organic layer was extracted, and the solvent was distilled off under reduced pressure. The residue was reslurried with acetone to the titled compound (180 mg).

MS m/z: 577(M+1)

Example 411:
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethoxycarbonylacetyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of the product of Example 315 (250 mg) in THF (3.0 ml) was added LDA (0.51 mol/L THF-hexane solution, 3.0 ml) at -78°C, and the mixture stirred at room temperature for 20 minutes. The reaction mixture was cooled to -78°C again, and added ethyl cyanoformate (76 μl), stirred at room temperature for 1 hour. Saturated aqueous ammonium chloride and aqueous sodium chloride were added to the mixture, and the aqueous layer was extracted with ethyl acetate. The organic layer was 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 chloroform-methanol (10:1) to give the titled compound (280 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.26(3H, t), 1.67-1.85(2H, m), 1.93-2.13(2H, m), 2.28-2.47(4H, m), 2.47-2.60(2H, m), 2.60-2.76(2H, m), 3.94(2H, s), 4.21(2H, q),

5.60(2H, brs), 6.22(1H, t), 6.88(1H, d), 7.29-7.34(3H, m), 7.43(2H, d), 7.59(1H, d), 7.71(1H, dd), 7.97(1H, d), 8.53(1H, d).
MS m/z: 561(M+1)

Example 412:
4-(4-fluorophenyl)-1-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

To a solution of 5-(3-bromopropylidene)-5,11-dihydro-7-hydroxy-[1]benzoxepino[2,3-b] pyridine (2.59 g) in DMF (10 ml) was added 4-(4-Fluorophenyl)-4-hydroxypiperidine (1.02 g) and triethylamine (835 μM). The solution was stirred at room temperature for 23 hours. The reaction was quenched with water, extracted with ethyl acetate, and evaporated *in vacuo*. The residue was purified by silica gel chromatography (87:10:3 ethyl acetate: methanol: triethylamine) to yield 0.9 g (39%) of the title compound. ^{1}H-NMR (DMSO) d: 1.64-1.69 (2H, m), 1.74-1.85 (2H, m), 2.27-2.52 (8H, m), 4.81 (1H, s), 5.16 (2H, brs), 6.08 (1H, t), 6.62-6.71 (3H, m), 7.12 (2H, t), 7.40-7.51 (3H, m), 7.72 (1H, dd), 8.48 (1H, dd), 9.09 (1H, s).
ESI-MS m/z: 447 (M + 1).

Example 413:
4-(4-fluorophenyl)-1-[3-(5,11-dihydro-7-carboxy[1]benzoxepino[2, 3-b]pyridin-5-ylidene)propyl] piperidine-4-ol

The titled compound was prepared by following the procedure of example 118, but replacing the compound of Example 169 with the triflate derived from compound 412.
^{1}H-NMR (MeOD) δ:1.78-1.85 (2H, m), 2.25-2.40 (2H, m), 2.57-2.70 (2H, m), 3.06-3.35 (7H, m), 5.06-5.81 (2H, brs), 6.23 (1H, t), 6.77 (1H, d), 7.00-7.11 (2H, m), 7.37-7.56 (3H, m), 7.65-7.80 (2H, m), 8.01 (1H, d), 8.48 (1H, dd).
MS m/z: 475

Example 414:

4-(4-fluorophenyl)-1-[3-(5,11-dihydro-7-(1-hydroxy-1-methylethyl)-[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine-4-ol

The titled compound was prepared by following the procedure of Example 27, but starting with the methyl ester of the compound of Example 413.

^{1}H-NMR ($CDCl_3$) δ: 1.57-2.14 (12H,m), 2.34-2.45 (4H,m), 2.50-2.61 (2H,m), 2.63-2.78 (2H,m), 5.22-5.43 (2H, brs), 6.14 (1H,t), 6.95-7.10 (2H,m), 7.25-7.35 92H,m), 7.40-7.60 (4H,m), 8.50 (1H,dd).

MS m/z: 489

Example 415:

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

The titled compound was prepared by following the procedure of Example 316, but replacing dimethylamine with diethylamine.

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.30 (6H, m), 1.65 (2H, d), 1.80 (1H, s), 2.05 (2H, dt), 2.30-2.45 (4H, m), 2.50 (2H, t), 2.60-2.70 (2H, m), 3.35-3.50 (4H, m), 5.30 (2H, brs), 6.15 (1H, t), 6.83 (1H, d), 6.90 (1H, dd), 7.10 (1H, dd), 7.23-7.35 (3H, m), 7.40 (2H, d), 7.56 (1H, dd), 8.50 (1H, dd).

MS m/z: 563

Example 416:

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

To a solution of the compound of Example 44 (0.511 g, 1.1 mmol) in dry THF (20 mL) was added sodium hydride (60% in mineral oil, 48 mg, 1.2 mmol), and the slurry heated at 40°C under argon with stirring for 20 minutes. Phenylsulfonylisocyanate (160 μL, 1.2 mmol) was added and the mixture was stirred for 14 hours. The solvent was then removed by rotary evaporation to give the crude product. The solid material was washed twice with 20 mL CH_2Cl_2, and

then twice with 20 mL MeoH: CH_2Cl_2 (1:1) to give the title compound (274 mg).
MS m/z:647

Example 417:
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxycarbonyl-carbamoyl-[1]benzoxepono[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

To a solution of the compound of Example 44 (0.214 g, 0.46 mmol) in dry THF (5mL) was added sodium hydride (60% in mineral oil, 28 mg, 0.7 mmol), and the slurry heated at 50°C under argon with stirring for 20 minutes. Methyl isocyanatoformate (56 μl, 0.7 mmol) was added and the mixture was stirred for 14 hours. The solvent was then removed by rotary evaporation to give the crude product. The residue was purified by silica gel chromatography eluting with a dichloromethane/2.0 M ammonia in methanol gradient (0 to 4% MeOH over 1 hour) to give the title compound (102 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.60-1.65 (2H, m), 1.80 (1H, s), 2.05 (2H, dt), 2.30-2.45 (4H, m), 2.50 (2H, t), 2.60-2.70 (2H, m), 3.35 (3H, s), 5.30 (2H, brs), 6.15 (1H, t), 6.83 (1H, d), 6.90 (1H, dd), 7.10 (1H, dd), 7.23-7.35 (3H, m), 7.40 (2H, d), 7.56 (1H, dd), 8.50 (1H, dd).
MS m/z: 565

Example 418:
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(R-3-ethoxycarbonyl-piperidine-1-yl)-carbamoyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol
Step 1:

R-ethyl nipecotate-L-tartrate (1.53 g) was freebased with aqueous sodium hydroxide and ethyl acetate. The organic layers were evaporated, and the resulting amine was redissolved in THF (10 mL) and treated with carbonyl-diimidazole (0.81 g). The resulting solution was stirred at room temperature for 23 hours, concentrated *in vacuo*, and redissolved in acetonitrile (5 mL). This solution was treated with methyl iodide (0.347 mL) and stirred for 18 hours at room temperature.

Step 2:

The compound of Example 44 (0.7 g) was suspended in THF (25 mL) and treated with sodium hydride (0.036 g) and stirred at room temperature for one hour. The resulting anion was added to the imidazolium salt prepared in Step 1, and the solution was heated to reflux for 18 hr. The crude material was then loaded on silica gel and purified by silica gel chromatography (87:10:3 ethyl acetate:methanol:triethylamine) to yield 0.278 g (64%) of the title compound.
^{1}H-NMR (DMSO) δ: 1.11-1.21 (3H, m), 1.45-2.0 (8H, m), 2.15-2.40 (6H, m), 3.05-3.15 (2H, m), 3.31 (2H, m), 3.95-4.15 (3H, m), 5.31 (2H, brs), 6.14 (1H, t), 6.78 (1H, d), 6.92 (1H, dd), 7.05 (1H, d), 7.33 (2H, d), 7.42-7.47 (3H, m), 7.72 (1H, dd), 8.50 (1H, dd).
ESI-MS m/z: 646 (M + 1).

Example 419:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(R-3-ethoxycarbonyl-piperidine-1-yl)-carbamoyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol
The compound of Example 418 (0.195 g) was dissolved in THF (1 mL) and treated with aqueous lithium hydroxide (0.0084 g) and stirred at room temperature for 18 hours. The resulting solution was concentrated *in vacuo*, and the residue was purified by chromatography on a reverse-phase solid-phase-extraction column, eluting with water-acetonitrile, 0.1% formic acid, to yield 0.153 g (77%) of the title compound.
^{1}H-NMR (DMSO) δ: 1.55-2.25 (8H, m), 2.30-2.80 (10H, m), 3.22 (1H, m), 4.15-4.35 (2H, m), 5.41 (2H, brs), 6.35 (1H, t), 6.98 (1H, d), 7.13 (1H, dd), 7.25 (1H, d), 7.54 (2H, d), 7.64 (3H, m), 7.90 (1H, dd), 8.50 (1H, s), 8.70 (1H, dd).
ESI-MS m/z: 618 (M + 1).

Example 420:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(4-ethoxycarbonyl-piperidine-1-yl)-carbamoyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The titled compound was prepared by following the procedure of Example 418, but replacing R-ethyl nipecotate-L-tartrate with ethyl isonipecotate.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t), 1.60-1.80 (4H, m), 1.90-2.05 (4H, m), 2.25-2.65 (10H, m), 2.90-3.15 (2H, m), 4.05-4.25 (4H, m), 5.30 (2H, brs), 6.15 (1H, t), 6.75-6.90 (2H, m), 7.05 (1H, d), 7.20-7.40 (3H, m), 7.40 (2H, d), 7.56 (1H, dd), 8.45 (1H, dd).

MS m/z: 647

Example 421:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(4-carboxy-piperidine-1-yl)-carbamoyl-[1]benzoxepino [2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

A solution of the compound of Example 420 (91 mg, 0.14 mmol) in MeOH (5 mL) was treated with a 0.4 M solution of lithium hydroxide (5 mL, 2 mmol) and stirred for 3 hours. After addition of 5 mL of 0.4 N HCl, the solvent was removed under reduced pressure to give the crude product. The residue was purified using silica gel chromatography eluting with a dichloromethane:methanol gradient (0 to 50% MeOH over 1 hour) to give the title compound (48 mg).

^{1}H-NMR (MeOD) δ: 1.60-1.65 (2H, m) 2.10-2.70 (10H, m), 5.30 (2H, brs), 6.15 (1H, t), 6.80-6.90 (2H, m), 7.20-7.50 (6H, m), 7.62 (1H, dd), 8.48 (1H, dd).

MS m/z:619

Example 422:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(S-3-ethoxycarbonyl-piperidine-1-yl)-carbamoyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The titled compound was prepared by following the procedure of Example 418, but replacing R-ethyl nipecotate-L-tartrate with ethyl (S)-nipecotate-D-tartrate.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t), 1.30-1.70 (5H, m), 1.94-2.05 (3H, m), 2.25-2.65 (11H, m), 3.05-3.15 (1H, m), 4.05-4.25 (4H, m), 5.30 (2H, brs), 6.15 (1H, t), 6.75-6.90 (2H, m), 7.05 (1H, d), 7.20-7.40 (3H, m), 7.40 (2H, d), 7.56 (1H, dd), 8.45 (1H, dd).

MS m/z: 647

Example 423:

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

The compound of Example 169 (0.166 g) was dissolved in DMF (1 mL) and treated with palladium (II) acetate (0.007 g), 1,3-bis-diphenylphosphinopropane (0.012 g), triethylamine (0.1 mL) and ethanol (1 mL), and stirred at 60°C for 18 hours under a CO balloon. The resulting solution was quenched with water, extracted with ethyl acetate, concentrated *in vacuo*, and purified by silica gel chromatography (87:10:3 ethyl acetate:methanol:triethylamine). The residue was further purified by chromatography on a reverse-phase solid-phase-extraction column, eluting with water-acetonitrile, 0.1% formic acid, to yield 0.114 g (73%) of the title compound.

^{1}H-NMR (DMSO) δ: 1.28 (3H, t), 1.40-1.55 (2H, m), 1.71-1.85 (2H, m), 2.20-2.60 (6H, m), 3.22 (2H, m), 4.28 (2H, q), 5.00-5.60 (2H, brs), 6.21 (1H, t), 6.92 (1H, d), 7.40-7.80 (8H, m), 8.50 (1H, d).

ESI-MS m/z: 519 (M + 1).

Example 424:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(ethoxycarbonylmethyl)-oxycarbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The procedure of Example 423 was followed, but replacing ethanol with ethyl glyoxylate to yield 0.041 g (26%) of the title compound.

^{1}H-NMR (DMSO) δ: 1.10-1.30 (3H, m), 1.35-1.55 (2H, m), 1.60-1.85 (2H, m), 2.20-2.60 (6H, m), 3.32 (2H, m), 4.05-4.25 (2H, m), 4.87 (2H, s), 5.00-5.60 (2H, brs), 6.21 (1H, t), 6.92 (1H, d), 7.2-7.90 (8H, m), 8.50 (1H, d).

ESI-MS m/z: 577 (M + 1).

Example 425:

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

The procedure of Example 423 was followed, but replacing ethanol with cyclohexanol to yield 0.050 g (32%) of the title compound.

^{1}H-NMR (MeOD) δ: 1.30-2.20 (14H, m), 2.53-2.60 (2H, m), 2.95-3.32 (6H, m), 5.00 (1H, m), 5.00-5.60 (2H, brs), 6.28 (1H, t), 6.92 (1H, d), 7.40-7.55 (8H, m), 7.95 (2H, m), 8.05 (1H, s), 8.50 (2H, m).

ESI-MS m/z: 573 (M + 1).

Example 426:

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

To a solution of the compound of Example 118 (109 mg, 0.22 mmol) in dry DMF (5 mL) was added potassium carbonate (91 mg) followed by propyl iodide (24 μL, 0.66 mmol). The mixture was heated to 55°C for 14 hours. The mixture was diluted with ethyl acetate (200 mL), washed twice with water (200 mL) and then with brine (100 mL), and dried with sodium sulfate. The organic solvent was removed under reduced pressure and the residue subjected to silica gel chromatography using a dichloromethane : methanol gradient (0 to 5% MeOH over 1 hour) to give the title compound (103 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, t), 1.50-2.10 (4H, m), 2.14-2.25 (2H, m), 2.31-2.75 (10H, m), 4.28 (2H, t), 6.15 (1H, t), 6.83 (1H, d), 7.24-7.38 (3H, m), 7.42 (2H, d), 7.59 (1H, dd), 7.78 (1H, dd), 8.00 (1H, d), 8.50 (1H, dd).

MS m/z: 533

Example 427:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-butoxy)carbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The procedure of Example 423 was followed, but replacing ethanol with n-butanol to yield 0.065 g (45%) of the title compound.

^{1}H-NMR (MeOD) δ: 0.85-0.91 (3H, m), 1.25-1.45 (2H, m),1.55-1.70 (2H, m), 1.70-1.85 (2H, m), 2.10-2.28 (2H, m), 2.53-2.60 (2H, m), 3.15-3.38 (6H, m), 4.12-4.21 (2H, m), 5.00-5.60 (2H, brs), 6.10 (1H, t), 6.76 (1H, d), 7.22-7.40 (3H, m), 7.71 (1H, m), 7.95 (1H, m), 8.05 (1H, s), 8.30 (1H, s), 8.41 (1H, m).
ESI-MS m/z: 547 (M + 1).

Example 428:
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-propoxy)carbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The titled compound was prepared by following the procedure of Example 426, but replacing propyl iodide with 2-bromopropane.
^{1}H-NMR ($CDCl_3$) δ: 1.30-2.10 (8H, m), 2.14-2.25 (2H, m), 2.31-2.75 (10H, m), 5.15-5.60 (2H, m), 6.15 (1H, t), 6.83 (1H, d), 7.24-7.38 (3H, m), 7.44 (2H, d), 7.59 (1H, dd), 7.80 (1H, dd), 8.02 (1H, d), 8.50 (1H, dd).
MS m/z: 533

Example 429:
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-cyclopentyl-oxycarbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The titled compound was prepared by following the procedure of Example 426, but replacing propyl iodide with cyclopentyl bormide.
^{1}H-NMR (MeOD) δ : 1.23-1.33 (1H, m), 1.50-2.04 (10H, m), 2.27-2.41 (2H, m), 2.70-2.90 (2H, m), 3.30-3.62 (5H, m), 5.21-5.85 (3H, m), 6.15 (1H, t), 6.85 (1H, d), 7.38 (2H, d), 7.42 (2H, d), 7.60-7.82 (2H, m), 8.04 (1H, d), 8.61 (1H, dd).
MS m/z:559

Example 430:
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-morpholinoethyl-1-yl)-oxycarbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The titled compound was prepared by following the procedure of Example

426, but replacing propyl iodide with 2-morpholinoethyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.62-1.70 (2H, m) 1.90-2.13 (2H, m), 2.30-2.80 (14 H, m), 3.62-3.75 (4H, m), 4.41 (2H, t), 5.11-5.62 (2H, brs), 6.19 (1H, t), 6.83 (1H, d), 7.23-7.38 (3H, m), 7.42 (2H, d), 7.59 (1H, dd), 7.78 (1H, dd), 8.00 (1H, d), 8.50 (1H, dd).

MS m/z: 604

Example 431:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2,2-diethylaminoethyl-1-yl)-oxycarbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The titled compound was prepared by following the procedure of Example 426, but replacing propyl iodide with 2-(N,N-diethylamino)ethyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.06 (6H, t), 1.62-1.71 (2H, m), 1.93-2.10 (2H, m), 2.30-2.75 (12H, m), 2.85 (2H, t), 4.38 (2H, t), 5.20-5.58 (2H, brs), 6.15 (1H, t), 6.83 (1H, d), 7.24-7.38 (3H, m), 7.42 (2H, d), 7.59 (1H, dd), 7.78 (1H, dd), 8.00 (1H, d), 8.50 (1H, dd).

MS m/z: 590

Example 432:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-2,2-dimethylpropionyl-oxymethyl)-oxycarbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The procedure of Example 426 was followed, but replacing with chloromethyl pivalate to yield 0.36 g (77%) of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 1.18 (9H, s), 1.58-1.72 (2H, m), 1.85-2.85 (10H, m), 5.00-5.60 (2H, brs), 5.94 (2H, s), 6.17 (1H, t), 6.82 (1H, d), 7.22-7.42 (5H, m), 7.56 (1H, dd), 7.80 (1H, dd), 7.99 (1H, d), 8.05 (1H, d), 8.46 (1H, dd).

ESI-MS m/z: 605 (M + 1).

Example 433:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-hydroxyethyl-1-yl)-oxycarbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The procedure of Example 423 was followed, but replacing ethanol with ethylene glycol to yield 0.076 g (42%) of the title compound.
^{1}H-NMR (MeOD) δ: 1.80-2.00 (4H, m), 2.25-2.35 (2H, m), 2.55-2.65 (2H, m), 3.15-3.45 (5H, m), 3.75 (2H, dd), 4.24 (2H, dd), 5.00-5.60 (2H, brs), 6.10 (1H, t), 6.76 (1H, d), 7.18-7.42 (5H, m), 7.71 (2H, m), 7.99 (1H, m), 8.05 (1H, s), 8.30 (1H, s), 8.41 (1H, m).
ESI-MS m/z: 535 (M + 1).

Example 434:
5-{3-[4-(4-Chloro-phenyl)-4-hydroxy-3-methyl-piperidin-1-yl]-propylidene}-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-ol

Step 1: 3-Methyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester

In a Parr shaker flask, 1-benzyl-3-methyl-4-piperidone (19 g, 93 mmol), di-*tert*-butyl dicarbonate (27g, 121 mmol) and palladium hydroxide (2.6 g) were suspended in methanol (75 mL) and then purged with argon. The reaction mixture was then purged with hydrogen and placed on a Parr shaker apparatus for about 16 hours at about 44 psi of hydrogen. The catalyst was filtered over celite and washed with methanol. The crude product was chromatographed on silica gel, eluting with EtOAc /hexane (1:5) to give a white crystalline solid.
^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d), 1.45 (9H, s), 2.37-2.53 (3H, m), 2.80 (1H, brs), 3.16-3.26 (1H, m), 4.11-4.18 (2H, m).
ESI-MS m/z: 158 [M - CH=C(CH_3)$_2$ + 1].

Step 2: 4-(4-Chloro-phenyl)-4-hydroxy-3-methyl-piperidine-1-carboxylic acid tert-butyl ester

To 4-chlorophenyl magnesium bromide (49 mL, 49 mmol, 1M in diethyl ether) at about 0 °C under argon, was added 3-Methyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester (7 g, 32.8 mmol) in THF (50 mL) over a period of about 1 hour. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with water, then brine and dried over sodium sulfate. The solvent was evaporated and the crude residue was recrystallized in EtOAc to give a white solid.

^{1}H-NMR ($CDCl_3$) δ: 0.58 (3H, d), 1.45 (9H, s), 1.50-1.69 (2H, m), 1.76-2.13 (2H, m), 2.80 (1H, t), 3.10 (1H, t), 3.96 (2H, brs), 7.29 (4H, m).

ESI-MS m/z: 252 [M - CH=C(CH_3)$_2$ - H_2O + 1].

Step 3: 4-(4-Chloro-phenyl)-3-methyl-piperidin-4-ol

To a solution of 4-(4-Chloro-phenyl)-4-hydroxy-3-methyl-piperidine-1-carboxylic acid tert-butyl ester (1.5 g, 4.6 mmol) in dichloromethane (40 mL) at about 0°C was added trifluoroacetic acid (10 mL). The solution was stirred for about 2 hours. The solvent was evaporated and the residue was dissolved in ethyl acetate. The solution was neutralized with saturated sodium bicarbonate, and washed with brine and dried over magnesium sulfate. The solvent was removed to give a yellow solid. No purification was needed.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, d), 1.85 (1H, d), 2.52 (2H, m), 3.05 (1H, t), 3.27 (1H, dd), 3.34 (2H, d), 7.40 (4H, m).

ESI-MS m/z: 240 [M + 1].

5-{3-[4-(4-Chloro-phenyl)-4-hydroxy-3-methyl-piperidin-1-yl]-propylidene}-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-ol

To a solution of 4-(4-Chloro-phenyl)-3-methyl-piperidin-4-ol (1.0 g, 4.6 mmol) in DMF (10 mL) with triethylamine (1.75 mL, 12.54 mmol), was added 5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-ol (1.38 g, 4.18 mmol) dropwise for over a period of about 1.5 hours at about 50 °C. The reaction was stirred overnight at about 50 °C. The reaction was quenched with water, extracted with ethyl acetate, and evaporated *in vacuo*. The residue was purified by silica gel chromatography (87:10:3 ethyl acetate:methanol:triethylamine) to yield a brown solid of the title compound.

[1]H-NMR ($CDCl_3$) δ: 0.53 (3H, d), 1.60-1.69 (2H, m), 2.07-2.30 (3H, m), 2.34-2.51 (3H, m), 2.56-2.75 (3H, m), 2.76-2.87 (1H, m), 2.98-3.11 (1H, m), 5.25 (2H, brs), 6.12 (1H, t), 6.64-6.79 (3H, m), 7.20-7.40 (5H, m), 7.53 (1H, d), 8.50 (1H, d).
ESI-MS m/z: 477 [M + 1].

Example 435:
Trifluoro-methanesulfonic acid 5-{3-[4-(4-chloro-phenyl)-4-hydroxy-3-methyl-piperidin-1-yl]-propylidene}-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl ester

The title compound was prepared according to the procedure of Example 169 and obtained as a brown solid.
[1]H-NMR ($CDCl_3$) δ: 0.55 (3H, d), 1.55-1.68 (2H, m), 1.92-2.18 (2H, m), 2.24-2.69 (7H, m), 5.36 (2H, brs), 6.15 (1H, t), 6.88 (1H, d), 7.05 (1H, dd), 7.19-7.43 (6H, m), 7.60 (1H, d), 8.54 (1H, d).
ESI-MS m/z: 609 [M + 1].

Example 436:
5-{3-[4-(4-Chloro-phenyl)-4-hydroxy-3-methyl-piperidin-1-yl]-propylidene}-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene-7-carboxylic acid methyl ester

The title compound was prepared according to the procedure of Example 423 and obtained as a brown solid (formate salt).
[1]H-NMR ($CDCl_3$) δ: 0.62 (3H, d), 1.75 (1H, d), 2.41-2.71 (5H, m), 2.90-3.14 (4H, m), 3.27 (1H, d), 3.89 (3H, s), 5.00-5.70 (2H, brs), 6.08 (1H, t), 6.86 (1H, d), 7.26-7.39 (5H, m), 7.59 (1H, d), 7.83 (1H, d), 7.98 (1h, s), 8.34 (1H, s), 8.56 (1H, d).
ESI-MS m/z: 519 [M + 1].

Example 437:
4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene]-propyl}-3-methyl-piperidin-4-ol

The title compound was prepared according to the procedure of Example 27. The racemic compound was resolved using preparative chiral HPLC (ChiralPak AD, 20mm X 250 mm, isocrati elution with 10% ethanol:90% hexane, 15 mL/min., 35 minute run time). The more active enantiomer eluted first, at 17 minutes. The less active enantiomer eluted second, at 23 minutes. white solid (formate salt).
^{1}H-NMR ($CDCl_3$) δ: 0.61 (3H, d), 1.57 (6H, s), 1.76 (1H, d), 2.43-2.72 (5H, m), 2.91-3.12 (4H, m), 3.25 (1H, d), 5.04-5.46 (2H, brs), 6.01 (1H, t), 6.82 (1H, d), 7.22-7.37 (5H, m), 7.46 (1H, s), 7.55 (1H, d), 8.30-8.40 (1H, brs), 8.52 (1H, d).
ESI-MS m/z: 519 [M + 1].

Example 438:
5-{3-[4-(4-Chloro-phenyl)-4-hydroxy-3-methyl-piperidin-1-yl]-propylidene}-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene-7-carboxylic acid

The title compound was prepared according to the procedure of Example 118 and obtained as a brown solid (formate salt).
^{1}H-NMR ($CDCl_3$) δ: 0.49 (3H, d), 1.63 (1H, d), 2.29-2.43 (2H, m), 2.45-2.63 (3H, m), 2.78-3.18 (5H, m), 4.82-5.85 (2H, brs), 6.13 (1H, t), 6.67 (1H, d), 7.19-7.31 (5H, m), 7.55 (1H, d), 7.67 (1H, d), 7.87 (1h, s), 8.19 (1H, s), 8.40 (1H, d).
ESI-MS m/z: 505 [M + 1].

Example 439:
5-{3-[4-(4-Chloro-phenyl)-4-hydroxy-3,5-dimethyl-piperidin-1-yl]-propylidene}-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-ol

Step 1: 1-Benzyl-3,5-dimethyl-piperidin-4-one

To 1-benzyl-3-methyl-4-piperidone (2.0 g, 9.8 mmol) in THF at about –78 °C under argon, was added Lithium diisopropylamide (7.35 mL, 14.7 mmol, 2 M in heptane/THF/ethylbenzene). After stirring for about 1 hour at about –78 °C, iodomethane (0.73 mL, 11.8 mmol) was added. The reaction mixture was stirred for about 1 hour at about –78 °C, then warmed to room temperature. Stirring was continued overnight at room temperature. The reaction was quenched with saturated ammonium chloride solution, and extracted with ethyl acetate. The organic layer was washed with water, then brine and dried over magnesium sulfate. The crude product was chromatographed on silica gel, eluting with EtOAc /hexane (3:10) to give a yellow oil of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 0.96 (6H, d), 2.04 (2H, t), 2.62-2.78 (2H, m), 3.12-3.17 (2H, m), 3.59 (2H, s), 7.23-7.38 (5H, m).

ESI-MS m/z: 218 [M + 1].

Step 2: 3,5-Dimethyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared according to the procedure of Example 434, step 1 and obtained as a white crystalline solid.

^{1}H-NMR ($CDCl_3$) δ: 1.02 (6H, d), 1.5 (9H, s), 2.47-2.75 (4H, m), 4.25-4.54 (2H, brs).

ESI-MS m/z: 172 [M - CH=C(CH_3)$_2$ + 1].

Step 3: 4-(4-Chloro-phenyl)-4-hydroxy-3,5-dimethyl-piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared according to the procedure of Example 434, step 2 and obtained as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 0.57 (6H, d), 1.49 (9H, s), 1.98-2.08 (2H, m), 2.71-2.98 (2H, m), 3.79-4.10 (2H, m), 7.29-7.36 (4H, m).

ESI-MS m/z: 266 [M - CH=C(CH_3)$_2$ - H_2O + 1].

Step 4: 4-(4-Chloro-phenyl)-3,5-dimethyl-piperidin-4-ol

The title compound was prepared according to the procedure of Example 434, step 3 and obtained as a light yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 0.54 (6H, d), 1.97-2.11 (4H, m), 2.75 (2H, t), 2.88 (2H, d), 7.27-7.32 (4H, m).

ESI-MS m/z: 240 [M + 1].

5-{3-[4-(4-Chloro-phenyl)-4-hydroxy-3,5-dimethyl-piperidin-1-yl]-propylidene}-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-ol

The title compound was prepared according to the procedure of Example 434, and obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 0.58 (6H, d), 2.50-2.80 (6H, m), 2.94-3.06 (2H, m), 3.17 (2H, d), 5.14-5.29 (2H, brs), 5.87 (1H, t), 6.75-6.90 (2H, m), 7.10-7.45 (6H, m), 8.44 (1H, d), 8.52 (1H, s).

ESI-MS m/z: 491[M + 1].

Example 440:

4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene]-propyl}-3,5-dimethyl-piperidin-4-ol

The title compound was prepared according to the procedure of Example 439 but using 2-[5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl]-propan-2-ol, and was obtained as a white solid (formate salt).

^{1}H-NMR ($CDCl_3$) δ: 0.59 (6H, d), 1.58 (6H, s), 2.49-2.74 (6H, m), 2.97-3.10 (2H, m), 3.16 (2H, d), 5.20-5.45 (2H, brs), 6.06 (1H, t), 6.83 (1H, d), 7.12-7.43 (6H, m), 7.49 (1H, s), 7.60 (1H, d), 8.38 (1H, s), 8.54 (1H, m).

ESI-MS m/z: 533 [M + 1].

Examples 441 and 442:

4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene]-propyl}-3-methyl-piperidin-4-ol

and

4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-azadibenzo[a,d]cyclohepten-5-ylidene]-propyl}-4-methyl-piperidin-3-ol

Step 1: 4-(4-Chloro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester

To a solution of di-tert-butyl-dicarbonate (3.27 g, 15.0 mmol) in CH_2Cl_2 (50 mL) was added 4-(4-chlorophenyl)-1,2,3,6-tetrahydropiperidine hydrochloride (3.02 g, 13.1 mmol) and triethylamine (3.6 mL, 20 mmol). The solution was stirred at about room temperature for about 15 hours. Gas evolution was observed. The reaction was quenched with aqueous ammonium chloride, extracted with CH_2Cl_2, and the organic layers were evaporated *in vacuo*. The residue was purified by plug filtration through silica gel to yield the title compound as a colorless oil.

^{1}H-NMR ($CDCL_3$) d: 1.50 (9H, s), 2.46 (2H, br s), 3.62 (2H, br s), 4.05 (2H, br s), 6.01 (1H, br s), 7.25 (4H, s).

Step 2: 6-(4-Chloro-phenyl)-7-oxa-3-aza-bicyclo[4.1.0]heptane-3-carboxylic acid tert-butyl ester

To a solution of 4-(4-Chloro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (3.8 g, 13 mmol) in CH_2Cl_2 (50 mL) was added 3-chloroperbenzoic acid (3.8 g, 17.0 mmol) and triethylamine (3.6 mL, 20 mmol). The solution was stirred at room temperature for about 4 hours. A white precipitate was observed. The reaction was quenched with aqueous sodium bicarbonate, extracted with CH_2Cl_2, and the organic layers were evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (35g SiO_2, gradient elution from 100% hexane to 100% ethyl acetate) to yield the title compound as a colorless oil.

^{1}H-NMR ($CDCL_3$) ∂: 1.50 (9H, s), 2.15 (1H, m), 3.15 (2H, m), 3.6-4.2 (4H, m), 7.31 (4H, s).

Step 3: 4-(4-Chloro-phenyl)-4-hydroxy-3-methyl-piperidine-1-carboxylic acid tert-butyl ester and 4-(4-Chloro-phenyl)-3-hydroxy-4-methyl-piperidine-1-carboxylic acid tert-butyl ester

A suspension of copper(I) iodide (0.38 g, 2 mmol) in THF (20 mL) was cooled to about 4°C, and treated with methylmagnesium bromide (6 mL of 3M solution in diethyl ether, 18 mmol). To the cooled suspension of cuprate was added 6-(4-Chloro-phenyl)-7-oxa-3-aza-bicyclo[4.1.0]heptane-3-carboxylic acid tert-butyl ester (1.9 g, 6.1 mmol) in THF (5 mL). The solution was stirred and allowed to warm to about room temperature for about 4 hours. The reaction was quenched with aqueous ammonium chloride, extracted with ethyl acetate, and the organic layers were evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (35g SiO_2, gradient elution from 100% hexane to 50% ethyl acetate) to yield a mixture of the title compounds as a white foam. This mixture was carried on to the next step.

Step 4: Synthesis of 4-(4-Chloro-phenyl)-3-methyl-piperidin-4-ol and 4-(4-Chloro-phenyl)-4-methyl-piperidin-3-ol

The BOC-protected amino-alcohol mixture (0.8 g, 2.5 mmol) was dissolved in 4M HCl/Dioxane (5 mL, 20 mmol). The solution was stirred at room temperature for about 1 hour. The solvent was removed *in vacuo*. The residue was quenched with aqueous sodium hydroxide, extracted with ethyl acetate, and the organic layers were dried over sodium sulfate and evaporated *in vacuo* to yield the title compound as a brown solid.

ESI-MS m/z: 226 (M + 1), 208 (M+1-H_2O). The mixture was carried on to the next step without further purification.

4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene]-propyl}-3-methyl-piperidin-4-ol

and

4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-azadibenzo[a,d]cyclohepten-5-ylidene]-propyl}-4-methyl-piperidin-3-ol

To a solution of the amino alcohol mixture (0.53 g, 2.3 mmol) in isopropanol (10 mL) was added 2,6-lutidine (0.23 mL, 2.0 mmol) and catalytic potassium iodide. This mixture was heated to about 80°C, and treated with 2-[5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl]-propan-2-ol (0.37 g, 1.0 mmol), added in portions over about 2 hours. The solution was then stirred at about 80°C for about an additional 2 hours. The reaction was concentrated *in vacuo*, then purified by flash chromatography on silica gel (35g SiO_2, gradient elution from 100% ethyl acetate to 87% ethyl acetate:10% methanol:3% triethylamine) to yield the title compounds.

The faster eluting isomer: 4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene]-propyl}-3-methyl-piperidin-4-ol, a brown semisolid. ^{1}H-NMR ($CDCL_3$) ∂: 0.70 (3H, d, J = 7.2 Hz), 1.53 (6H, s), 1.92 (3H, m), 2.28-2.69 (8H, m), 5.30 (2H, br s), 6.15 (1H, t, J = 1.4 Hz), 6.79 (2H, d, J = 8.4 Hz), 7.18-7.45 (7H, m), 7.59 (1H, d, J = 8 Hz), 8.45 (1H, m). ESI-MS m/z: 519(M + 1).

The slower eluting isomer: 4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-, a brown semisolid. ^{1}H-NMR ($CDCL_3$) ∂: 1.16 (3H, s), 1.55 (6H, s), 2.28-2.69 (5H, m), 3.86 (1H, br s), 5.30 (2H, br s), 6.07 (1H, t, J = 1.4 Hz), 6.79 (2H, d, J = 8.4 Hz), 7.18-7.45 (7H, m), 8.45 (1H, m). ESI-MS m/z: 519(M + 1).

Example 443:
4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene]-propyl}-3,3-dimethyl-piperidin-4-ol

Step 1: 1-Benzyl-3,3-dimethyl-piperidin-4-one

To a solution of 1-Benzyl-3-methyl-piperidin-4-one (2.03 g, 10 mmol) in THF (10 mL) was added potassium t-Butoxide (1.1g, 10 mmol) and methyl iodide (0.62 mL, 10 mmol). The solution was then stirred at room temperature for about 72 hours. The reaction was quenched with brine and extracted with ethyl acetate. The combined organic layers were concentrated *in vacuo*, then purified by flash chromatography on silica gel (35g SiO_2, gradient elution from 100% hexane to 100% ethyl acetate) to yield the title compound as a colorless oil.

^{1}H-NMR ($CDCL_3$) ∂: 1.12 (6H, s), 2.41 (2H, s), 2.52 (2H, m), 2.73 (2H, m), 3.56 (2H, s), 7.20-7.40 (5H, m). ESI-MS m/z: 218 (M + 1).

Step 2: 3,3-Dimethyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester

To a solution of 1-Benzyl-3,3-dimethyl-piperidin-4-one (2.48 g, 11 mmol) in ethanol (100 mL) was added di-tert-butyl dicarbonate (2.18, 10 mmol) and palladium hydroxide (0.10 g), The suspension was then shaken under a hydrogen atmosphere (40 PSI) at room temperature for about an additional 12 hours. The reaction was filtered through celite and evaporated *in vacuo* to yield the title compound as a white solid.

^{1}H-NMR ($CDCL_3$) ∂: 1.12 (6H, br s), 1.48 (9H, s), 2.45-2.80 (3H, m), 3.12 (1H, m), 3.42 (1H, br s), 3.70 (1H, m).

Step 3: 4-(4-Chloro-phenyl)-4-hydroxy-3,3-dimethyl-piperidine-1-carboxylic acid tert-butyl ester

To an ice-cooled solution 3,3-Dimethyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester (1.6 g, 7.2 mmol) in THF (20 mL) was added 4-chlorophenylmagnesium bromide (1 M in ether, 15 mL, 15 mmol). The solution was allowed to warm to about room temperature, then stirred at room temperature for about 22 hours. The reaction was quenched with aqueous ammonium chloride and extracted with ethyl acetate. The combined organic layers were concentrated *in vacuo*, then purified by flash chromatography on silica gel (35g SiO_2, gradient elution from 100% hexane to 100% ethyl acetate) to yield the title compound as a colorless oil.

^{1}H-NMR ($CDCL_3$) ∂: 1.12 (6H, s), 1.50 (11H, m), 2.60 (1H, m), 3.20 (2H, m), 3.56 (1H, m), 4.20 (1H, m), 7.20-7.40 (4H, m). ESI-MS m/z: 218 (M + 1).

Step 4: 4-(4-Chloro-phenyl)-3,3-dimethyl-piperidin-4-ol

4-(4-Chloro-phenyl)-4-hydroxy-3,3-dimethyl-piperidine-1-carboxylic acid tert-butyl ester (0.25 g, 0.73 mmol) was dissolved in 4M HCl/Dioxane (2 mL, 8 mmol). The solution was stirred at room temperature for about 4 hours. The solvent was removed *in vacuo*. The residue was quenched with aqueous sodium hydroxide, extracted with ethyl acetate, and the organic layers were dried over sodium sulfate and evaporated *in vacuo* to yield the title compound as a yellow solid. The mixture was carried on to the next step without further purification.

4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene]-propyl}-3,3-dimethyl-piperidin-4-ol

To a solution of the amino alcohol mixture (0.17 g, 0.7mmol) in isopropanol (5 mL) was added 2,6-lutidine (0.23 mL, 2.0 mmol) and catalytic potassium iodide. This mixture was heated to about 80°C, and treated with 2-[5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl]-propan-2-ol (0.19 g, 0.5 mmol), added in portions over about 2 hours. The solution was then stirred at about 80°C for an additional 2 hours. The reaction was concentrated *in vacuo*, then purified by flash chromatography on silica gel (10g SiO_2, gradient elution from 100% ethyl acetate to 87% ethyl acetate:10% methanol:3% triethylamine) to yield the title compound as a brown semisolid.
^{1}H-NMR ($CDCL_3$) ∂: 0.78 (3H, s), 0.90 (3H, s), 1.45 (2H, m), 1.53 (6H, s), 2.28-2.80 (9H, m), 5.30 (2H, br s), 6.15 (1H, t, J = 1.4 Hz), 6.79 (2H, d, J = 8.4 Hz), 7.18-7.45 (7H, m), 7.59 (1H, d, J = 8 Hz), 8.45 (1H, m). ESI-MS m/z: 533 (M + 1).

Example 456
4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11*H*-10-oxa-1-aza-dibenzo-[*a*,*d*]cyclohepten-5-ylidene]-propyl}-piperidine-4-carbonitrile

Step 1: Bis-(2-chloroethyl)-carbamic acid *tert*-butyl ester

To a solution of bis-(2-chloroethyl)-amine hydrochloride (7.12g, 40 mmol) in dichloromethane (65ml) was added *N,N*-diisopropylethylamine (34.8ml, 200 mmol) and catalytic amount of 4-dimethylaminopyridine, followed by portionwise addition of di-*tert*-butyl dicarbonate (8.72g, 40 mmol). The solution was stirred at room temperature for 72 hours. The reaction mixture was concentrated and triturated with ether (70 ml). The solid was filtered and the filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography eluting with hexane-ethyl acetate (9:1) to give the title compound (2.02 g, 21%).

^{1}H-NMR ($CDCl_3$) δ: 1.5 (9H, s), 3.5-3.6 (8H, m).

Step 2: 4-(4-Chloro-phenyl)-4-cyano-piperidine-1-carboxylic acid *tert*-butyl ester

To 1.26 g (8.37 mmol) 4-chloro-benzylcyanide was added bis-(2-chloroethyl)-carbamic acid *tert*-butyl ester (2.02 g, 8.37 mmol) in 25 ml *N, N*-dimethylformamide. The resulting mixture was stirred and cooled in an ice bath, then sodium hydride (60% suspension in mineral oil) (1.1 g, 42 mmol) was added portionwise. The reaction was brought to room temperature and then heated in an oil bath at 60 °C for 16 hours. The reaction mixture was quenched by addition of ice water and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed twice with water, once with brine, dried with magnesium sulfate and concentrated *in vacuo*. The residual brown oil was purified by silica gel chromatography eluting with hexane-ethyl acetate (9:1) to give the title compound (1.44 g, 54%).

^{1}H-NMR ($CDCl_3$) δ: 1.5 (9H, s), 1.8-2.0 (2H, m), 2.1 (2H, d), 3.2 (2H, t), 4.3 (2H, brs), 7.4 (4H, m).

MS m/z: 221 (M+1-100)

Step 3: 4-(4-Chloro-phenyl)-piperdine-4-carbonitrile

To a chilled solution of 4-(4-chloro-phenyl)-4-cyano-piperidine-1-carboxylic acid *tert*-butyl ester (315 mg, 1mmol) in 5 ml dichloromethane was added 1 ml trifluoroacetic acid. The reaction was stirred at 0 °C for 3 hours, then concentrated under vacuum. The resulting oil was diluted with dichloromethane and washed twice with saturated aqueous sodium bicarbonate. The aqueous washings were extracted three times with dichloromethane. The combined organic layers were dried with magnesium sulfate and concentrated under vacuum to yield the title compound (180 mg, 82%).

^{1}H-NMR ($CDCl_3$) δ: 1.9-2.1 (4H, m), 3.0-3.2 (4H, m), 7.3-7.5 (4H, m).

MS m/z: 221 (M+1)

Step 4

To a suspension of 4-(4-chloro-phenyl)-piperdine-4-carbonitrile (180 mg, 0.8 mmol) in acetonitrile/water (4/1) was added potassium carbonate (221 mg, 1.6 mmol), followed by 2-[5-(3-bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-7-yl]-propan-2-ol (150 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 48 hours and then concentrated *in vacuo*. The resulting residue was treated with water and extracted with ethyl acetate. Solvent was evaporated from the combined dried ($MgSO_4$) organic extracts, and the residue was purified by column chromatography on silica gel using hexane-ethyl acetate (6:4) to afford the title compound.

^{1}H-NMR ($CDCl_3$) δ: 1.5 (6H, s), 1.8-2.0 (4H, m), 2.4 (4H, m), 2.55 (2H, m), 2.8 (2H, d), 5.3 (2H, brs), 6.1 (1H, t), 6.8 (1H, d), 7.27-7.4 (7H, m), 7.5 (1H,d), 8.5 (1H, d)

MS m/z: 514 (M+1)

Example 457

1-(4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11*H*-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-piperidin-4-yl)-ethanone

Step 1: 1-[4-(4-Chloro-phenyl)-piperidin-4-yl]-ethanone

To a dry round bottom flask was added via syringe 10 ml methyl magnesium bromide in toluene/tetrahydrofuran (75:25, 1.4 M). The flask was cooled in an ice bath under a stream of nitrogen. A solution of 4-(4-Chloro-phenyl)-4-cyano-piperidine-1-carboxylic acid *tert*-butyl ester (357 mg, 1.11 mmol) in 4 ml tetrahydrofuran was added dropwise to the flask over 20 minutes and the resulting mixture was stirred at 0 °C for 8 hours. The reaction mixture was warmed to room temperature and stirred for 5 days. The reaction was quenched by slowly pouring 150 ml saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined organic phases were dried over magnesium sulfate and concentrated under vacuum. The yellow residue was purified by reverse phase HPLC to get the formate salt of the title compound (106 mg, 40%).

MS m/z: 238 (M+1)

Step 2

To a suspension of 1-[4-(4-chloro-phenyl)-piperidin-4-yl]-ethanone in acetonitrile/water (4/1) was added potassium carbonate (221 mg, 1.6 mmol), followed by 2-[5-(3-bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-7-yl]-propan-2-ol (150 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 48 hours and then concentrated *in vacuo*. The resulting residue was treated with water and extracted with ethyl acetate. Solvent was evaporate from the combined dried ($MgSO_4$) organic extracts. Purification on silica gel chromatography using dichloromethane-methanol (9.5:0.5) afforded the title compound.

^{1}H-NMR ($CDCl_3$) δ: 1.3 (2H, m), 1.5 (6H, s), 1.9 (3H, s),2.1-2.5 (10H, m), 5.3 (2H, brs), 5.9 (1H, t), 6.8 (1H, d), 7.3 (6H, m), 7.4 (1H, d), 7.6 (1H,d), 8.5 (1H, d)

MS m/z: 531 (M+1)

Example 458

4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11*H*-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-piperidine-4-carboxylic acid methyl ester

Step 1: 4-(4-Chloro-phenyl)-piperidine-1,4-dicarboxylic acid mono-*tert*-butyl ester

To a solution of 4-(4-chloro-phenyl)-4-cyano-piperidine-1-carboxylic acid *tert*-butyl ester (1.1 g, 3.44 mmol) in 40 ml ethanol was added 10 ml 10 N aqueous sodium hydroxide. The resulting solution was warmed to reflux for 48 hours, cooled to room temperature, poured into 1 N aqueous hydrochloric acid, and extracted into ethyl acetate. The organic extracts were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. Recovered orange oil was purified by silica gel chromatography, eluting with dichloromethane-methanol (9.5:0.5) to give the title compound (1.0 g, 86%).
MS m/z: 338 (M-1)

Step 2: 4-(4-Chloro-phenyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-methyl ester

To a stirred 4-(4-chloro-phenyl)-piperidine-1,4-dicarboxylic acid mono-*tert*-butyl ester (852 mg, 2.5 mmol) in methanol (5 ml)-benzene (17.5 ml) was added 15 ml (trimethylsilyl)diazomethane (2.0 M solution in hexanes) at room temperature. The mixture was stirred for 16 hours at room temperature and concentrated *in vacuo*. The residual yellow oil was purified by silica gel chromatography eluting with hexane-ethyl acetate (9:1) to give the corresponding ester (780 mg, 88%).
^{1}H-NMR ($CDCl_3$) δ: 1.5 (9H, s), 2.8-2.9 (2H, m), 2.5 (2H,d), 3.0 (2H, t). 3.7 (3H, s), 4.0 (2H, d), 7.4 (4H, m).
MS m/z: 354 (M+1)

Step 3: 4-(4-Chloro-phenyl)-piperidine-4-carboxylic acid methyl ester

The title compound was prepared by following the procedure of Example 456, Step 3, but replacing 4-(4-chloro-phenyl)-4-cyano-piperidine-1-carboxylic acid *tert*-butyl ester with 4-(4-chloro-phenyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-methyl ester.
^{1}H-NMR ($CDCl_3$) δ: 1.9 (2H, t), 2.55 (2H, d), 2.9 (2H, t), 3.25 (2H, d), 3.8 (3H, s), 7.2 (4H, m)
MS m/z: 254 (M+1)

Step 4

To a suspension of 4-(4-chloro-phenyl)-piperidine-4-carboxylic acid methyl ester in acetonitrile/water (4/1) was added potassium carbonate (221 mg, 1.6 mmol), followed by 2-[5-(3-bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-7-yl]-propan-2-ol (150 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 48 hours and then concentrated *in vacuo*. The resulting residue was treated with water and extracted with ethyl acetate. Solvent was evaporate from the combined dried ($MgSO_4$) organic extracts. Purification on silica gel chromatography using dichloromethane-methanol (9.6:0.4) afforded the title compound.

^{1}H-NMR ($CDCl_3$) δ: 1.5 (6H, s), 1.8-2.0 (4H, m), 2.1 (2H, m), 2.4-2.5 (7H, m), 2.6 (2H, m), 5.3 (2H, brs), 6.1 (1H, t), 6.8 (1H, d), 7.3 (6H, m), 7.4 (1H, d), 7.6 (1H,d), 8.5 (1H, d)

MS m/z: 547 (M+1)

Example 459

4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11*H*-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-piperidine-4-carboxylic acid

To a solution 4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11*H*-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-piperidine-4-carboxylic acid methyl ester (110 mg, 0.2 mmol) in methanol (5 ml) was added 1 ml 1 N aqueous sodium hydroxide. The resulting solution was warmed to 50 °C for 16 hours, cooled to room temperature, and concentrated under a stream of nitrogen. The residue was purified by reverse phase HPLC to get the formate salt of the title compound (96 mg. 90%).

^{1}H-NMR ($CDCl_3$) δ: 1.5 (6H, s), 1.8-1.9 (2H, m), 2.4 (4H, m), 2.55 (2H, m),2.6-2.8 (4H, d), 5.3 (2H, brs), 5.9 (1H, t), 6.8 (1H, d), 7.27-7.4 (7H, m), 7.5 (1H,m), 8.5 (1H, d)

MS m/z: 533 (M+1)

Example 460

4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11*H*-10-oxa-1-aza-dibenzo[*a*,*d*]cyclohepten-5-ylidene]-propyl}-piperidine-4-carboxylic acid amide

Step 1: 4-Carbamoyl-4-(4-chloro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

To a solution of 4-(4-chloro-phenyl)-4-cyano-piperidine-1-carboxylic acid *tert*-butyl ester (500 mg, 1.56 mmol) in ethanol (15 ml) was added 2 ml 10 N aqueous sodium hydroxide. The resulting solution was warmed to reflux for 2 hours, cooled to room temperature, poured into 1 N aqueous hydrochloric acid, and extracted into ethyl acetate. The organic extracts were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. Recovered yellow oil was purified by silica gel chromatography, eluting with dichloromethane-methanol (9.6:0.4) to give the title compound (306 mg, 58%). MS m/z: 339 (M+1)

Step 2: 4-(4-Chloro-phenyl)-piperidine-4-carboxylic acid amide

The title compound was prepared by following the procedure of Example 456, step 3, but replacing 4-(4-chloro-phenyl)-4-cyano-piperidine-1-carboxylic acid *tert*-butyl ester with 4-carbamoyl-4-(4-chloro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester.

MS m/z: 239 (M+1)

Step 3

The title compound was prepared by following the procedure of Example 456, step 4 but replacing 4-(4-chloro-phenyl)-piperdine-4-carbonitrile with 4-(4-chloro-phenyl)-piperidine-4-carboxylic acid amide. Purification on silica gel chromatography using dichloromethane-methanol (9:1) afforded the title compound. ^{1}H-NMR ($CDCl_3$) δ: 1.5 (6H, s), 1.8-2.0 (6H, m), 2.3-2.6 (6H, m), 5.3 (2H, brs), 6.1 (1H, t), 6.8 (1H, d), 7.3 (6H, m),7.4 (1H, d), 7.5 (1H,d), 8.5 (1H, d)

MS m/z: 532 (m+1)

Example 461
2-(5-{3-[4-(4-Chloro-phenyl)-4-hydroxymethyl-piperidin-1-yl]-propylidene}-5,11-dihydro-10-oxa-1-aza-dibenzo[*a*,*d*]cyclohepten-7-yl)-propan-2-ol

Step 1: 4-(4-Chloro-phenyl)-4-hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester

To a chilled solution of 4-(4-chloro-phenyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-methyl ester (700 mg, 1.98mmol) in 6 ml ether was added dropwise 2ml lithium aluminium hydride 1M solution in ether. The reaction was stirred at 0 °C for 3 hours, then water (100 ml) was slowly added. The resulting gel was filtered and the aqueous filtrate was extracted three times with ether. The combined organic layers were dried with magnesium sulfate and concentrated under vacuum. Recovered oil was purified by silica gel chromatography, eluting with hexane-ethyl acetate (6:4) to give the title compound (297 mg, 46%).

^{1}H-NMR ($CDCl_3$) δ: 1.5 (9H,s), 1.7-1.8 (2H, m), 2.1 (2H,d), 3.0 (2H, m), 3.5 (2H, s), 3.7 (2H, d), 7.4 (4H, m)
MS m/z: 324 (M-1)

Step 2: [4-(4-Chloro-phenyl)-piperidin-4-yl]-methanol

The title compound was prepared by following the procedure of Example 456, step 3, but replacing 4-(4-chloro-phenyl)-4-cyano-piperidine-1-carboxylic acid *tert*-butyl ester with 4-(4-chloro-phenyl)-4-hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester.
MS m/z: 224 (M-1)

Step 3

The title compound was prepared by following the procedure of Example 456, step 4, but replacing 4-(4-chloro-phenyl)-piperdine-4-carbonitrile with [4-(4-

chloro-phenyl)-piperidin-4-yl]-methanol. Purification on silica gel chromatography using dichloromethane-methanol (9.5:0.5) afforded the title compound.

^{1}H-NMR ($CDCl_3$) δ: 1.5 (6H, s), 2.0 (2H, m), 2.2-2.3 (4H, m) 2.4 (2H, m), 2.55 (2H, m), 2.8 (2H, d), 3.5 (2H, s), 5.3 (2H, brs), 6.0 (1H, t), 6.8 (1H, d), 7.27-7.4 (7H, m), 7.5 (1H,d), 8.5 (1H, d)

MS m/z: 517 (M-1)

Example 462

2-(5-{3-[4-(4-chloro-phenyl)-4-(1-hydroxy-ethyl)-piperidin-1-yl]-propylidene}-5,11-dihydro-10-oxa-1-aza-dibenzo[*a*,*d*]cyclohepten-7-yl)-propan-2-ol

To a chilled solution of 1-(4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11*H*-10-oxa-1-aza-dibenzo[*a*,*d*]cyclohepten-5-ylidene]-propyl}-piperidin-4-yl)-ethanone (70 mg, 0.13 mmol) in 5 ml methanol was added sodium borohydride (20 mg, 0.53 mmol). The reaction mixture was stirred at 0 °C for 4 hours, then concentrated down under a stream of nitrogen. The residue was purified by reverse phase HPLC to get the formate salt of the title compound (39 mg, 56%).

^{1}H-NMR ($CDCl_3$) δ: 0.8 (4H, d), 1.5 (6H, s), 2.1-2.7 (10H, m), 3.1 (2H, m), 5.3 (2H, brs), 5.95 (1H, t), 6.8 (1H, d), 7.27-7.4 (7H, m), 7.5 (1H,d), 8.5 (H, d)

MS m/z: 533 (M+1)

Example 463

2-(5-{3-[4-(4-Chloro-phenyl)-4-(1-hydroxy-1-methyl-ethyl)-piperidin-1-yl]-propylidene}-5,11-dihydro-10-oxa-1-aza-dibenzo[*a*,*d*]cyclohepten-7-yl)-propan-2-ol

Step 1: 4-Acetyl-4-(4-chloro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

To a chilled solution of 1-[4-(4-chloro-phenyl)-piperidin-4-yl]-ethanone (540 mg, 1.98 mmol) in dichloromethane (10ml) was added triethylamine (0.6 ml, 3.82 mmol), followed by portionwise addition of di-*tert*-butyl dicarbonate (470 mg, 1.98 mmol). The solution was stirred at room temperature for 16 hours. The reaction mixture was concentrated down, quenched with 1 N aqueous hydrochloric acid, and extracted into dichloromethane. The organic extracts were washed with saturated aqueous sodium bicarbonate solution, brine, dried over magnesium sulfate, and concentrated *in vacuo*. Recovered oil was purified by silica gel chromatography, eluting with hexane-ethyl acetate (8:2) to give the title compound (445 mg, 67%).

^{1}H-NMR ($CDCl_3$) δ: 1.5 (9H, s), 1.9 (5H, m), 2.3-2.4 (2H, m), 3.1 (2H, t), 3.7-3.8 (2H, m), 7.4 (4H, m)

MS m/z: 338 (M+1)

Step 2: 4-(4-Chloro-phenyl)-4-(1-hydroxy-1-methyl-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester

To a dry round bottom flask was added via syringe 16 ml methyl magnesium bromide in toluene/tetrahydrofuran (75:25, 1.4 M). The flask was cooled in an ice bath under a stream of nitrogen. A solution 4-acetyl-4-(4-chloro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester (337 mg, 1.02 mmol) in 5 ml tetrahydrofuran was added dropwise to the flask over 20 minutes and the resulting mixture was stirred at 0 °C for 8 hours. The reaction mixture was warmed to room temperature and stirred for 5 days. The reaction was quenched by slow addition of 150 ml saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated under vacuum. The yellow residue was purified by silica gel chromatography, eluting with hexane-ethyl acetate (7.5:2.5) to give the title compound (242 mg, 67%).

^{1}H-NMR ($CDCl_3$) δ: 1.1 (6H, s), 1.4 (9H, s), 1.8-1.9 (2H, m), 2.3-2.4 (2H, d), 2.6 (2H, t), 3.9 (2H, d), 7.3 (4H, m)

MS m/z: 354 (M+1)

Step 3: 2-[4-(4-Chloro-phenyl)-piperidin-4-yl]-propan-2-ol

The title compound was prepared by following the procedure of Example

456, step 3, but replacing 4-(4-chloro-phenyl)-4-cyano-piperidine-1-carboxylic acid *tert*-butyl ester with : 4-(4-chloro-phenyl)-4-(1-hydroxy-1-methyl-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester.

MS m/z: 254 (M+1)

Step 4

The title compound was prepared by following the procedure of Example 456, step 4, but replacing 4-(4-chloro-phenyl)-piperdine-4-carbonitrile with 2-[4-(4-chloro-phenyl)-piperidin-4-yl]-propan-2-ol. Purification on silica gel chromatography using dichloromethane-methanol (9:1) afforded the title compound.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (6H, s), 1.5 (6H, s), 1.8 (2H, m), 2.3-2.6 (10H, m), 5.3 (2H, brs), 5.95 (1H, t), 6.8 (1H, d), 7.27-7.4 (7H, m), 7.5 (1H,d), 8.5 (1H, d)

MS m/z: 547 (M+1)

Example 464

4-(4-Chloro-phenylamino)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene]-propyl}-piperidine-4-carbonitrile

Step 1: 1-Benzyl-4-(4-chloro-phenylamino)-piperidine-4-carbonitrile

To a solution of 1-Benzyl-piperidin-4-one (2.68g, 14.20mmol) in acetic acid (13ml, glacial) was added 4-Chloro-phenylamine (1.99g, 15.6mmol). The reaction was cooled in a cool temperature water bath. Trimethylsilylcyanide (1.89ml, 14.20mmol) was added slowly. The reaction mixture was allowed to warm to room temperature and stir overnight under N_2. The reaction was cooled to 0°C. Concentrated ammonium hydroxide (15ml) was added slowly. Next added was cold water. The pH of the mixture was ≈ 10. The mixture was extracted three times with methylene chloride, and the organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Ether was added to the residue, and the white solid was filtered off and dried under high vacuum to give the titled compound (3.73g, 81%)

^{1}H-NMR ($CDCl_3$) δ: 1.90-2.01(2H,t), 2.3-2.4(2H,m), 2.45-2.55(2H,t), 2.81-2.93(2H,m), 3.61(2H,s), 3.68(1H,s) 6.87(1H,s), 6.90(1H,s) 7.2-7.38(7H,m).
MS m/z: 326 (M+1).

Step 2: 4-(4-Chloro-phenylamino)-piperidine-4-carbonitrile

To 1-Benzyl-4-(4-chloro-phenylamino)-piperidine-4-carbonitrile (163mg, 0.5002mmol) in dichloroethane (5ml) was added 1-chloroethyl chloroformate (65μl, 0.600mmol). The mixture was heated to reflux and stirred under N_2. After 1 hour 15 minutes, an additional 86μl (0.800mmol) of the chloroformate was added to the reaction and stirred for an additional 2 hours at reflux. After cooling to room temperature the reaction was concentrated under reduced pressure. To this residue was added methanol (5ml) and the reaction was heated at reflux for 2 hours. Next, the reaction was allowed to cool to room temperature and concentrated under reduced pressure. The residue was diluted with ethyl acetate and water. The organic layer was removed and sodium hydroxide (1*N*) was added to the aqueous layer until pH≈9. The aqueous layer was extracted with ethyl acetate 2 times and dried over magnesium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound (84mg, 71%).
^{1}H-NMR ($CDCl_3$) δ: 1.66-1.68(1H,d), 1.70-1.75(2H,d), 2.22-2.28(2H,d), 2.87-3.12(4H,m), 3.61(1H,bs), 6.53-7.27(4H,m)
MS m/z: 236 (M+1).

Step 3

The title compound was prepared by dissolving 2-[5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl]-propan-2-ol (106.7mg, 0.285mmol) in water (4ml) and acetonitrile (1ml). To this was added potassium carbonate (82.7mg, 0.599mmol) and 4-(4-Chloro-phenylamino)-piperidine-4-carbonitrile (84.0mg, 0.356mmol). The reaction was heated to 50 °C and stirred overnight. The next day the reaction was allowed to cool to room temperature and diluted with ethyl acetate and water. The organic layer was washed twice with water, dried over magnesium sulfate, and concentrated under reduced pressure. The crude residue was purified by reverse phase HPLC to give the title compound (11.5mg, 8% yield, 88%pure by LC/MS).

^{1}H–NMR($CDCl_3$) δ: 1.52(6H,bs), 2.2-2.8(12H, m), 3.4(1H,b), 5.16-5.36(2H,b), 6.00-6.10(1H,m), 6.75-6.80(2H,m), 6.95-7.55(7H,m), 8.45-8.76(1H,m)

MS m/z: 529 (M + 1).

Example 465

4-(4-Chloro-phenylamino)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo [a,d] cyclohepten-5-ylidene]-propyl}-piperidine-4-carboxylic acid methyl ester

Step 1: 1-Benzyl-4-(4-chloro-phenylamino)-piperidine-4-carboxylic acid amide

To 1-Benzyl-4-(4-chloro-phenylamino)-piperidine-4-carbonitrile (1.97g, 6.05mmol) was added concentrated sulfuric acid (50ml). The reaction stirred at room temperature as an orange homogeneous solution. After 24 hours the reaction was cooled to 0°C and very slowly poured into concentrated ammonium hydroxide in ice. The precipitate was filtered and washed with water to give a white solid (202mg, 71%).

^{1}H–NMR($CDCl_3$) δ: 1.87-1.92(2H,bd), 2.06-2.14 (2H,t) 2.27-2.38(2H,m), 2.70-2.78(2H,bd), 3.50(2H,s), 3.05(1H,s), 5.42-5.44(1H,bs), 6.55-6.57(2H,d), 6.76-6.82(1H,bs), 7.10-7.15(2H,d), 7.24-7.31(5H,m)

MS m/z: 344 (M+1).

Step 2: 1-Benzyl-4-(4-chloro-phenylamino)-piperidine-4-carboxylic acid methyl ester

To a solution of 1-Benzyl-4-(4-chloro-phenylamino)-piperidine-4-carboxylic acid amide (1.19g 3.46mmol) in methanol (10ml) in a sealed tube was added toluene sulfonic acid (2.33g, 12.11mmol). The reaction was heated to 120°C, and stirred at that temperature behind a blast shield for 5 days. The reaction was then allowed to cool to room temperature at which time it was worked up by diluting with water, then by adding concentrated ammonium hydroxide until the pH≈8. The mixture was extracted three times with ethyl acetate and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The yellow oil was used crude (744mg, 60%).

^{1}H–NMR($CDCl_3$) δ: 1.93-2.03(2H,bd), 2.19-2.28(2H,dt), 2.32-2.48(2H,m), 2.55-2.64(2H,m), 3.51(2H,s), 3.68(3H,s), 3.85 (1H,s) 6.47-6.51(2H,bd), 7.07-7.10(2H,bd), 7.21-7.35(5H,m)

MS m/z: 359(M+1)

Step 3: 4-(4-Chloro-phenylamino)-piperidine-4-carboxylic acid methyl ester

The titled compound was prepared by following the procedure of Example 464, step 2, but replacing 1-Benzyl-4-(4-chloro-phenylamino)-piperidine-4-carbonitrile with 1-Benzyl-4-(4-chloro-phenyl amino)-piperidine-4-carboxylic acid methyl ester. This compound was also purified on a sep-pak silica column eluted with 2% - 10% $MeOH/CH_2Cl_2$.

^{1}H–NMR($CDCl_3$) δ: 1.92-1.99(2H,bd), 2.11-2.22(2H,m), 2.73-3.03(4H,m), 3.69(3H,s), 3.94(1H,s), 6.50-6.53(2H,bd), 7.09-7.12(2H,bd)

MS m/z: 269(M+1)

Step 4

The titled compound was prepared by following the procedure of Example 464, step 3, but replacing 4-(4-chlorophenylamino)-piperidine-4-carbonitrile with 4-(4-Chloro-phenylamino)-piperidine-4-carboxylic acid methyl ester. The residue was purified by reverse phase HPLC to give the title compound (62mg, 32%).

^{1}H–NMR($CDCl_3$) δ: 1.58(6H,s) 2.09-2.20(2H,m), 2.36-2.47(2H,m), 2.51-2.60(2H,m), 2.85-3.02(6H, m), 3.69(3H,s), 5.19-5.41(3H,bs), 6.01-6.06(1H,t), 6.51-6.54(2H,d), 6.82-6.84(1H,d), 7.10-7.13(2H,d), 7.24-7.34(2H,m), 7.43-7.44(1H,d), 7.55-7.58(1H,d), 8.26(1H,s), 8.53-8.55(1H,dd)

MS m/z: 562 (M)

Example 466

4-(4-Chloro-phenylamino)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo [a,d]cyclohepten-5-ylidene]-propyl}-piperidine-4-carboxylic acid amide

Step 1: 4-(4-Chloro-phenylamino)-piperidine-4-carboxylic acid amide

The titled compound was prepared by following the procedure of Example 464, step 2, but replacing 1-Benzyl-4-(4-chloro-phenylamino)-piperidine-4-carbonitrile with 1-Benzyl-4-(4-chloro-phenyl amino)-piperidine-4-carboxylic acid amide.

^{1}H–NMR($CDCl_3$) δ: 1.82-1.92(2H,bd), 2.10-2.37(3H,m), 2.69-2.79(2H,m), 2.89-3.03(2H,m), 5.42-5.46(1H,bs), 6.47-6.59(2H,m), 6.76-6.82(1H,bs), 7.08-7.15(2H,bd).

MS m/z: 254 (M+1)

Step 2

The titled compound was prepared by following the procedure of Example 464, step 3, but replacing 4-(4-chlorophenylamino)-piperidine-4-carbonitrile with 4-(4-Chloro-phenylamino)-piperidine-4-carboxylic acid amide. The sample was purified using reverse phase HPLC to give the title compound (25mg, 25%).

^{1}H–NMR($CDCl_3$) δ: 1.53-1.55(7H,s), 1.97-2.07(2H,m), 2.40-2.61(3H,m), 2.67-2.76(3H,m), 2.86-2.96(2H,m), 5.20-5.38(2H,bs), 6.04-6.09(1H,t), 6.51-6.54(2H,bd), 6.77-6.80(1H,bd), 7.08-7.11(2H,bd), 7.19-7.29(2H,m), 7.42-7.43(1H,bd), 7.51-7.55(1H,dd), 8.18(1H,bs), 8.48-8.50(1H,dd)

MS m/z: 547 (M)

Example 467

2-(5-{3-[4-(4-Chloro-phenyl)-4-fluoro-piperidin-1-yl]-propylidene}-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl)-propan-2-ol

Step 1

To a cooled (0 °C) solution of hydrogen fluoride (65 – 70 %) in pyridine (4 mL) was added 4-(4-chloro-phenyl)-piperidin-4-ol (500 mg, 2.36 mmol). The resulting solution was stirred at 0 °C for 15 min and then warmed to rt and stirred 1h. The mixture was *slowly* poured into a saturated aqueous sodium bicarbonate solution (30 mL) and extracted with methylene chloride (100 mL; ADD SOLVENT AND EXTRACT SLOWLY AND WITH CAUTION).

Excess hydrogen fluoride was neutralized with solid sodium carbonate. The organic phase was washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography, eluting with a methylene chloride to methylene chloride/methanol/ammonium hydroxide (8.5/1/0.5) gradient to give 4-(4-Chloro-phenyl)-4-fluoro-piperidine (260 mg, 52 %).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.98 – 3.14 (m, 4 H), 1.87 – 2.10 (m, 4 H), 7.33 – 7.36 (m, 4 H).

^{19}F-NMR ($CDCl_3$, 282 MHz) d: -160.40 - -160.20 (m).

MS m/z: 214 (M + 1).

Step 2

To a solution of the product of Step 1 (252 mg, 1.18 mmol) in isopropyl alcohol (5 mL) was added 2,6-lutidine (197 mg, 214 uL, 1.84 mmol) and potassium iodide (few mg). The resulting suspension was warmed to 80 °C. Solid 2-[5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl]-propan-2-ol (221 mg, 0.591 mmol) was added in approximately equal portions over 2 h. Stirring was continued an additional 20 h at 80 °C. The mixture was concentrated and the resulting residue purified by silica gel chromatography (methylene chloride to methylene/methanol 95:5 gradient) to afford the title compound (160 mg, 54 %).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.57 – 1.66 (m, 8 H), 1.88 – 1.97 (m, 3 H), 2.31 – 2.46 (m, 4 H), 2.52 – 2.62 (m, 2 H), 2.67 – 2.76 (m, 2 H), 5.20 – 5.45 (br s, 2 H), 6.14, (t, 1 H), 6.83 (d, 1 H), 7.22 – 7.37 (m, 6 H), 7.45 (d, 1 H), 7.59 (dd, 1 H), 8.51 (dd, 1 H).

^{19}F-NMR ($CDCl_3$, 282 MHz) δ: -160.30 - -160.50 (m).

MS m/z: 507 (M + 1).

Example 468

4-(4-Chloro-phenyl)-4-fluoro-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene]-propyl}-piperidin-3-ol

Step 1

To a solution of 4-(4-chloro-phenyl)-3,4-dihydroxy-piperidine-1-carboxylic acid tert-butyl ester (1.213 g, 3.34 mmol) in methylene chloride (30 mL) at -78 °C was added diethylaminosulfur trifluoride (DAST, 3 mL). The resulting solution was stirred at -78 °C 4h. Methanol (20 mL) was added to quench excess DAST and the mixture was allowed to remain at -78 °C 5 min before warming to rt. The mixture was concentrated and purified by silica gel chromatography (80 % hexanes / 20 % ethyl acetate gradient) to afford 4-(4-chloro-phenyl)-4-fluoro-piperidin-3-ol (262 mg, 24 %).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.48 (s, 9 H), 1.84 (br dd, 1 H), 2.50 (dddd, 1 H), 3.15 (br dd, 1 H), 3.38 (d, 1 H), 3.76 (s, 1 H), 4.04 – 4.36 (m, 2 H), 7.33 – 7.44 (m, 4 H).

^{19}F-NMR ($CDCl_3$, 282 MHz) δ: -159.90 (d).

Step 2

4-(4-Chloro-phenyl)-4-fluoro-piperidin-3-ol was prepared as in step 3 of Example 502, substituting 4-(4-chloro-phenyl)-4-fluoro-3-hydroxy-piperidine-1-carboxylic acid tert-butyl ester for 4-(4-chloro-phenyl)-4-hydroxy-3,3-dimethyl-piperidine-1-carboxylic acid tert-butyl ester. Following isolation from the crude mixture, the free amine was used immediately without further purification .

^{1}H-NMR ($CDCl_3$, 300 MHz). 4-(4-Chloro-phenyl)-4-fluoro-piperidin-3-ol appears as the major constituent of a mixture of compounds.

MS m/z: 230 (M + 1; major peak in chromatogram).

Step 3

The titled compound was prepared as in step 5 of Example 502, substituting 4-(4-chloro-phenyl)-4-fluoro-piperidin-3-ol for S-4-(4-chloro-phenyl)-3,3-dimethyl-piperidin-4-ol.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.58 (s, 6 H), 1.74 – 1.96 (m, 2 H), 2.31 – 2.75 (m, 8 H), 2.80 (br d, 1 H), 3.06 (d, 1 H), 3.67 (br d, 1 H), 5.20 – 5.45 (br s, 2 H), 6.11 (t, 1 H), 6.84 (d, 1 H), 7.22 – 7.36 (m, 4 H), 7.39 – 7.47 (m, 3 H), 7.57 (d, 1 H), 8.56 (dd,1 H).

^{19}F-NMR ($CDCl_3$, 282 MHz) δ: -158.30 (d).

MS m/z: 523 (M + 1).

Example 469

2-(5-{3-[4-(4-Chloro-phenyl)-4-fluoro-3-methyl-piperidin-1-yl]-propylidene}-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl)-propan-2-ol

Step 1

4-(4-Chloro-phenyl)-4-fluoro-3-methyl-piperidine was prepared following the procedure in Step 1 in Example 467, replacing 4-(4-chloro-phenyl)-piperidin-4-ol with 4-(4-Chloro-phenyl)-3-methyl-piperidin-4-ol.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.67 (d, 3 H), 1.91 – 2.26 (m, 2 H), 2.84 (t, 1 H), 3.02 (dd, 1 H), 3.06 – 3.21 (m, 2 H), 3.33 (br s, 2 H), 7.27 (d, 2 H), 7.34 (d, 2 H).

^{19}F-NMR ($CDCl_3$, 282 MHz) δ: -180.60 (ddd).

MS m/z: 228 (M + 1).

Step 2

The titled compound was prepared following the procedure step 2 of Example 467, replacing 4-(4-chloro-phenyl)-4-fluoro-piperidine with 4-(4-chloro-phenyl)-4-fluoro-3-methyl-piperidine.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.63 (d, 3 H), 1.58 (s, 6 H), 1.76 – 1.96 (m, 2 H), 2.09 – 2.52 (m, 6 H), 2.55 – 2.88 (m, 4 H), 5.18 – 5.50 (br s, 2 H), 6.12 (t, 1 H), 6.83 (d, 1 H), 7.22 – 7.36 (m, 6 H), 7.46 (dd, 1 H), 7.59 (d, 1 H), 8.51 (d, 1 H).
MS m/z: 521 (M + 1).

Example 470

4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene]-propyl}-piperidine-3,4-diol

Step 1

To a suspension of 4-(4-Chloro-phenyl)-1,2,3,6-tetrahydro-pyridine hydrochloride (2 g, 8.73 mmol) in methylene chloride (50 mL) was added triethylamine (1.42 g, 1.95 mL, 14.0 mol). The resulting mixture was cooled to 0 °C and di-*tert*-butyl-dicarbonate (2.19 g, 10.0 mmol) was added in a single portion. After 10 min at 0 °C, the mixture was warmed to rt and stirred 90 min. The contents of the flask were poured into 250 mL methylene chloride and washed with 1 N hydrochloric acid/brine (3:1), saturated aqueous sodium bicarbonate and brine. The organic phase was dried over magnesium sulfate, filtered, concentrated and the resulting oil filtered through a plug of silica with methylene chloride elution, to afford 2.88g (>100 %) of 4-(4-Chloro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.49 (s, 9 H), 2.45 – 2.52 (m, 2 H), 3.63 (t, 2 H), 4.07 (q, 2 H), 6.02 (br s, 1 H), 7.29 (s, 4 H).

Step 2

The product of step 1 (2.88 g, approx. 8.7 mmol) was dissolved in 15 mL of a 5:1 acetone:water solution. Osmium tetroxide (2.5 % in *tert*-butyl alcohol, 1 mL) was added followed by 4-methyl morpholine *N*-oxide (1.13 g, 9.65 mmol). The mixture was stirred at rt 16 h. Saturated aqueous sodium bisulfite (5 mL) was added and the acetone was removed under reduced pressure. The resulting aqueous phase was extracted with methylene chloride and the extracts washed with an aliquot of saturated aqueous sodium bisulfite, 1 N hydrochloric acid, saturated aqueous sodium bicarbonate and brine. The extracts were then dried over magnesium sulfate, filtered and concentrated to afford an oil which was purified by silica gel chromatography (100 % methylene chloride to 90:10 methylene chloride:methanol gradient). 4-(4-Chloro-phenyl)-3,4-dihydroxy-piperidine-1-carboxylic acid tert-butyl ester was afforded as an oil (2.64 g, 83 %, 2 steps).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.44 (s, 9 H), 1.62 (br d, 1 H), 1.82 (br s, 2 H), 2.69 (br s, 1 H), 2.99 (br t, 1 H), 3.12 (br s, 1 H), 3.90 – 4.30 (m, 3 H), 7.33 (d, 2 H), 7.41 (d, 2 H).

Step 3

The product of step 2 (500 mg, 1.37 mmol) was dissolved in methylene chloride (10 mL) and the resulting solution cooled to 0 °C. Trifluoroacetic acid (3 mL) was slowly added and the reaction was allowed to stir at 0 °C for 2 h, before concentration under reduced pressure. The trifluoroacetate salt was dissolved in tetrahydrofuran and excess triethylamine was added. Solids generated were removed by suction filtration and the supernatant solution was concentrated to afford 4-(4-chloro-phenyl)-piperidine-3,4-diol.

^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.91 (ddd, 1 H), 2.13 (ddd, 1 H), 3.12 – 3.28 (m, 4 H), 4.08 (dd, 1 H), 7.37 (ddd, 2 H), 7.51 (ddd, 2 H).

Step 4

The titled compound was prepared following the procedure in step 2 of Example 467, but replacing 4-(4-Chloro-phenyl)-4-fluoro-piperidine with 4-(4-Chloro-phenyl)-piperidine-3,4-diol.

^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.51 (s, 6 H), 1.80 (br d, 1 H), 2.03 – 2.11 (m, 1 H), 2.56 (q, 2 H), 2.68 – 3.12 (m, 6 H), 4.00 (dd, 1 H), 5.00 – 5.50 (br s, 2 H), 6.17 (t, 1 H), 6.76 (d, 2 H), 7.27 (dd, 1 H), 7.33 (ddd, 2 H), 7.44 – 7.49 (m, 4 H), 7.80 (dd, 1 H), 8.48 (dd, 1 H).

MS m/z: 521 (M + 1).

Example 471

4-(4-Chloro-phenyl)-3-ethyl-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene]-propyl}-piperidin-4-ol

Step 1

A solution of 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (5 g, 25.1 mmol), pyrollidine (5 mL) and *p*-toluenesulfonic acid (25 mg) in benzene (100 mL) was heated at reflux for 16 h with azeotropic distillation of water. The resulting enamine solution was cooled to rt and concentrated. The crude enamine was dissolved in acetonitrile (50 mL); iodoethane (4.67 g, 30.1 mmoL) was added and the mixture was heated at 100 °C for 0.5 h, cooled to rt and concentrated. The mixture was dissolved in ethyl acetate (200 mL), washed with 1 N hydrochloric acid, saturated aqueous sodium bicarbonate, and brine. The extract was dried over magnesium sulfate, filtered and concentrated. The crude compound was purified by silica gel chromatography (80 % hexanes / 20 % ethyl acetate) to afford 3-ethyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester (680 mg).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.95 (t, 3 H), 1.26 – 1.42 (m, 1 H), 1.50 (s, 9 H), 1.69 – 1.85 (m, 1 H), 2.30 (br s, 1 H), 2.43 (q, 2 H), 2.90 – 4.36 (m, 4 H).

Step2

4-(4-Chloro-phenyl)-3-ethyl-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester was prepared following the procedure in step 2 of Example 502, substituting 3-ethyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester for 3,3-dimethyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.80 (t, 3 H), 0.91 – 1.13 (m, 2 H), 1.18 – 1.28 (m, 1 H), 1.48 (s, 9 H), 1.57 – 1.64 (br d, 1 H), 1.75 – 1.91 (m, 2 H), 2.79 (t, 1 H), 3.14 (ddd, 1 H), 4.02 (br d, 1 H), 4.19 (br d, 1 H), 7.28 – 7.37 (m, 4 H).

Step 3

4-(4-Chloro-phenyl)-3-ethyl-piperidin-4-ol was prepared according to the procedure of step 3 in Example 502, substituting 4-(4-chloro-phenyl)-3-ethyl-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester for 4-(4-chloro-phenyl)-4-hydroxy-3,3-dimethyl-piperidine-1-carboxylic acid tert-butyl ester.
^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.75 (t, 3 H), 0.88 – 1.17 (m, 2 H), 1.26 (t, 1 H), 1.65 (br d, 2 H), 1.83 – 2.02 (m, 2 H), 2.75 (t, 1 H), 2.95 – 3.21 (m, 3 H), 7.32 (d, 2 H), 7.40 (d, 2 H).
MS m/z: 240 (M + 1).

Step 4

The titled compound was prepared following the procedure in step 5 of Example 502, substituting 4-(4-chloro-phenyl)-3-ethyl-piperidin-4-ol for 4-(4-chloro-phenyl)-3,3-dimethyl-piperidin-4-ol.
^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.70 (t, 3 H), 0.81 – 1.11 (m, 3 H), 1.56 – 1.64 (m, 7 H), 1.77 – 2.09 (m, 4 H), 2.23 – 2.86 (m, 7 H), 5.00 – 5.60 (m, 2 H), 6.13 (t, 1 H), 6.83 (d, 1 H), 7.23 – 7.47 (m, 6 H), 7.46 (d, 1 H), 7.59 (dd, 1 H), 8.49 (dd, 1 H).
MS m/z: 533 (M + 1).

Example 472

5-Chloro-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[a,d]-cyclohepten-5-ylidene]-propyl}-spiro[3-oxo-1,3-dihydroisobenzofuran-1,4'-piperidine]

Step 1

To a suspension of 2-bromo-5-chlorobenzoic acid (1.5 g, 6.4 mmol) in methylene chloride (15 mL) at room temperature was added oxalyl chloride (969 mg, 666 μL, 7.64 mmol) and 2 drops of dimethylformamide; bubbling commenced and the mixture ultimately became homogenous. The mixture was stirred at room temperature for 7 hours and concentrated. The resulting acid chloride residue was dissolved in methylene chloride (15 mL). Triethylamine (325 mg, 450 μL, 3.2 mmol) was added, followed by 2-amino-2-methyl-1-propanol (627 mg, 672 μL, 7.04 mmol) and the reaction was allowed to stir at rt 3h. The mixture was poured into 1 N hydrochloric acid (50 mL), extracted with methylene chloride (2 x 75 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate, brine and dried over magnesium sulfate, filtered and concentrated and dried *in vacuo*. The crude amide residue was dissolved in methylene chloride (15 mL) and thionyl chloride (1.29 g, 794 μL, 10.9 mmol) was added. Stirring at room temperature was carried out for 4 h after which the mixture was poured into saturated sodium bicarbonate (50 mL). The pH was adjusted to 9 by the addition of solid sodium bicarbonate and further basified by the addition of several milliliters of aqueous sodium hydroxide (5 N). The biphasic mixture was extracted with methylene chloride (150 + 50 mL). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated to afford the crude residue which was purified by silica gel chromatography (80 % hexanes / 20 % ethyl acetate gradient) to yield 2-(2-bromo-5-chloro-phenyl)-4,4-dimethyl-4,5-dihydro-oxazole (1.15 g, 62 %).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.42 (s, 6 H), 4.14 (s, 2 H), 7.25 (dd, 1 H), 7.55m (d, 1 H), 7.67 (d, 1 H).

Step 2

To a cold (- 78 °C) solution of the product of step 1 (1.09 g, 4.63 mmol) in anhydrous tetrahydrofuran (10 mL) was added a solution of n-butyllithium (1.6 M in hexanes, 2.89 mL, 4.63 mmol) and the contents of the reaction were allowed to react for 0.5 h. A solution of 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (922 mg, 4.63 mmol) in tetrahydrofuran (10 mL) was added and the combined contents stirred for 2 h at -78 °C. Reaction was quenched by the addition of saturated aqueous ammonium chloride (30 mL), followed by warming to rt. The biphasic mixture was extracted with ethyl acetate (150 mL); washed with water and brine; dried over magnesium sulfate; filtered and concentrated. 4-[4-Chloro-2-(4,4-dimethyl-4,5-

dihydro-oxazol-2-yl)-phenyl]-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester was isolated (412 mg, 22 %) following silica gel chromatography (80 % hexanes / 20 % ethyl acetate).

^{1}H-NMR ($CDCl_3$, 300 MHz, mixture; spectrum of major component:) δ: 1.36 (s, 6 H), 1.50 (s, 9 H), 1.66 (d, 2 H), 1.96 (dd, 2 H), 3.19 (br d, 2 H), 3.42 (d, 2 H), 4.24 (br s, 2 H), 7.16 (d, 1 H), 7.45 (dd, 1 H), 7.71 (br s, 1 H).

MS m/z: 409 (M + 1).

Step 3

To a solution of the product of step 2 (200 mg, 0.49 mmol) in tetrahydrofuran (5 mL) was added water (5 mL) and oxalic acid (300 mg). Stir at rt for about 4 days. The solids were separated and dissolved in ethyl acetate (50 mL); the resulting solution was washed with saturated aqueous sodium bicarbonate and brine. The extracts were dried over magnesium sulfate; filtered and concentrated. The 5-chlorospiro[3-oxo-1,3-dihydroisobenzofuran-1,4'-piperidine]-1-carboxylic acid tert-butyl ester thus afforded (100 mg, 61 %) was used without further purification.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.49 (s, 9 H), 1.67 (d, 2 H), 2.04 (ddd, 2 H), 3.24 (dd, 2 H), 4.21 (br s, 2 H), 7.32 (d, 1H), 7.64 (dd, 1H), 7.85 (d, 1 H).

MS m/z: 238 (M + 1 - 100).

Step 4

5-Chlorospiro[3-oxo-1,3-dihydroisobenzofuran-1,4'-piperidine] was prepared according to the procedure in step 3 of Example 502, using 5-chlorospiro[3-oxo-1,3-dihydroisobenzofuran-1,4'-piperidine]-1-carboxylic acid tert-butyl ester instead of 4-(4-chloro-phenyl)-4-hydroxy-3,3-dimethyl-piperidine-1-carboxylic acid tert-butyl ester.

^{1}H-NMR ($CDCl_3$, 300 MHζ) δ: 1.71 (d, 2 H), 2.09 – 2.22 (m, 2 H), 3.13 – 3.28 (m, 4 H), 7.37 (d, 1 H), 7.64 (dd, 1 H), 7.84 (d, 1 H).

MS m/z: 238 (M + 1).

Step 5

The titled compound was prepared according to the procedure in step 2 of Example 467, substituting 5-chlorospiro[3-oxo-1,3-dihydroisobenzofuran-1,4'-piperidine] for 4-(4-chloro-phenyl)-4-fluoro-piperidine.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.58 (s, 6 H), 1.64 (d, 2 H), 2.04 – 2.15 (m, 3 H), 2.33 – 2.50 (m, 3 H), 2.57 (t, 2 H), 2.76 (d, 2 H), 5.20 – 5.50 (br s, 2 H), 6.12 (t, 1 H), 6.81 (d, 1 H), 7.22 – 7.34 (m, 3 H), 7.45 (d, 2 H), 7.55 – 7.63 (m, 2 H), 7.81 (d, 1 H), 8.48 (dd, 1 H).

MS m/z: 531 (M + 1).

Example 473

4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene]-propyl}-4-methoxy-3-methyl-piperidin-3-ol

Step 1

To a suspension of 4-(4-chloro-phenyl)-1,2,3,6-tetrahydro-pyridine hydrochloride (5 g, 21.8 mmol) in methylene chloride (100 mL) was added triethylamine (3.6 g, 4.9 mL, 35 mmol). The resulting solution was cooled to 0 °C in an ice-water bath. Di-*tert*-butyl-dicarbonate (5.4 g, 25 mmol) was added and the resulting reaction was allowed to warm to rt and stir over night. The mixture was poured into 100 mL of a 1:1 1 N HCl:brine solution and diluted with methylene chloride (300 mL). The organic phase was washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 4-(4-Chloro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (6.68 g, 93 %) as a colorless oil, which was used without further purification.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.48 (s, 9 H), 2.45 – 2.55 (m, 2 H), 3.63 (t, 2 H), 4.07 (q, 2 H), 6.03 (br s, 1 H), 7.29 (m, 4 H).

Step 2

To a cooled (0 °C) solution of 4-(4-chloro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (7.10 g, approx. 24.1 mmol) in methylene chloride (150 mL) was added a solution of 3-chloroperbenzoic acid (75 %, 8.34 g, 36.2 mmol) in methylene chloride (120 mL) over 40 min. The mixture was warmed to rt and allowed to stir over night (16 h). The solution was washed twice with a half-saturated aqueous solution of sodium bisfulfite to destroy excess oxidant. The mixture was then twice washed with half-saturated aqueous potassium carbonate, and brine. The extracts were dried over magnesium sulfate, filtered and concentrated to afford a crude oil which was purified by silica gel chromatography (100 % hexanes – 80 % hexanes / 20 % ethyl acetate gradient) to afford pure 6-(4-Chloro-phenyl)-7-oxa-3-aza-bicyclo[4.1.0]heptane-3-carboxylic acid tert-butyl ester (5.34 g, 71 %) as a clear, colorless oil which solidified on standing.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.48 (s, 9 H), 2.06 – 2.22 (m, 1 H), 2.42 (ddd, 1 H), 3.08 – 3.23 (m, 2 H), 3.57 – 4.19 (m, 3 H), 7.26 – 7.36 (m, 4 H).

Step 3

To a solution of 6-(4-Chloro-phenyl)-7-oxa-3-aza-bicyclo[4.1.0]heptane-3-carboxylic acid tert-butyl ester (2.4 g, 7.8 mmol) in methanol (100 mL) was added a catalytic amount of p-toluenesulfonic acid (ca. 50 mg). The resulting solution was heated at reflux 24h, cooled and concentrated. The crude residue was purified by silica gel chromatography (100 % hexanes – 80 % hexanes/20 % ethyl acetate gradient) to afford 4-(4-chloro-phenyl)-3-hydroxy-4-methoxy-piperidine-1-carboxylic acid tert-butyl ester (2.05 g, 77 %); note the diol moiety has the trans-orientation.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.47 (s, 9 H), 1.95 (d, 1 H), 2.37 (ddd, 1 H), 2.97 (s, 3 H), 3.47 (d, 1 H), 3.67 (br s, 1 H), 3.98 – 4.17 (m, 3 H), 7.29 – 7.42 (m, 4 H).

Step 4

A solution of 4-(4-chloro-phenyl)-3-hydroxy-4-methoxy-piperidine-1-carboxylic acid tert-butyl ester (2.05 g, 6.0 mmol) in methylene chloride (75 mL) was cooled to 0 °C. Dess-Martin periodinane (3.30 g, 7.8 mmol) was added, followed by water (200 uL) and the reaction allowed to stir at rt 2 h. The reaction was quenched by the addition of a solution consisting of equal parts saturated aqueous sodium thiosulfate and saturated aqueous sodium bicarbonate; the resulting reaction was stirred until the mixture formed two homogenous phases. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine and dried over magnesium sulfate, filtered and concentrated. The crude mixture was purified by silica gel chromatography to afford recovered starting material (1.17 g, 57 %) and 4-(4-chloro-phenyl)-4-methoxy-3-oxo-piperidine-1-carboxylic acid tert-butyl ester (540 mg, 27 % (62 % brsm)).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.43 (s, 9 H), 2.16 – 2.40 (m, 2 H), 3.12 (s, 3 H), 3.55 (ddd, 1 H), 3.80 (br s, 1 H), 3.96 (d, 1 H), 4.34 (br s, 1 H), 7.23 – 7.40 (m, 4 H).

Step 5

To a solution of 4-(4-chloro-phenyl)-4-methoxy-3-oxo-piperidine-1-carboxylic acid tert-butyl ester (470 mg, 1.38 mmol) in anhydrous tetrahydrofuran (10 mL) at 0 °C was added methylmagnesium bromide (1.4 M in diethyl ether, 2.96 mL, 4.15 mmol) and the resulting mixture was stirred at that temperature for 3 h. Excess organomagnesium was quenched by the addition of saturated aqueous ammonium chloride and the reaction was allowed to warm to rt. To the biphasic mixture was added water and ethyl acetate. The phases were separated and the organic phase washed with brine, dried over magnesium sulfate, filtered, dried and concentrated to afford a crude residue which was purified by silica gel chromatography (100 % methylene chloride – 97.5 % methylene chloride / 2.5 % methanol gradient) to afford pure 4-(4-chloro-phenyl)-3-hydroxy-4-methoxy-3-methyl-piperidine-1-carboxylic acid tert-butyl ester (269 mg, 58 %).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.97 (s, 3 H), 1.50 (s, 9 H), 1.81 (d, 1 H), 2.59 (ddd, 1 H), 2.96 (br t, 1 H), 3.11 (s, 3 H), 3.31 (s, 3 H), 3.72 – 3.88 (m, 1 H), 7.27 – 7.37 (m, 4 H).

Step 6

4-(4-Chloro-phenyl)-3-hydroxy-4-methoxy-3-methyl-piperidine-1-carboxylic acid tert-butyl ester (260 mg, 0.74 mmol) was dissolved in methylene chloride (5 mL) and the resulting solution was cooled to 0 °C. Trifluoroacetic acid (1 mL) was added and the mixture was stirred 2h. Solvents were then removed under reduced pressure and the residue dissolved in ethyl acetate. Water and 6 N aqueous sodium hydroxide were added until the pH = 10. The organic phase was washed with brine and dried over magnesium sulfate, filtered and concentrated to afford 4-(4-chloro-phenyl)-4-methoxy-3-methyl-piperidin-3-ol.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.94 (s, 3 H), 1.91 (d, 1 H), 2.65 – 2.81 (m, 2 H), 2.94 (ddd, 1 H), 3.13 (s, 3 H), 3.25 (d, 1 H), 3.30 (m, 1 H), 7.37 (s, 4 H).

MS m/z: 256 (M + 1).

Step 7

To a solution of 4-(4-chloro-phenyl)-4-methoxy-3-methyl-piperidin-3-ol (206 mg, 1.24 mmol) in acetonitrile/water (4:1, 20 mL) was added potassium carbonate (171 mg, 1.24 mmol) followed by 2-[5-(3-bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl]-propan-2-ol (417 mg, 1.12 mmol). The mixture was stirred at rt 40h and concentrated. The product residue was partitioned between ethyl acetate and water and the organic phase was washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by silica gel chromatography (100 % methylene chloride – 90 % methylene chloride / 10 % methanol gradient) to afford the titled compound (232 mg, 35 %) as an off-white solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.83 (s, 3 H), 1.57 (s, 6 H), 1.76 – 1.94 (m, 2 H), 2.20 (t, 1 H), 2.29 – 2.72 (m, 7 H), 3.06 (s, 3 H), 3.39 (br s, 1 H), 5.19 – 5.54 (br s, 2

H), 6.12 (t, 1 H), 6.82 (d, 1 H), 7.21 – 7.34 (m, 6 H), 7.46 (d, 1 H), 7.58 (d, 1 H), 8.51 (d, 1 H).
MS m/z: 549 (M + 1).

Example 474
4-(4-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene]-propyl}-4-methoxy-piperidin-3-ol

Step 1

4-(4-Chloro-phenyl)-4-methoxy-piperidin-3-ol was prepared following the procedure in Step 6 of Example 473, replacing 4-(4-chloro-phenyl)-3-hydroxy-4-methoxy-3-methyl-piperidine-1-carboxylic acid tert-butyl ester with 4-(4-chloro-phenyl)-3-hydroxy-4-methoxy-piperidine-1-carboxylic acid tert-butyl ester.
MS m/z: 242 (M + 1).

Step 2

The titled compound was prepared following the procedure of Step 7 in Example 473, replacing 4-(4-chloro-phenyl)-4-methoxy-3-methyl-piperidin-3-ol with the product of Step 1 in Example 474.
^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.58 (s, 6 H), 1.63 – 1.82 (m, 3 H), 1.95 (d, 1 H), 2.21 – 2.78 (m, 8 H), 2.91 (s, 3 H), 3.63 (br s, 1 H), 5.32 (br s, 2 H), 6.11 (t, 1 H), 6.81 (d, 1 H), 7.21 – 7.37 (m, 6 H), 7.44 (d, 1 H), 7.57 (dd, 1 H), 8.51 (dd, 1 H).
MS m/z: 535 (M + 1).

Example 475
2-(5-{3-[4-(4-Chloro-phenyl)-3,4-dimethoxy-piperidin-1-yl]-propylidene}-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl)-propan-2-ol

Step 1

The product of Step 3 in Example 473 (259 mg, 0.76 mmol) was dissolved in tetrahydrofuran (5 mL) and cooled to 0 °C. Sodium hydride (60 % dispersion in mineral oil, 46 mg, 1.15 mmol) was added in a single portion and the mixture stirred 5 min. Methyl iodide was added and the mixture was warmed to rt and stirred 48 h. Excess base was quenched by the addition of saturated aq. NH_4Cl and water. The biphasic mixture was extracted twice with ethyl acetate. The extracts were combined, washed with brine and dried over sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (hexanes – 80 hexanes/20 ethyl acetate gradient) to afford 4-(4-chloro-phenyl)-3,4-dimethoxy-piperidine-1-carboxylic acid tert-butyl ester (191 mg, 71 %).
^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.47 (s, 9 H), 1.90 (d, 1 H), 2.31 (ddd, 1 H), 2.91 – 3.38 (m, 9 H), 3.93 – 4.37 (br m, 2 H), 7.24 – 7.37 (m, 4 H).

Step 2

4-(4-Chloro-phenyl)-3,4-dimethoxy-piperidine was prepared following the procedure in Step 6 of Example 473, substituting the product of Step 1 for 4-(4-Chloro-phenyl)-3-hydroxy-4-methoxy-3-methyl-piperidine-1-carboxylic acid tert-butyl ester.
^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.96 (d, 1 H), 2.27 (dddd, 1 H), 2.71 – 3.03 (m, 9 H), 3.04 – 3.15 (m, 2 H), 7.30 – 7.41 (m, 4 H).
MS m/z: 256 (M + 1).

Step 3

The titled compound was prepared following the procedure in Step 7 of Example 473, substituting the product of Step 2 for 4-(4-chloro-phenyl)-4-methoxy-3-methyl-piperidin-3-ol.
^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.58 (s, 6 H), 1.67 (br s, 2 H), 1.77 (s, 1 H), 1.91 (d, 1 H), 2.18 – 2.31 (m, 1 H), 2.33 – 2.47 (m, 2 H), 2.48 – 2.62 (m, 2 H), 2.65 – 2.75 (m, 1 H), 2.83 – 2.90 (m, 4 H), 2.92 (s, 3 H), 3.07 (br s, 1 H), 5.06 – 5.57 (br s, 2 H),

6.10 (t, 1 H), 6.82 (d, 1 H), 7.22 – 7.35 (m, 6 H), 7.44 (d, 1 H), 7.59 (d, 1 H), 8.50 (d, 1 H).

MS m/z: 549 (M + 1).

Example 476

3-Azido-4-(4-chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11*H*-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene}-propyl}-piperidin-4-ol

Step 1: 4-(4-Chloro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester

To a solution of di-tert-butyl-dicarbonate (9.96 g, 45.6 mmol) in CH_2Cl_2 (500 mL) was added 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (10.00 g, 43.5 mmol) and triethylamine (12.42 mL, 89 mmol). The solution was stirred at rt for 4h. Gas evolution was observed. The reaction was quenched with 1N HCl and extracted with CH_2Cl_2 (3X), and the organic layers were collected together, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified to yield the title compound as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (9H, s), 2.46 (2H, br s), 3.62 (2H, br s), 4.05 (2H, br s), 6.01 (1H, br s), 7.25 (4H, s).

Step 2: 6-(4-Chloro-phenyl)-7-oxa-3-aza-bicyclo[4.1.0]heptane-3-carboxylic acid tert-butyl ester

To a solution of 4-(4-chloro-phenyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid tert-butyl ester (4.0 g, 13.6 mmol) in CH_2Cl_2 (136 mL) cooled to 0°C. 3-Chloroperbenzoic acid (4.07 g, 20.4 mmol) was dissolved in CH_2Cl_2 and added portion wise over 45 min. A white precipitate was observed. The solution was allowed to stir at room temperature for 14h. The reaction was washed with 1 x 10% $NaSO_3$, 1 x 10% Na_2CO_3, 1 x brine and dried over Mg_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by Biotage flash system (90% hexane/10% ethyl acetate to 80% hexane/20% ethyl acetate to yield the title compound as a colorless oil (2.75 g, 65%). ^{1}H-NMR ($CDCl_3$) δ: 1.50 (9H, s), 2.15 (1H, m), 3.15 (2H, m), 3.6-4.2 (4H, m), 7.31 (4H, s).

Step 3: 4-Azido-4-(4-chloro-phenyl)-3-hydroxy-piperidine-1-carboxylic acid tert-butyl ester and 3-azido-4-(4-chloro-phenyl)-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester

To a solution of 6-(4-chloro-phenyl)-7-oxa-3-aza-bicyclo[4.1.0]heptane-3-carboxylic acid tert-butyl ester (0.960g, 3.1 mmol) in 31mL of DMSO was added sodium azide (0.970g, 14.9 mmol). The solution was allowed to heat at 100°C for 24 h and cooled to room temperature. The reaction was washed with water, dried over Mg_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by Biotage flash system (90% hexane/10% ethyl acetate to 80% hexane/20% ethyl acetate to 70% hexane/30% ethyl acetate to yield two compounds. The faster eluting isomer 4-azido-4-(4-chloro-phenyl)-3-hydroxy-piperdine-1-carboxylic acid tert-butyl ester (0.010g, 9%) ^{1}H-NMR ($CDCl_3$) δ: 1.46(s, 9H), 1.93(d, 1H), 2.51(dt, 1H), 3.10(bt, 1H), 3.34(d, 1H), 3.80(bs, 1H), 4.08(m, 2H), 7.41 (s, 4H). The slower eluting isomer 3-azido-4-(4-chloro-phenyl)-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (0.361g, 33%) ^{1}H-NMR ($CDCl_3$) δ: 1.43(s, 9H), 1.57(m, 1H), 2.40(t, 1H), 2.93(m, 1H), 3.11(t, 1H), 3.50(s, 1H), 3.56(d, 1H), 4.07(m, 2H), 7.33(d, 2H), 7.40 (d, 2H).

Step 4

The Boc-protected azido-alcohol (0.184 g, 0.5 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C and TFA (0.790 mL) was added. The solution was allowed to stir at 0° C for 1 h. The solvent was evaporated *in vacuo* and the residue was partitioned between $NaHCO_3$ and CH_2Cl_2. The aqueous solution was extracted (3x) and then washed with brine and dried over Na_2SO_4. The residue was carried onto the next step without further purification.

Step 5

To a solution of the azido piperidine (0.142 g, 0.56 mmol) in isopropanol

(5.6 mL) was added 2,6-lutidine (0.066 mL, 0.8 mmol) and catalytic potassium iodide. This mixture was heated to 80°C, and treated with 2-[5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-7-yl]-propan-2-ol (0.025 g, 0.067mmol), added in portions over 2h. The solution was then stirred at 80 °C for an additional 14 h. The reaction was concentrated *in vacuo*, then purified by Biotage flash chromatography (75% EtOAc/25% Hexane to 100% ethyl acetate) to yield the title compound (0.135 g, 66%). ^{1}H-NMR ($CDCl_3$): δ 1.56(6H, s), 1.65(d, 1H), 1.85(s, 1H), 2.13(s, 1H), 2.36-2.94(m, 8H), 3.51(s, 1H), 5.24(bs, 2H), 6.16(t, 1H), 6.80(d, 1H), 7.21-7.45(m, 7H), 7.58(d, 1H), 8.44(d, 1H). ESI-MS m/z: 546(M + 1), retention time 1.55.

Example 477

4-Azido-4-(4-chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11*H*-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene}-propyl}-piperidin-3-ol

Step 1

The Boc-protected azido-alcohol (Example 476, step 3) (0.050 g, 0.2 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C and TFA (0.2 mL) was added. The solution was allowed to stir at 0° C for 1 h. The solvent was evaporated *in vacuo* and the residue was partitioned between $NaHCO_3$ and CH_2Cl_2. The aqueous solution was extracted (3x) and then washed with brine and dried over Na_2SO_4. The residue was carried onto the next step without further purification.

Step 2

To a solution of the azido piperidine (0.025 g, 0.1 mmol) in isopropanol (1.0 mL) was added 2,6-lutidine (0.012 mL, 0.1 mmol) and catalytic potassium iodide. This mixture was heated to 80 °C, and treated with 2-[5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo*[a,d]*cyclohepten-7-yl]-propan-2-ol (0.025 g, 0.067mmol), added in portions over 2h. The solution was then stirred at 80°C for an additional 14 h. The reaction was concentrated *in vacuo*, then purified by Biotage flash chromatography (100% ethyl acetate) to yield the title compound (0.013 g, 36%). ^{1}H-NMR ($CDCl_3$): δ 1.56 (s, 6H), 1.65 (d, 1H), 1.85 (s, 1H), 2.13 (s, 1H), 2.36-2.94 (m, 8H), 3.51 (s, 1H), 5.24 (bs, 2H), 6.16 (t, 1H), 6.80 (d, 1H), 6.93 (d, 1H), 7.21-7.46 (m, 8H), 7.58 (d, 1H), 8.42 (d, 1H). ESI-MS m/z: 546(M + 1), retention time 1.71.

Example 478

N-[4-(4-Chloro-phenyl)-4-hydroxy-1-{3-[7-(hydroxyl-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-piperidin-3-yl)-propionamide

Step 1: 3-Amino-4-(4-chloro-phenyl)-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester

3-azido-4-(4-chloro-phenyl)-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (0.67 g, 0.2 mmol) was dissolved in Et_2O (2 mL) and cooled to 0°C and $LiAlH_4$ (0.280 mL, 0.23mmol) was added. The solution was allowed to warm to room temperature and stir for 2h. A white precipitate formed. The reaction mixture was quenched with water and extracted with Et_2O (3x). The organic layers were collected together, dried over $MgSO_4$ and evaporated *in vacuo* to give the amino alcohol which was used directly in the next reaction.

Step 2: 4-(4-Chloro-phenyl)-4-hydroxy 3-propionylamino-piperidine-1-carboxylic acid tert-butyl ester

3-Amino-4-(4-chloro-phenyl)-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (0.116 g, 0.35 mmol) was dissolved in CH_2Cl_2. Propionyl chloride (0.034 mL, 0.39 mmol) and triethylamine (0.109 mL, 0.78 mmol) were added and the solution was stirred for 24 h at room temperature. The reaction was concentrated *in vacuo*, then purified by Biotage flash chromatography (30% ethyl acetate/70% hexane to 50% ethyl acetate/50%hexane) to yield the title compound (0.133 g, 97%). ^{1}H-NMR ($CDCl_3$): δ 0.87 (t, 3H), 1.44 (s, 9H), 1.78-1.95 (m, 3H), 2.20 (dt, 1H), 3.24 (t, 1H), 3.50 (d, 1H), 3.90 (t, 1H), 4.08 (q, 2H), 4.28 (d, 1H), 5.48 (bd, 1H), 7.26 (d, 2H), 7.37 (d, 2H). ESI-MS m/z: 383 (M + 1), retention time 2.21.

Step 3

The Boc-protected 3-N-acyl-alcohol (0.180 g, 0.47 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C and TFA (2 mL) was added. The solution was allowed to stir at 0° C for 1 h. The solvent was evaporated *in vacuo* and the residue was partitioned between $NaHCO_3$ and CH_2Cl_2. The aqueous solution was extracted (3x) and then washed with brine and dried over Na_2SO_4. The residue was carried onto the next step without further purification.

Step 4

To a solution of the N-[4-(4-chloro-phenyl)-4-hydroxy –piperidin-3-yl]-propionamide (0.133 g, 0.47 mmol) in isopropanol (5.0 mL) was added 2,6-lutidine (0.055 mL, 0.47 mmol) and catalytic potassium iodide. This mixture was heated to 80 °C, and treated with 2-[5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-7-yl]-propan-2-ol (0.176 g, 0.35mmol), added in portions over 2h. The solution was then stirred at 80°C for an additional 14 h. The reaction was concentrated *in vacuo*, then purified by HPLC (acetonitrile/H_2O/Formic acid) to yield the title compound as a white formate salt (0.085 g, 27%). ^{1}H-NMR ($CDCl_3$): δ 0.780 (t, 3H), 1.55 (s, 6H), 1.90 (m, 3H), 2.60 (m, 2H), 2.92-3.28 (m, 6H), 4.50 (d, 1H), 5.26 (bs, 2H), 6.00 (t, 1H), 6.82 (d, 1H), 7.22-7.37 (m, 6H), 7.44 (s, 1H), 7.56 (d, 1H), 8.20 (d, 1H), 8.34 (s, 1H), 8.47 (d, 1H). ESI-MS m/z: 576(M + 1), retention time 1.43.

Example 479

Trans-4-(4-Chloro-phenyl)-4-hydroxy-1-{3-[7-(1-hydroxyl-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-piperidin-3-carbonitrile

Step 1: Cis and *trans* -4-(4-chloro-phenyl)-3-cyano-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester

Acetone cyanohydrin (0.917 mL, 10 mmol) was added to THF (22 mL) and cooled to 0°C. To the solution was added lithium hydride (0.077 g, 9.7 mmol) in several portions over 20 min. and then stirred at room temperature for 1 h. 6-(4-Chloro-phenyl)-7-oxa-3-aza-bicyclo[4.1.0]heptane-3-carboxylic acid tert-butyl ester (1.00 g, 3.2 mmol) dissolved in THF (10 mL) was added to the above solution and heated to reflux for 7 ½ h. The reaction was diluted with H_2O and extracted (3x). The reaction was washed with water, dried over Mg_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by Biotage flash system (90% hexane/10% ethyl acetate to 80% hexane/20% ethyl acetate to 70% hexane/30% ethyl acetate to yield two compounds. The faster eluting isomer *cis*-4-(4-chloro-phenyl)-3-cyano-4-hydroxy-piperdine-1-carboxylic acid tert-butyl ester (0.210g, 19%) ^{1}H-NMR ($CDCl_3$): δ 1.35 (s, 9H), 1.59-1.86 (m, 2H), 2.83-3.30 (m, 3H), 3.88 (bs, 2H), 4.16 (m, 1H), 7.23 (d, 2H), 7.33 (d, 2H).

The second eluting isomer was the *trans* -4-(4-chloro-phenyl)-3-cyano-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (0.560g, 51%).^{1}H-NMR ($CDCl_3$): δ 1.43 (s, 9H), 1.70 (d, 1H), 2.47 (dt, 1H), 2.76 (bs, 2H), 3.10-3.54 (m, 2H), 4.18 (m, 2H), 7.31 (d, 2H), 7.44 (d, 2H).

Step 2

Trans -4-(4-chloro-phenyl)-3-cyano-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (0.210 g, 0.62 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C and TFA (1.0 mL) was added. The solution was allowed to stir at 0° C for 1 h. The solvent was evaporated *in vacuo* and the residue was partitioned between $NaHCO_3$ and CH_2Cl_2. The aqueous solution was extracted (3x) and then washed with brine and dried over Na_2SO_4. The residue was carried onto the next step without further purification.

Step 3

To a solution of the *trans*-3-cyano-4-hydroxypiperidine (0.137 g, 0.58 mmol) in isopropanol (5.7 mL) was added 2,6-lutidine (0.067 mL, 0.58 mmol) and catalytic potassium iodide. This mixture was heated to 80°C, and treated with 2-[5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-7-yl]-propan-2-ol (0.108 g, 0.29mmol), added in portions over 2h. The solution was then stirred at 80 °C for an additional 14 h. The reaction was concentrated *in vacuo*, then purified by Biotage flash chromatography (50% ethyl acetate/50% hexane to 75% ethyl acetate/ 25% hexane to 100% ethyl acetate) to yield the title compound (0.040g, 26%). ^{1}H-NMR ($CDCl_3$): δ 1.50 (d, 6H), 1.63 (s, 1H), 1.78 (d, 1H), 2.08 (s, 1H), 2.35 (m, 2H), 2.51-3.03 (m, 6H), 3.48 (s, 1H), 5.29 (bs, 2H), 6.42 (t, 1H), 6.79 (d, 1H), 7.15 (d, 1H), 7.28 (m, 1H), 7.37 (d, 2H), 7.50 (d, 2H), 7.55 (s, 1H), 7.58 (d, 1H), 8.46 (d, 1H). ESI-MS m/z: 530.2(M + 1), retention time 1.50.

Example 480

Cis-4-(4-Chloro-phenyl)-4-hydroxy-1-{3-[7-(1-hydroxyl-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-piperidin-3-carbonitrile

Step 1

Cis-4-(4-chloro-phenyl)-3-cyano-4-hydroxy-piperdine-1-carboxylic acid tert-butyl ester (0.210 g, 0.62 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C and TFA (1 mL) was added. The solution was allowed to stir at 0° C for 1 h. The solvent was evaporated *in vacuo* and the residue was partitioned between $NaHCO_3$ and CH_2Cl_2. The aqueous solution was extracted (3x) and then washed with brine and dried over Na_2SO_4. The residue was carried onto the next step without further purification.

Step 2

To a solution of the *cis*-3-cyano-4-hydroxypiperidine (0.125 g, 0.53 mmol) in isopropanol (5.8 mL) was added 2,6-lutidene (0.061 mL, 0.53 mmol) and catalytic potassium iodide. This mixture was heated to 80 °C, and treated with 2-[5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-7-yl]-propan-2-ol (0.100 g, 0.26mmol), added in portions over 2h. The solution was then stirred at 80°C for an additional 14 h. The reaction was concentrated *in vacuo*, then purified by Biotage flash chromatography (50% ethyl acetate/ 50% hexane to 75% ethyl acetate/ 25% hexane to 100% ethyl acetate) to yield the title compound (0.050 g, 35%). ^{1}H-NMR ($CDCl_3$): δ 1.53 (d, 1H), 1.57(s, 6H), 1.74 (d, 1H), 1.89 (s, 1H), 2.35-2.68(m, 7H), 2.88 (d, 1H), 3.11 (d, 1H), 5.30 (bs, 2H), 6.11 (t, 1H), 6.82 (d, 1H), 7.23-7:45 (m, 7H), 7.57 (d, 1H), 8.48 (d, 1H). ESI-MS m/z: 530.2(M + 1), retention time 1.58.

Example 481

4-(4-Chloro-phenyl)-4-hydroxy-1-{3-[7-(hydroxyl-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-3-methyl-piperidine-3-carboxylic acid methyl ester

Step 1: 4-Oxo-piperidine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester

To a solution of di-tert-butyl-dicarbonate (3.08 g, 14.1 mmol) in CH_2Cl_2 (134 mL) was added methyl-4-oxo-3-piperdine carboxylate HCl (2.6 g, 13.4 mmol) and triethylamine (3.84 mL, 27.5 mmol). The solution was stirred at rt for 12h. Gas evolution was observed. The reaction was quenched with 1N HCl and extracted with CH_2Cl_2 (3X), and the organic layers were collected together, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified to yield the title compound as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9H), 2.36 (t, 2H), 3.55 (t, 2H), 3.77 (s, 4H), 4.04 (s, 2H).

Step 2: 3-Methyl-4-oxo-piperidine-1,3-dicarboxylic acid-1-*tert*-butyl ester 3-methyl ester

4-Oxo-piperidine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (2.00g, 6.8 mmol) was dissolved in tetrahydrofuran and cooled to 0 °C. To the solution was added NaH (0.300 g, 12.5 mmol) portionwise over 1h. $H_{2(g)}$ was evolved during the addition. The reaction was allowed to stir for 30 minutes at 0 °C and then methyl iodide (0.422 mL, 6.8 mmol) was added and allowed to stir at room temperature for 13 h. The reaction was quenched with ice water and concentrated down. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with EtOAc (3x), the organics were collected together dried over Mg_2SO_4, filtered and evaporated *in vacuo*, then purified by Biotage flash chromatography (10% ethyl acetate/ 90% hexane to yield the title compound (1.1 g, 52 %).^{1}H-NMR ($CDCl_3$): δ 1.29 (s, 3H), 1.47 (s, 9H), 2.47 (dt, 1H), 2.76 (m, 1H), 3.07 (d, 1H), 3.33 (dt, 1H), 3.71 (s, 3H), 4.11 (m, 1H), 4.50 (d, 1H).

Step 3: 4-(4-Chloro-phenyl)-4-hydroxy-3-methyl-piperdine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester

3-Methyl-4-oxo-piperdine-1,3-dicarboxylic acid-1-*tert*-butyl ester 3-methyl ester (1.1 g, 4.07 mmol) was dissolved in tetrahydrofuran and cooled to 0 °C. To the solution was added 4-chlorophenyl magnesium bromide (12.2 mL, 12.2 mmol) dropwise over ~1/2 h and then stirred at 0 °C for 1h. The reaction was quenched with saturated solution of NH_4Cl and extracted with ethyl acetate (3x). The organics were collected, dried over Mg_2SO_4, filtered and evaporated *in vacuo*, then purified by Biotage flash chromatography (10% ethyl acetate/ 90% hexane to 20% ethyl acetate/80% hexane) to yield the title compound (1.1 g, 70 %).^{1}H-NMR ($CDCl_3$): δ 1.17 (s, 3H), 1.44 (s, 9H), 1.55 (m ,1H), 1.96 (d, 1H)3.00 (m, 1H), 3.37 (m, 2H), 3.53 (s, 3H), 3.91 (m, 2H), 4.07 (d, 1H), 7.27 (d, 2H), 7.43 (d, 2H). ESI-MS m/z: 384.1 (M + 1), retention time 2.95.

Step 4

4-(4-Chloro-phenyl)-4-hydroxy-3-methyl-piperidine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (1.1 g, 2.87 mmol) was dissolved in CH_2Cl_2 (35 mL) and cooled to 0°C and TFA (8 mL) was added dropwise. The solution was allowed to stir at 0° C for 1 h. The solvent was evaporated *in vacuo* and the residue was partitioned between 1N NaOH and CH_2Cl_2. The aqueous solution was extracted (3x) and then washed with brine and dried over Na_2SO_4. The residue was carried onto the next step without further purification.

Step 5

To a solution of 4-(4-chloro-phenyl)-4-hydroxy-3-methyl-piperidine-3-carboxylic acid methyl ester (0.71 g, 2.5 mmol) in acetonitrile/water (8:2) (25 mL) was added K_2CO_3 (1.40g, 10.0 mmol) and 2-[5-(3-bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl]-propan-2-ol (0.937 g, 2.5 mmol). The solution was allowed to stir at room temperature for 48 h. The reaction was concentrated and partitioned between EtOAc/H_2O, extracted with EtOAc (3x). The organics were collected together dried over Mg_2SO_4, filtered and evaporated *in vacuo*, then purified by Biotage flash chromatography (50% ethyl acetate/ 50% hexane to 75% ethyl acetate/ 25% hexane to 100% ethyl acetate) to yield the title compound (0.835 g, 58 %).^{1}H-NMR ($CDCl_3$): 1.30 (s, 3H), 1.57 (s, 6H), 1.76 (d, 1H), 2.24-2.53 (m, 7H), 2.65 (d, 1H), 2.86 (d, 2H), 3.44 (s, 3H), 5.30 (bs, 2H), 6.16 (d, 1H), 6.82 (d, 1H), 7.26 (m, 4H), 7.45 (s, 1H), 7.53 (d, 1H), 7.58 (d, 1H), 8.49 (d, 1H). ESI-MS m/z: 577 (M + 1), retention time 1.50.

Example 482

4-(4-Chloro-phenyl)-3-hydroxymethyl-1-{3-[7-(hydroxyl-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-3-methyl-piperidine-4-ol

4-(4-Chloro-phenyl)-4-hydroxy-1-{3-[7-(hydroxyl-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-3-methyl-piperidine-3-carboxylic acid methyl ester (0.250 g, 0.43 mmol) was dissolved in tetrahydrofuran and cooled to 0°C. To the solution was added $LiAlH_4$ (1.3 mL, 1.3 mmol) dropwise and the reaction was allowed to stir at 0°C for 3h. The reaction was quenched with ice water slowly and diluted with ethyl acetate. The reaction mixture was allowed to stir at room temperature for 45 min. to break up any aluminum complexes. The organics were separated and the aqueous layer was extracted (2x) more. All of the organics were collected, dried over Mg_2SO_4, filtered and evaporated *in vacuo*, then purified by Biotage flash chromatography (50% ethyl acetate/ 50% hexane to 75% ethyl acetate/ 25% hexane) to yield the title compound (0.103 g, 43 %).^{1}H-NMR ($CDCl_3$): δ 0.53 (s, 3H), 1.55 (d, 6H), 1.62 (m, 1H), 2.40 (q, 2H), 2.55 (q, 3H), 2.72-2.86 (m, 4H), 3.19 (dd, 1H), 3.24 (d, 1H), 3.41 (d, 1H), 5.33 (bs, 2H), 6.17 (t, 1H), 6.44 (bs, 1H), 6.79 (d, 1H), 7.17 (d, 1H), 7.26-7.59 (m, 7H), 8.50 (d, 1H). ESI-MS m/z: 549 (M + 1), retention time 1.39.

Example 483-1, Example 483-2

Racemic 4-(4-Chloro-phenyl)-3-hydroxymethyl-1-{3-[7-(hydroxyl-1-methyl-ethyl)-11H-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-3-methyl-piperdine-4-ol was resolved using a ChiralPak AD column eluting with 5/5/90 methanol/ethanol/hexane. Peak One is the more active enantiomer, Example 483-1. Peak Two is the less active enantiomer, Example 483-2.

Example 484

4-(4-Chloro-phenyl)-3-ethoxymethyl-1-{3[7-(-hydroxy-1-methyl-ethyl)-11*H*-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-3-methyl-piperidin-4-ol

Step 1

To a solution of 4-(4-chloro-phenyl)-4-hydroxy-3-hydroxymethyl-3-methyl-piperidine-1-carboxylic acid-*tert*-butyl ester (0.270 g, 0.76 mmol) in THF (4.8 mL) was added NaH (0.075 g, 1.9 mmol) and stirred for 20 min at room temperature. Ethyl iodide (0.066 mL, 0.83 mmol) was added and the solution was heated to 50°C for 1h. The reaction was quenched with water and extracted with ethyl acetate (3x). The organics were collected together dried over Mg_2SO_4, filtered and evaporated *in vacuo*, then purified by Biotage flash chromatography (10% ethyl acetate/ 90% hexane to 20% ethyl acetate/ 80% hexane to 30% ethyl acetate/ 70% hexane) to yield the title compound (0.110 g, 37 %). ^{1}H-NMR ($CDCl_3$): 0.79 (s, 3H), 1.10 (t, 3H), 1.26 (s, 1H), 1.45 (s, 9H), 1.84 (s, 1H), 2.74 (m, 2H), 2.98 (d, 1H), 3.18 (m, 1H), 3.28 (q, 2H), 3.97 (d, 2H), 7.26-7.39 (m, 4H).

Step 2

4-(4-Chloro-phenyl)-3-ethoxymethyl-4-hydroxy-3-methyl-piperidine-1-carboxylic acid-*tert*-butyl ester (0.052 g, 0.14 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C and TFA (1 mL) was added. The solution was allowed to stir at 0° C for 1 h. The solvent was evaporated *in vacuo* and used directly in the next reaction.

Step 3

To a solution of 4-(4-chloro-phenyl)-3-ethoxymethyl-3-methyl-piperidin-4-ol (0.038g, 0.13 mmol) in acetonitrile/water (8:2) (1.3 mL) was added K_2CO_3 (0.075g, 0.53 mmol) and 2-[5-(3-bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl]-propan-2-ol (0.050g, 0.13 mmol). The solution was allowed to stir at room temperature for 48 h. The reaction was concentrated and partitioned between EtOAc/H_2O, extracted with EtOAc (3x). The organics were collected, dried over $MgSO_4$, filtered and evaporated *in vacuo*, then purified by Biotage flash chromatography (75% ethyl acetate/ 25% hexane) to yield the title compound in 65% yield. ^{1}H-NMR ($CDCl_3$): δ 0.81 (s, 3H), 0.98 (t, 3H), 1.58 (s, 6H), 1.84 (s, 1H), 2.31-2.49 (m, 5H), 2.58 (d, 1H), 2.67 (s, 1H), 2.77 (d, 2H), 3.26 (q, 2H), 3.65 (d, 2H), 5.33 (bs, 2H), 6.16 (t, 1H), 6.82 (d, 1H), 7.22-7.36 (m, 7H), 7.45 (d, 1H), 7.60 (d, 1H). ESI-MS m/z: 577 (M + 1), retention time 1.58.

Example 485

(4-(4-Chloro-phenyl)-4-hydroxy-1-{3[7-(1-hydroxy-1-methyl-ethyl)-11*H*-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-3-methyl-piperidin-3-ylmethoxy)-acetic acid ethyl ester

Step 1

To a solution of 4-(4-chloro-phenyl)-4-hydroxy-3-hydroxymethyl-3-methyl-piperidine-1-carboxylic acid-*tert*-butyl ester (0.080 g, 0.22 mmol) in THF (2.2 mL) was added NaH (0.031 g, 0.78 mmol) and stirred for 20 min at room temperature. Ethyl bromoacetate (0.027 mL, 0.30 mmol) was added and the solution was heated to 50°C for 1h. The reaction was quenched with water and extracted with ethyl acetate (3x). The organics were collected together dried over Mg_2SO_4, filtered and evaporated *in vacuo*, then purified by Biotage flash chromatography (10% ethyl acetate/ 90% hexane to 20% ethyl acetate/ 80% hexane) to yield the ethyl ester (0.050 g, 50 %). ^{1}H-NMR ($CDCl_3$): 0.85 (bs, 3H), 1.22 (t, 3H), 1.45 (s, 9H), 1.66 (s, 1h), 2.64-3.39 (m, 6H), 3.96 (d, 2H), 4.12 (q, 2H), 7.26-7.38 (m, 4H).

Step 2

4-(4-Chloro-phenyl)-3-ethoxycarbonylmethoxymethyl-4-hydroxy-3-methyl-piperidine-1-carboxylic acid-*tert*-butyl ester (0.060 g, 0.14 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C and TFA (1 mL) was added. The solution was allowed to stir at 0° C for 1 h. The solvent was evaporated *in vacuo* and used directly in the next reaction.

Step 3

To a solution of 4-(4-chloro-phenyl)-4-hydroxy-3-methyl-piperidin-3-ylmethoxy]-acetic acid ethyl ester (0.046g, 0.13 mmol) in acetonitrile/water (8:2) (1.3 mL) was added K_2CO_3 (0.075g, 0.53 mmol) and 2-[5-(3-bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl]-propan-2-ol (0.051g, 0.13 mmol). The solution was allowed to stir at room temperature for 48 h. The reaction was concentrated down and partitioned between EtOAc/H_2O, extracted with EtOAc (3x). The organics were collected together dried over Mg_2SO_4, filtered and evaporated *in vacuo*, then purified by Biotage flash chromatography (75% ethyl acetate/ 25% hexane) to yield the title compound in 54% yield. ^{1}H-NMR ($CDCl_3$): δ 0.86 (s, 3H),l 1.16 (t, 3H), 1.57 (s, 6H), 1.78 (s, 1H), 2.37 (t, 1H), 2.46-2.71 (m, 5H), 2.81 (t, 1H), 3.80 (d, 2H), 3.97 (d, 2H), 4.06 (q, 2H), 5.30 (bs, 2H), 6.18 (t, 1H), 6,82 (d, 1H), 7.22 (dd, 1H), 7.26-7.36 (m, 7H), 7.47 (d, 1H), 7.60 (d, 1H). ESI-MS m/z: 635 (M + 1), retention time 1.62.

Example 486

4-(4-Chloro-phenyl)-3-(2-diethylamino-ethoxymethyl)-4-hydroxy-3-methyl-piperidine-1-carboxylic acid-*tert*-butyl ester

Step 1

To a solution of 4-(4-chloro-phenyl)-4-hydroxy-3-hydroxymethyl-3-methyl-piperidine-1-carboxylic acid-*tert*-butyl ester (0.071 g, 0.15 mmol) in THF (1.5 mL) was added NaH (0.016 g, 0.39 mmol) and stirred for 20 min at room temperature. 2-Bromo-N,N-diethylethylamine HBr (0.044 mL, 0.17 mmol) was added and the solution was heated to 50°C for 1h. The reaction was quenched with water and extracted with ethyl acetate (3x). The organics were collected, dried over $MgSO_4$, filtered and evaporated *in vacuo*, then purified by Biotage flash chromatography (10% ethyl acetate/ 90% hexane to 20% ethyl acetate/ 80% hexane) to yield the diethylamine (0.035 g).

Step 2

4-(4-Chloro-phenyl)-3-(2-diethylamino-ethoxymethyl)-4-hydroxy-3-methyl-piperidine-1-carboxylic acid-*tert*-butyl ester (0.035 g, 0.62 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C and TFA (1 mL) was added. The solution was allowed to stir at 0° C for 1 h. The solvent was evaporated *in vacuo* and used directly in the next reaction.

Step 3

To a solution of 4-(4-chloro-phenyl)-3-(2-diethylamino-ethoxymethyl)-3-methyl-piperidin-4-ol in acetonitrile/water (8:2) (3.2 mL) was added K_2CO_3 and 2-[5-(3-bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-

yl]-propan-2-ol. The solution was allowed to stir at room temperature for 48 h. The reaction was concentrated down and partitioned between EtOAc/H_2O, extracted with EtOAc (3x). The organics were collected, dried over $MgSO_4$, filtered and evaporated *in vacuo*, then purified by Biotage flash chromatography (5% methanol/ 95% methylene chloride to 10% methanol/ 90% methylene chloride to 15% methanol/85% methylene chloride) to yield the title compound. ^{1}H-NMR ($CDCl_3$): 0.50 (s, 3H), 0.97 (t, 6H), 1.52 (s, 6H), 2.40-2.66 (m, 12H), 3.16-3.30 (m, 6 H), 5.32 (bs, 2H), 6.06 (t, 1H), 6.80 (t, 1H), 7.20 (dd, 1H), 7.29 (dd, 1H), 7.29-7.31 (m,6H), 7.58 (d, 2H), 8.51 (d, 1H). δ ESI-MS m/z: 648 (M + 1), retention time 1.19.

Example 487

2-[5-(3-{4-[(4-Chloro-benzyl)ethyl-amino]-piperidin-1-yl}-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-7-yl]-propan-2-ol

Step 1: 4-(4-Chloro-benzylamino)-piperidine-1-carboxylic acid *tert*-butyl ester

4-Amino-1-*N*-Boc piperidine (1.80g, 8.9 mmol) was dissolved in CH_2Cl_2 and 4-chlorobenzylbromide (1.84g, 8.9 mmol) and triethylamine (1.25 mL, 8.9 mmol) were added. The solution was allowed to stir for 14h at room temperature and evaporated *in vacuo* and partitioned between ether/ 1N NaOH. The aqueous layer was removed and the ether was washed with brine and dried over $MgSO_4$, filtered and evaporated *in vacuo*, then purified by Biotage flash chromatography (5% methanol/ 95% methylene chloride) to yield the title compound (0.800 g, 27 %).^{1}H-NMR ($CDCl_3$): δ 1.26 (m, 1H), 1.44 (s, 9H), 1.83 (d, 2H), 2.63 (t, 1H), 2.78 (t, 2H), 3.46 (s, 2H), 3.78 (s, 2H), 4.00 (bs, 2H), 7.26 (bs, 4H). ESI-MS m/z: 325.1 (M + 1), retention time 1.86.

Step 2

(4-Chloro-benzyl)-ethyl-amino]-piperidine-1-carboxylic acid *tert*-butyl ester (0.500g , 1.4 mmol) dissolved in 4M HCl/Dioxane (100 mL). The solution was stirred at rt for 1h. The solvent was removed *in vacuo* and the mixture was carried on to the next step without further purification as the hydrochloride salt.

Step 3: (4-Chloro-benzyl)-ethyl-piperdin-4-yl-amine

4-(4-Chloro-benzylamino)-piperidine-1-carboxylic acid *tert*-butyl ester was dissolved in CH_2Cl_2 and acetaldehyde (0.678g, 3.2 mmol), $Na(OAc)_3BH$ (0.163g, 3.7 mmol) and 1 drop of AcOH was added. The solution was stirred in a sealed vessel for 10 h. The reaction mixture was washed with 1N NaOH, brine and dried over Mg_2SO_4, filtered and evaporated *in vacuo*, then purified by Biotage flash chromatography (15% ethyl acetate/ 85% hexane) to yield the title compound (0.350 g, 40 %).

Step 4

To a solution of (4-chloro-benzyl)-ethyl-piperidin-4-yl-amine hydrochloride (0.200 g, 0.83 mmol) in acetonitrile/water (8:2) (8 mL) was added K_2CO_3 (0.476g, 3.4 mmol) and 2-[5-(3-bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl]-propan-2-ol (0.282 g, 7.5 mmol). The solution was allowed to stir at room temperature for 48 h. The reaction was concentrated and partitioned between EtOAc/H_2O, extracted with EtOAc (3x). The organics were collected, dried over $MgSO_4$, filtered and evaporated *in vacuo*, then purified by Biotage flash chromatography (5 % methanol/ 95 % methylene chloride to 10% methanol/ 90% methylene chloride) to yield the title compound (0.240 g, 60 %).^{1}H-NMR ($CDCl_3$): δ 0.988 (t, 3H), 1.57 (s, 6H), 1.67 (d, 2H), 1.85 (t, 2H), 2.32-2.46 (m, 5H), 2.51 (q, 2H), 2.84 (d, 2H), 3.47 (s, 2H), 3.56 (s, 2H), 5.29 (bs, 2H), 6.07 (t, 1H), 6.80 (d, 1H), 7.21-7.28 (m, 6H), 7.42 (s, 1H), 7.56 (d, 1H), 8.48 (d, 1H). ESI-MS m/z: 546 (M + 1), retention time 1.87.

Example 488

1-{3-[7-(1-Hydroxy-1-methyl-ethyl)-11*H*-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-4-phenyl-piperidin-4-ol

To a solution of the 4-phenyl-piperidin-4-ol (0.212 g, 1.2 mmol) in isopropanol was added 2,6-lutidine (0.240 mL, 2.1 mmol) and catalytic potassium iodide. This mixture was heated to 80°C, and treated with 2-[5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl]-propan-2-ol (0.224 g, 0.6mmol), added in portions over 1 h. The solution was then stirred at 80 °C for an additional 14 h. The reaction was concentrated *in vacuo*, then purified by Isco flash chromatography (15% methanol/85% methylene chloride) to yield the title compound (0.140 g, 50%). ^{1}H-NMR ($CDCl_3$): δ 1.12 (t, 3H), 1.57(s, 6H), 2.67-2.80 (m, 4H), 1.95-2.11 (m, 2H), 2.34-2.41 (m, 2H), 2.43 -2.54 (m, 2H), 2.88 (d, 2H), 3.22 (q, 2H), 3.43 (m, 1H), 5.28 (bs, 2H), 6.12 (t, 1H), 6.60 (d, 2H), 6.80 (d, 1H), 7.13 (d, 2H), 7.21-7.30 (m, 2H), 7.45 (s, 1H), 7.56 (d, 1H), 8.48 (dd, 1H). ESI-MS m/z: 534 (M + 1), retention time 2.47.

Example 489

4-(2-Chloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11*H*-10-oxa-1-aza dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-piperidin-4-ol

Step 1

To a 1-bromo-2-chloro-benzene (0.97 mL, 8.3 mmol) in ether was added magnesium (0.238 g, 9.8 mmol) and catalytic iodide at room temperature for 2h. This mixture was cooled to 0 °C, and treated with 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (1.5 g, 7.5 mmol) dissolved in ether (8 mL) and added to the reaction mixture slowly. The reaction was heated to reflux for 1h. The reaction was quenched with ammonium chloride and the aqueous phase extracted with ethyl acetate. The organics were combined and dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by Isco flash system (75% hexane/25% ethyl acetate) to yield the alcohol (0.600 g, 38%).

Step 2

4-(2-Chloro-phenyl)-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (0.600 g, 1.9 mmol) was dissolved in CH_2Cl_2 (19 mL) and cooled to 0°C and TFA (4 mL) was added. The solution was allowed to stir at 0° C for 1 h. The solvent was evaporated *in vacuo* and the residue was partitioned between $NaHCO_3$ and CH_2Cl_2. The aqueous solution was extracted (3x) and then washed with brine and dried over Na_2SO_4. The residue was carried onto the next step without further purification.

Step 3

To a solution of the 4-(2-chloro-phenyl)-piperidin-4-ol (0.210 g, 1.0 mmol) in isopropanol was added 2,6-lutidine (0.31 mL, 2.7 mmol) and catalytic potassium iodide. This mixture was heated to 80°C, and treated with 2-[5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl]-propan-2-ol (0.287 g, 0.77 mmol), added in portions over 1 h. The solution was then stirred at 80 °C for an additional 14 h. The reaction was concentrated *in vacuo*, then purified by Isco flash chromatography (15% methanol/85% methylene chloride) to yield the title compound (0.200 g, 52%). ^{1}H-NMR ($CDCl_3$): δ 1.55 (s, 6H), 1.70 (d, 2H), 2.10-2.30 (m, 2H), 2.36-2.54 (m, 2H), 2.57-2.92 (m, 6H), 5.30 (bs, 2H), 6.16 (t, 1H), 6.77 (d, 1H), 7.16-7.36 (m, 5H), 7.48 (s, 2H), 7.58 (d, 1H), 8.37 (dd, 1H). ESI-MS m/z: 505 (M + 1), retention time 1.48.

Example 490

4-(4-Chloro-2-methyl-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11*H*-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-piperidin-4-ol

Step 1

To 4-chloro-2-methylphenylmagnesium bromide (15 mL, 7.5 mmol) in ether cooled to 0 °C was added 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (1.0 g, 5.0 mmol) over 30 min. The resulting solution was heated to reflux for 1h. The reaction was quenched with ammonium chloride and the aqueous phase extracted with ethyl acetate. The organics were combined and dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by Isco flash system (75% hexane/25% ethyl acetate) to yield the alcohol (0.534 g, 33%).

Step 2

4-(4-Chloro-2-methyl-phenyl)-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (0.534 g, 1.6 mmol) was dissolved in CH_2Cl_2 (16 mL) and cooled to 0°C and TFA (3 mL) was added. The solution was allowed to stir at 0° C for 1 h. The solvent was evaporated *in vacuo* and the residue was partitioned between $NaHCO_3$ and CH_2Cl_2. The aqueous solution was extracted (3x) and then washed with brine and dried over Na_2SO_4. The residue was carried onto the next step without further purification.

Step 3

To a solution of the 4-(4-chloro-2-methyl-phenyl)-piperidin-4-ol (0.160 g, 0.71 mmol) in isopropanol was added 2,6-lutidine (0.24 mL, 2.1 mmol) and catalytic potassium iodide. This mixture was heated to 80°C, and treated with 2-[5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl]-propan-2-ol (0.221 g, 0.59 mmol), added in portions over 1 h. The solution was then stirred at 80 °C for an additional 14 h. The reaction was concentrated *in vacuo*, then purified by Isco flash chromatography (15% methanol/85% methylene chloride) to yield the title compound (0.130 g, 36%). ^{1}H-NMR ($CDCl_3$): δ 1.57 (s, 6H), 1.92 (d, 2H), 2.30 (t, 2H), 2.49 (s, 3H), 2.48-2.63 (m, 2H), 2.74-3.11 (m, 6H), 3.40 (s, 1H), 5.21 (bs, 2H), 6.09 (t, 1H), 6.75 (d, 1H), 7.06 (d, 1H), 7.08 (s, 1H), 7.20(d, 2H), 7.22-7.36 (m, 1H), 7.57 (d, 1H), 8.36 (dd, 1H). ESI-MS m/z: 519 (M + 1), retention time 1.61.

Example 491

4-(3,4-Dichloro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11*H*-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-piperidin-4-ol

Step 1

To 3,4-dichlorophenylmagnesium bromide (7.5 mL, 7.5 mmol) in ether cooled to 0°C was added 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (1.0 g, 5.0 mmol) over 30 min. The resulting solution was heated to reflux for 1h. The reaction was quenched with ammonium chloride and the aqueous phase extracted with ethyl acetate. The organics were combined and dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by Isco flash system (75% hexane/25% ethyl acetate) to yield the alcohol (0.630 g, 36%).

Step 2

4-(3,4-Dichloro-phenyl)-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (0.630 g, 1.8 mmol) was dissolved in CH_2Cl_2 and cooled to 0°C and TFA (3 mL) was added. The solution was allowed to stir at 0° C for 1 h. The solvent was evaporated *in vacuo* and the residue was partitioned between $NaHCO_3$ and CH_2Cl_2. The aqueous solution was extracted (3x) and then washed with brine and dried over Na_2SO_4. The residue was carried onto the next step without further purification.

Step 3

To a solution of the 4-(4-chloro-2-methyl-phenyl)-piperidin-4-ol (0.140 g, 0.57 mmol) in isopropanol was added 2,6-lutidine (0.23 mL, 2.0 mmol) and catalytic potassium iodide. This mixture was heated to 80°C, and treated with 2-[5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl]-propan-2-ol (0.213 g, 0.57 mmol), added in portions over 1 h. The solution was then stirred at 80 °C for an additional 14 h. The reaction was concentrated *in vacuo*, then purified by Isco flash chromatography (15% methanol/85% methylene chloride) to yield the title compound (0.110 g, 36%). ^{1}H-NMR ($CDCl_3$): δ1.55 (s, 6H), 1.70 (d, 2H), 2.10 -2.30 (m, 2H), 2.45 (m, 2H), 2.57-2.92 (m, 6H), 5.30 (bs, 2H), 6.16 (t, 1H), 6.77 (d, 1H), 7.16-7.40 (m, 4H), 7.08 (s, 1H), 7.57 (s, 2H), 8.36 (dd, 1H). ESI-MS m/z: 539 (M + 1), retention time 1.72.

Example 492

4-(4-Chloro-3-nitro-phenyl)-1-{3-[7-(1-hydroxy-1-methyl-ethyl)-11*H*-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-5-ylidene]-propyl}-piperidin-4-ol

Step 1

To fuming nitric acid (20 mL) was added 4-(4-chloro-phenyl)-piperidin-4-ol at 0 °C and stirred for 5 min. The solution was carefully neutralized with Na_2CO_3 and filtered. The resulting solid was trituated with water and then filtered to give a yellow solid. The solid was dissolved in sat $NaHCO_3$ and extrated with ethyl acetate (3x). The organics were collected together dried over Mg_2SO_4, filtered and evaporated *in vacuo* to give the 4-chloro-3-nitro compound (1.1 g, 18%).

Step 2

To a solution of the 4-(4-Chloro-3-nitro-phenyl)-piperidin-4-ol (0.295 g, 1.2 mmol) in isopropanol was added 2,6-lutidine (0.225 mL, 2.1 mmol) and catalytic potassium iodide. This mixture was heated to 80°C, and treated with 2-[5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-7-yl]-propan-2-ol (0.224 g, 0.6 mmol), added in portions over 1 h. The solution was then stirred at 80 °C for an additional 14 h. The reaction was concentrated *in vacuo*, then purified by Isco flash chromatography (15% methanol/85% methylene chloride) to yield the title compound (0.100 g, 30%). ^{1}H-NMR ($CDCl_3$): δ 1.53 (s, 6H), 1.70 (d, 2H), 1.81-2.18 (m, 4H), 2.3-2.44 (m, 4H), 2.56 (t, 2H), 2.69 (d, 2H), 5.32 (bs, 2H), 6.16 (t, 1H), 6.81 (d, 1H), 7.28 (t, 2H), 7.48 (t, 2H) , 7.58 (t, 2H), 8.06 (s, 1H). ESI-MS m/z: 550 (M + 1), retention time 1.51

Example 493

2-[5-(3-{4-[(4-Chloro-phenyl)-ethyl-amino]-piperidin-1-yl}-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl]-propan-2-ol

Step 1

4-Amino-piperidine-1-carboxylic acid tert-butyl ester (1.58 g, 7.9 mmol) and acetaldehyde (0.417g, 9.48 mmol) were mixed with sodium triacetoxy borohydride (3.35, 15.8 mmol) in dichloroethane containing acetic acid (1%) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate solution and brine and dried over sodium sulfate. The reaction was concentrated *in vacuo*, then purified by Isco flash chromatography (10% methanol/90% methylene chloride/ammonium hydroxide) to yield the tert-butyl ester (0.71 g, 39%).

Step 2

4-Ethylamino-piperidine-1-carboxylic acid tert-butyl ester (0.694 g, 3.04 mmol) and 1-Bromo-4-chloro-benzene (0.582, 3.04 mmol) was dissolved in toluene along with sodium t-butoxide (0.41, 4.26 mmol), $Pd_2(dba)_3$ (0.055 g, 0.061 mmol) and BINAP (0.037 g, 0.061 mmol). The solution was heated to 70 °C for 2 days and then filtered and the reaction was concentrated *in vacuo*, then purified by Isco flash chromatography (50% ethyl acetate/ 50 % hexane) to yield the tert-butyl ester (0.25 g, 24%).

Step 3

4-(Ethyl-phenyl-amino)-piperidine-1-carboxylic acid tert-butyl ester (0.251g, 1.0 mmol) was dissolved in 4M HCl/Dioxane (10 mL). The solution was stirred at rt for 1h. The solvent was removed *in vacuo* and the mixture was carried on to the next step without further purification as the hydrochloride salt.

Step 4

To a solution of the (4-chloro-phenyl)-ethyl-piperidin-4-yl-amine (0.150 g, 0.63 mmol) in isopropanol was added 2,6-lutidine (0.24 mL, 2.1 mmol) and catalytic potassium iodide. This mixture was heated to 80°C, and treated with 2-[5-(3-Bromo-propylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[*a,d*]cyclohepten-7-yl]-propan-2-ol (0.221 g, 0.6 mmol), added in portions over 1 h. The solution was then stirred at 80 °C for an additional 14 h. The reaction was concentrated *in vacuo*, then purified by Isco flash chromatography (15% methanol/85% methylene chloride) to yield the title compound (0.108 g, 34%). ^{1}H-NMR ($CDCl_3$): δ 1.12 (t, 3H), 1.57 (s, 6H), 2.67-2.80 (m, 4H), 2.00 (m, 2H), 2.34-2.41 (m, 2H), 2.43-2.54 (m, 2H), 2.88 (d, 2H), 3.22 (q, 2H), 3.37 -3.51 (m, 1H), 5.28 (bs, 2H), 6.12 (t, 1H), 6.60 (d, 2H), 6.80 (d, 1H), 7.13 (d, 2H), 7.21- 7.30 (m, 2H), 7.45 (s, 1H), 7.56 (d, 1H), 8.48 (dd, 1H). ESI-MS m/z: 532 (M + 1), retention time 2.47.

Example 494

2-(5-{3-[4-(4-Chloro-phenyl)-4-methoxy-piperidin-1-yl]-propylidene}-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cyclohepten-7-yl)-propan-2-ol

Step 1

4-(4-Chloro-phenyl)-4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (200 mg, 0.641 mmol) was added portionwise as a solid to a suspension of sodium hydride (0.018g, 0.770 mmol) in dimethylformamide (6 mL) at room temperature. After 30 minutes, methyl iodide (0.109g, 60 uL, 0.770 mmol) was added and the mixture was stirred overnight. The mixture was poured into an equal volume of water and extracted with ethyl acetate (2 X 10 mL). The ethyl acetate extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give a tan oil. The crude oil was purified by silica gel chromatography (hexane to 60:40 hexane/ethyl acetate gradient) to afford 4-(4-Chloro-phenyl)-4-methoxy-piperidine-1-carboxylic acid *tert*-butyl ester as a clear oil (108 mg, 52%).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.45 (s, 9H), 1.80(td, 2H), 1.97 (bd, 2H), 2.96 (s, 3H), 3.16 (td, 2H), 3.90 (bd, 2H), 7.36 (s, 4H)

MS m/z: 326 (M + 1)

Step 2

4-(4-Chloro-phenyl)-4-methoxy-piperidine-1-carboxylic acid *tert*-butyl ester (0.108g, 0.331 mmol) was dissolved in methylene chloride (6mL) and cooled in an

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JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __2___

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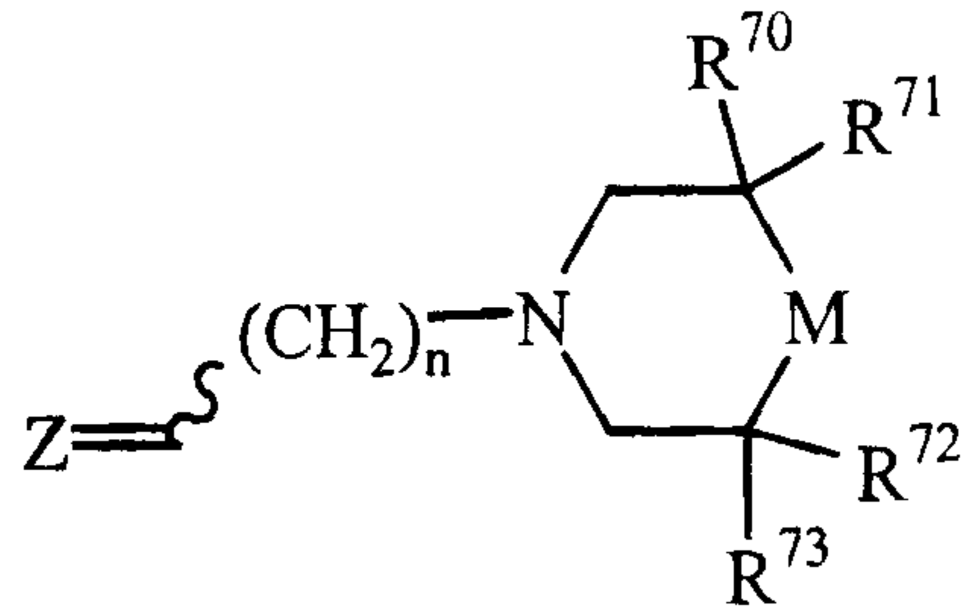
CLAIMS:

1. A compound having the formula:



or physiologically acceptable salt thereof, wherein:

n is 1 to 4;

M is $>NR^2$ or $>CR^1R^2$;

R^1 is -H, -OH, $-N_3$, a halogen, an aliphatic group, a substituted aliphatic group, an aminoalkyl 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), -COOH, -CN, $-CO-NR^3R^4$, or $-NR^3R^4$;

R^2 is -OH, a halogen, 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, a substituted non-aromatic heterocyclic group, -O-(substituted or unsubstituted aromatic group), -O-(substituted or unsubstituted aliphatic group), -C(O)-(substituted or unsubstituted aromatic group) or -C(O)-(substituted or unsubstituted aliphatic 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

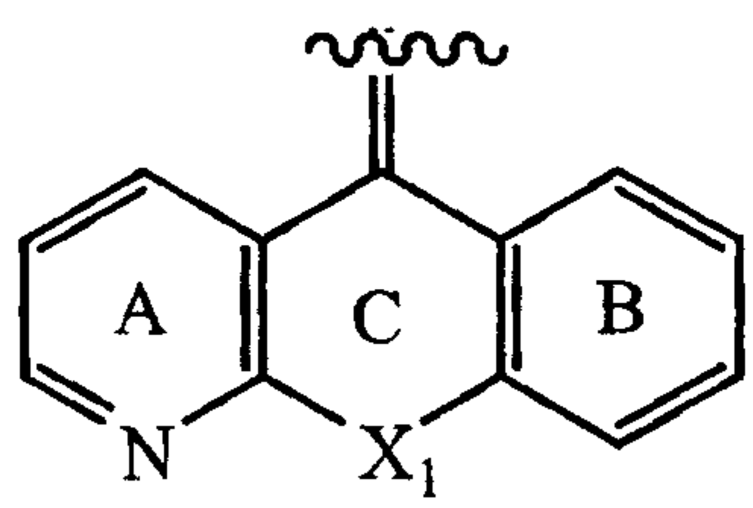
R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

R^{70} and R^{71} are independently -H, -OH, $-N_3$, a halogen, an aliphatic group, a substituted aliphatic group, an aminoalkyl 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), -COOH, -CN, -CO-NR^3R^4, -NR^3R^4, an acyl group, a substituted acyl group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group, or -O-(substituted or unsubstituted aromatic group);

R^{72} and R^{73} are independently -OH, -N_3, a halogen, an aliphatic group, a substituted aliphatic group, an aminoalkyl group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -O-C(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -COOH, -CN, -CO-NR^3R^4, -NR^3R^4, an acyl group, a substituted acyl group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group, or -O-(substituted or unsubstituted aromatic group);

Z is:



X_1 is -CH_2-O-, -O-CH_2-, -S-, -CH_2-, -CH_2-CH_2-, -CH_2-S-, -S-CH_2-,-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-, a bond, -O-, 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;

Rings A and B are independently unsubstituted or substituted;

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

said aliphatic group is a C_1-C_6 alkyl, alkenyl or alkynyl;

said aromatic group is selected from phenyl, 1-naphthyl, 2-naphthyl, 1-anthracyl, 2-anthracyl, *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, 5-oxazolyl, tetrahydronaphthyl, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 3-indolyl, 2-quinolinyl, 3-quinolinyl, 2-benzothiazolyl, 2-benzooxazolyl, 2-benzimidazolyl, 1-isoquinolinyl, 3-quinolinyl, 1-isoindolyl, 3-isoindolyl, acridinyl, 3-benzisoxazolyl, benzocyclopentyl, or benzocyclohexyl;

said non-aromatic heterocyclic group is a five to eight-membered non-aromatic ring which contains one or more heteroatoms which are independently nitrogen, oxygen or sulfur;

said substituted aliphatic group is substituted with one or more substituents selected from oxo group, epoxy group, non-aromatic heterocyclic ring, benzyl group, substituted benzyl group, aromatic group or substituted aromatic group electron withdrawing group, halo, azido, -CN, -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, guanidino, oxalo, -C(=NR^{60})NR^{21}R^{22}, =NR^{60}, -(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) or -Q-(CH$_2$)$_p$-(non-aromatic heterocyclic group);

said substituted non-aromatic heterocyclic ring is substituted with one or more substituents which are =O, =S, electron withdrawing group, halo, azido, -CN, -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, guanidino, oxalo, -C(=NR^{60})NR^{21}R^{22}, =NR^{60}, -(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) or -Q-(CH$_2$)$_p$-(non-aromatic heterocyclic group);

said substituted aromatic group, substituted benzyl group, Ring A when substituted and Ring B when substituted, are substituted with one or more substituents which are electron withdrawing group, aliphatic group, substituted aliphatic group, aromatic group, substituted aromatic group, halo, azido, -CN, -CONR^{24}R^{25}, -NR^{24}R^{25},

$-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, guanidino, oxalo, $-C(=NR^{60})NR^{21}R^{22}$, $=NR^{60}$, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$, -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) or $-Q-(CH_2)_p-$(non-aromatic heterocyclic group); 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)-, -NHC(O)-, -OC(O)NH-, -NH-C(O)-NH-, $-S(O)_2NH-$, $-NHS(O)_2-$, $-C(NR^{23})NHNH-$, $-NHNHC(NR^{23})-$, $-NR^{24}C(O)-$ or $-NR^{24}S(O)_2-$;R^{20}, R^{21} and R^{22} are independently -H, an aliphatic group, an 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, can form a substituted or unsubstituted non-aromatic heterocyclic ring;

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, an aliphatic group, a substituted aliphatic group, a benzyl group, an aryl group, non-aromatic heterocyclic group or R^{24} and R^{25} taken together with the nitrogen atom to which they are bonded can form a substituted or unsubstituted non-aromatic heterocyclic ring;

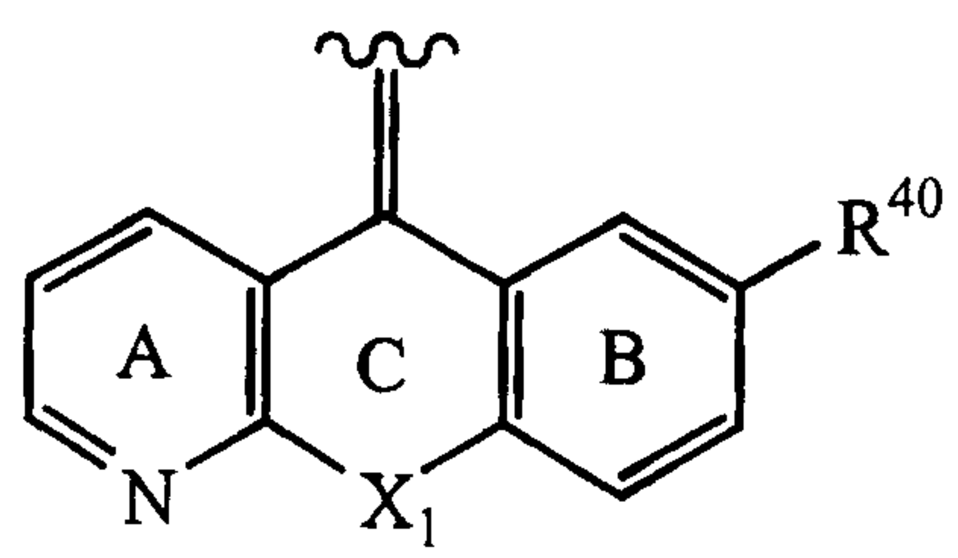
R^{60} is a -H, -OH, $-NH_2$, an aromatic group or a substituted aromatic group;

t is 0 to 3;

u is 0 or 1; and

p is 1 to 5.

2. The compound of claim 1 wherein Ring A is unsubstituted and B is substituted para to the carbon atom of ring B that is bonded to X_1 in ring C, and Z is represented by the structural formula:



wherein R^{40} is -OH, -COOH, $-NO_2$, halogen, aliphatic group, substituted aliphatic group, an aromatic group, a substituted aromatic group, $-NR^{24}R^{25}$, $-CONR^{24}R^{25}$, $-NR^{24}C(O)$-(aliphatic group), $-NR^{24}C(O)$-(substituted aliphatic group), $-NR^{24}S(O)_2$-(aliphatic group), $-NR^{24}S(O)_2$-(substituted aliphatic group), -C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -C(O)-(aliphatic group), -C(O)-(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 $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$;

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;

R^{24} and R^{25} are independently -H, an aliphatic group or a substituted aliphatic group;

u is 0 or 1; and

t is an integer from 0 to 3.

3. The compound of claim 2 wherein

M is $>CR^1R^2$;

R^1 is -H or -OH; and

R^2 is a substituted aromatic group, wherein said substituted aromatic group is 4-halophenyl.

4. The compound of claim 3 wherein said 4-halophenyl is 4-chlorophenyl, 4-bromophenyl or 4-fluorophenyl.

5. The compound of claim 3 wherein X_1 is $-CH_2-O-$.

6. The compound of claim 2 wherein at least one of R^{70}, R^{71}, R^{72} and R^{73} is an aliphatic group or a substititued aliphatic group; wherein

said aliphatic group is a C_1-C_6 alkyl and said substituted aliphatic group is a C_1-C_6 alkyl substituted with a -OH, -$(O)_u$-$(CH_2)_t$-C(O)OR_{20} or -O-(aliphatic group);

t is 0 to 3;

u is 0 or 1; and

R^{20} is C_1-C_6 alkyl.

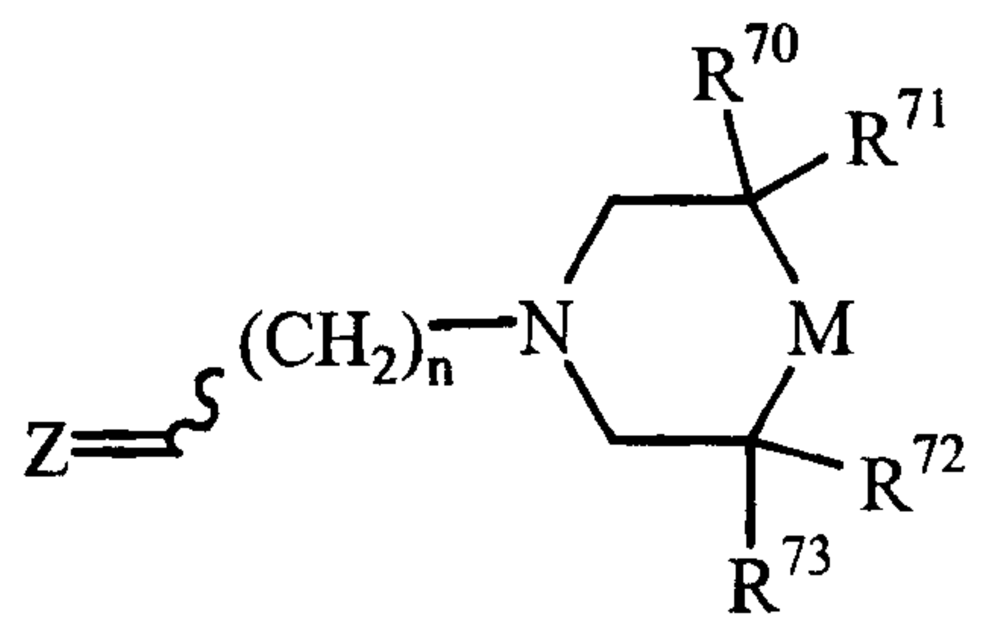
7. The compound of claim 6 wherein

R^{70} and R^{71} are both -H; and

R^{72} and R^{73} are independently C_1-C_6 alkyl or substititued C_1-C_6 alkyl.

8. The compound of claim 7 wherein R^{72} is -CH_3.

9. A compound having the formula:



or physiologically acceptable salt thereof, wherein:

n is 1 to 4;

M is >CR^1R^2;

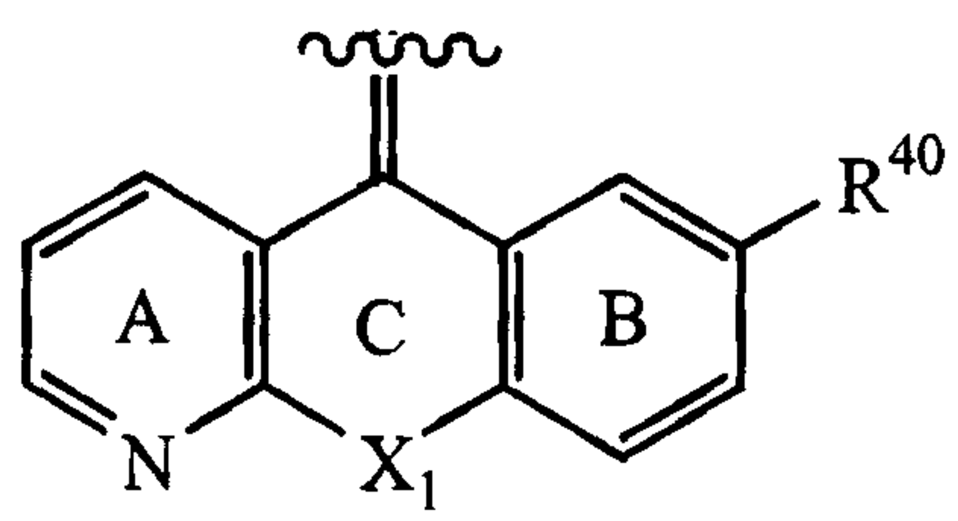
R^1 is -OH;

R^2 is 4-halophenyl;

R^{70} and R^{71} are -H, and R^{72} and R^{73} are -CH_3; or

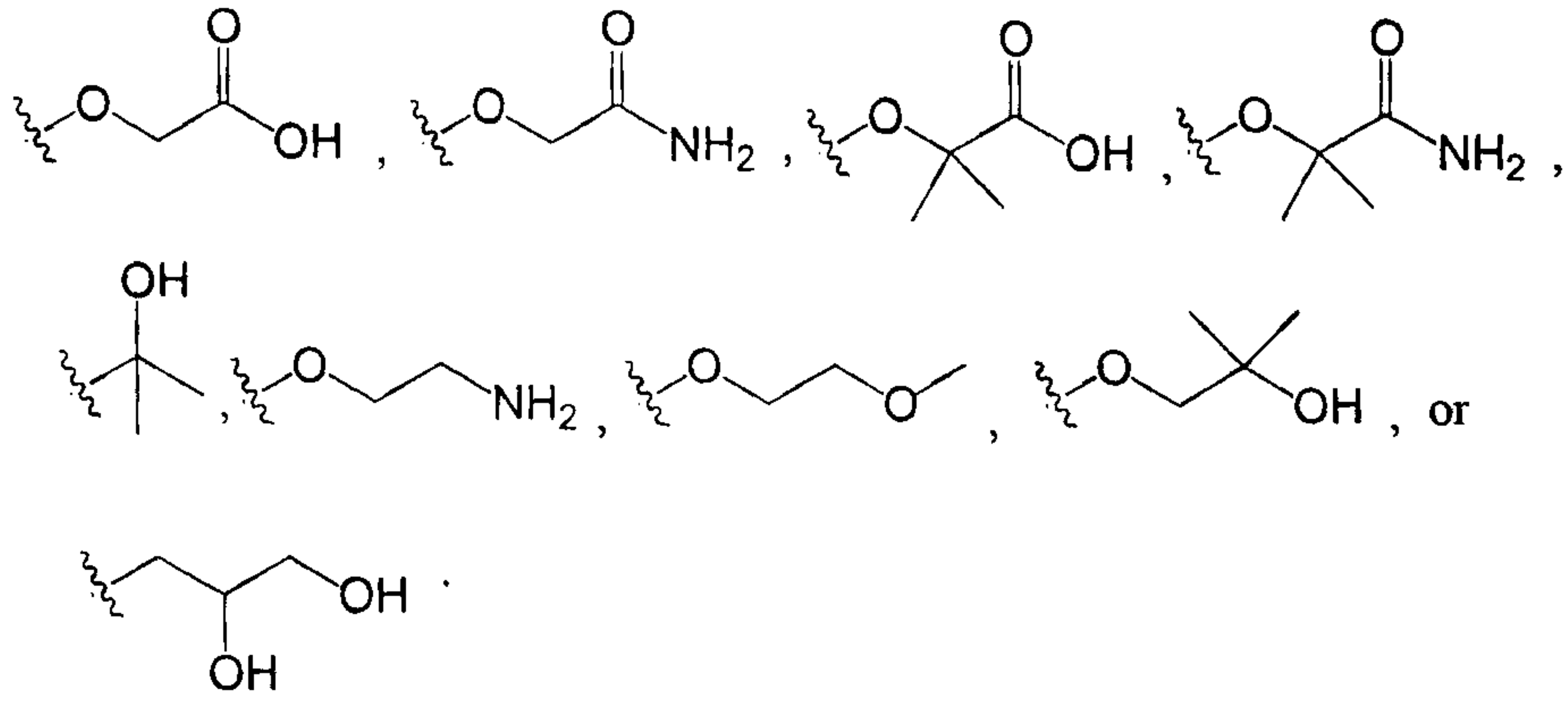
R^{70} and R^{71} are -CH_3, and R^{72} and R^{73} are -H;

Z is:



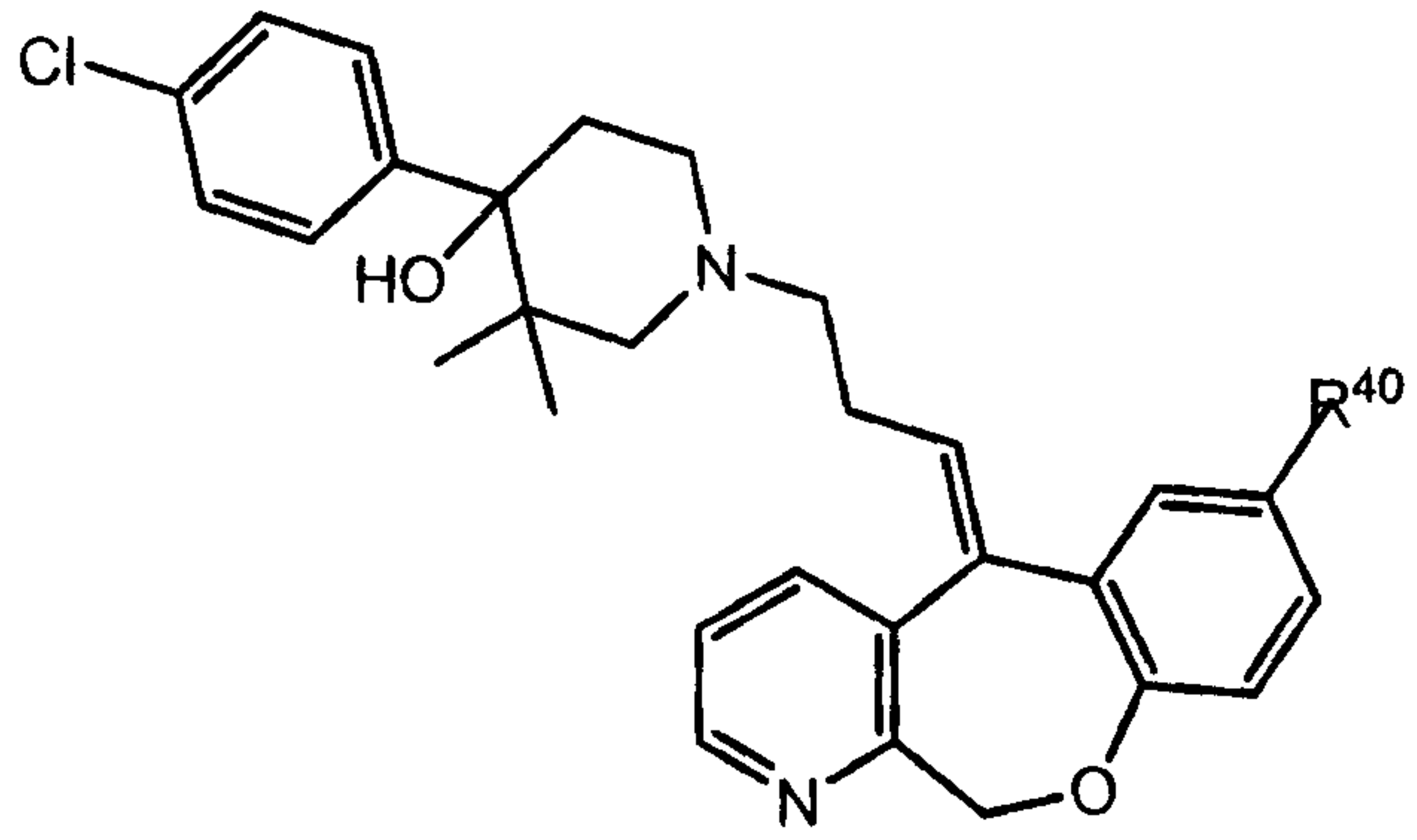
X_1 is -CH_2-O-; and

R^{40} is:

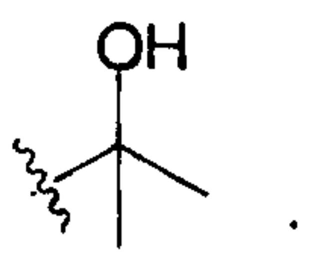


10. The compound of claim 9 wherein said 4-halophenyl is 4-chlorophenyl, 4-bromophenyl or 4-fluorophenyl.

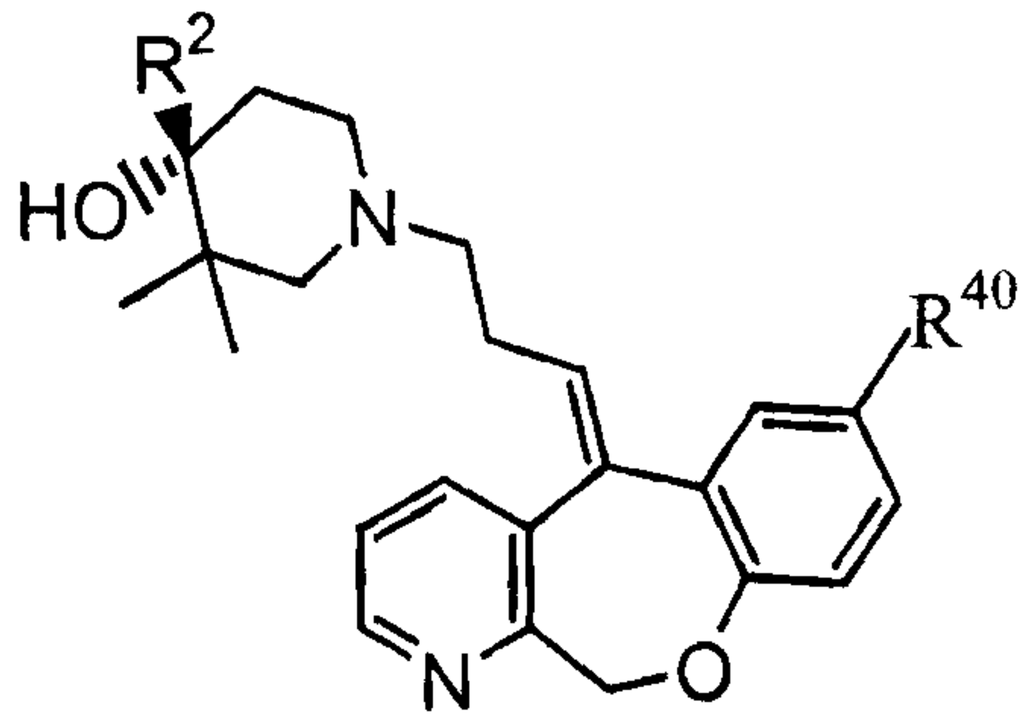
11. The compound of claim10 wherein R^{70} and R^{71} are -H, R^{72} and R^{73} are $-CH_3$, n is 2, and the compound has the structure:



12. The compound of claim 11 wherein R^{40} is:



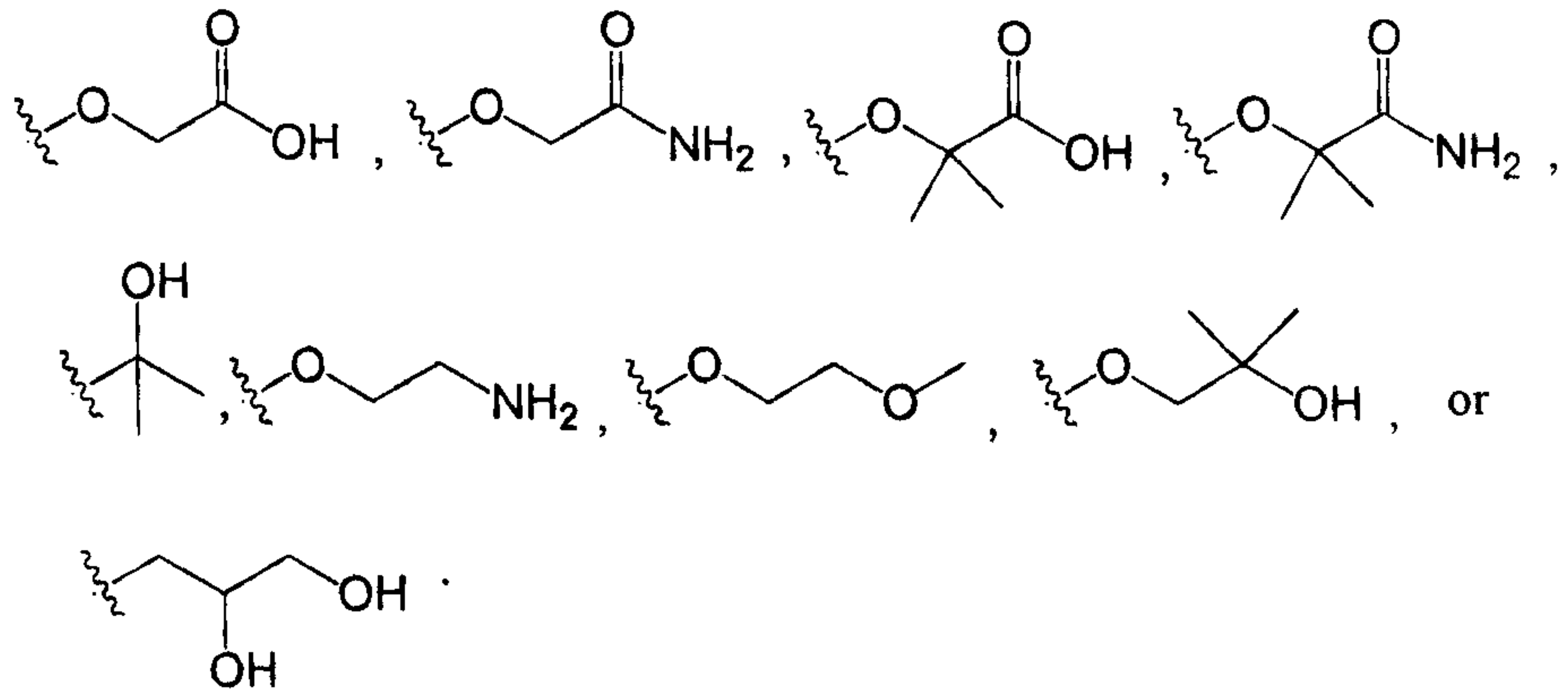
13. A compound having the structure:



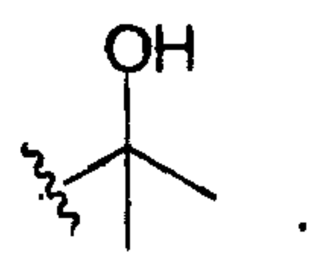
or a physiologically acceptable salt thereof, wherein

R^2 is 4-halophenyl; and

R^{40} is:



14. The compound of claim 13 wherein R^{40} is:



15. The compound of claim 13 wherein R^2 is 4-chlorophenyl, 4-bromophenyl or 4-fluorophenyl.

16. The compound of claim 15 wherein R^2 is 4-chlorophenyl.

17. A pharmaceutical composition comprising a compound according to any one of claims 1 to 16 and a physiologically acceptable carrier.

18. Use of a compound according to any one of claims 1 to 16 for the manufacture of a medicament for treating a disease associated with aberrant leukocyte recruitment, aberrant leukocyte activation or aberrant leukocyte recruitment and activation.

19. Use of claim 18, wherein said disease is arthritis, atherosclerosis, arteriosclerosis, restenosis, ischemia/reperfusion injury, diabetes mellitus, psoriasis, multiple sclerosis, inflammatory bowel diseases, rejection of a transplanted organ or tissue, graft versus host disease, allergy or asthma.

20. Use of a compound according to any one of claims 1 to 16 for the manufacture of a medicament for treating a chronic inflammatory disease.

21. Use of a compound according to any one of claims 1 to 16 for the manufacture of a medicament for treating multiple sclerosis.

22. Use of a compound according to any one of claims 1 to 16 for the manufacture of a medicament for treating arthritis.

23. Use of claim 22, wherein said arthritis is rheumatoid arthritis.

24. Use of a compound according to any one of claims 1 to 16 for treating a disease associated with aberrant leukocyte recruitment, aberrant leukocyte activation or aberrant leukocyte recruitment and activation.

25. Use of claim 24, wherein said disease is arthritis, atherosclerosis, arteriosclerosis, restenosis, ischemia/reperfusion injury, diabetes mellitus, psoriasis, multiple sclerosis, inflammatory bowel diseases, rejection of a transplanted organ or tissue, graft versus host disease, allergy or asthma.

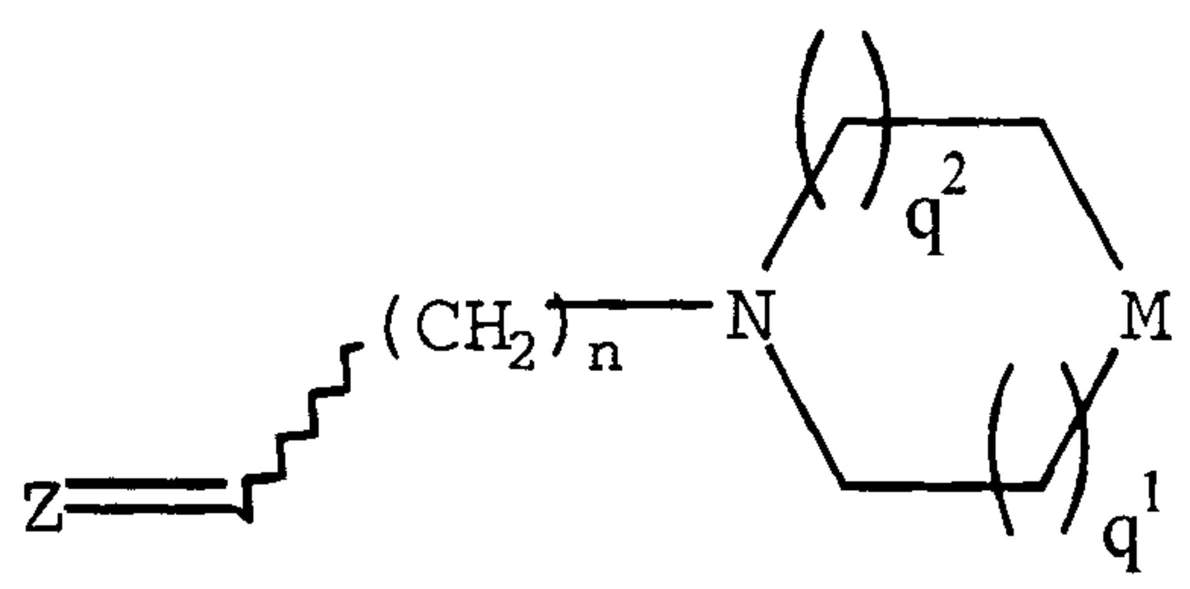
26. Use of a compound according to any one of claims 1 to 16 for treating a chronic inflammatory disease.

27. Use of a compound according to any one of claims 1 to 16 for treating multiple sclerosis.

28. Use of a compound according to any one of claims 1 to 16 for treating arthritis.

29. Use of claim 28, wherein said arthritis is rheumatoid arthritis.

30. A compound having the formula:



or physiologically acceptable salt thereof, wherein:

n is an integer from 1 to 4;

M is $>CR^1R^2$;

q^1 is 0;

q^2 is 1;

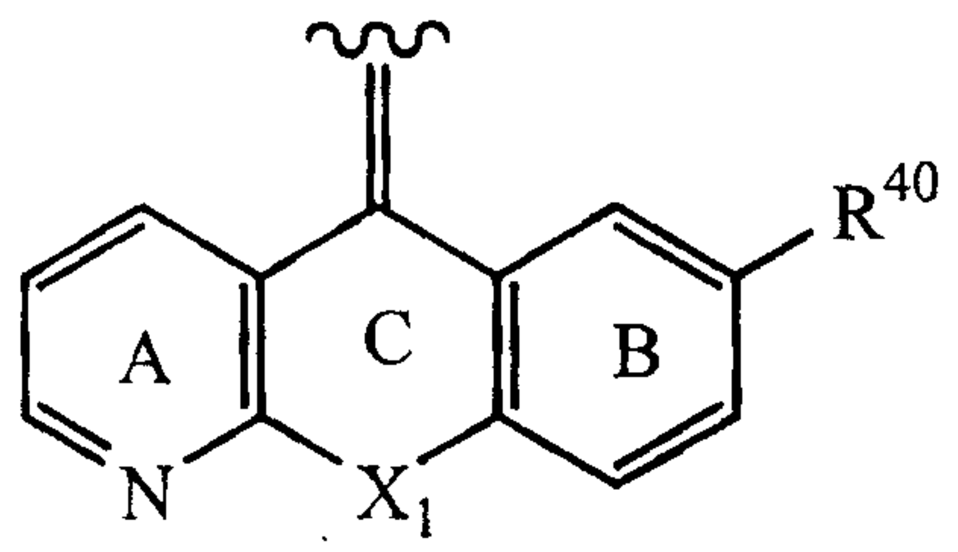
R^1 is -H, -OH, $-N_3$, a halogen, an aliphatic group, a substituted aliphatic group, an aminoalkyl group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -COOH, -CN, $-CO-NR^3R^4$, $-NR^3R^4$ or R^1 is a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M;

R^2 is -OH, a halogen, 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, a substituted non-aromatic heterocyclic group, -O-(substituted or unsubstituted aromatic group) or -O-(substituted or unsubstituted aliphatic 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;

Z is:



;

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-, $-NR_c-CO-$, a bond, -O-, 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;

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

said aliphatic group is a C_1-C_6 alkyl, alkenyl or alkynyl;

said aromatic group is phenyl, 1-naphthyl, 2-naphthyl, 1-anthracyl, 2-anthracyl, *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, 5-oxazolyl, tetrahydronaphthyl, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 3-indolyl, 2-quinolinyl, 3-quinolinyl, 2-benzothiazolyl, 2-benzooxazolyl, 2-benzimidazolyl, 1-isoquinolinyl, 3-quinolinyl, 1-isoindolyl, 3-isoindolyl, acridinyl, 3-benzisoxazolyl, benzocyclopentyl, or benzocyclohexyl;

said non-aromatic heterocyclic group is a five to eight-membered non-aromatic ring which contains one or more heteroatoms which are independently nitrogen, oxygen or sulfur;

said substituted aliphatic group is substituted with one or more substituents which are oxo group, epoxy group, non-aromatic heterocyclic ring, benzyl group, substituted benzyl group, aromatic group or substituted aromatic group, electron withdrawing group, halo, azido, -CN, -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, guanidino, oxalo, -C(=NR^{60})NR^{21}R^{22}, =NR^{60}, -(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) or -Q-(CH$_2$)$_p$-(non-aromatic heterocyclic group);

said substituted non-aromatic heterocyclic ring is substituted with one or more substituents which are =O, =S, electron withdrawing group, halo, azido, -CN, -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, guanidino, oxalo, -C(=NR^{60})NR^{21}R^{22}, =NR^{60}, -(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) or -Q-(CH$_2$)$_p$-(non-aromatic heterocyclic group);

said substituted aromatic group and substituted benzyl group are substituted with one or more substituents which are electron withdrawing group, halo, azido, -CN, -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, guanidino, oxalo, -C(=NR^{60})NR^{21}R^{22}, =NR^{60}, -(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) or -Q-(CH$_2$)$_p$-(non-aromatic heterocyclic group);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)-, -NHC(O)-, -OC(O)NH-, -NH-C(O)-NH-, -S(O)$_2$NH-, -NHS(O)$_2$-, -C(NR^{23})NHNH-, -NHNHC(NR^{23})-, -NR^{24}C(O)- or -NR^{24}S(O)$_2$-;

R^{20}, R^{21} and R^{22} are independently -H, an aliphatic group, an 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, can form a substituted or unsubstituted non-aromatic heterocyclic ring;

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, non-aromatic heterocyclic group; or R^{24} and R^{25} taken together with the nitrogen atom to which they are bonded can form a substituted or unsubstituted non-aromatic heterocyclic ring;

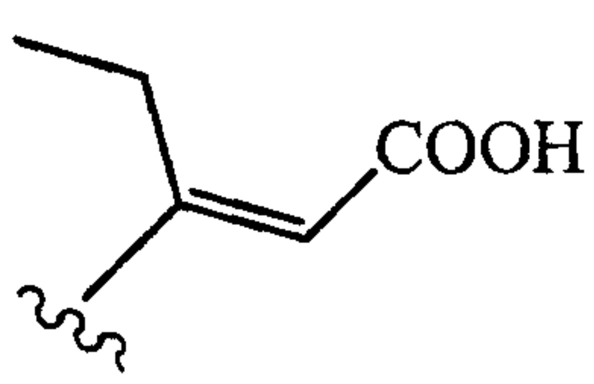
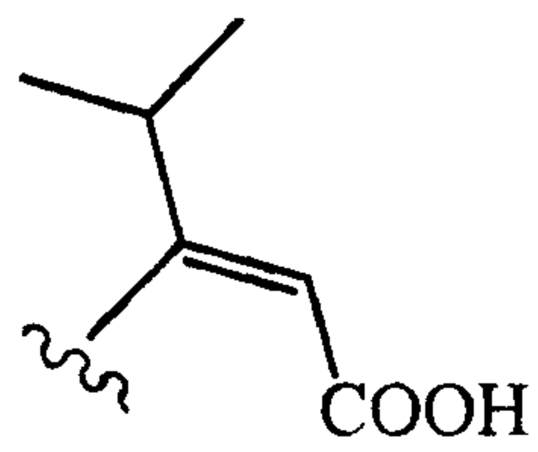
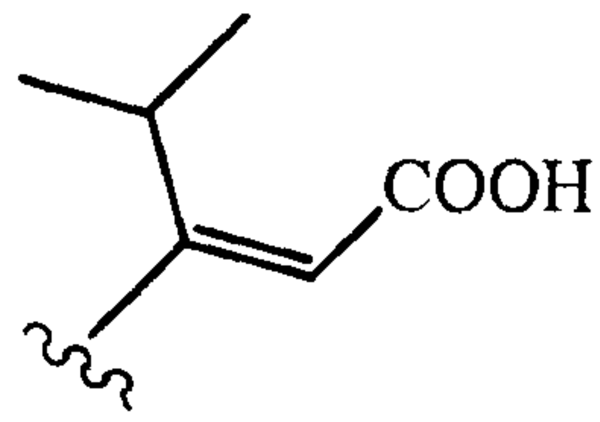
R^{60} is a -H, -OH, $-NH_2$, an aromatic group or a substituted aromatic group;

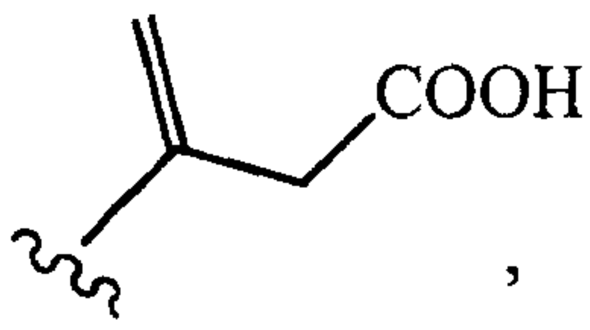
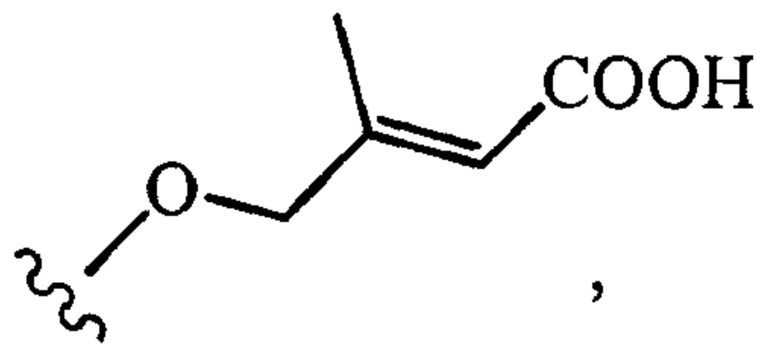
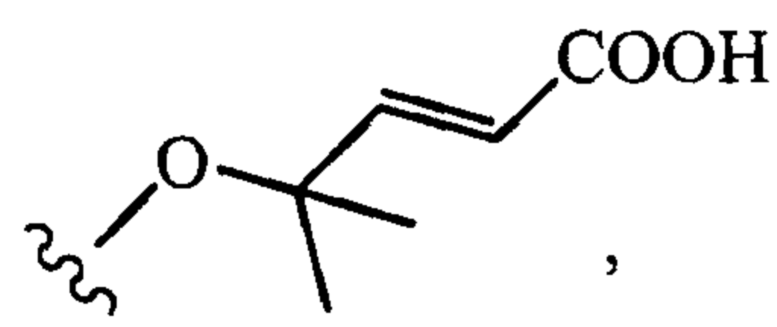
t is 0 to 3;

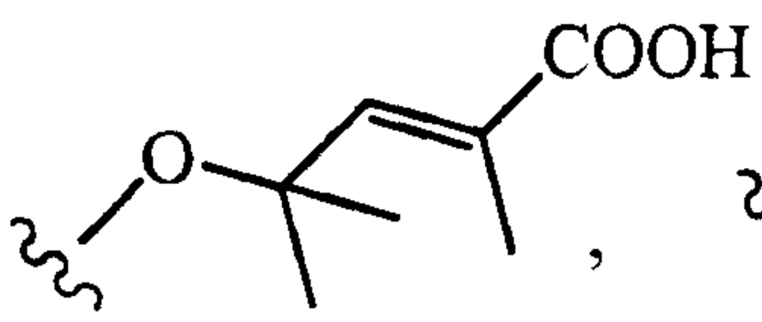
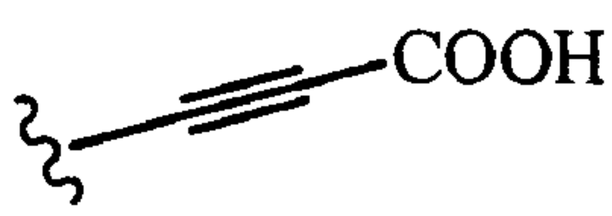
u is 0 or 1;

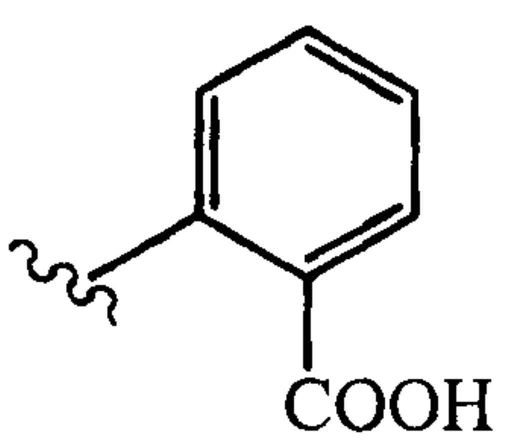
p is 1 to 5; and

R^{40} is:

 ,  , 

 ,  ,  ,

 ,  ,  or

 .

31. The compound of claim 30 wherein:

R^1 is -H or -OH; and

R^2 is a substituted aromatic group.

32. The compound of claim 31 wherein R^2 is phenyl substituted with a halogen.

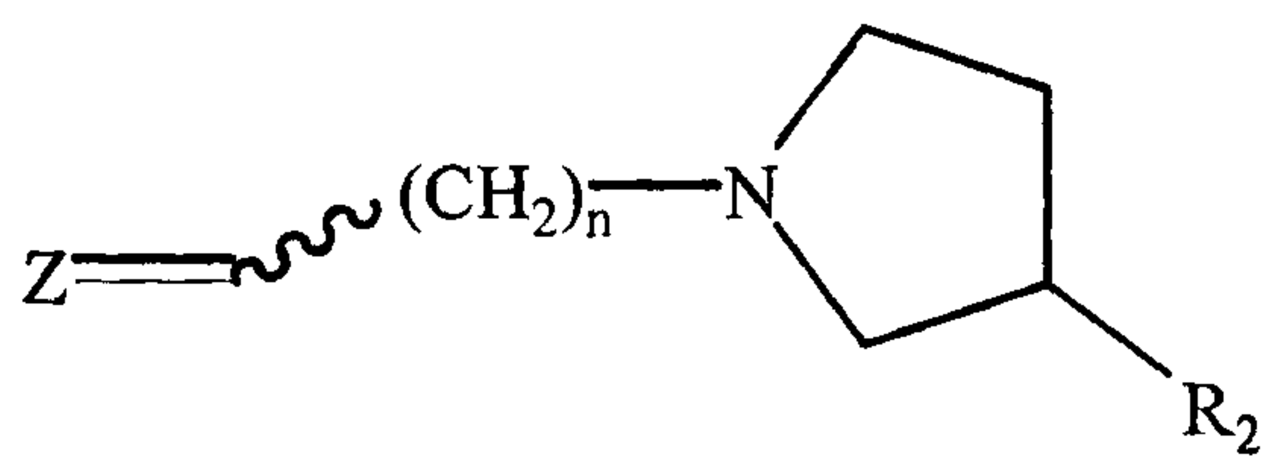
33. The compound of claim 32 wherein R^2 is 4-chlorophenyl.

34. The compound of claim 33 wherein n is 2, X_1 is $-CH_2-O-$, and R^1 is -OH.

35. Use of a compound of any one of claims 30 to 34 for the manufacture of a medicament for treating a disease associated with aberrant leukocyte recruitment, aberrant leukocyte activation, or aberrant leukocyte recruitment and activation.

36. A pharmaceutical composition comprising a compound of any one of claims 30 to 34 and a physiologically acceptable carrier.

37. A compound having the formula:



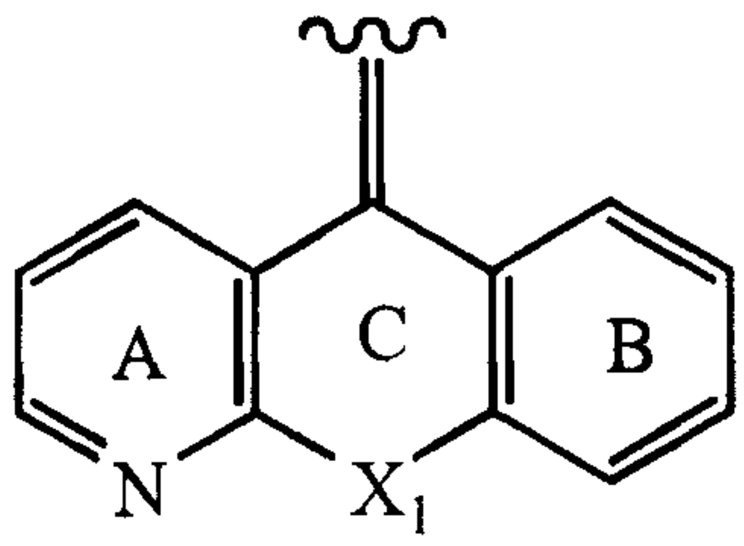
or physiologically acceptable salt thereof, wherein:

n is 1 to 4;

R^2 is -OH, a halogen, 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, a substituted non-aromatic heterocyclic group, -O-(substituted or unsubstituted aromatic group) or -O-(substituted or unsubstituted aliphatic group);

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^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;

Z is:



;

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-, $-NR_c-CO-$, a bond, -O-, 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;

Rings A and B are independently unsubstited or substituted;

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

said aliphatic group is a C_1-C_6 alkyl, alkenyl or alkynyl;

said aromatic group is phenyl, 1-naphthyl, 2-naphthyl, 1-anthracyl, 2-anthracyl, *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, 5-oxazolyl, tetrahydronaphthyl, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 3-indolyl, 2-quinolinyl, 3-quinolinyl, 2-benzothiazolyl, 2-benzooxazolyl, 2-benzimidazolyl, 1-isoquinolinyl, 3-quinolinyl, 1-isoindolyl, 3-isoindolyl, acridinyl, 3-benzisoxazolyl, benzocyclopentyl, or benzocyclohexyl;

said non-aromatic heterocyclic group is a five to eight-membered non-aromatic ring which contains one or more heteroatoms which are independently nitrogen, oxygen or sulfur;

said substituted aliphatic group is substituted with one or more substituents which are oxo group, epoxy group, non-aromatic heterocyclic ring, benzyl group, substituted benzyl group, aromatic group or substituted aromatic group electron withdrawing group, halo, azido, -CN, $-CONR^{24}R^{25}$, $-NR^{24}R^{25}$, $-OS(O)_2NR^{24}R^{25}$, $-S(O)_2NR^{24}R^{25}$, $-SO_3H$, guanidino, oxalo, $-C(=NR^{60})NR^{21}R^{22}$, $=NR^{60}$, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$, -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) or -Q-$(CH_2)_p$-(non-aromatic heterocyclic group);

said substituted non-aromatic heterocyclic ring is substituted with one or more substituents which are =O, =S, electron withdrawing group, halo, azido, -CN, -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, guanidino, oxalo, -C(=NR^{60})NR^{21}R^{22}, =NR^{60}, -(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) or -Q-$(CH_2)_p$-(non-aromatic heterocyclic group);

said substituted aromatic group, substituted benzyl group, Ring A when substituted and Ring B when substituted, are substituted with one or more substituents which are electron withdrawing group, halo, azido, -CN, -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, guanidino, oxalo, -C(=NR^{60})NR^{21}R^{22}, =NR^{60}, -(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) or -Q-$(CH_2)_p$-(non-aromatic heterocyclic group);

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)-, -NHC(O)-, -OC(O)NH-, -NH-C(O)-NH-, -S(O)$_2$NH-, -NHS(O)$_2$-, -C(NR^{23})NHNH-, -NHNHC(NR^{23})-, -NR^{24}C(O)- or -NR^{24}S(O)$_2$-;

R^{20}, R^{21} and R^{22} are independently -H, an aliphatic group, an 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, can form a substituted or unsubstituted non-aromatic heterocyclic ring;

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, non-aromatic heterocyclic group; or R^{24} and R^{25}

taken together with the nitrogen atom to which they are bonded can form a substituted or unsubstituted non-aromatic heterocyclic ring;

R^{60} is a -H, -OH, $-NH_2$, an aromatic group or a substituted aromatic group;

t is 0 to 3;

u is 0 or 1;

p is 1 to 5.

38. The compound according to claim 37 wherein R^2 is $-NR^5R^6$.

39. The compound of claim 38 wherein:

R^5 is aliphatic group or substituted aliphatic group; and

R^6 is benzyl or substituted benzyl; or

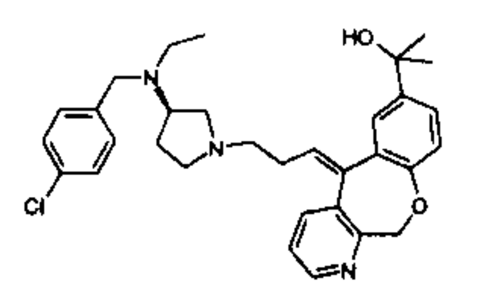
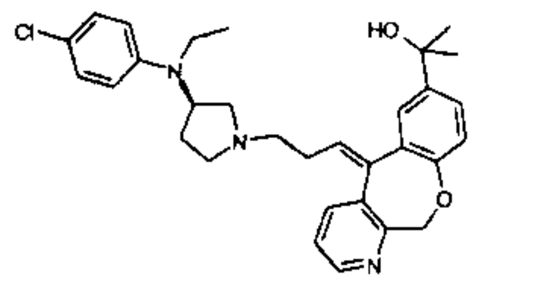
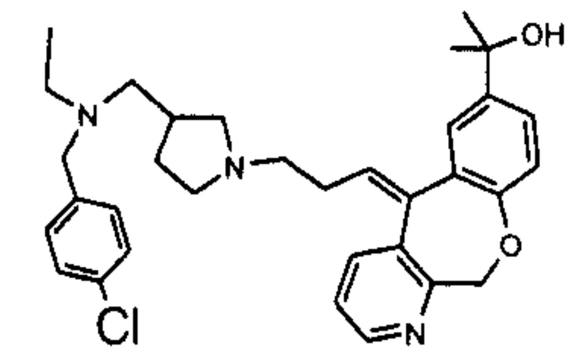
R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

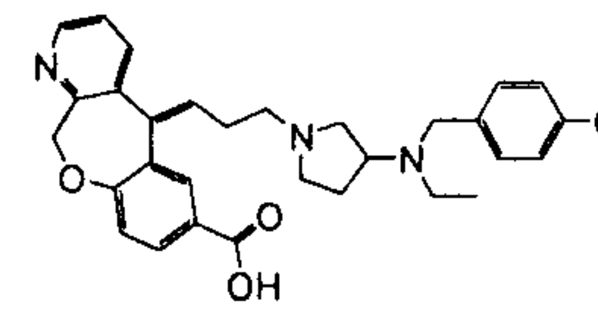
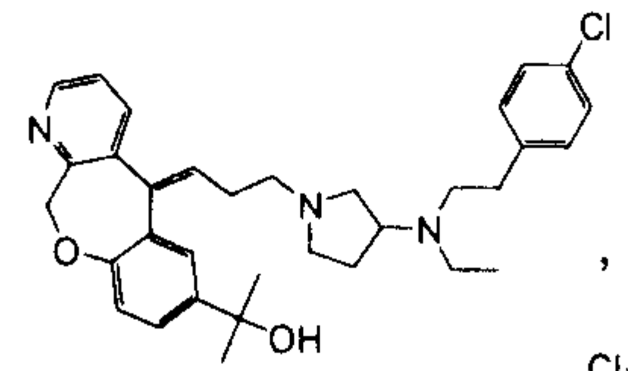
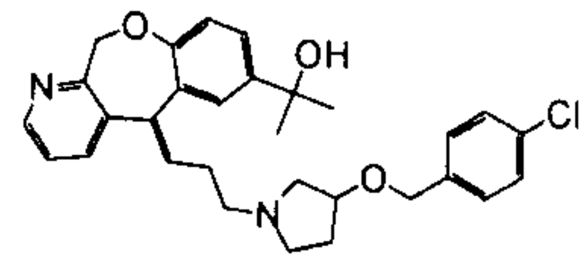
40. The compound of claim 39 wherein R^5 is ethyl, and R^6 is substituted benzyl, wherein said substituted benzyl is substituted with a halogen.

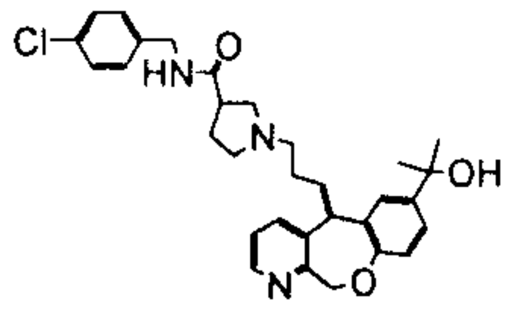
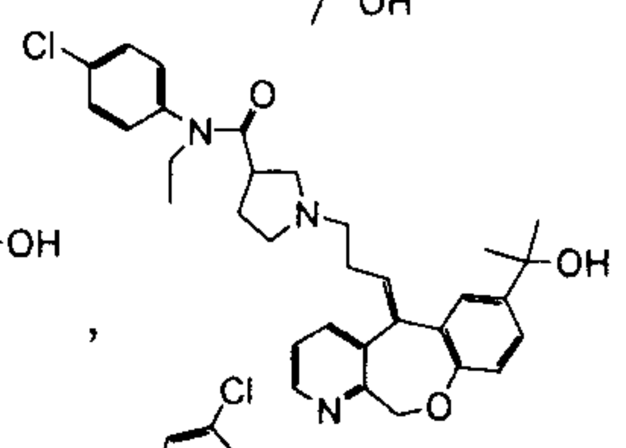
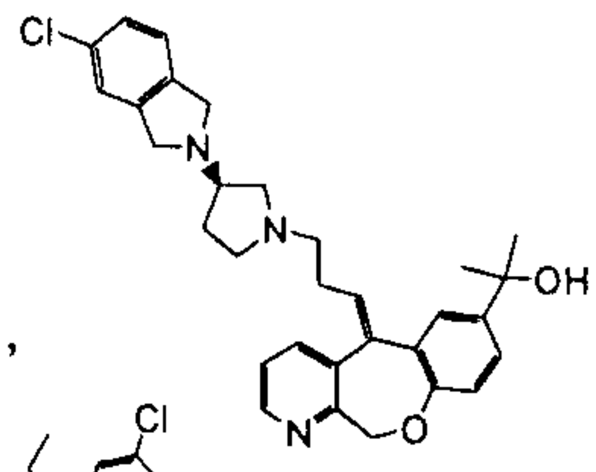
41. Use of a compound according to any one of claims 37 to 40 for the manufacture of a medicament for treating a disease associated with aberrant leukocyte recruitment, aberrant leukocyte activation or aberrant leukocyte recruitment and activation.

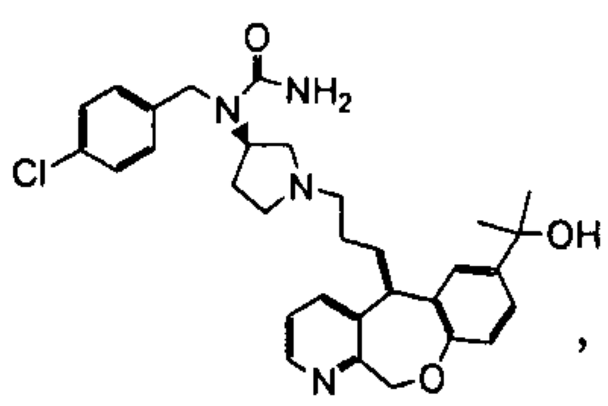
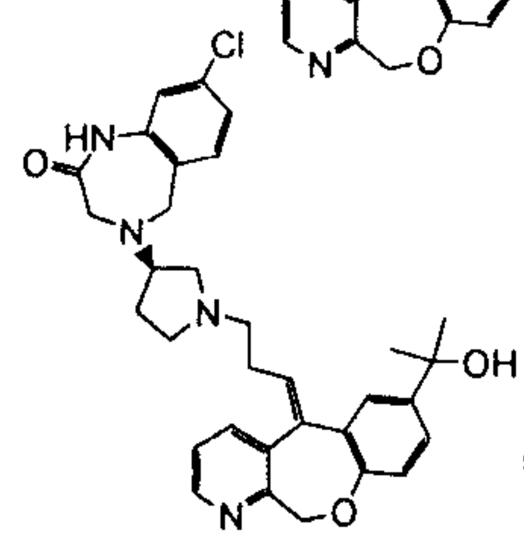
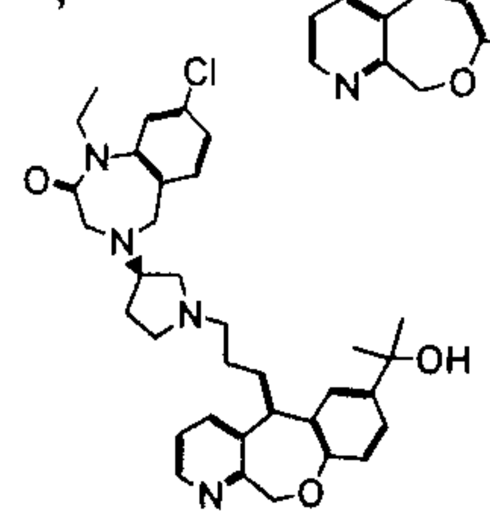
42. A pharmaceutical composition comprising a compound according to any one of claims 37 to 40 and a physiologically acceptable carrier.

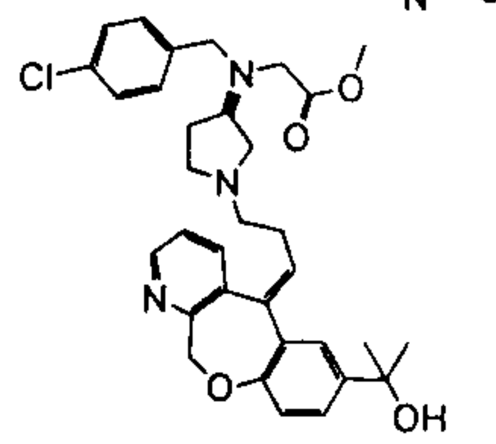
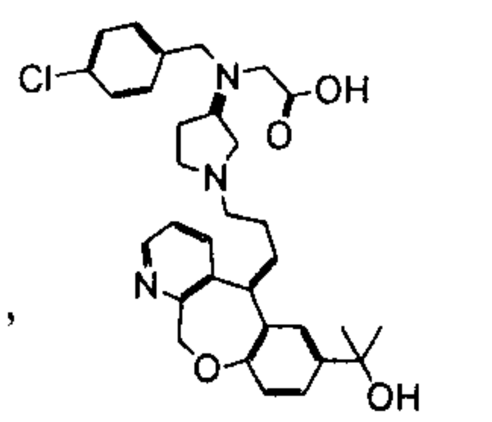
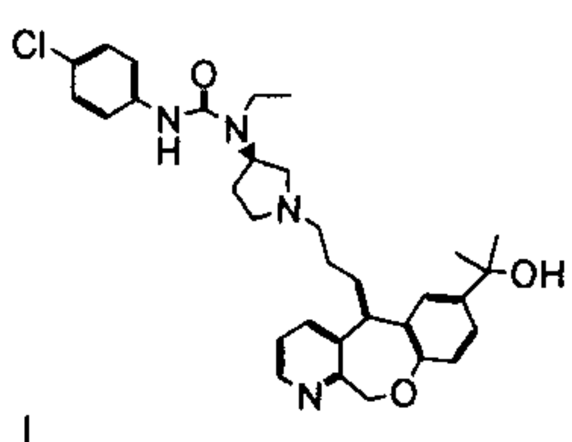
43. The compound of claim 37 wherein said compound is:

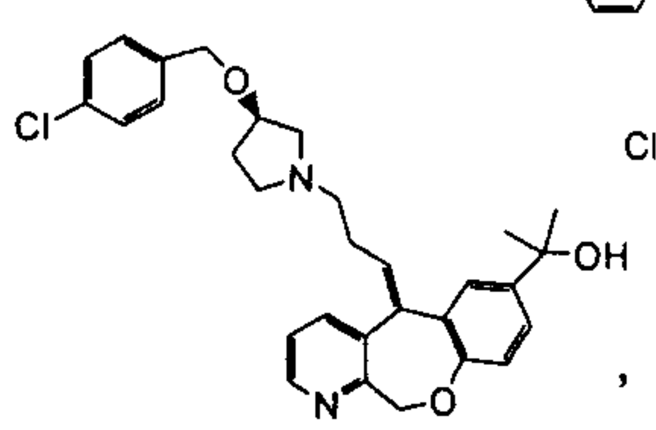
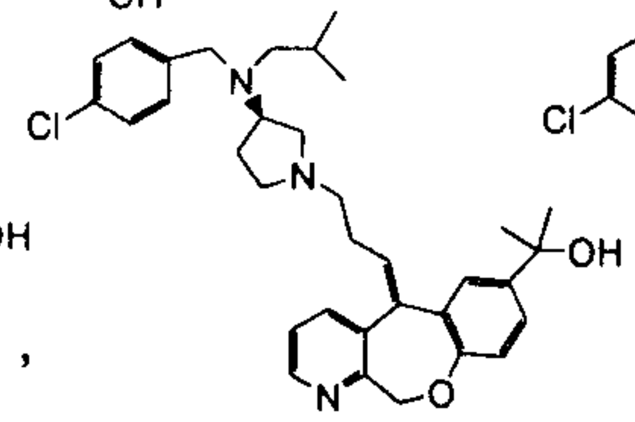
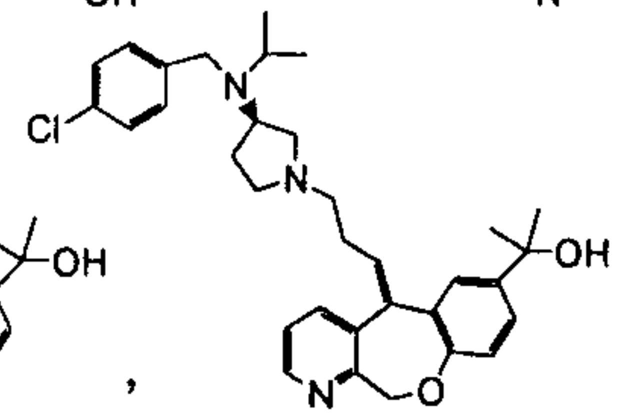
 ,  ,  ,

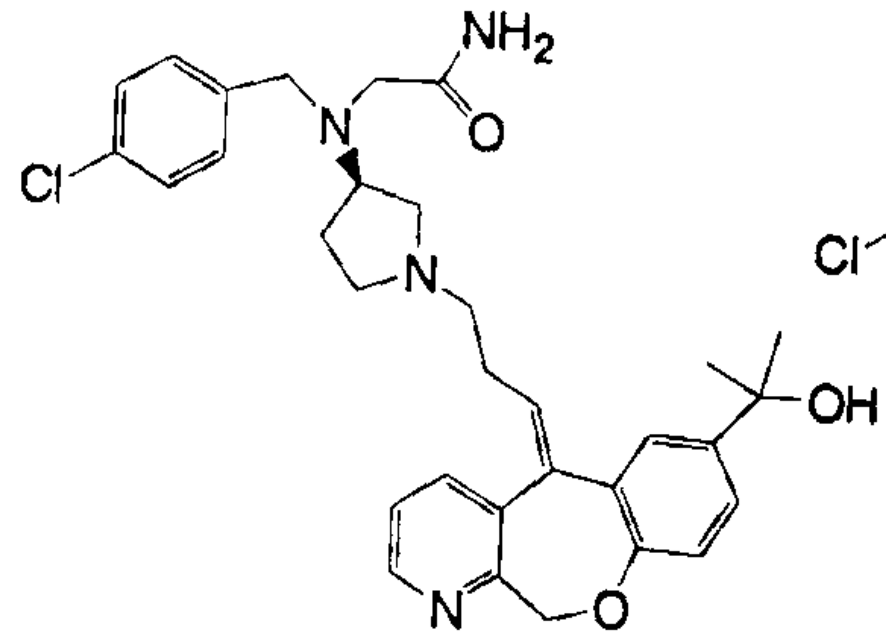
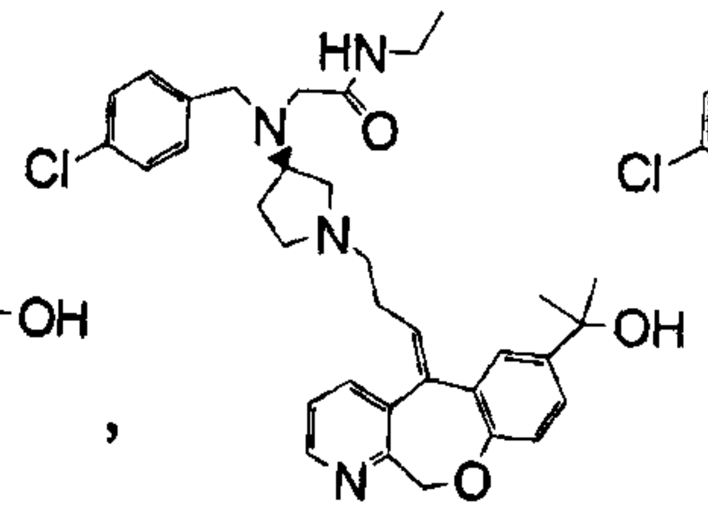
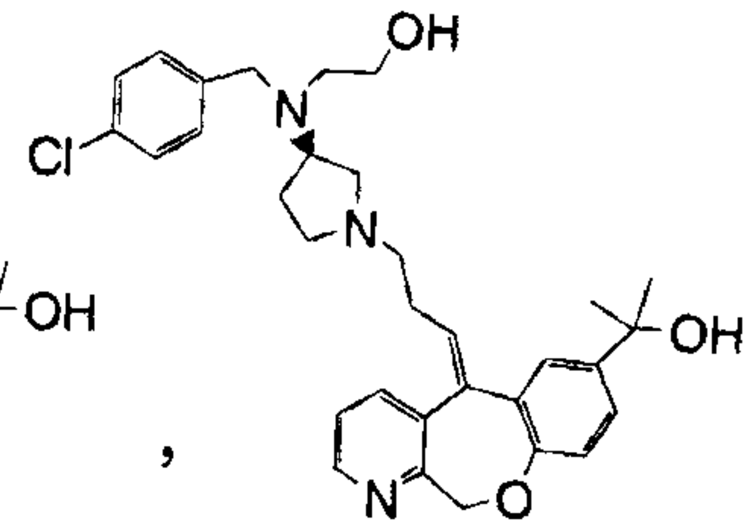
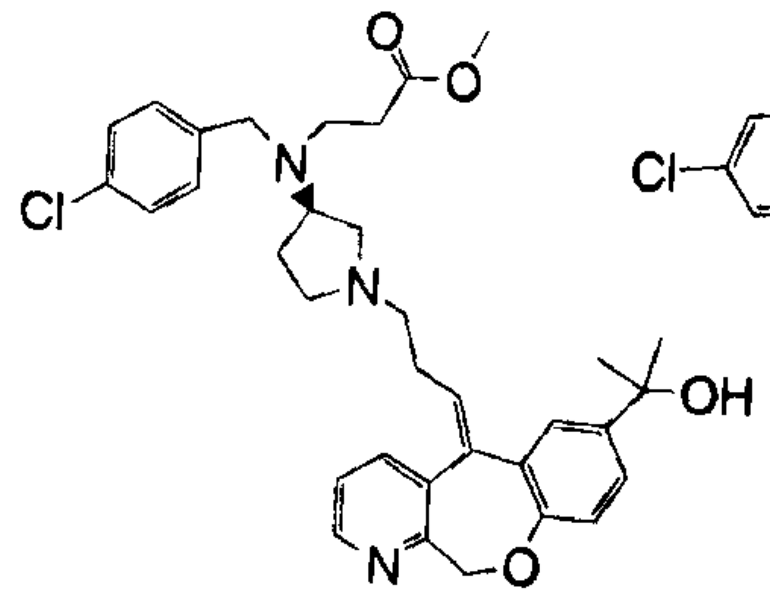
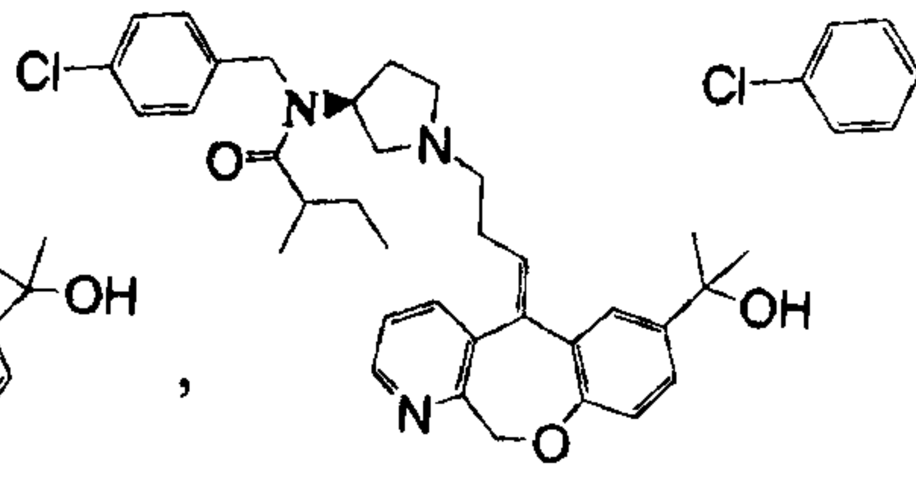
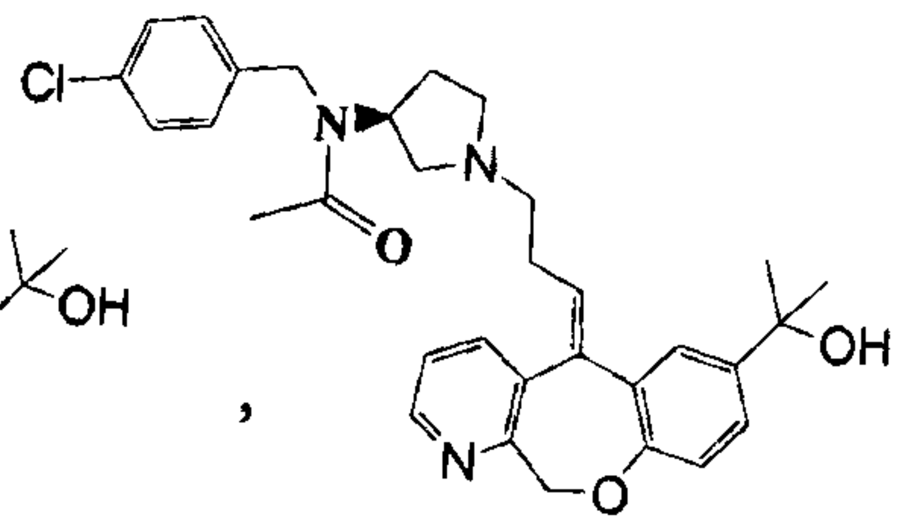
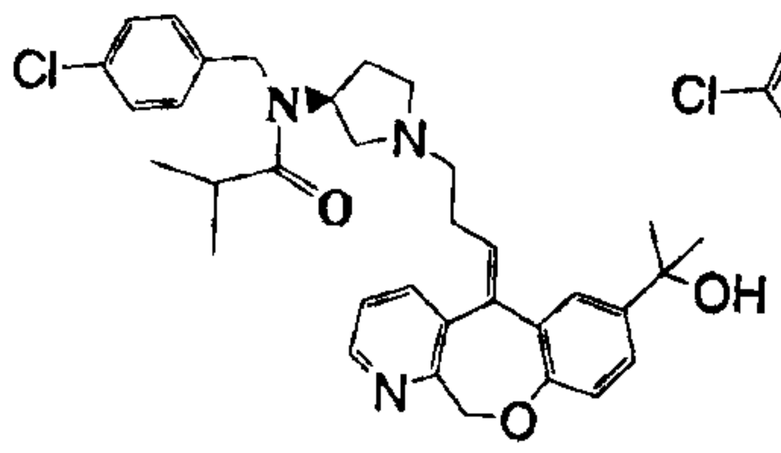
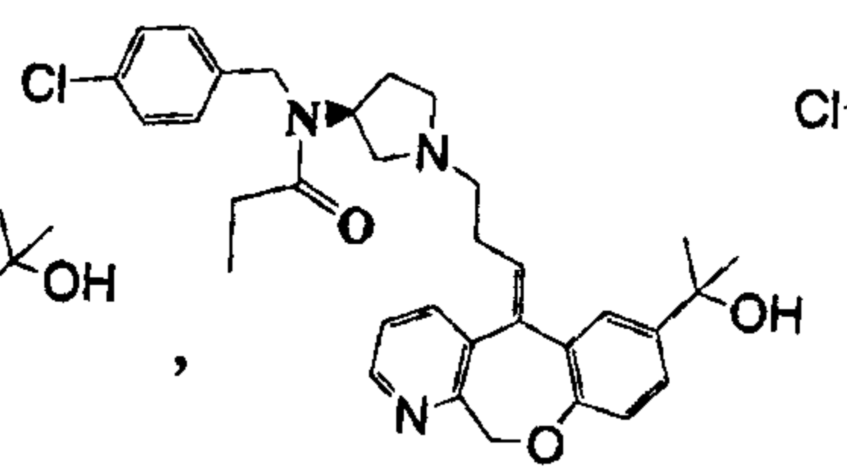
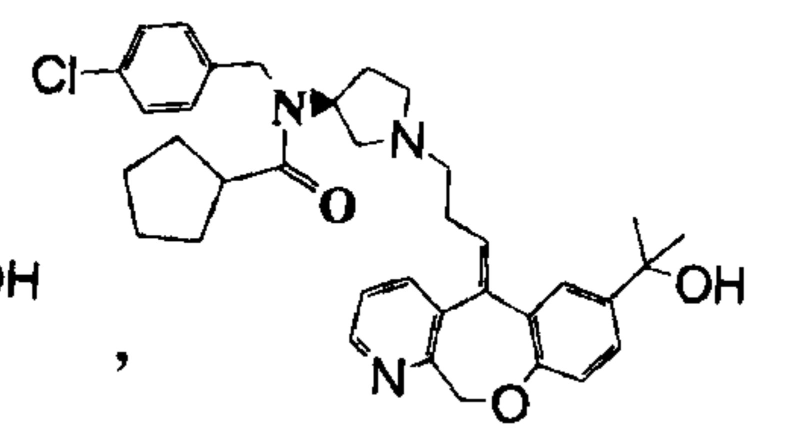
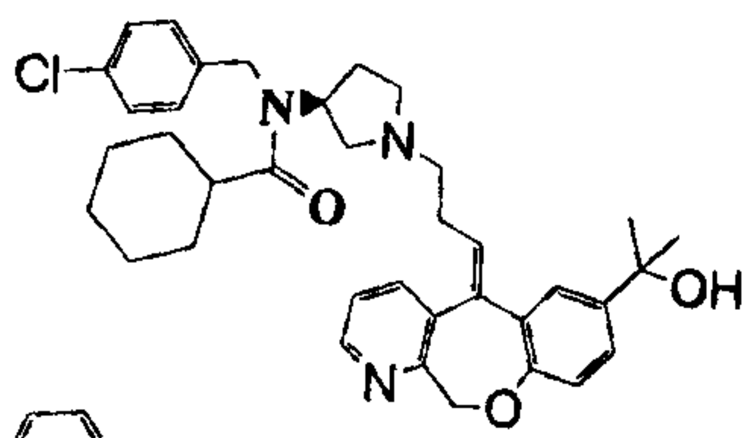
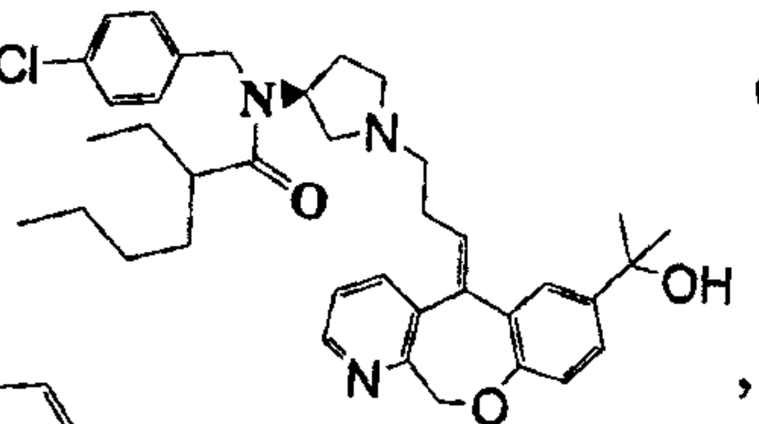
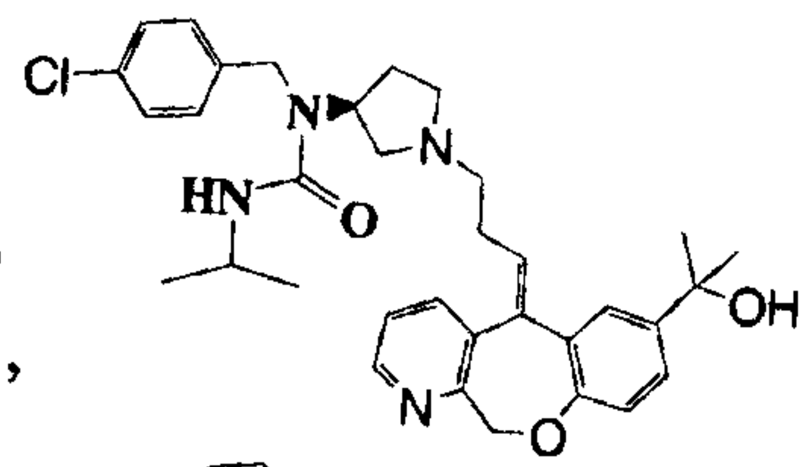
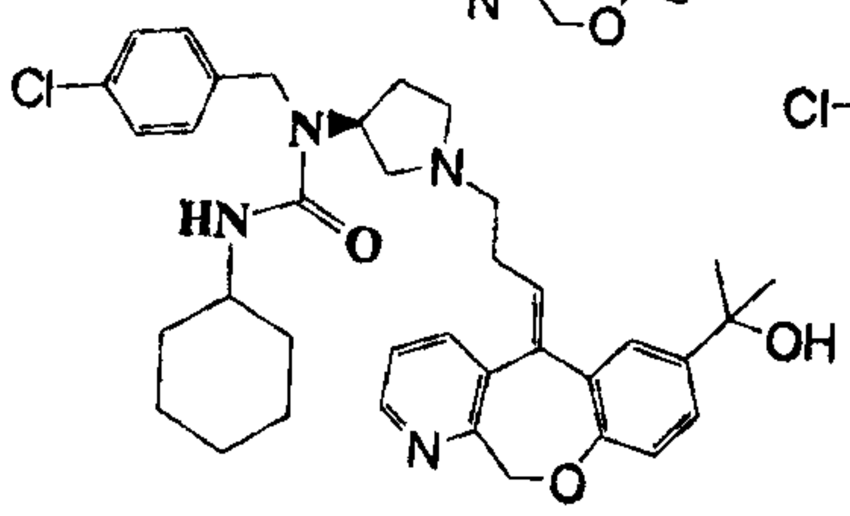
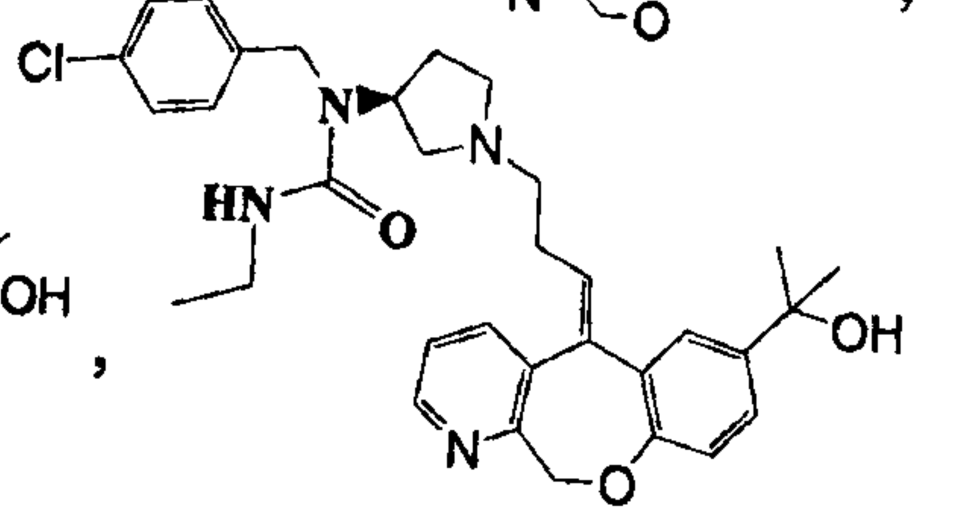
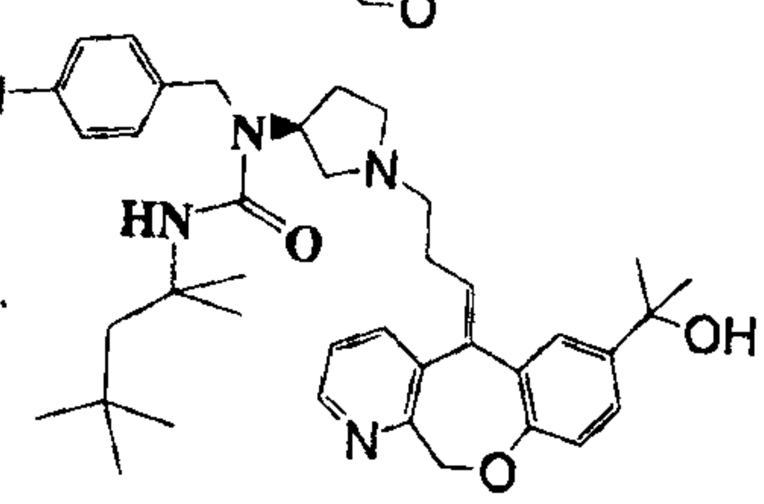
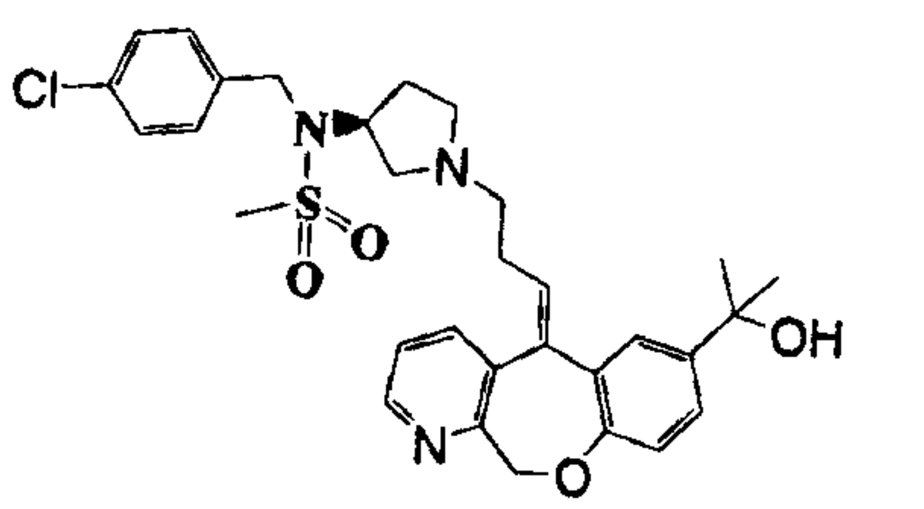
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

,
,
,
,
,
,
,
,
,
,
,
,
,
,
 ~~and~~ or
.

44. Use of a compound of claim 43 for the manufacture of a medicament for treating a disease associated with aberrant leukocyte recruitment, aberrant leukocyte activation, or aberrant leukocyte recruitment and activation.

45. A pharmaceutical composition comprising a compound of claim 43 and a physiologically acceptable carrier.

46. Use of any one of claims 35, 41 and 44, wherein said disease is arthritis, atherosclerosis, arteriosclerosis, restenosis, ischemia/reperfusion injury, diabetes mellitus, psoriasis, multiple sclerosis, inflammatory bowel diseases, rejection of a transplanted organ or tissue, graft versus host disease, allergy or asthma.

47. Use of a compound according to any one of claims 30 to 34, 37 to 40 and 43 for treating arthritis, atherosclerosis, arteriosclerosis, restenosis, ischemia/reperfusion injury, diabetes mellitus, psoriasis, multiple sclerosis, inflammatory bowel diseases, rejection of a transplanted organ or tissue, graft versus host disease, allergy or asthma.

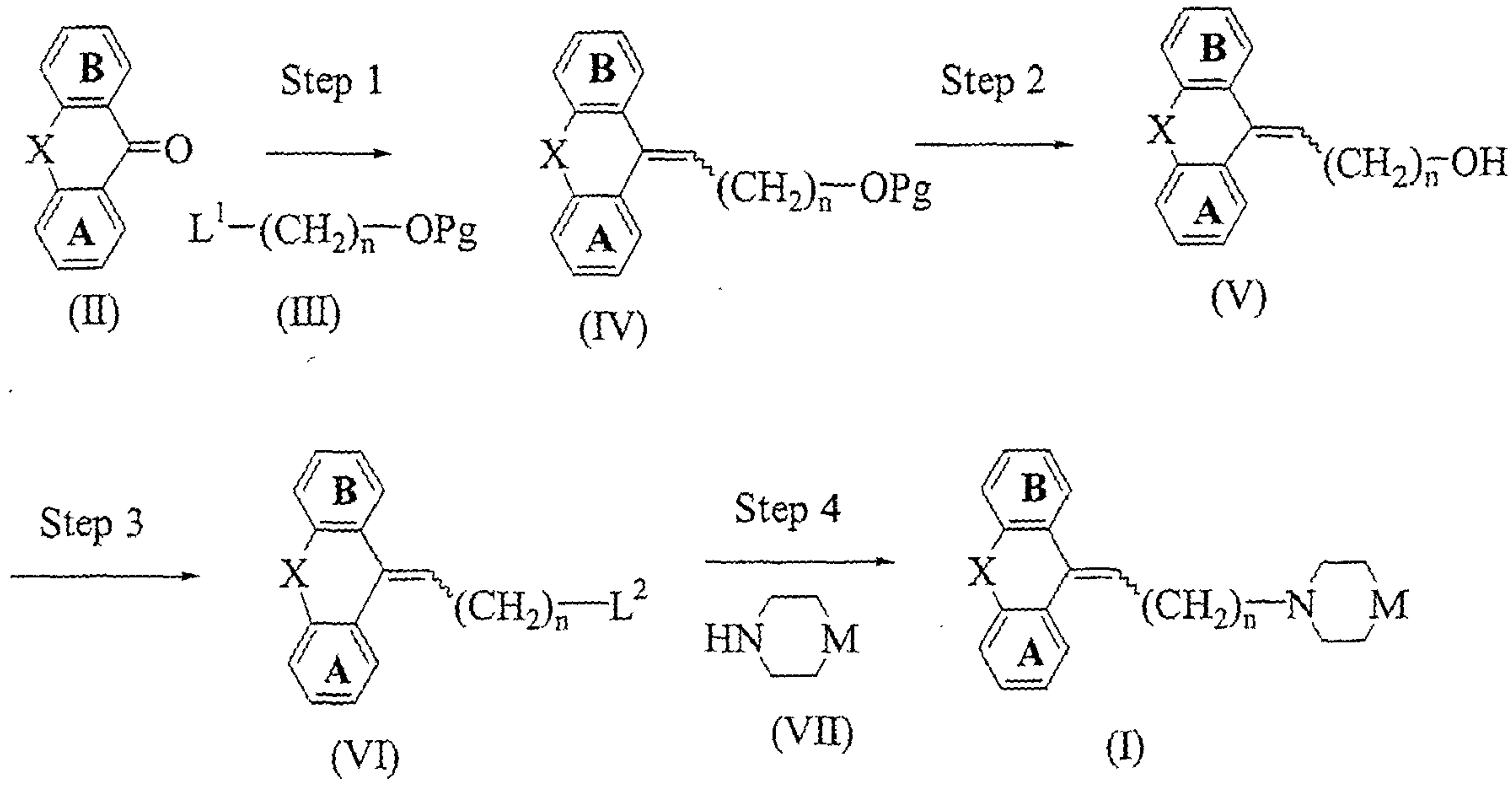

Step 1
Step 2
Step 3
Step 4
B
A
X
O
L1—(CH2)n—OPg
(CH2)n—OPg
(CH2)n—OH
(CH2)n—L2
HN M
(CH2)n—N M
(II)
(III)
(IV)
(V)
(VI)
(VII)
(I)

Figure 1

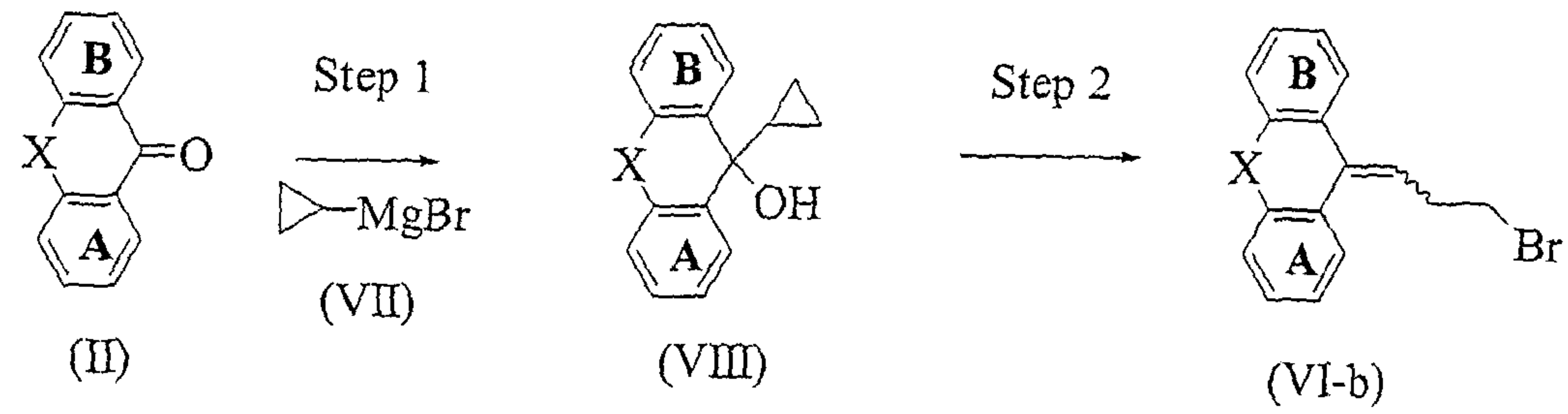


Figure 2

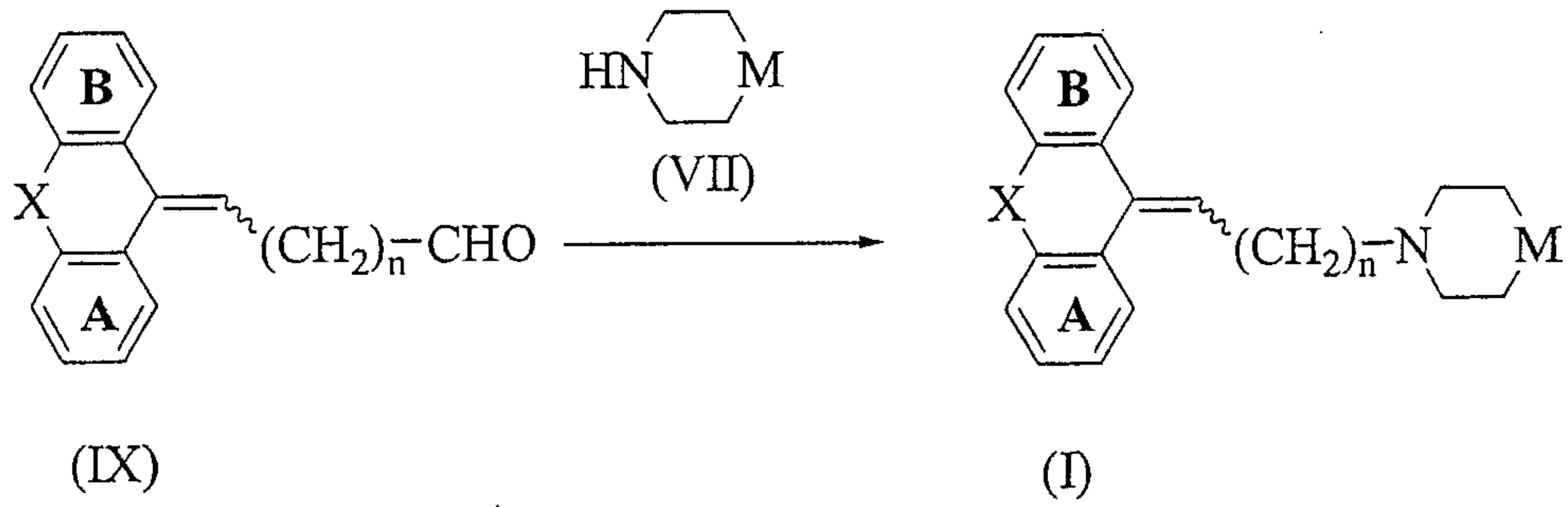
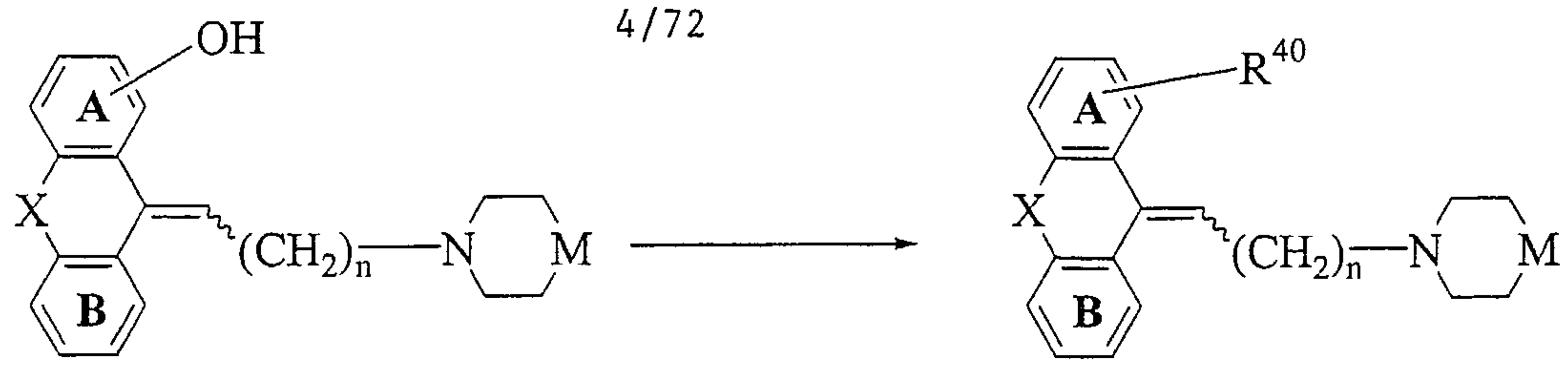
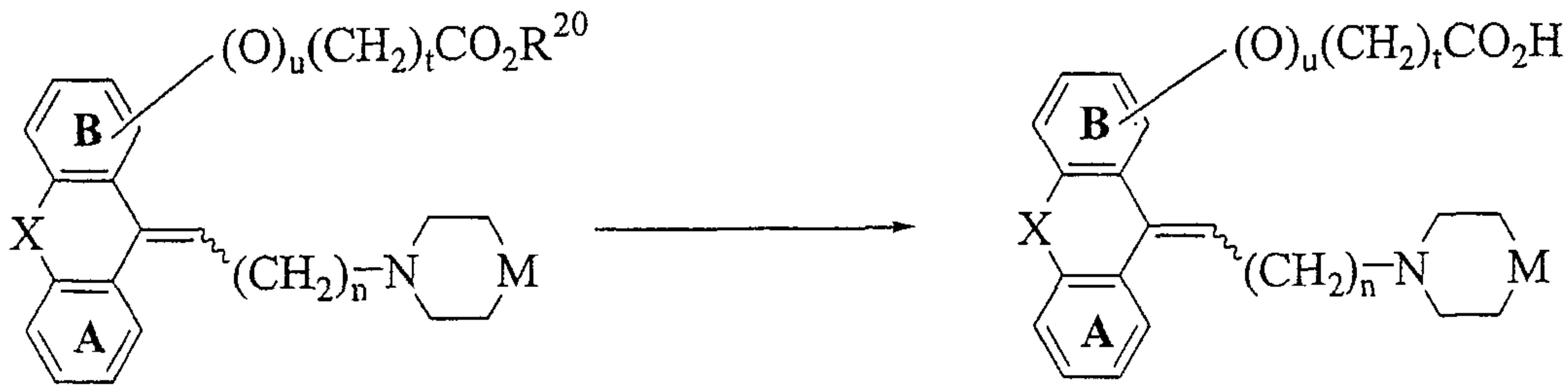


Figure 3

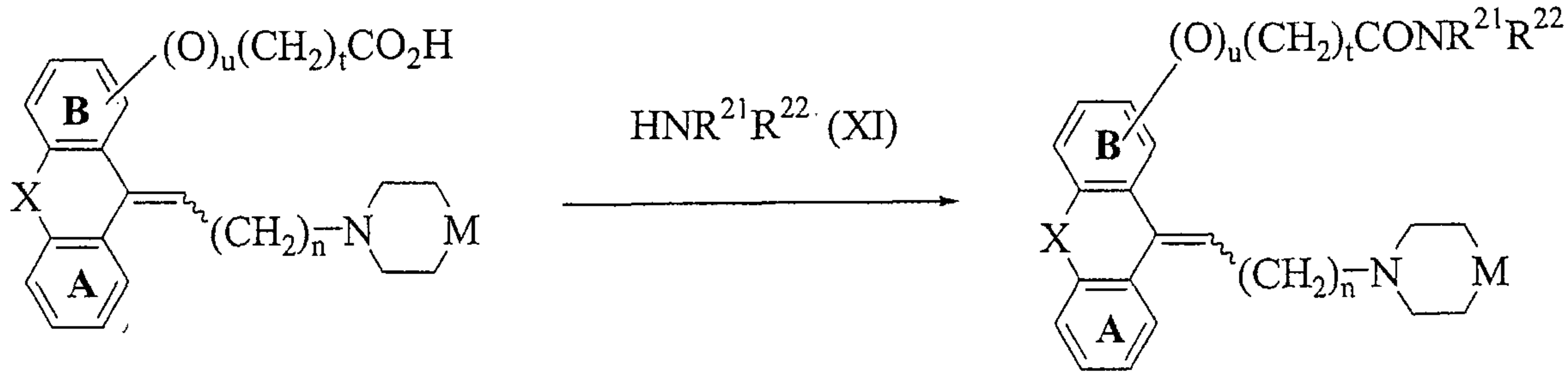


(I-a) (I-b)

Figure 4

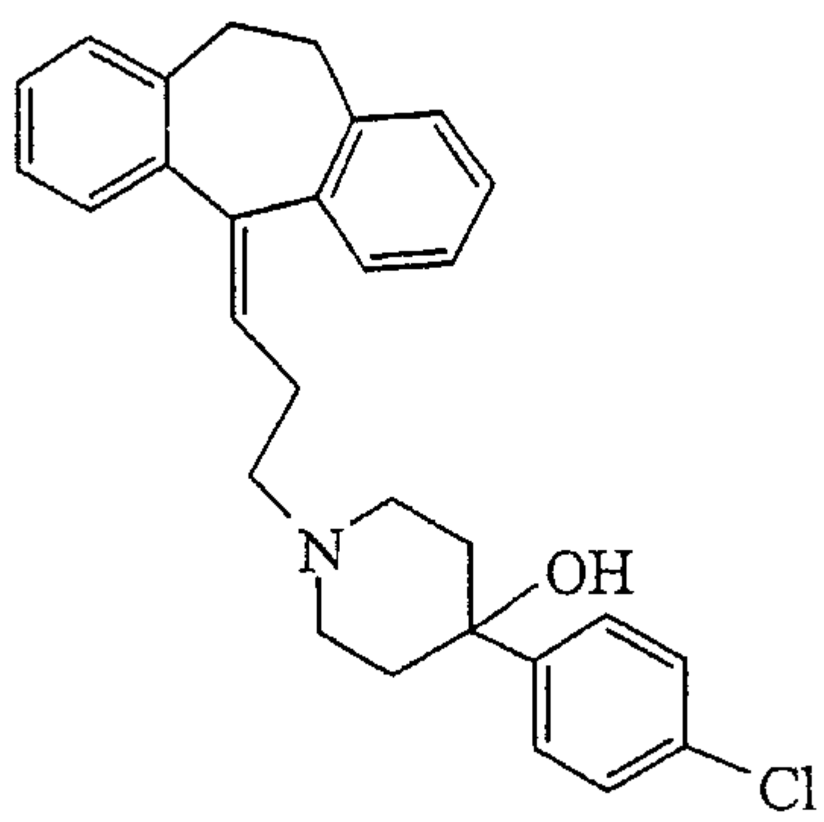


(I-c) (I-d)

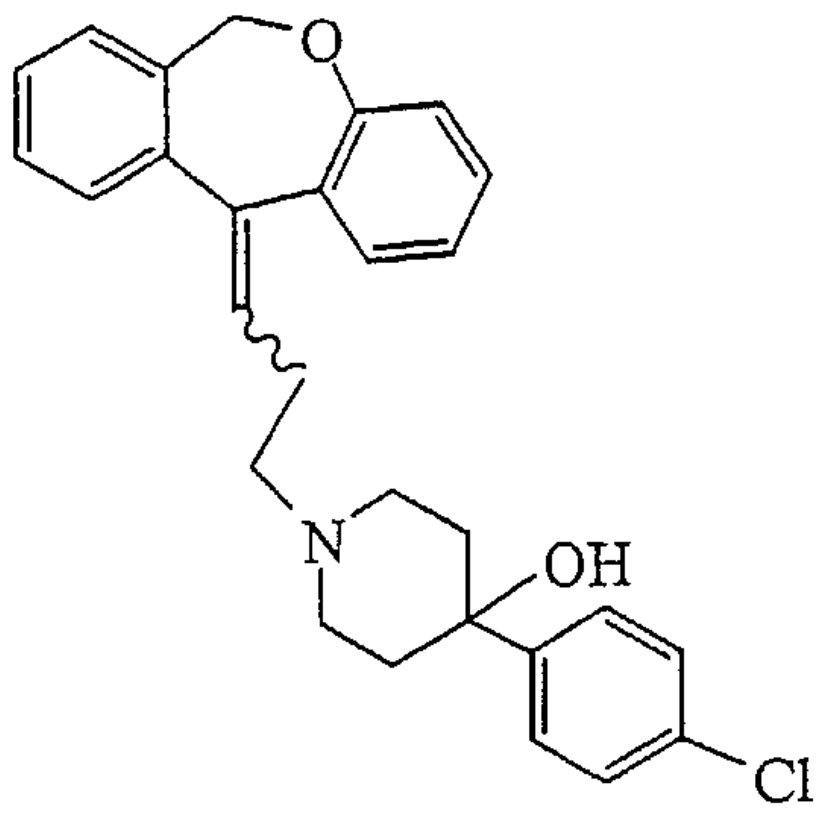


(I-d) (I-e)

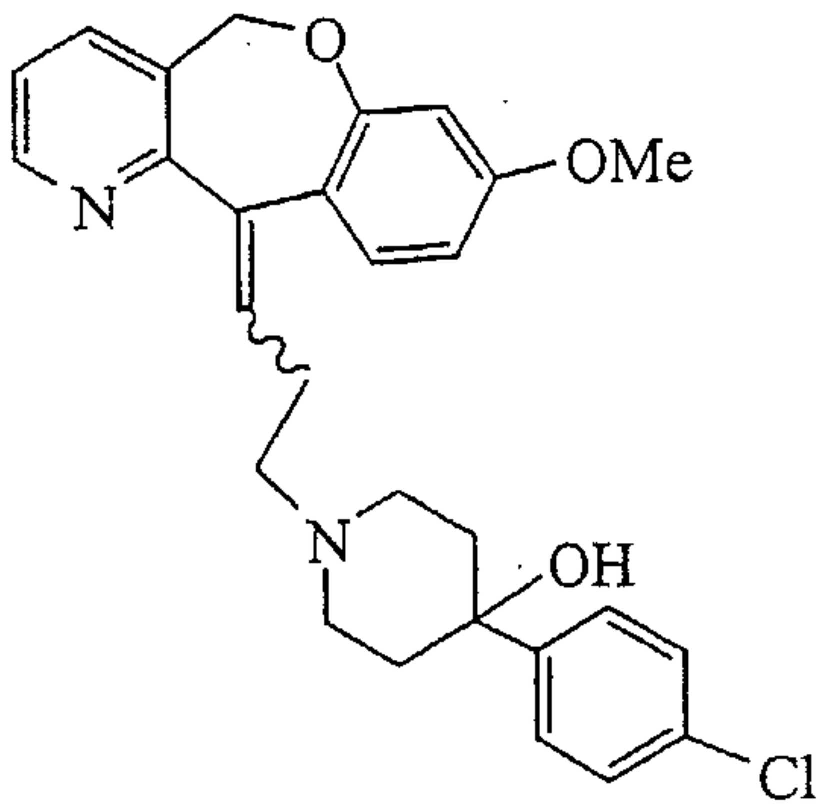
Figure 5



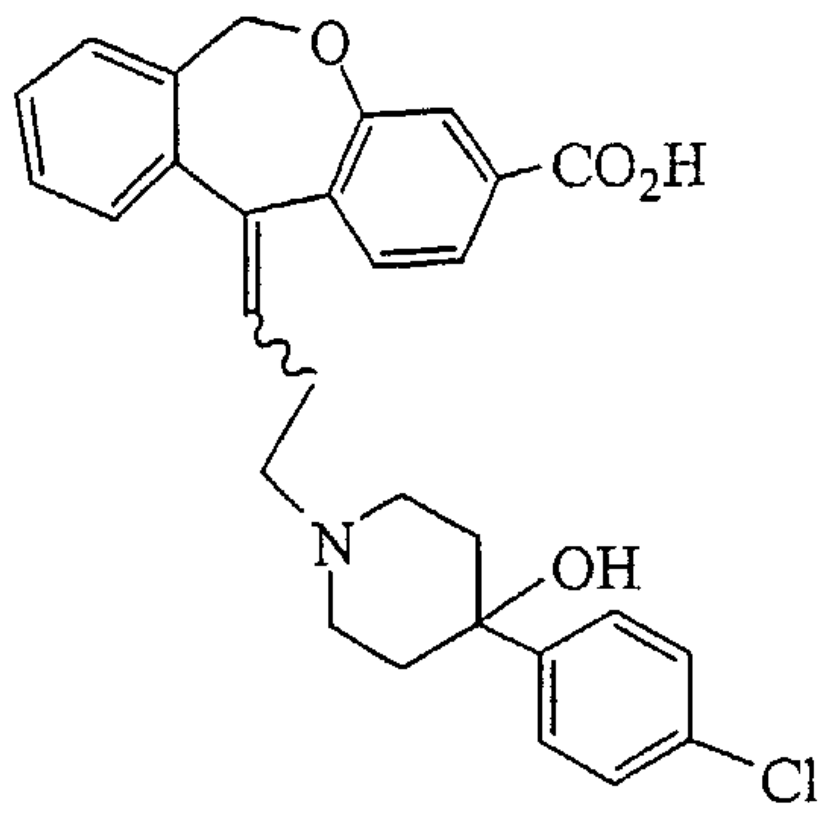
Example 1



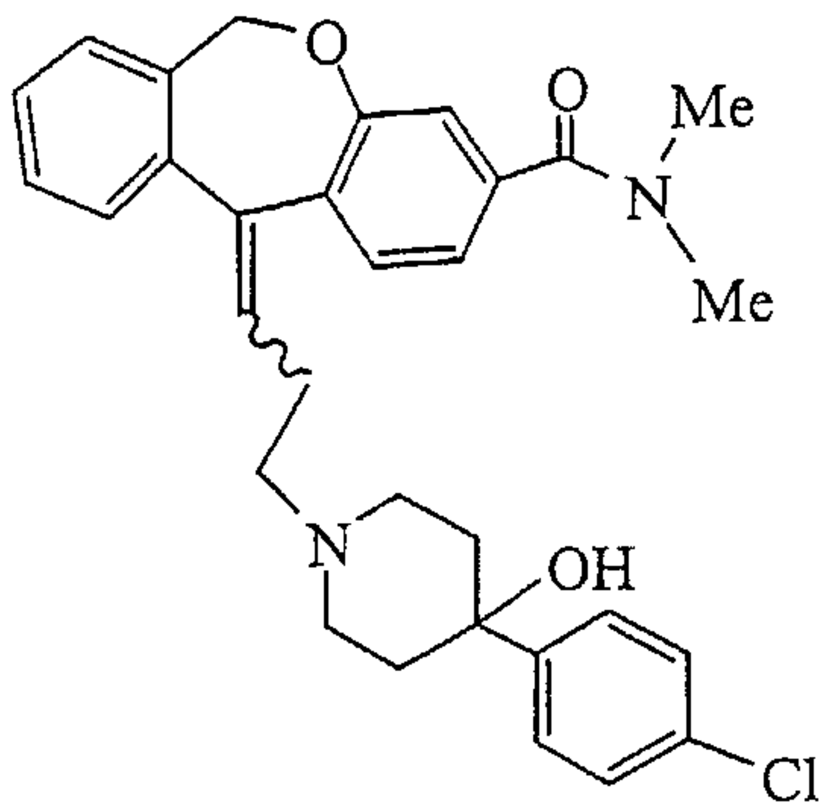
Example 2



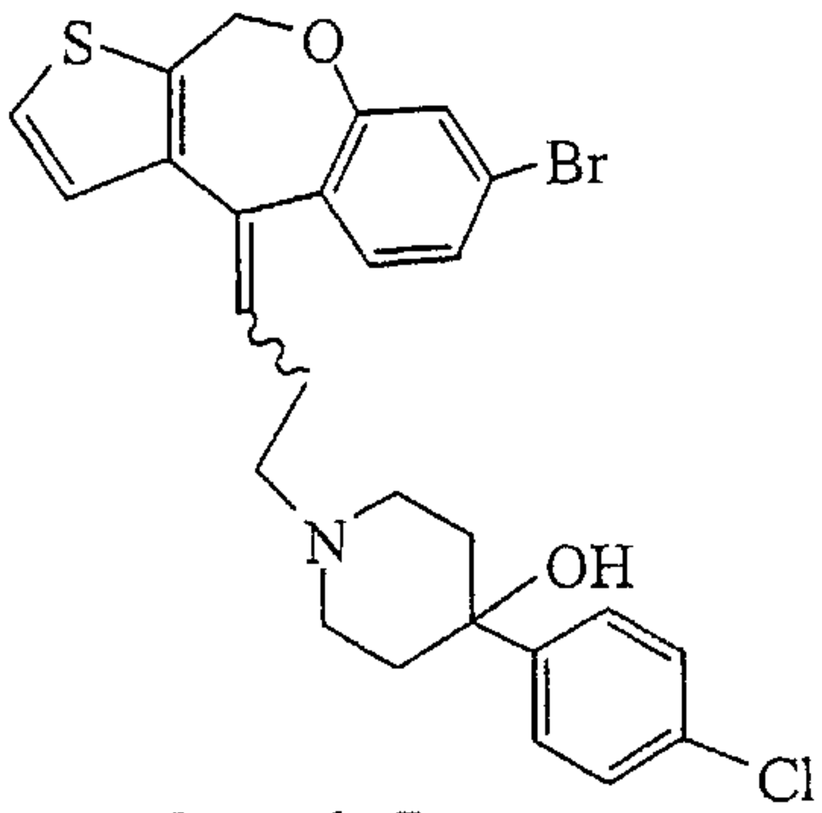
Example 4



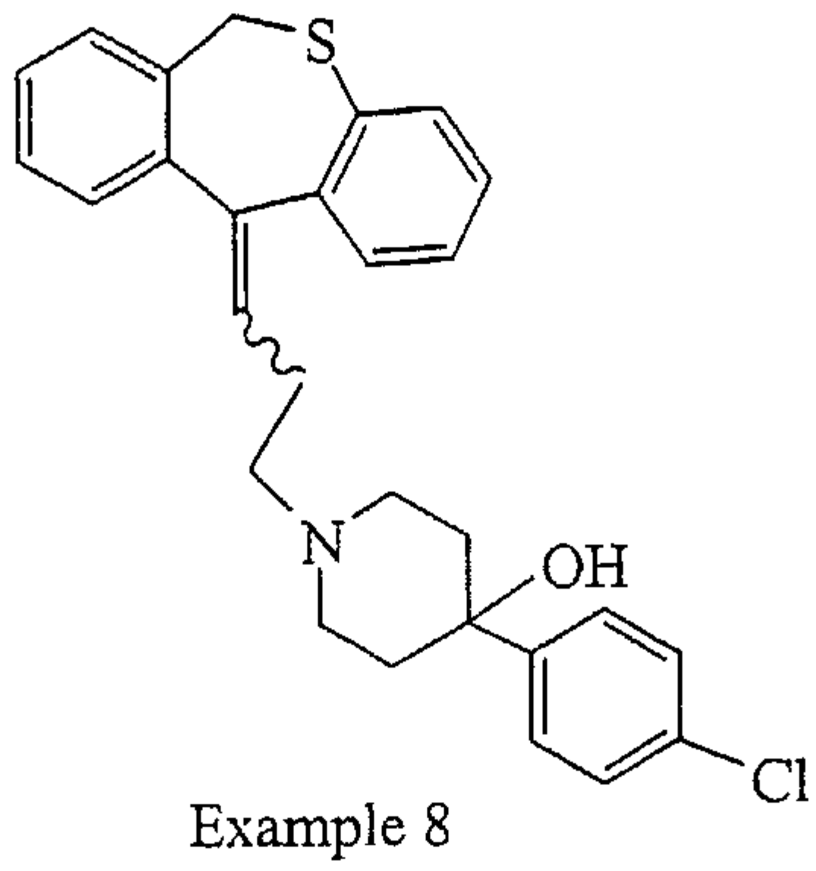
Example 5



Example 6



Example 7



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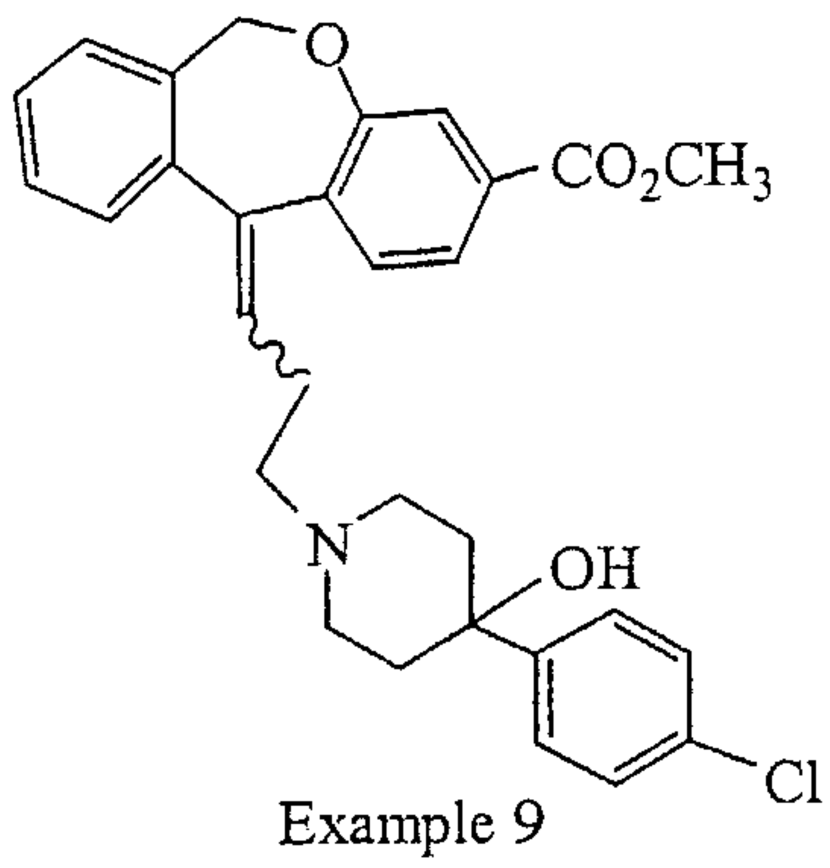

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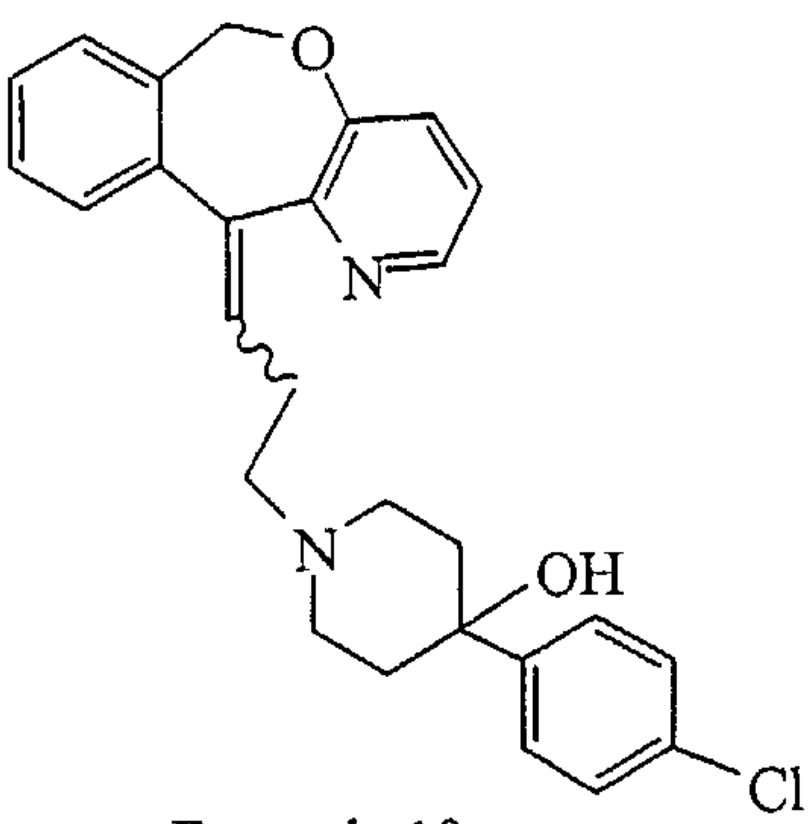
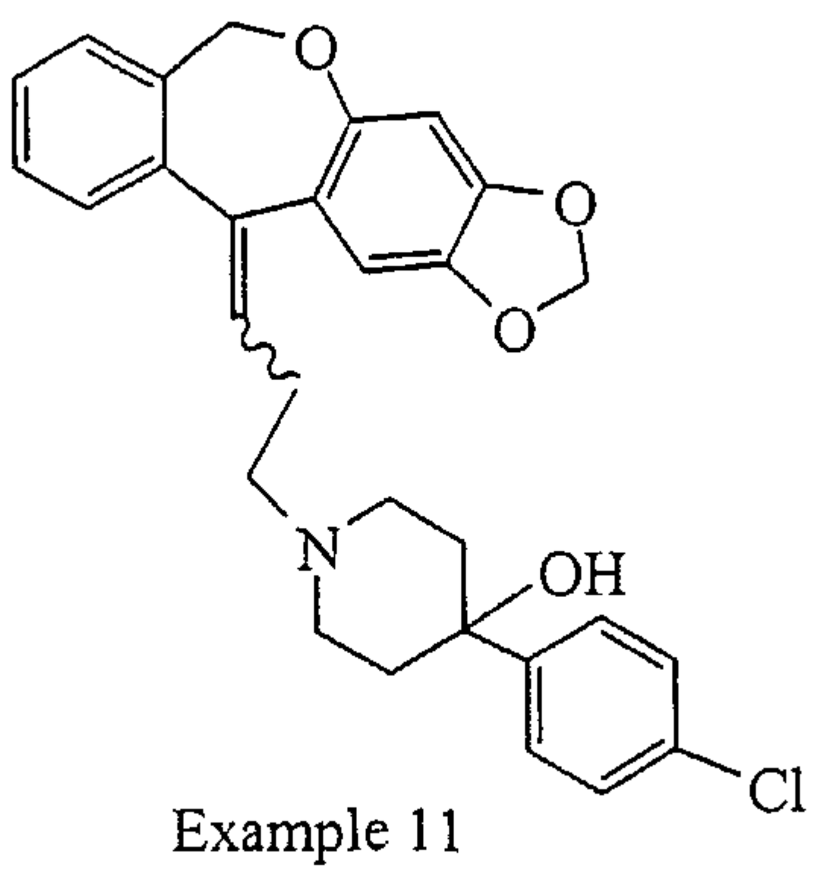
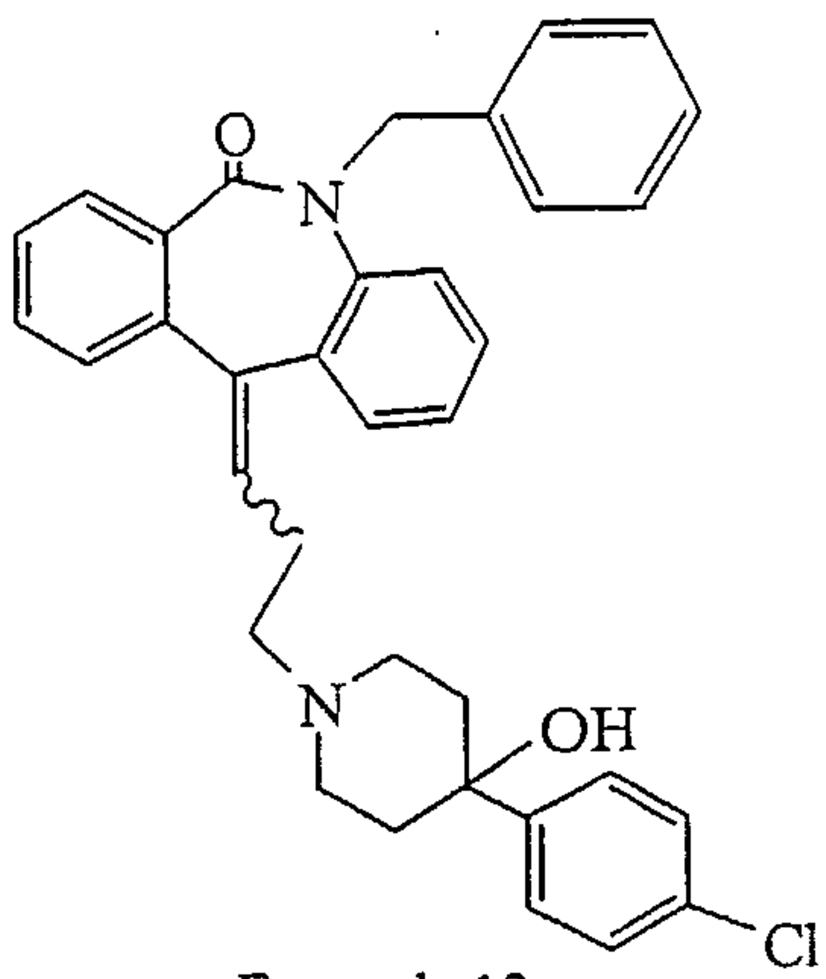


Example 10

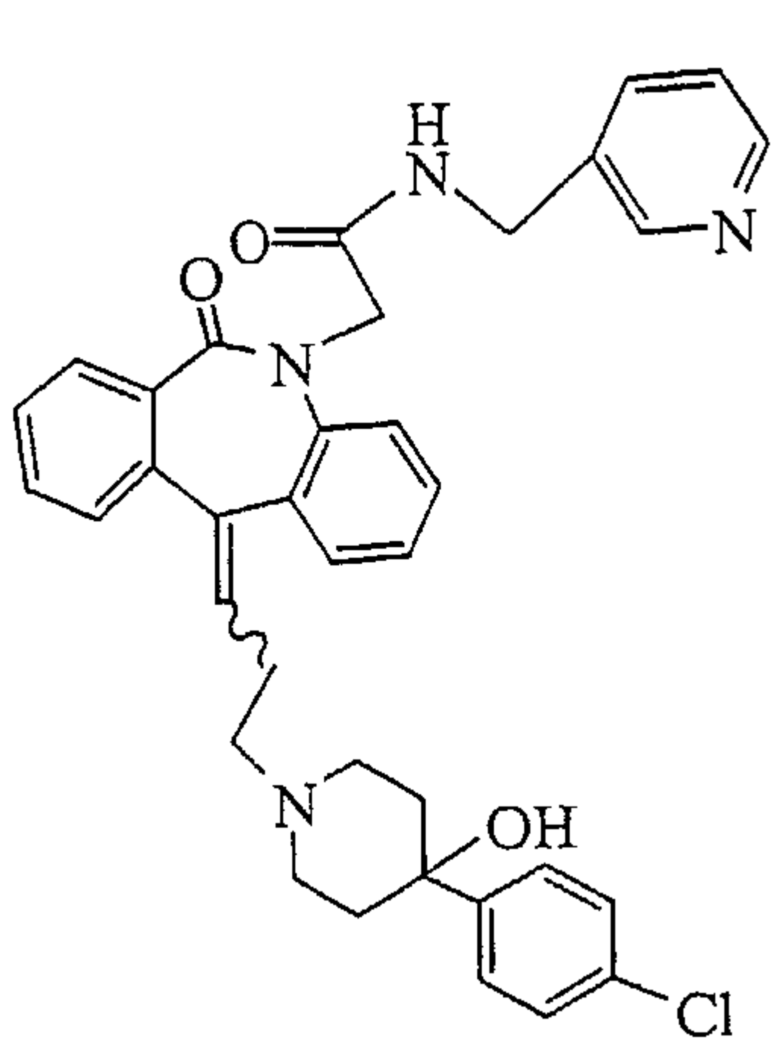


Example 11

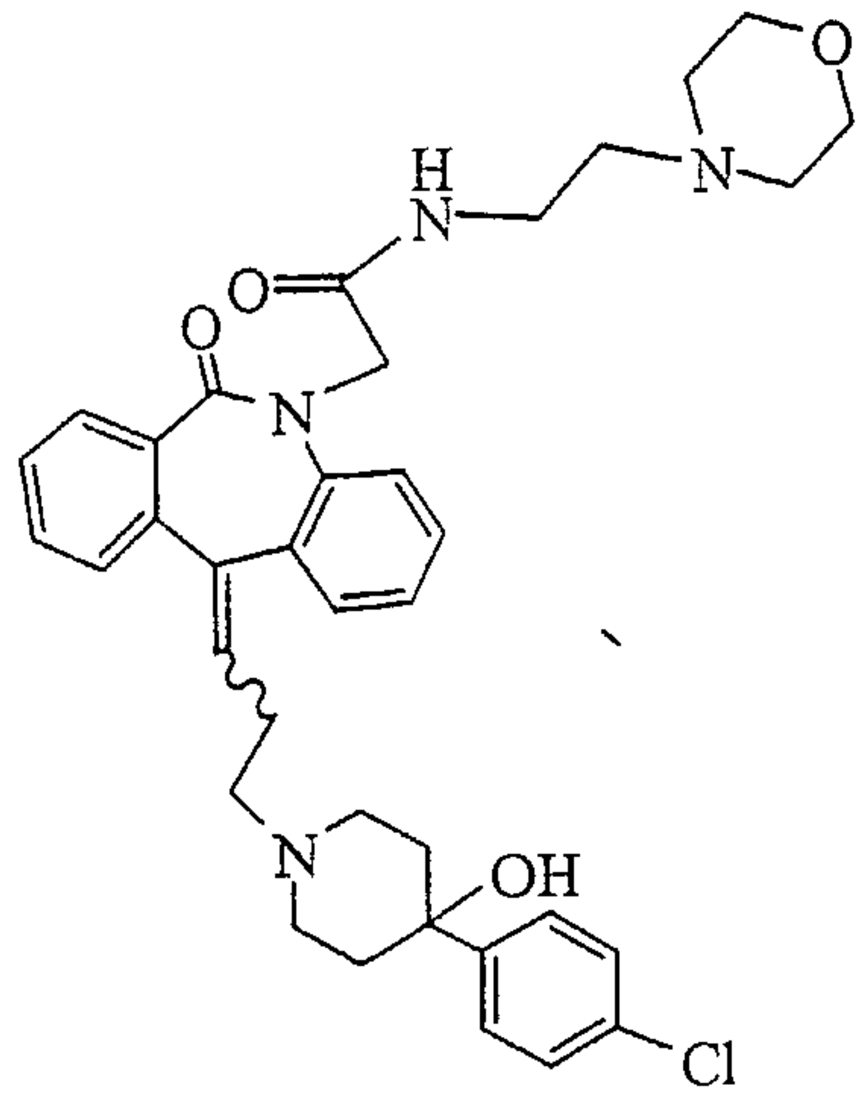


Example 12

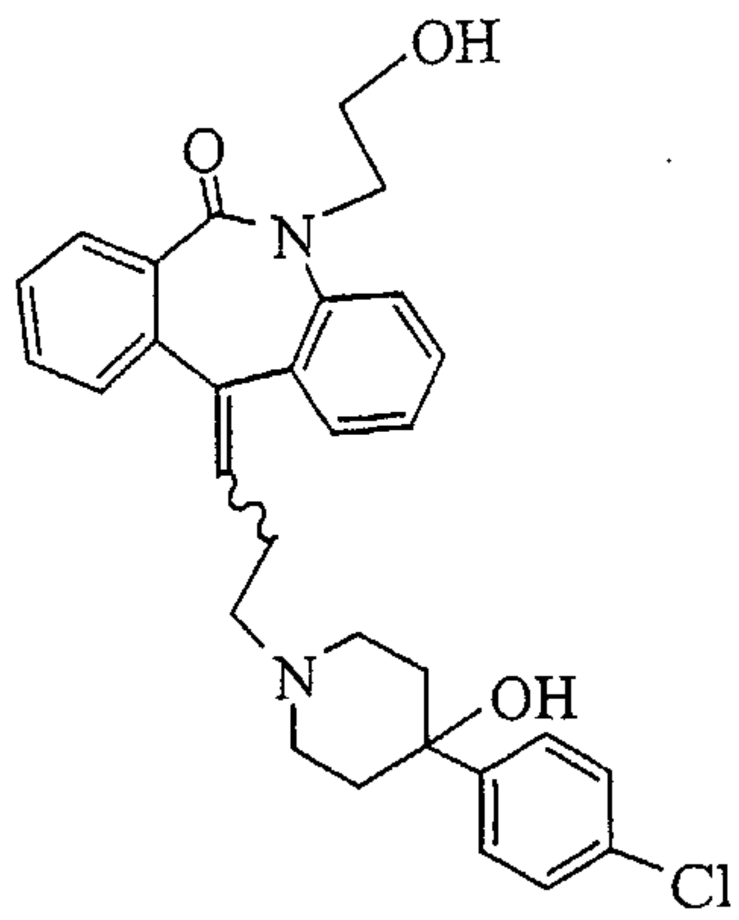
Figure 6A



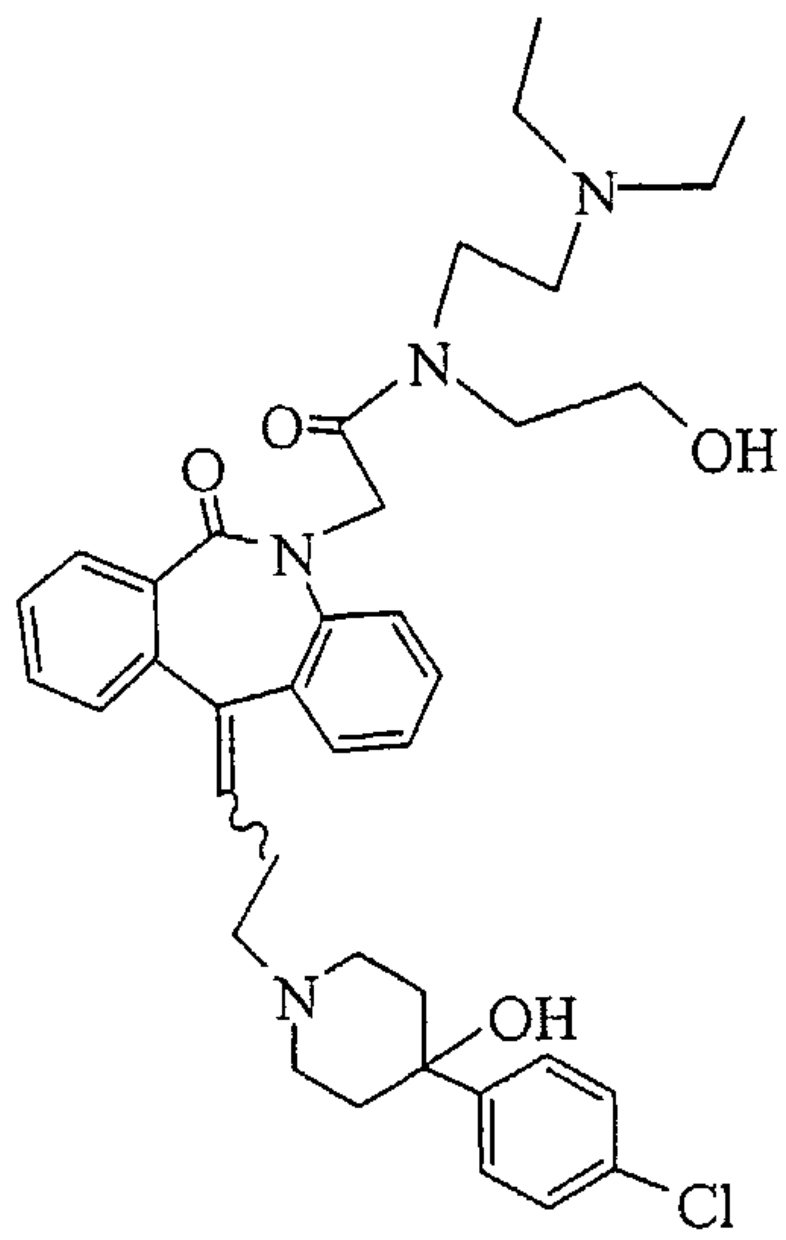
Example 13



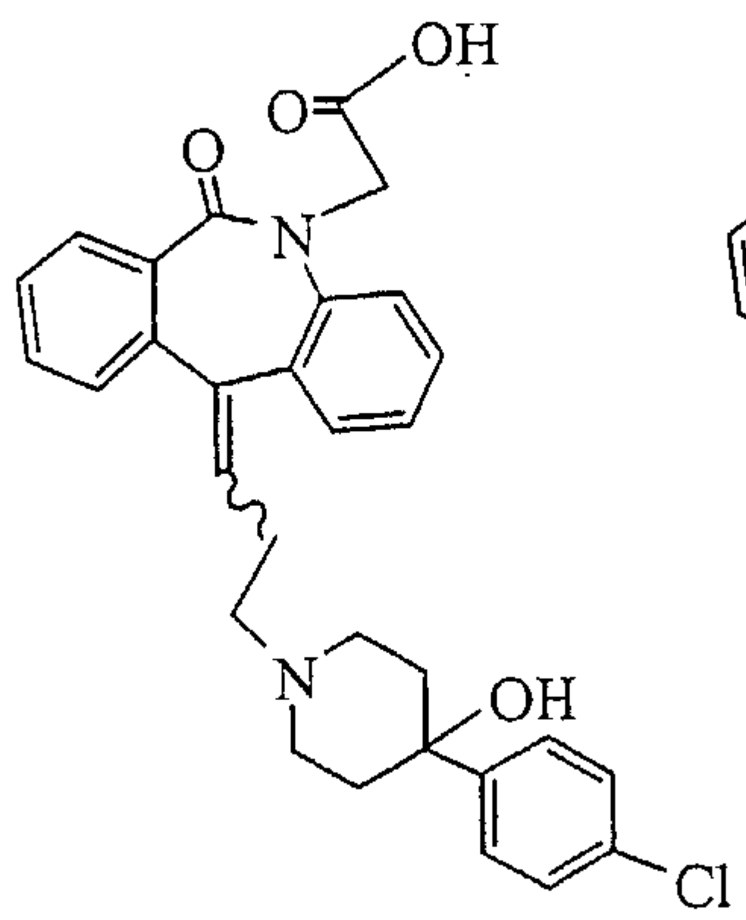
Example 14



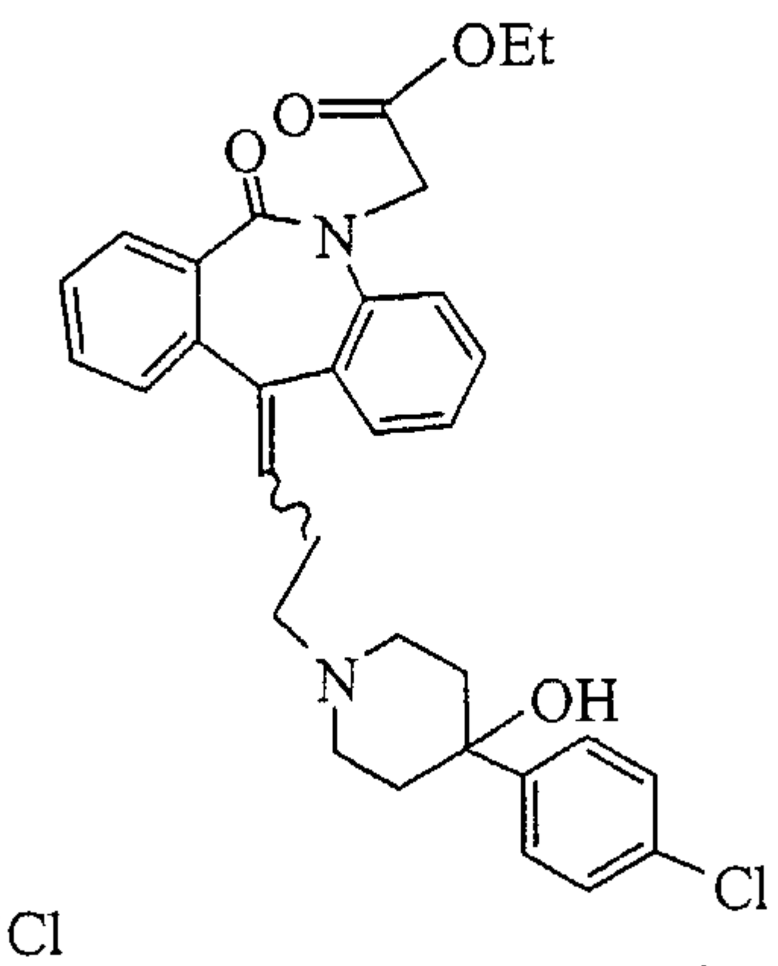
Example 15



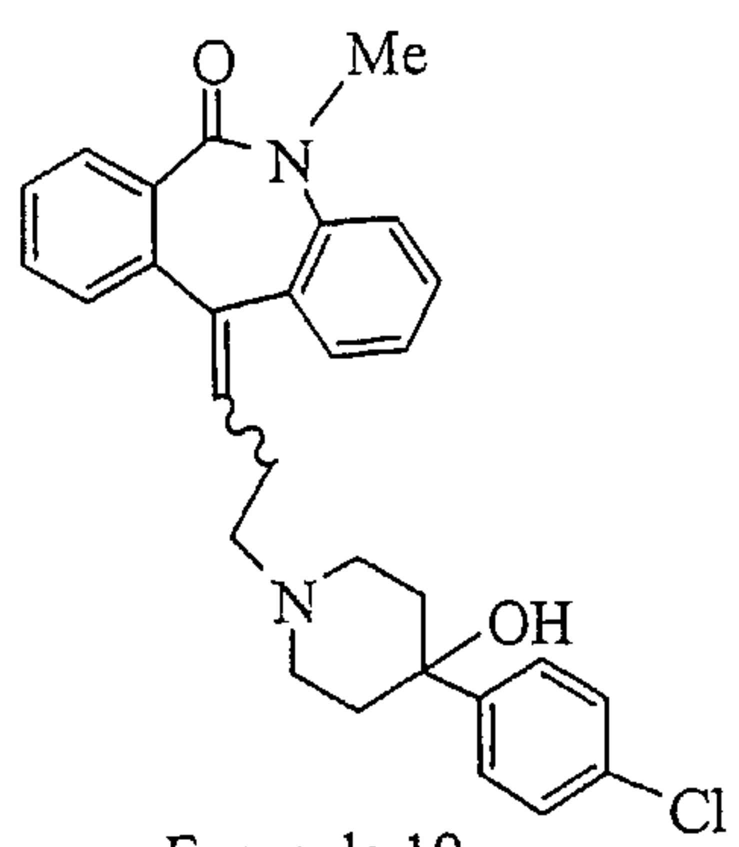
Example 16



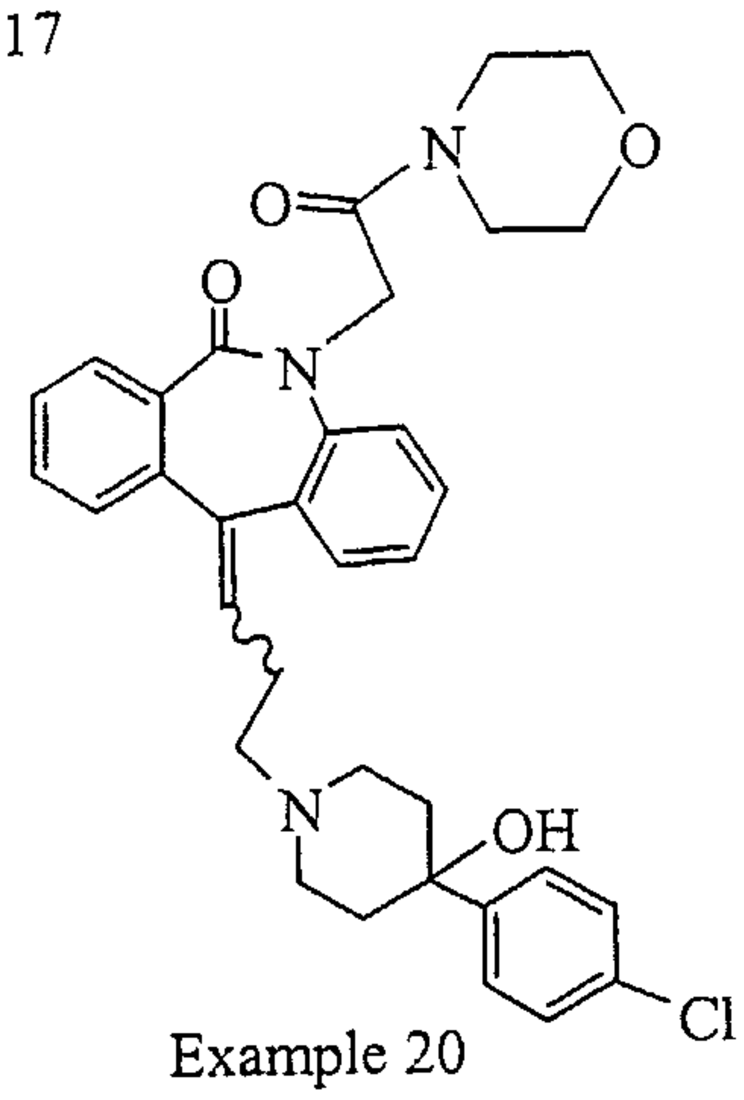
Example 17



Example 18

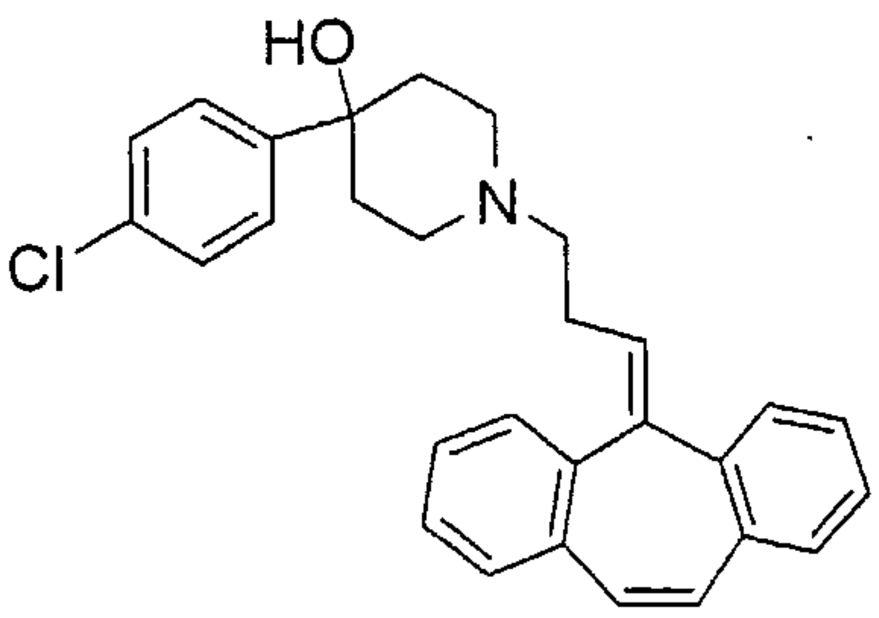


Example 19

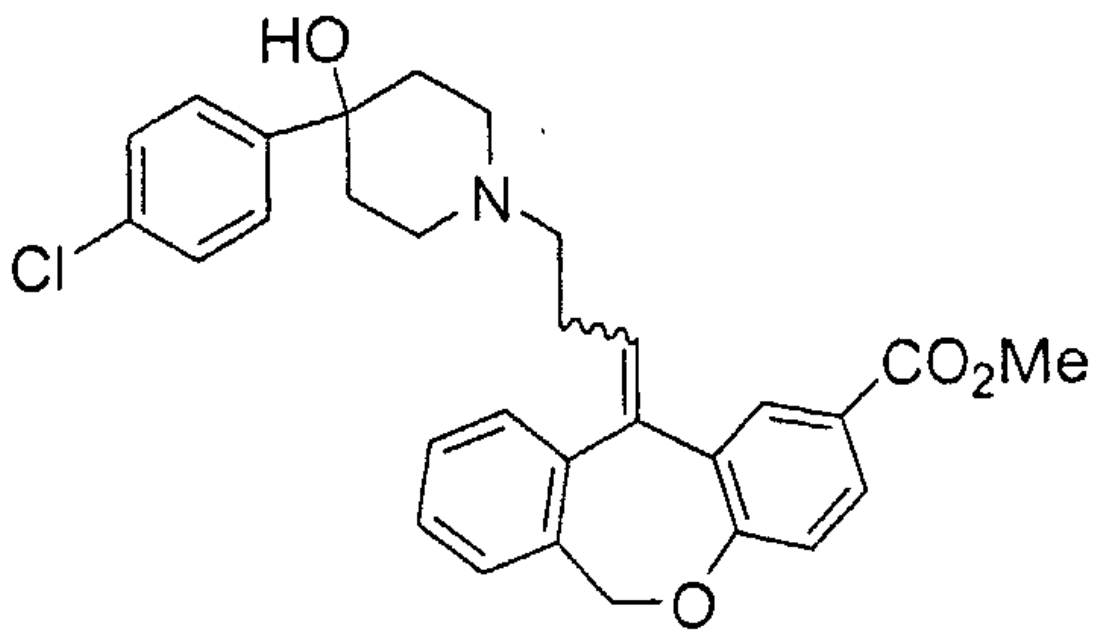


Example 20

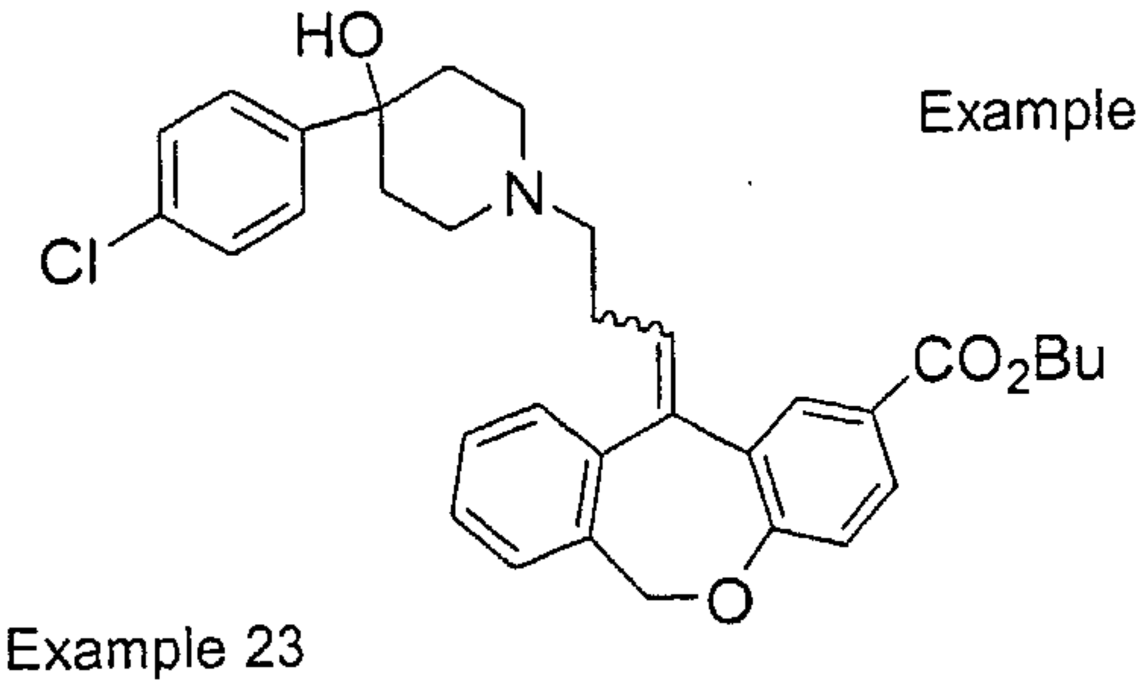
Figure 6B



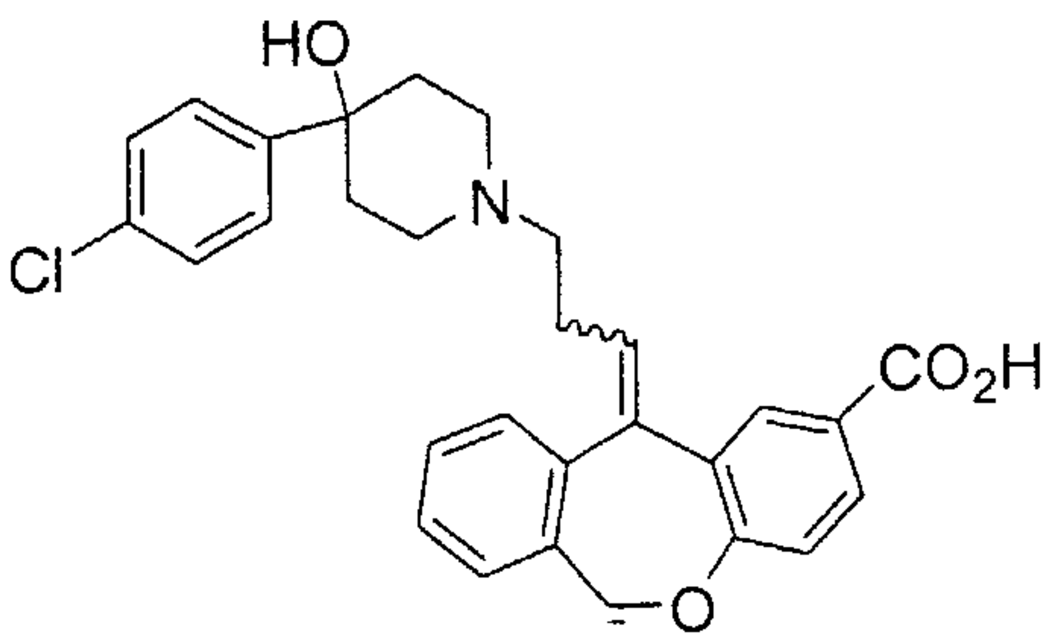
Example 21



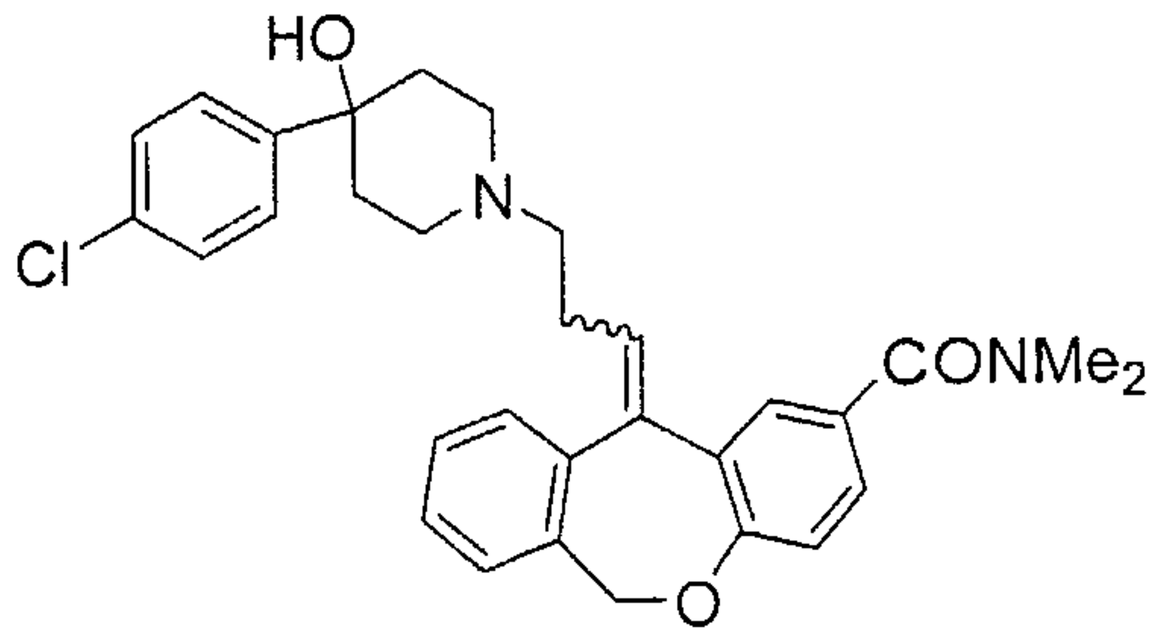
Example 22



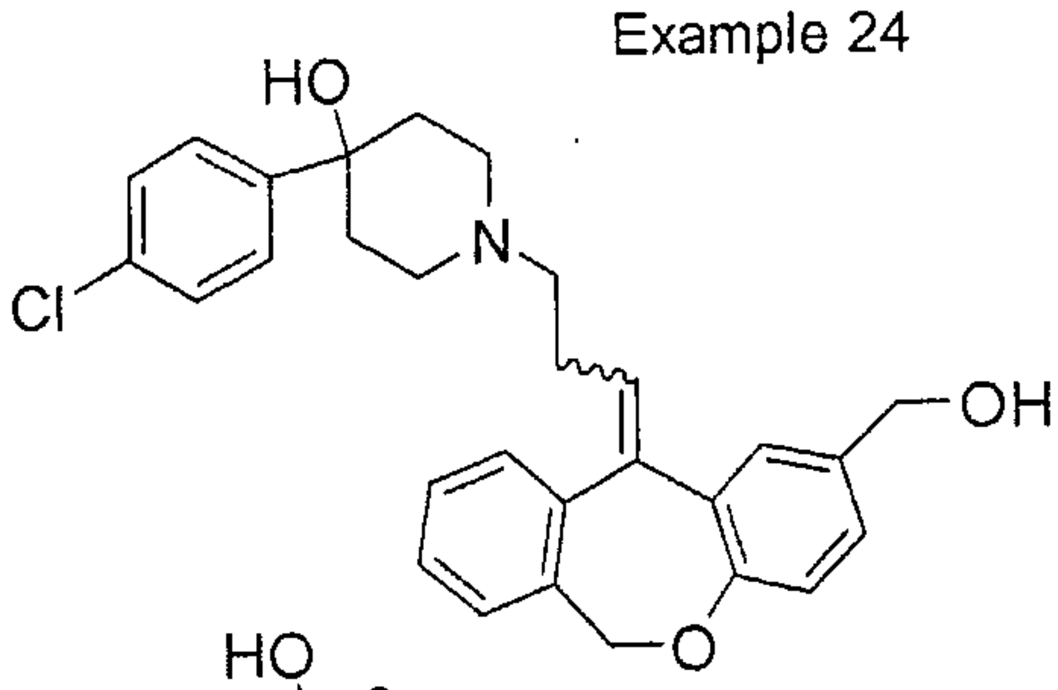
Example 23



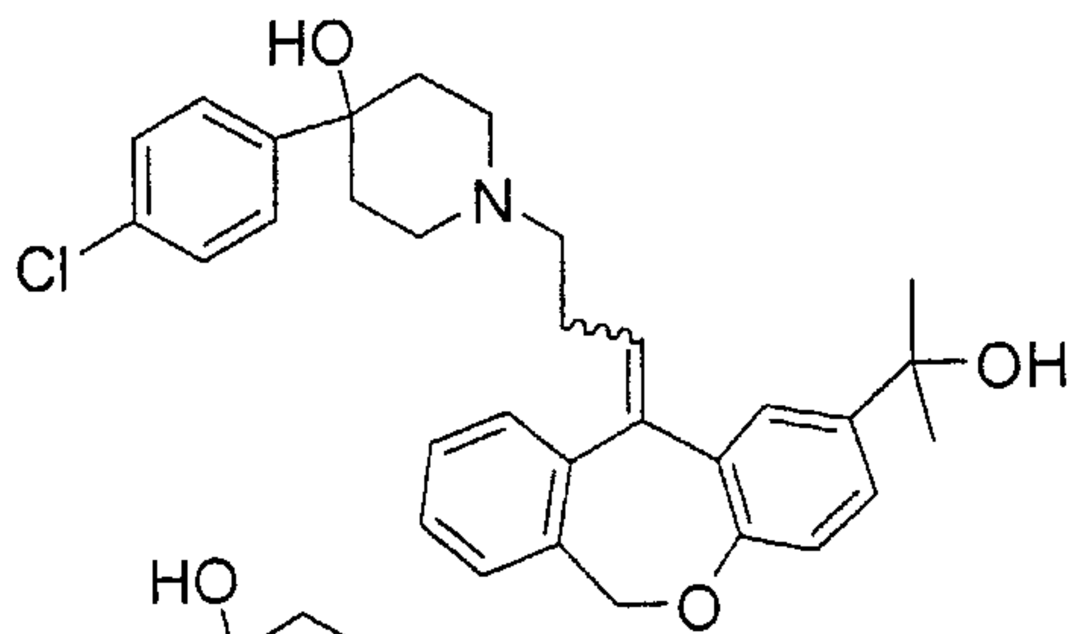
Example 24



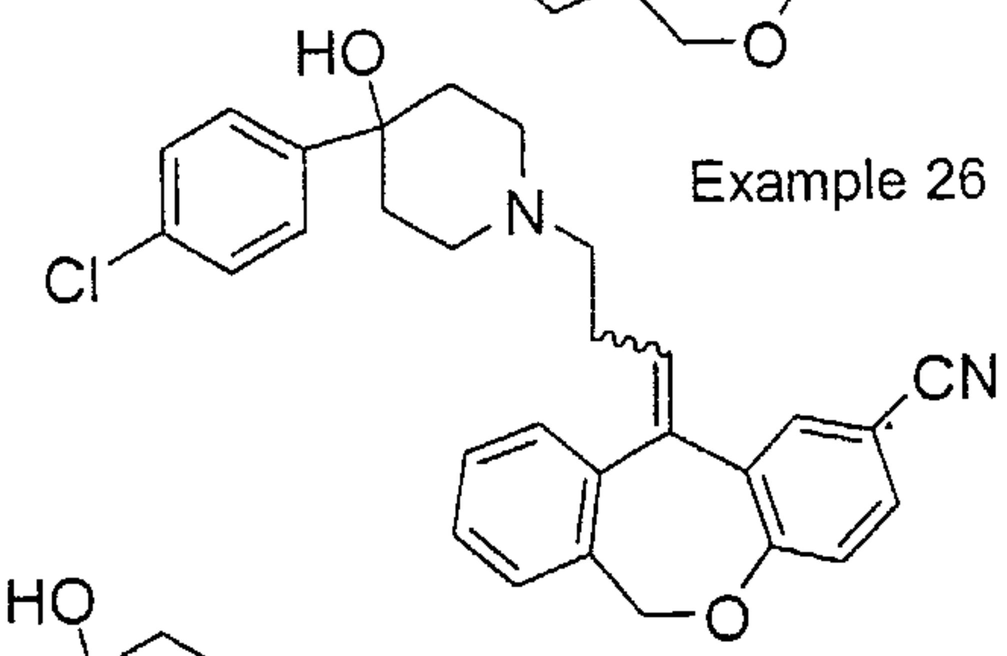
Example 25



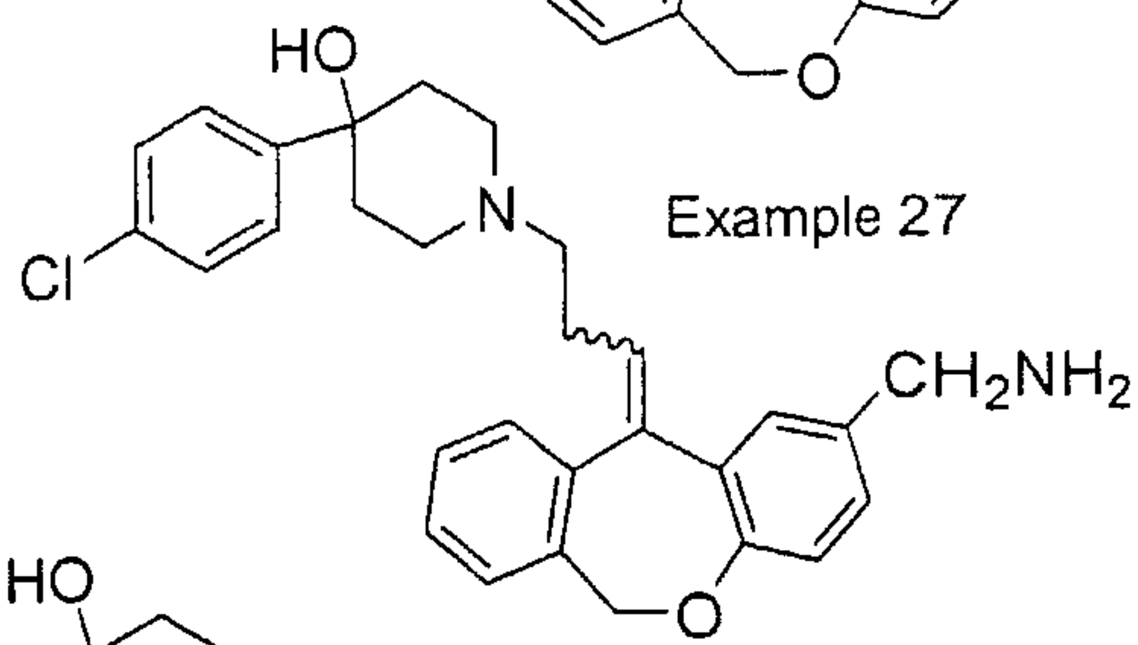
Example 26



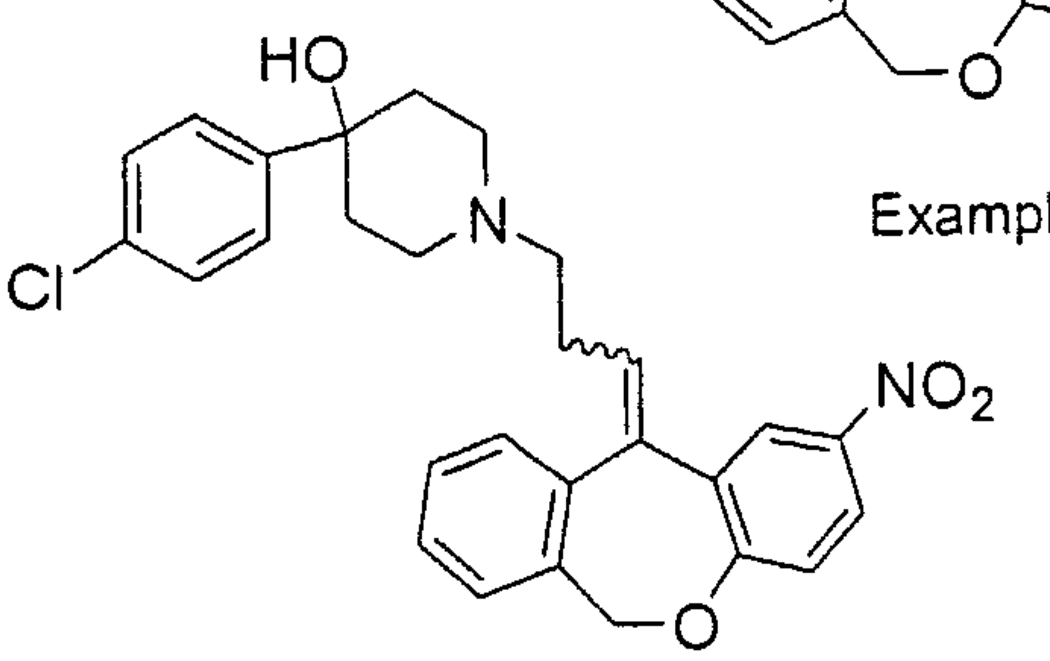
Example 27



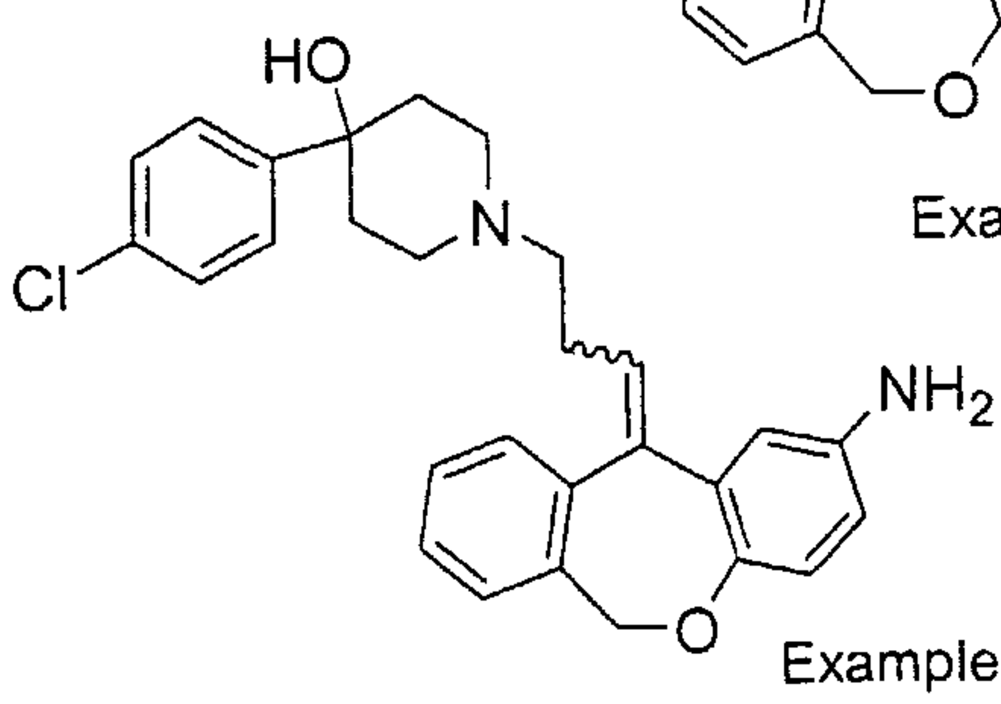
Example 28



Example 29

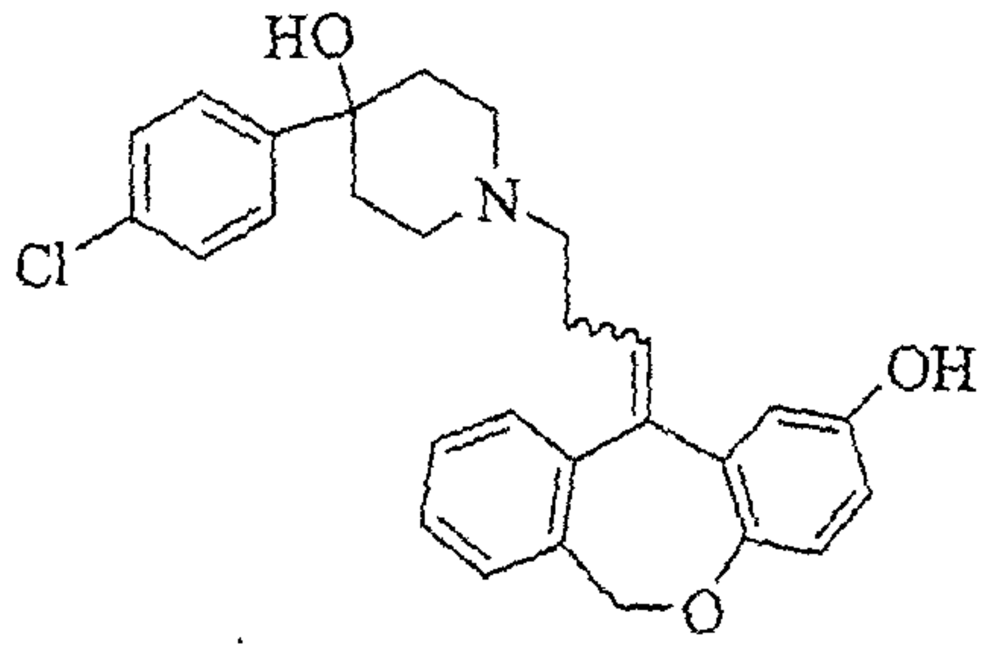


Example 30

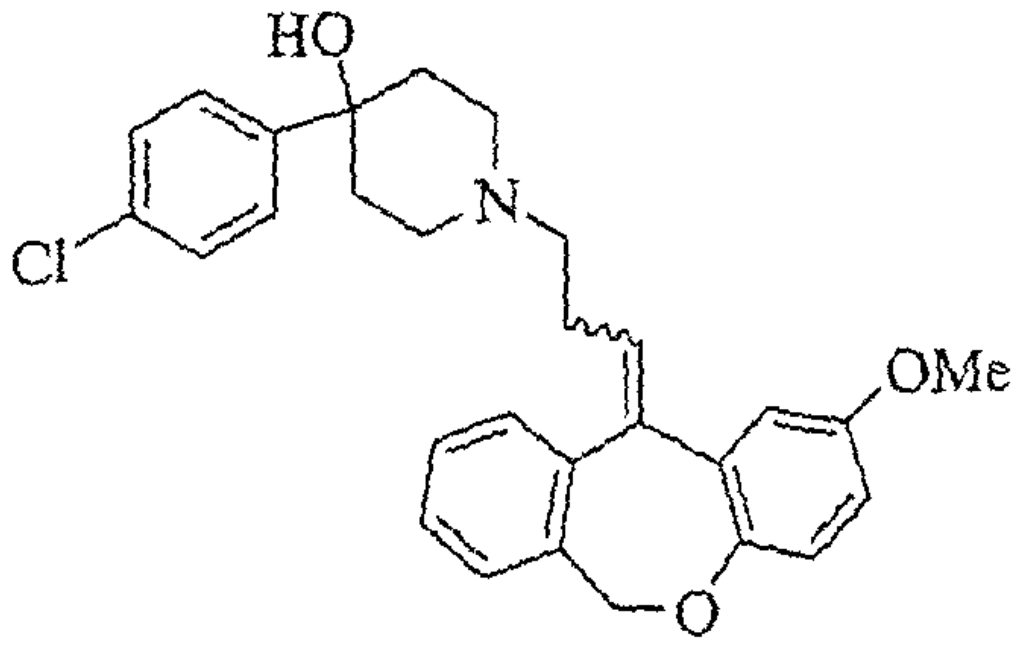


Example 31

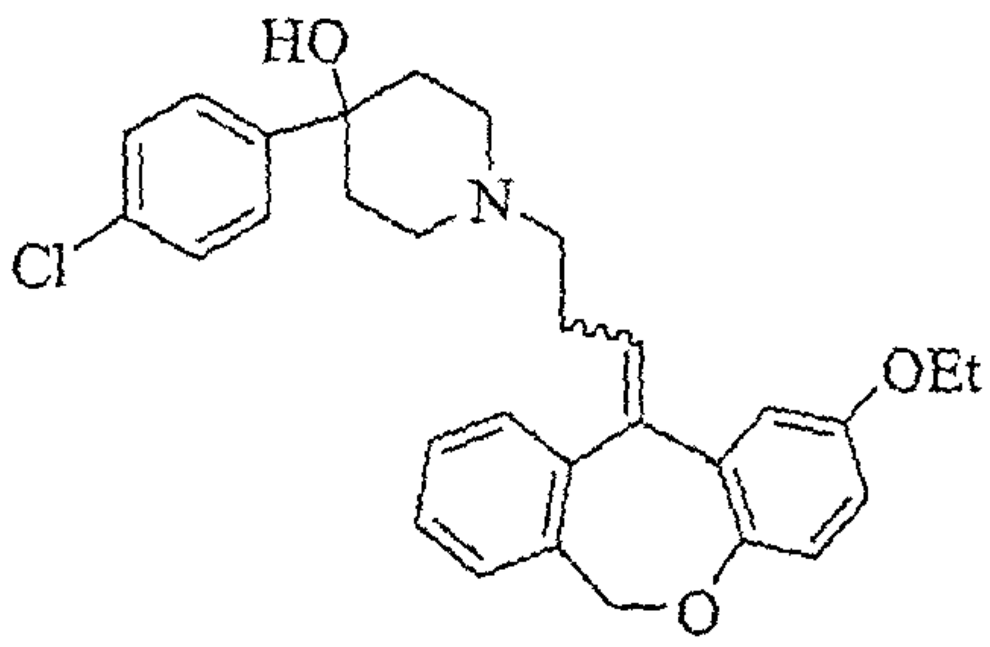
Figure 6C



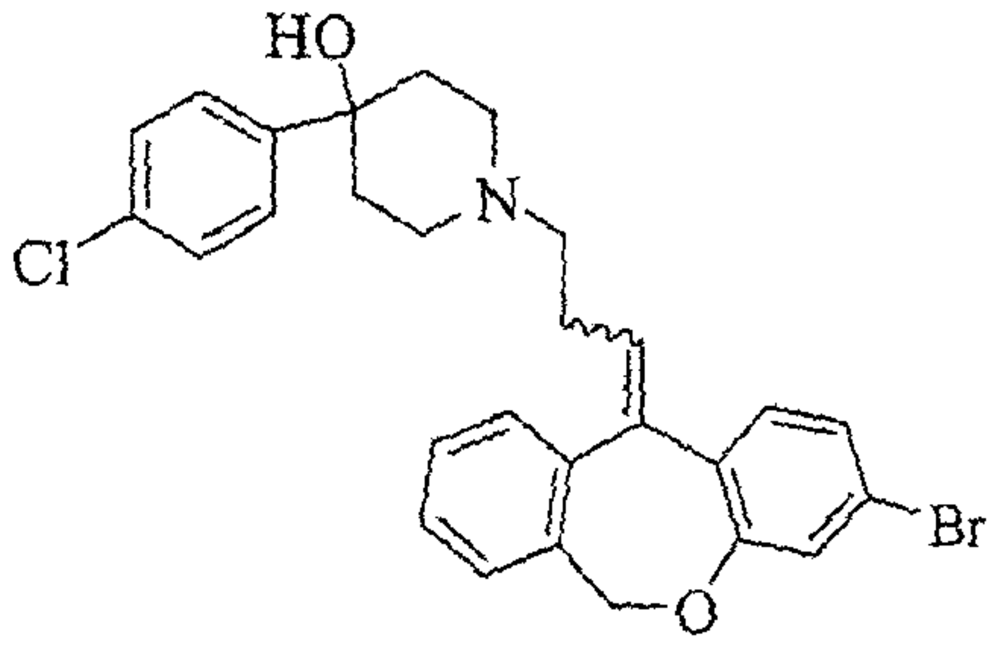
Example 32



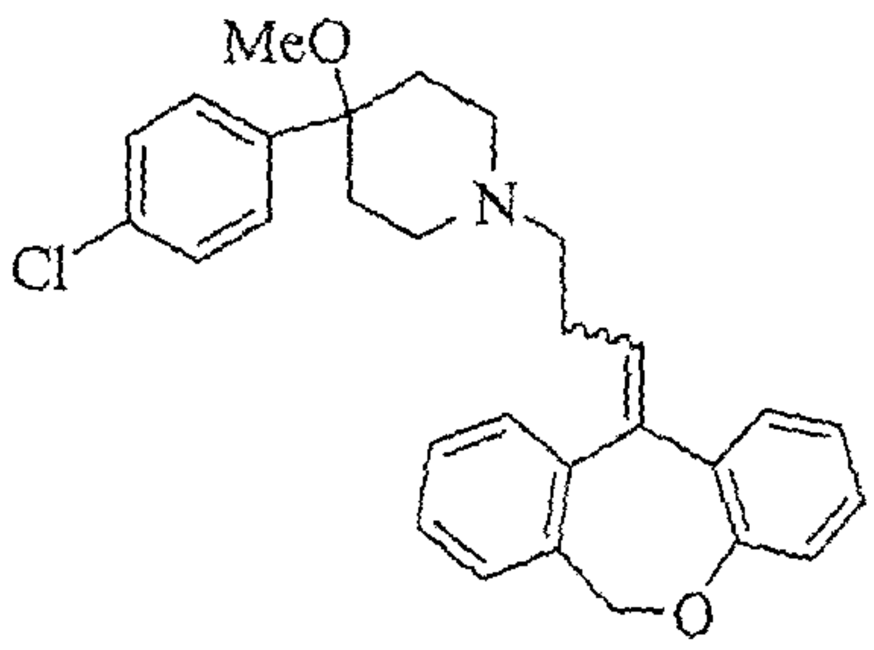
Example 33



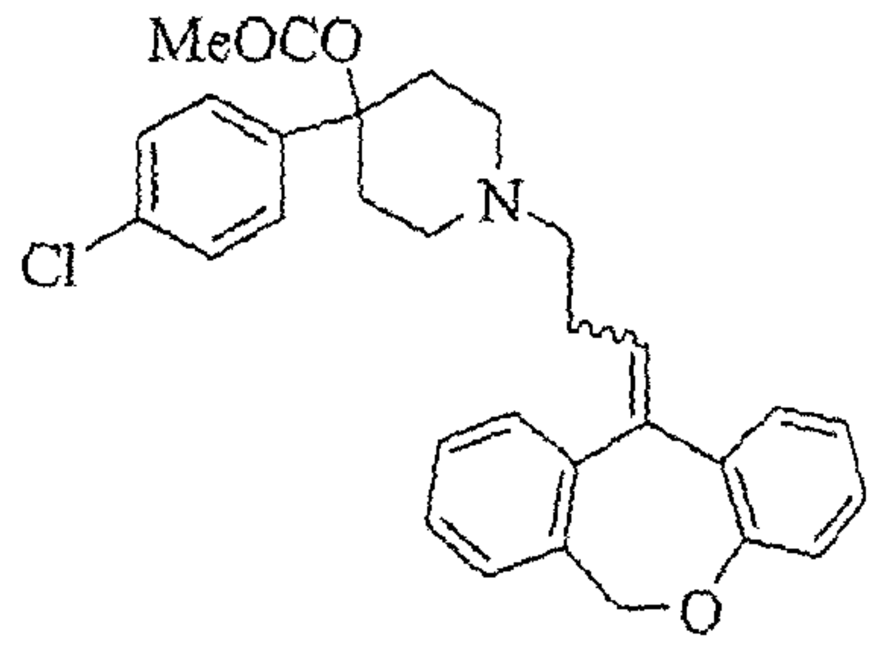
Example 34



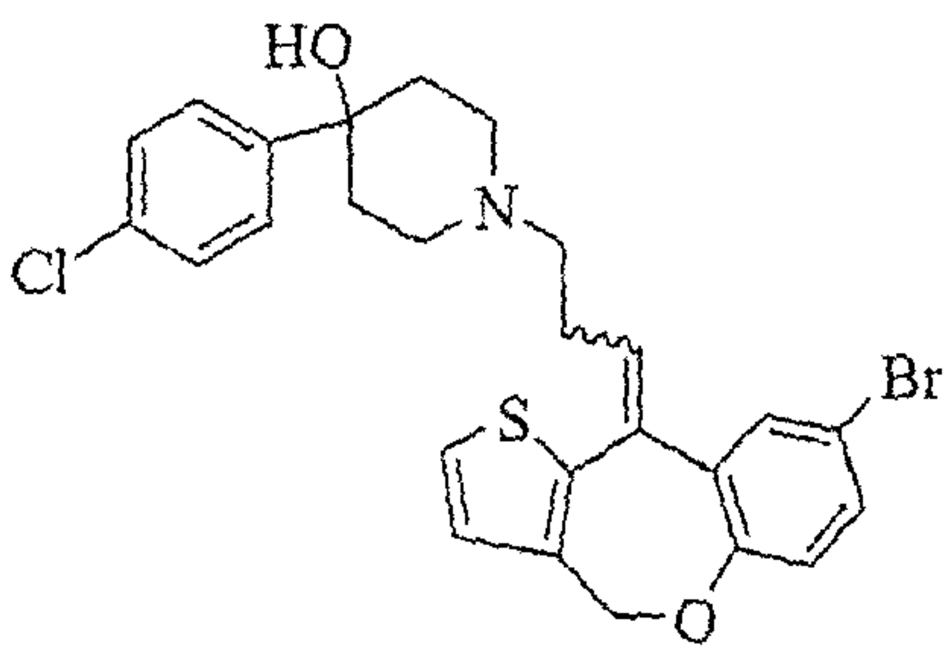
Example 35



Example 36

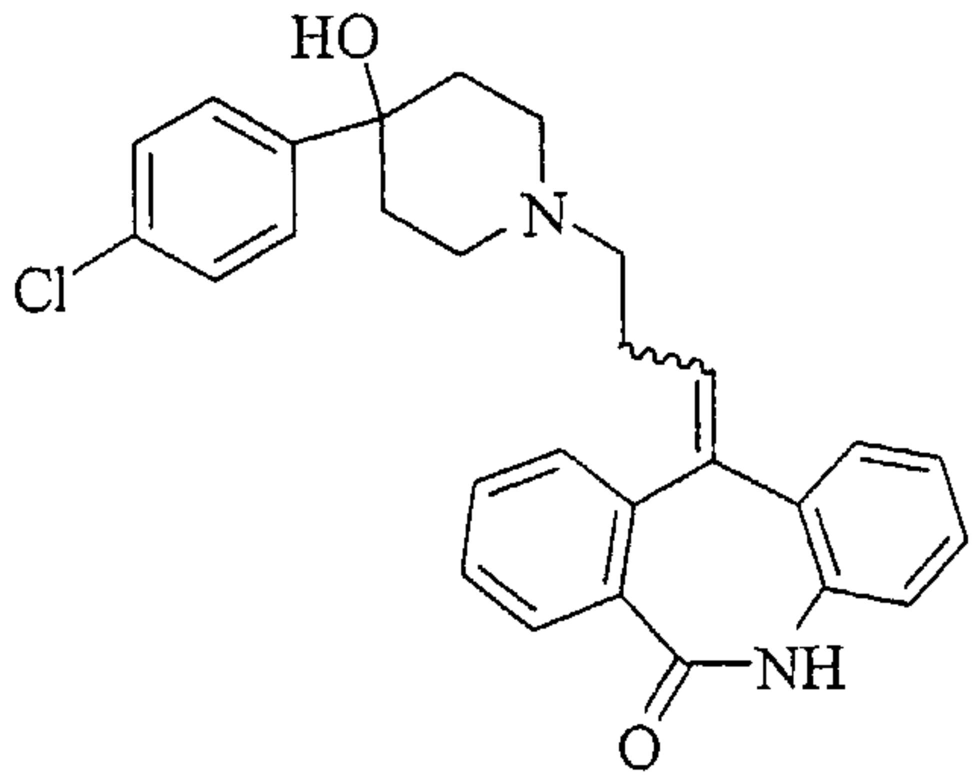


Example 37

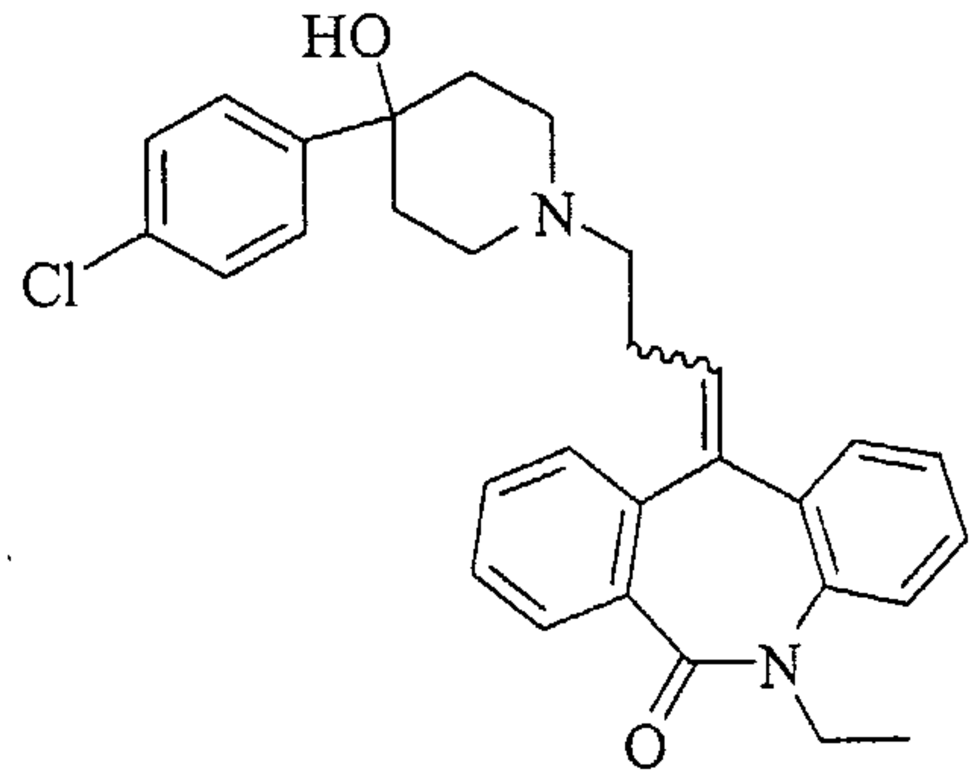


Example 38

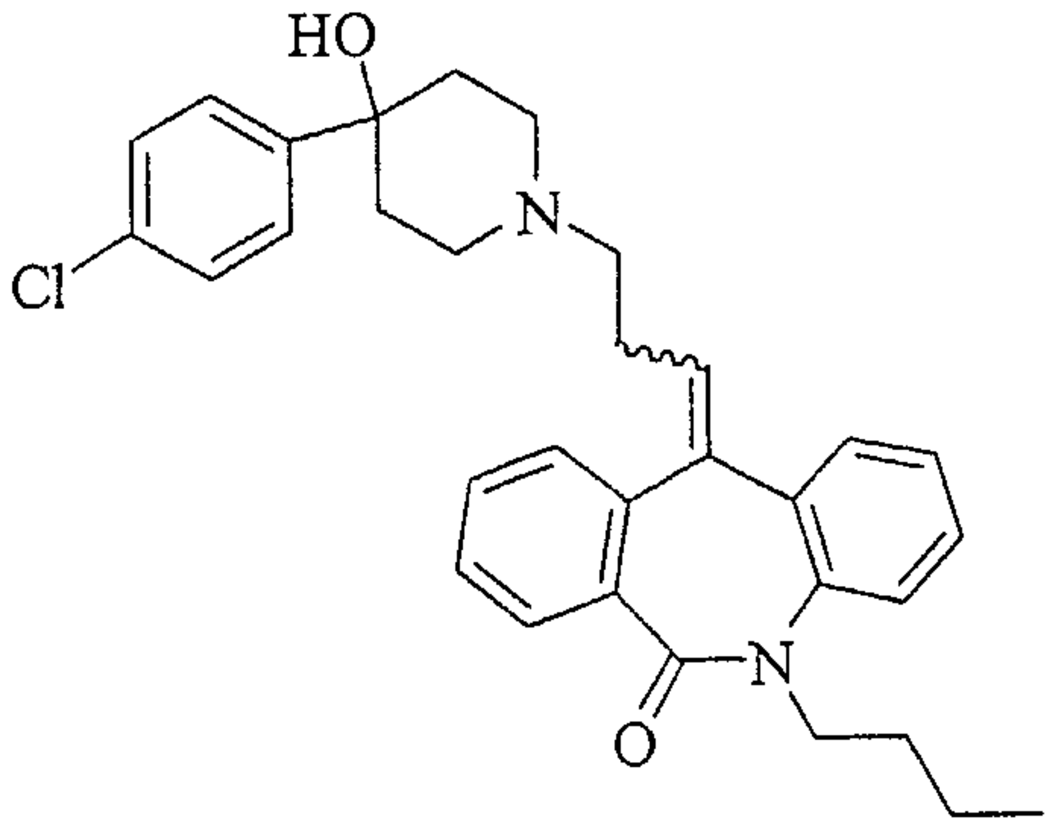
Figure 6D



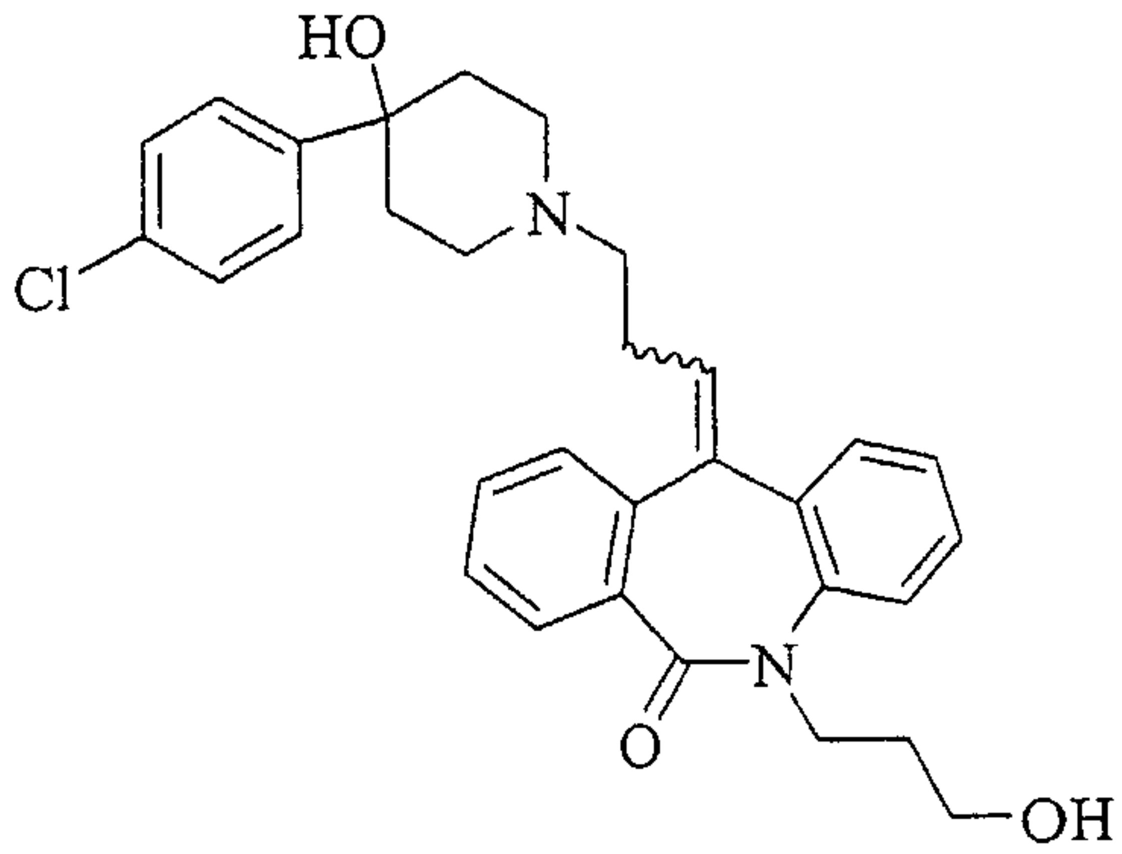
Example 39



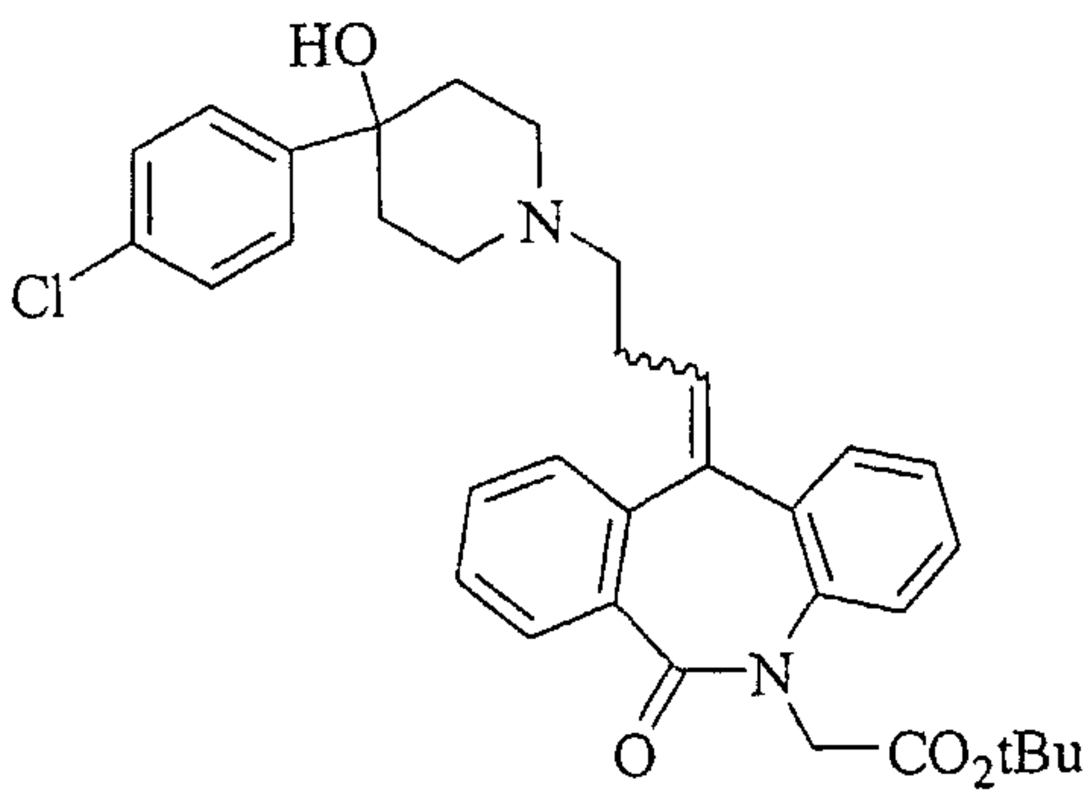
Example 40



Example 41

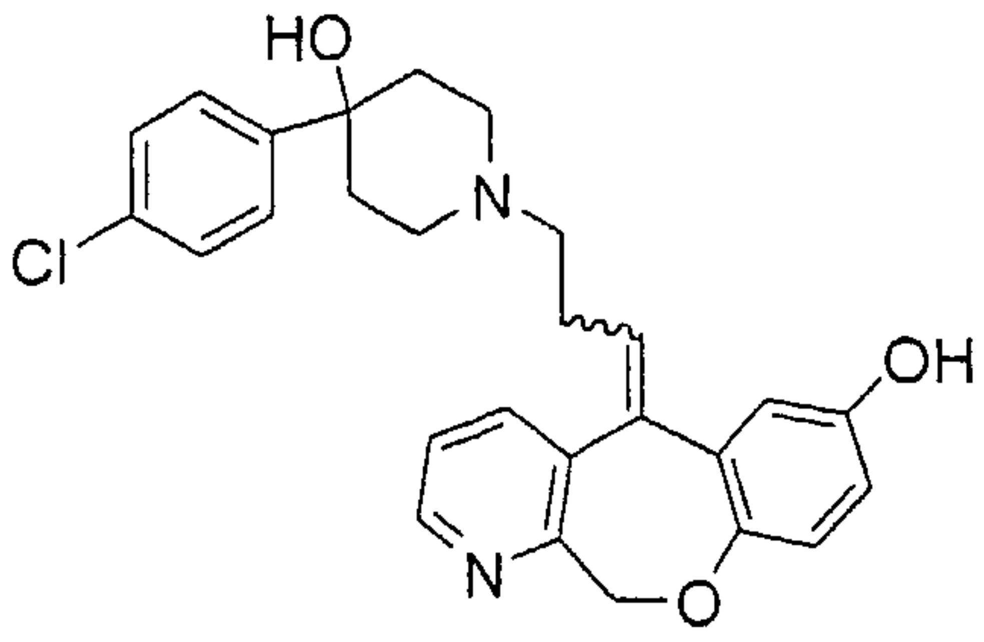


Example 42

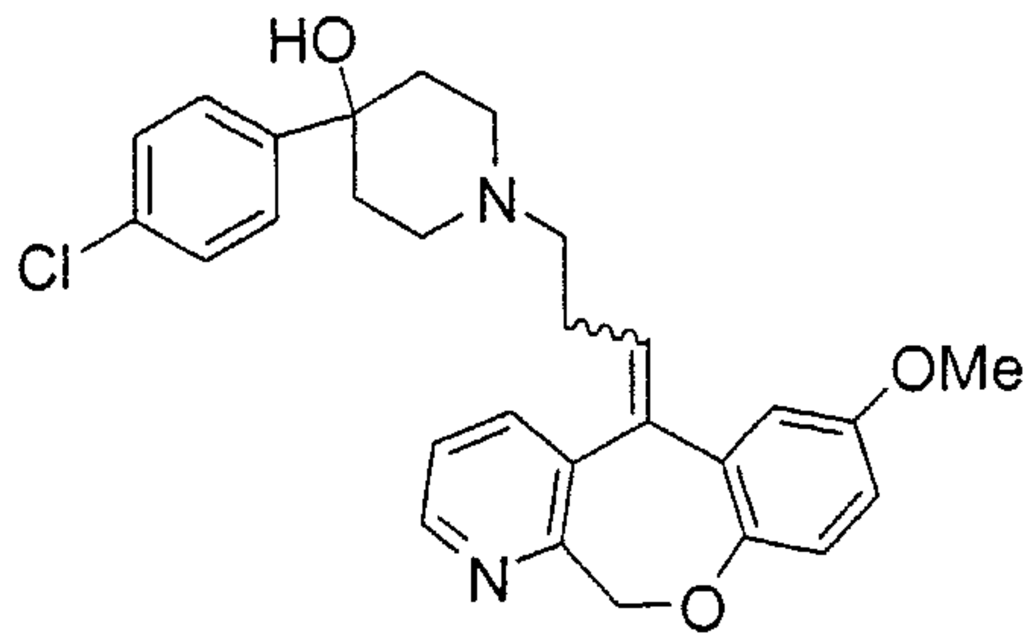


Example 43

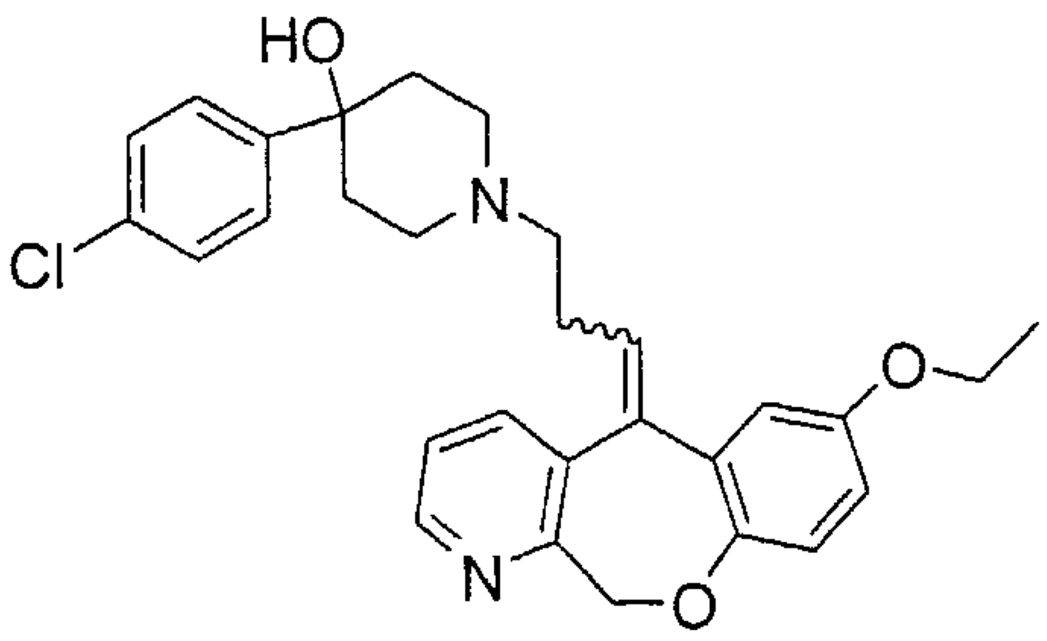
Figure 6E



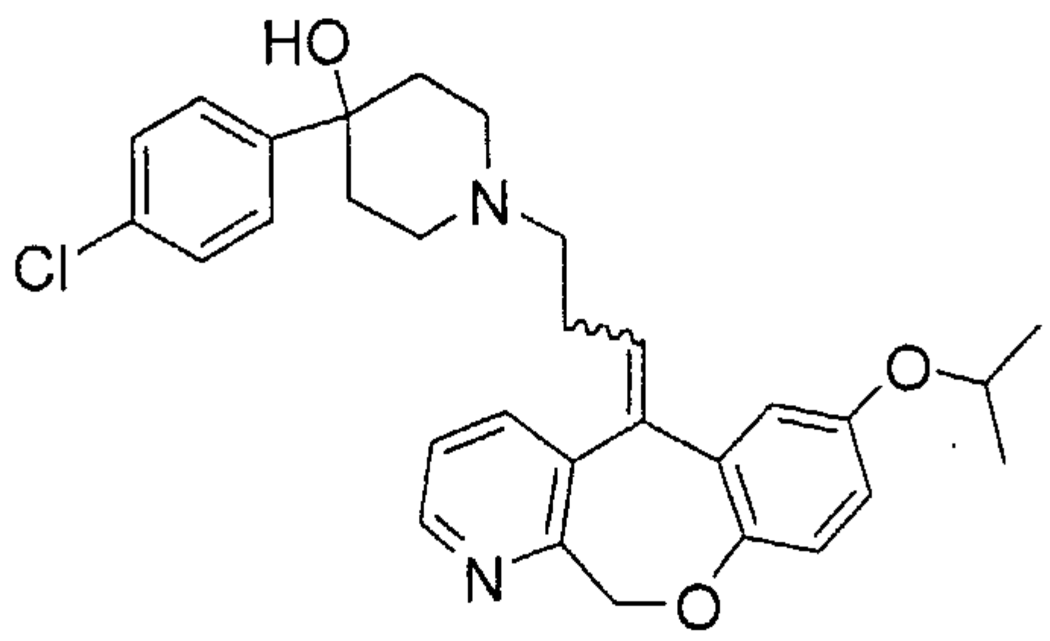
Example 44



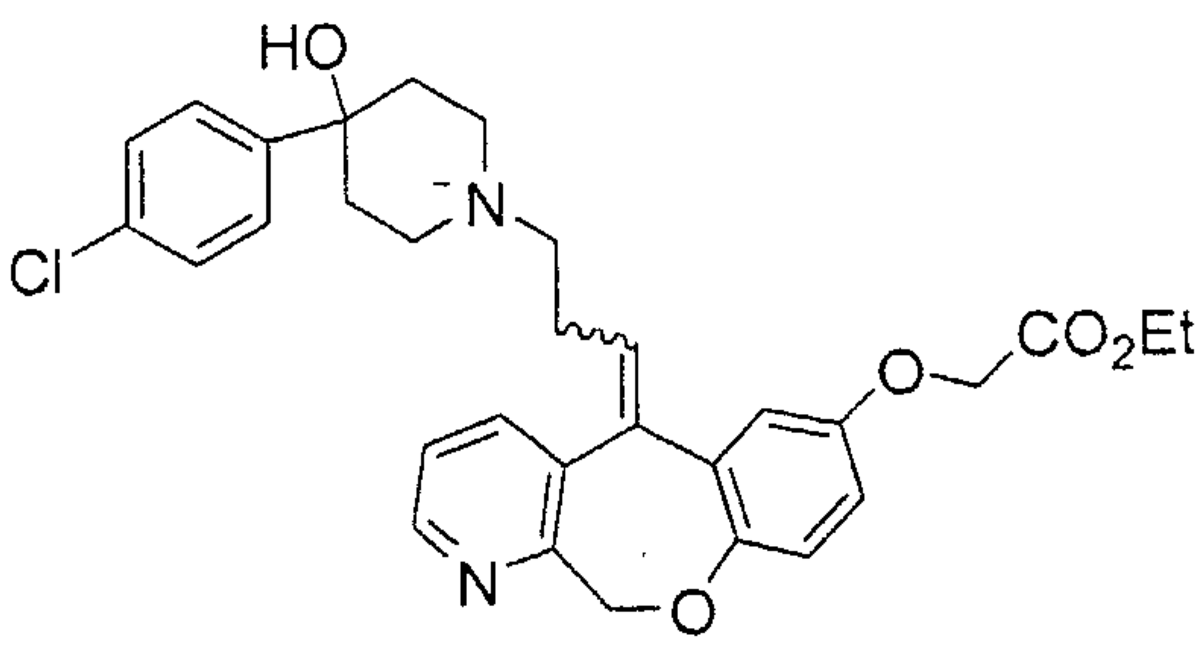
Example 45



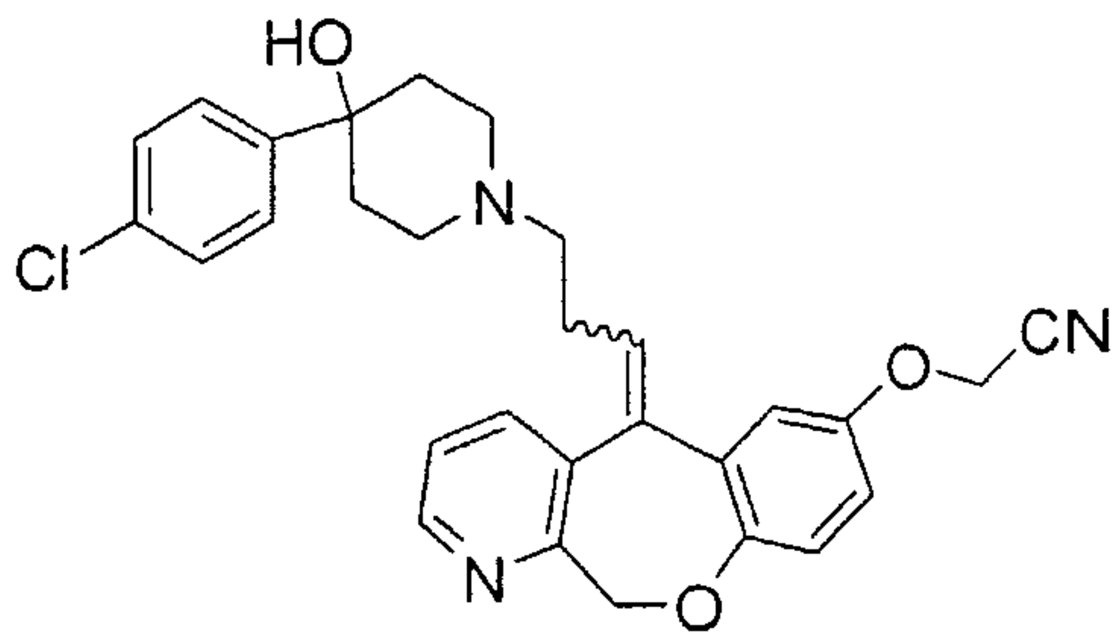
Example 46



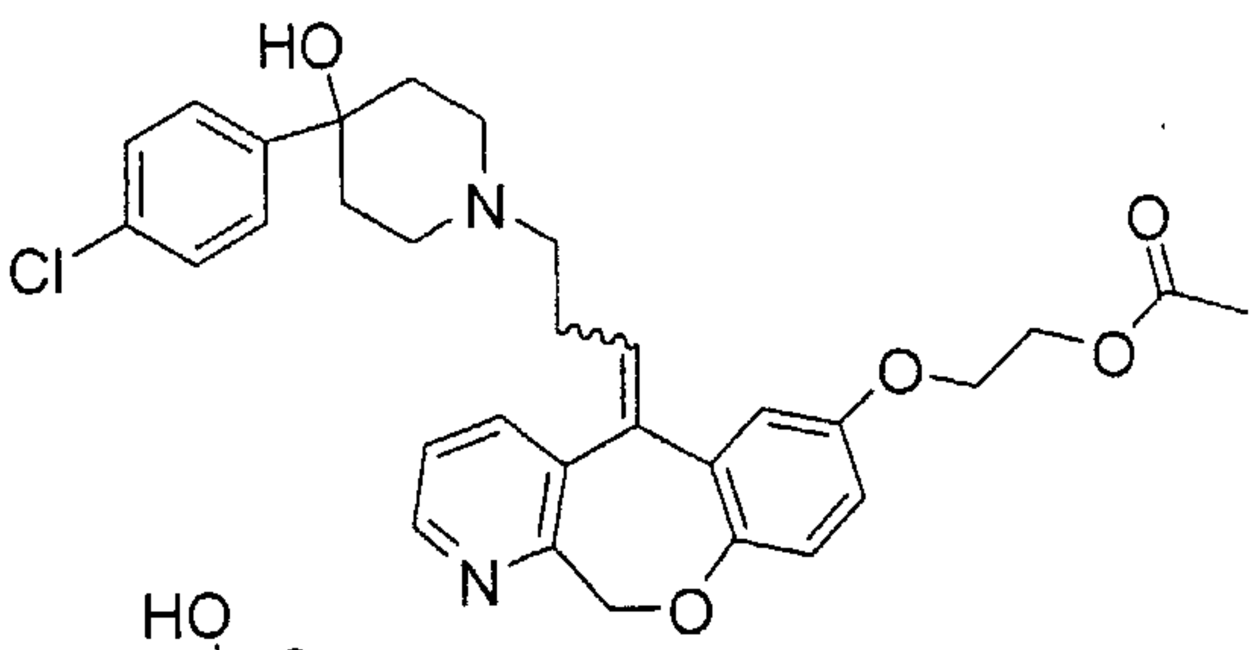
Example 47



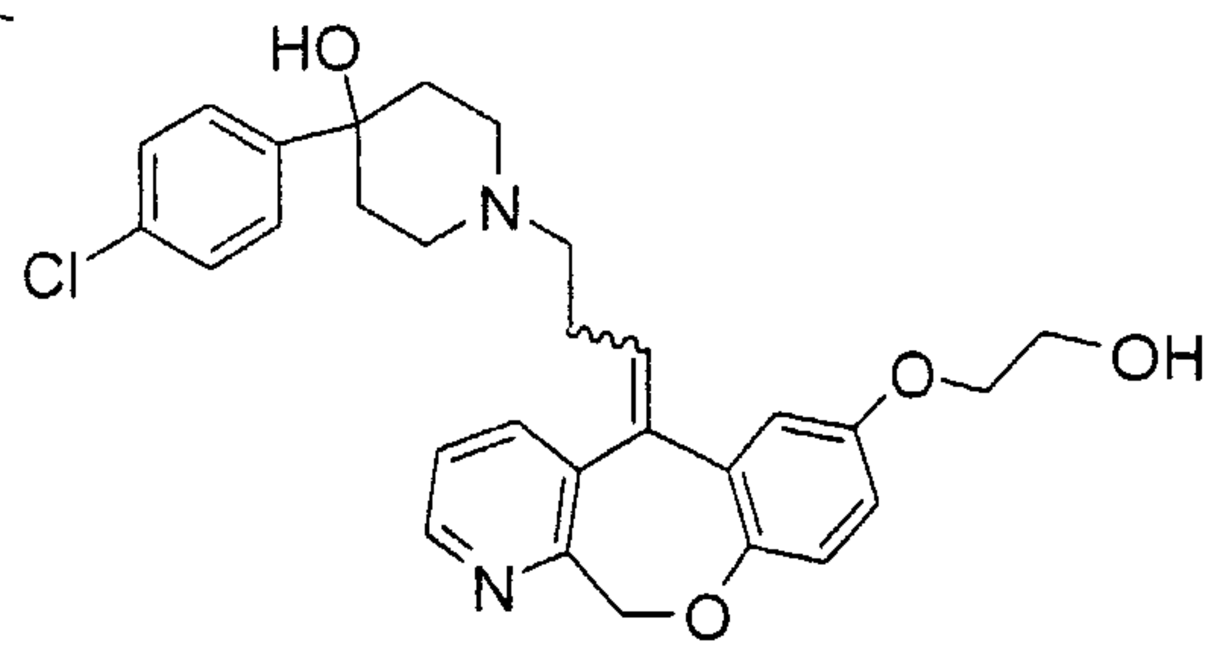
Example 48



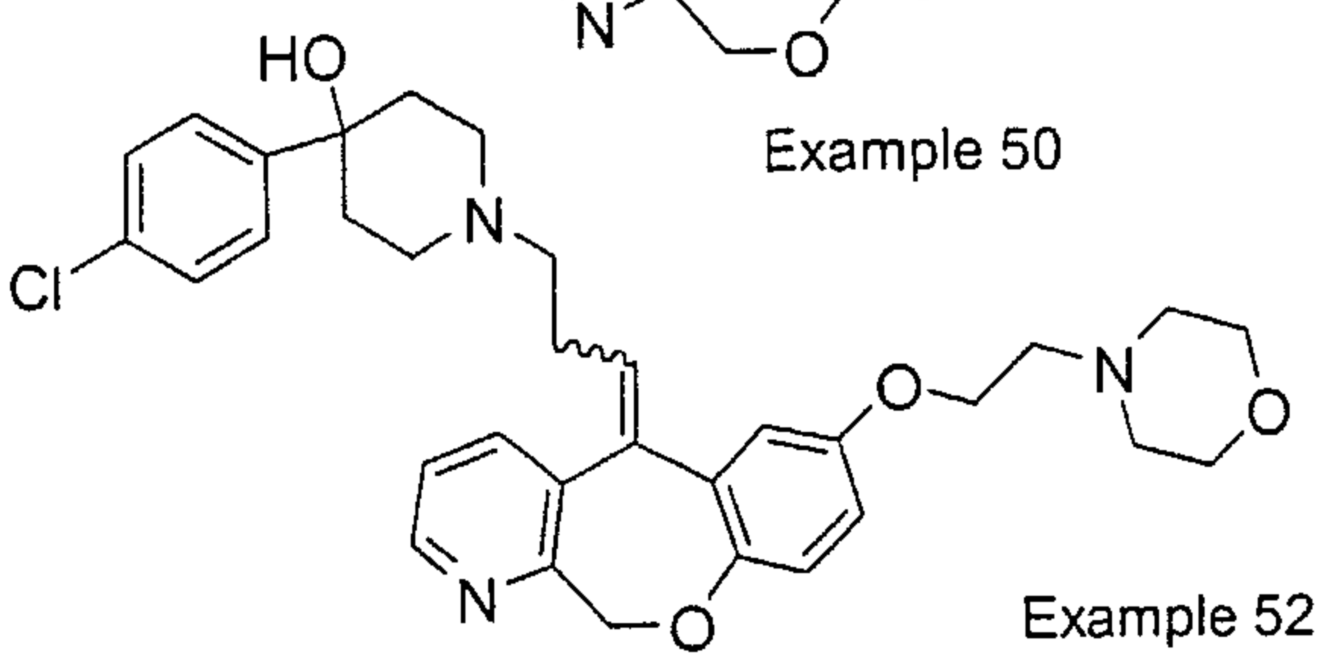
Example 49



Example 50

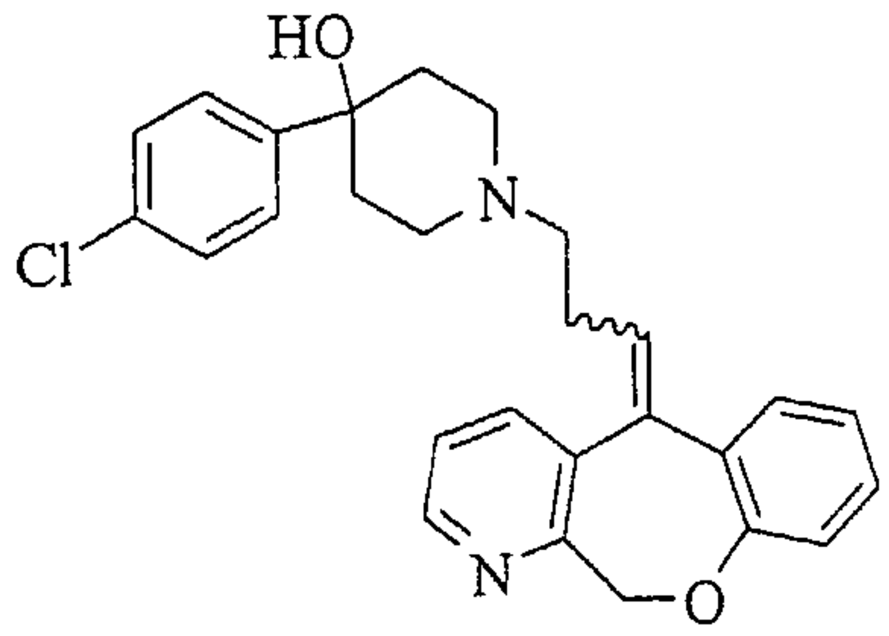


Example 51

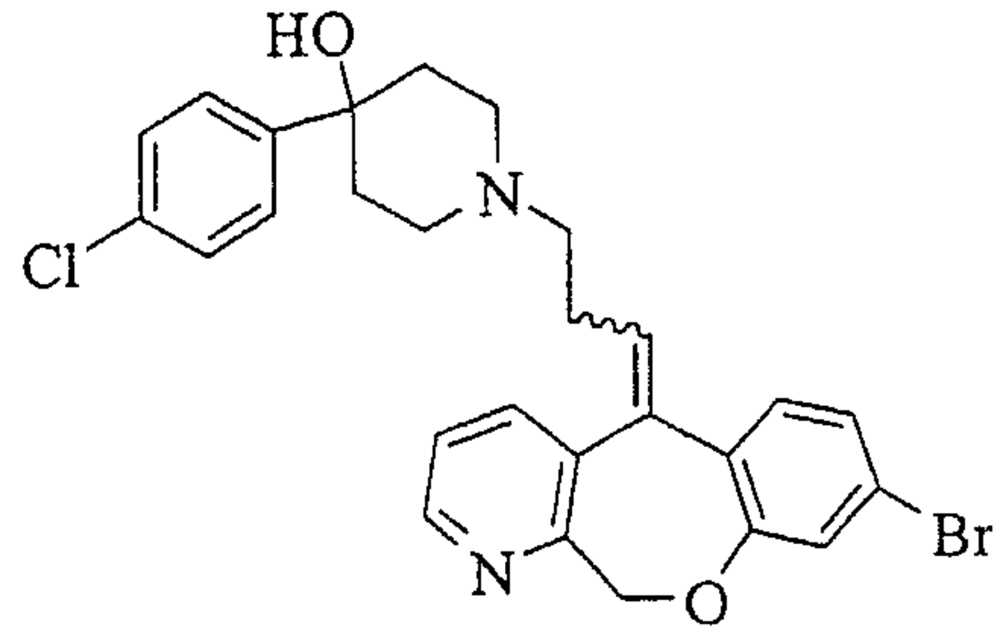


Example 52

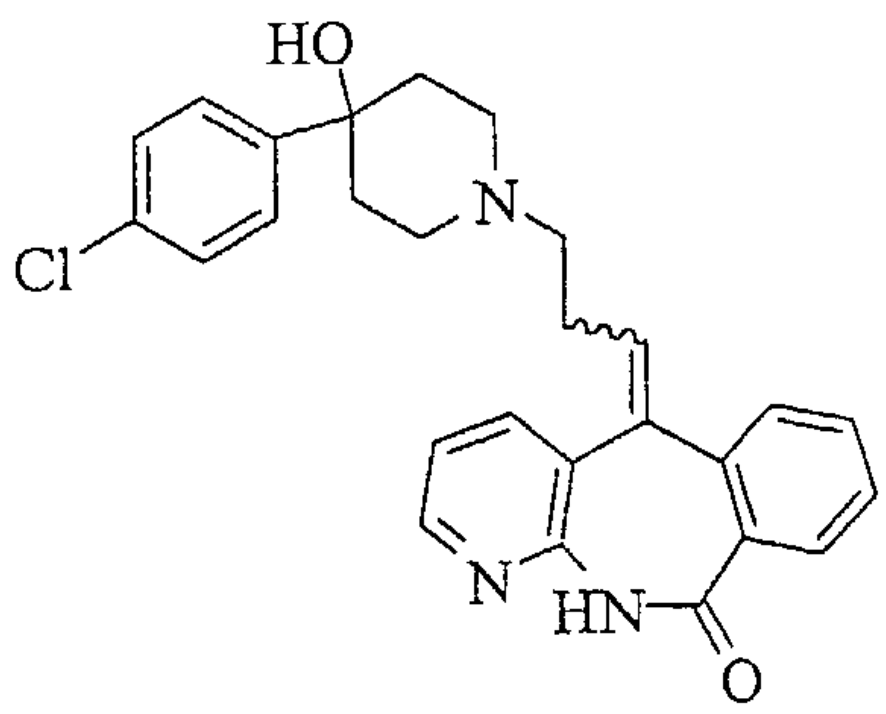
Figure 6F



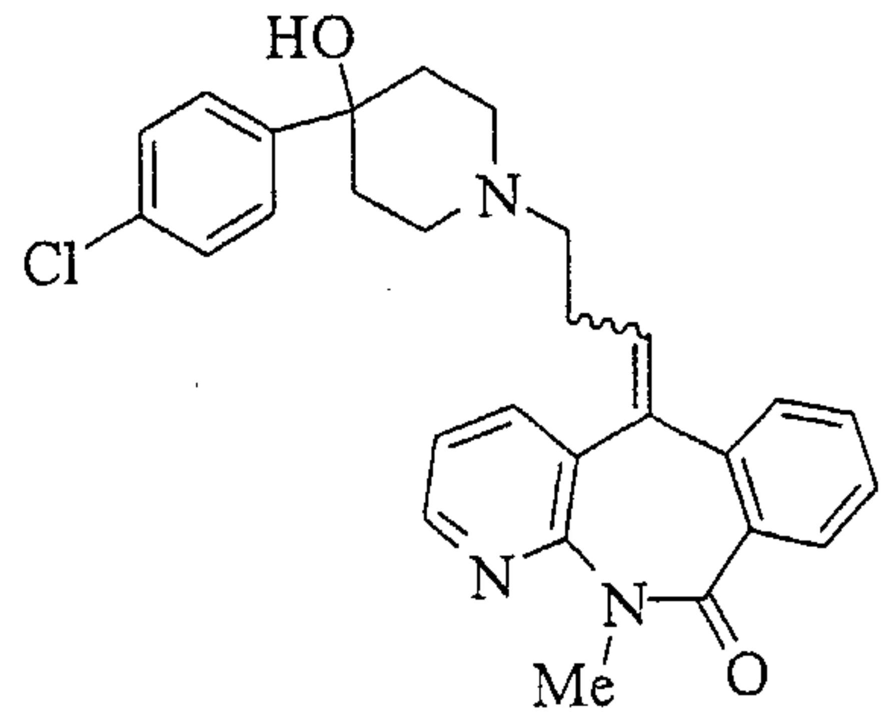
Example 53



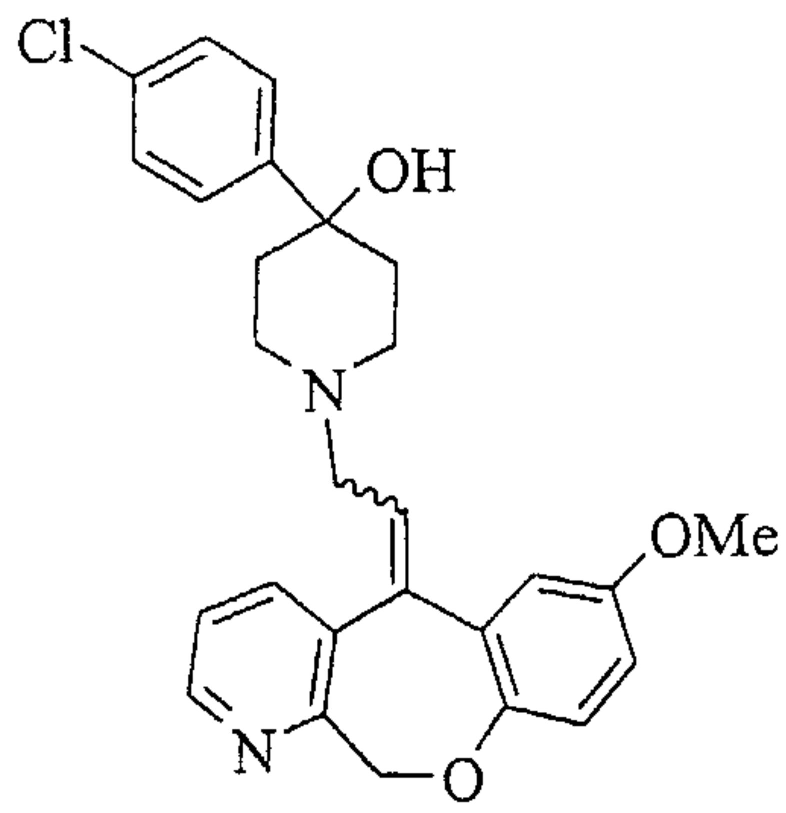
Example 54



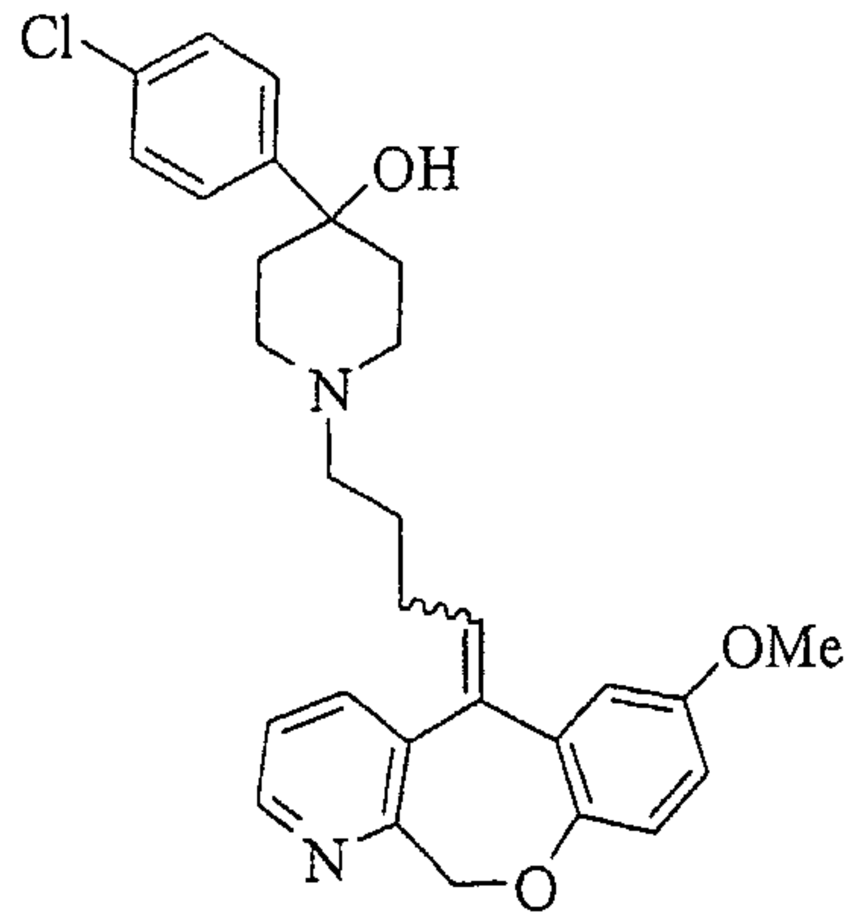
Example 55



Example 56

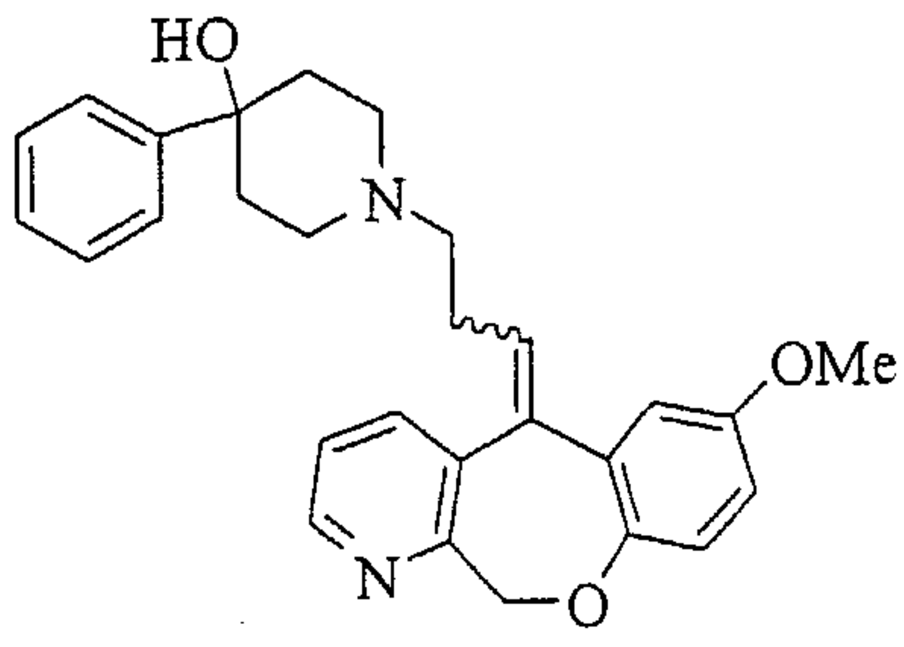


Example 57

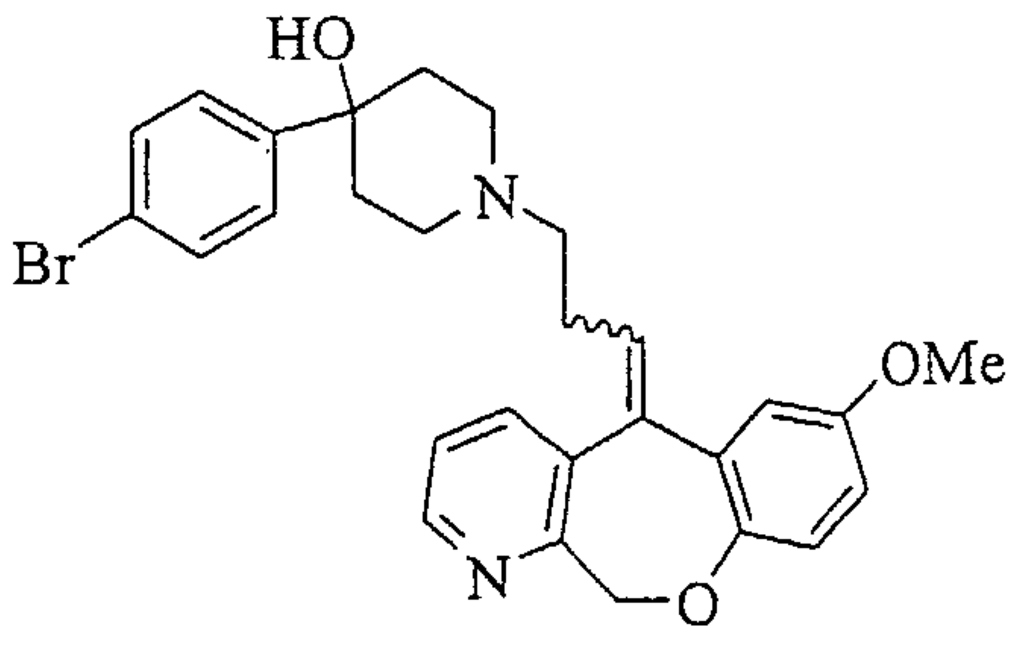


Example 58

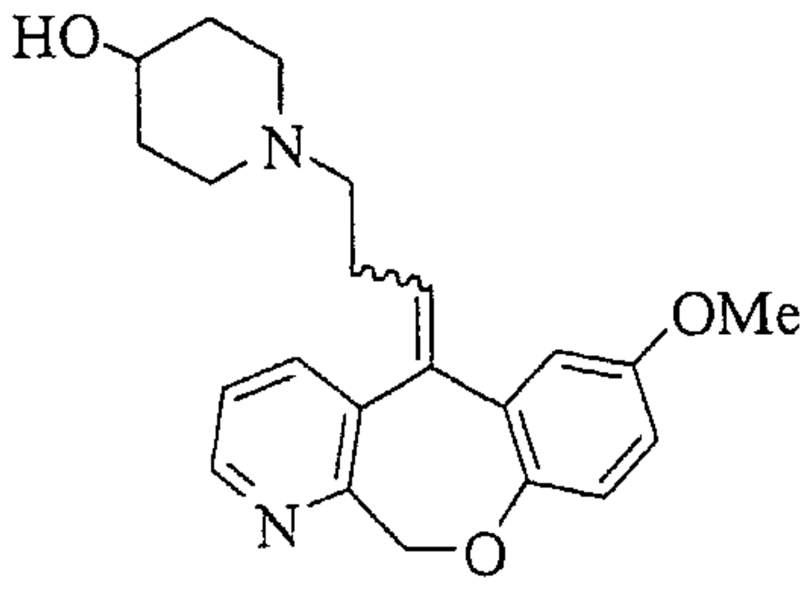
Figure 6G



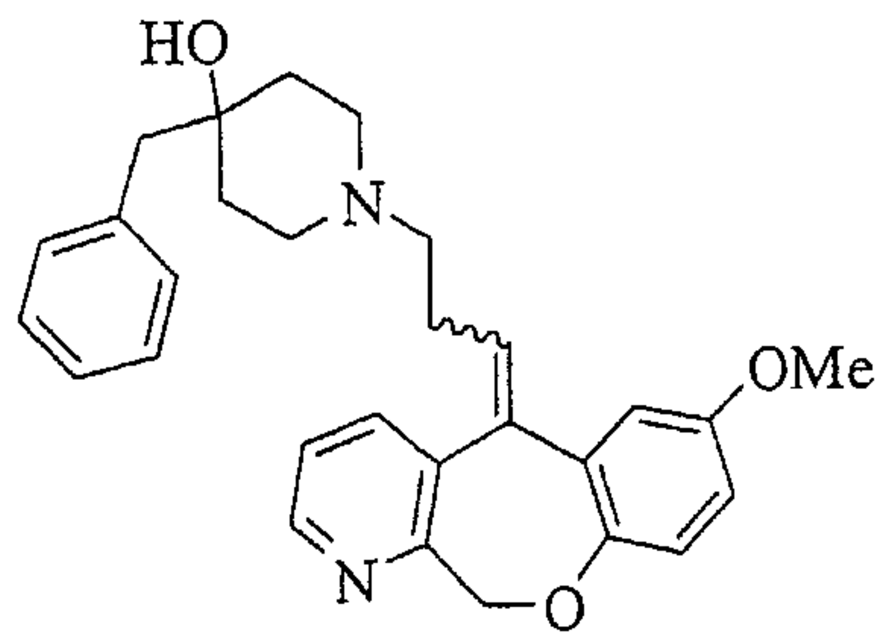
Example 59



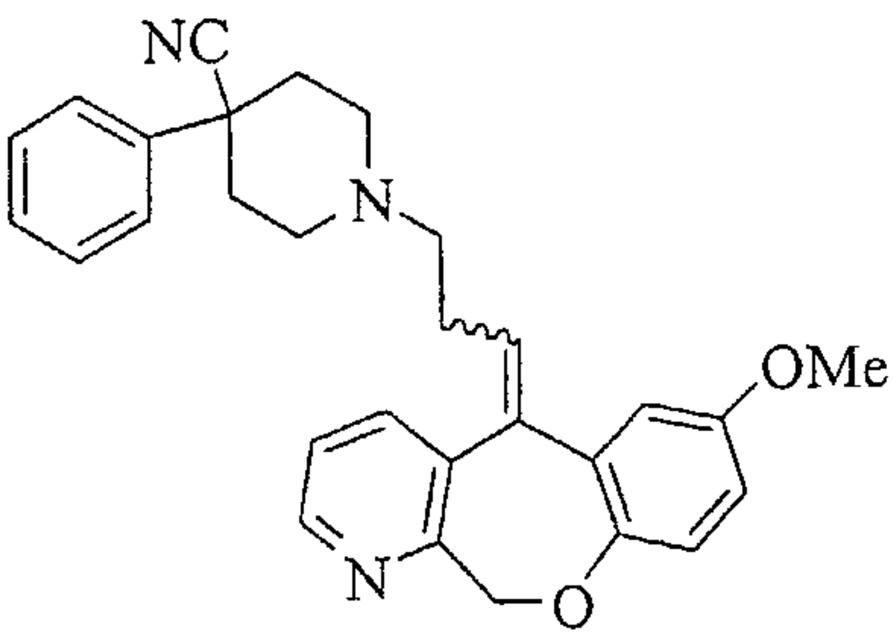
Example 60



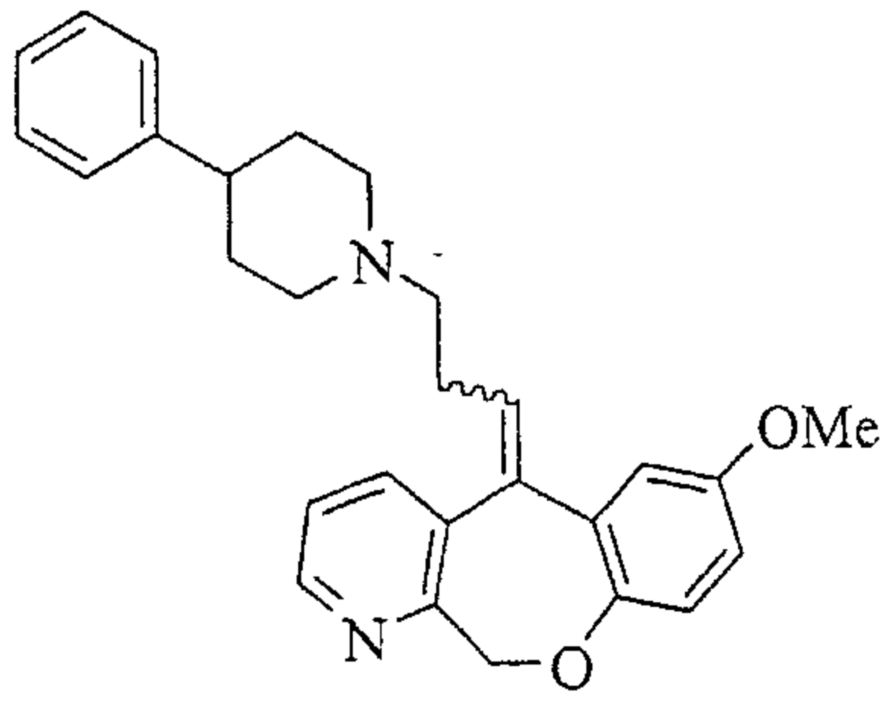
Example 61



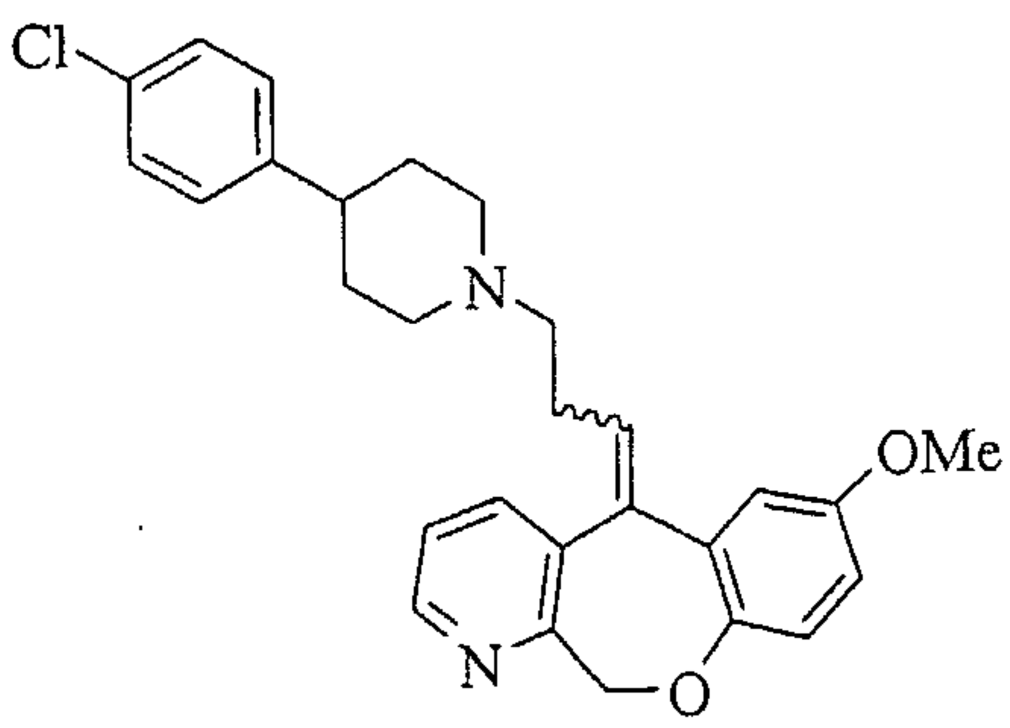
Example 62



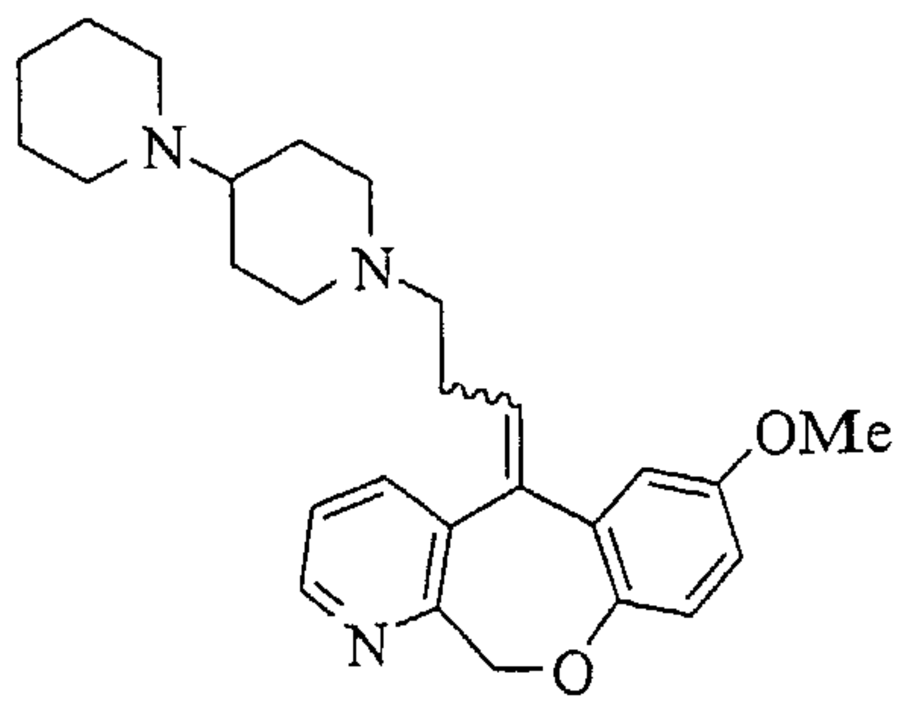
Example 63



Example 64

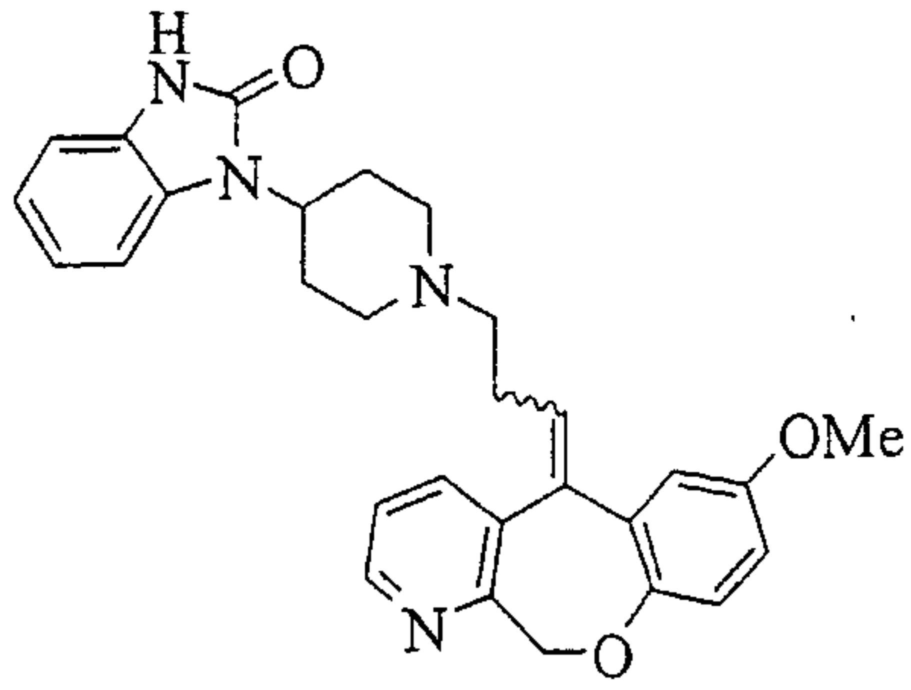


Example 65

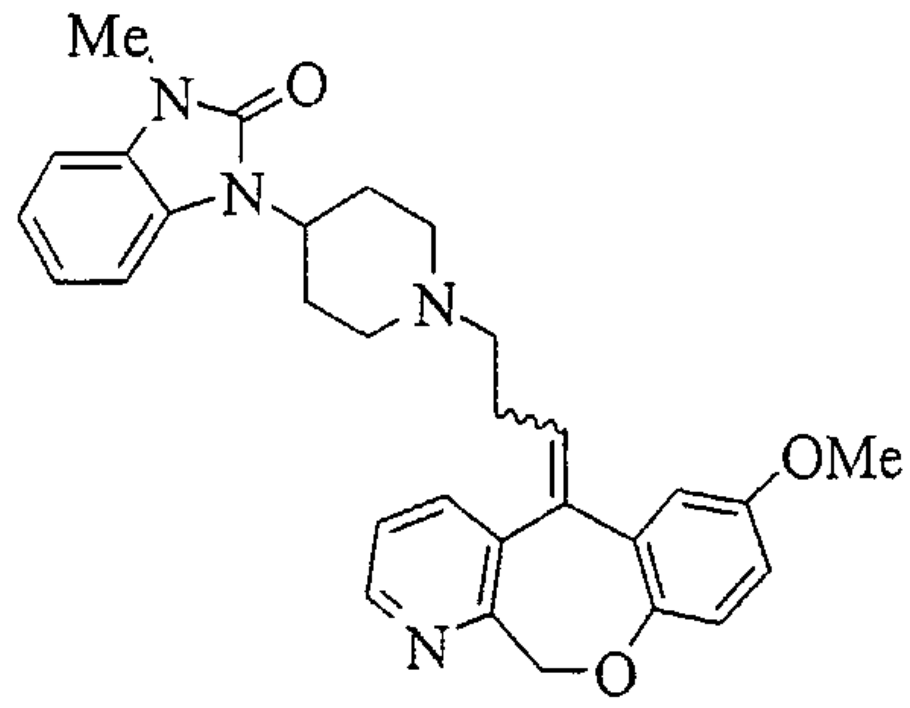


Example 66

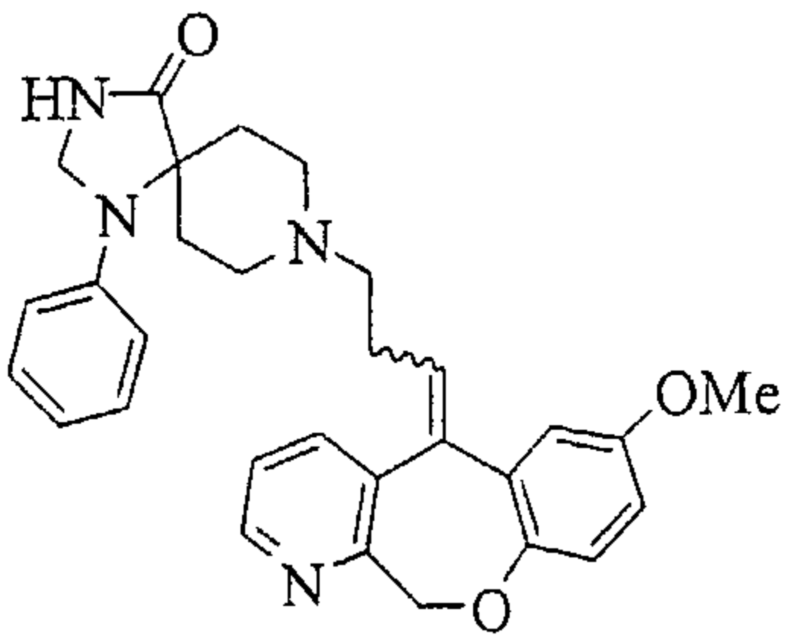
Figure 6H



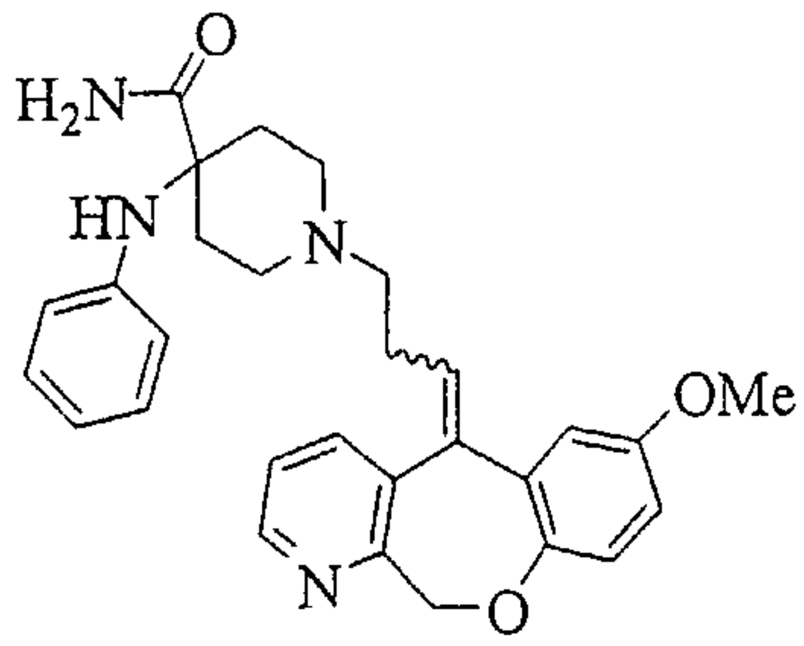
Example 67



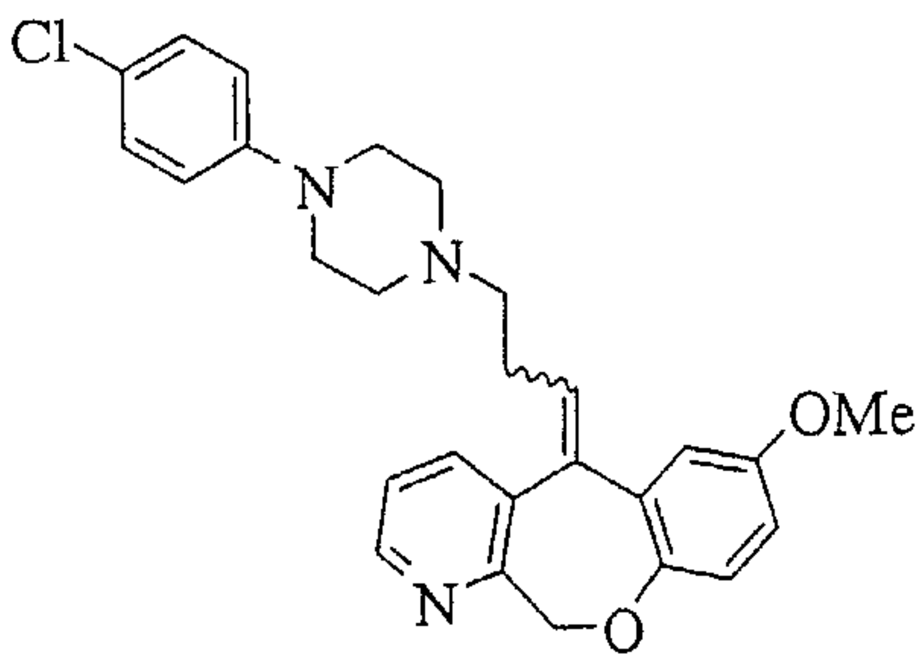
Example 68



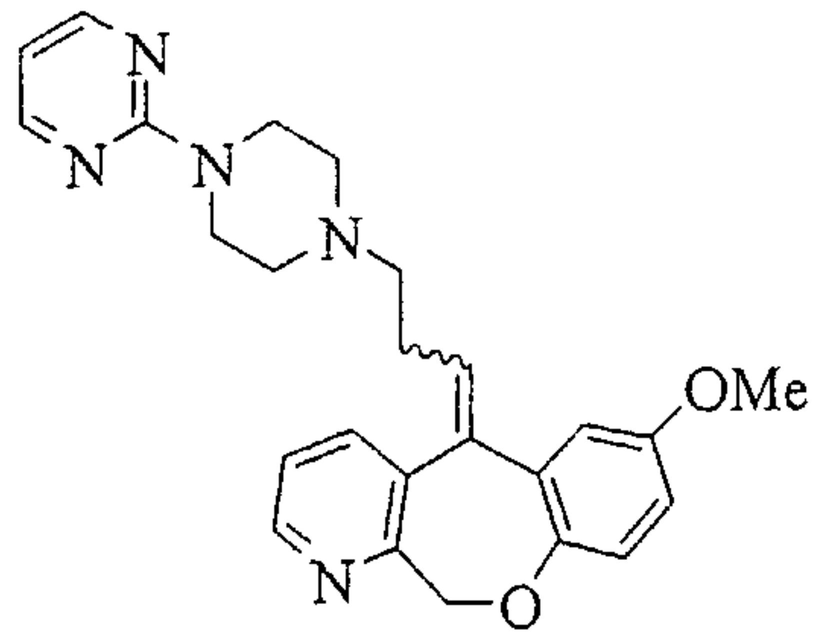
Example 69



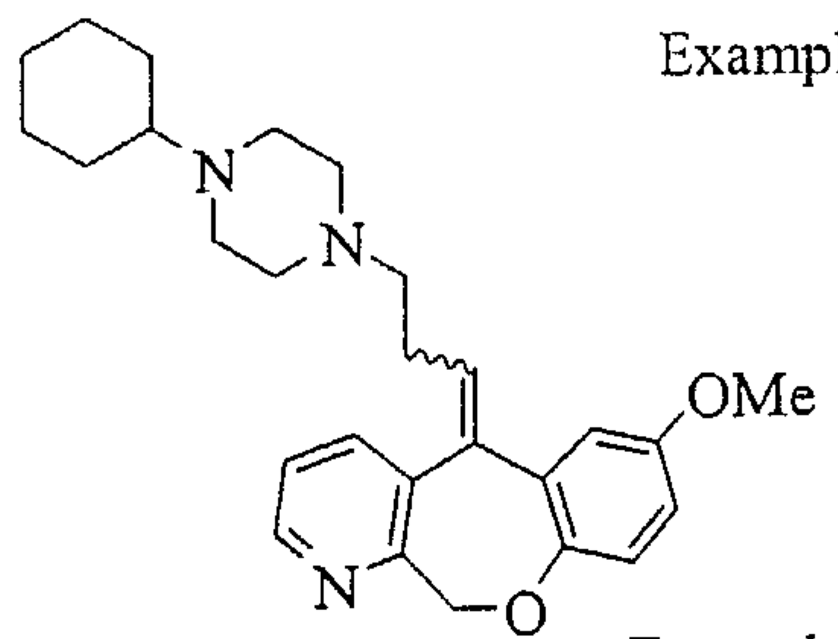
Example 70



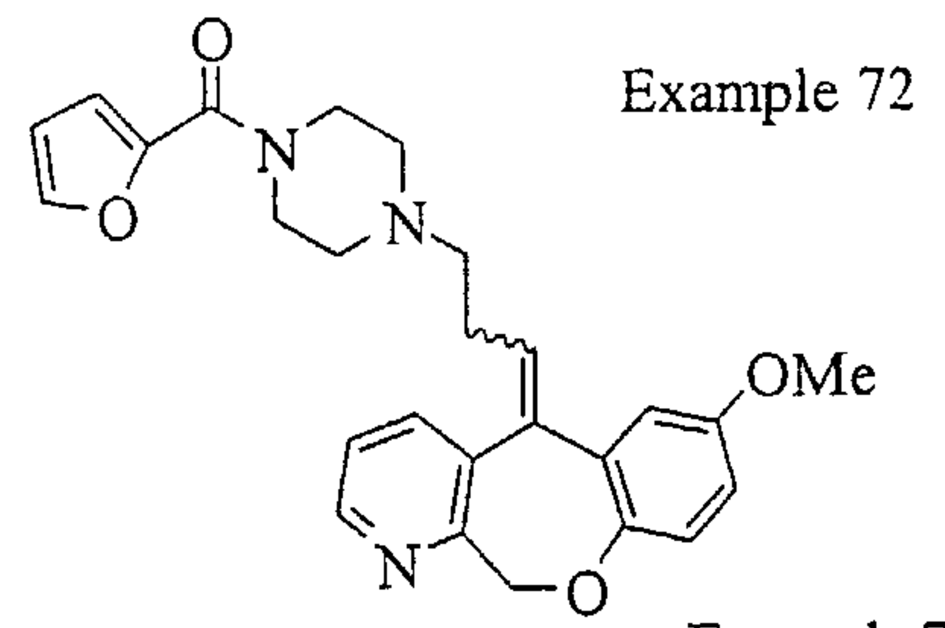
Example 71



Example 72

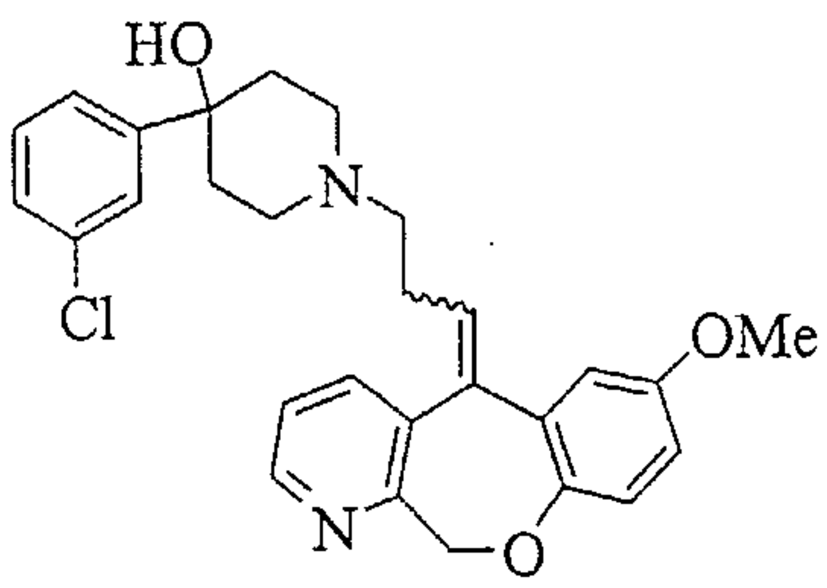


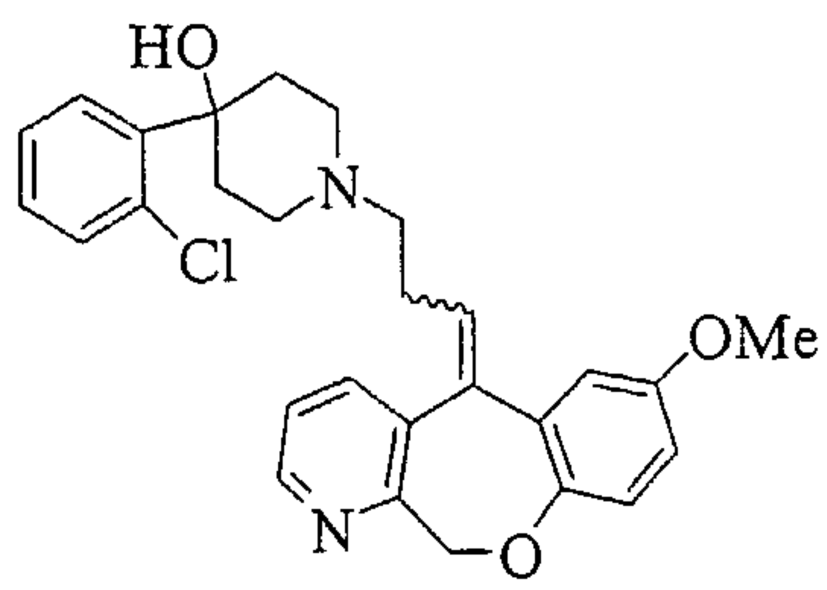
Example 73

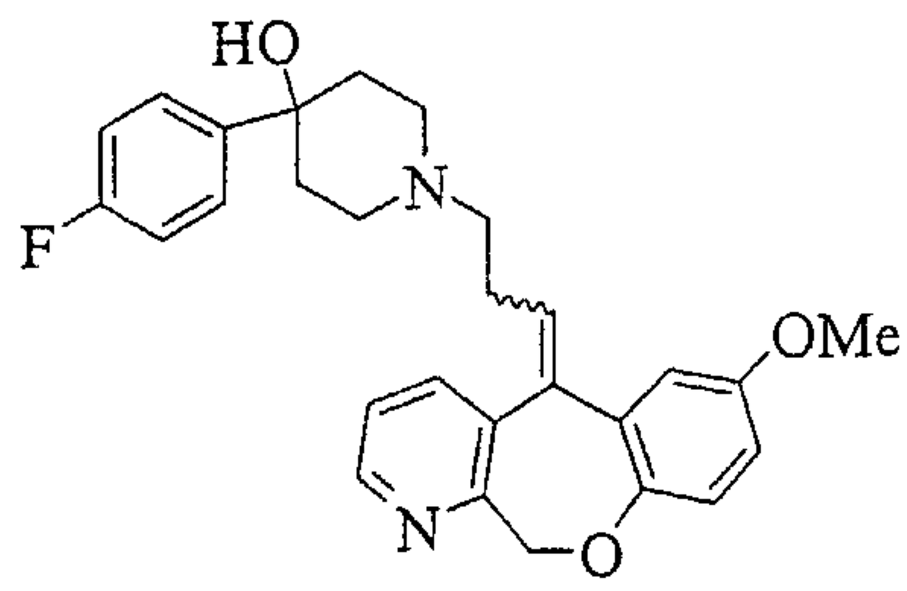


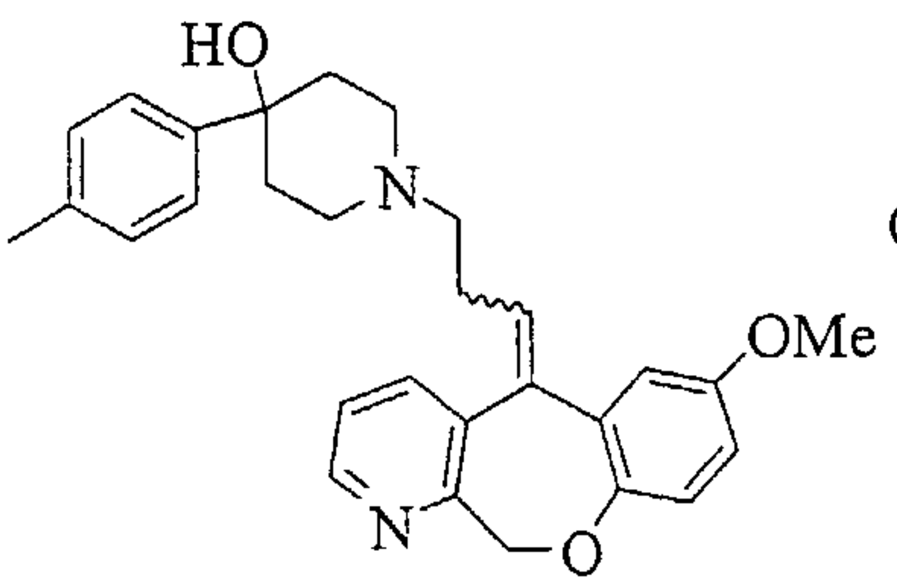
Example 74

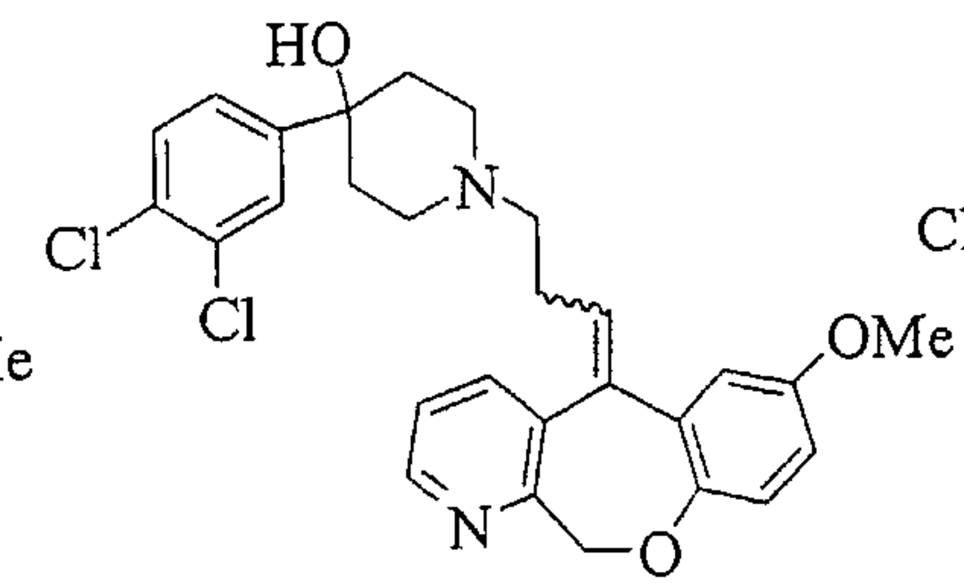
Figure 6I

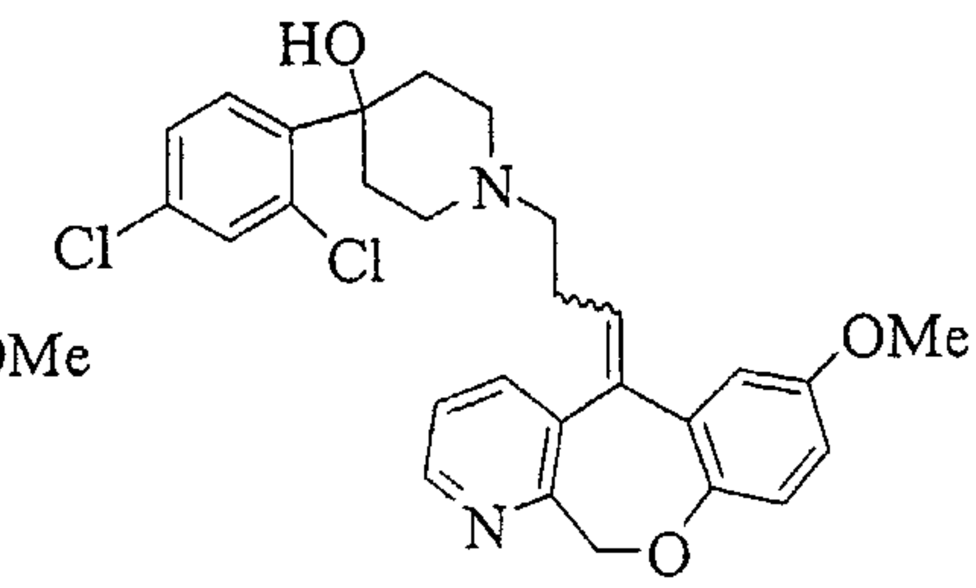

Example 75

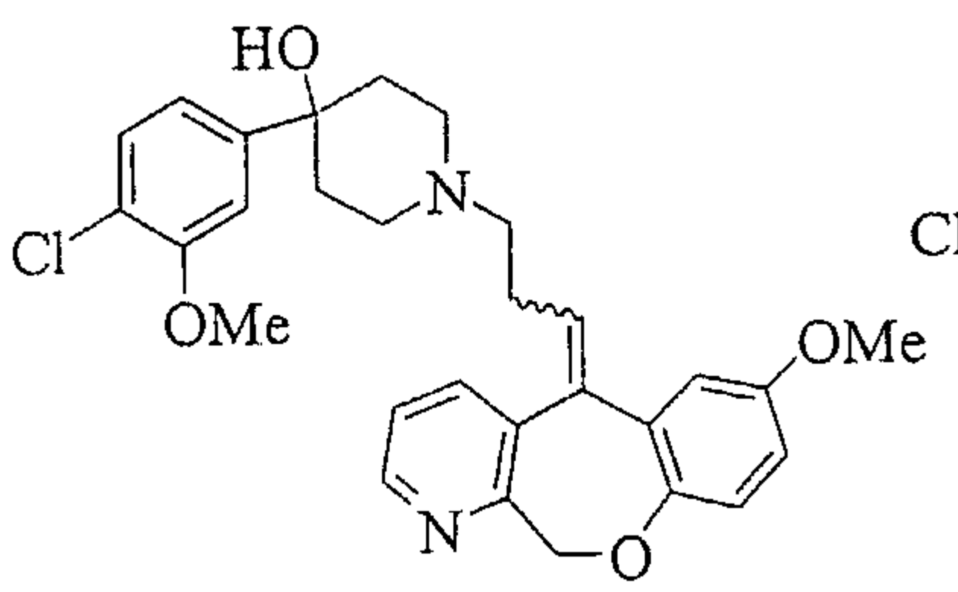

Example 76

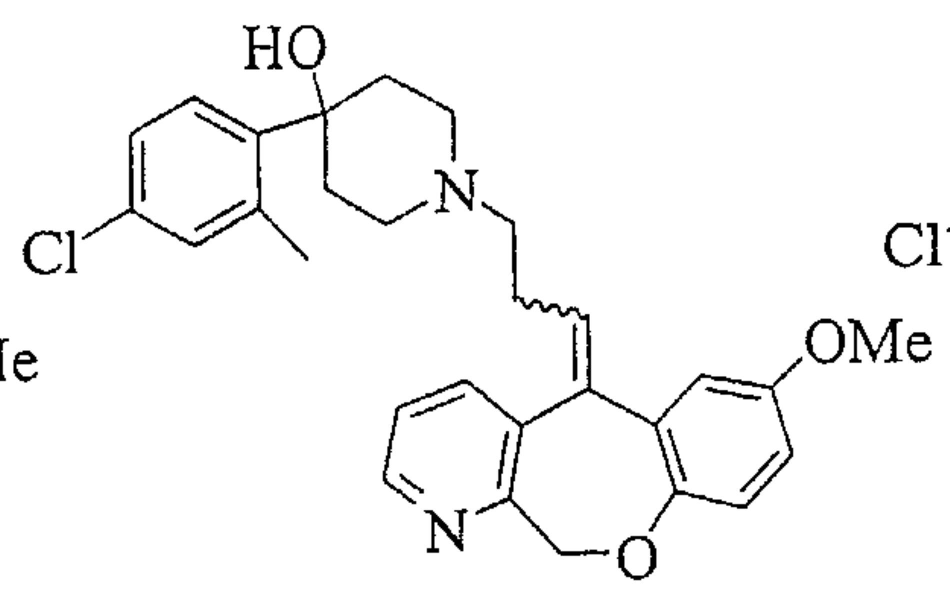

Example 77

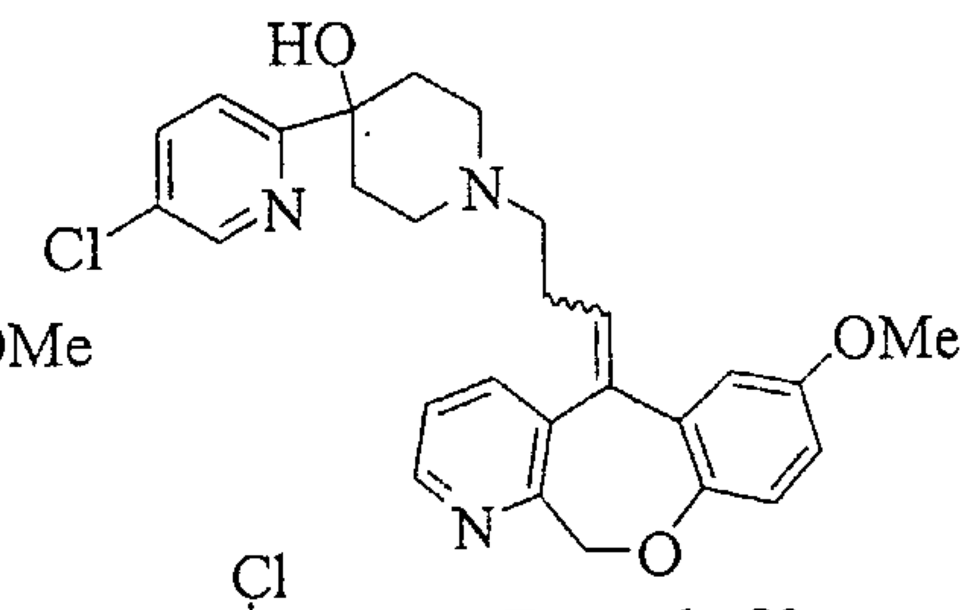

Example 78

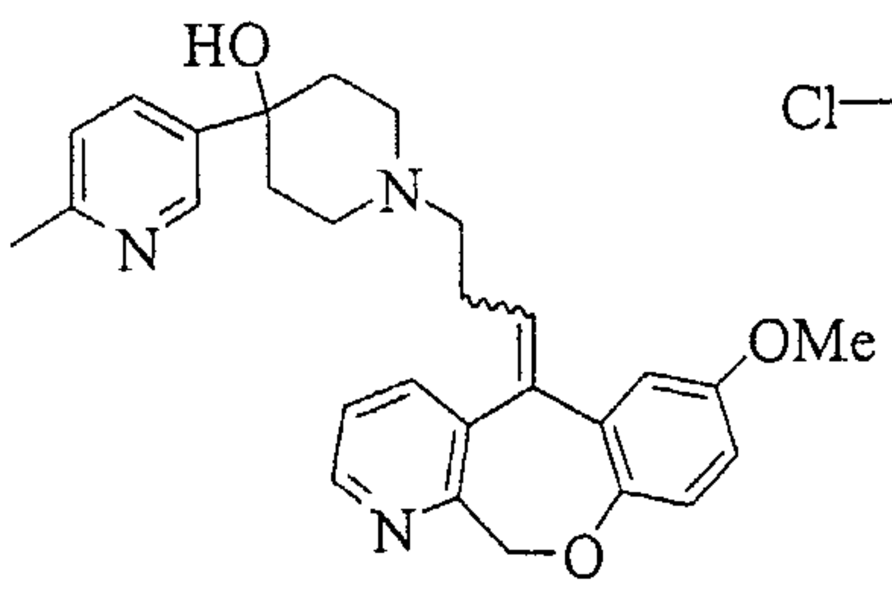

Example 79

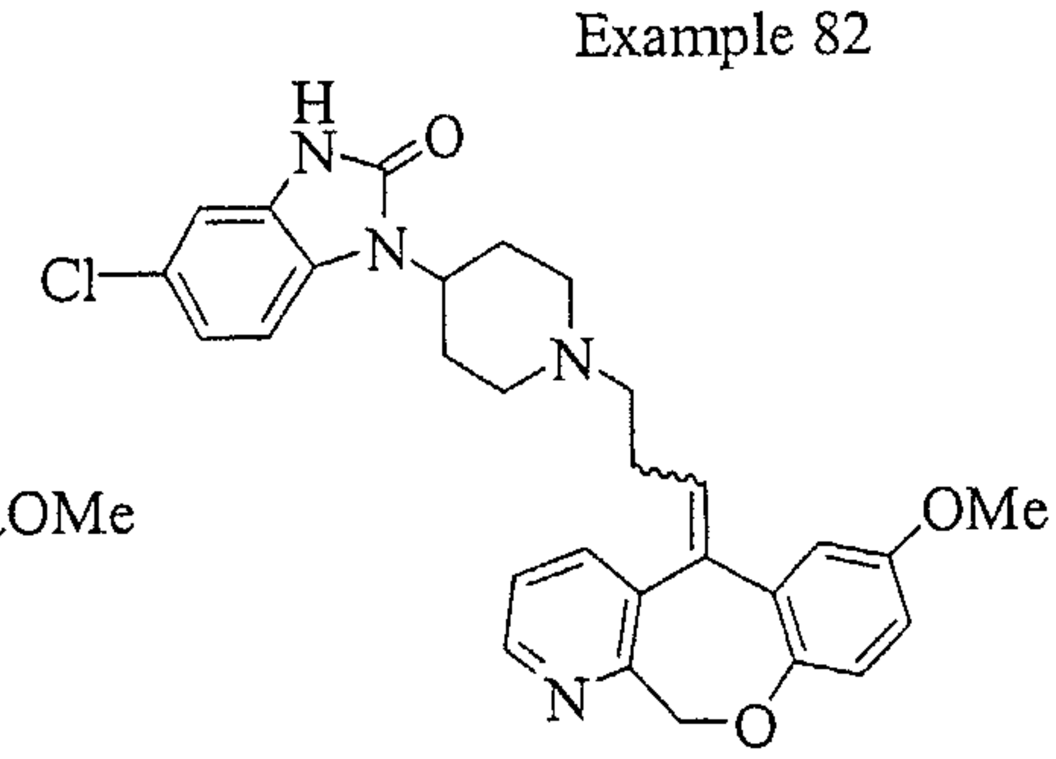

Example 80

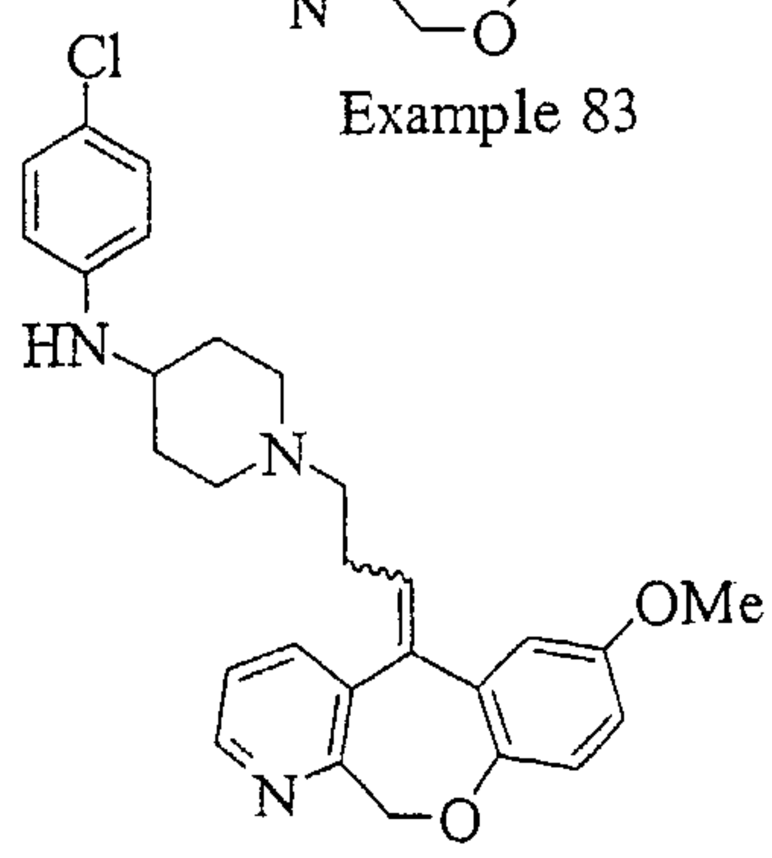

Example 81

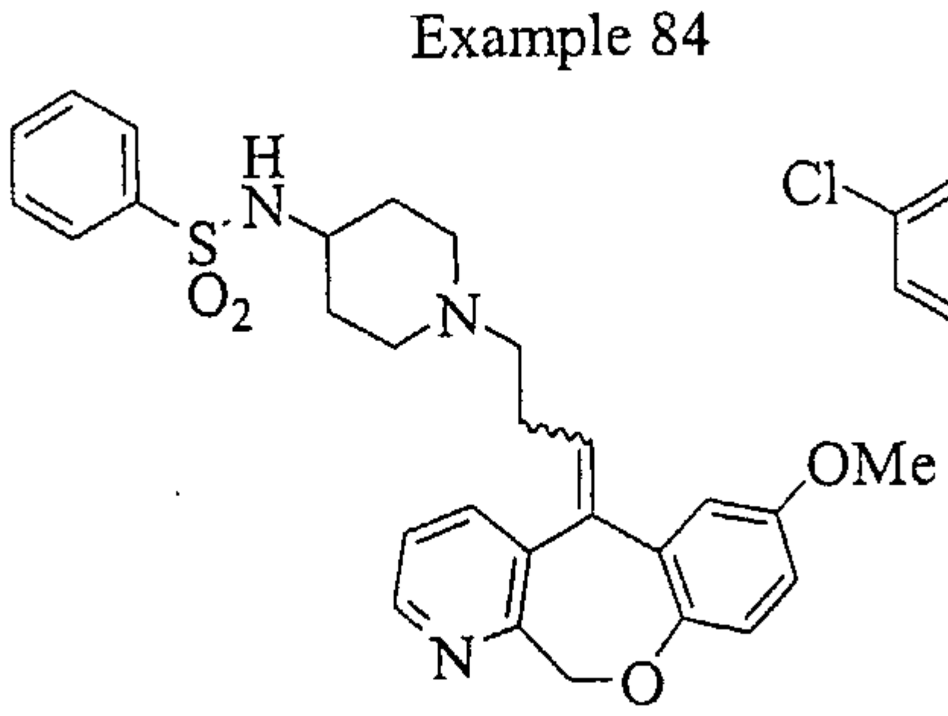

Example 82

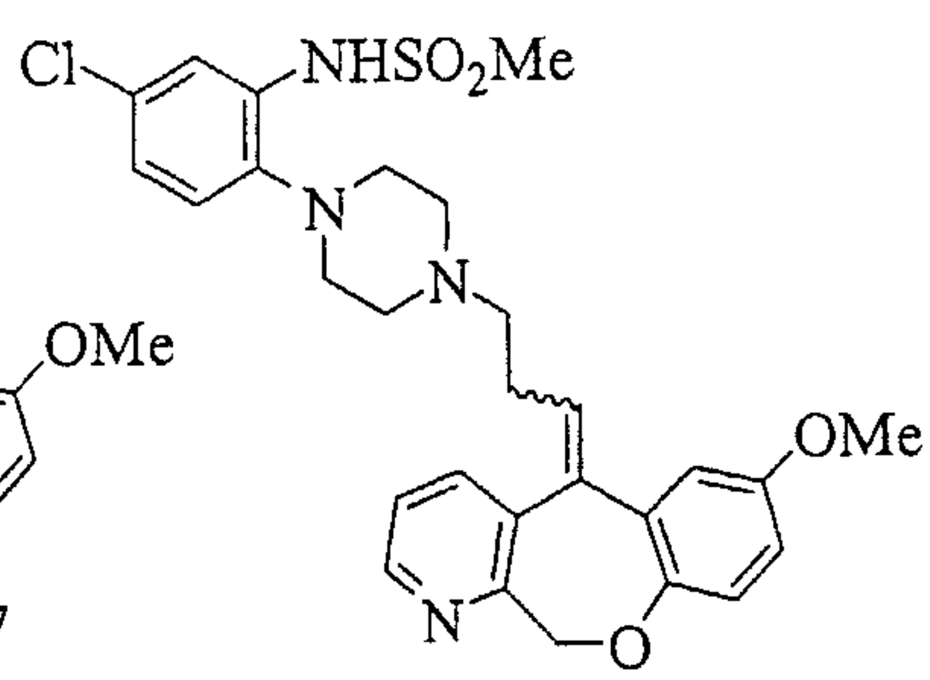

Example 83


Example 84


Example 85


Example 86


Example 87


Example 88

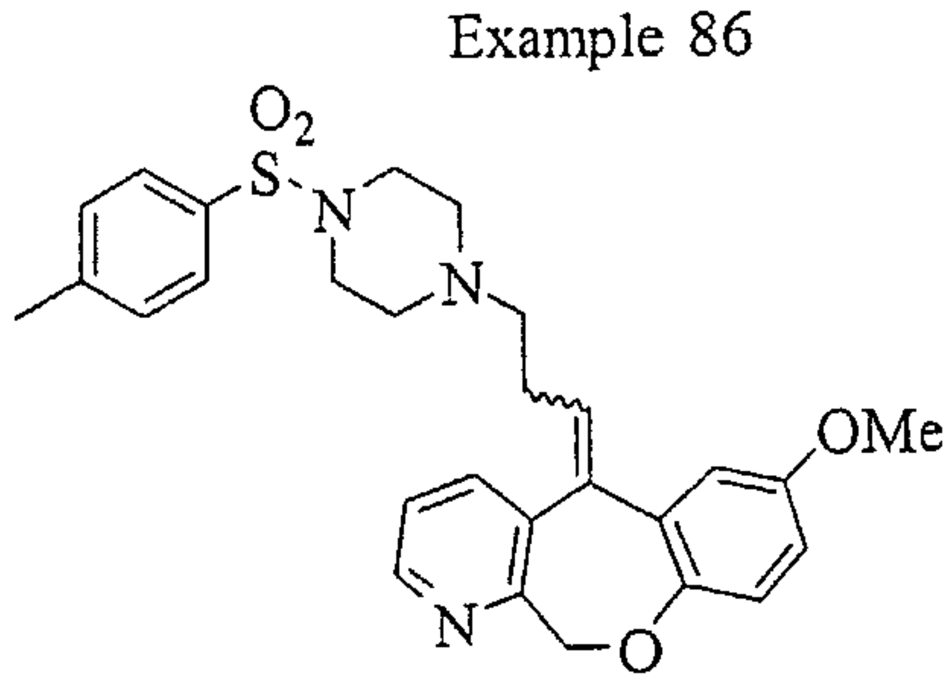
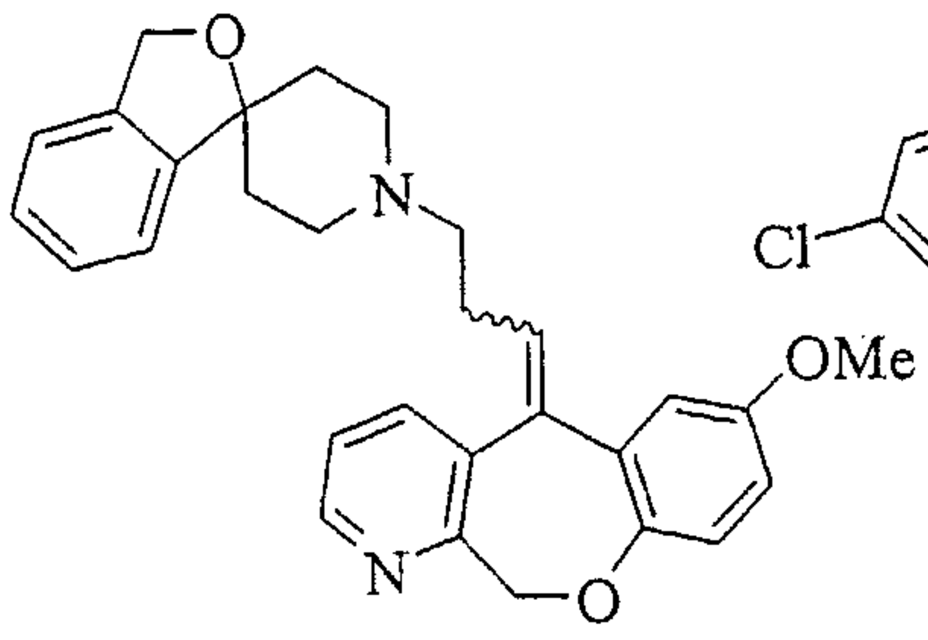
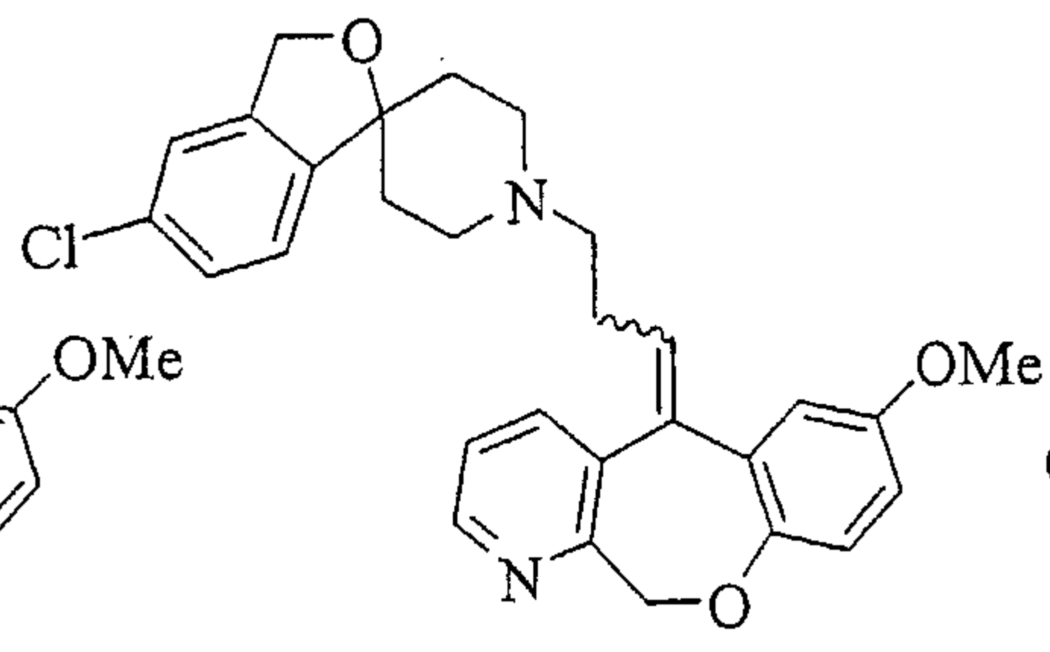
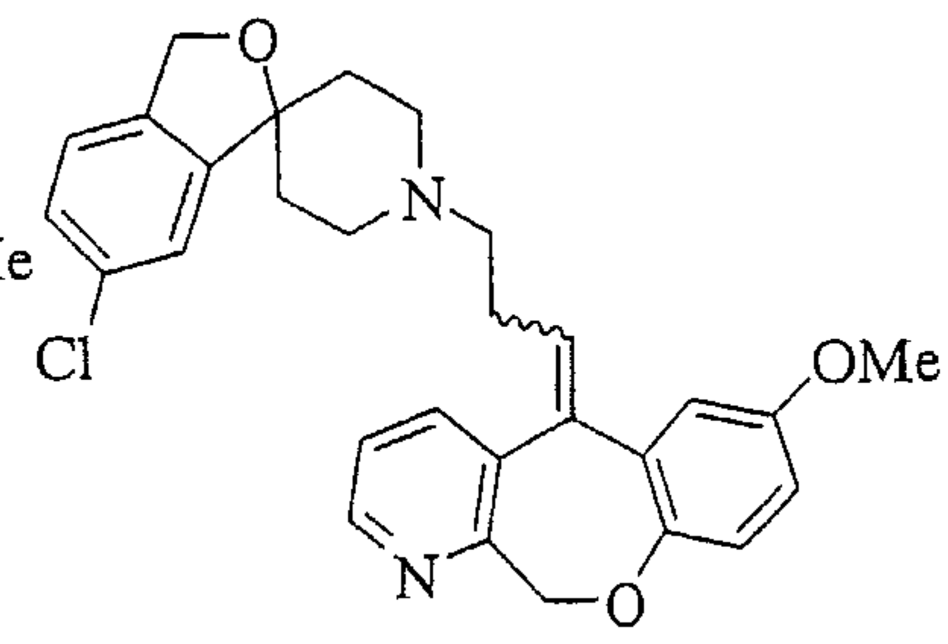
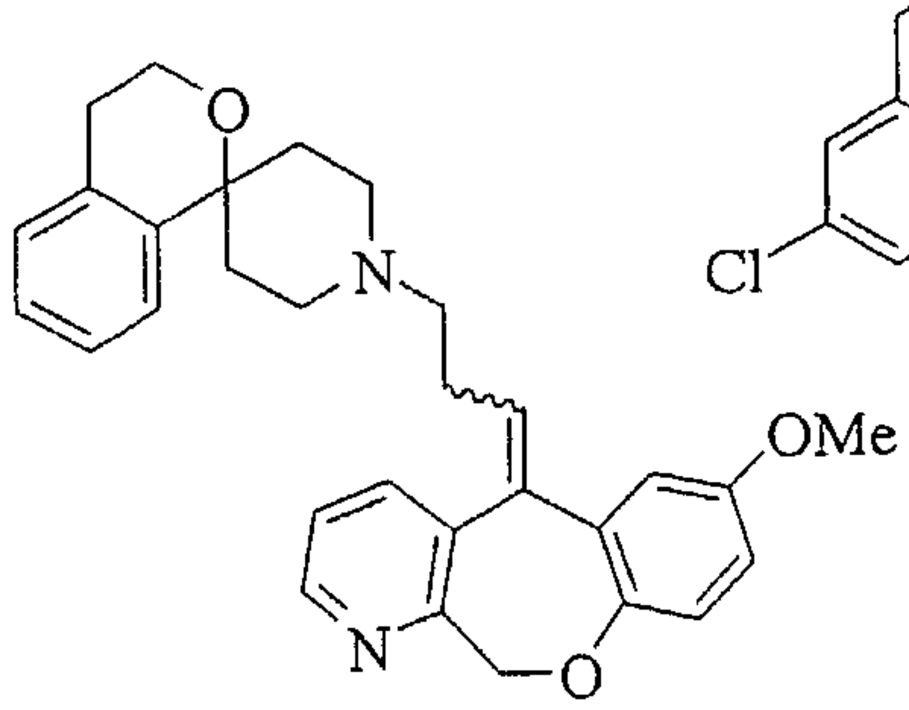

Example 89

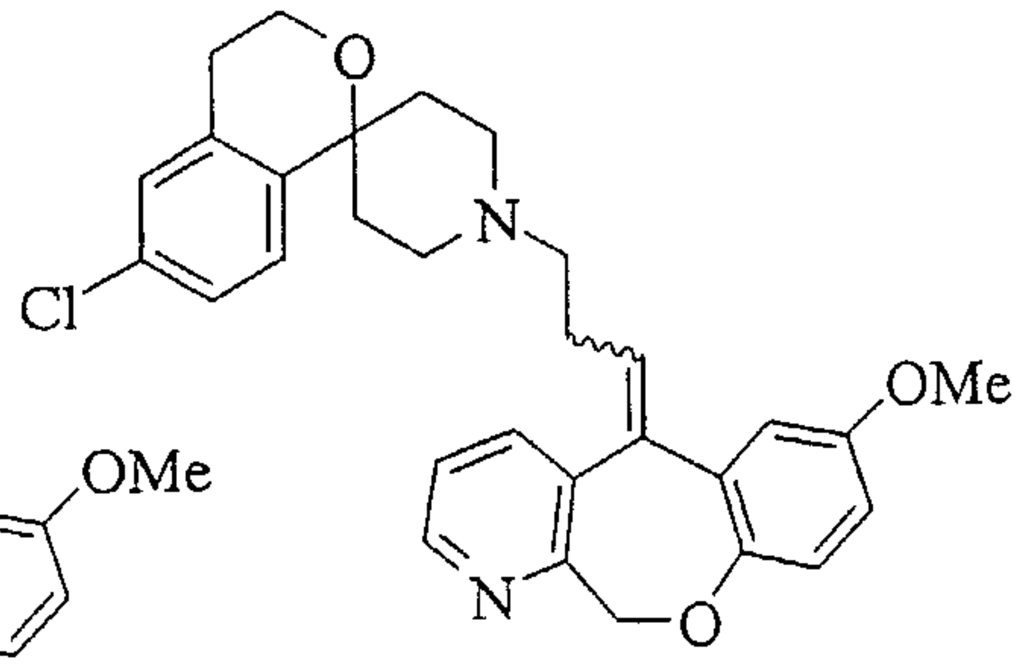
Figure 6J


Example 90


Example 91


Example 92


Example 93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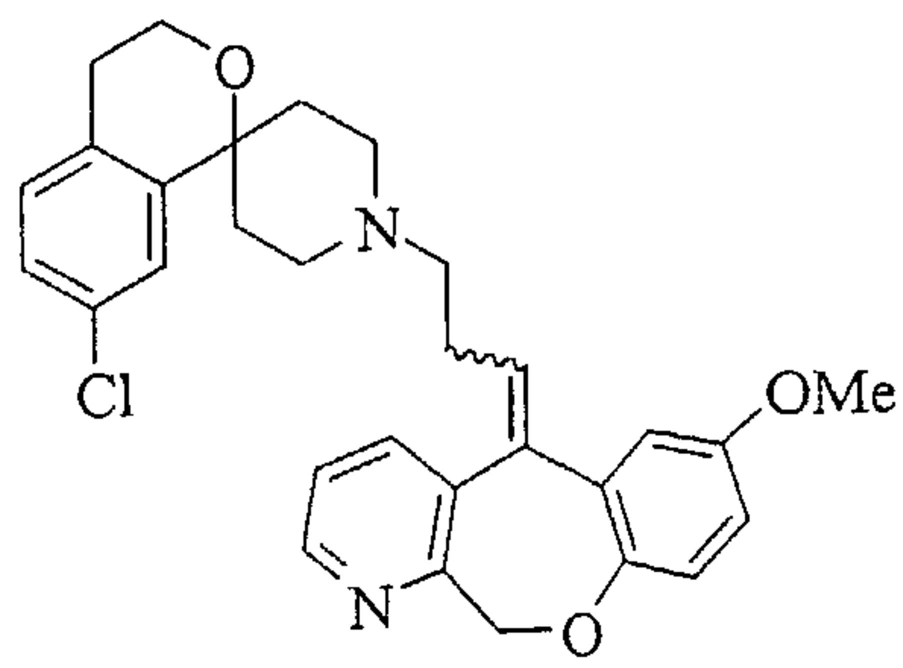
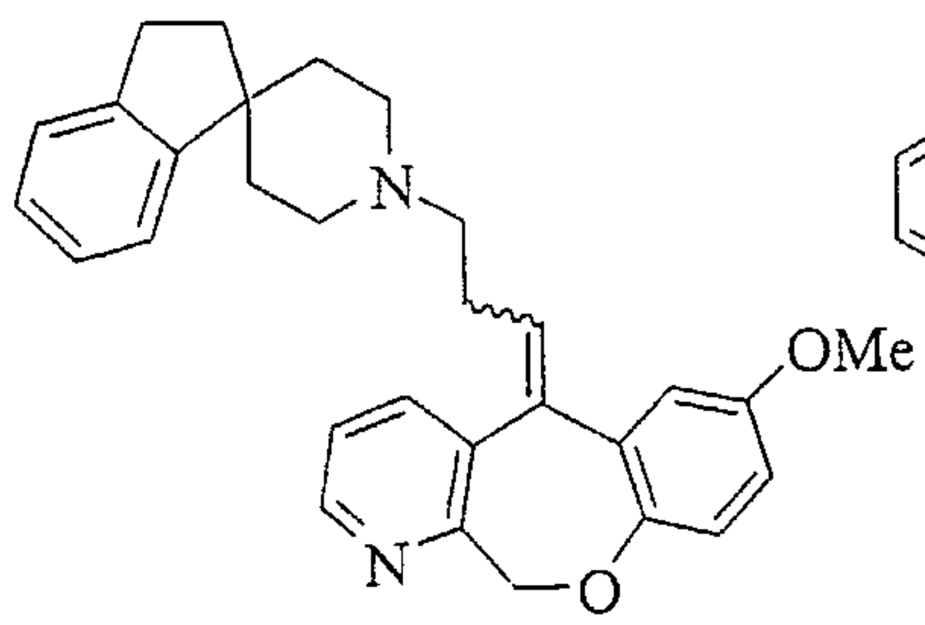
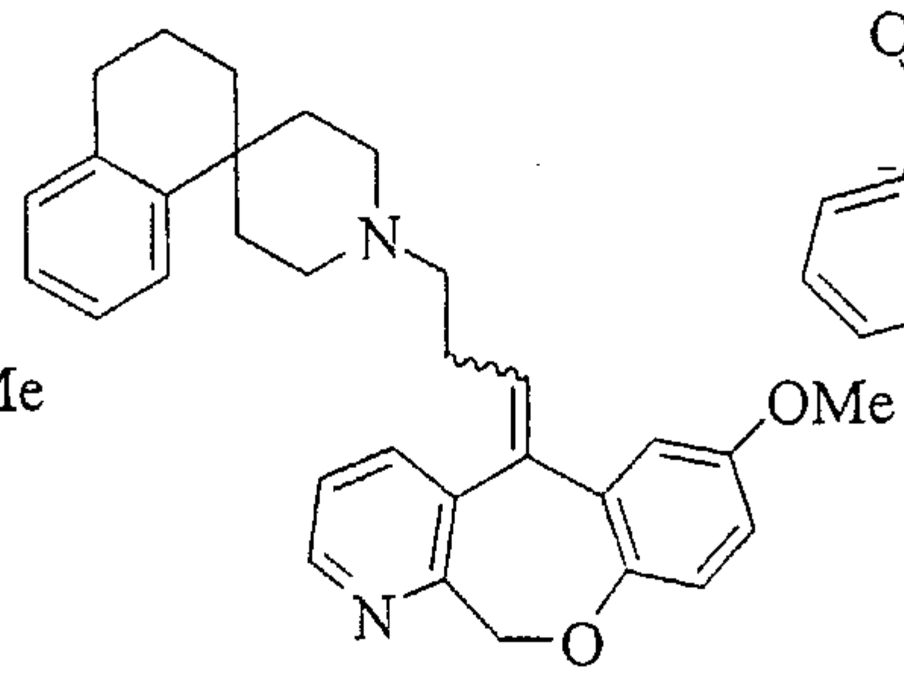
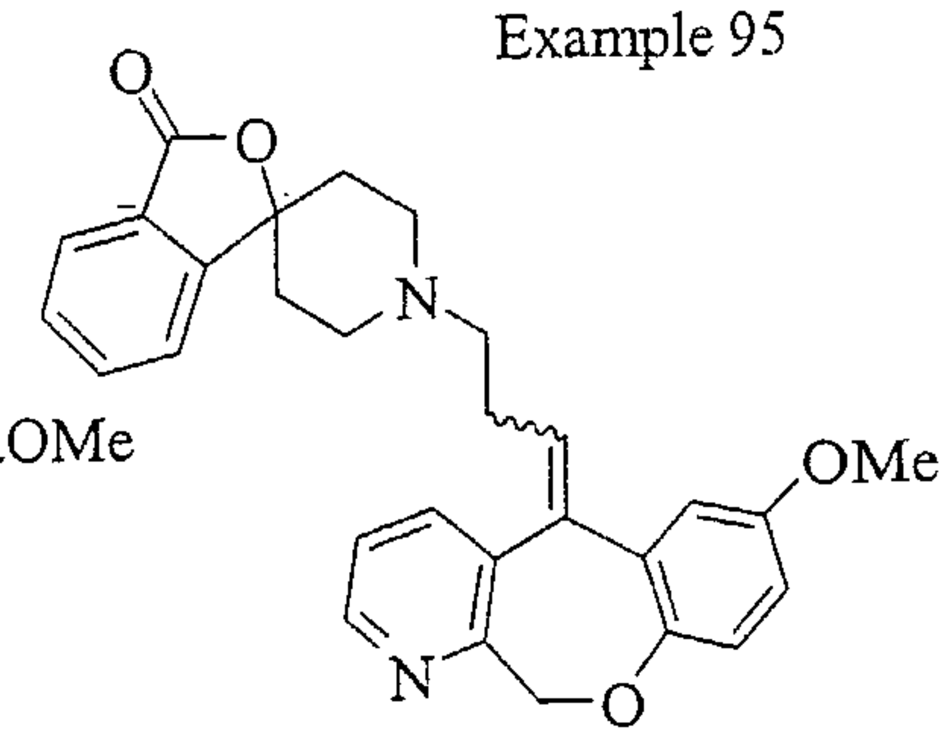
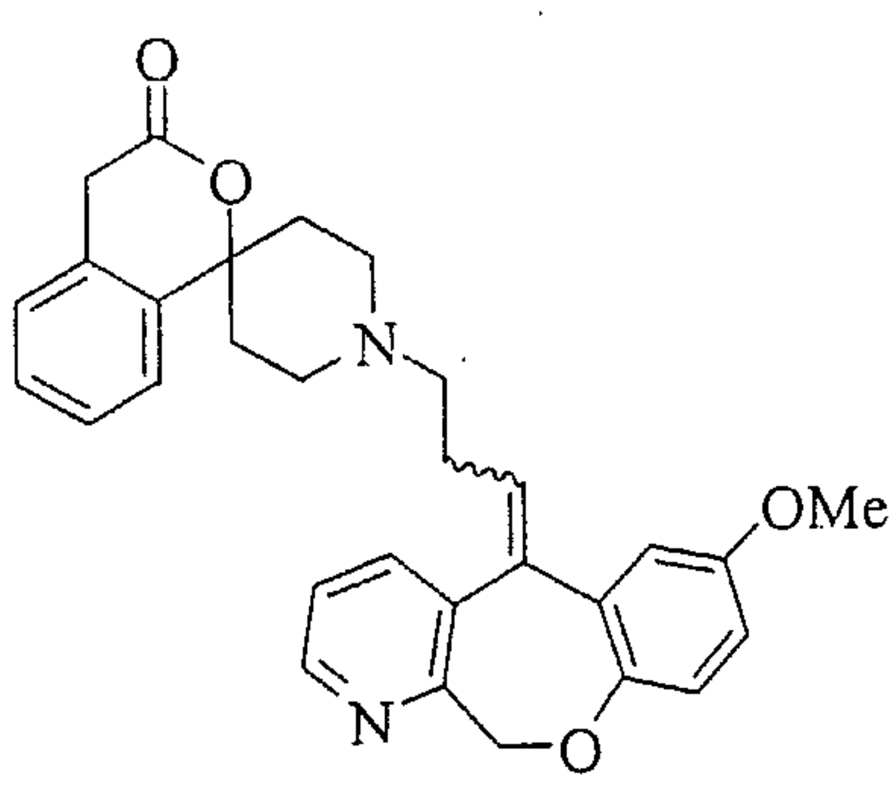
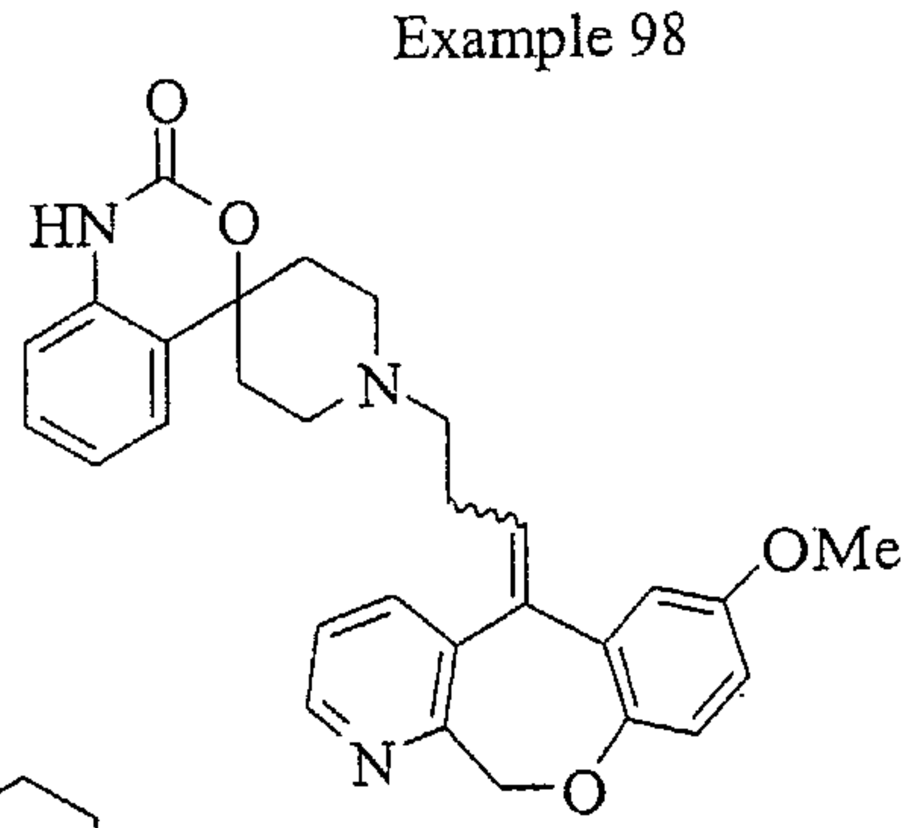

Example 95

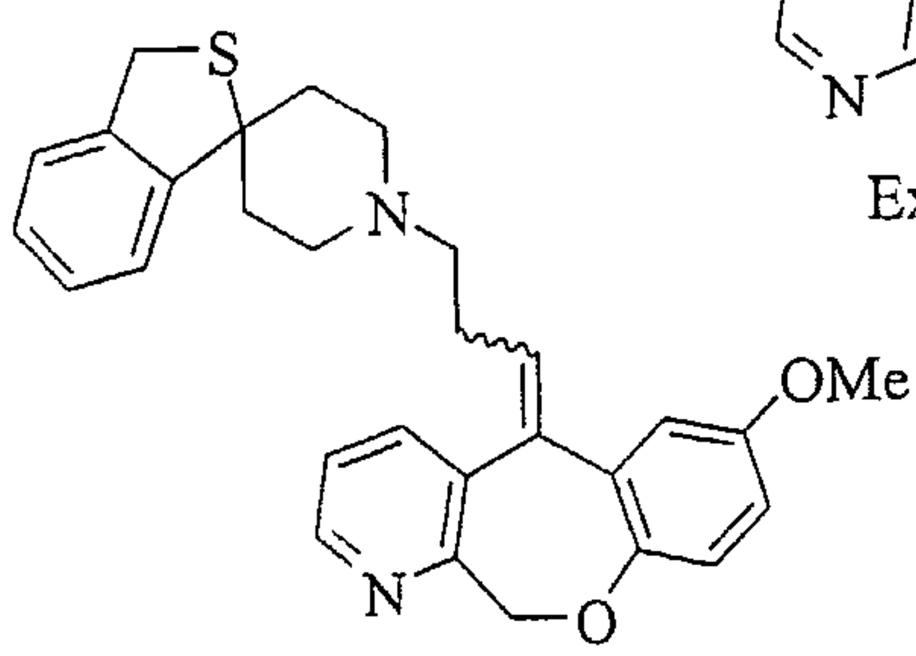

Example 96


Example 97


Example 98


Example 99


Example 100


Example 101

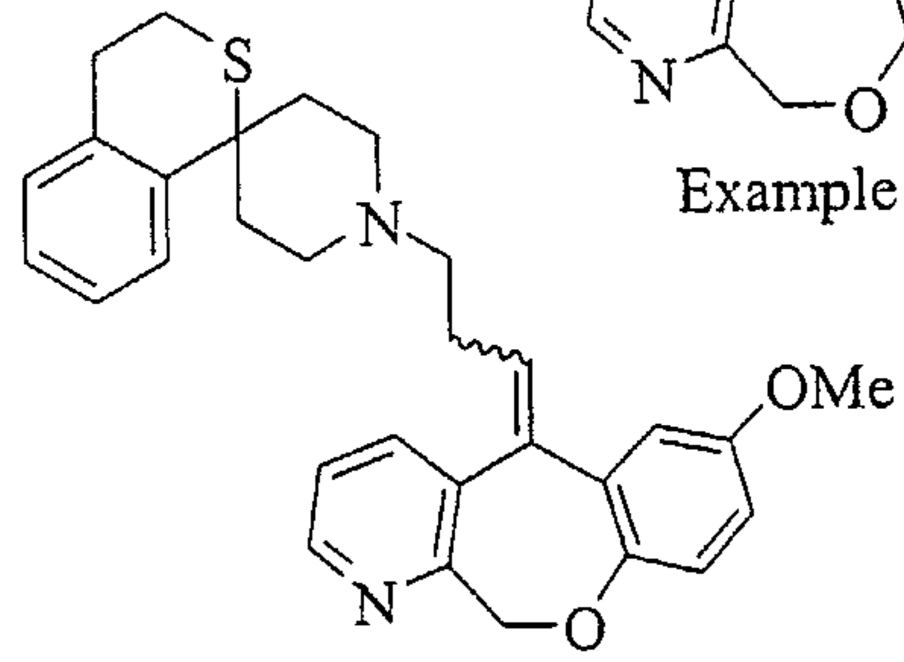
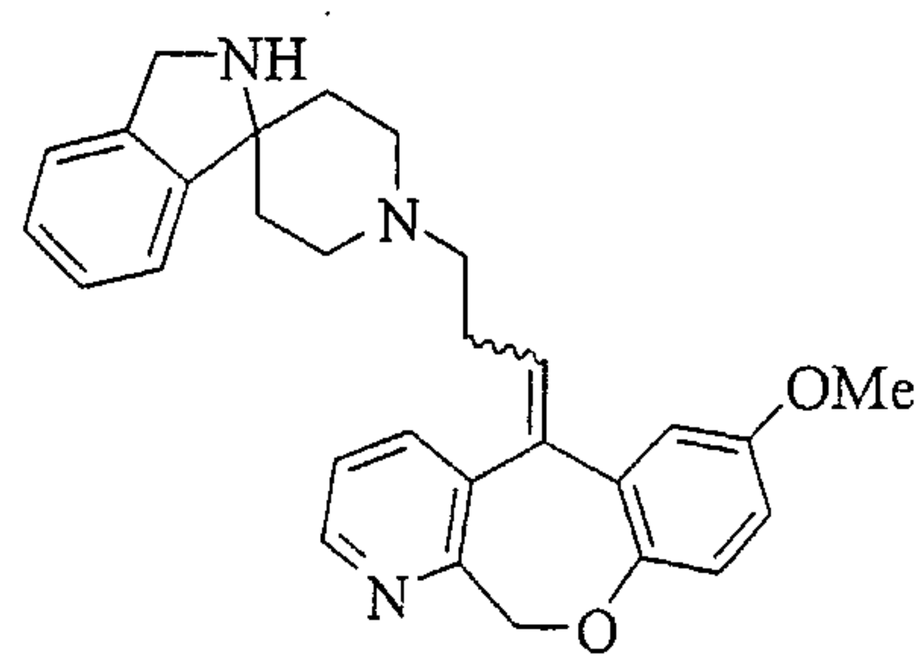
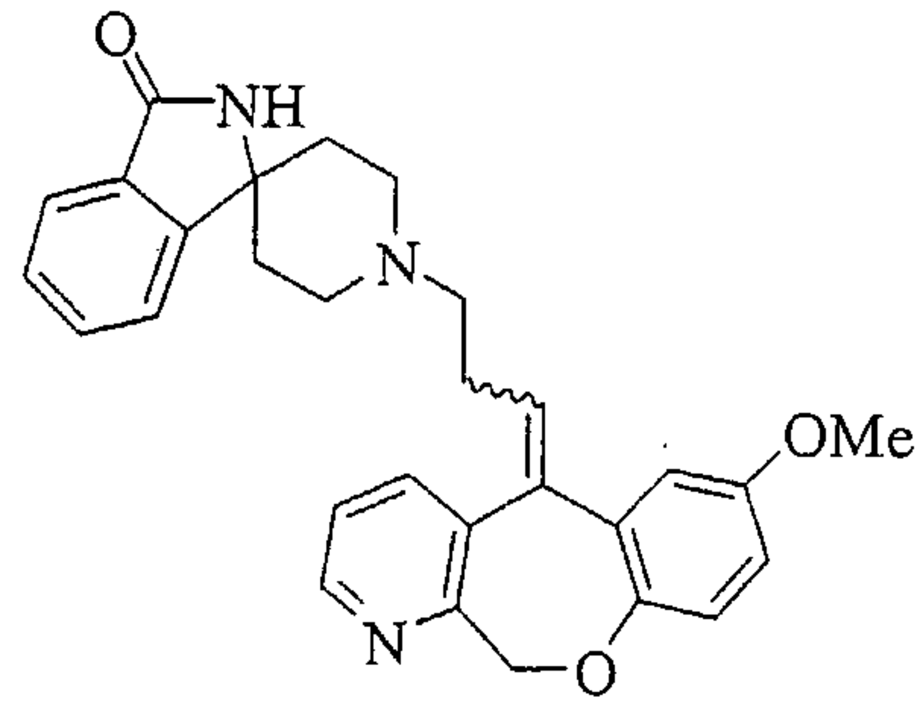

Example 102

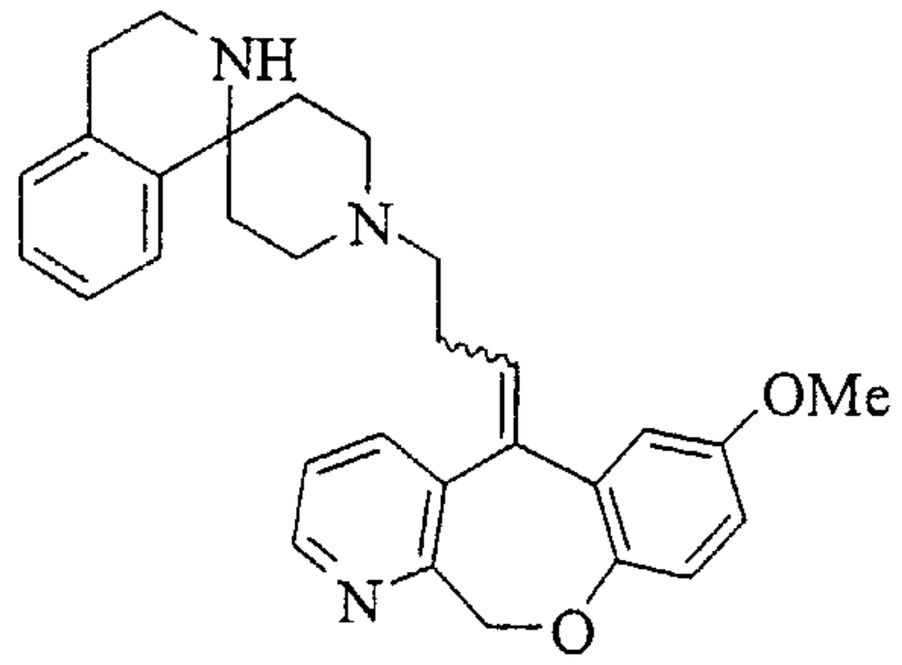
Figure 6K



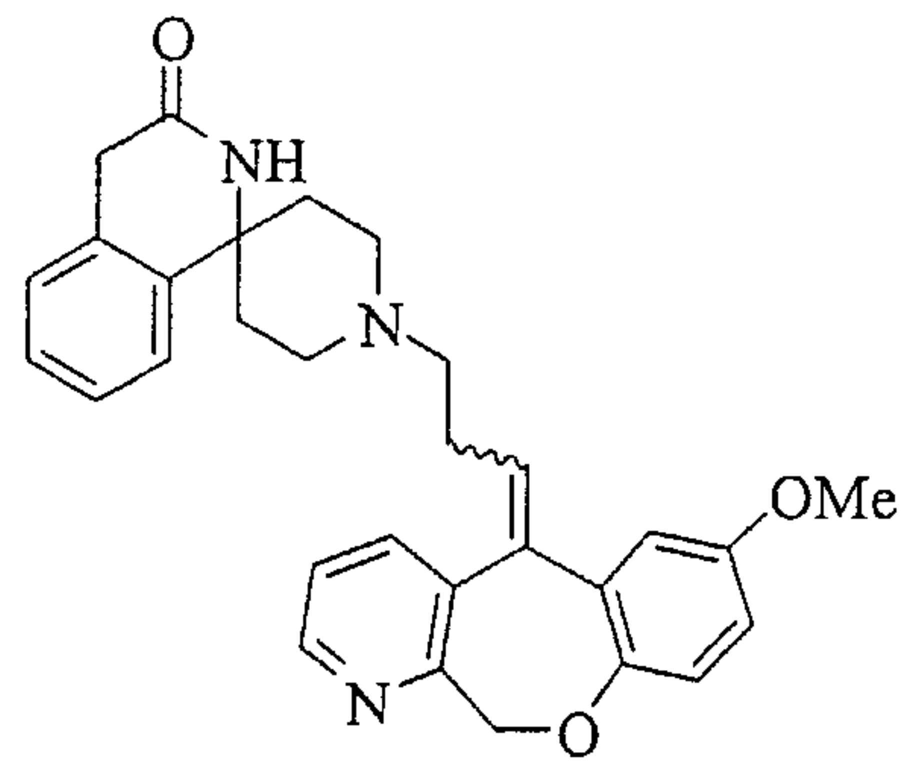
Example 103



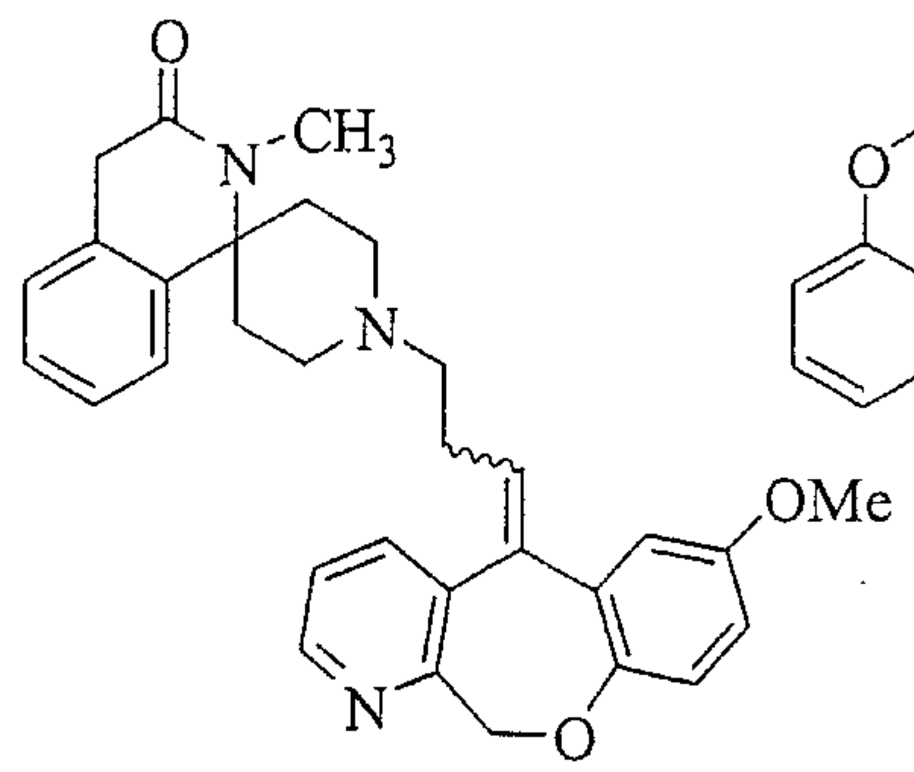
Example 104



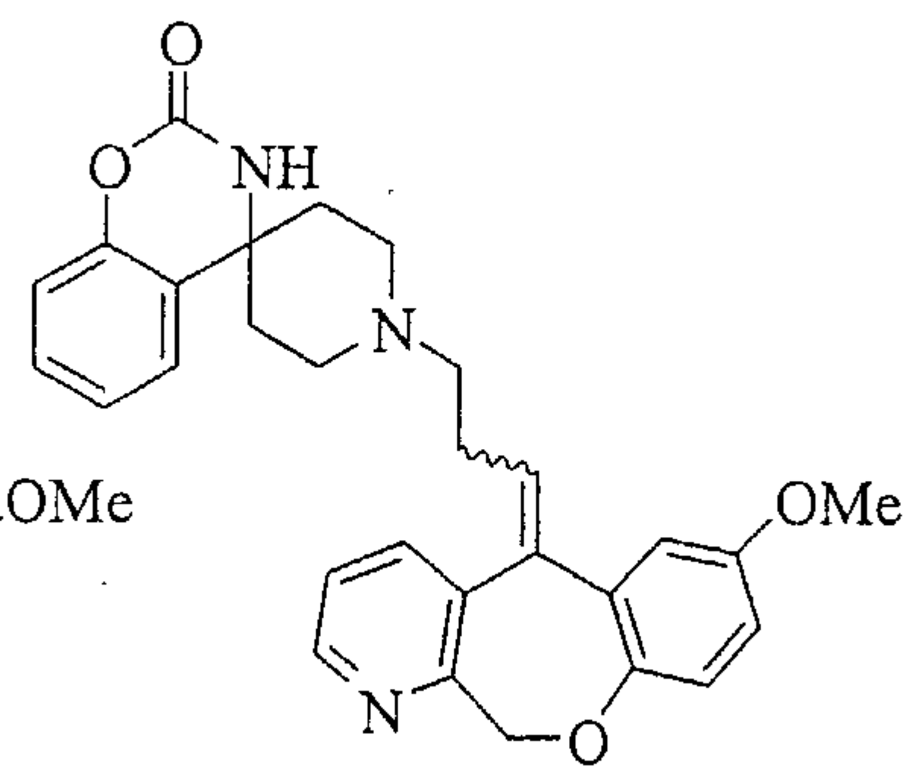
Example 105



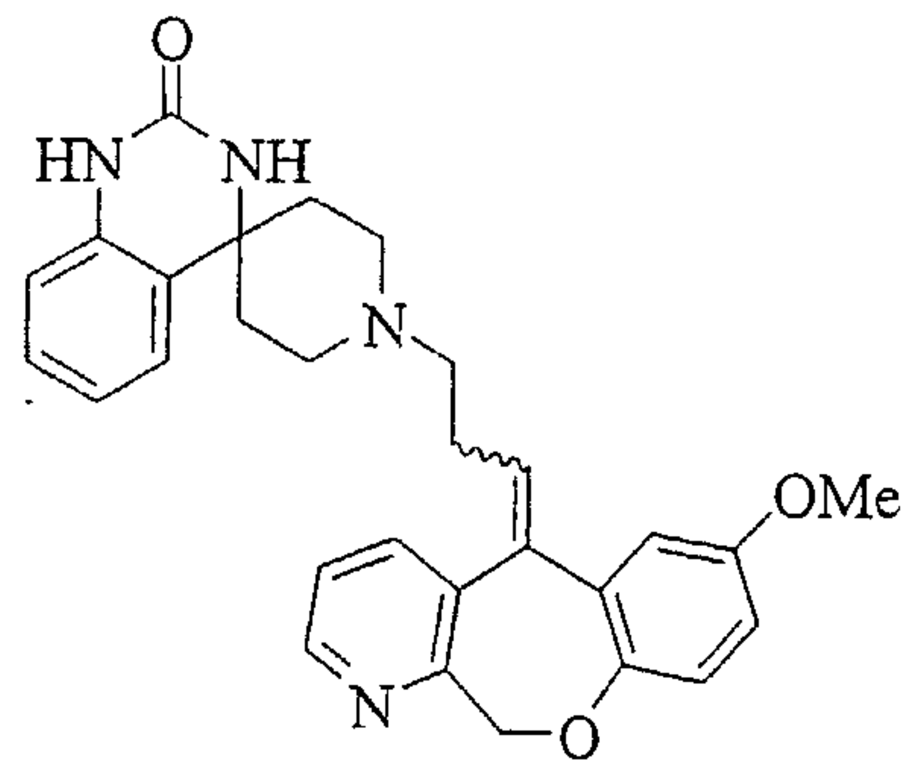
Example 106



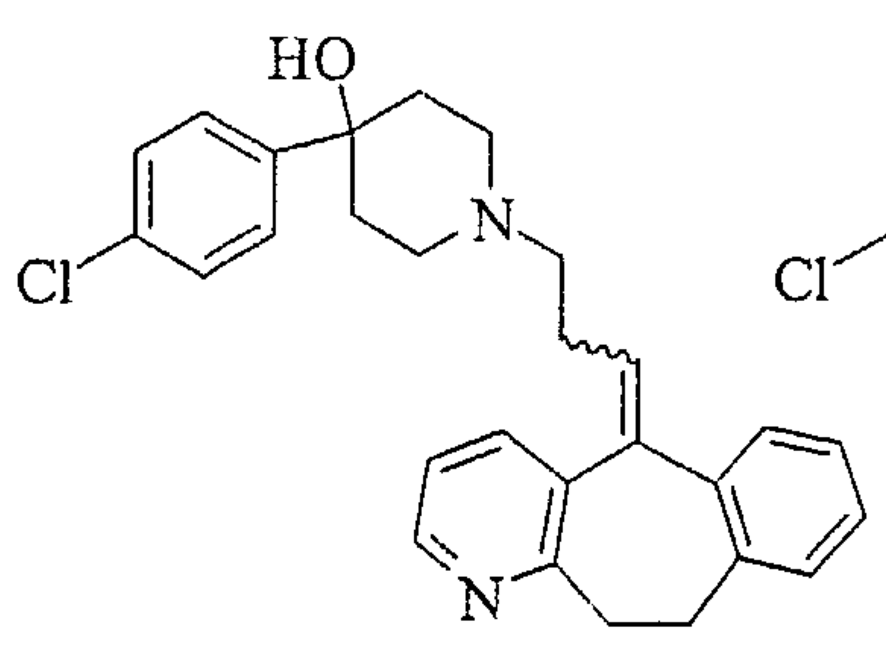
Example 107



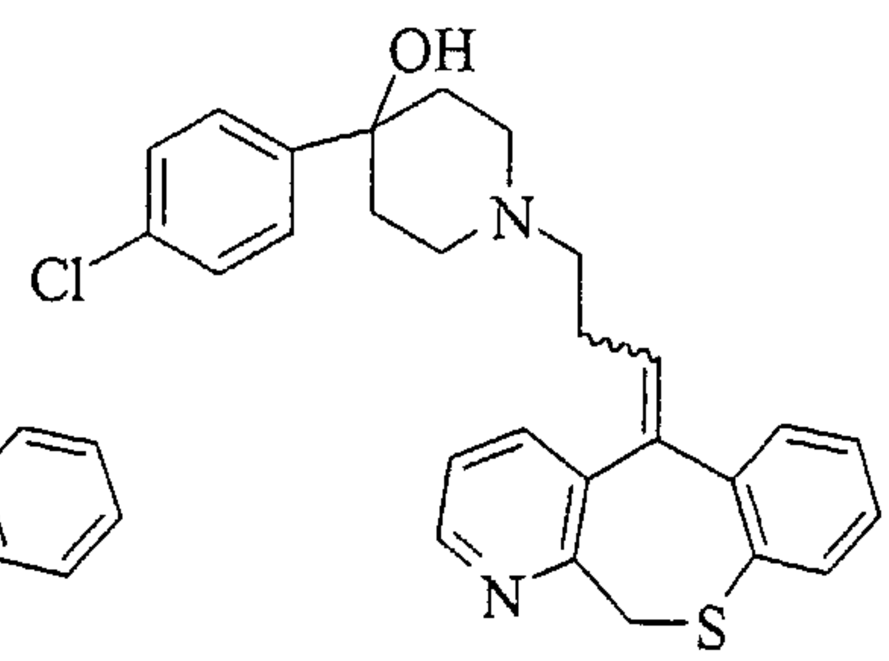
Example 108



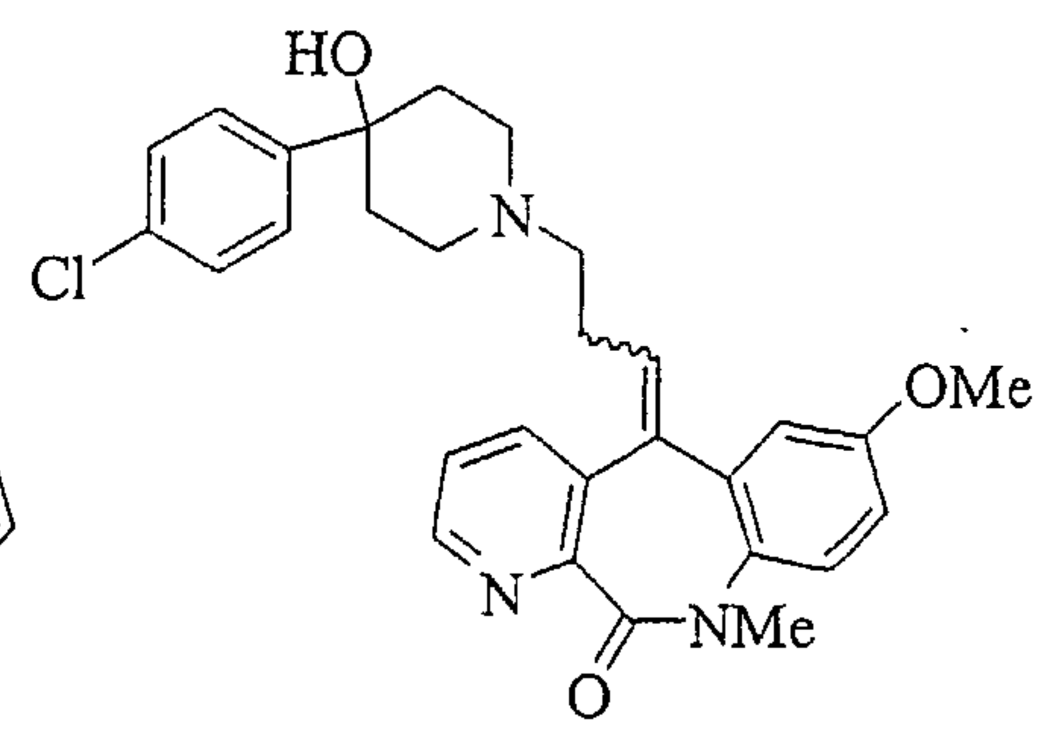
Example 109



Example 110

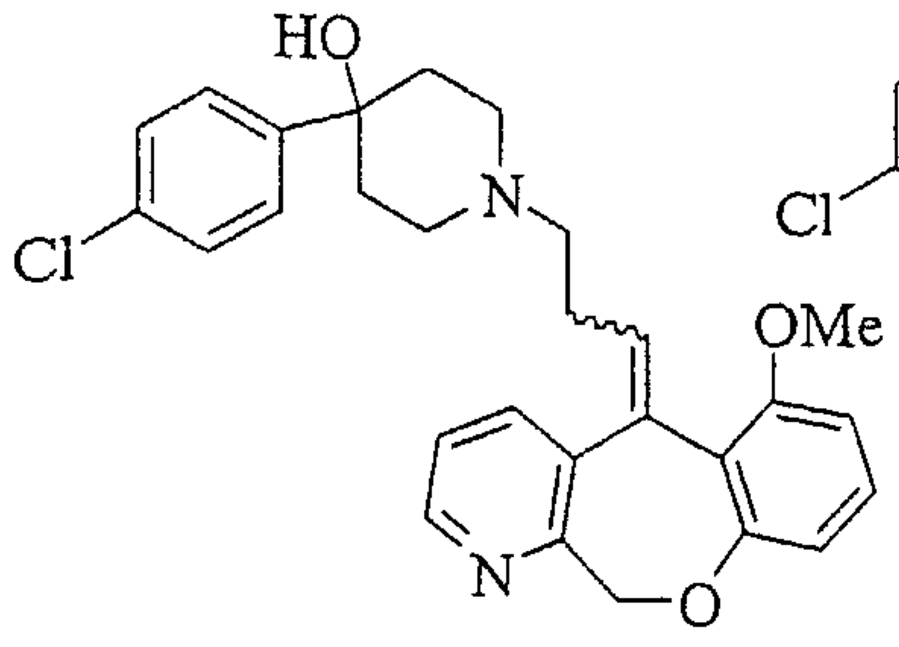


Example 111

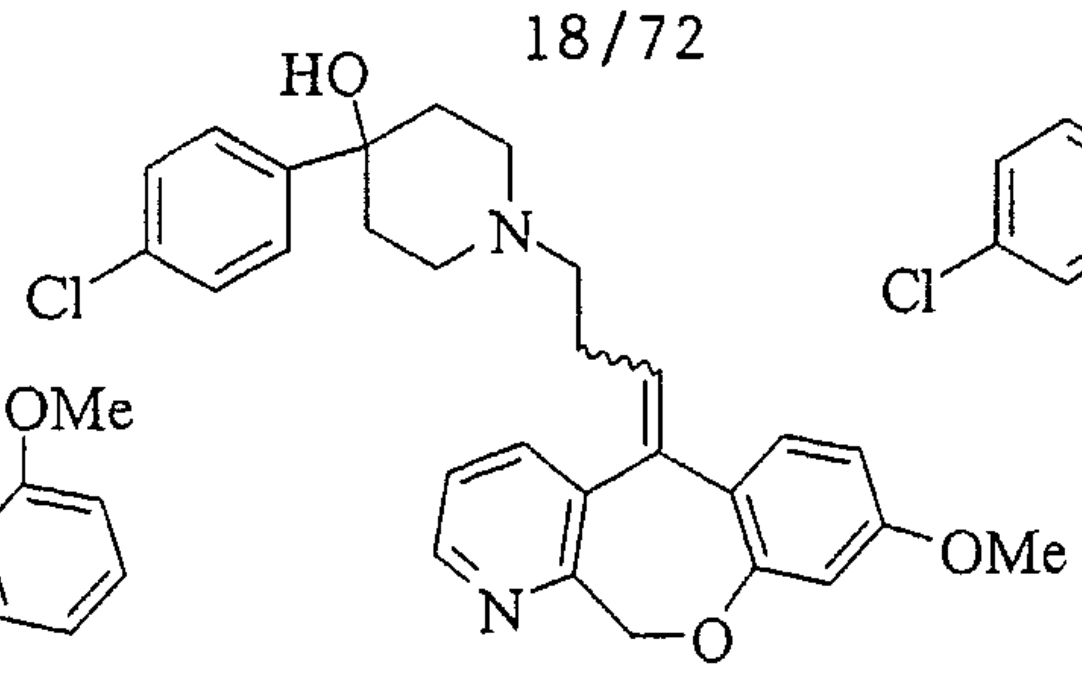


Example 112

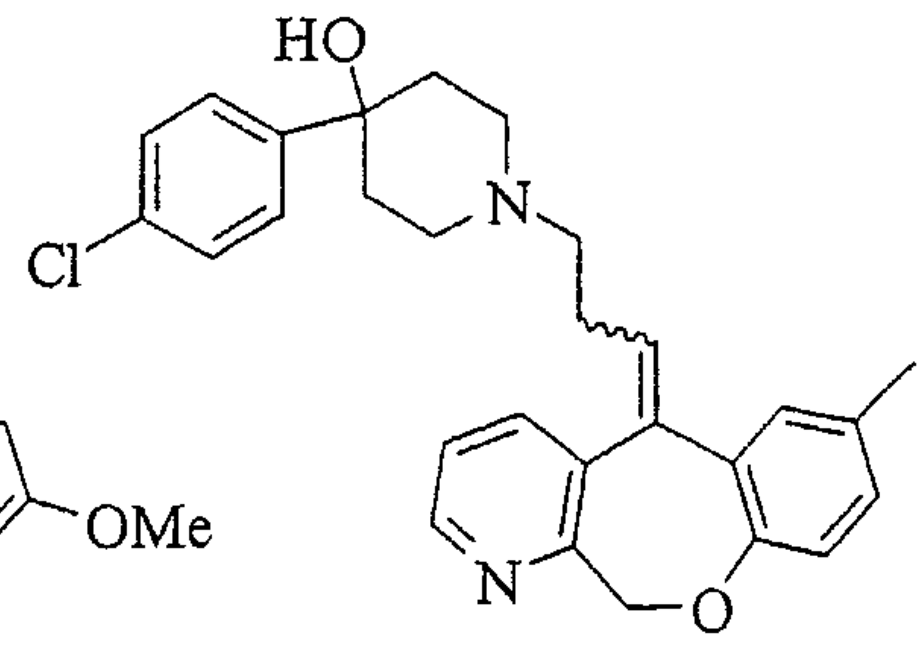
Figure 6L



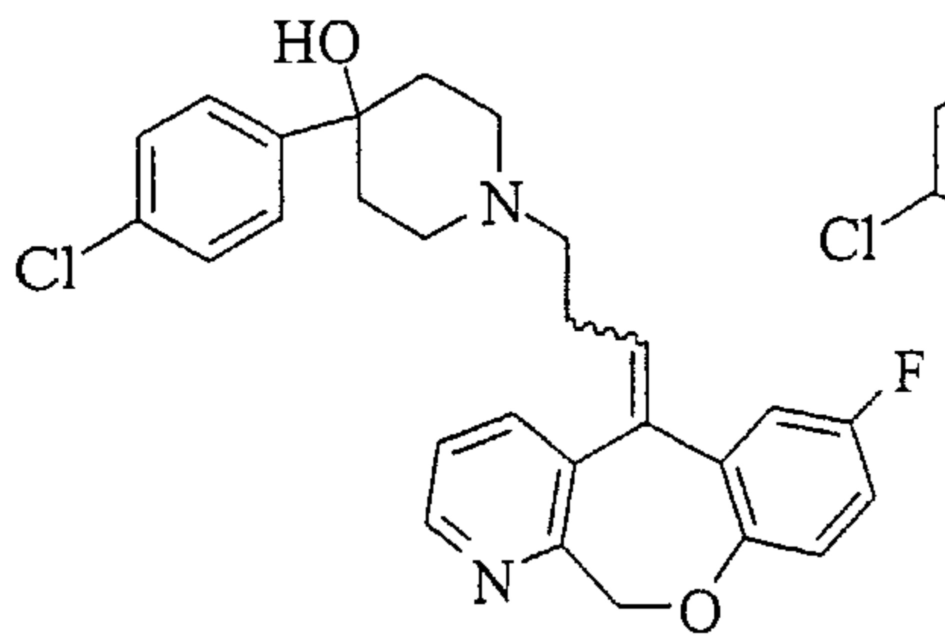
Example 113



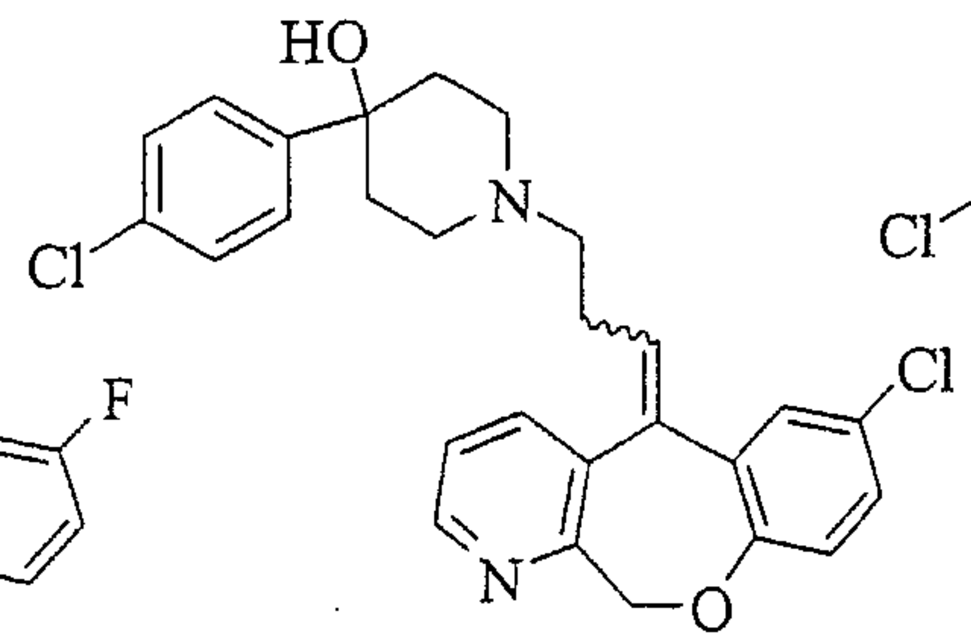
Example 114



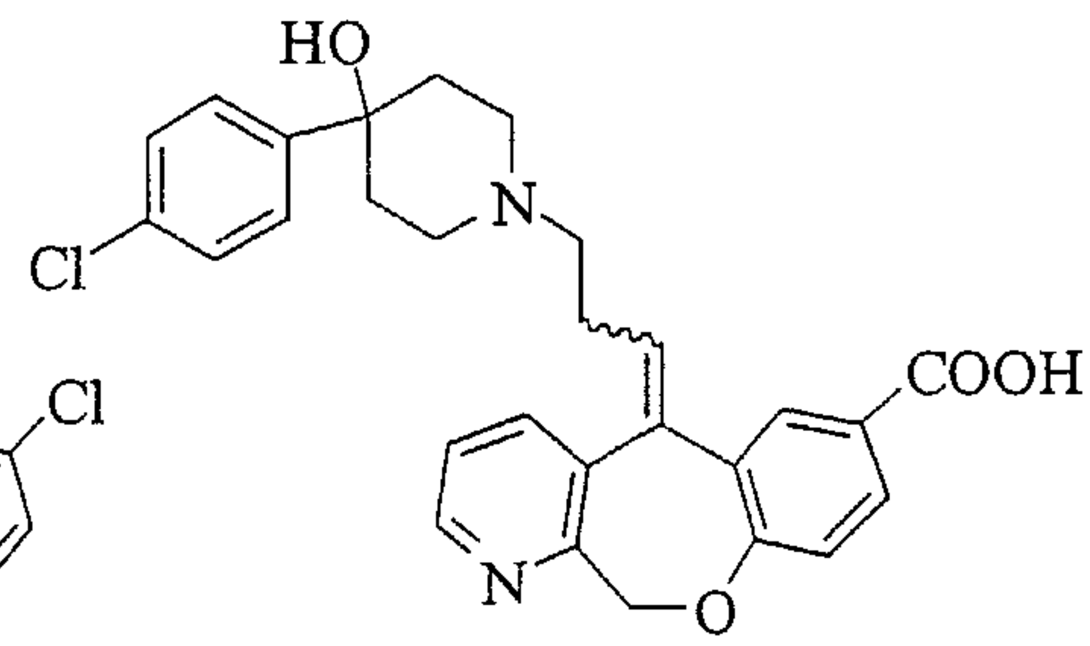
Example 115



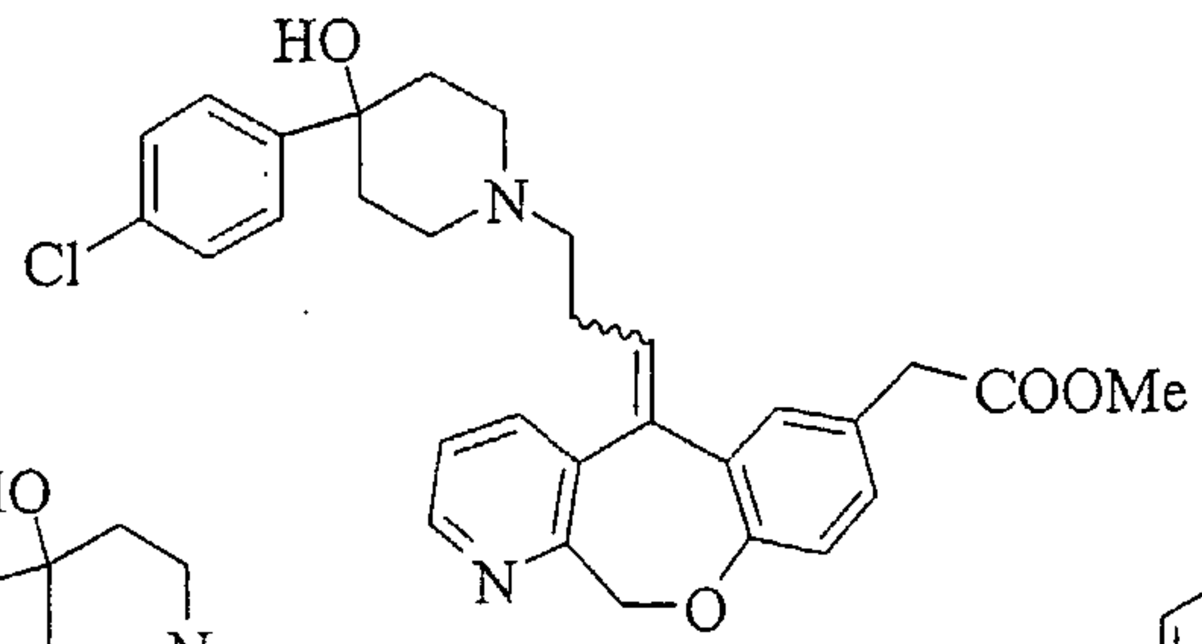
Example 116



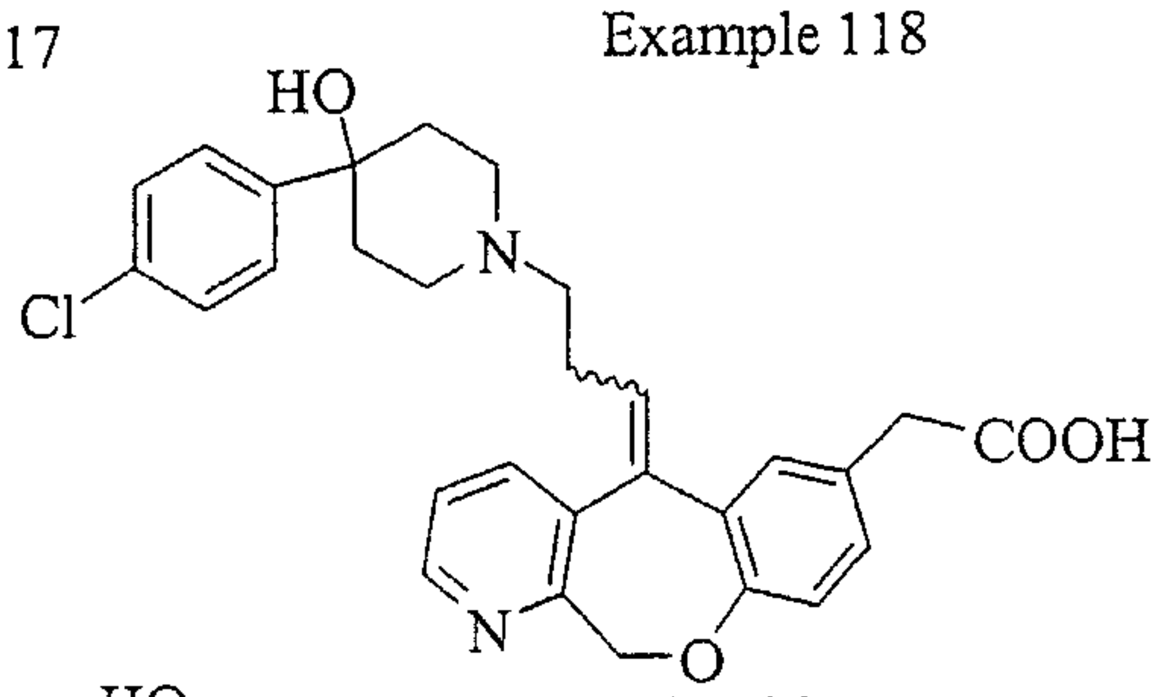
Example 117



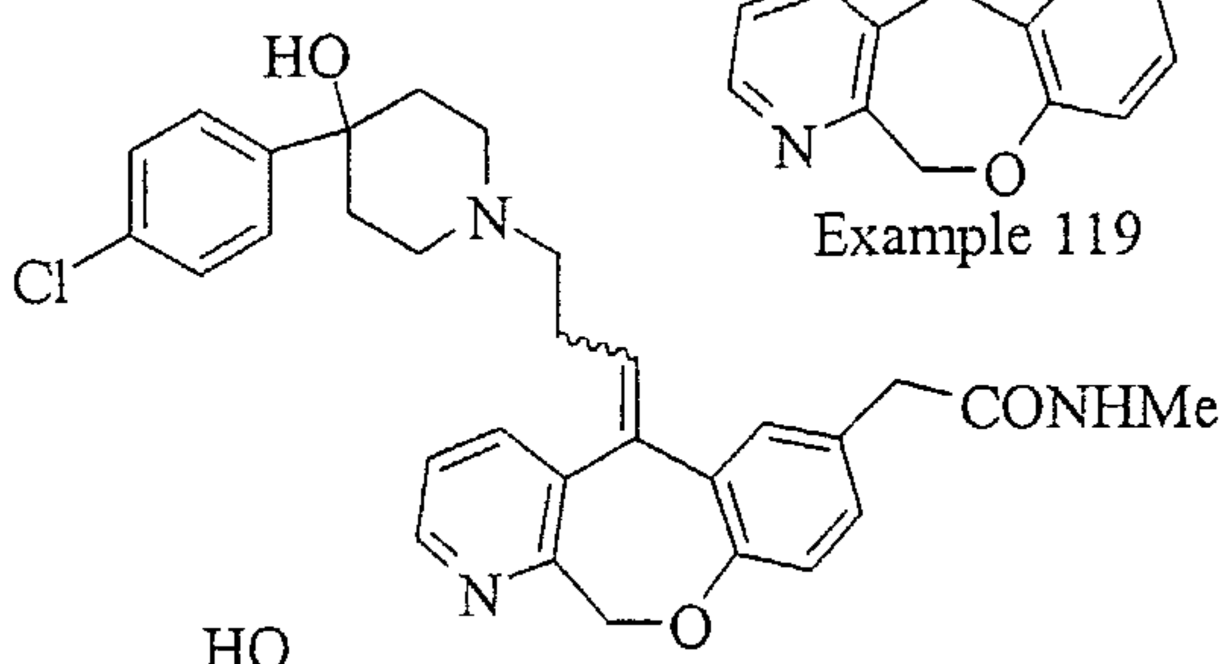
Example 118



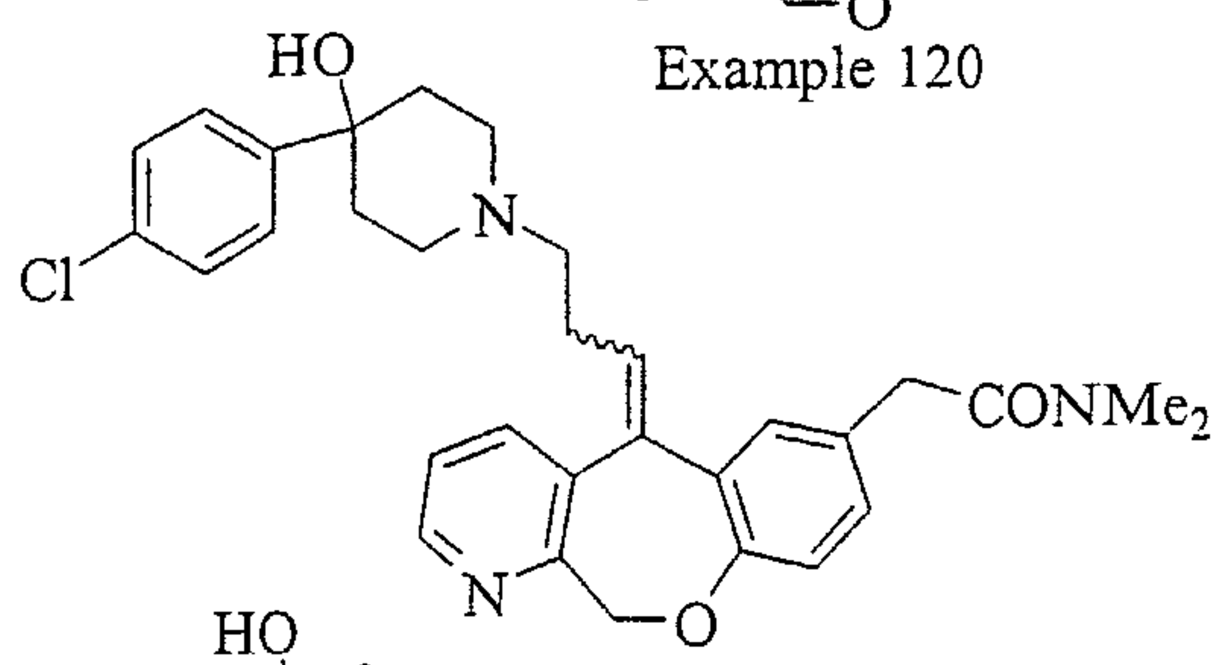
Example 119



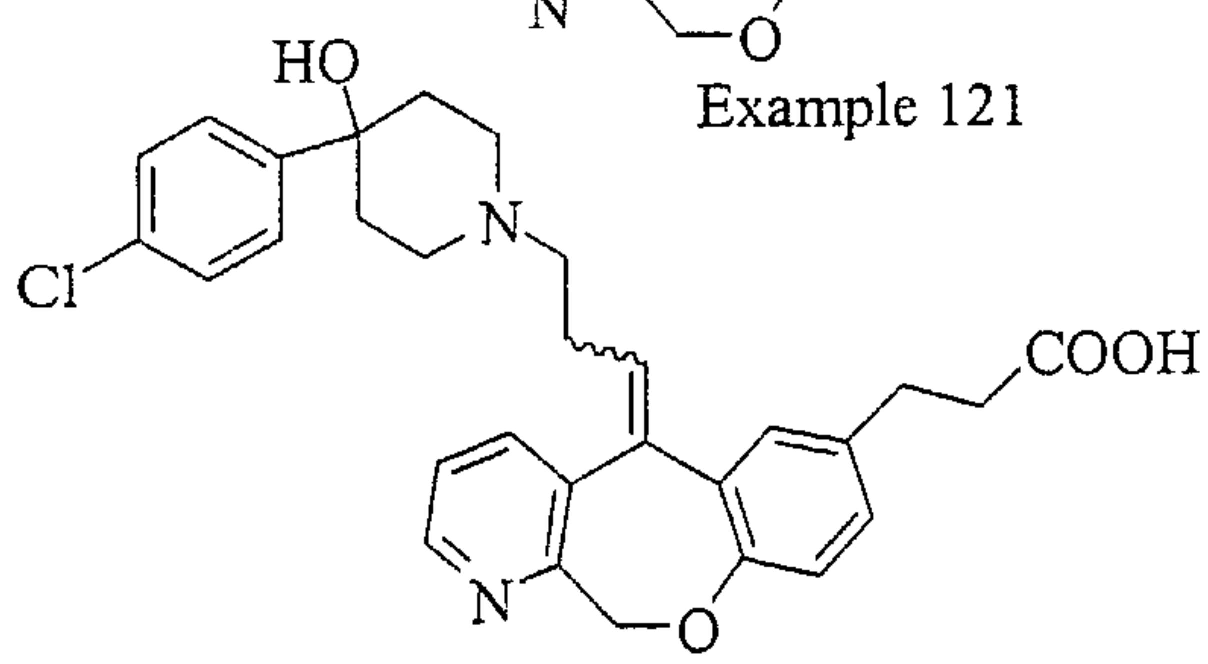
Example 120



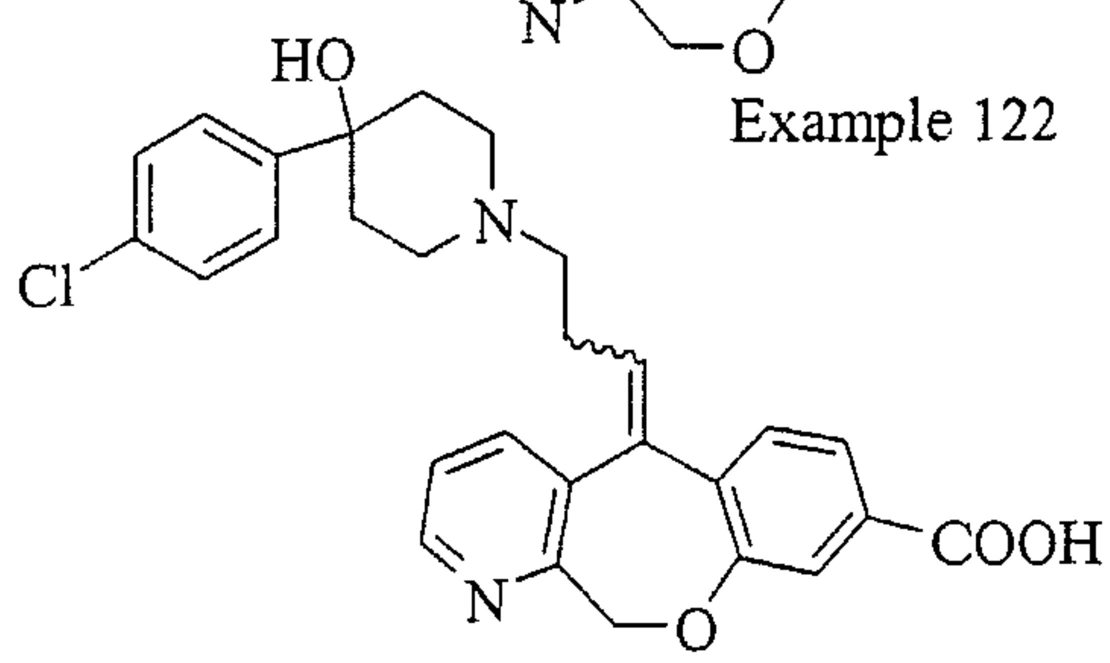
Example 121



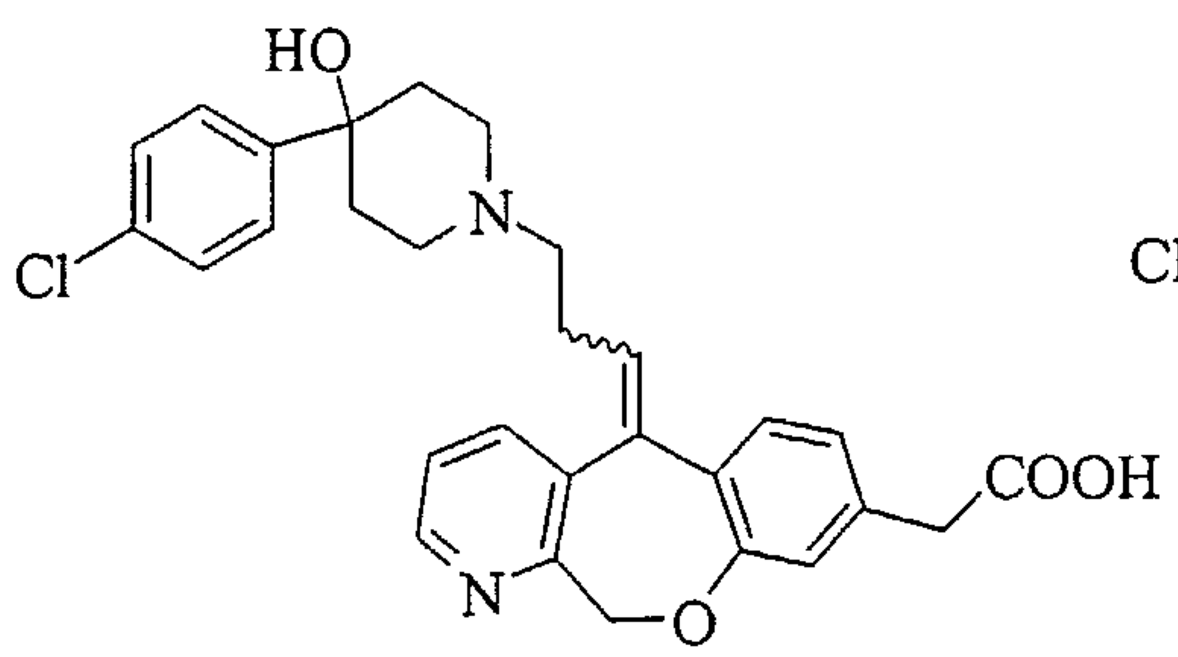
Example 122



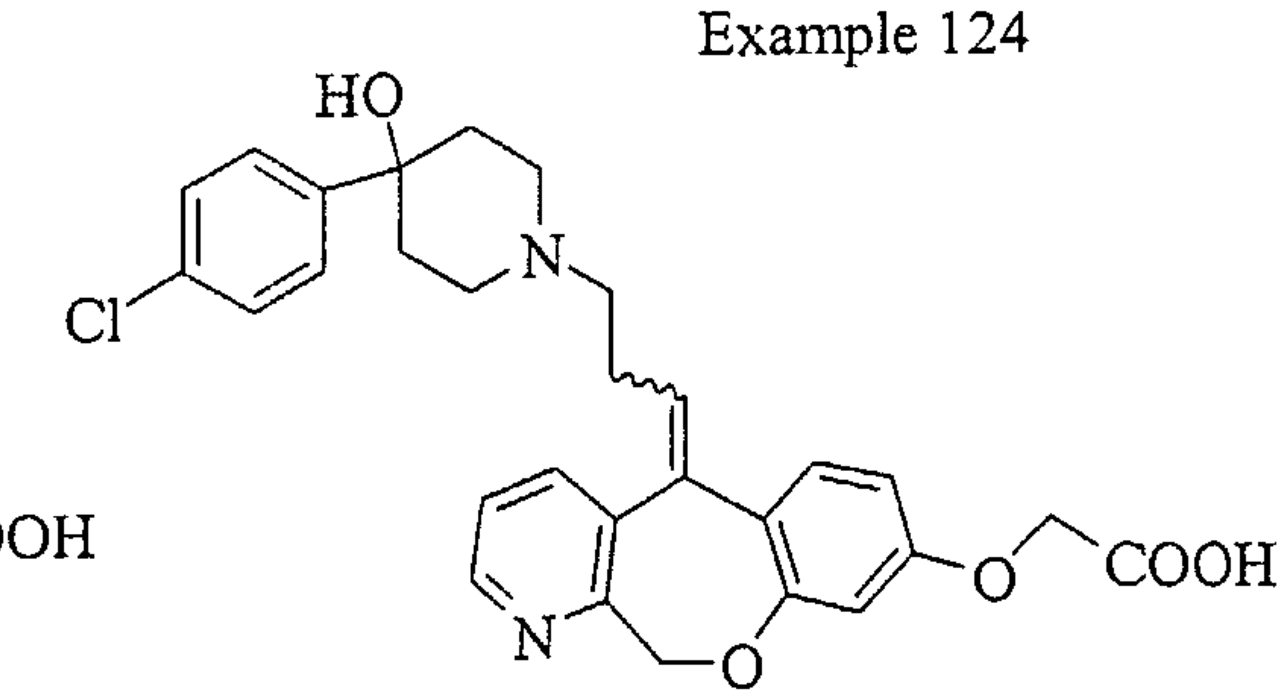
Example 123



Example 124

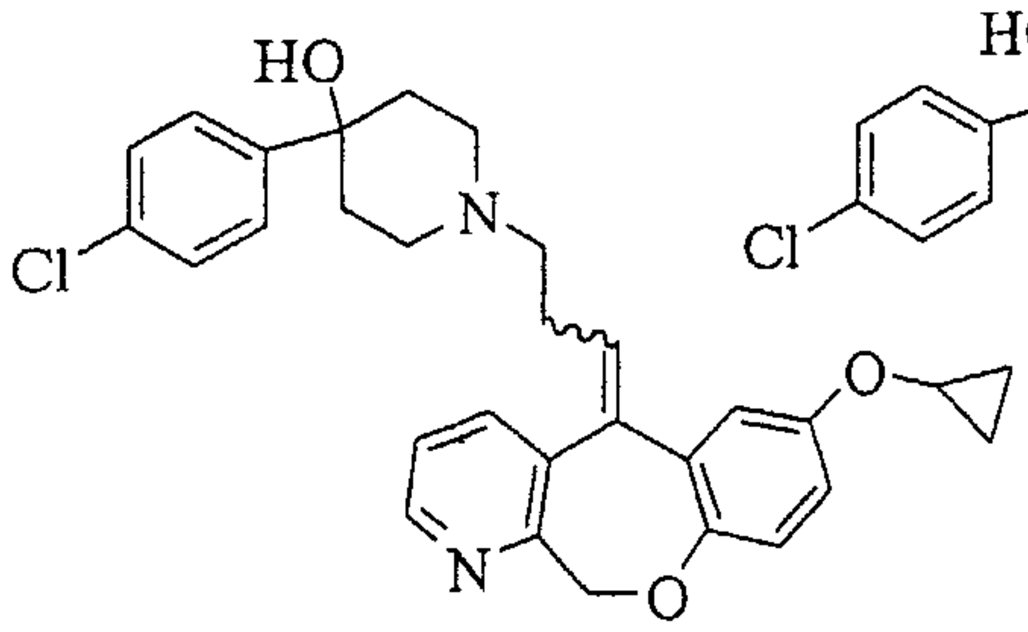


Example 125

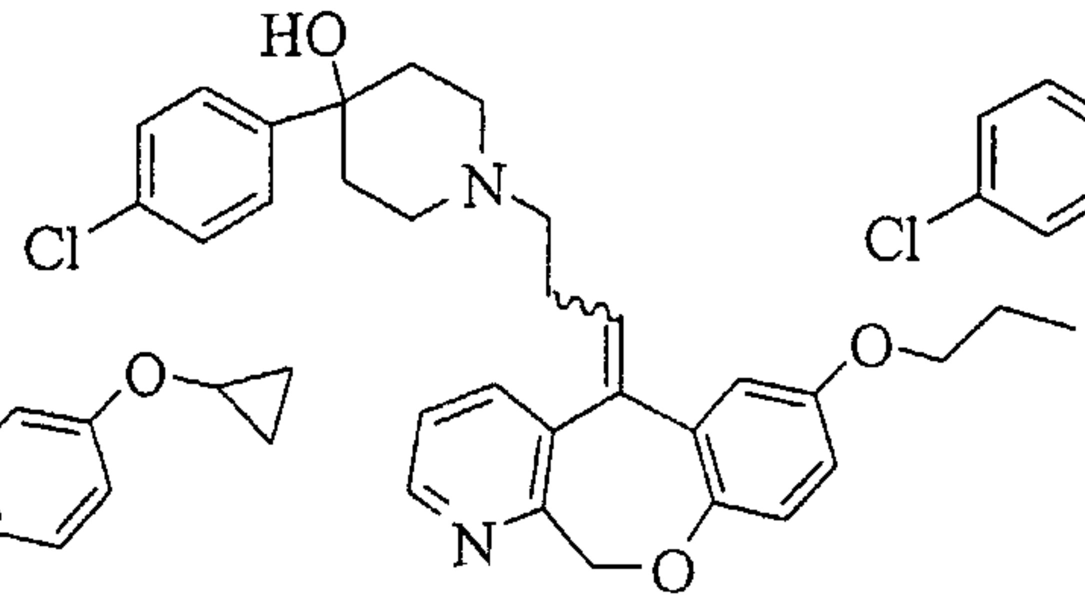


Example 126

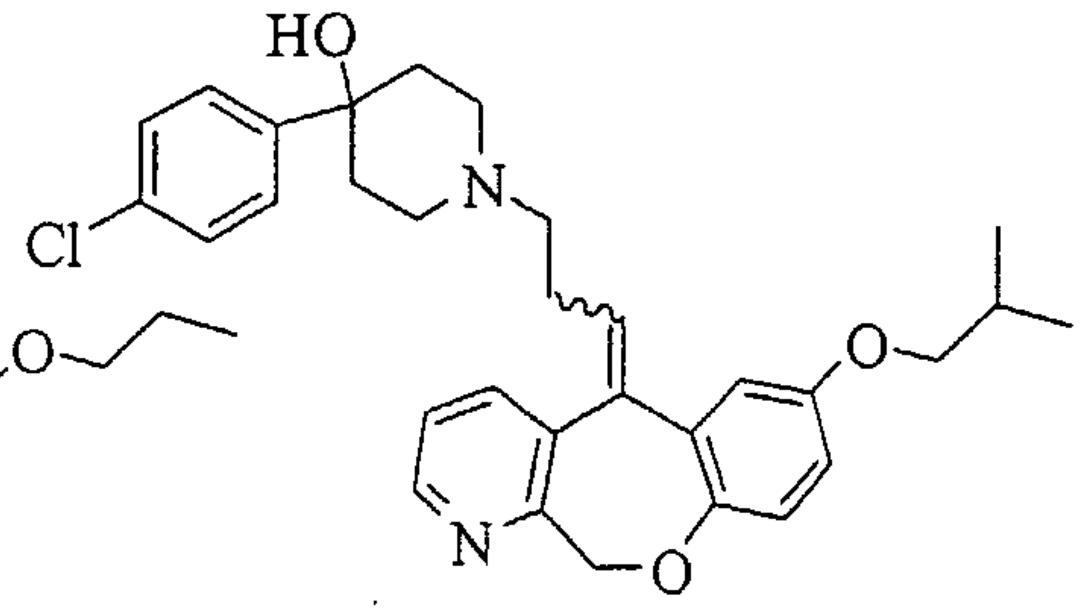
Figure 6M



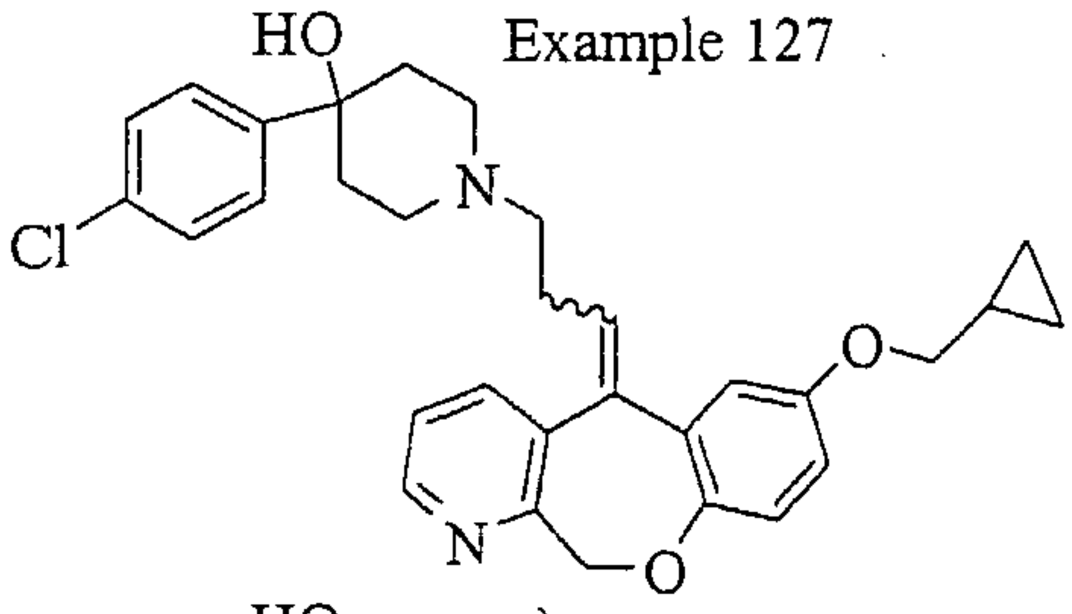
Example 127



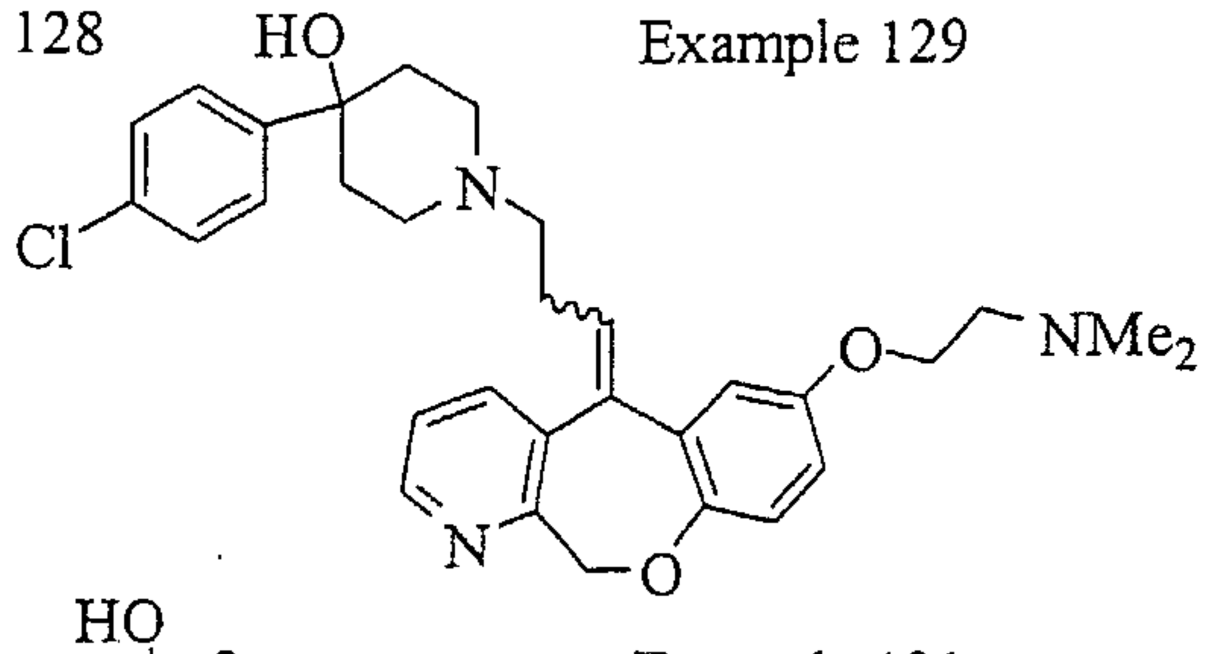
Example 128



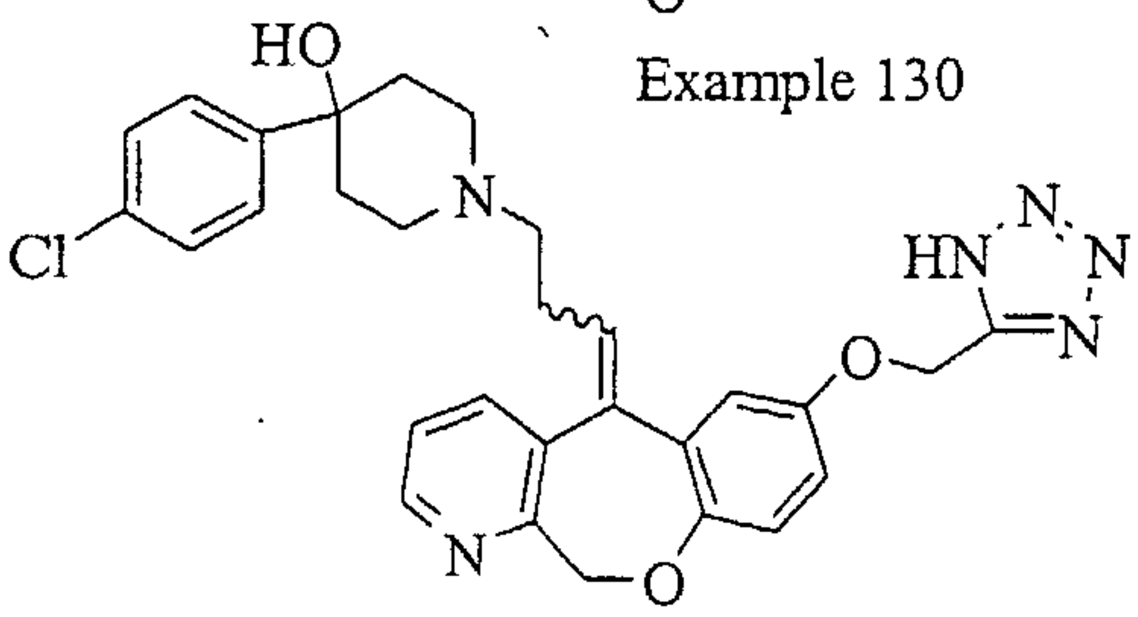
Example 129



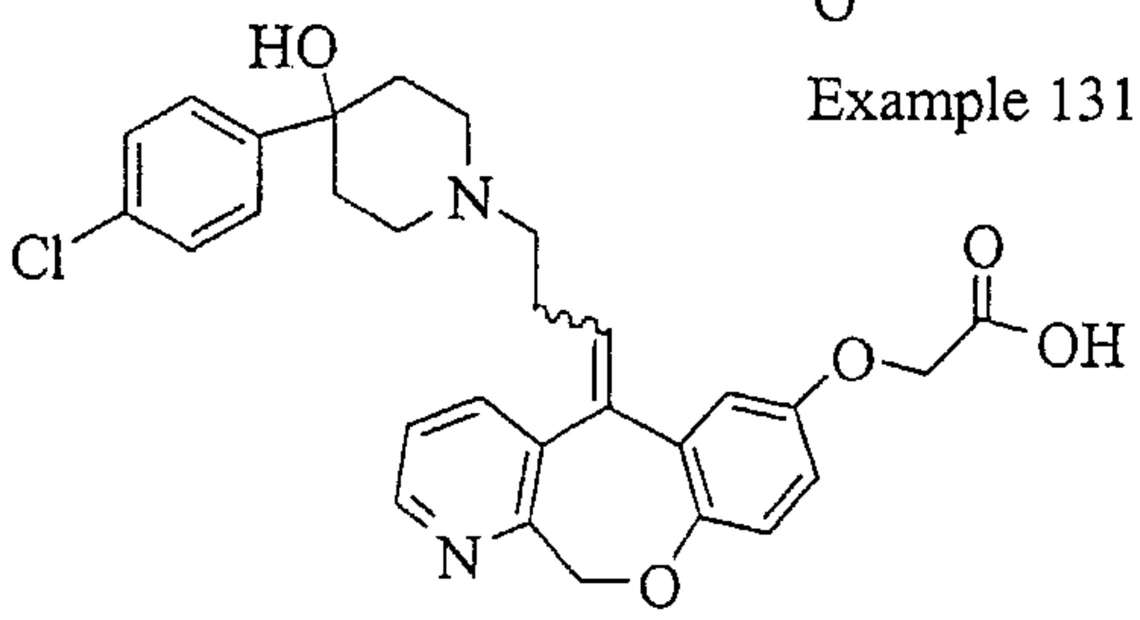
Example 130



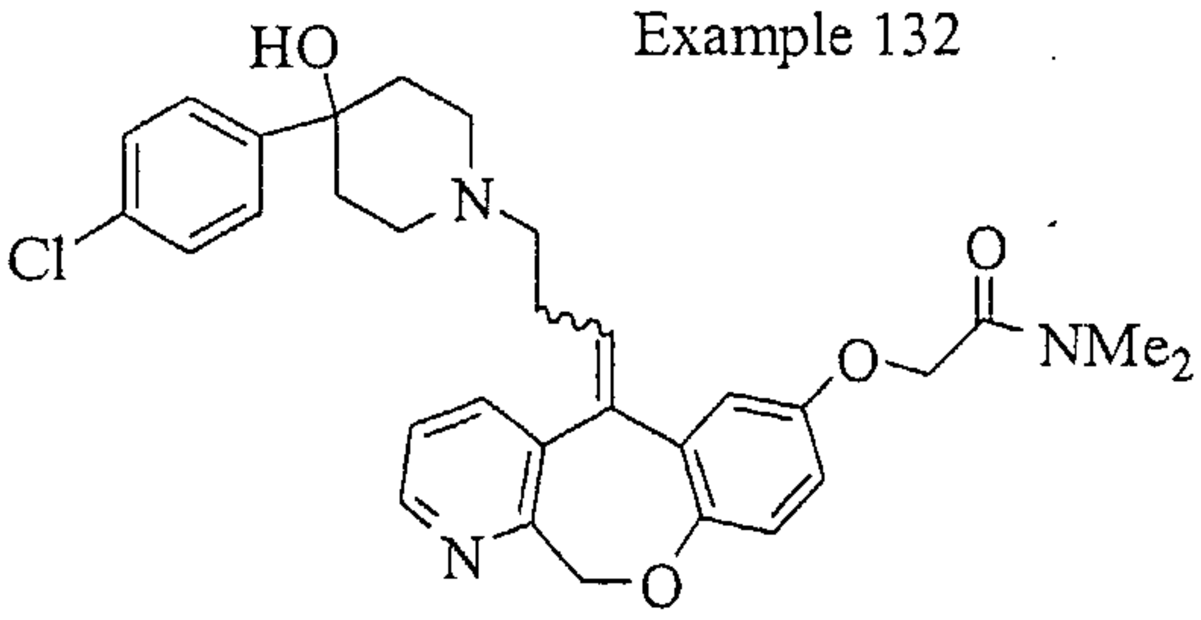
Example 131



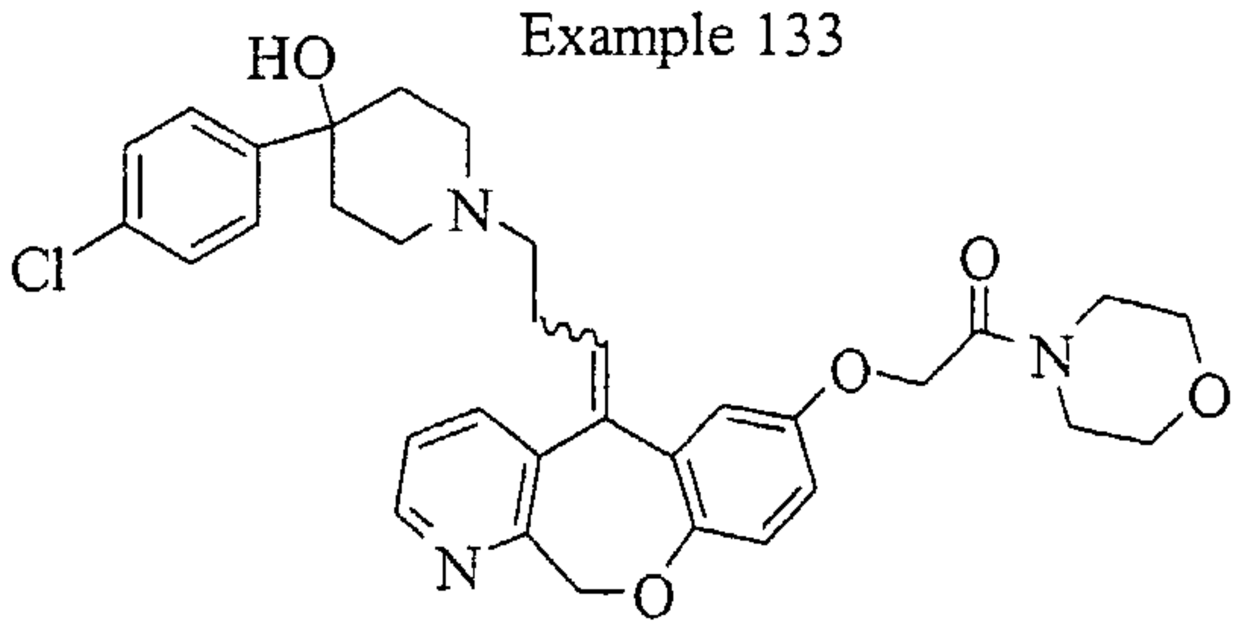
Example 132



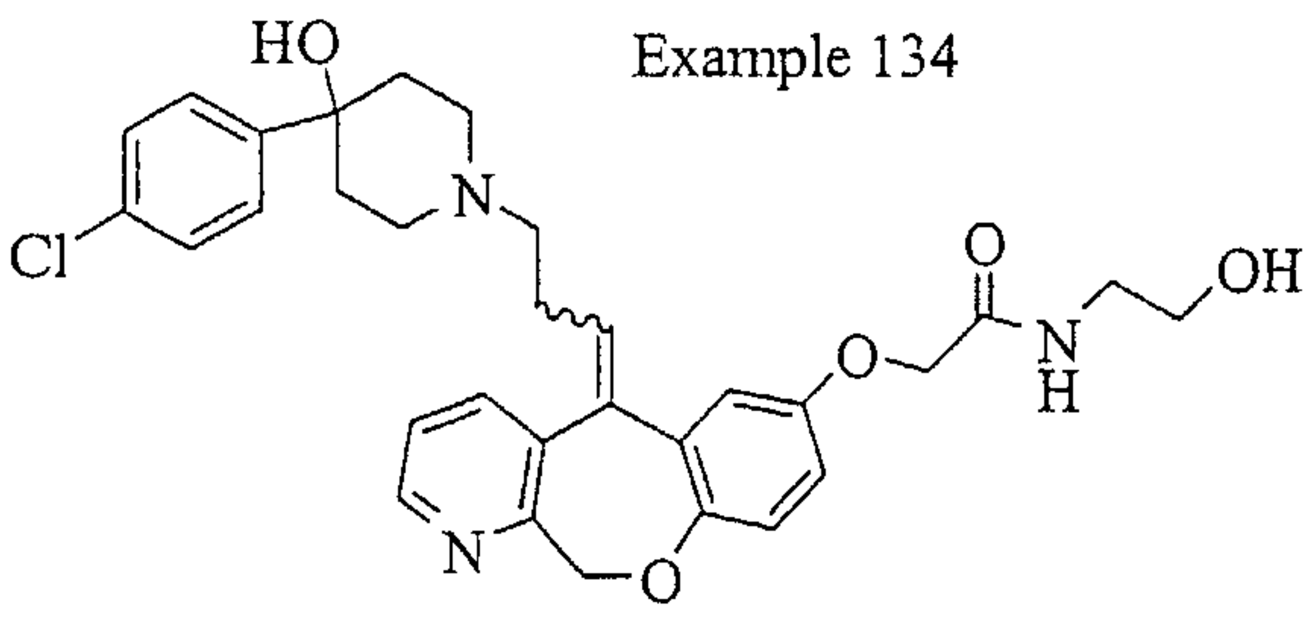
Example 133



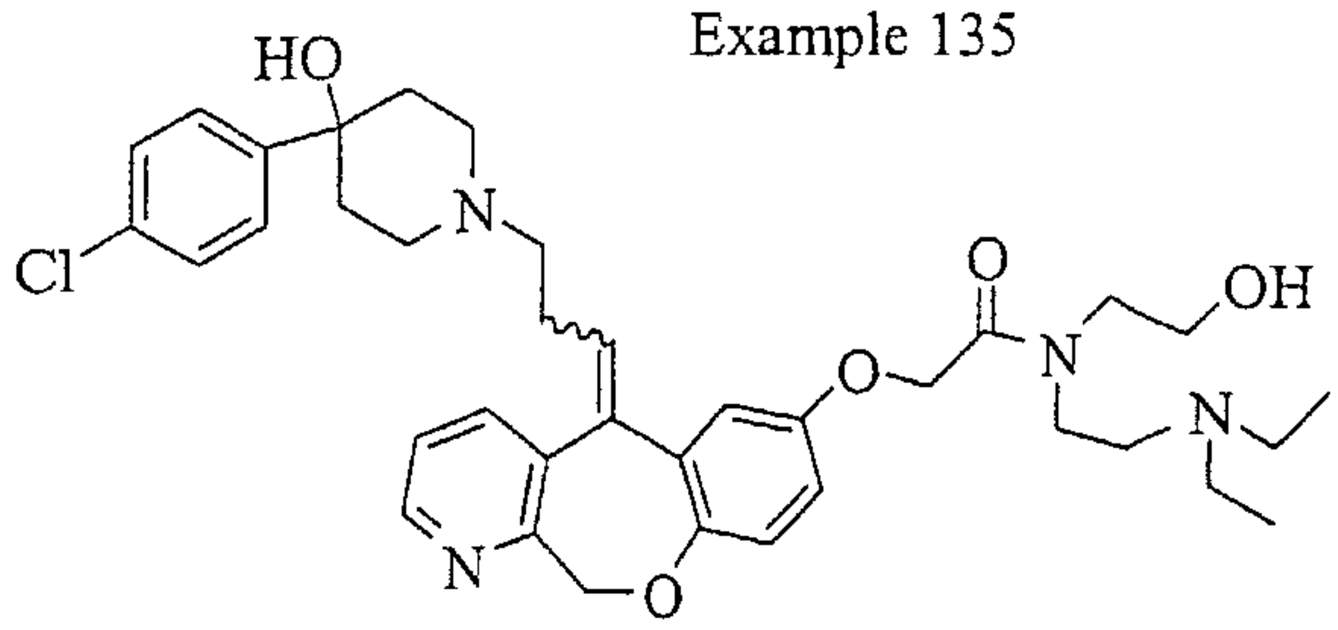
Example 134



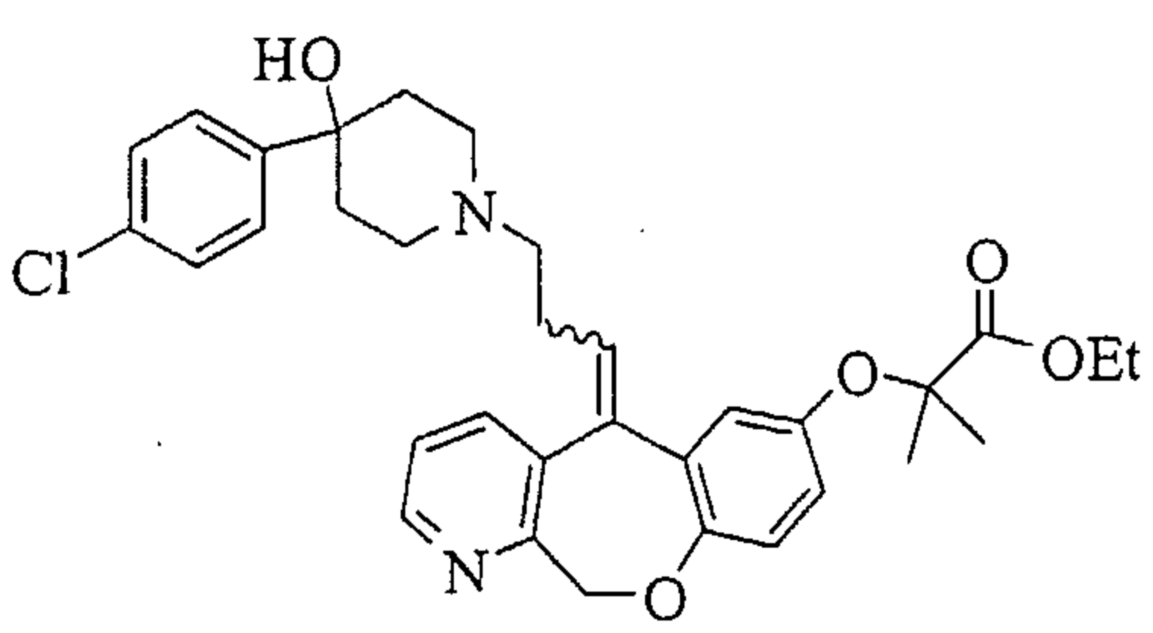
Example 135



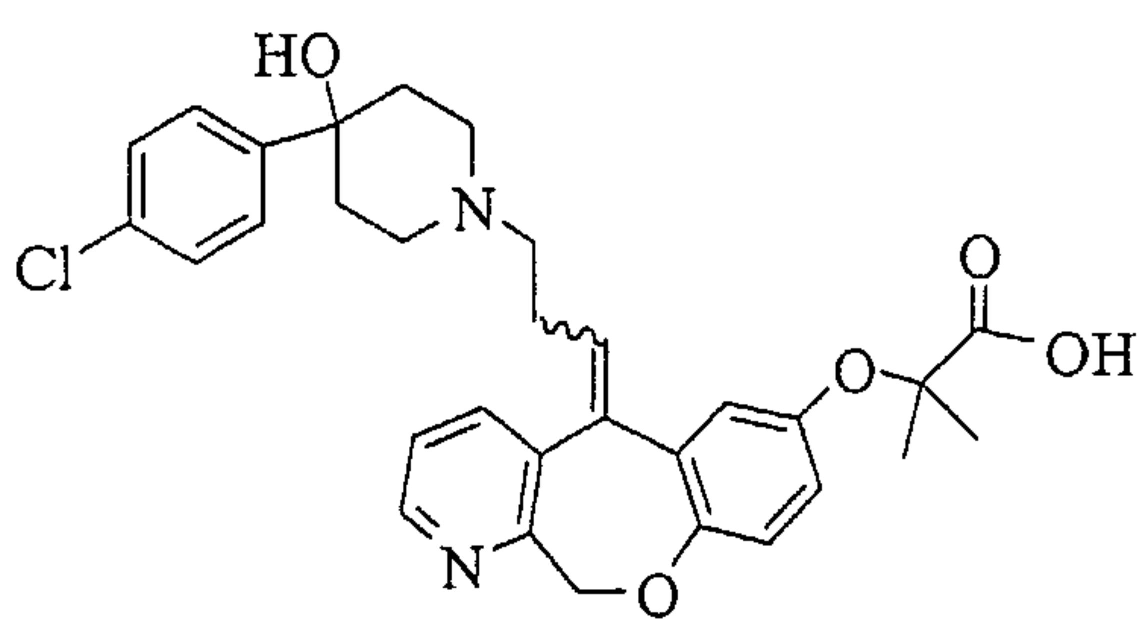
Example 136



Example 137

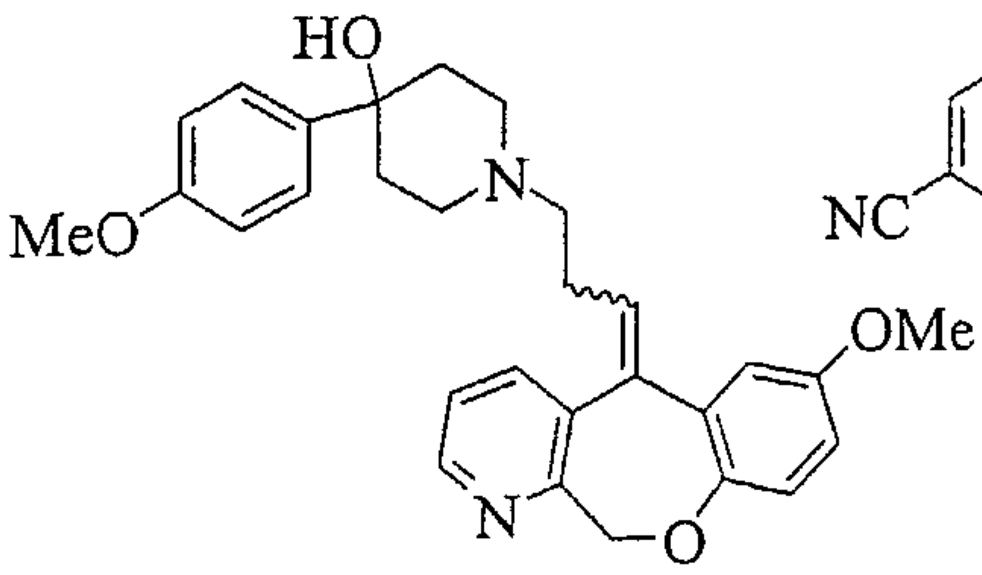


Example 138

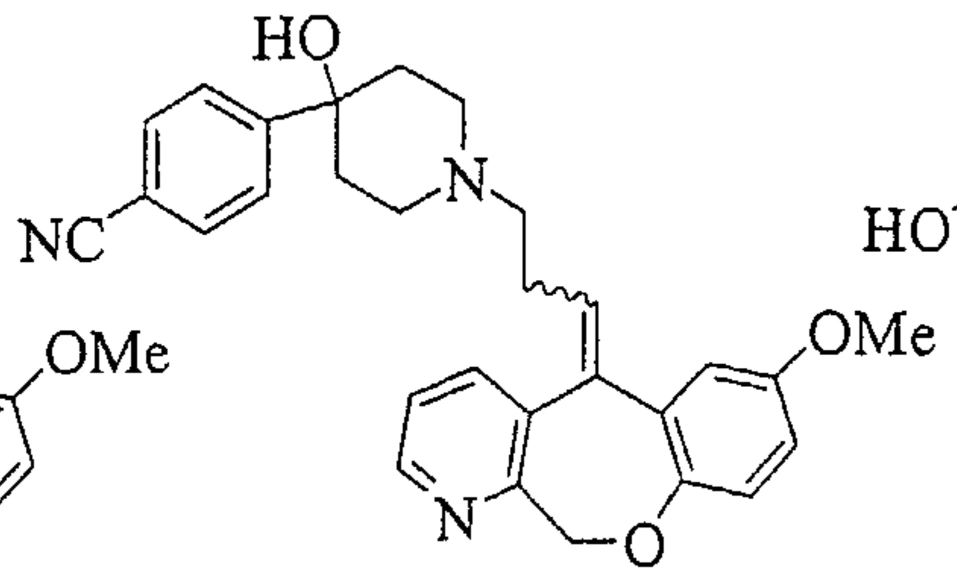


Example 139

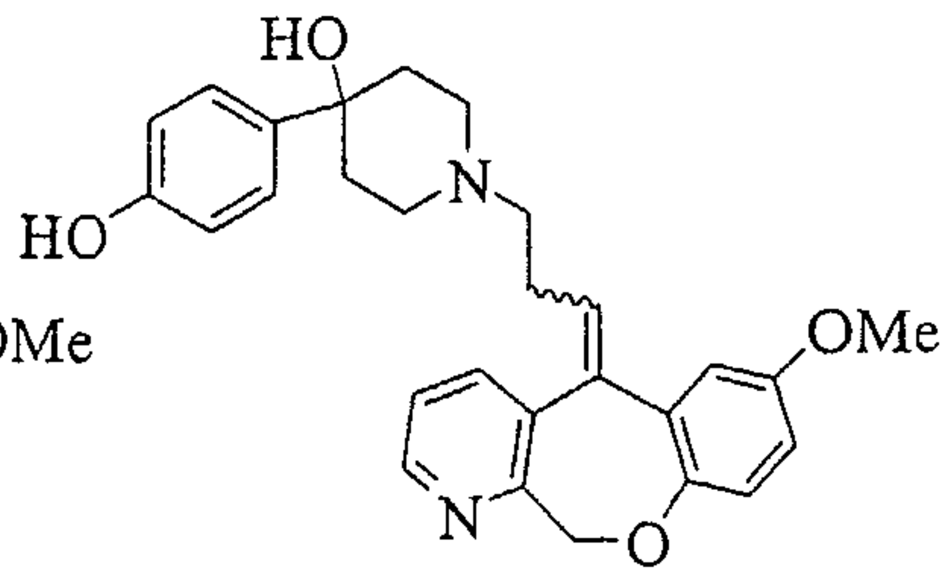
Figure 6N



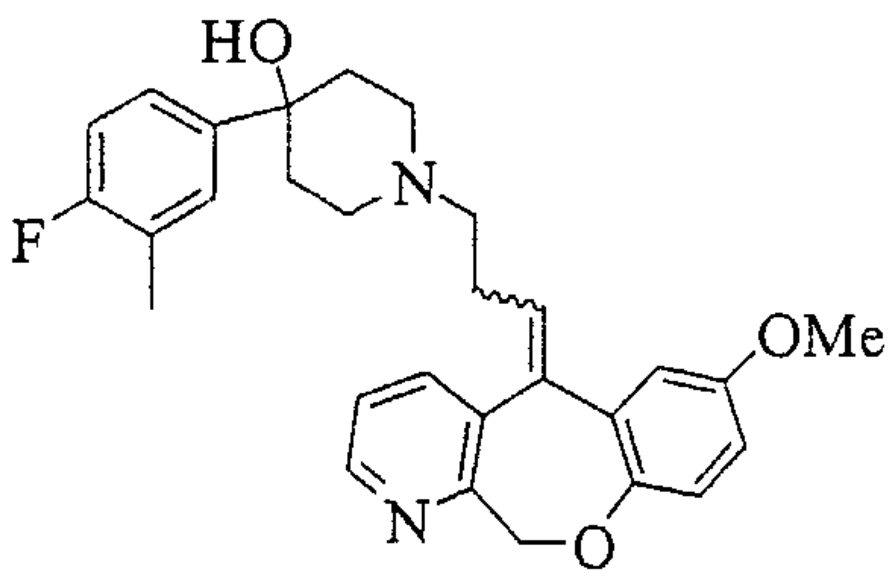
Example 140



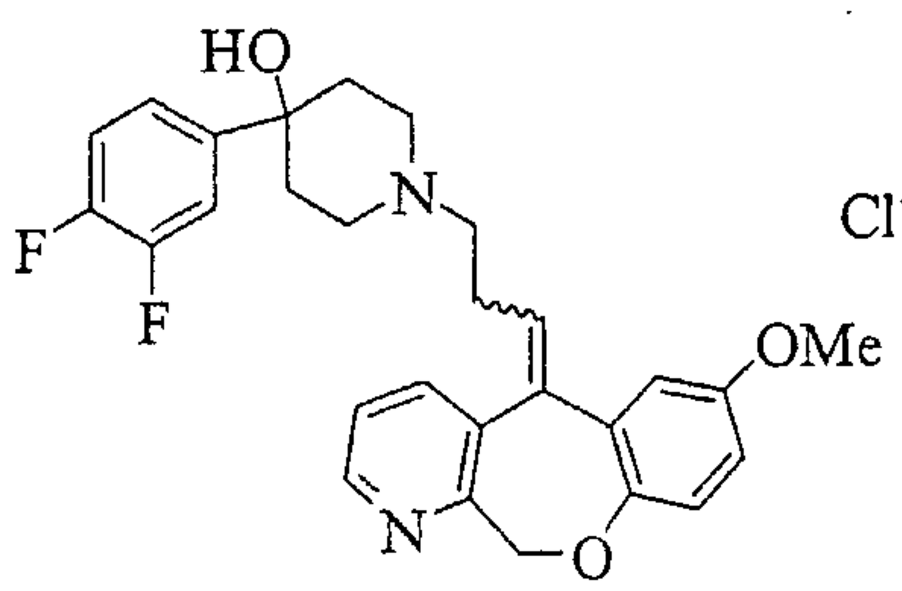
Example 141



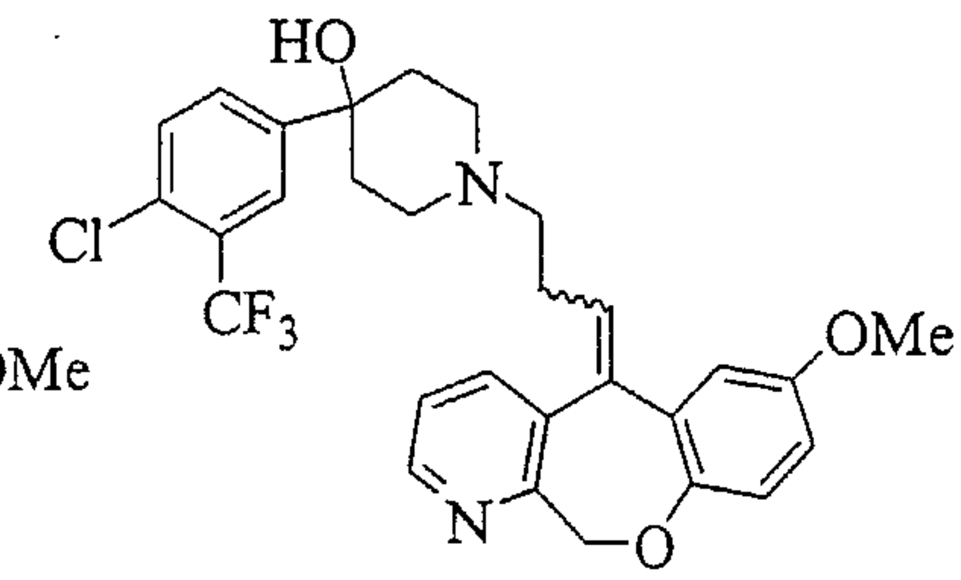
Example 142



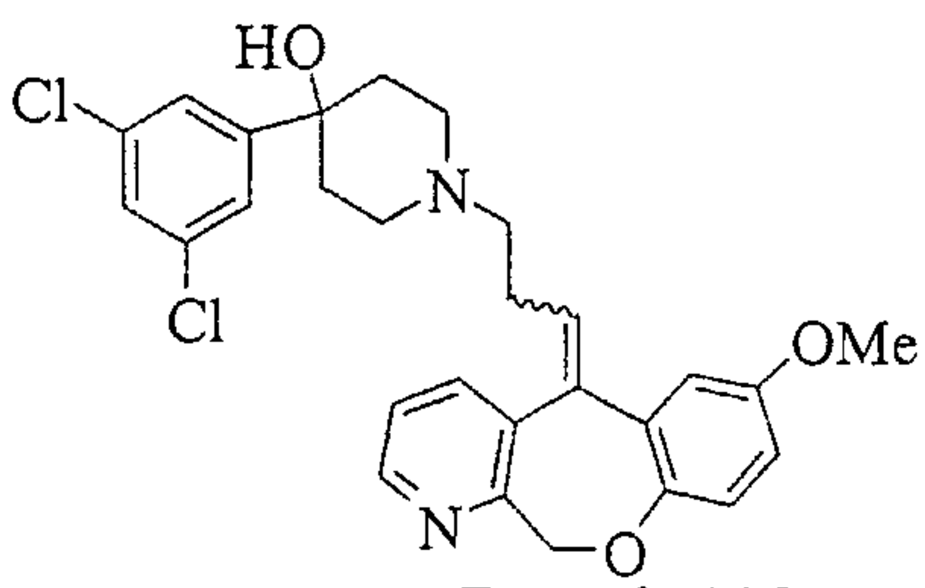
Example 143



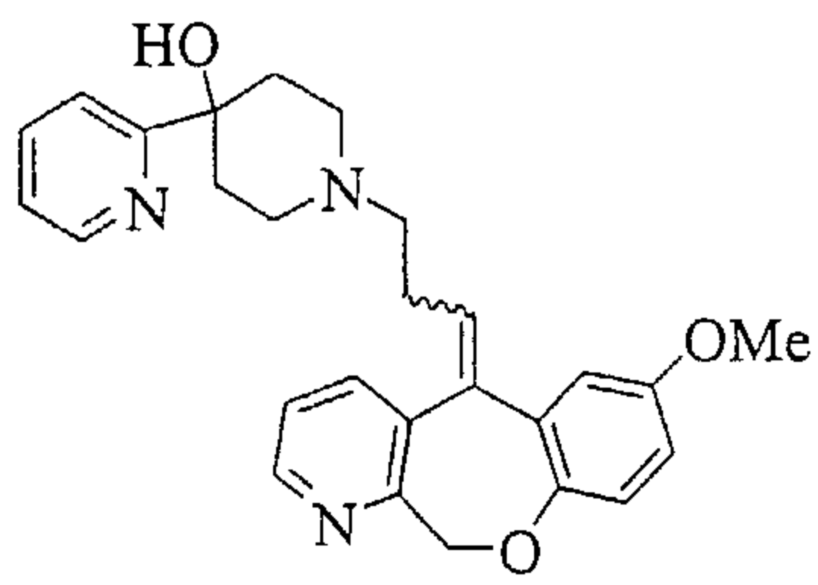
Example 144



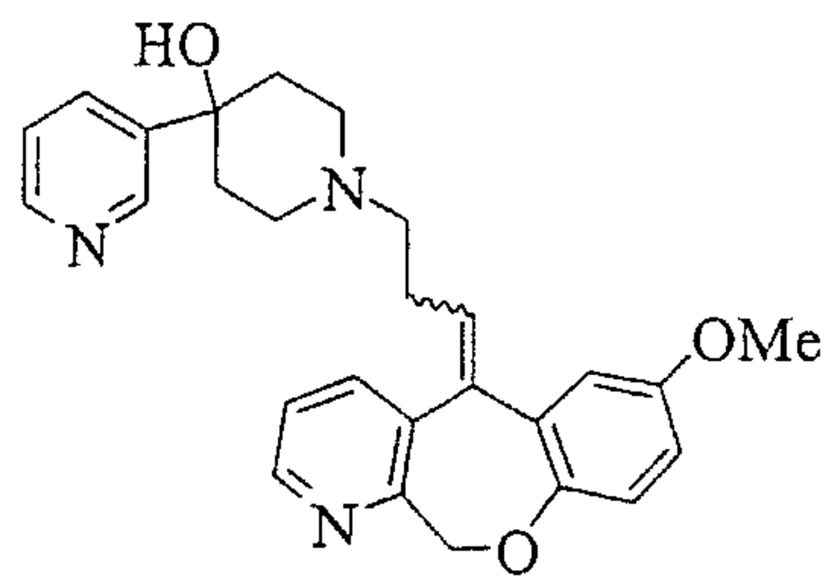
Example 145



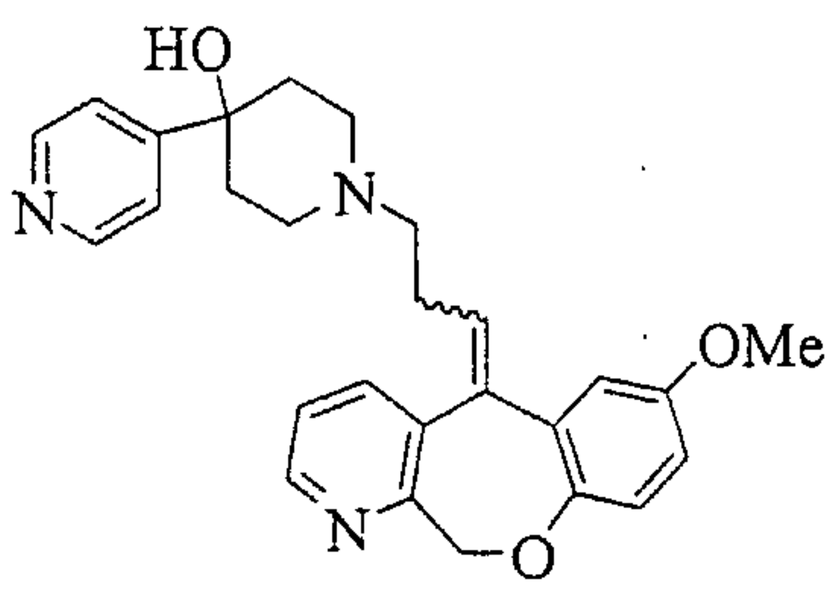
Example 146



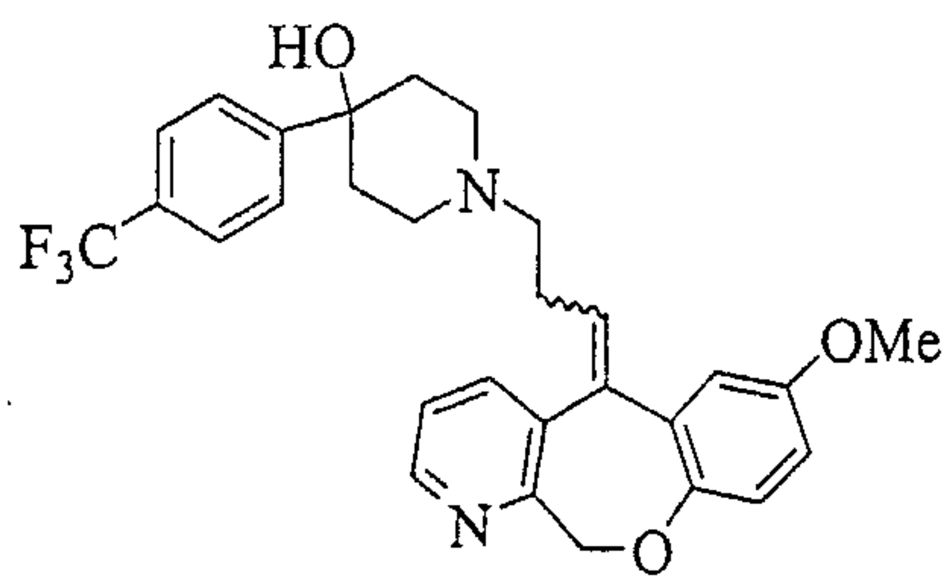
Example 147



Example 148

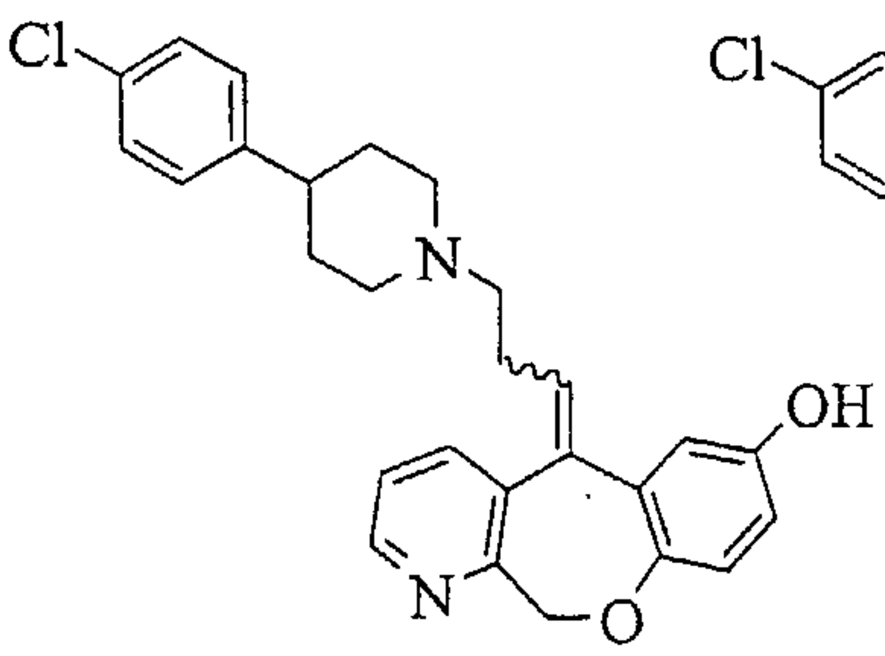


Example 149

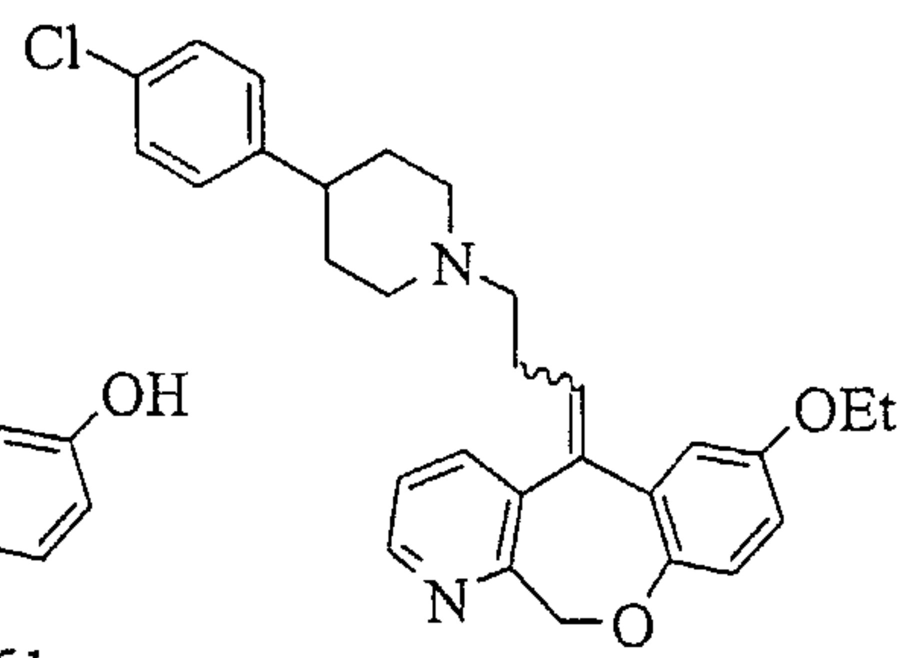


Example 150

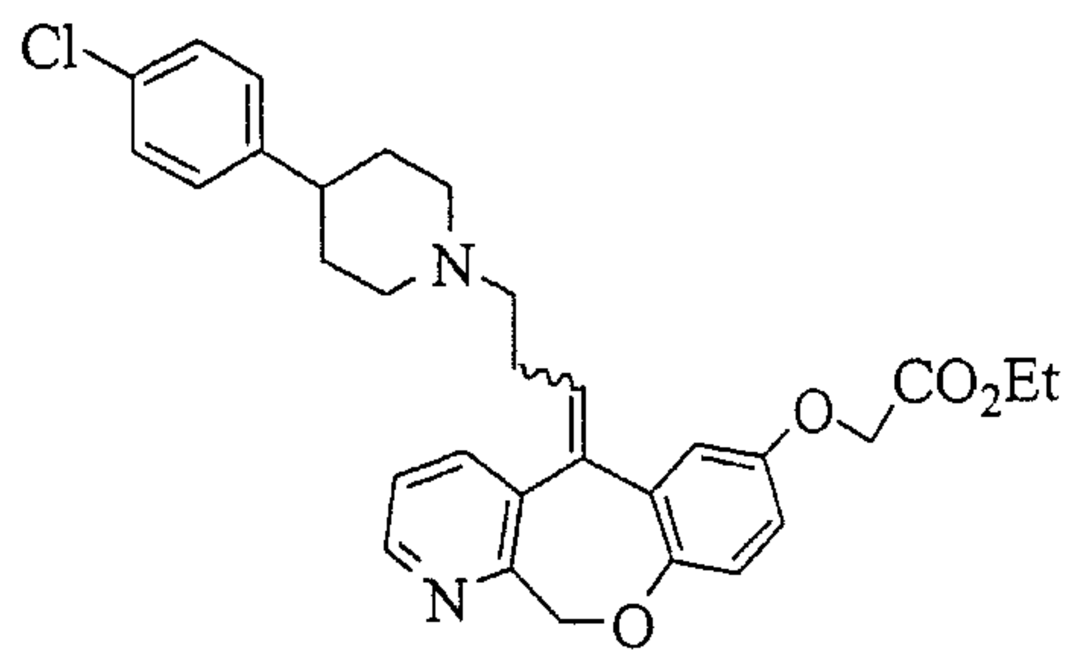
Figure 6O



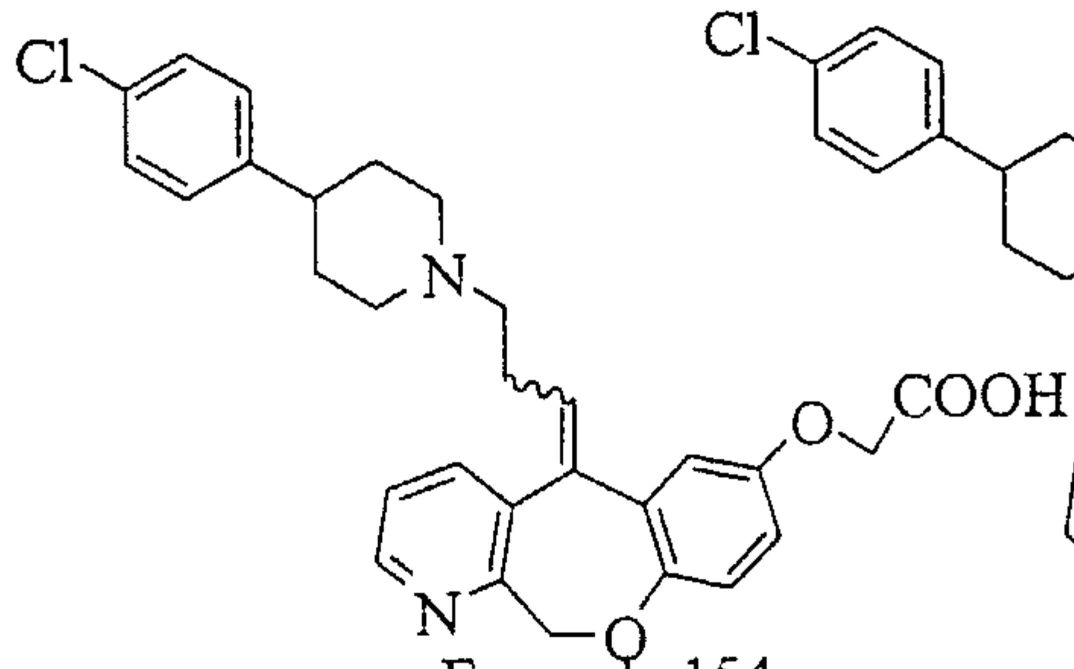
Example 151



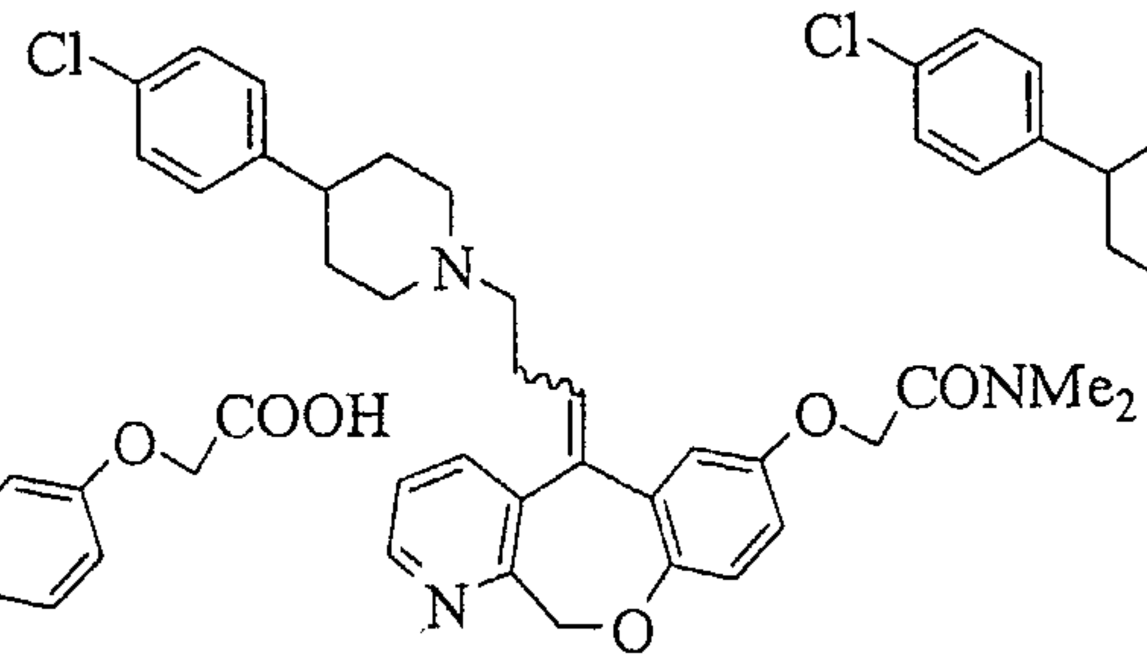
Example 152



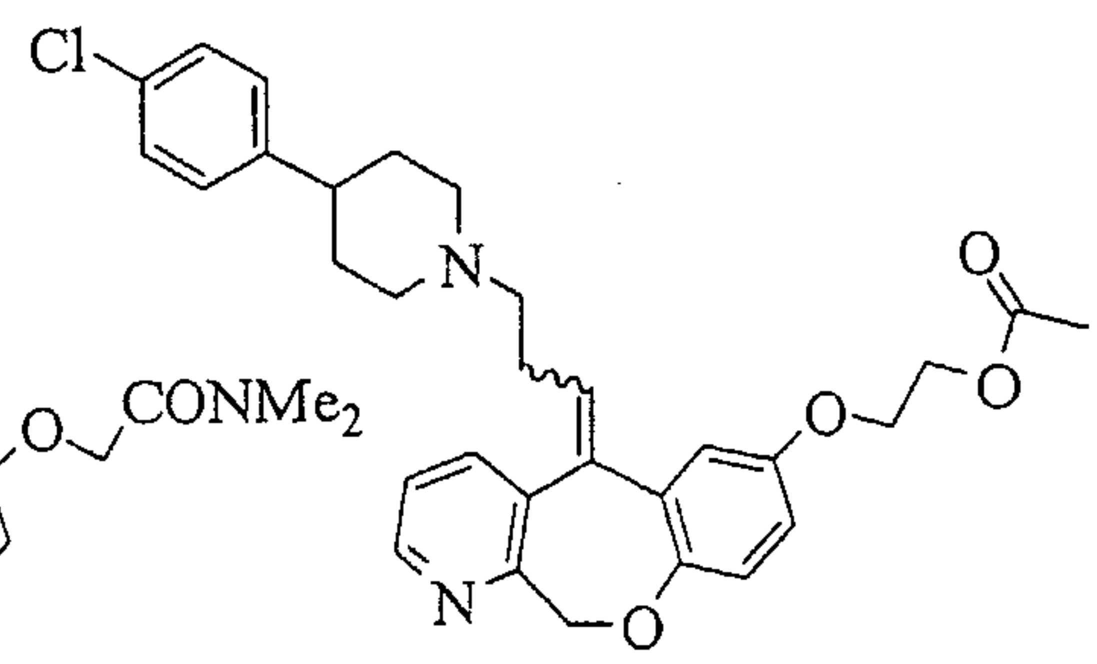
Example 153



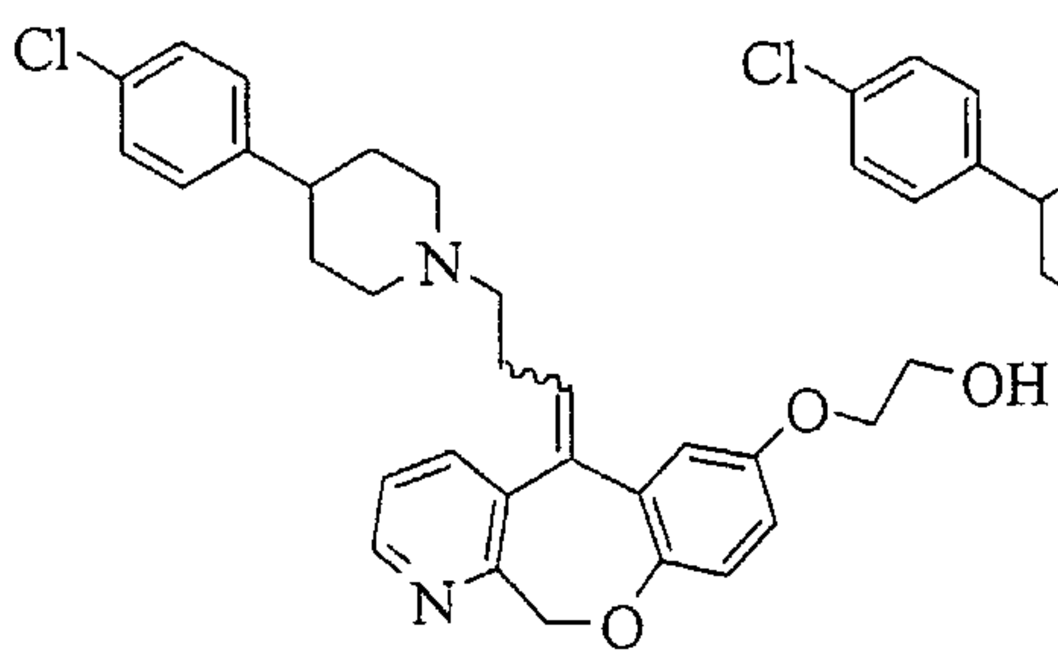
Example 154



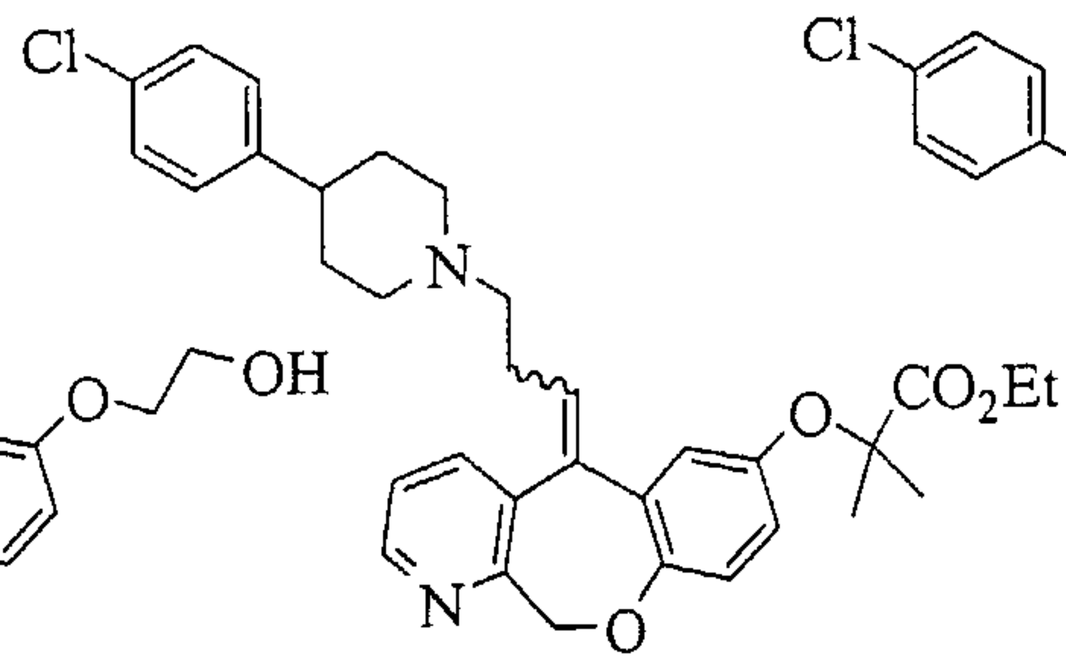
Example 155



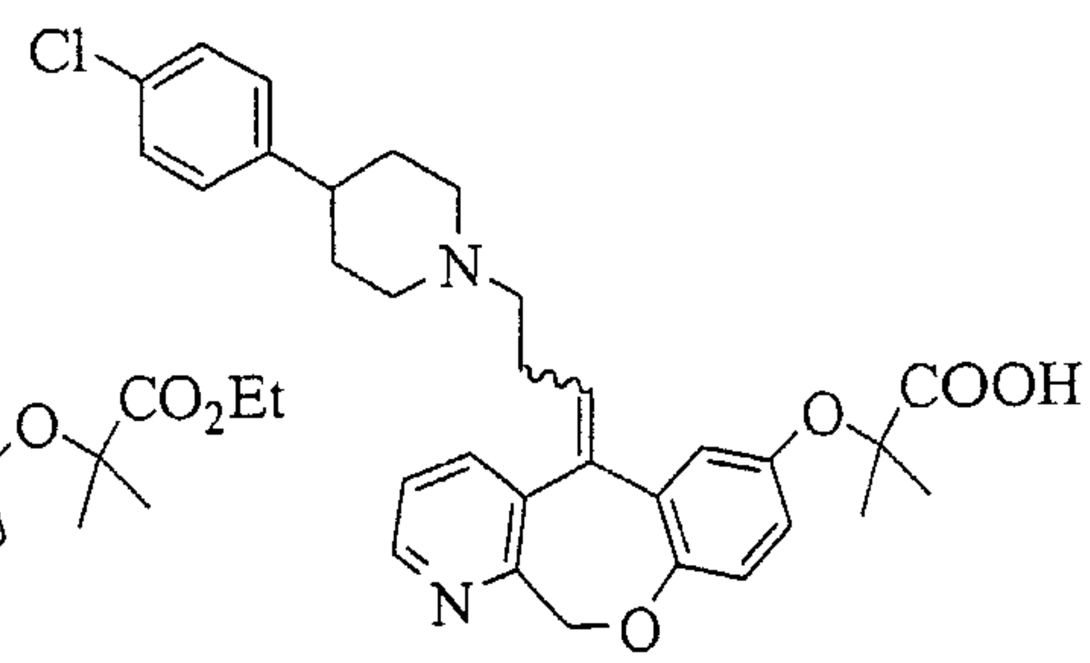
Example 156



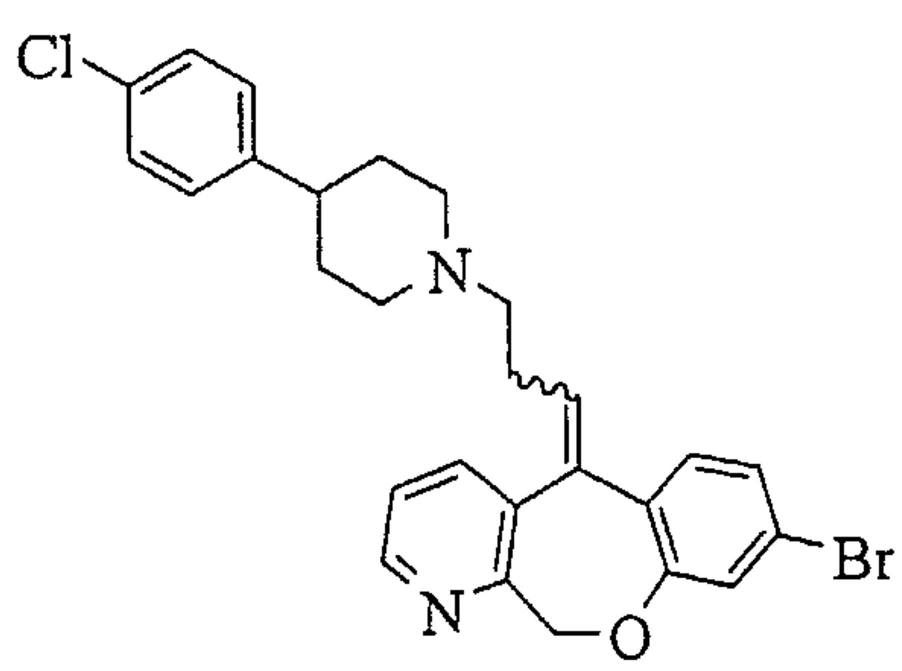
Example 157



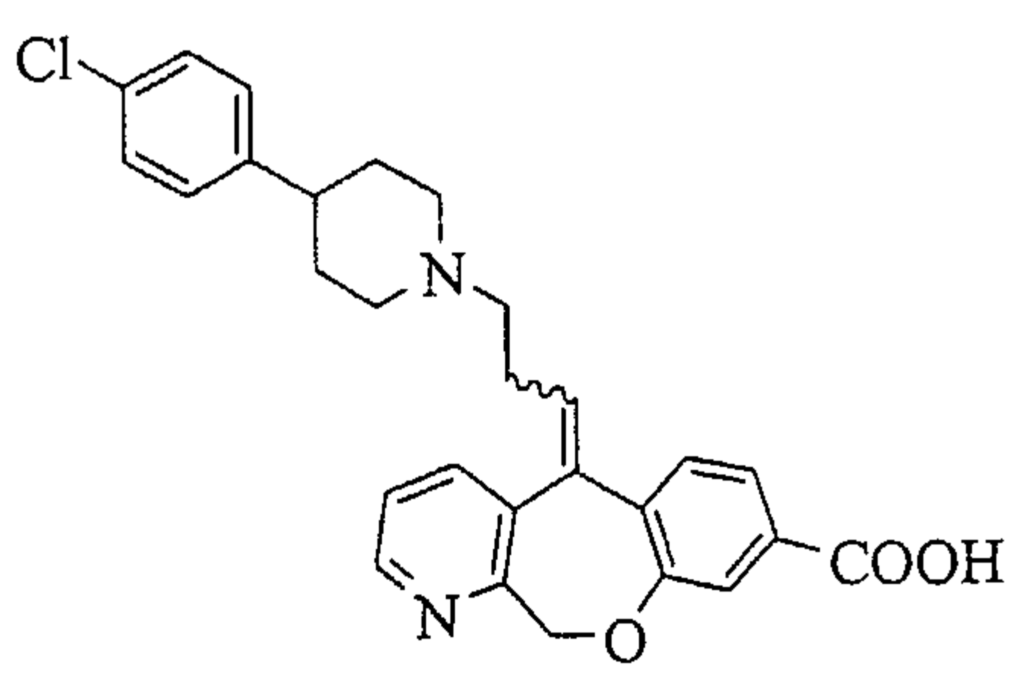
Example 158



Example 159

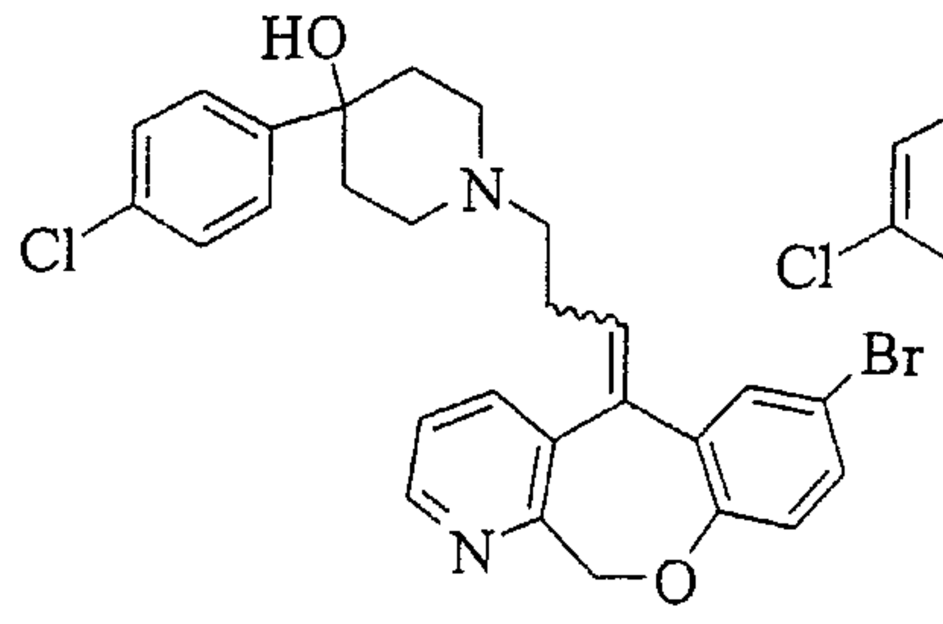


Example 160

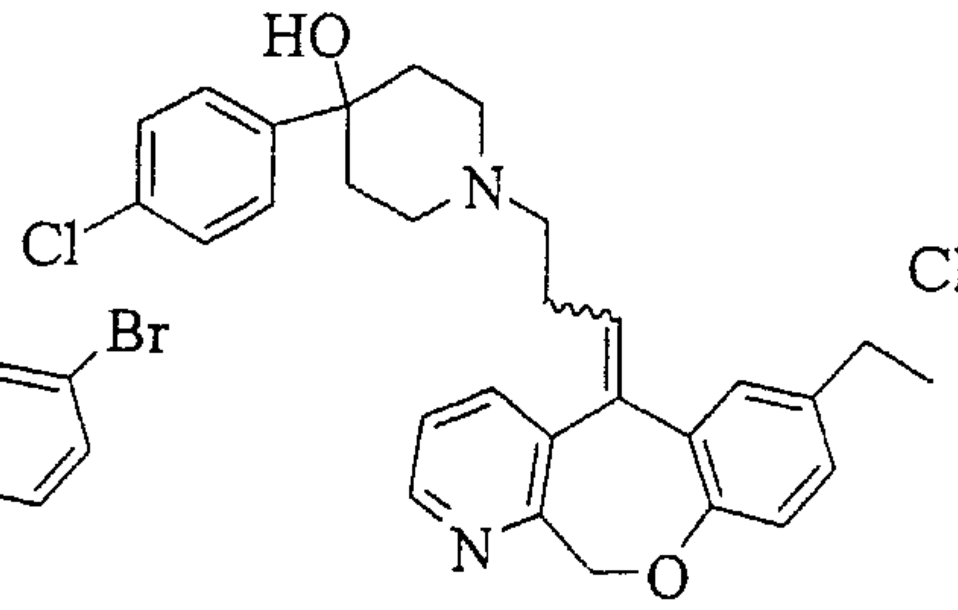


Example 161

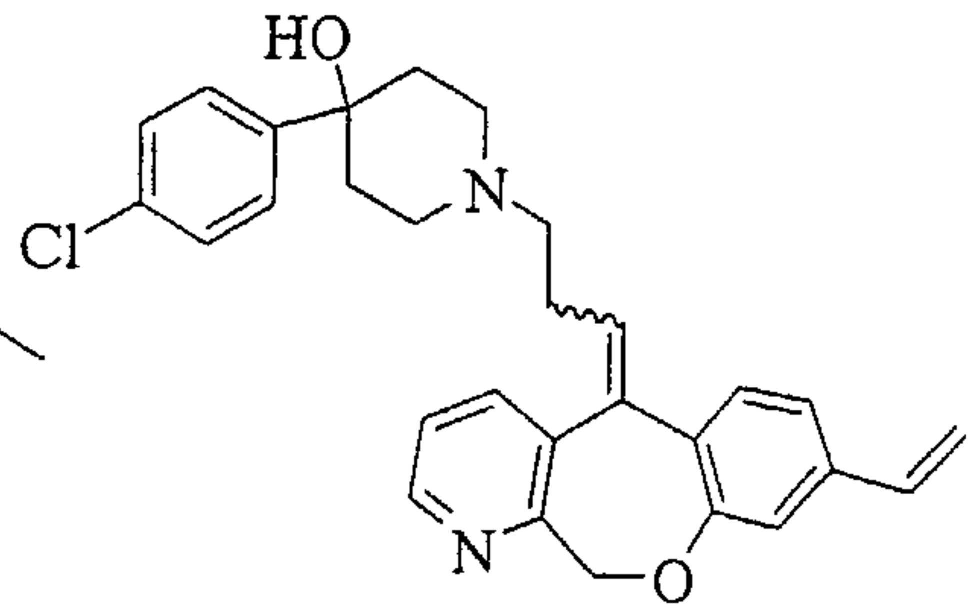
Figure 6P



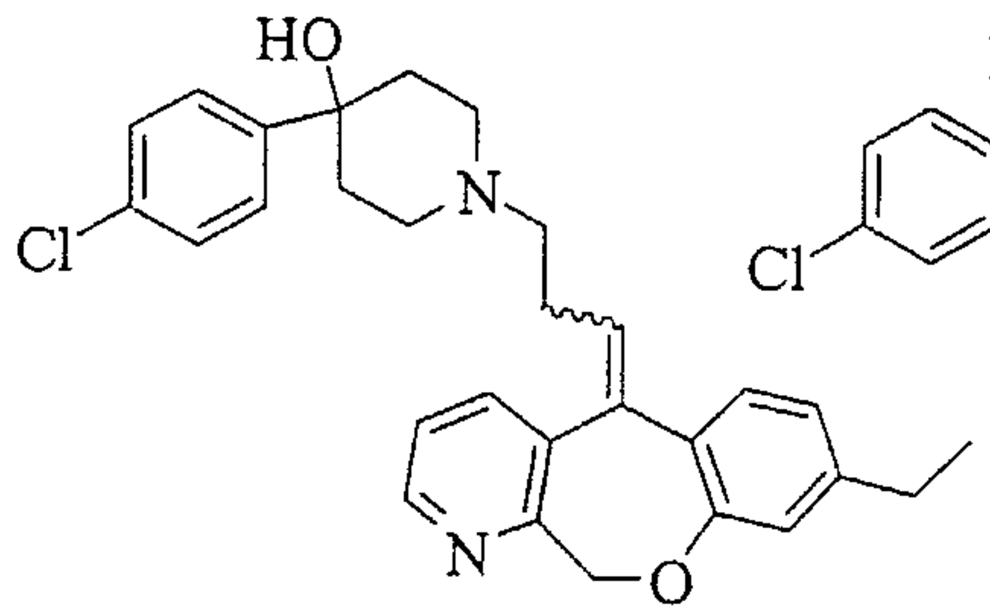
Example 162



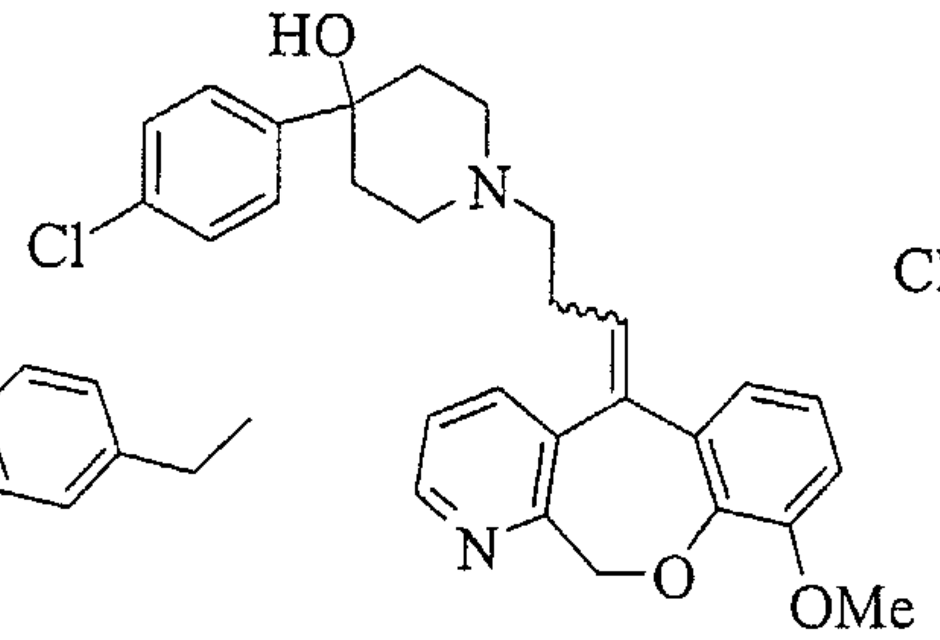
Example 163



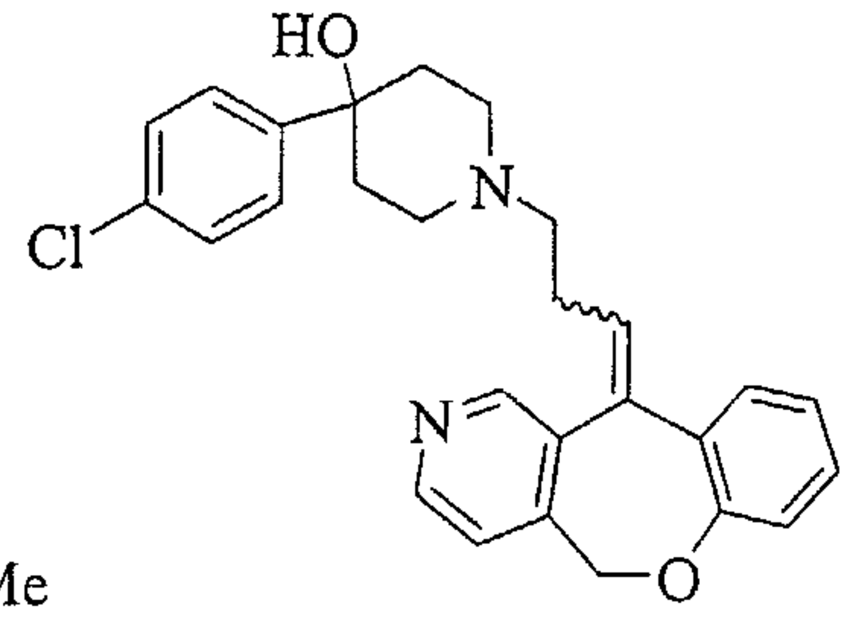
Example 164



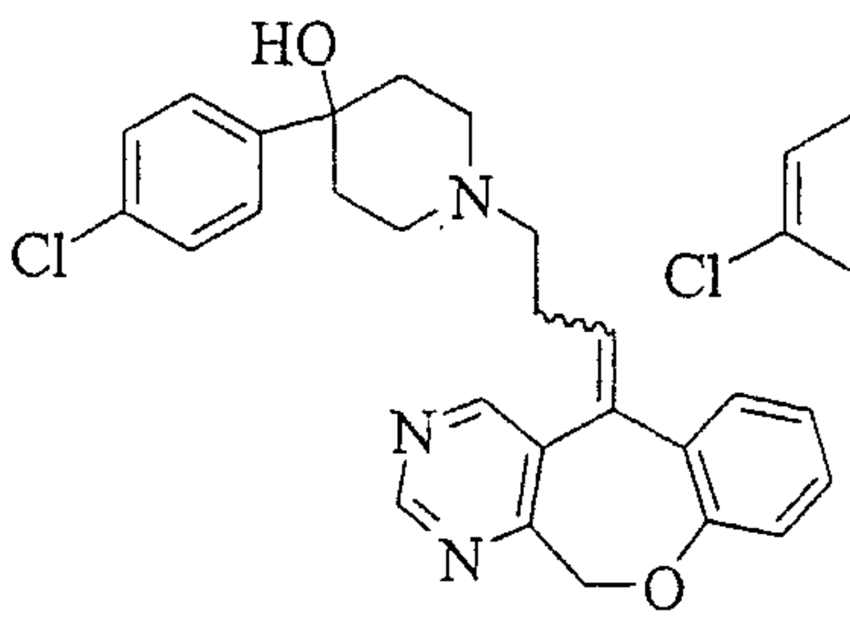
Example 165



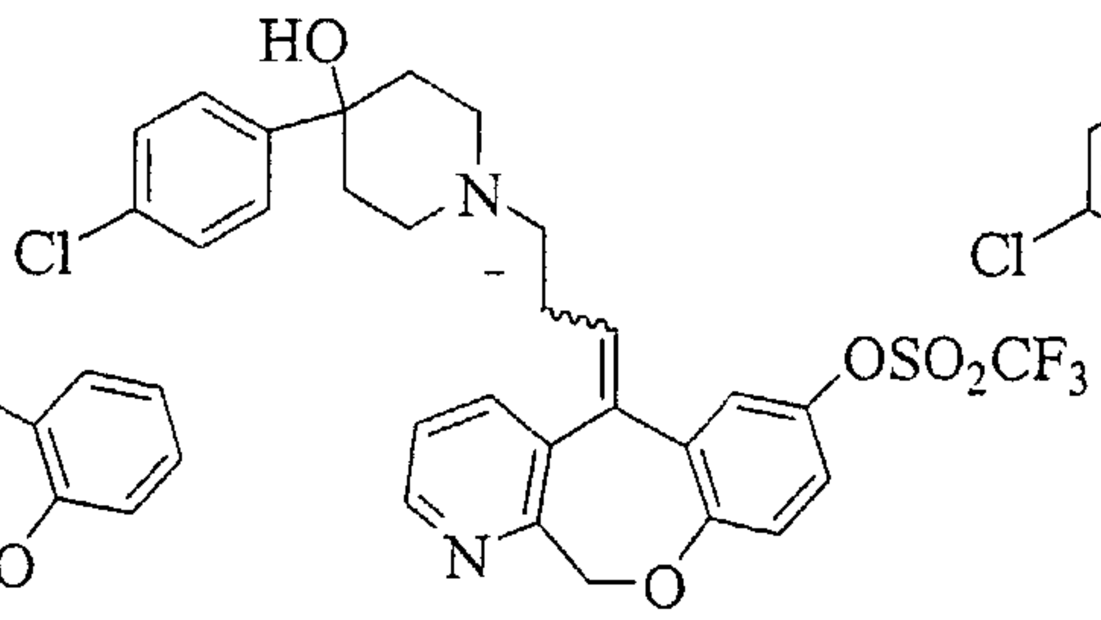
Example 166



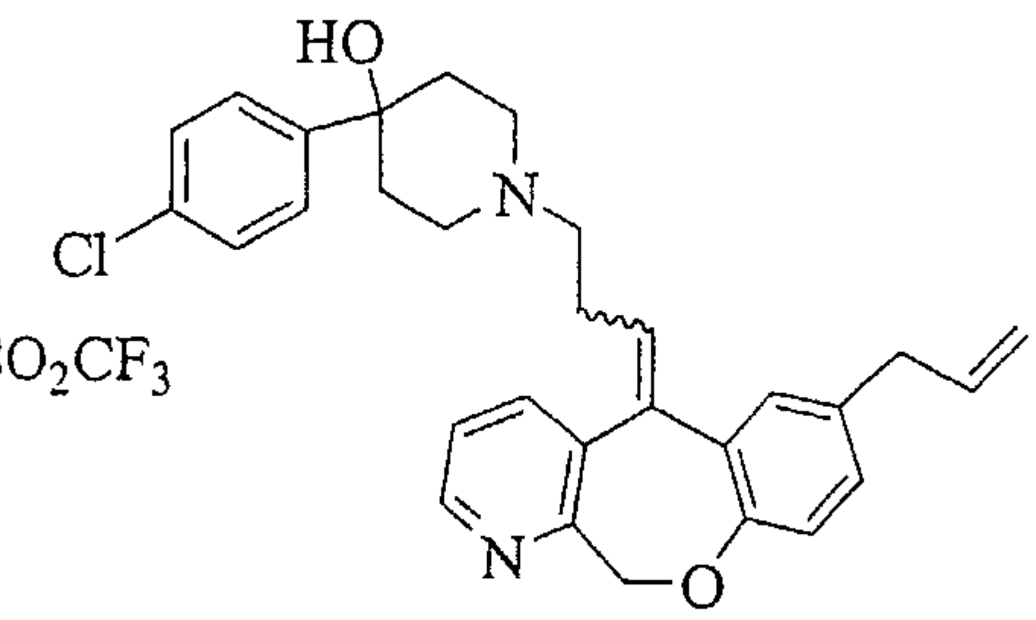
Example 167



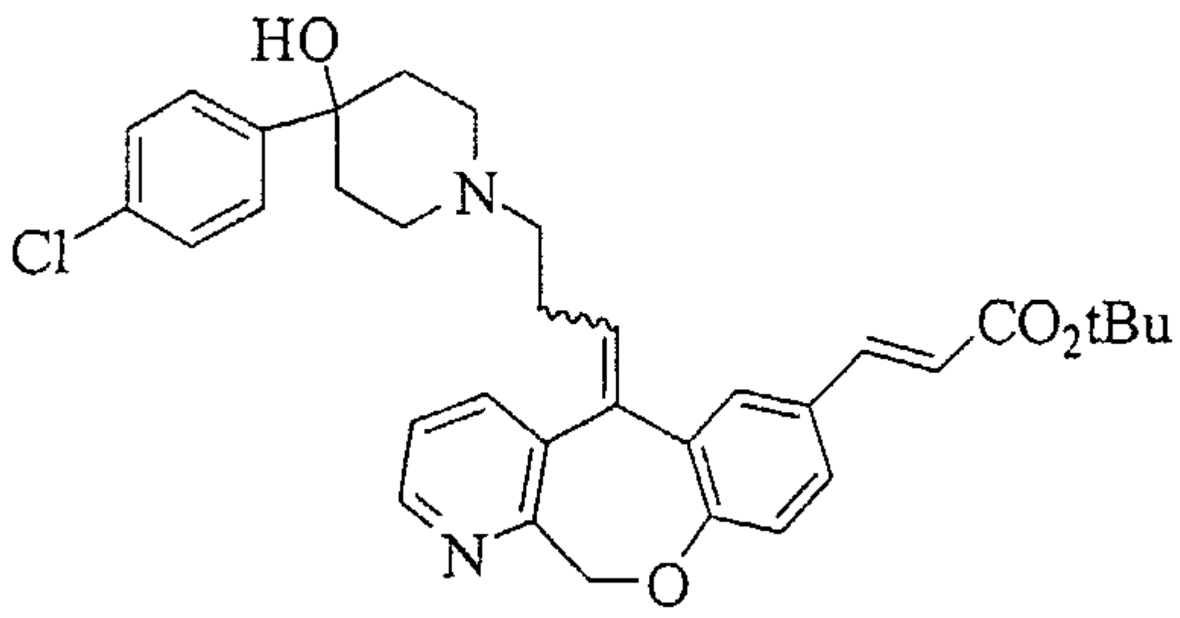
Example 168



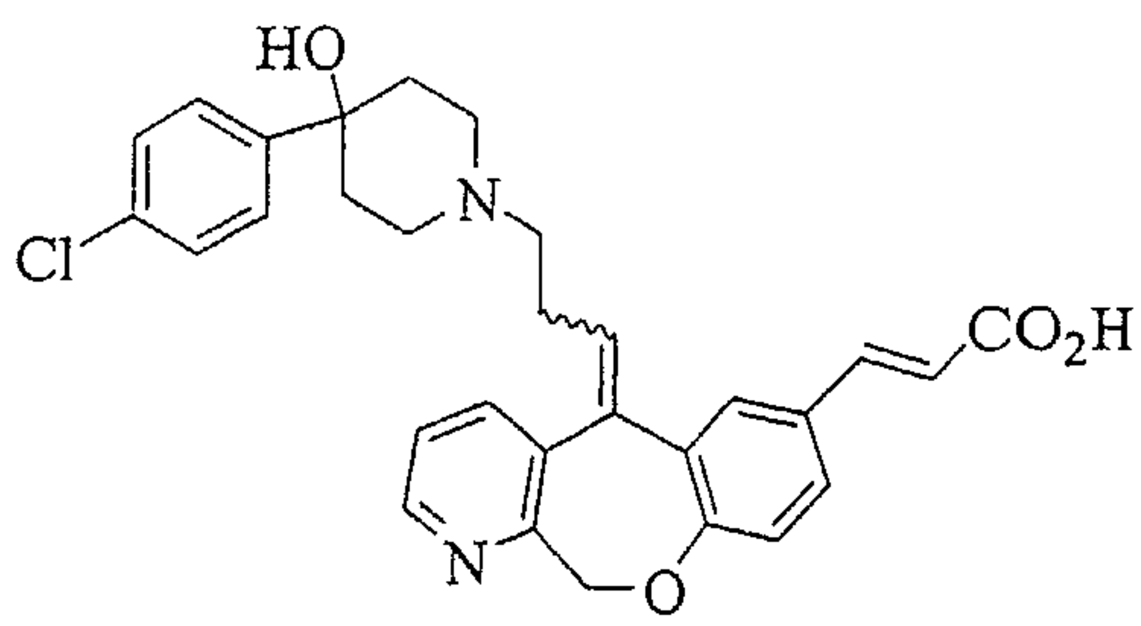
Example 169



Example 170

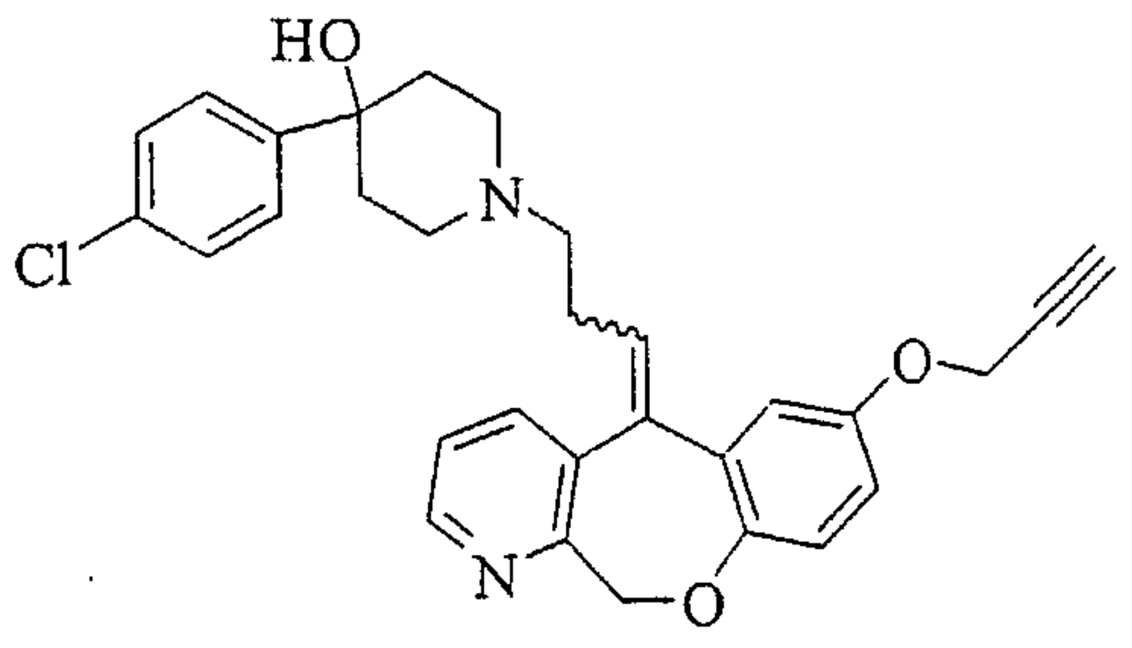


Example 171

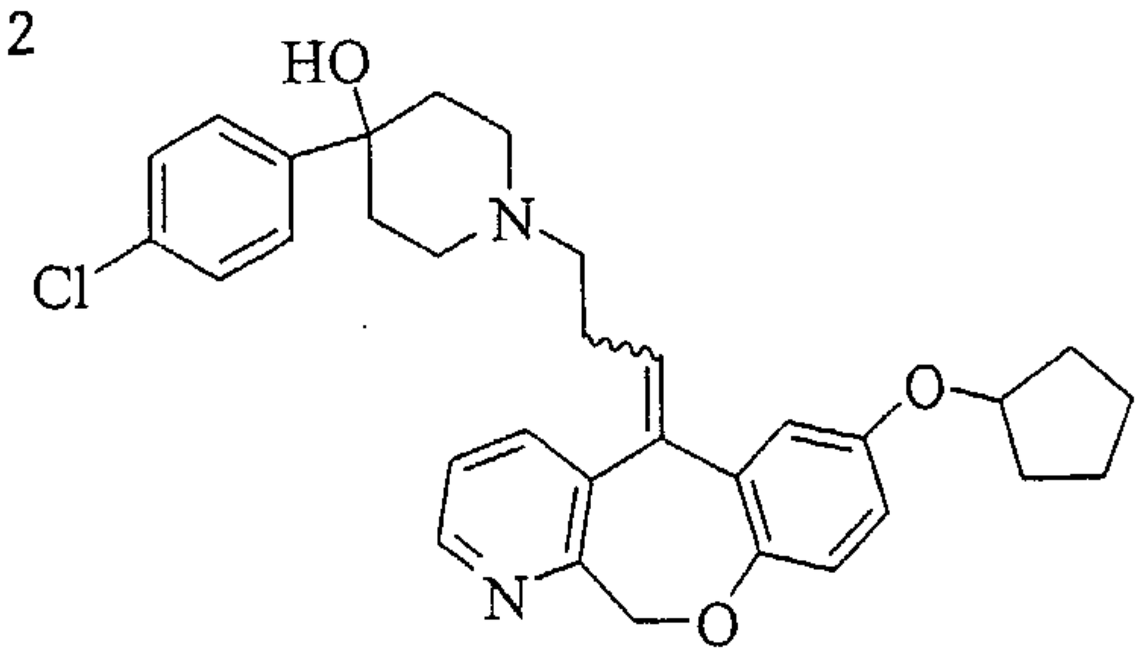


Example 172

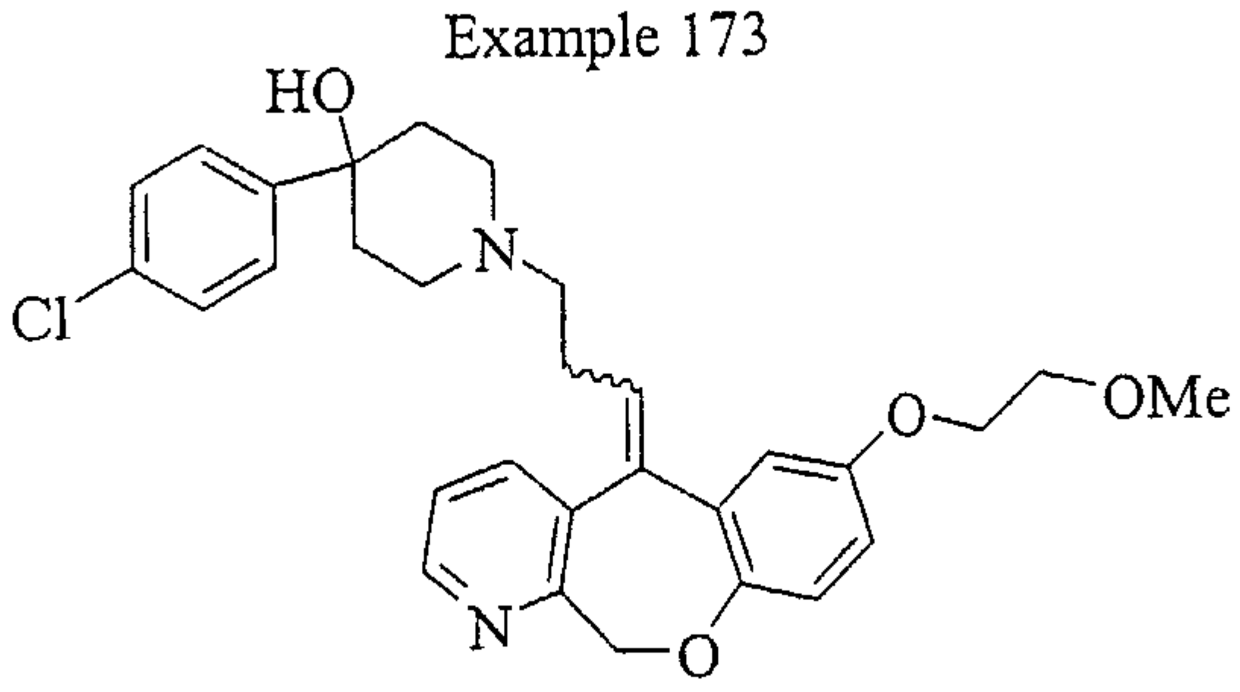
Figure 6Q



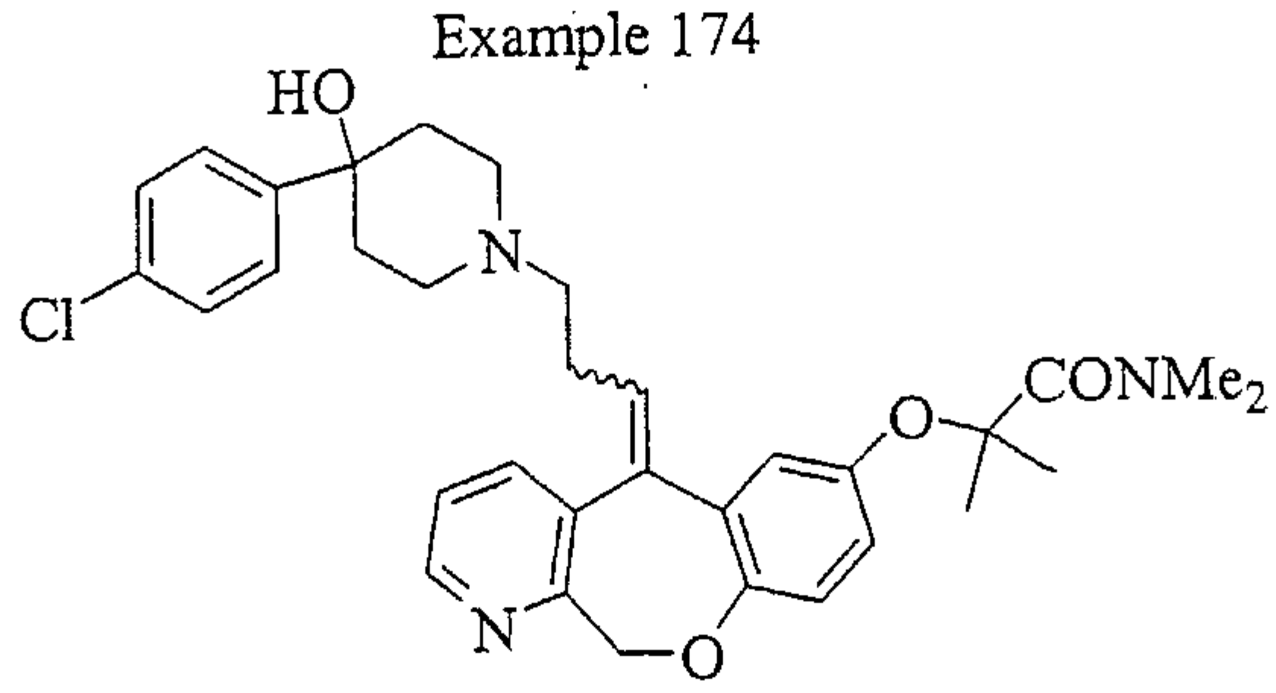
Example 173



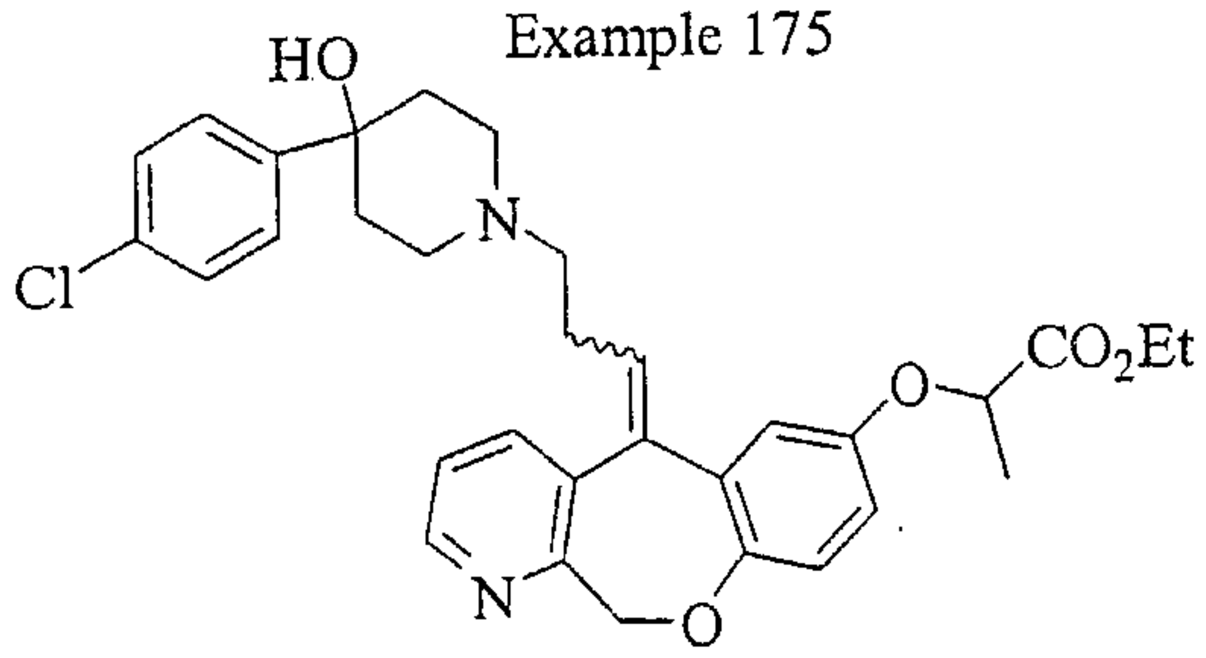
Example 174



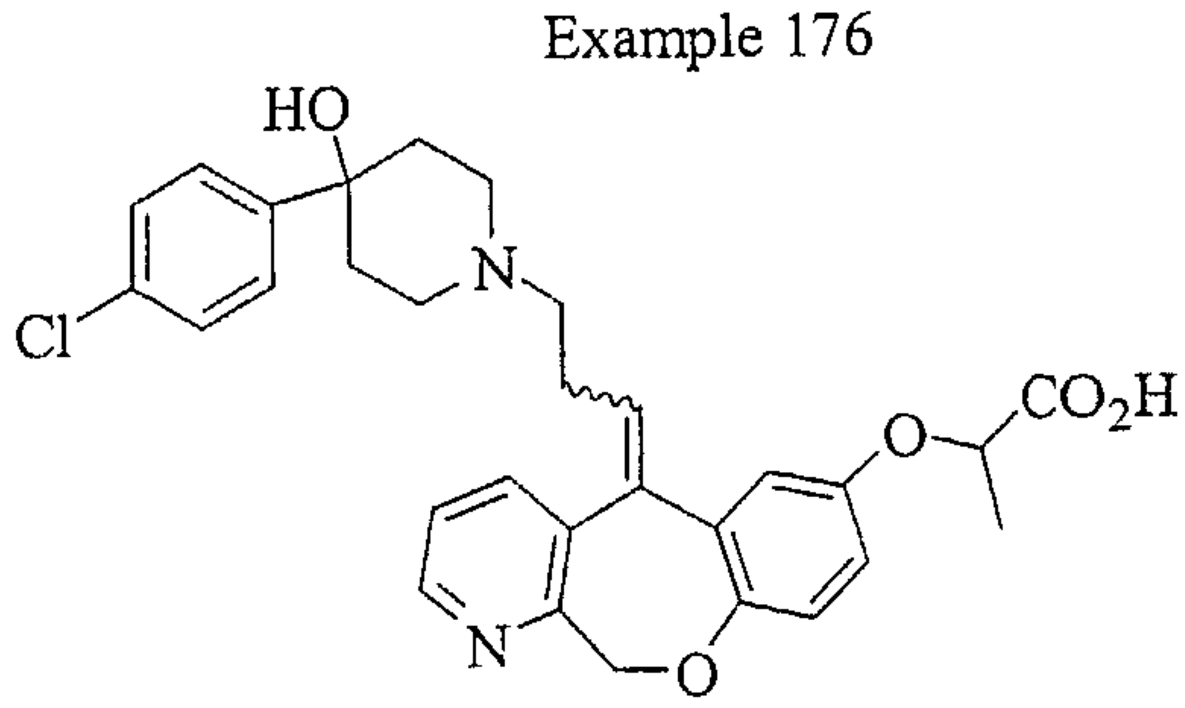
Example 175



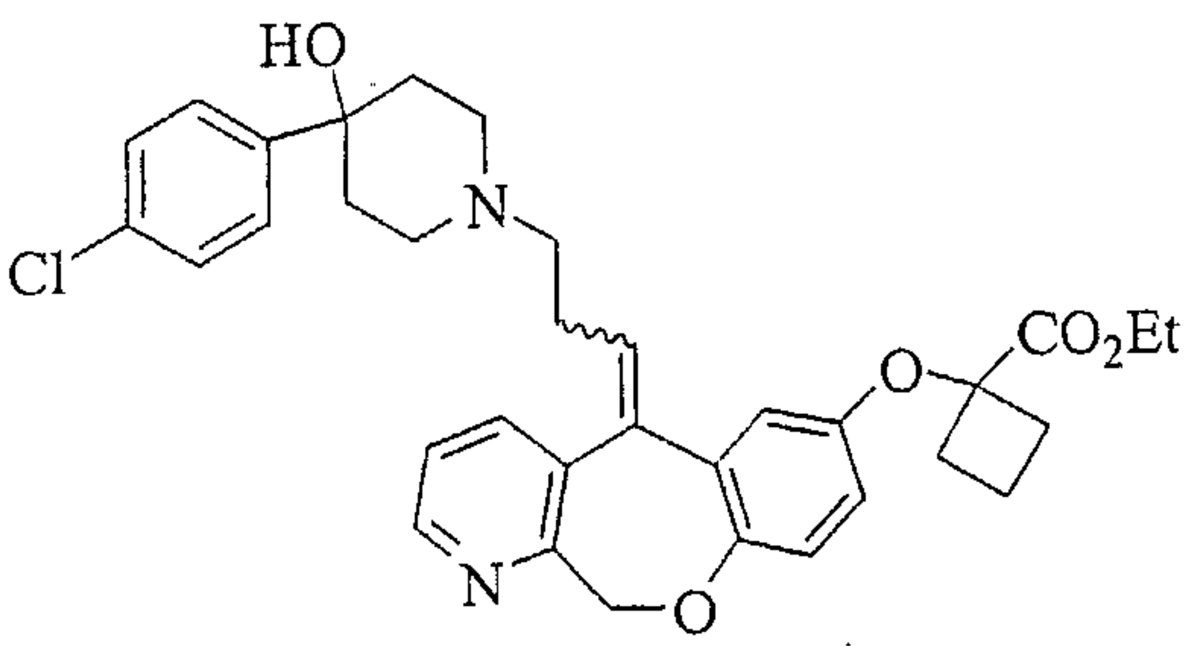
Example 176



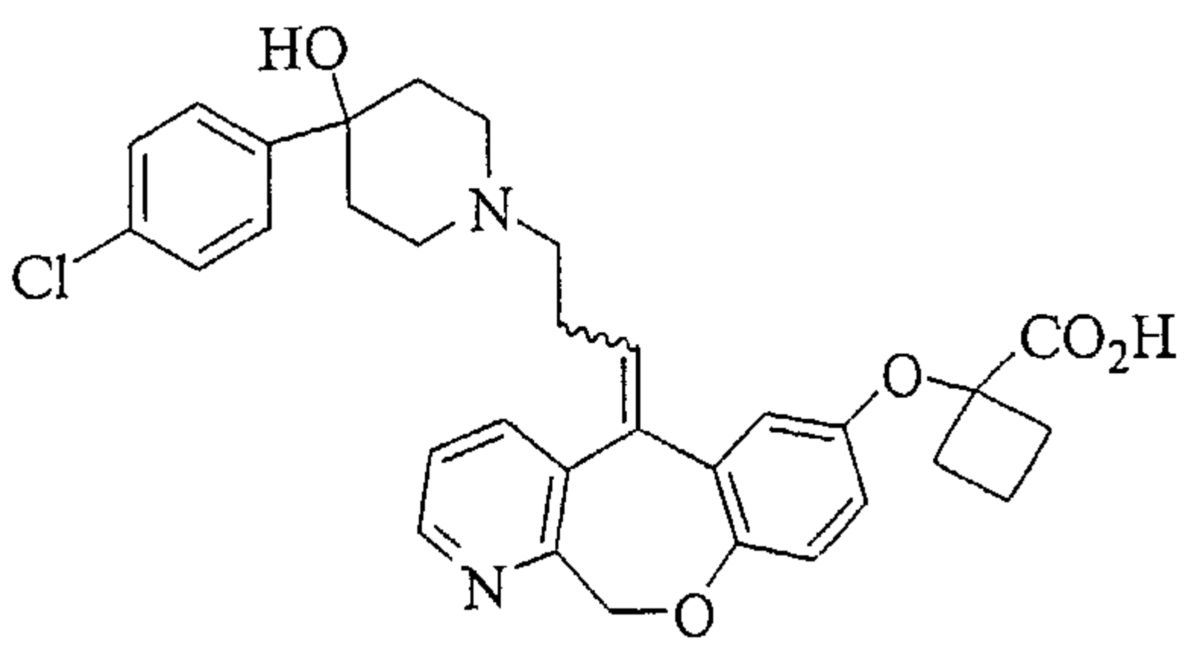
Example 177



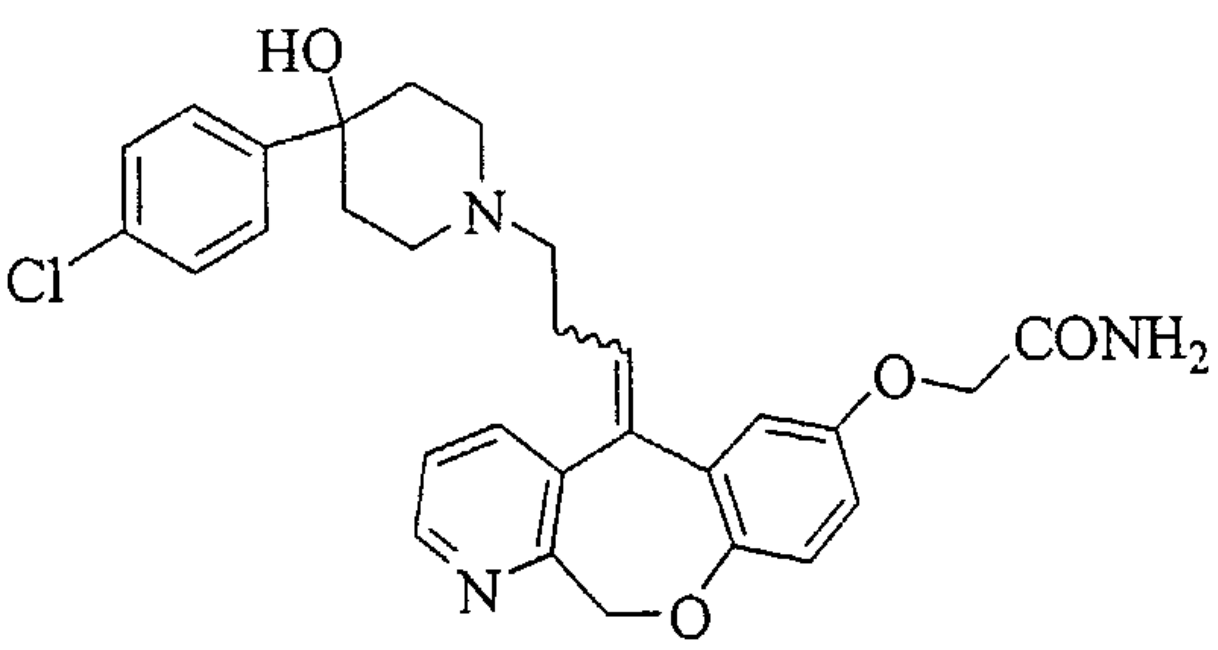
Example 178



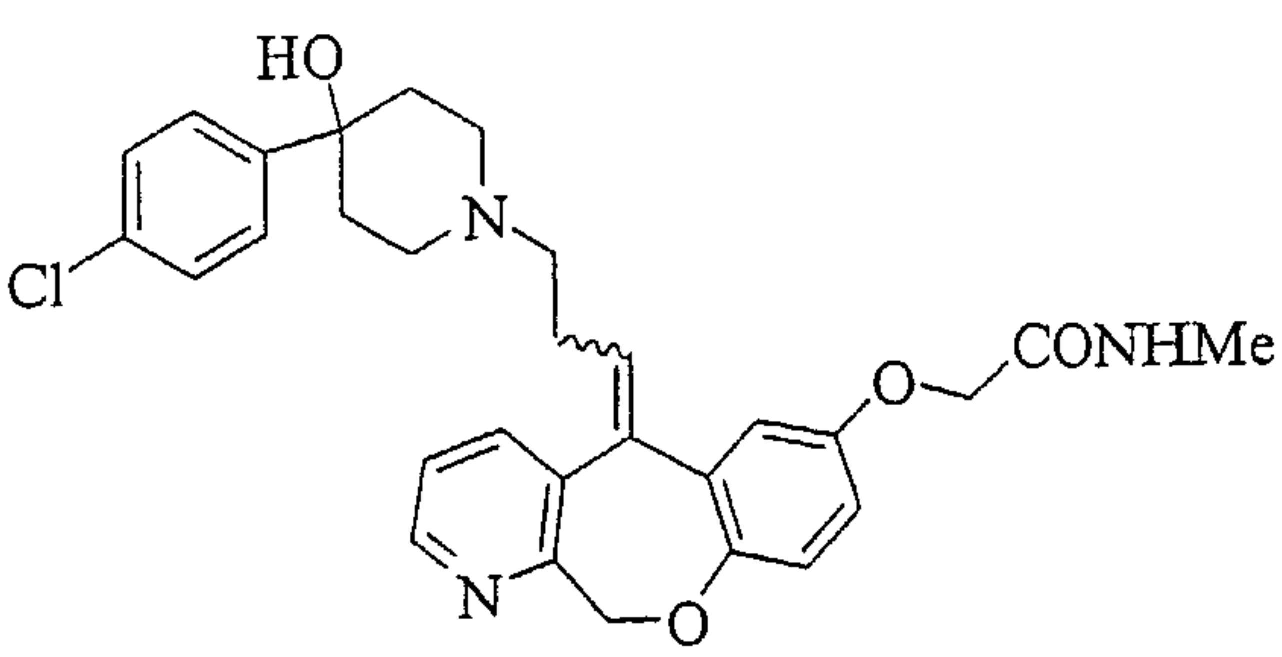
Example 179



Example 180

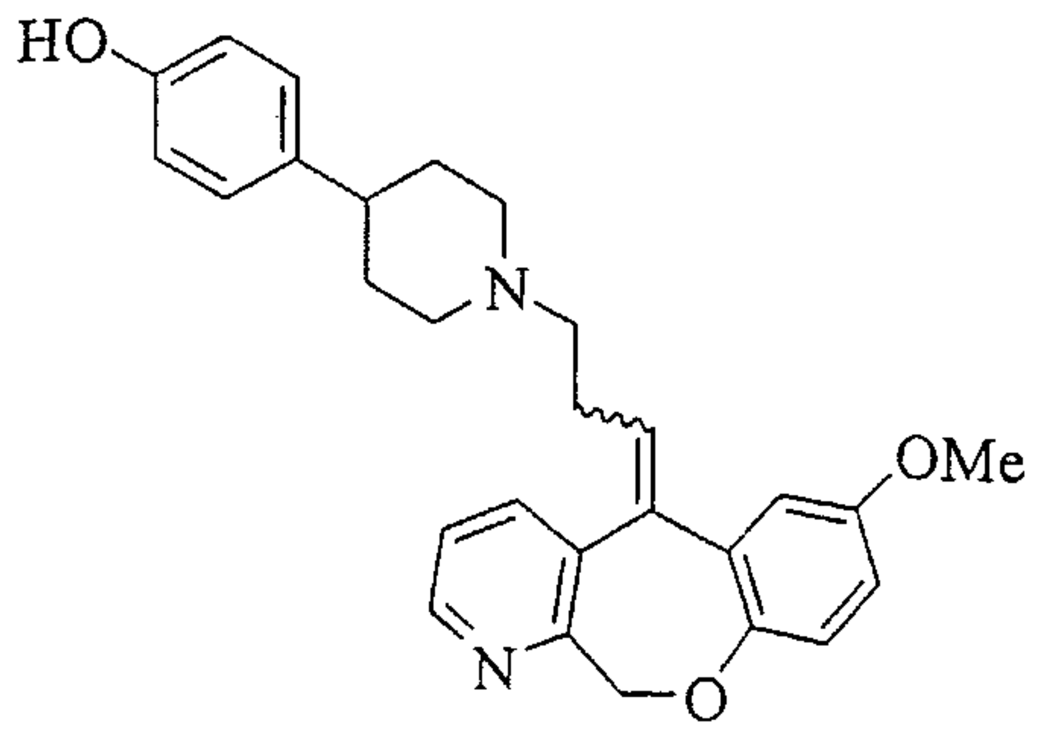


Example 181

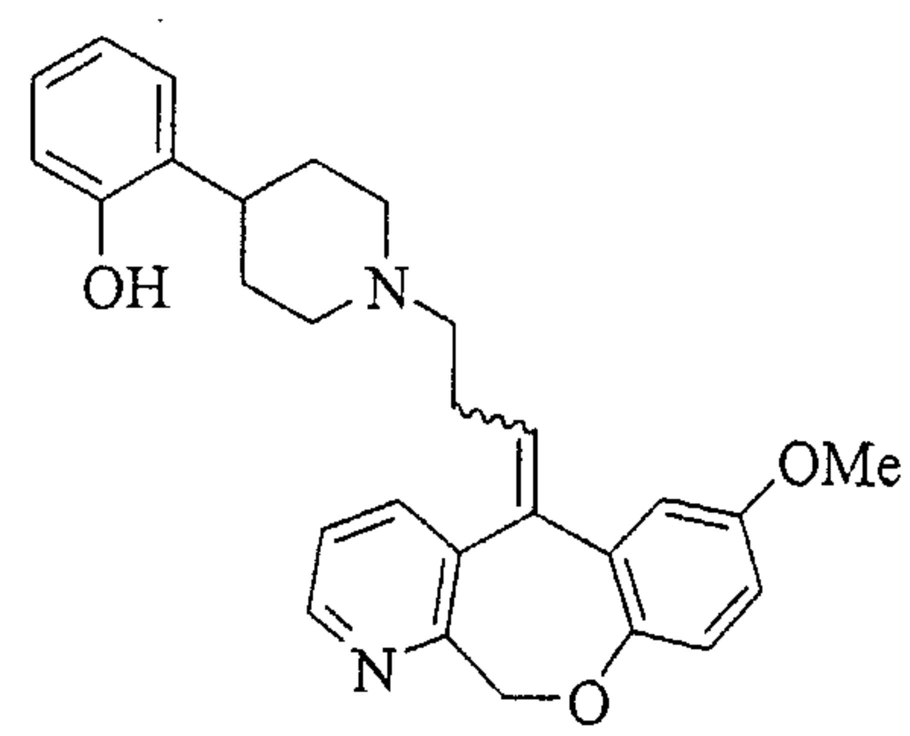


Example 182

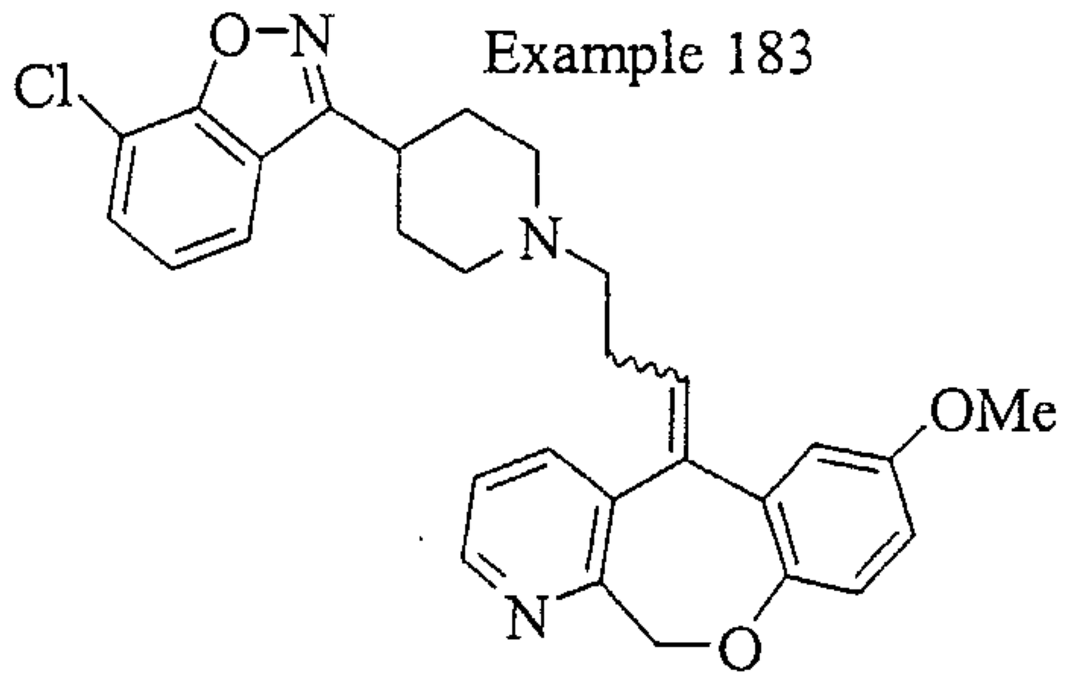
Figure 6R



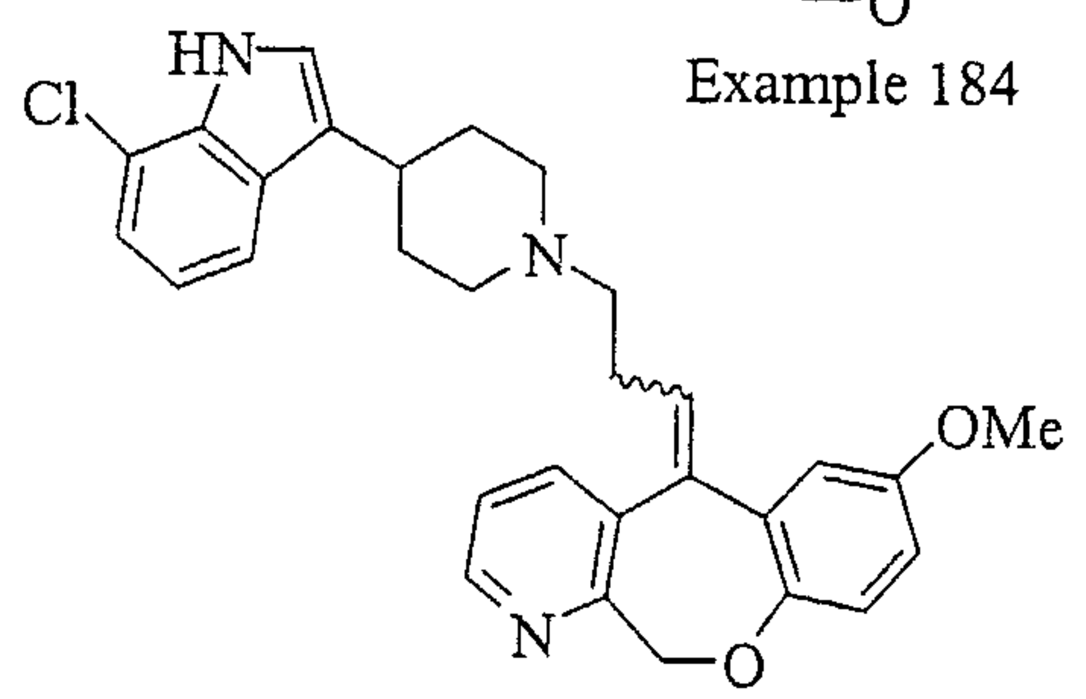
Example 183



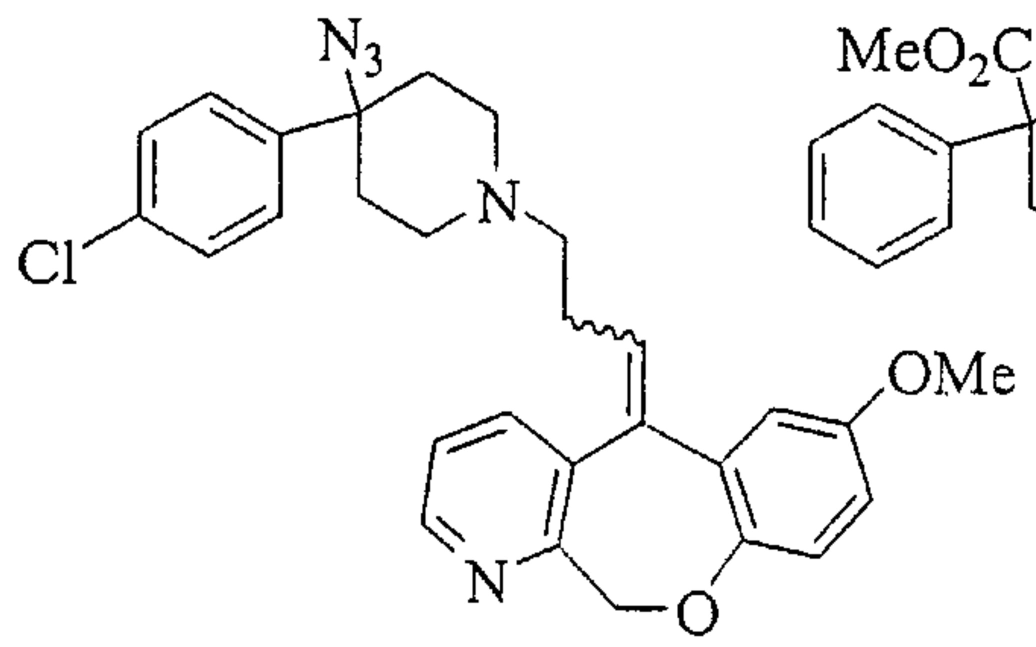
Example 184



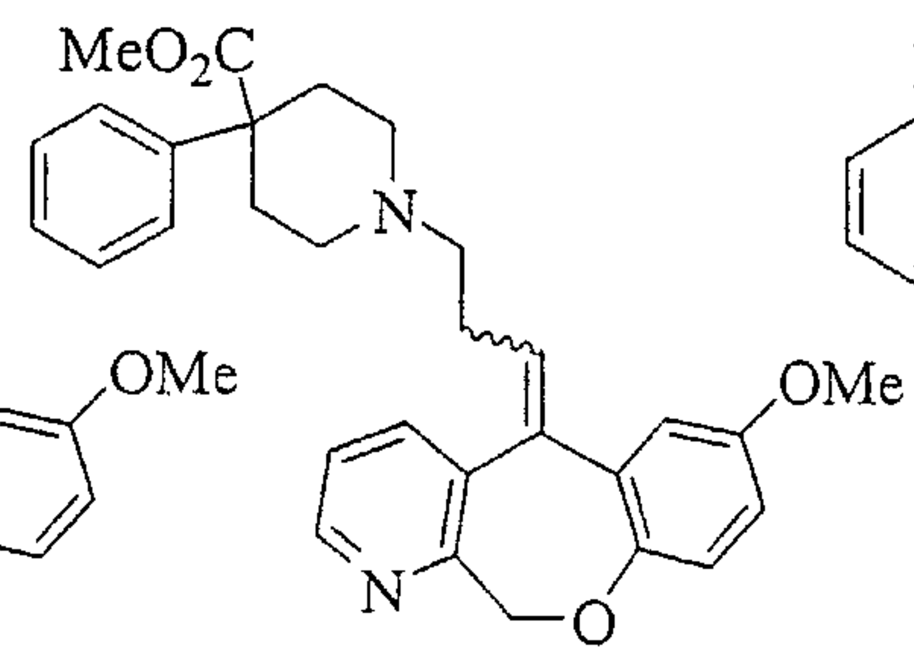
Example 185



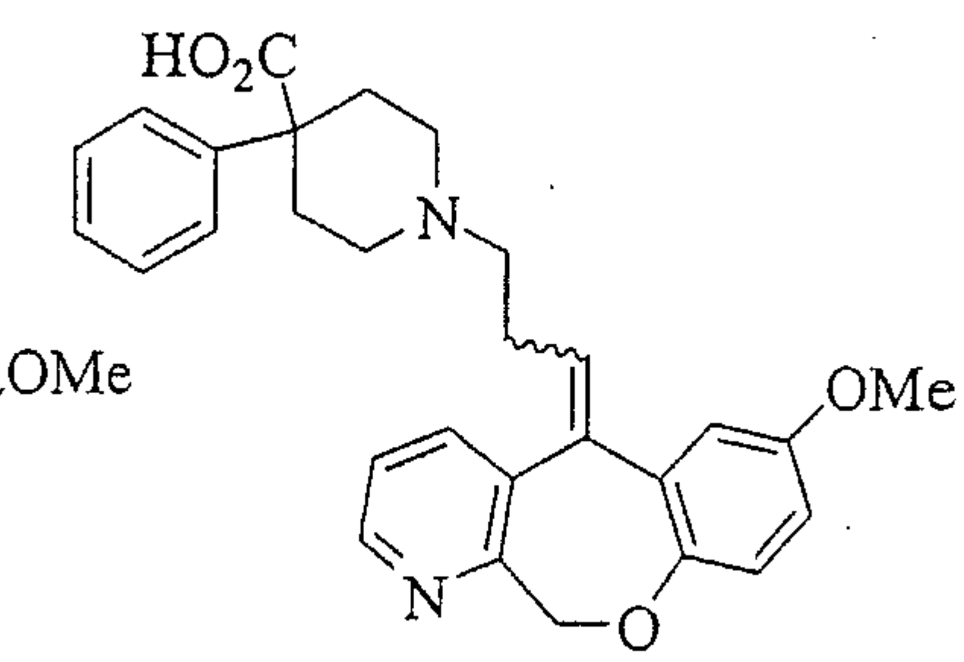
Example 186



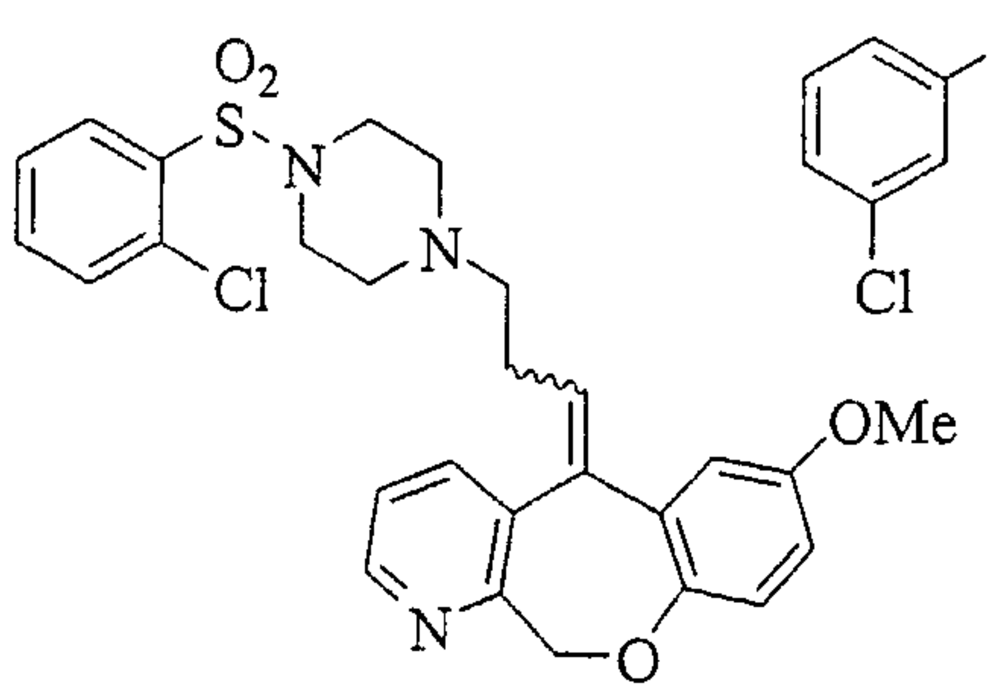
Example 187



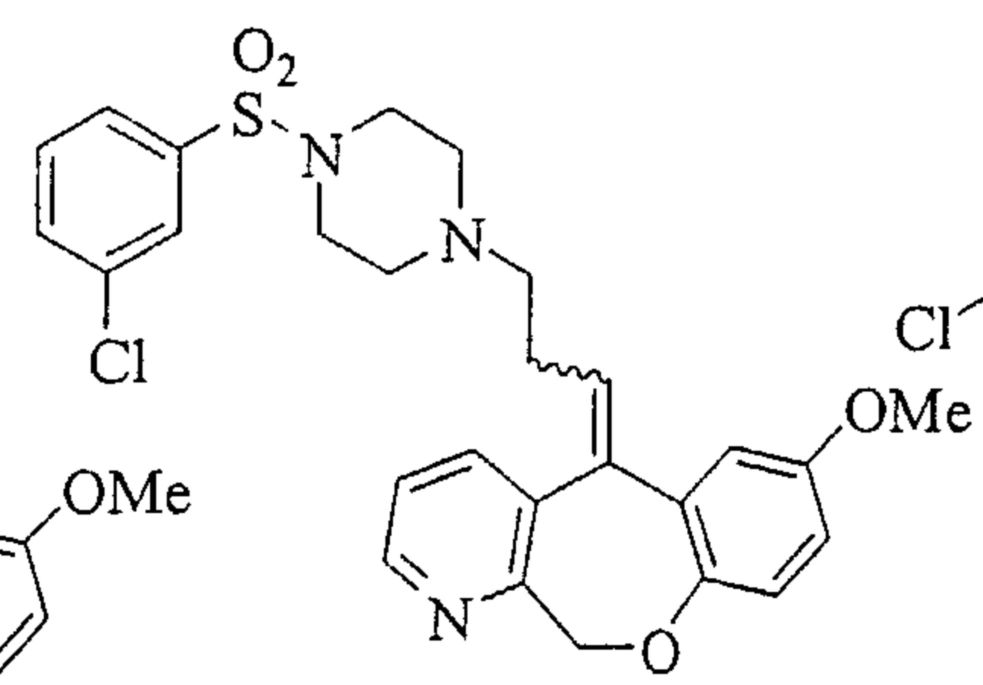
Example 188



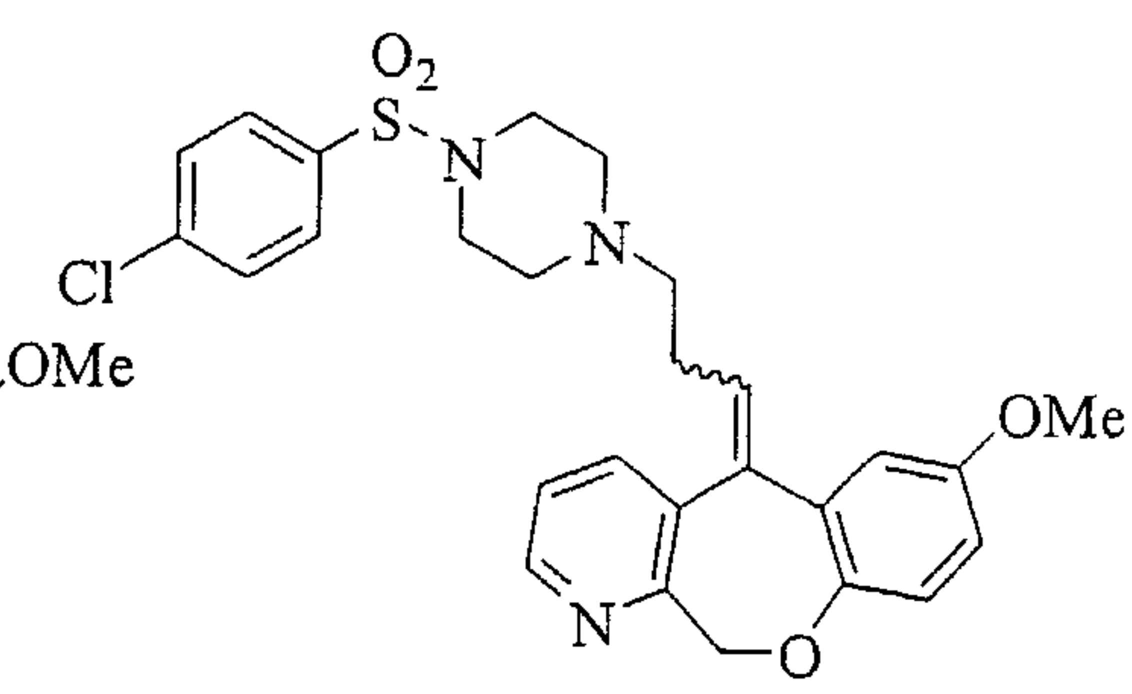
Example 189



Example 190

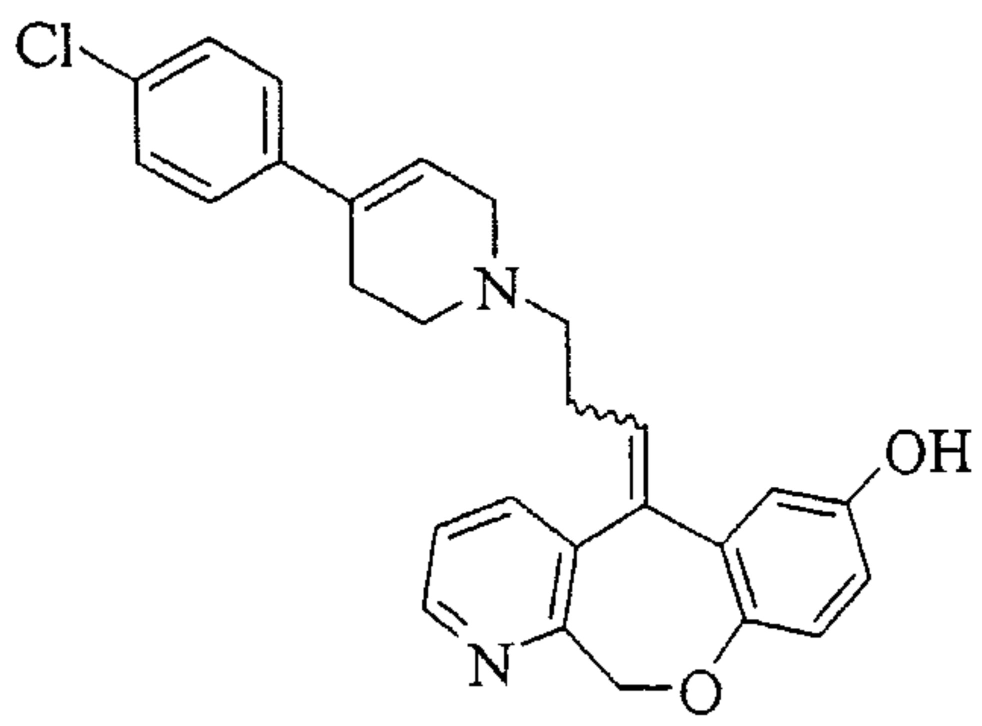


Example 191

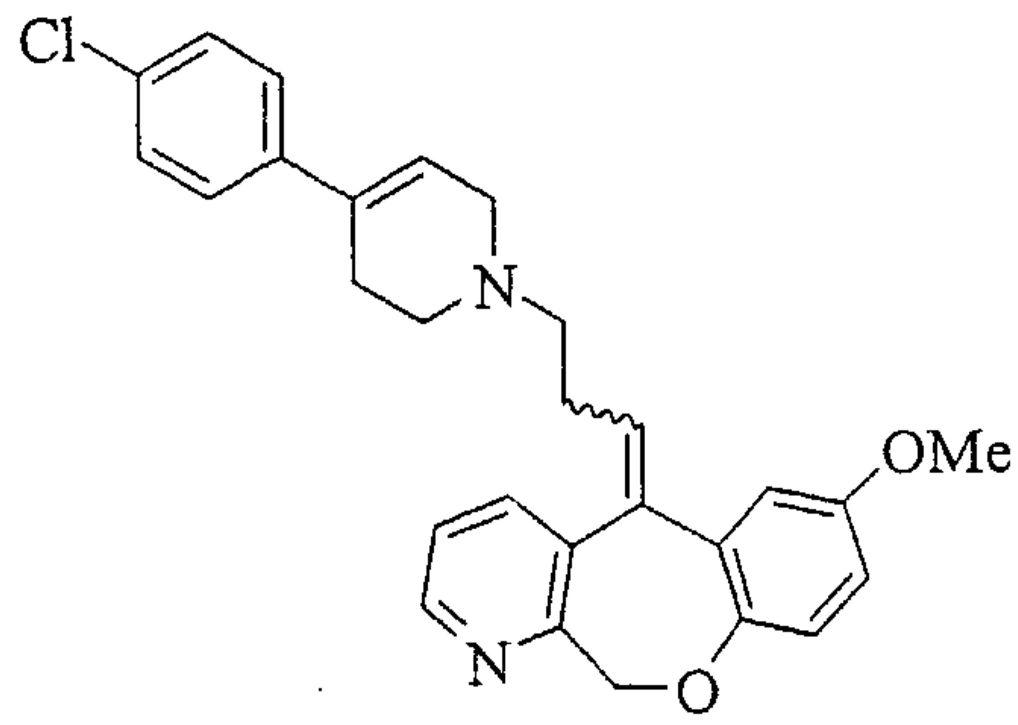


Example 192

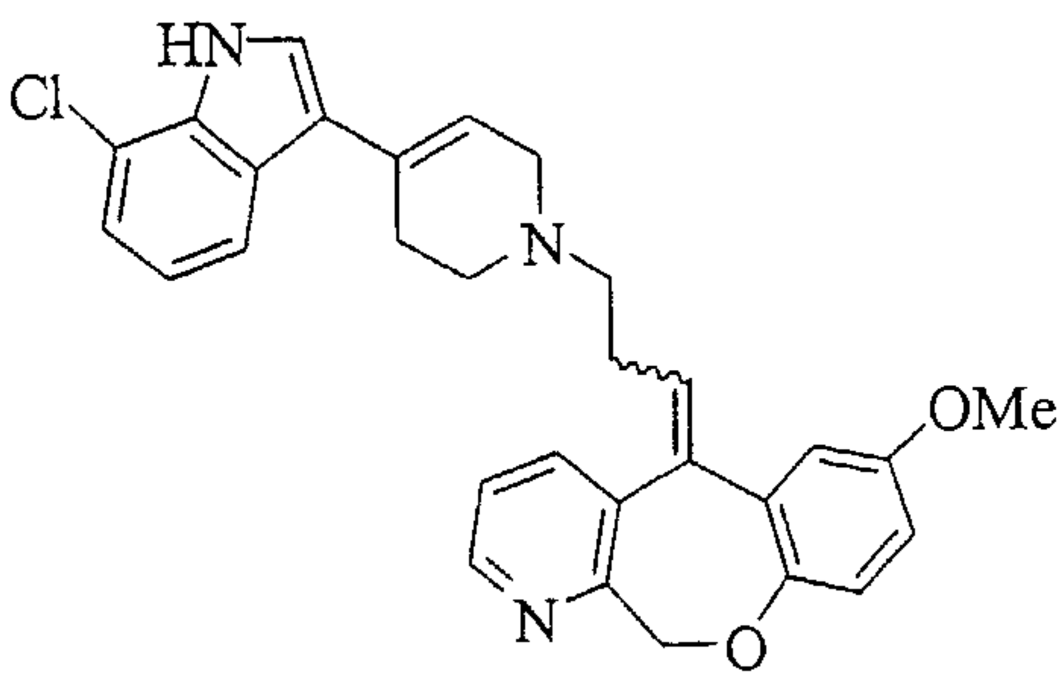
Figure 6S



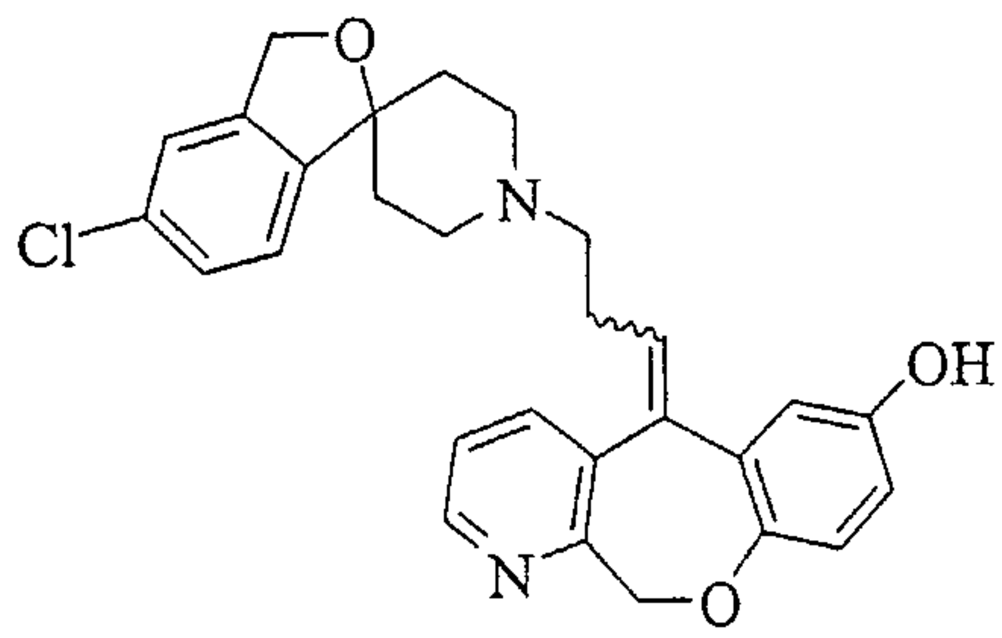
Example 193



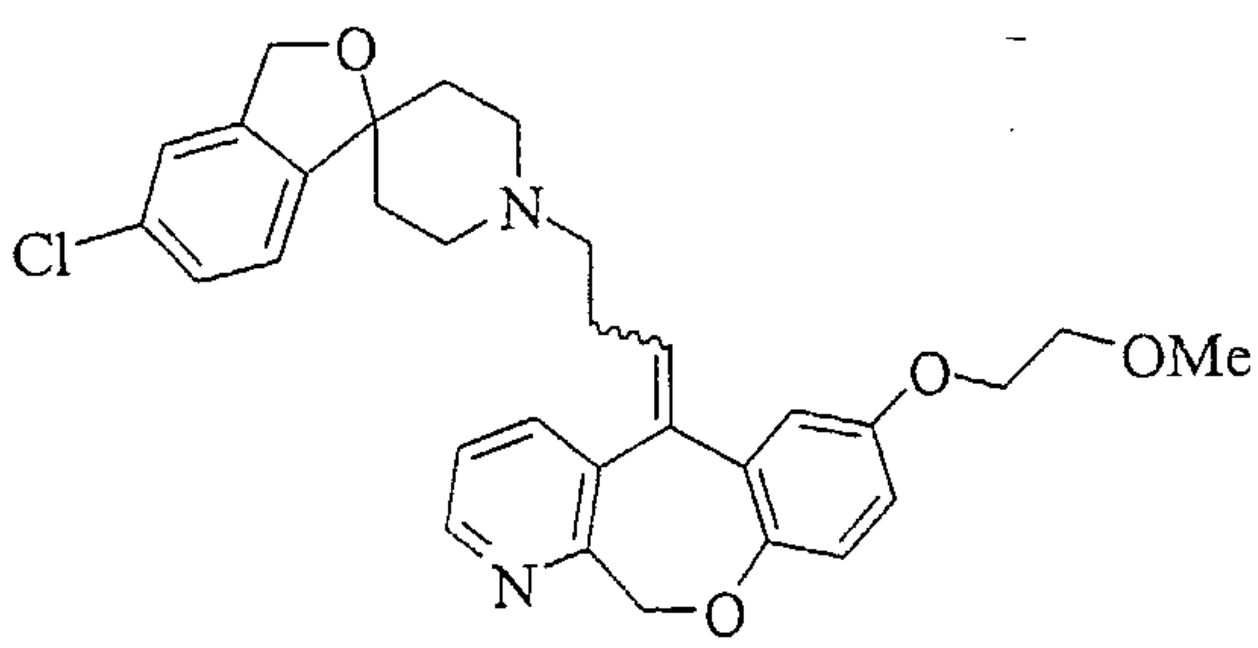
Example 194



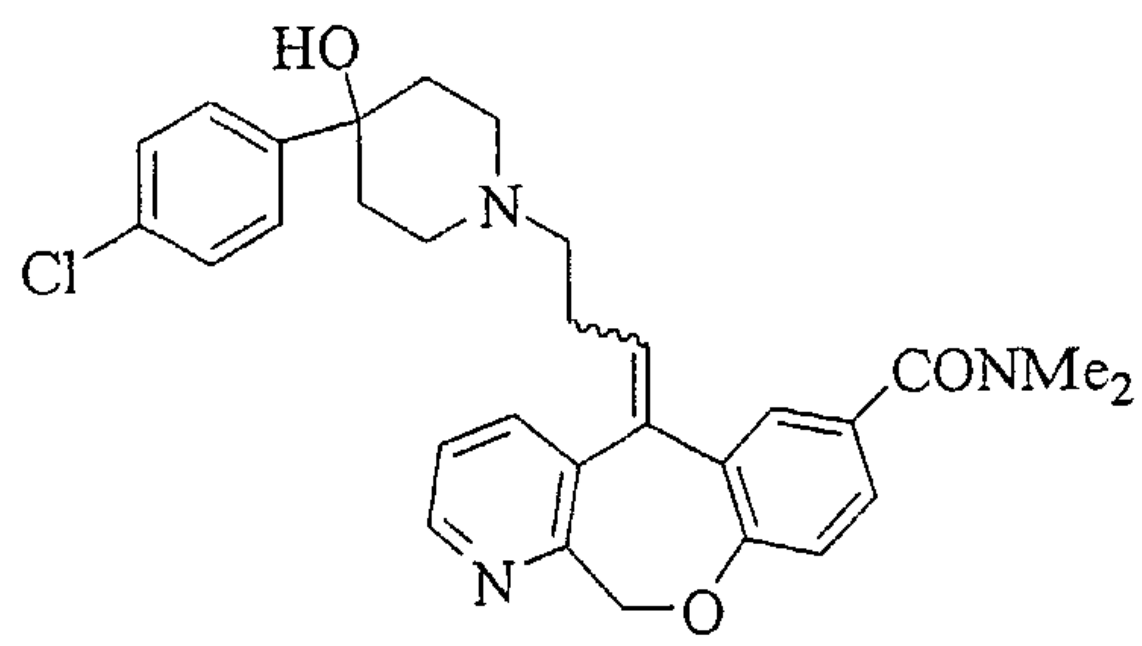
Example 195



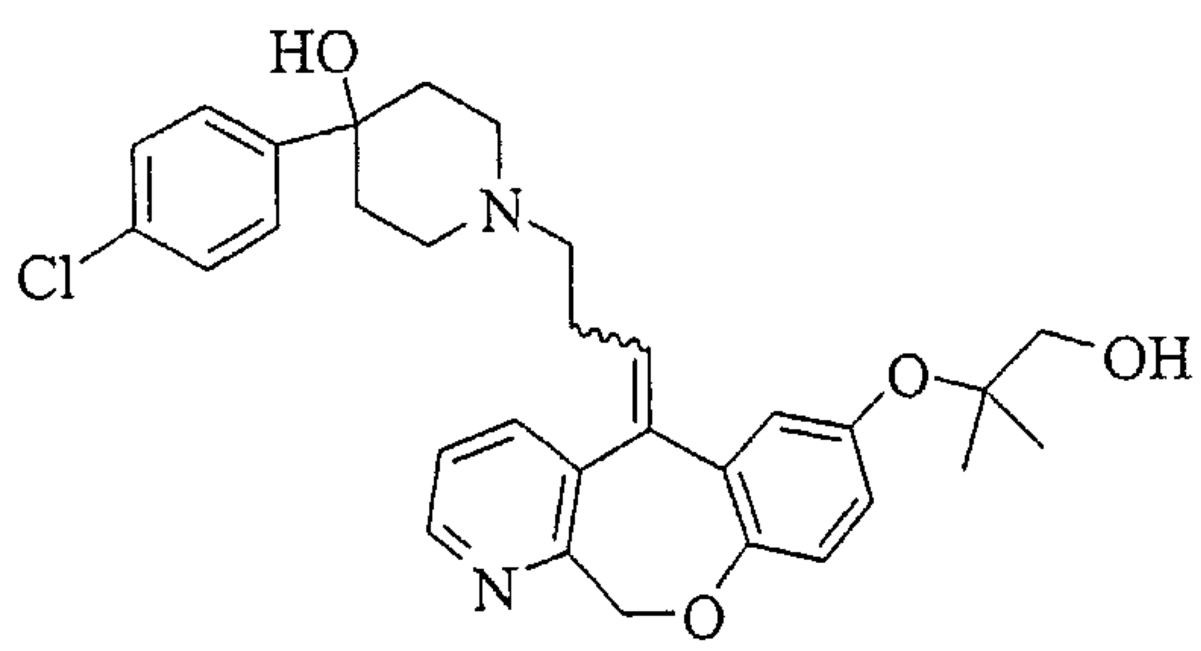
Example196



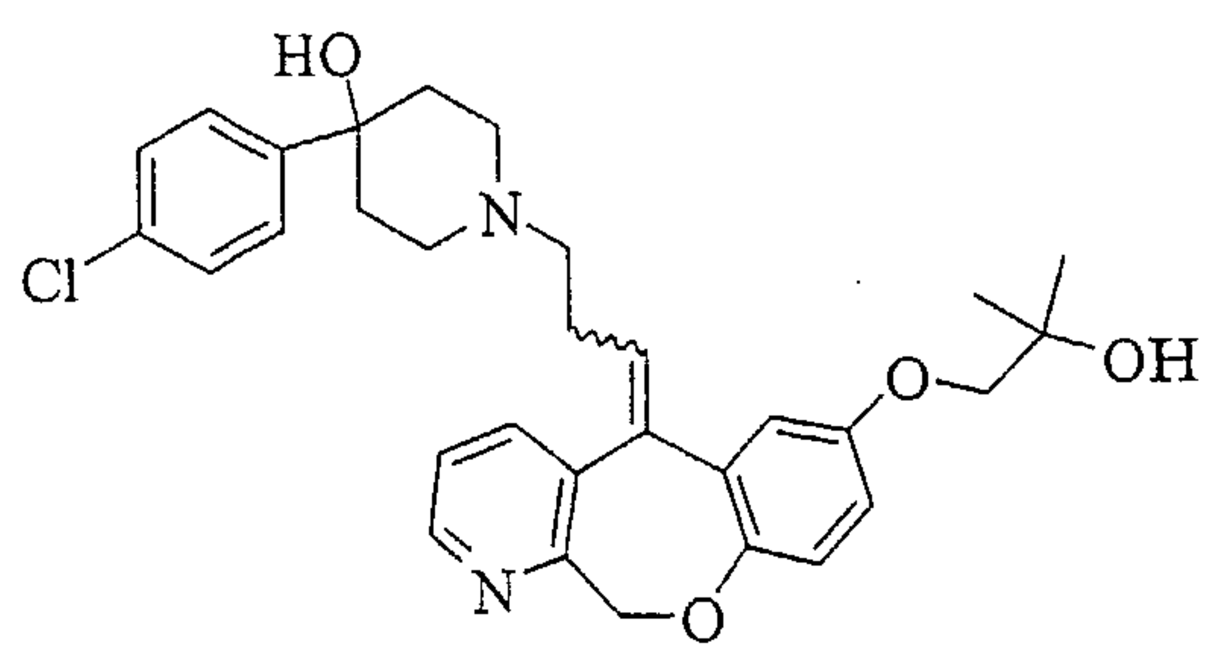
Example 197



Example 198

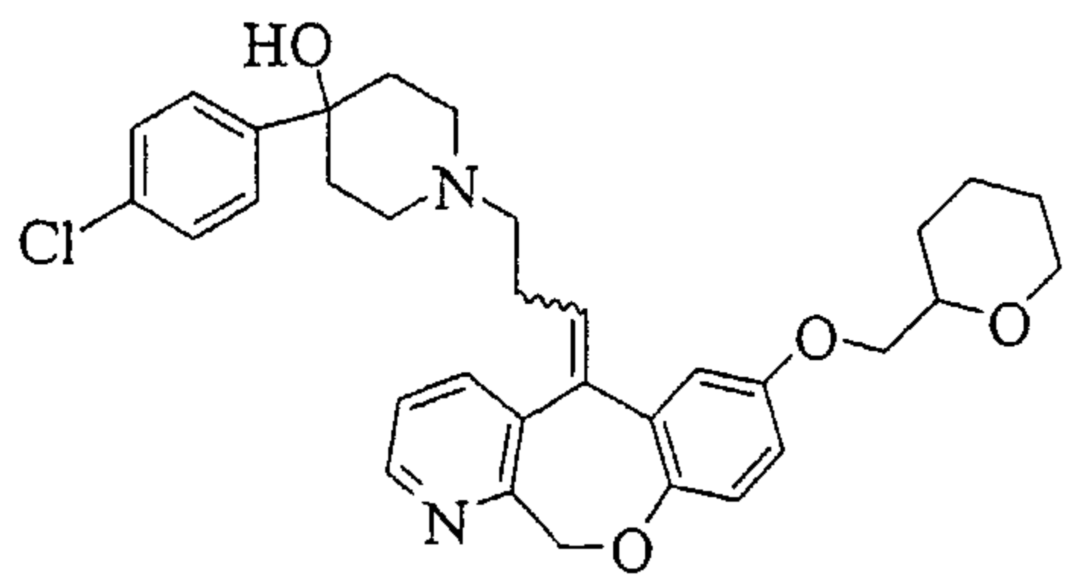


Example 199

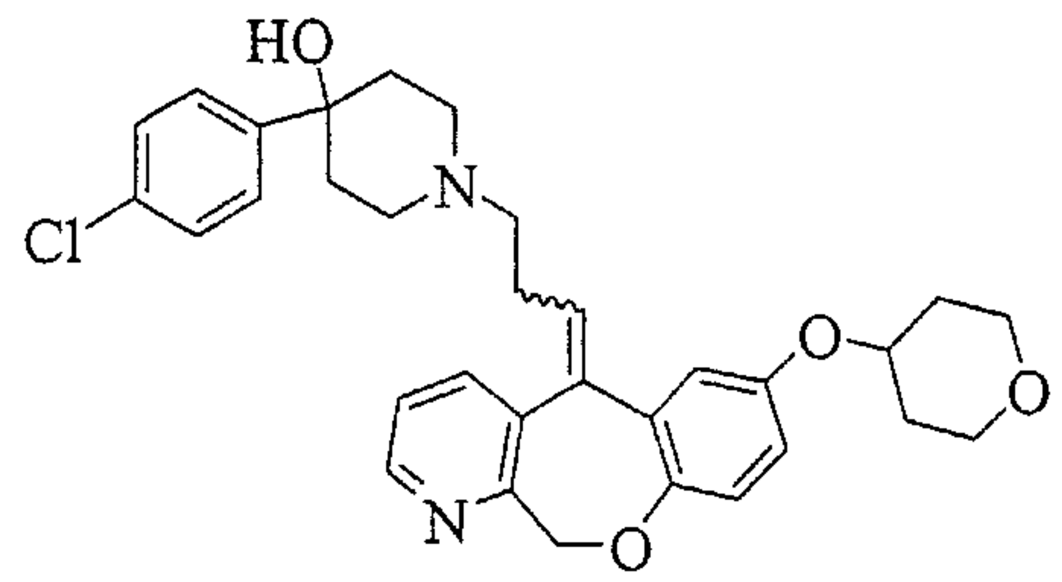


Example 200

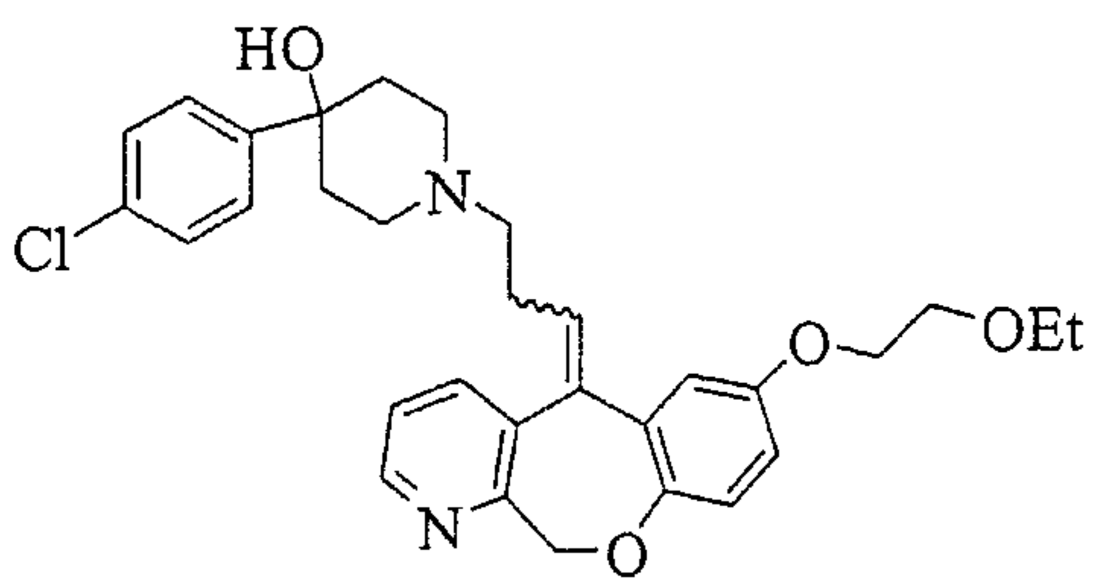
Figure 6T



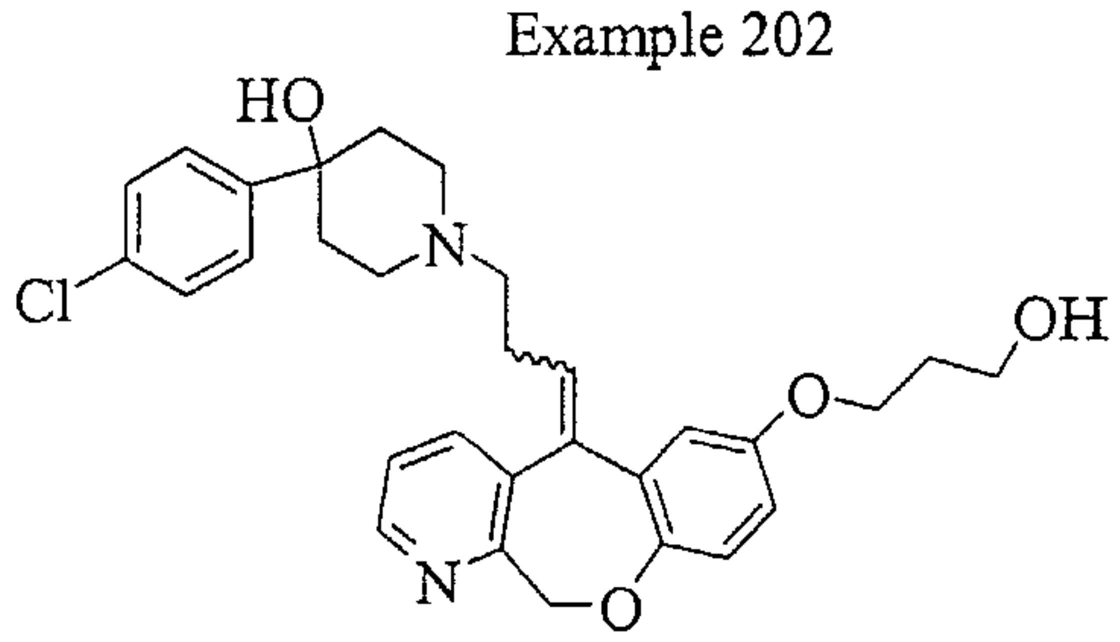
Example 201



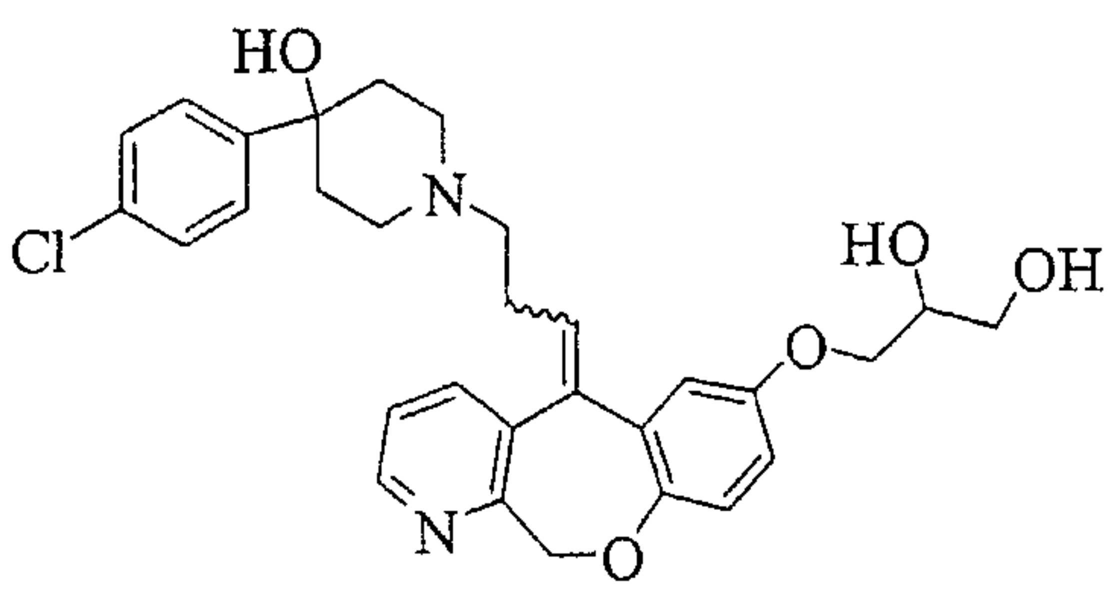
Example 202



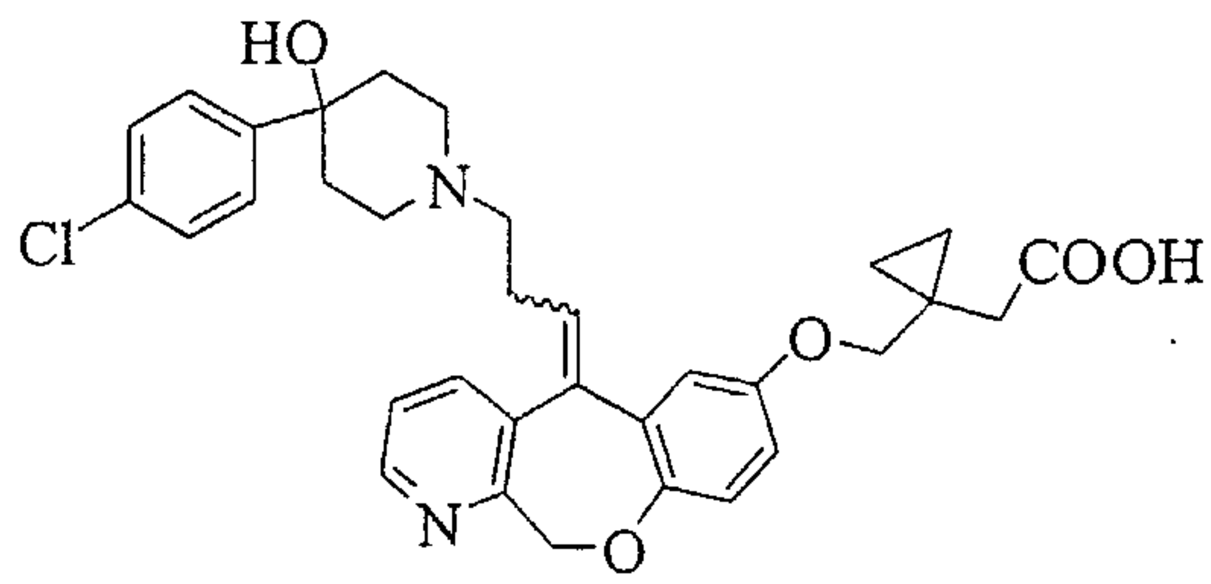
Example 203



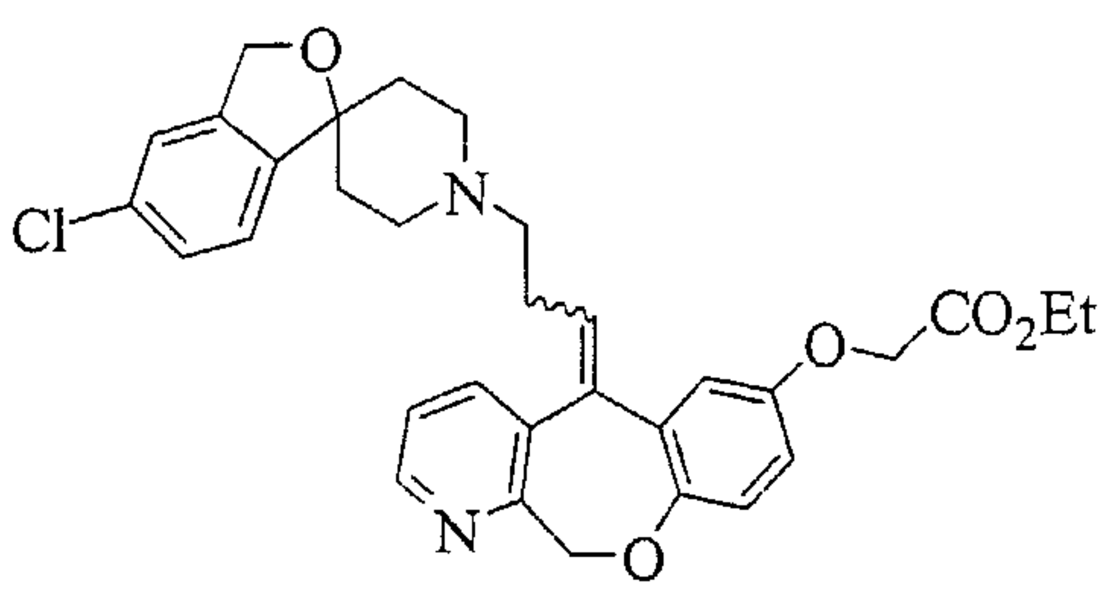
Example 204



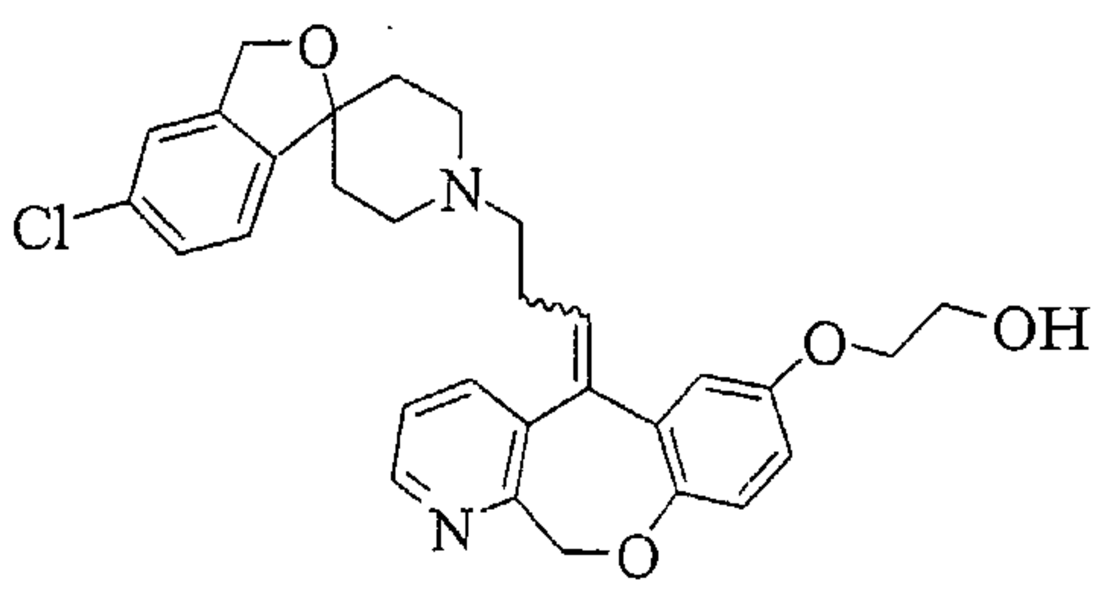
Example 205



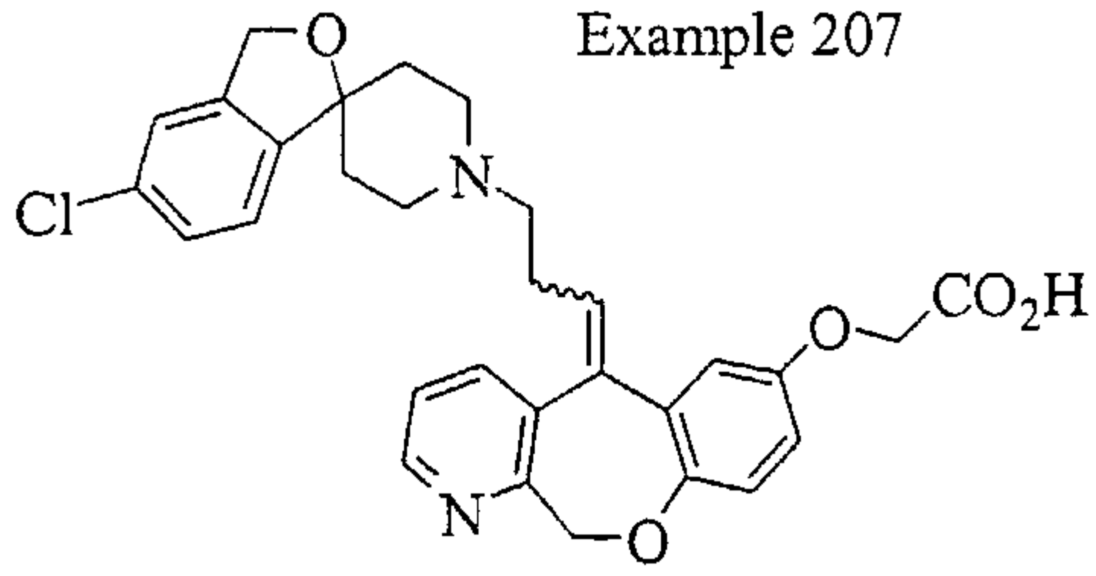
Example 206



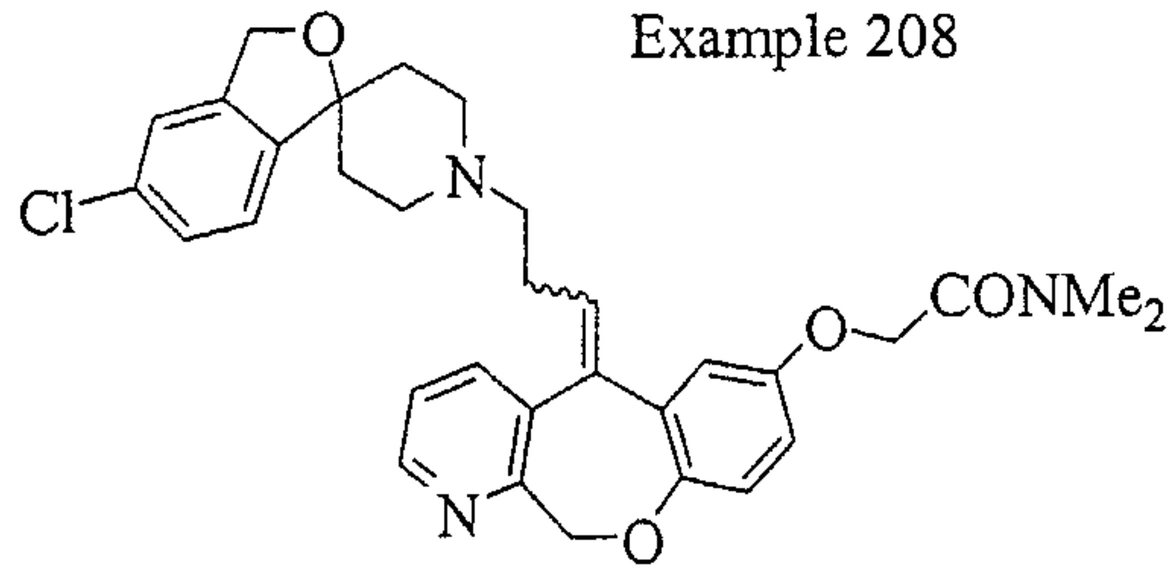
Example 207



Example 208

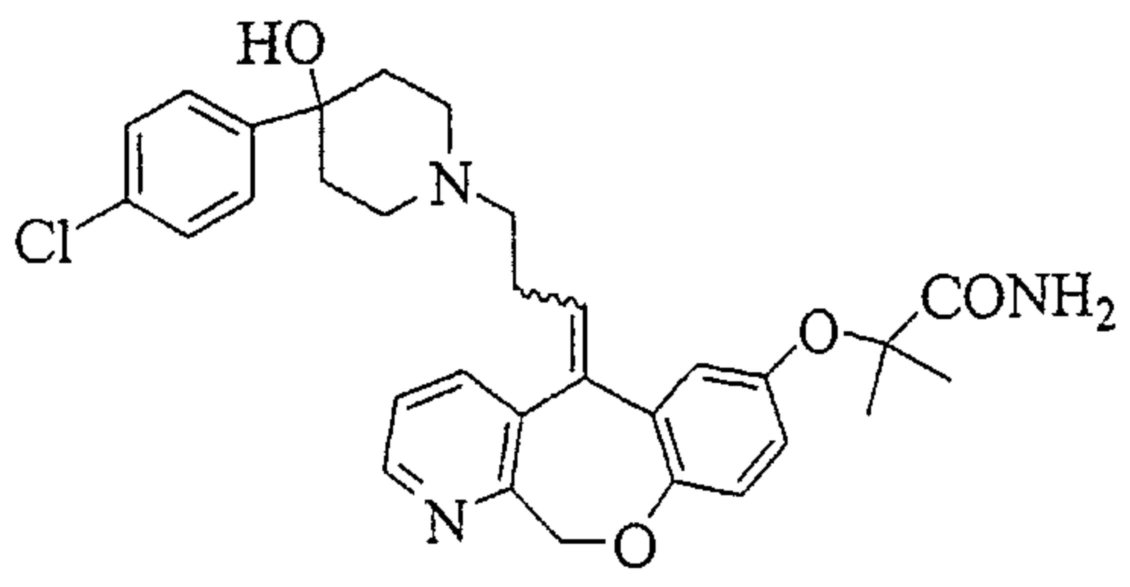


Example 209

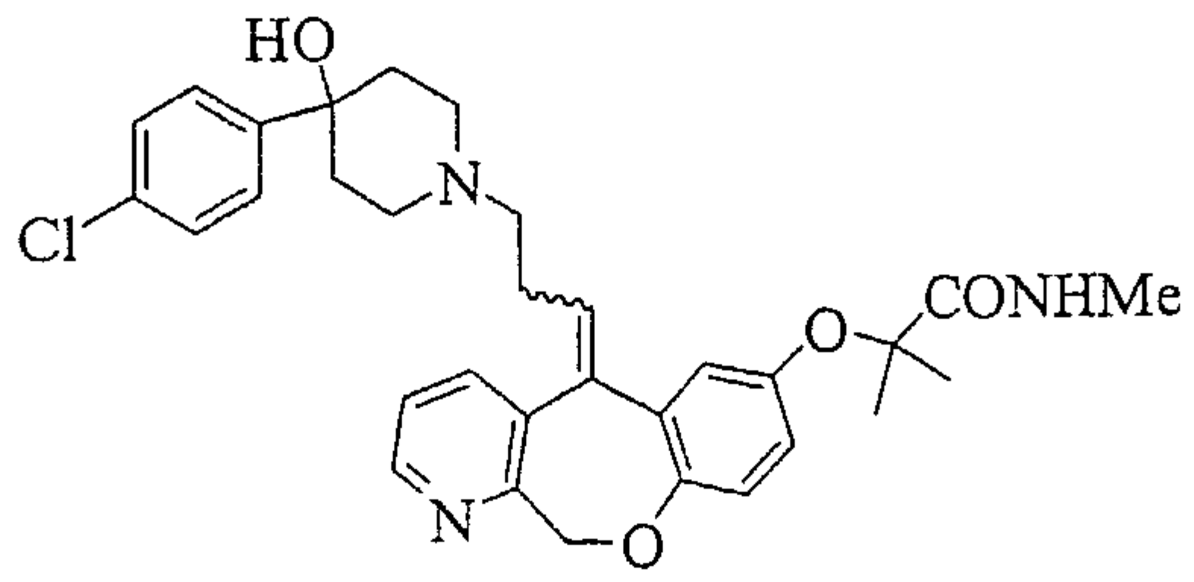


Example 210

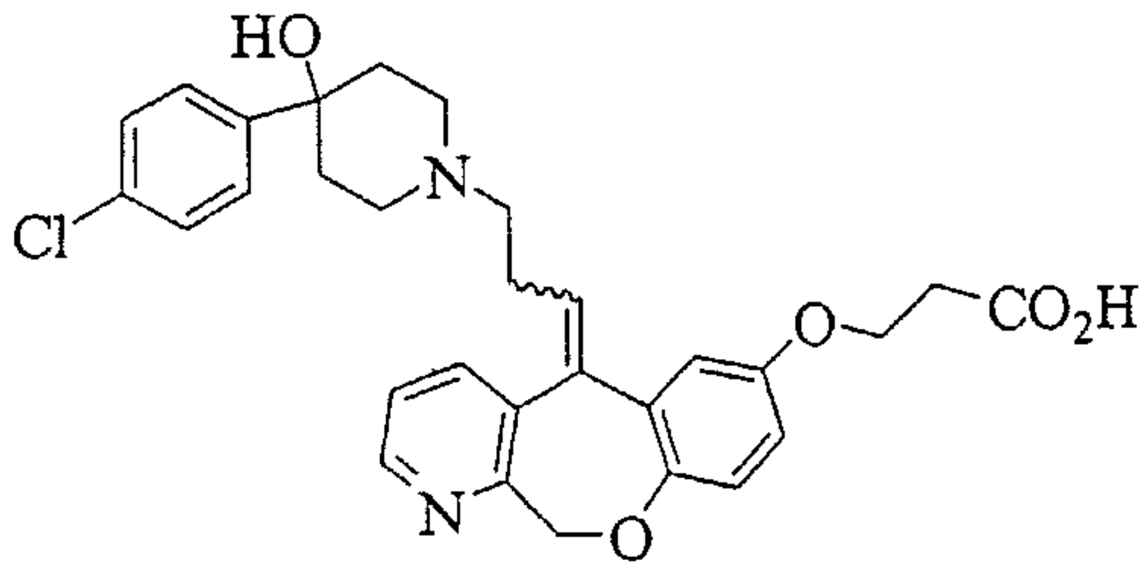
Figure 6U



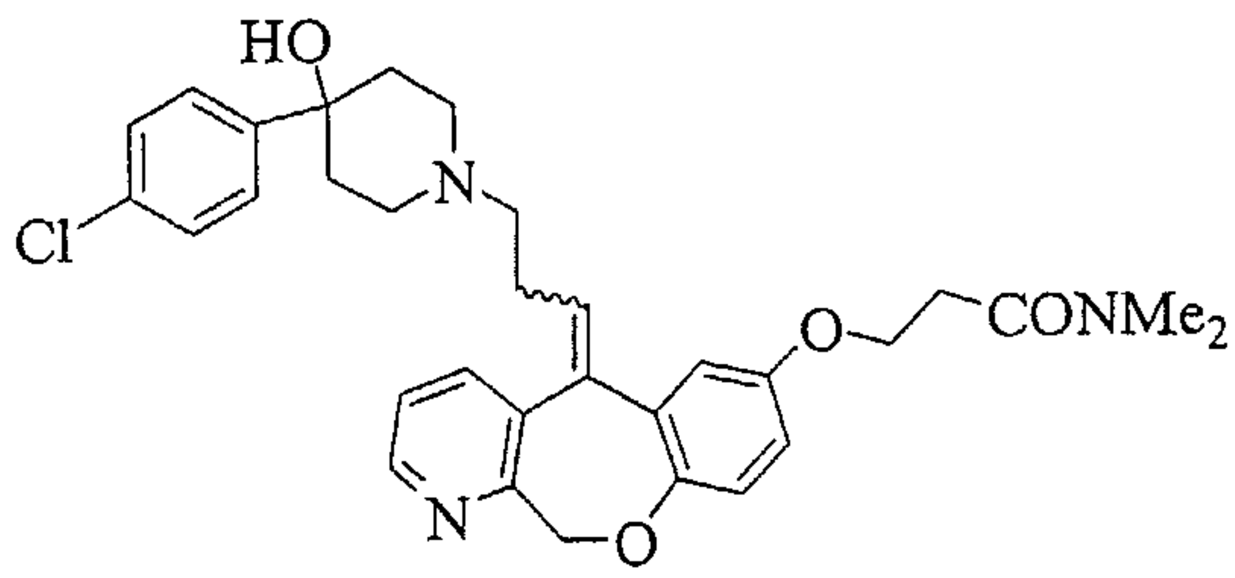
Example 211



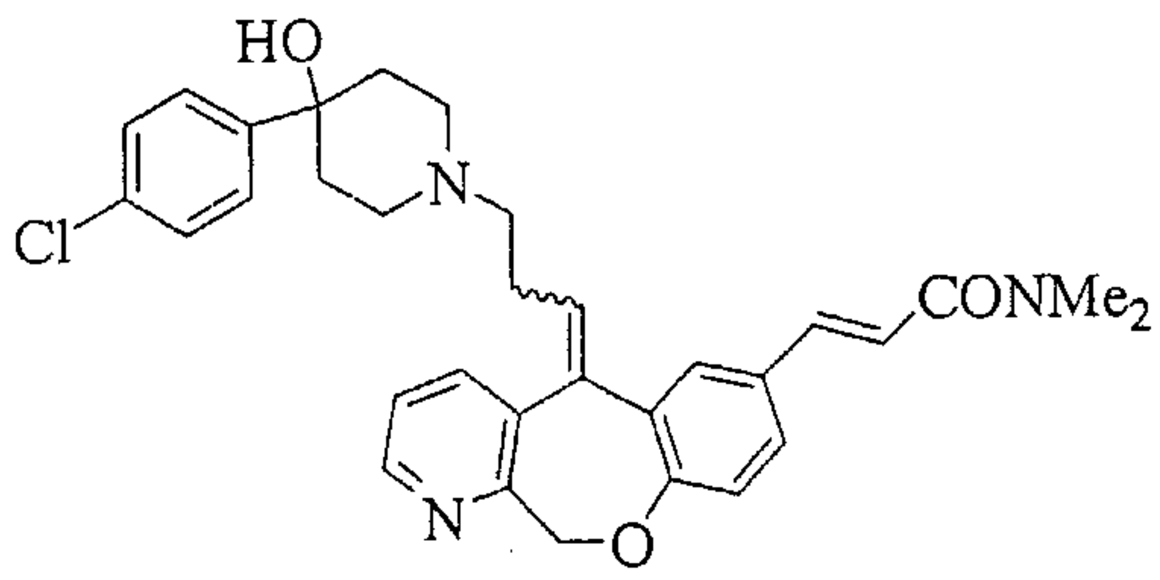
Example 212



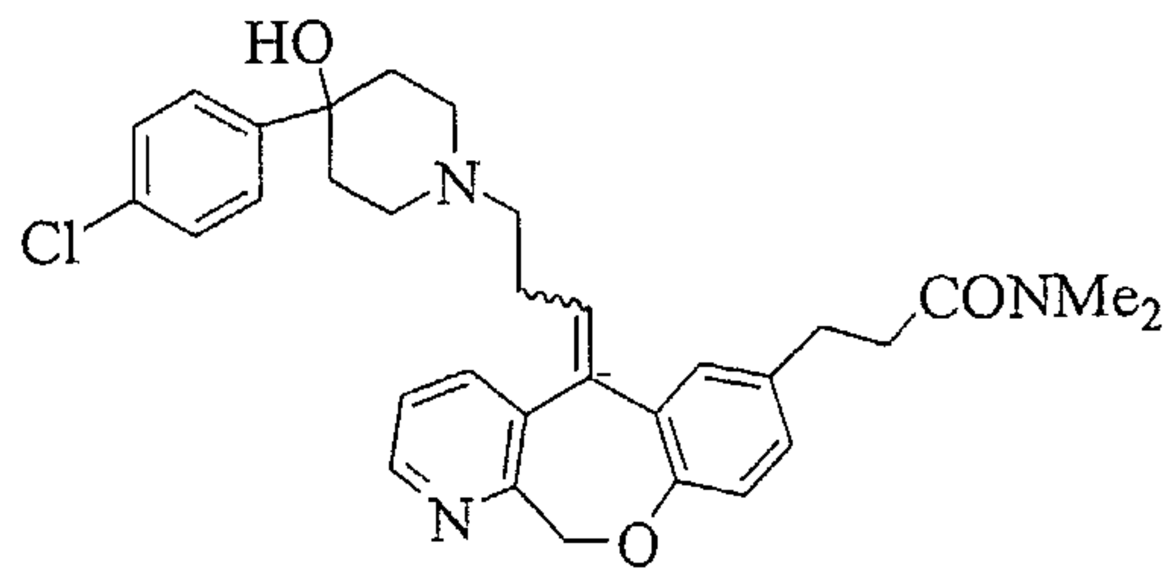
Example 213



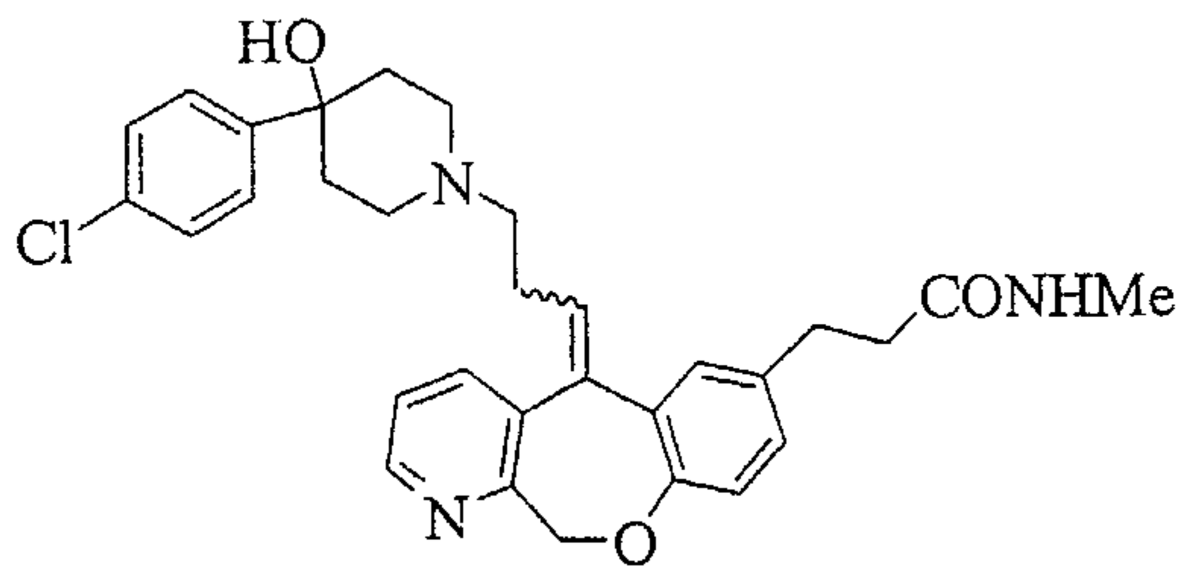
Example 214



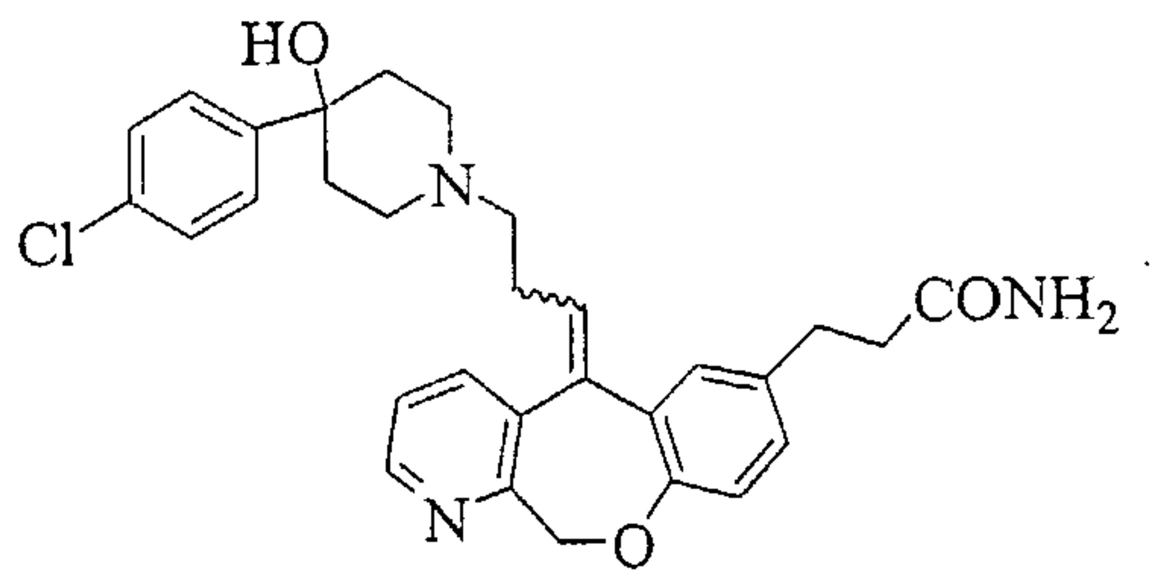
Example 215



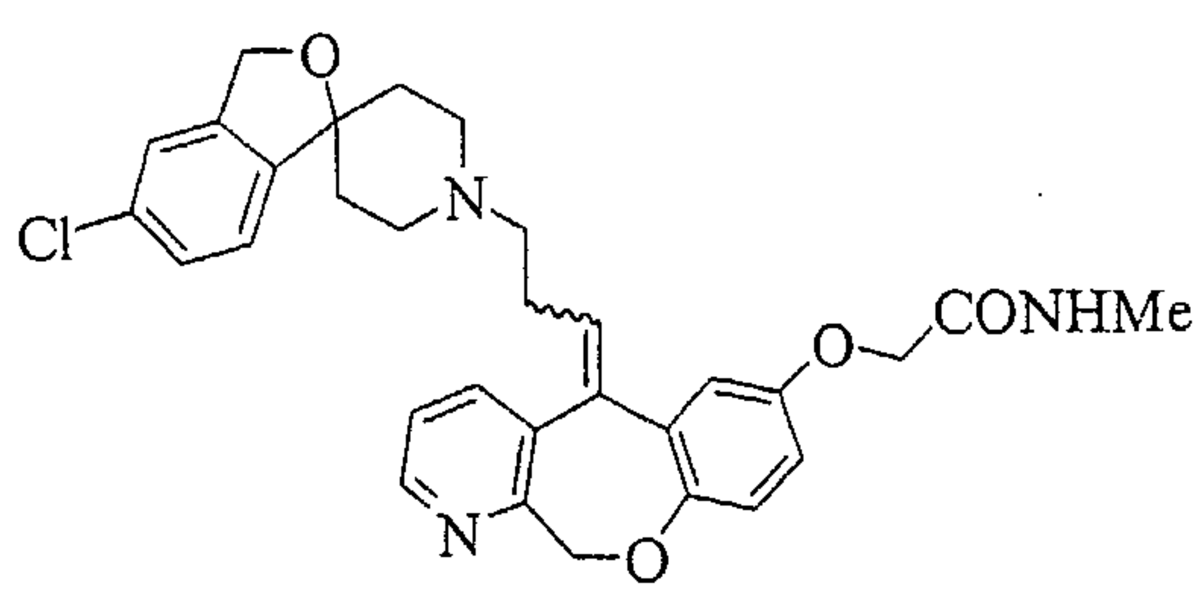
Example 216



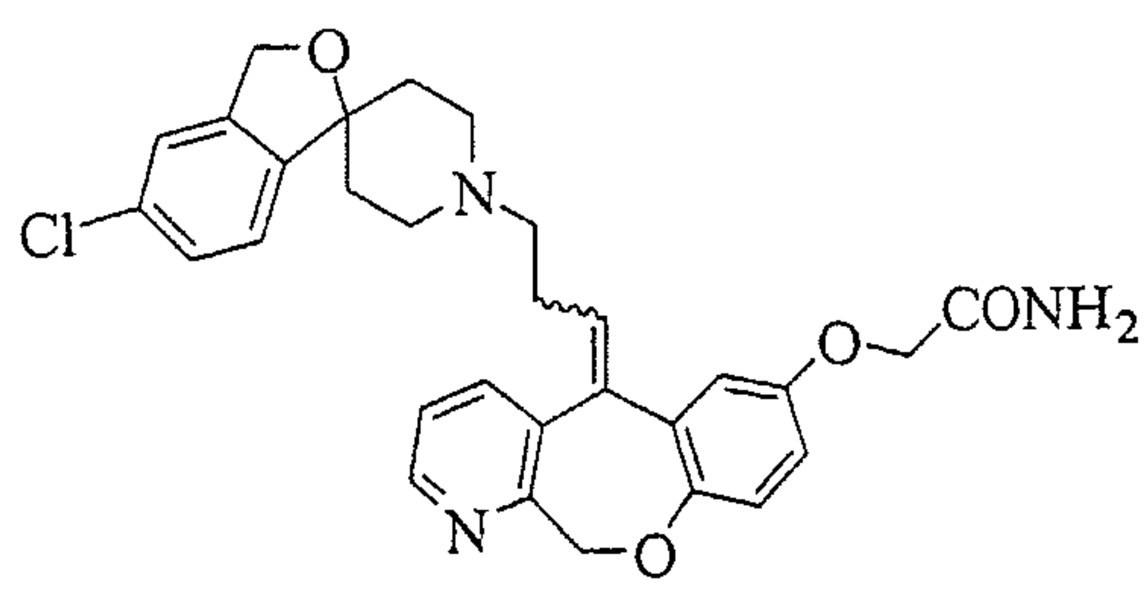
Example 217



Example 218

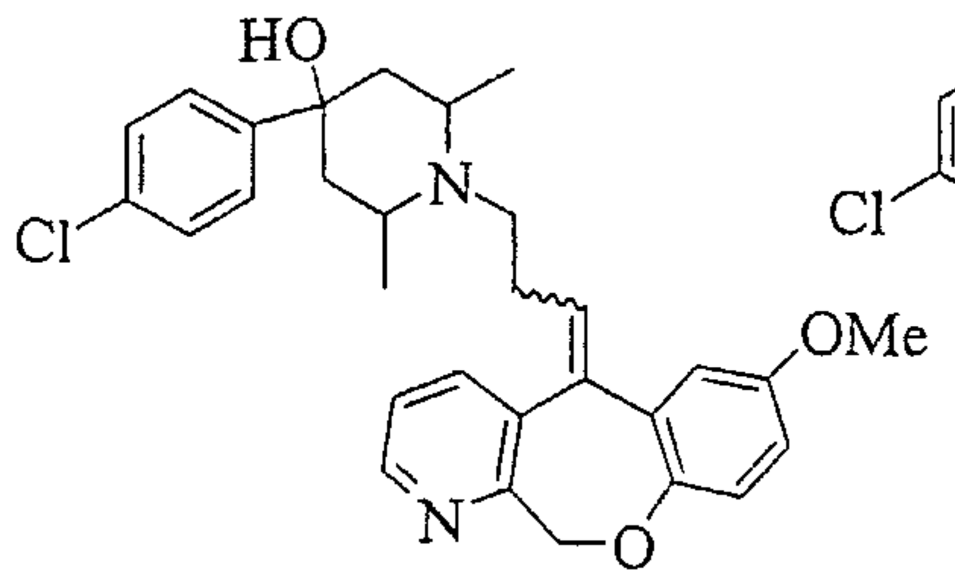


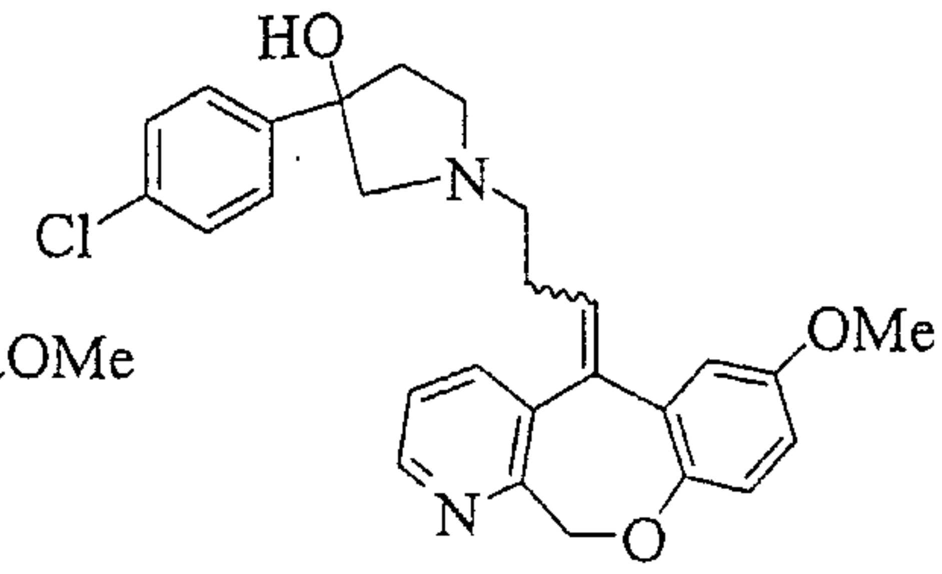
Example 219

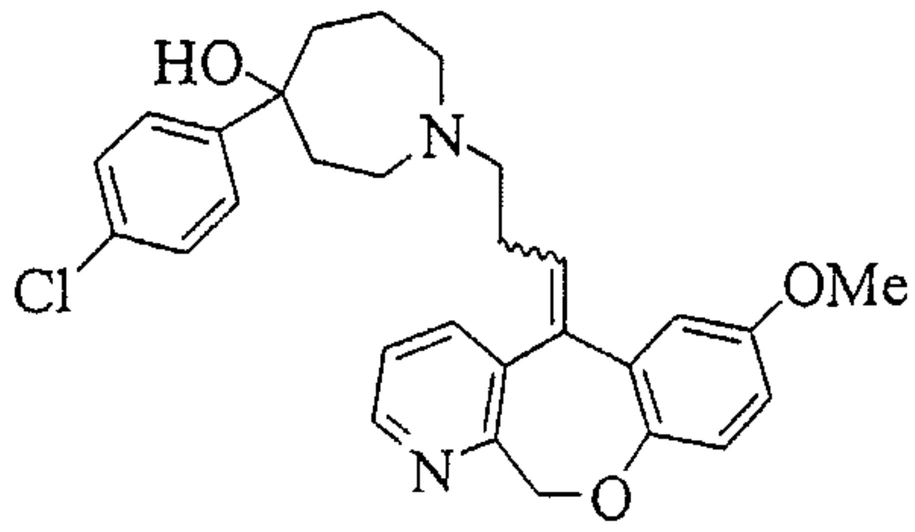


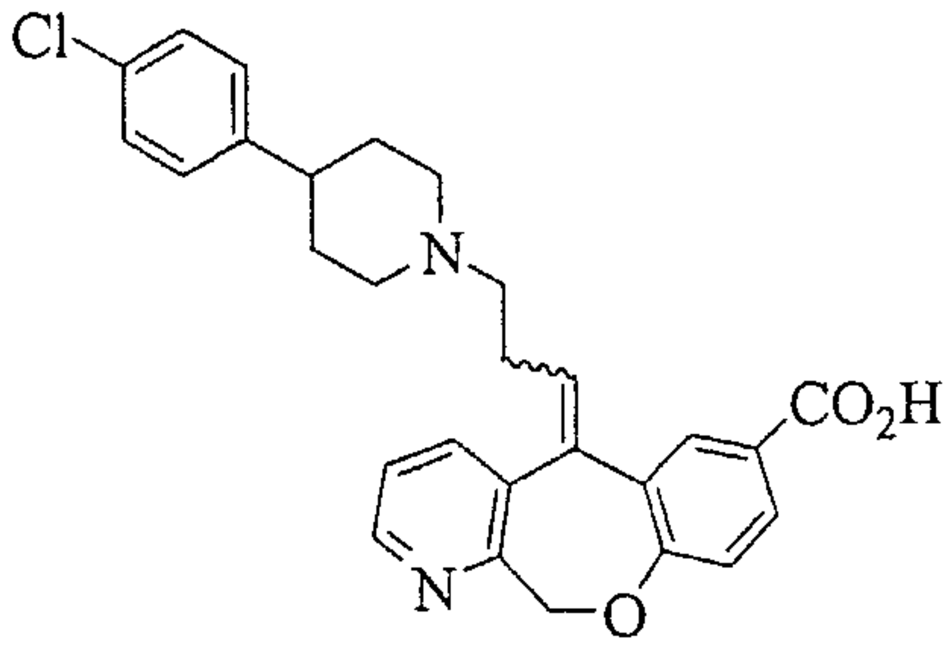
Example 220

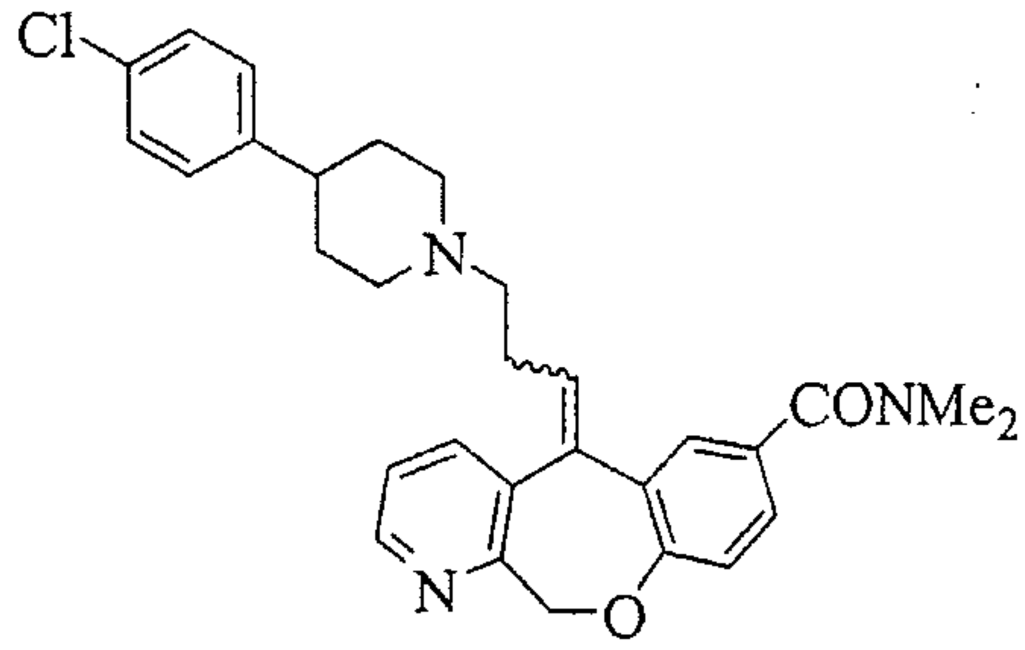
Figure 6V

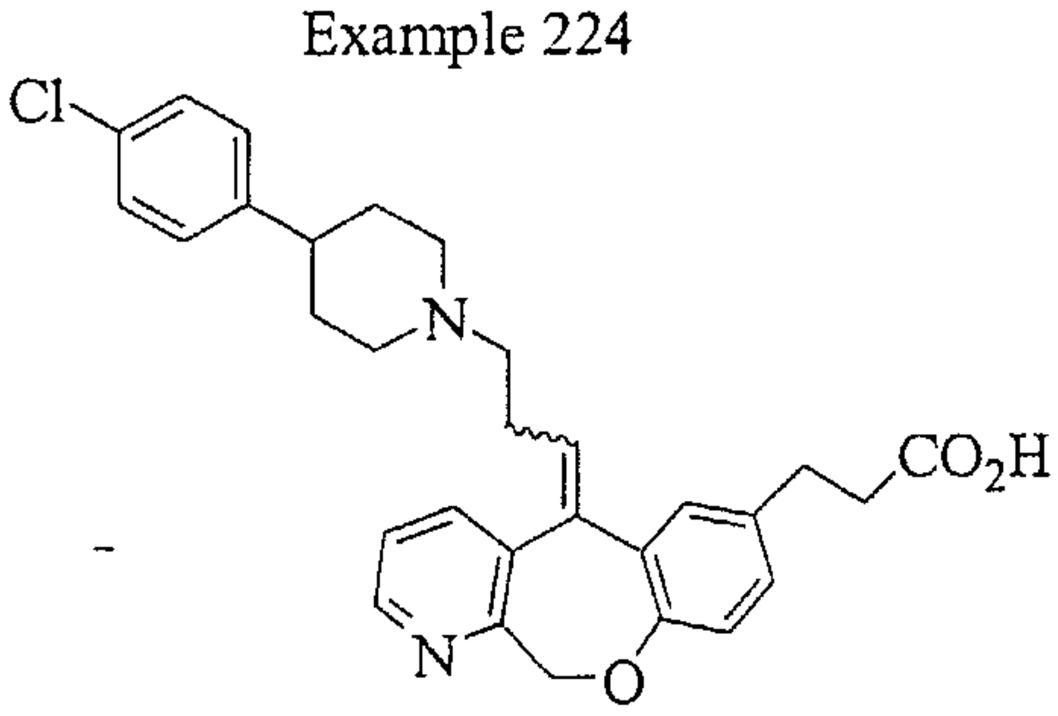

Example 221

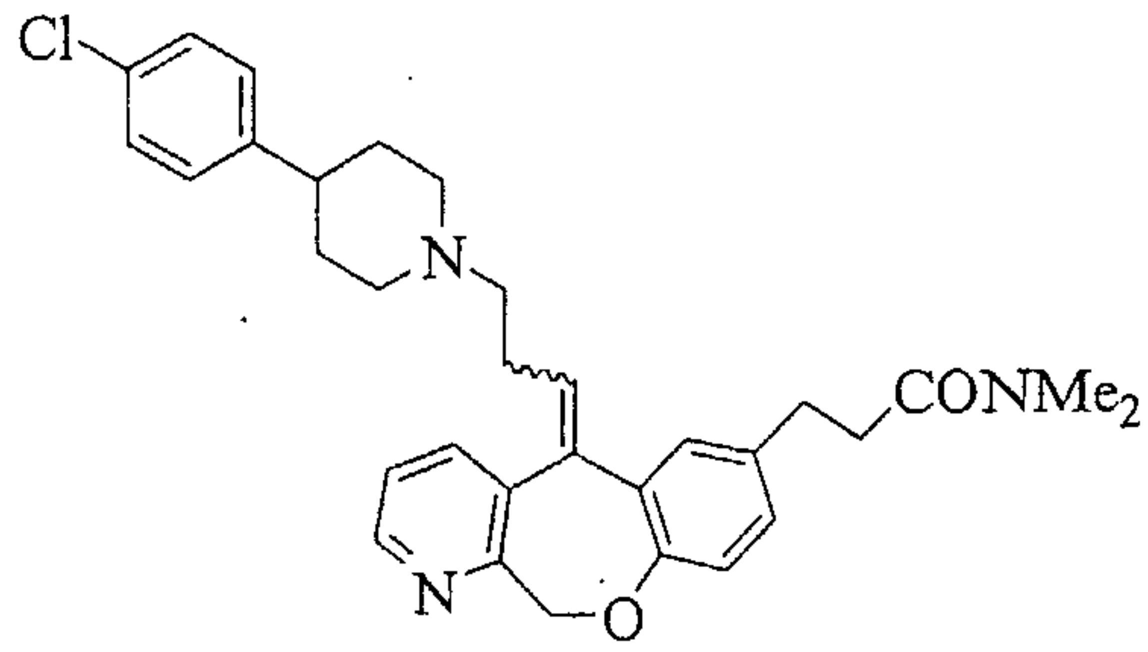

Example 222

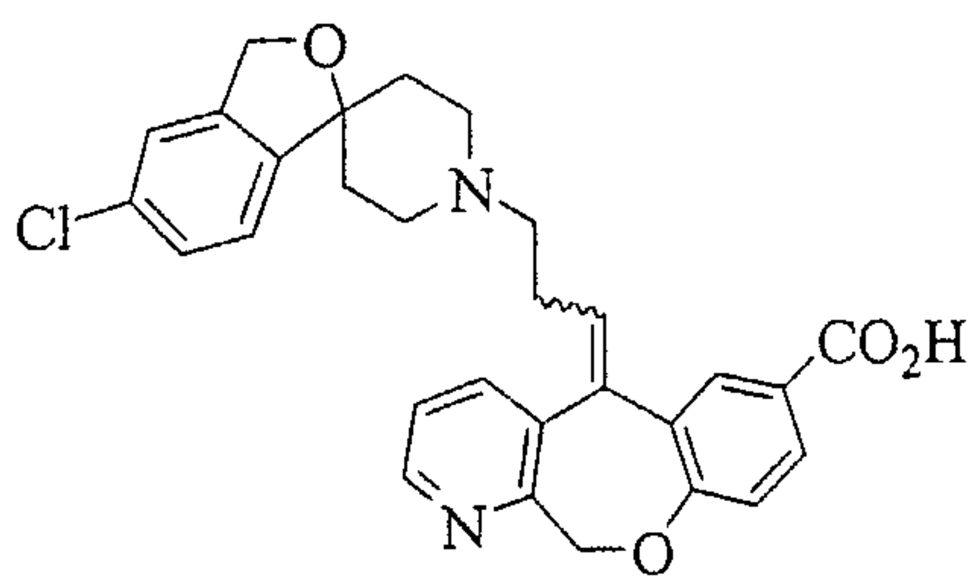

Example 223

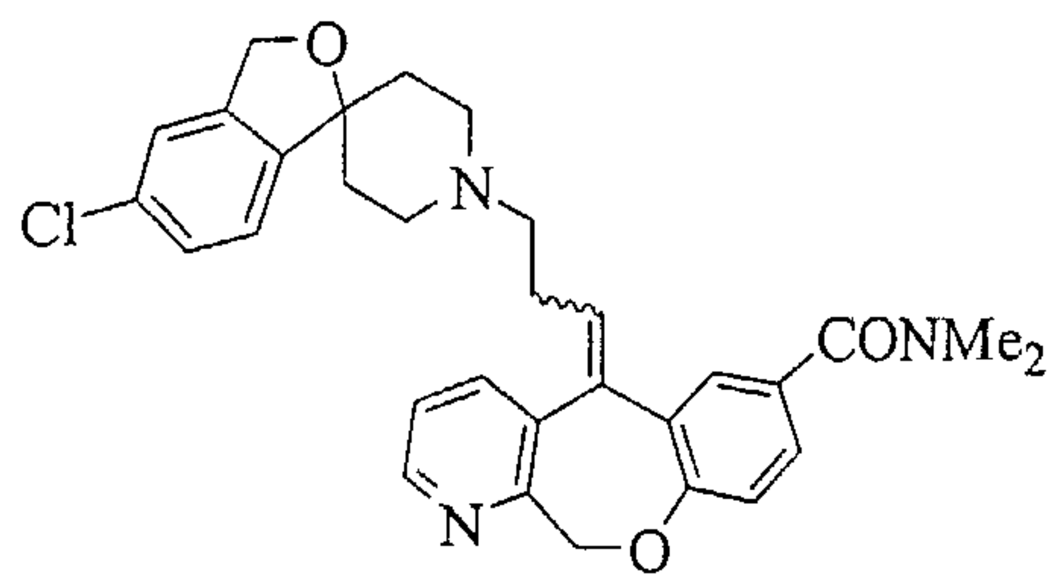

Example 224

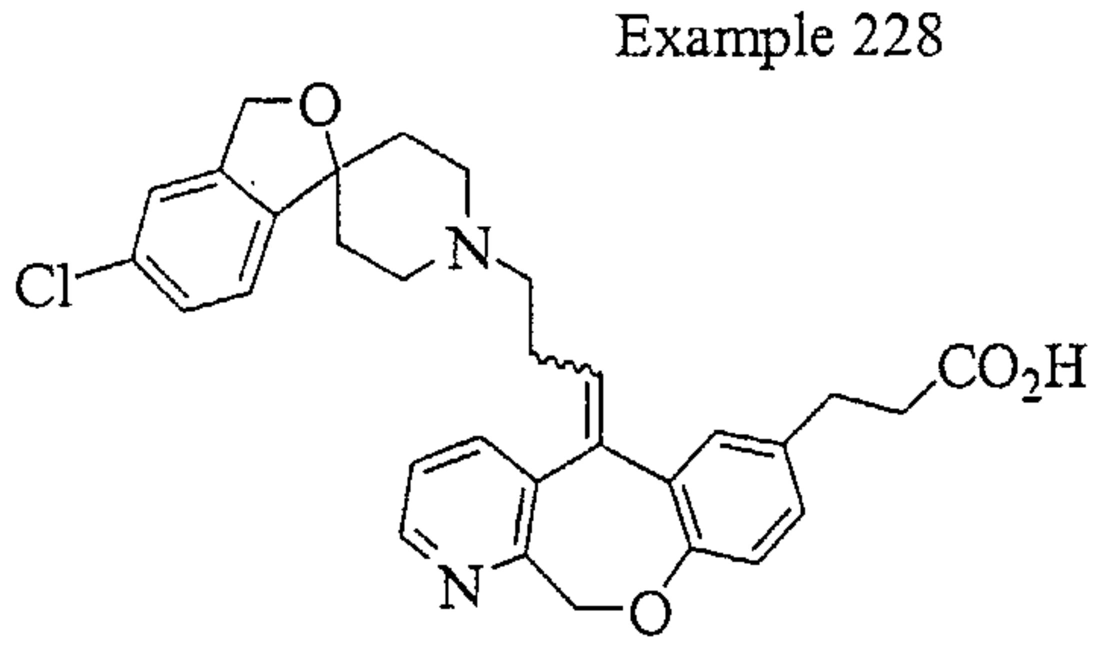

Example 225


Example 226


Example 227


Example 228


Example 229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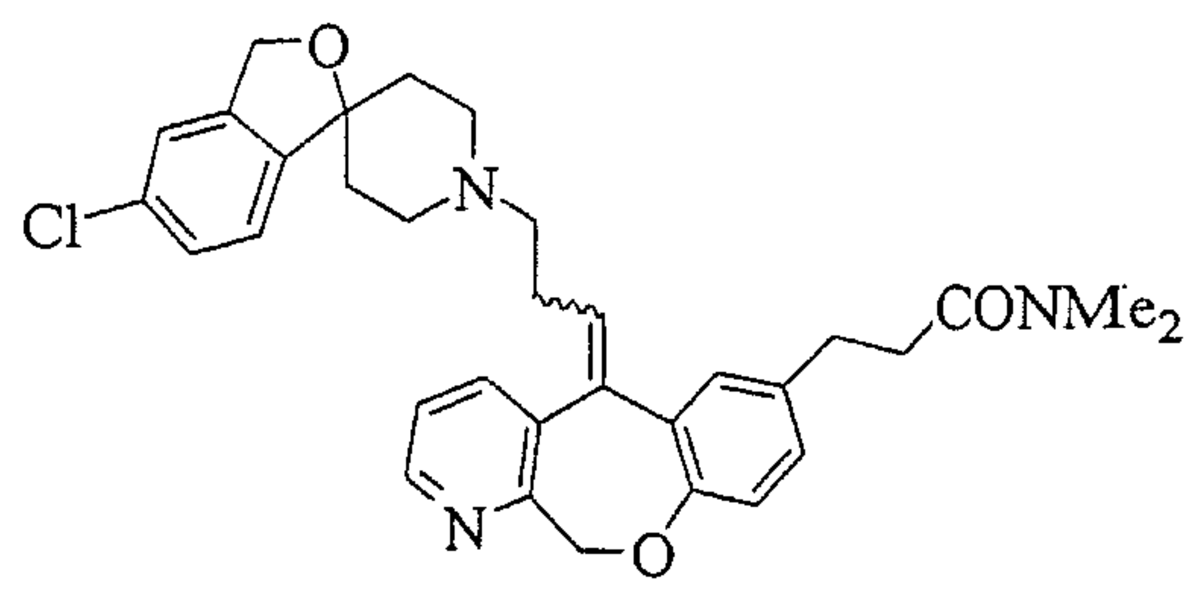
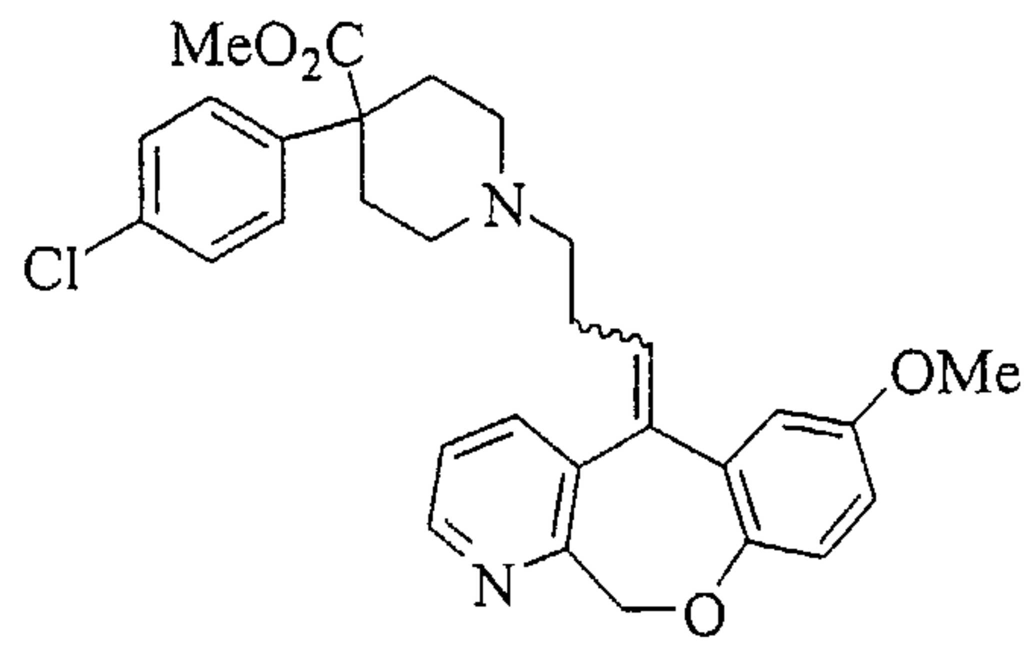
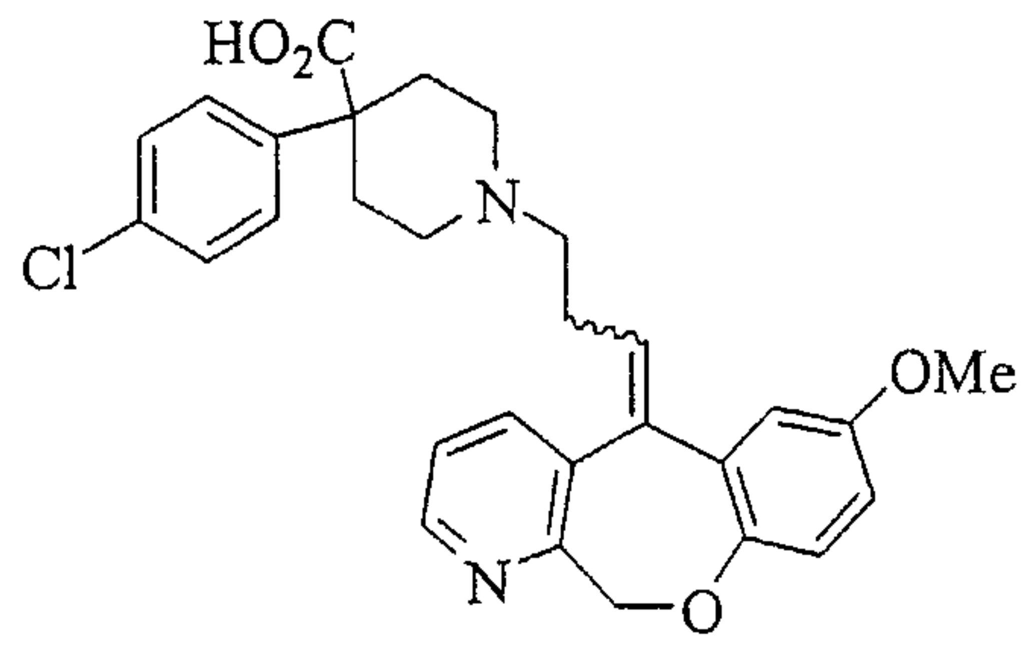

Example 231

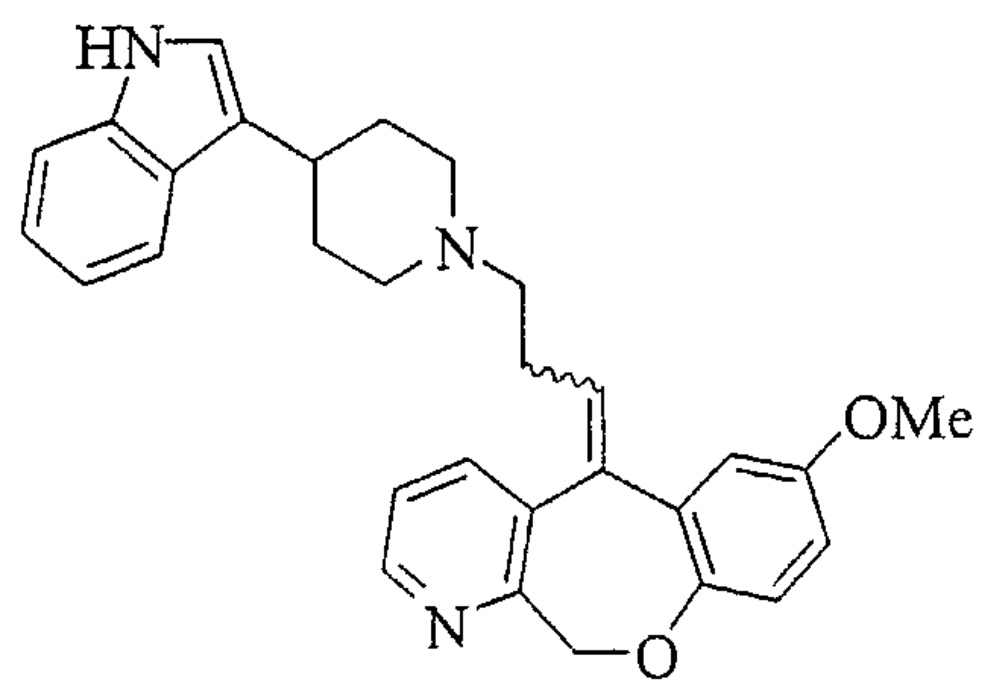
Figure 6W



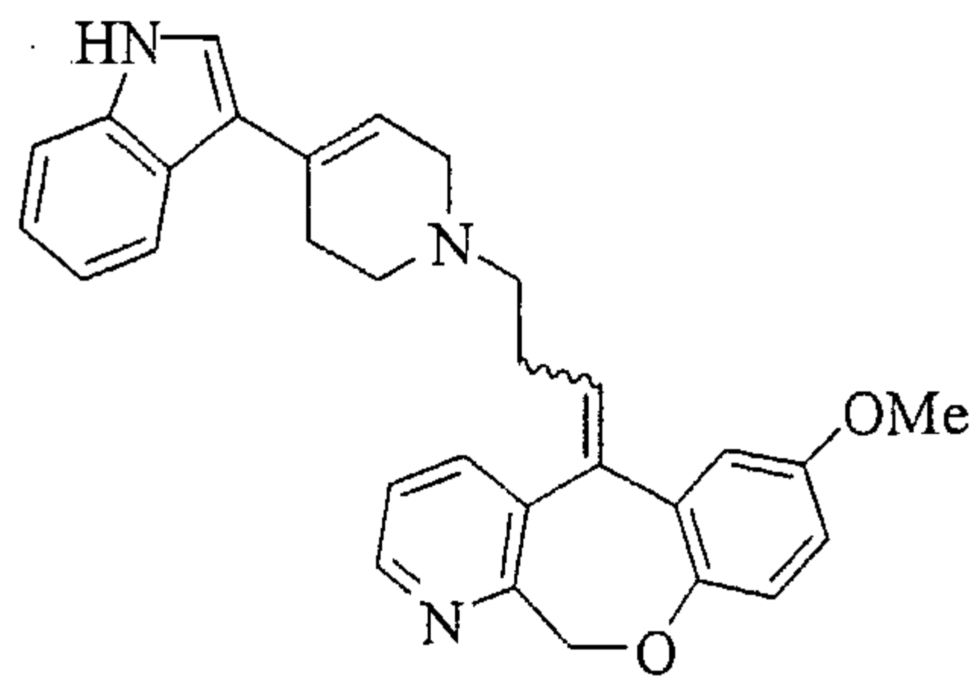
Example 232



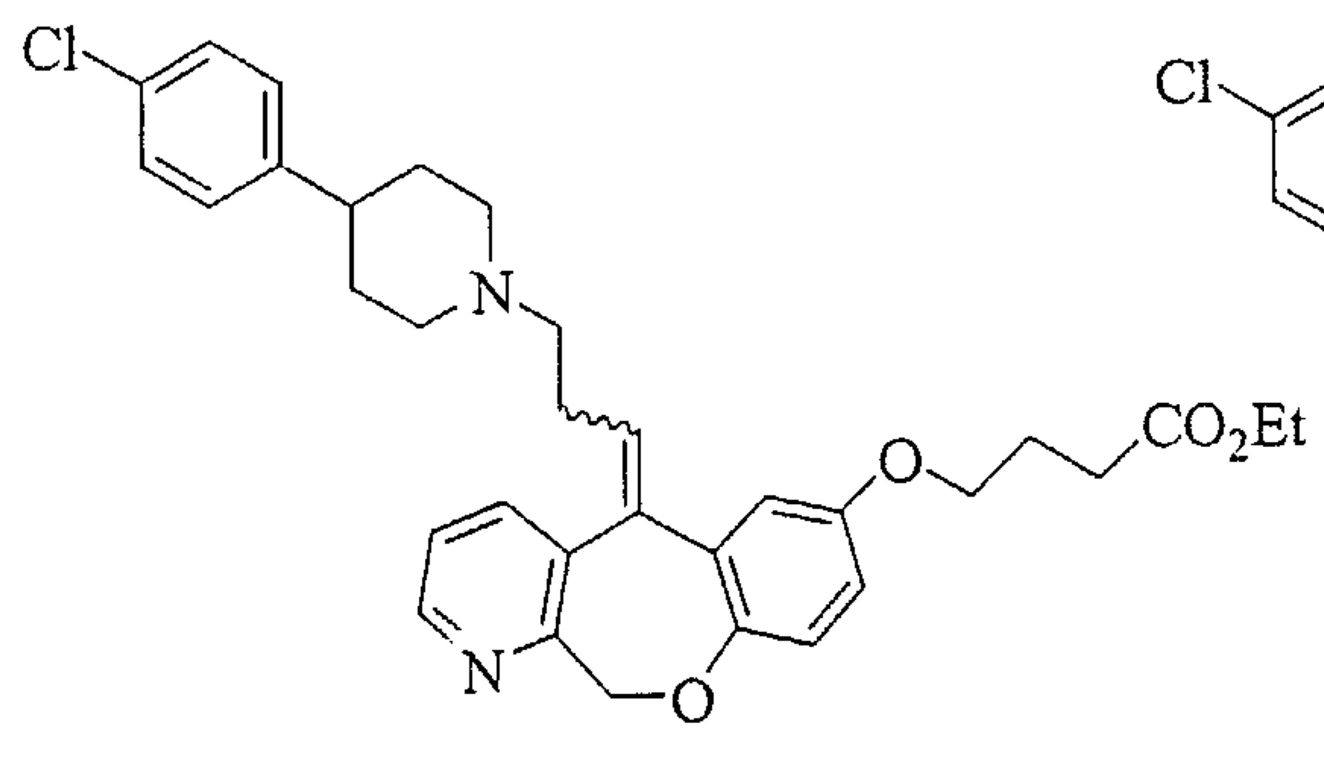
Example 233



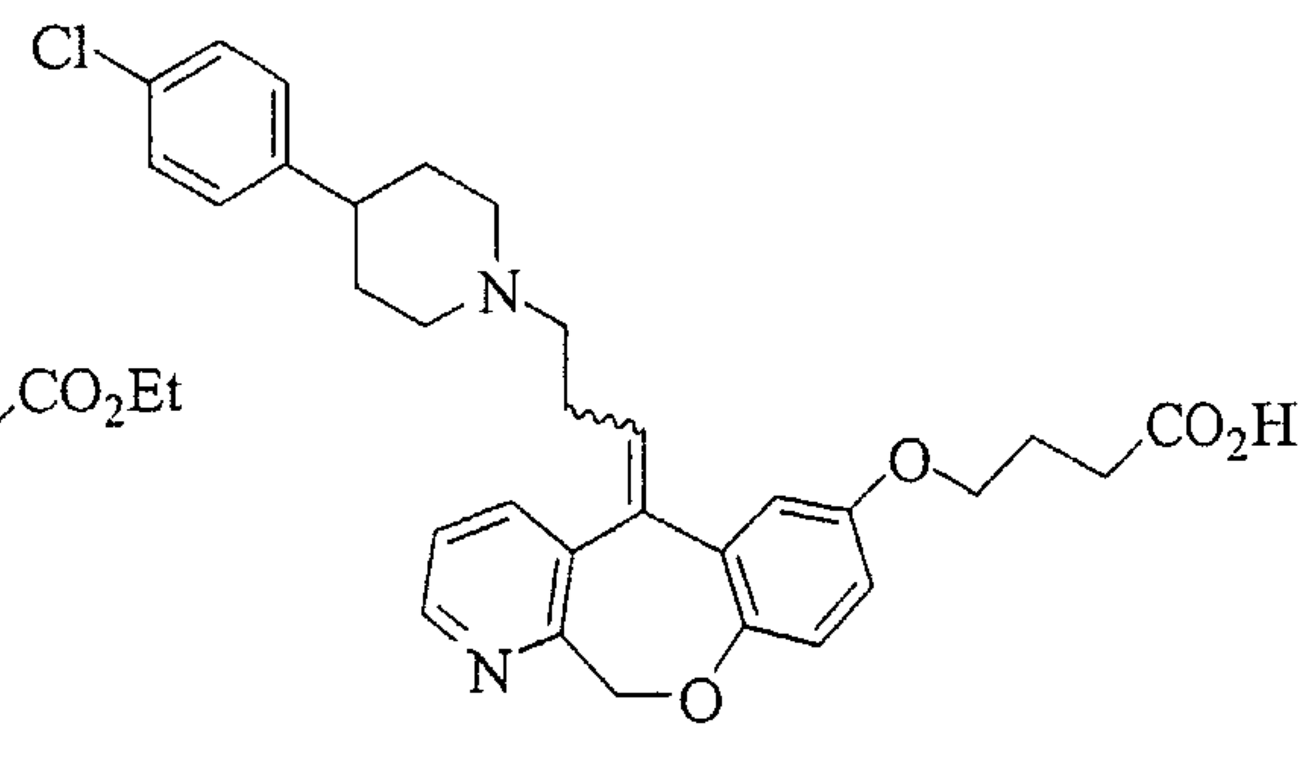
Example 234



Example 235

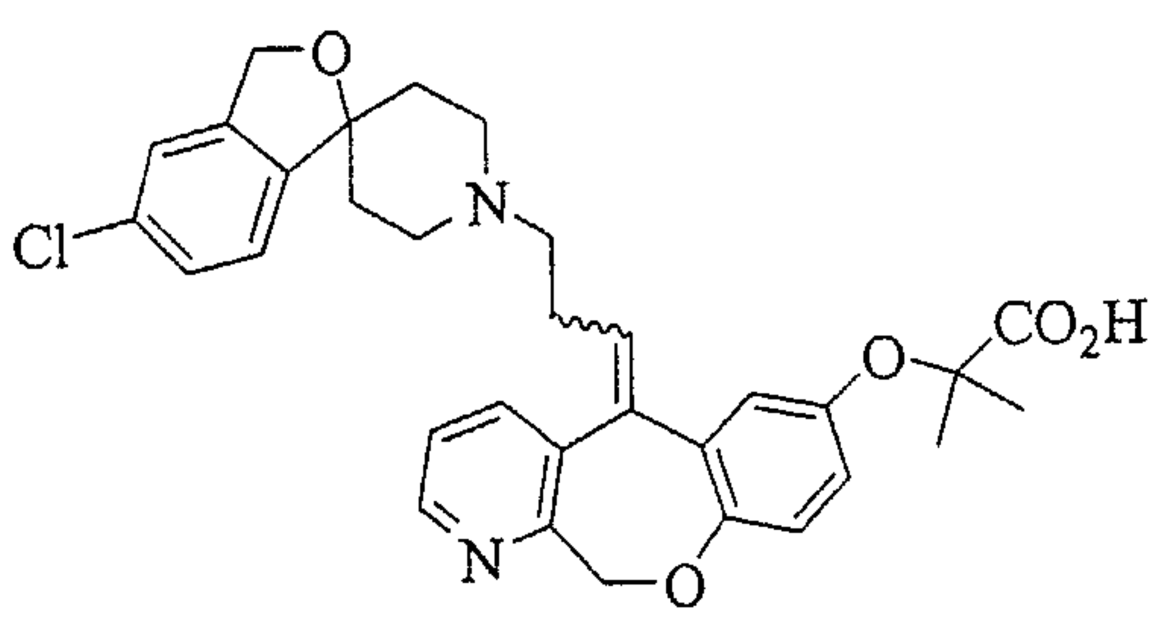


Example 236

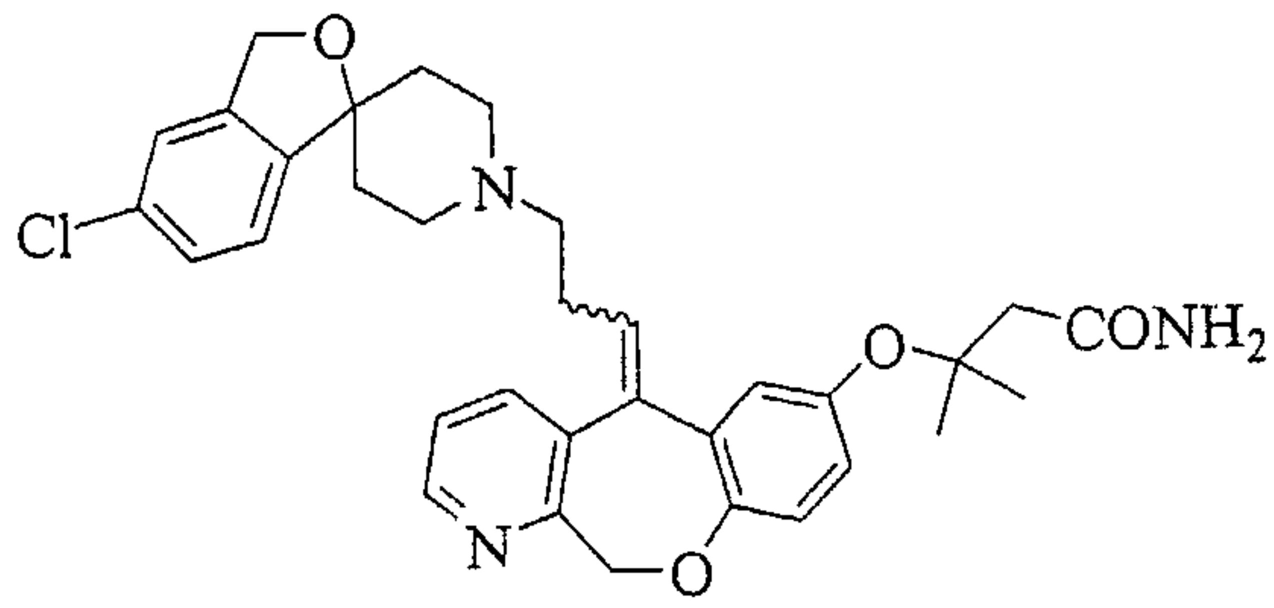


Example 237

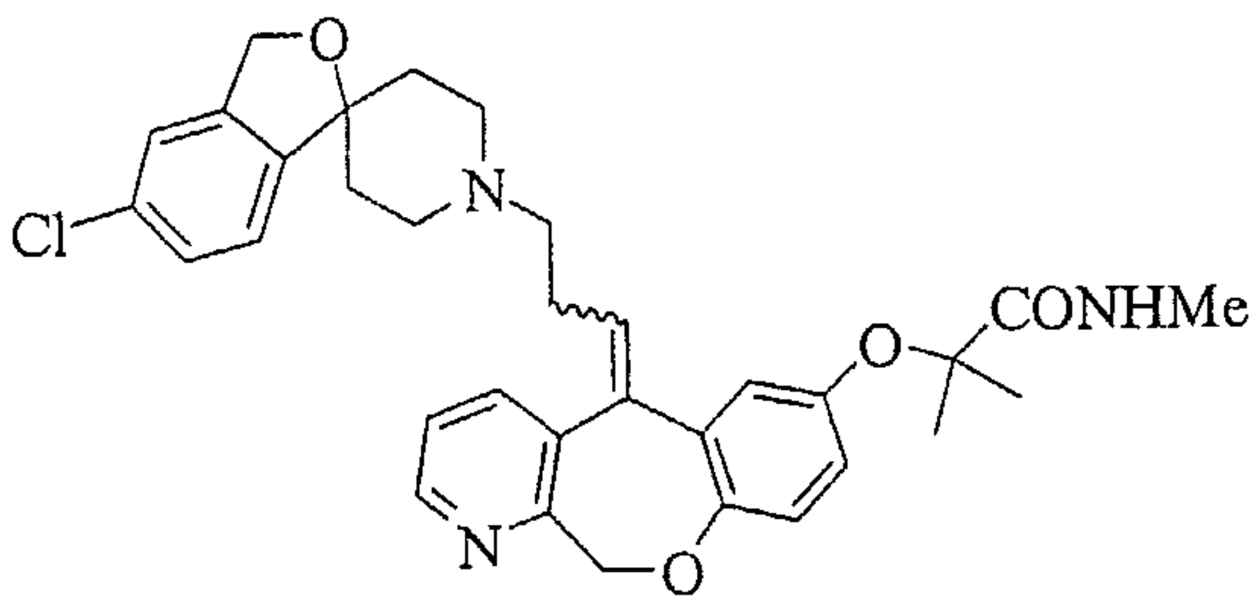
Figure 6X



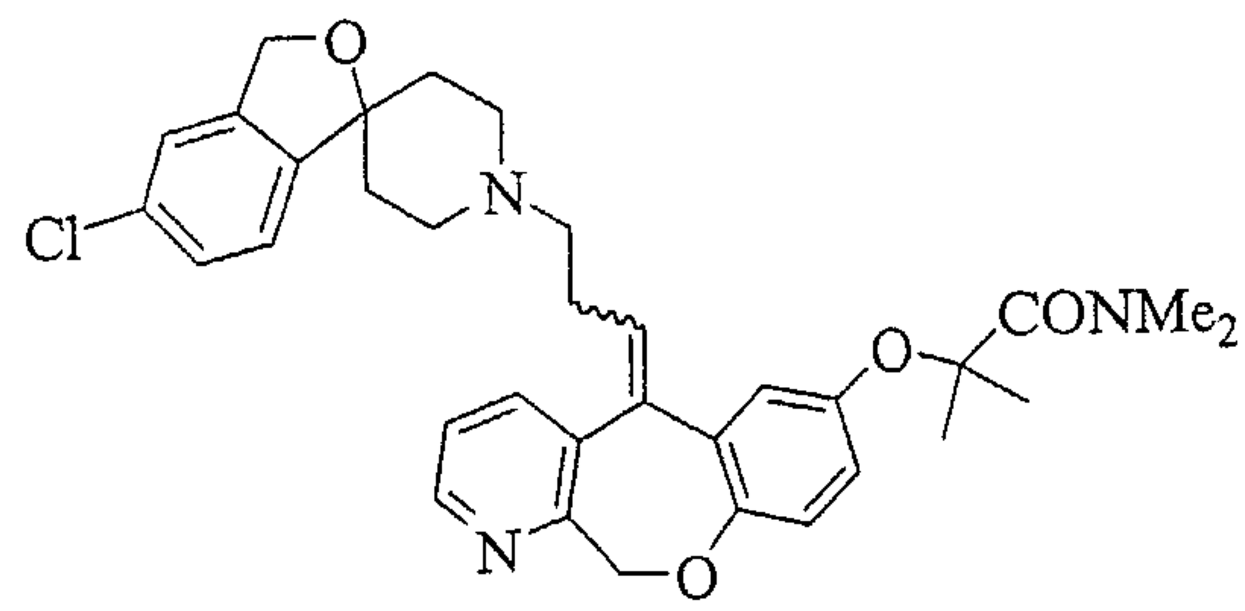
Example 238



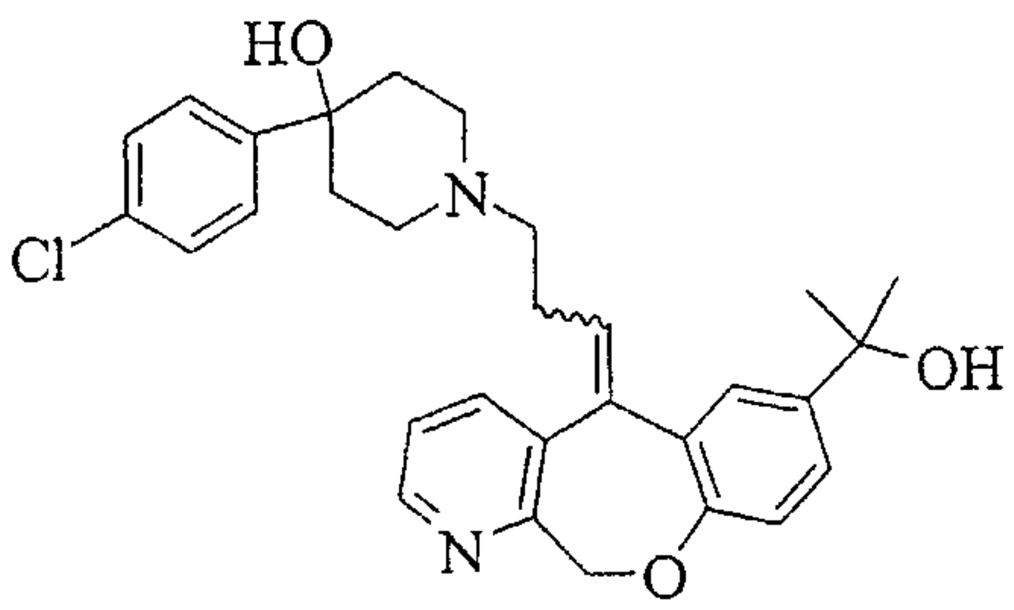
Example 239



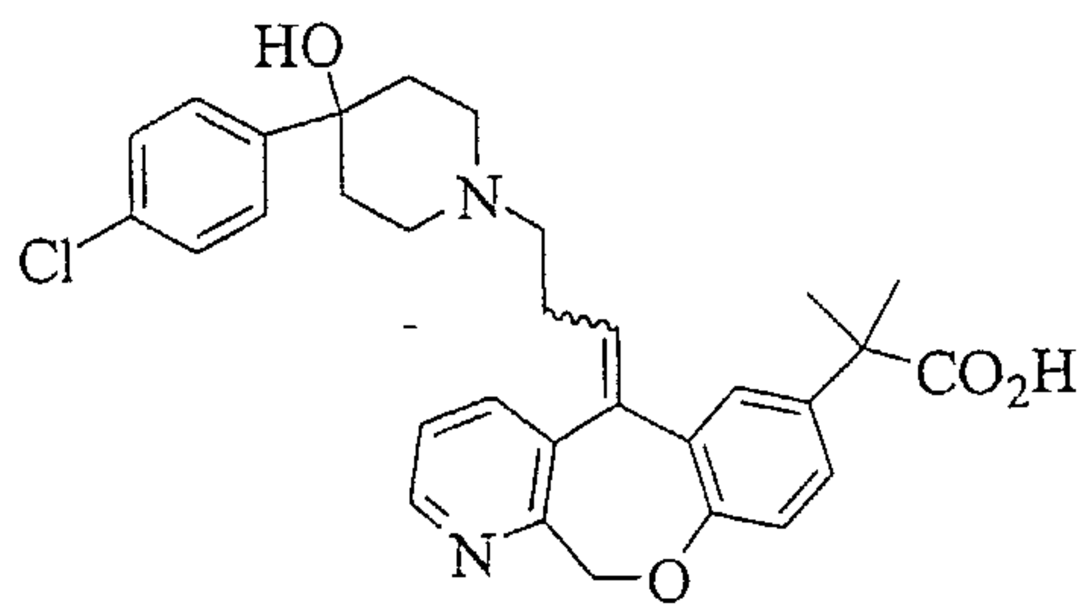
Example 240



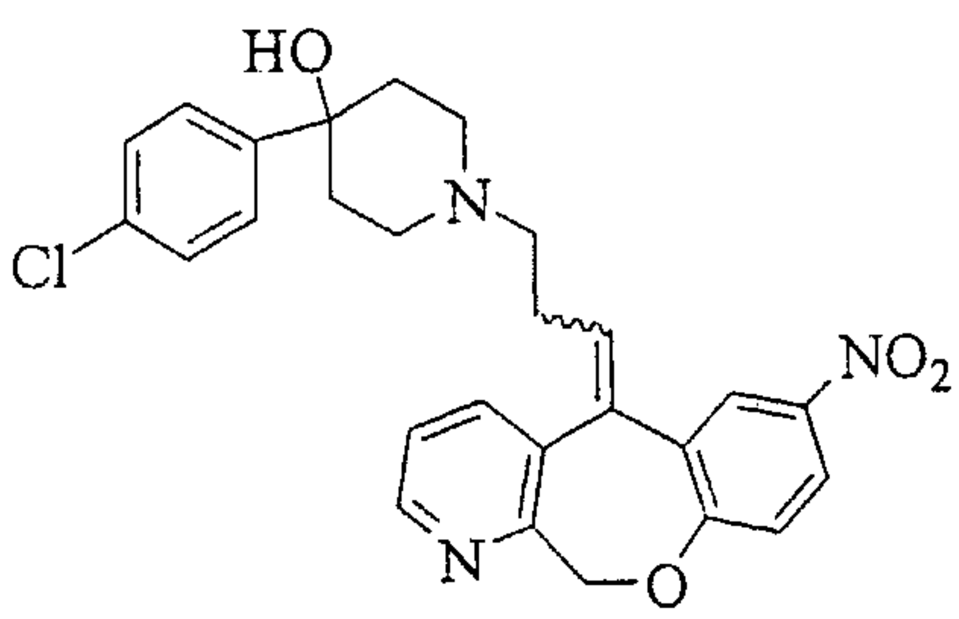
Example 241



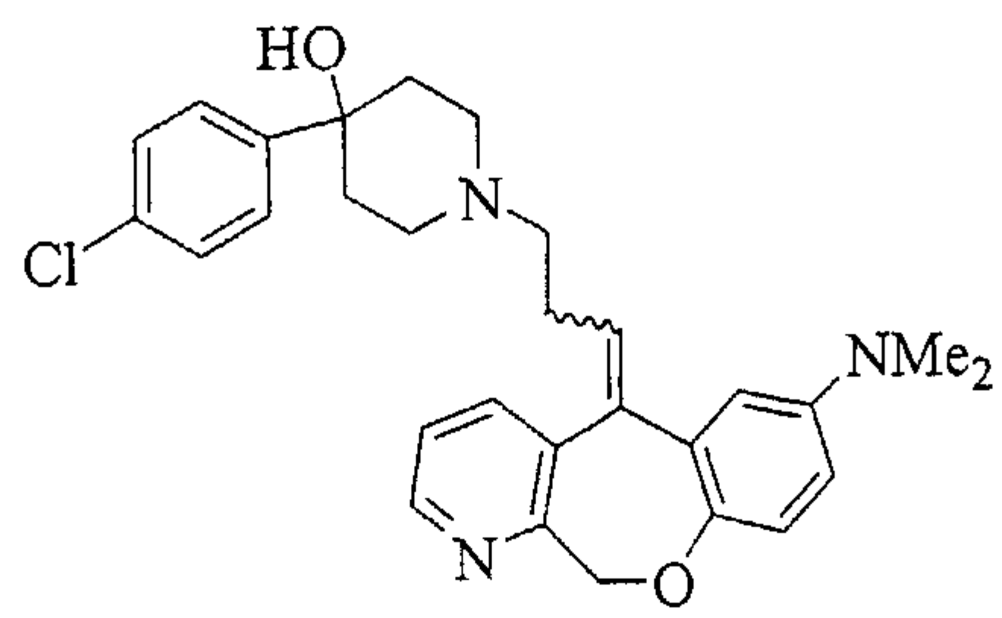
Example 242



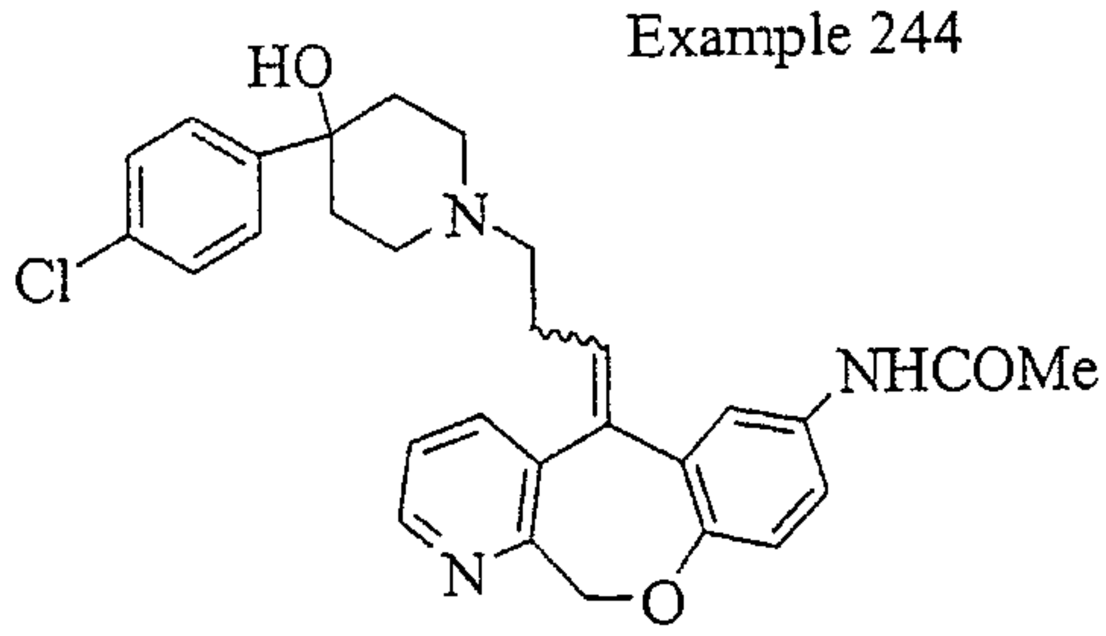
Example 243



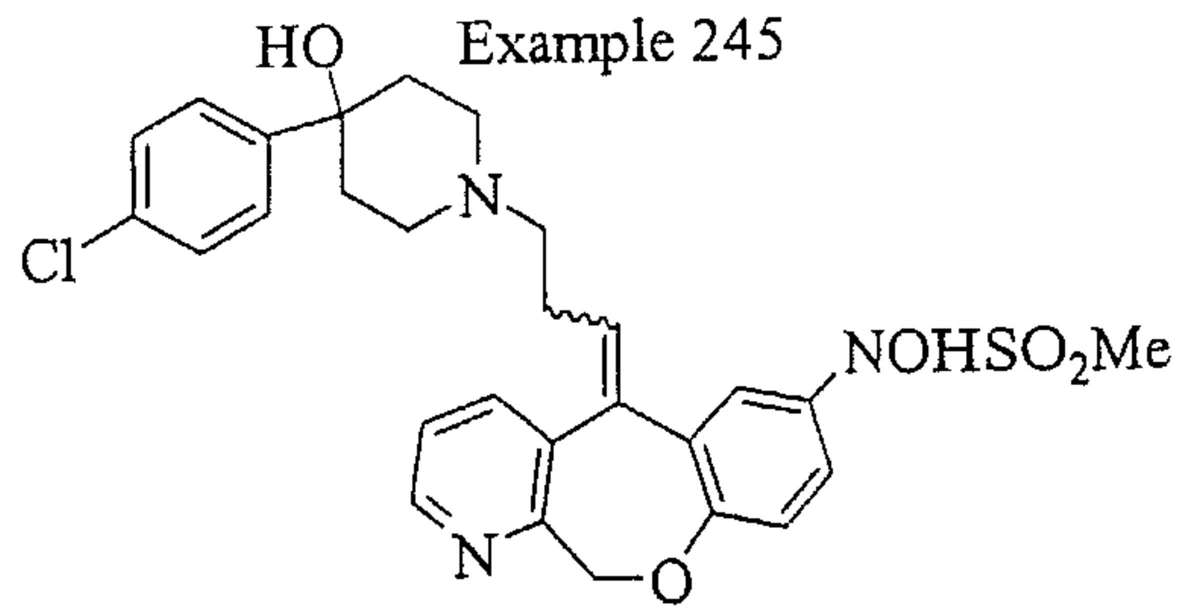
Example 244



Example 245

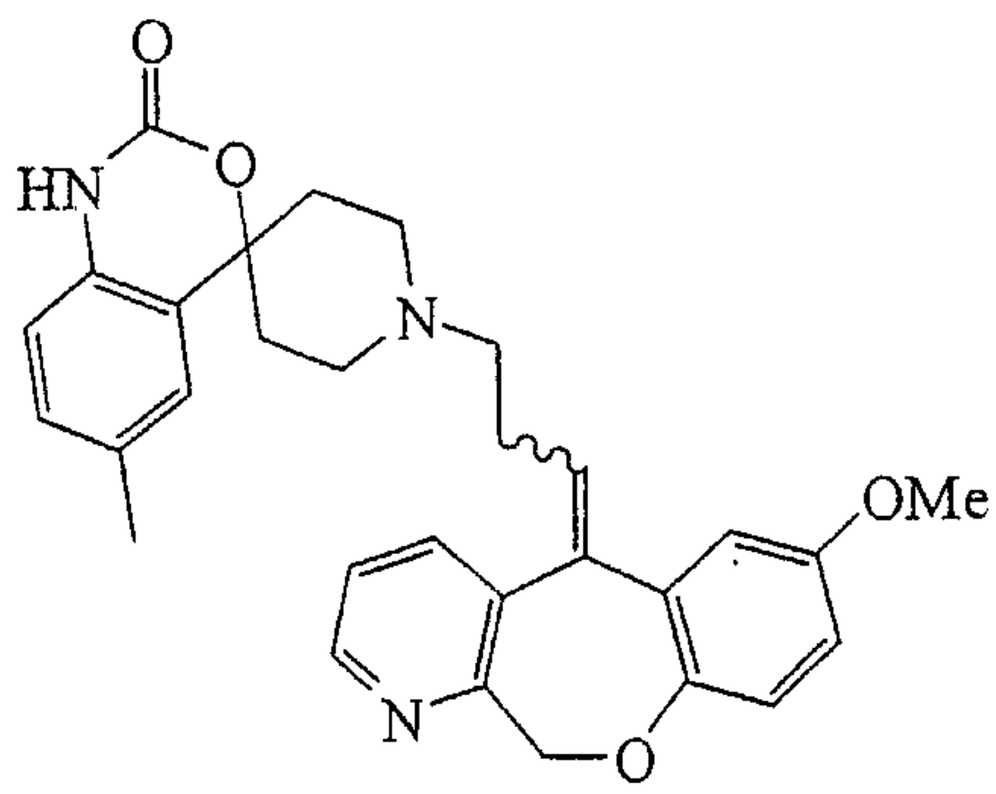


Example 246



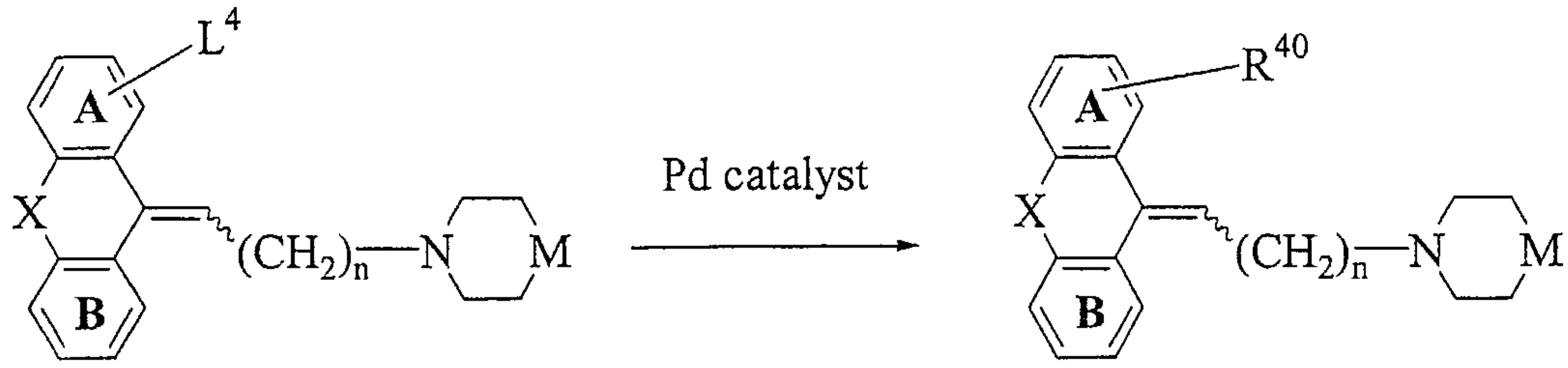
Example 247

Figure 6Y



Example 248

Figure 6Z



(I-f) (I-b)

Figure 7

Fig. 8a

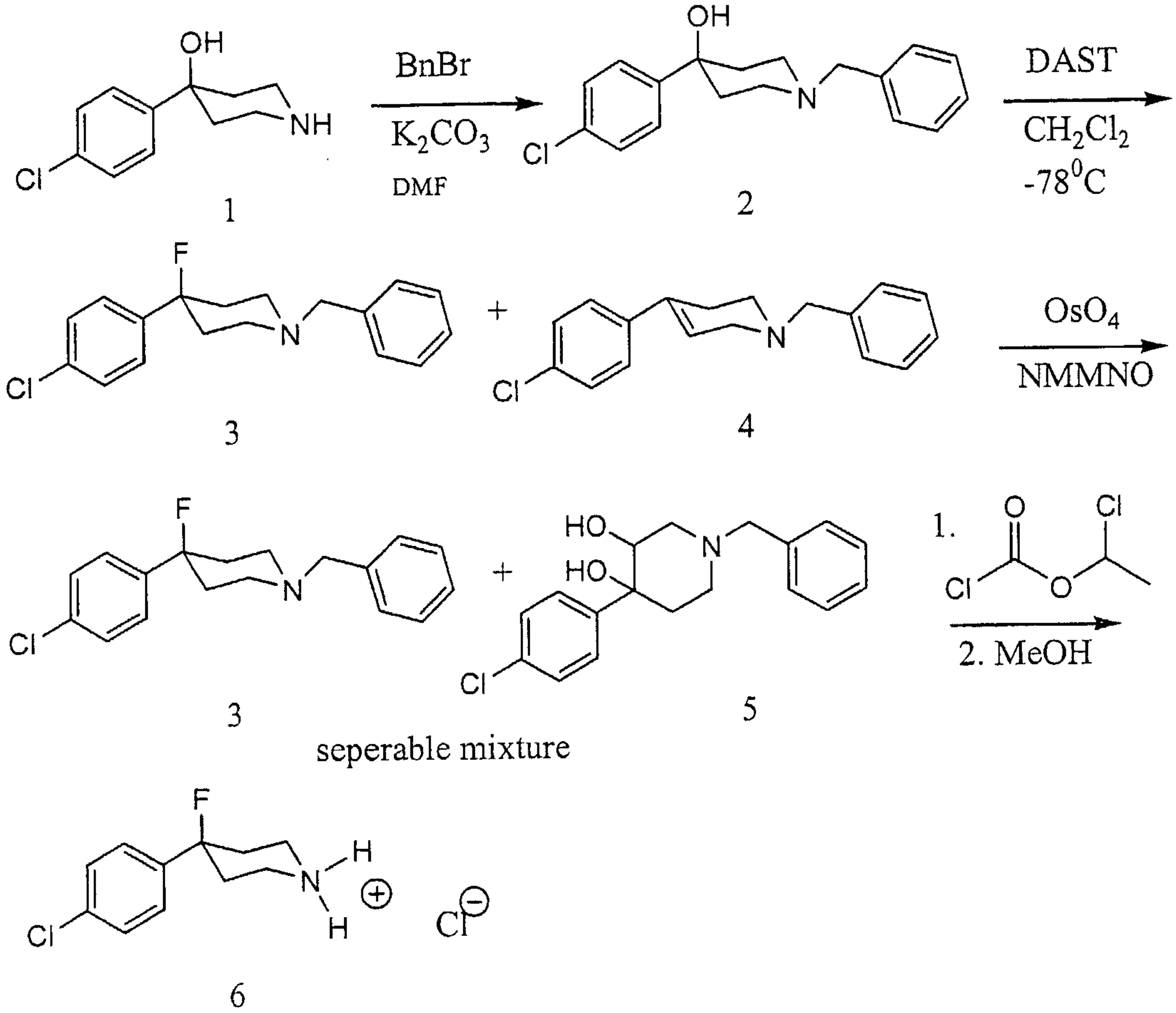

OH
NH
Cl
1
BnBr
K_2CO_3
DMF
2
DAST
CH_2Cl_2
-78^{0}C
F
N
3
4
OsO_4
NMMNO
HO
5
1.
O
Cl
2. MeOH
seperable mixture
H
6

Fig. 8b

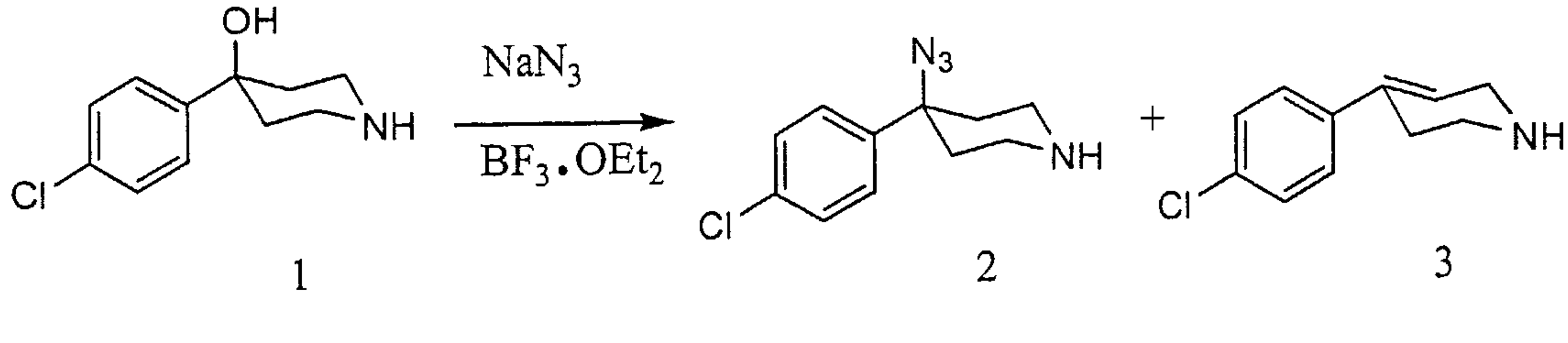

OH
NH
Cl
1
NaN_3
$BF_3 \cdot OEt_2$
N_3
2
3

Fig 8c.

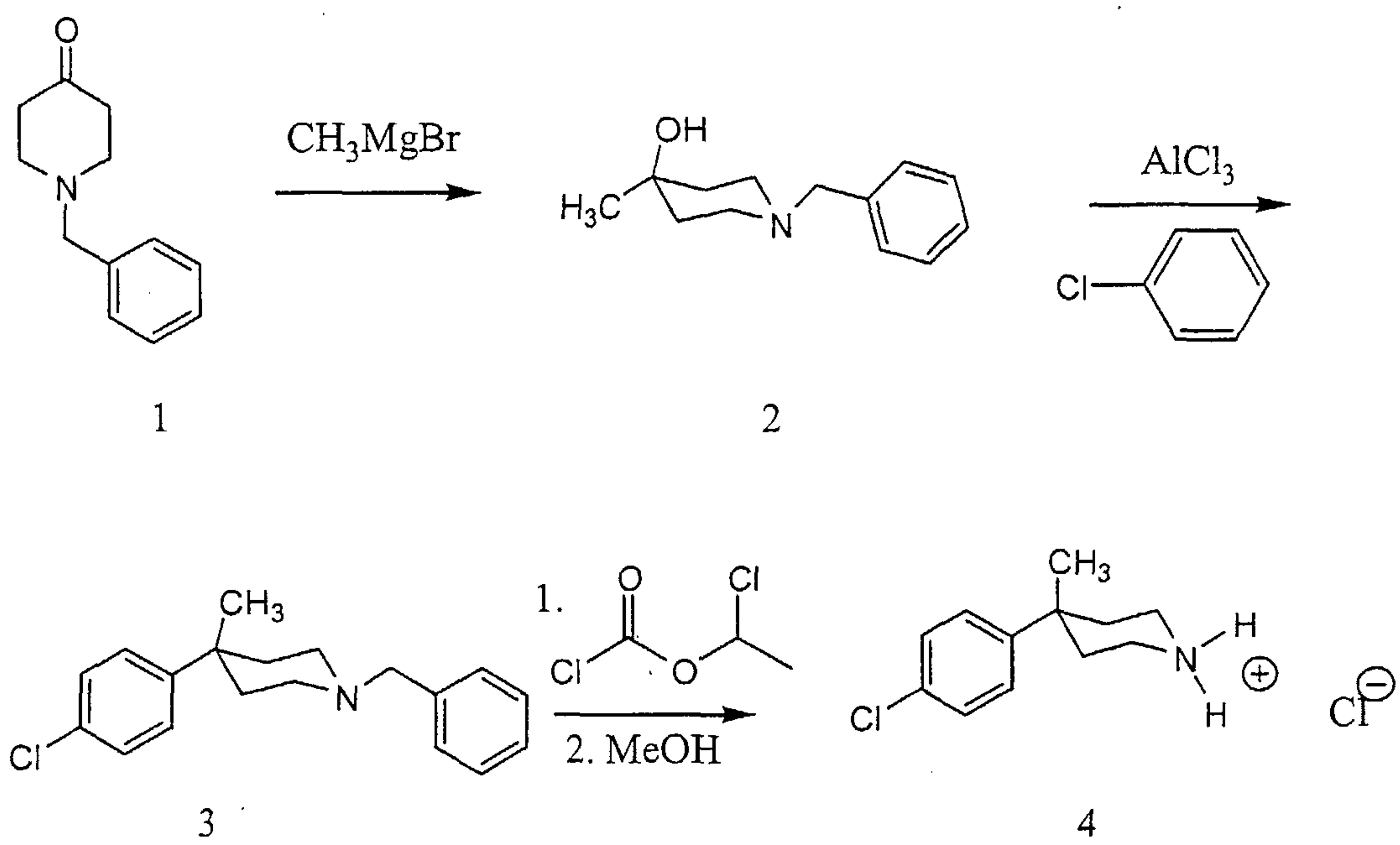
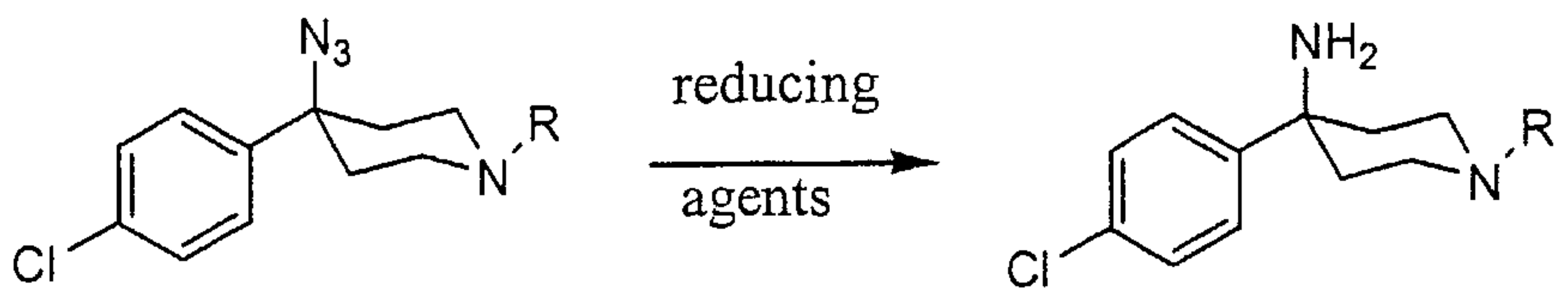
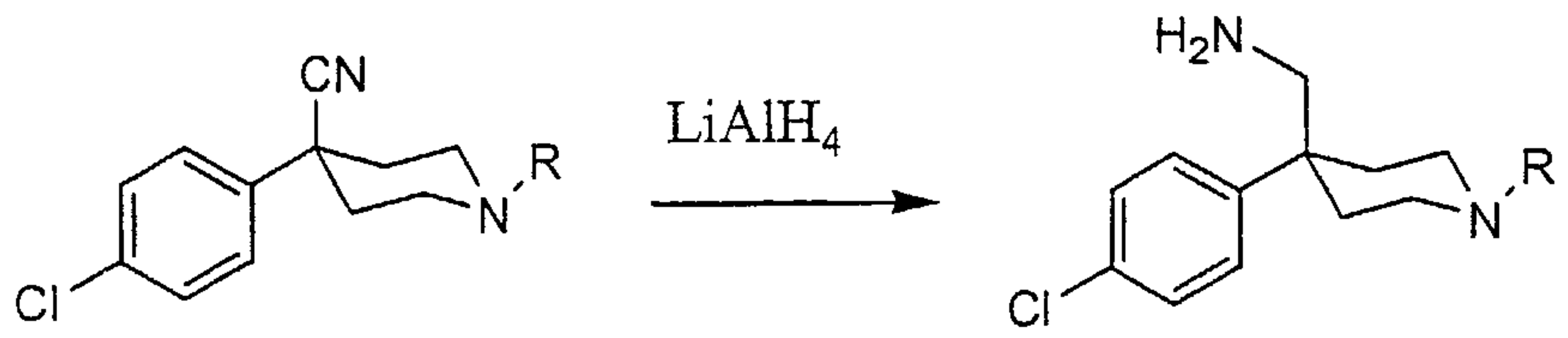

CH3MgBr
OH
H3C
N
AlCl3
Cl
1
2
CH3
N
Cl
3
1.
O
Cl
O
Cl
2. MeOH
CH3
N
H
H
Cl
Cl
4

Fig. 9a



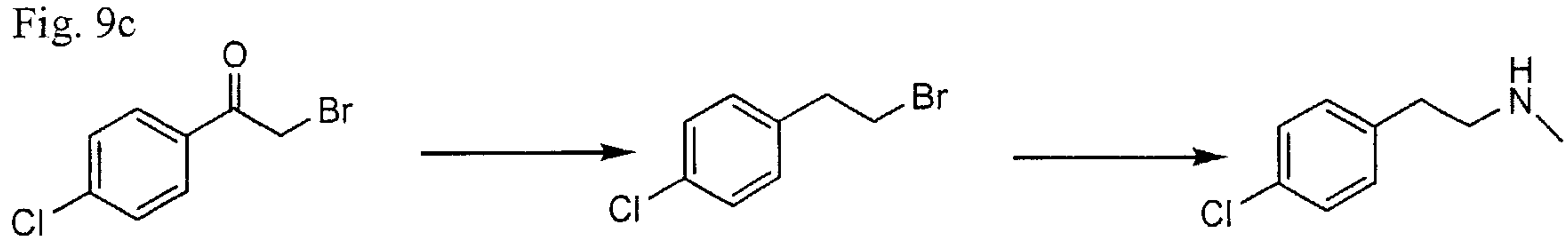
1 2

Fig. 9b



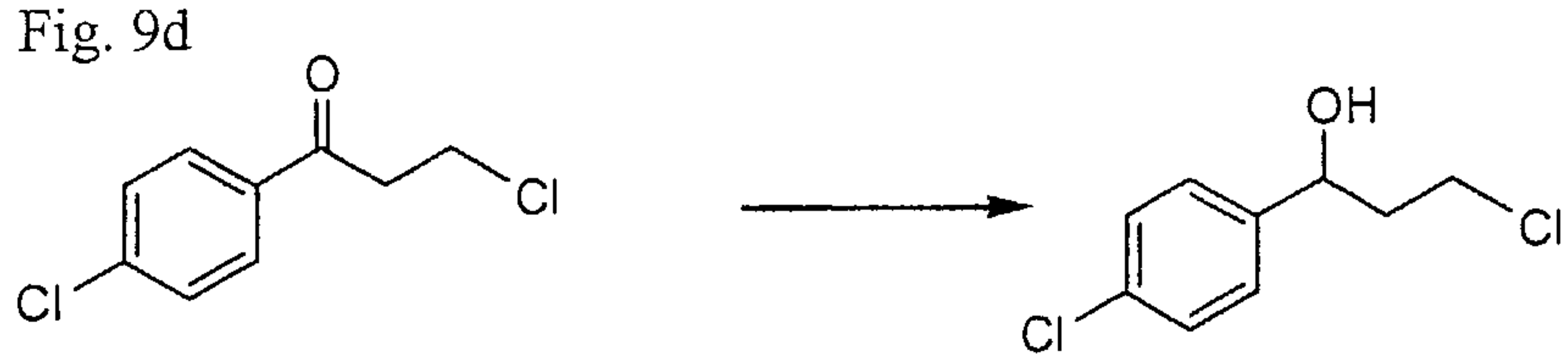
1 2

Fig. 9c



1 2 3

Fig. 9d

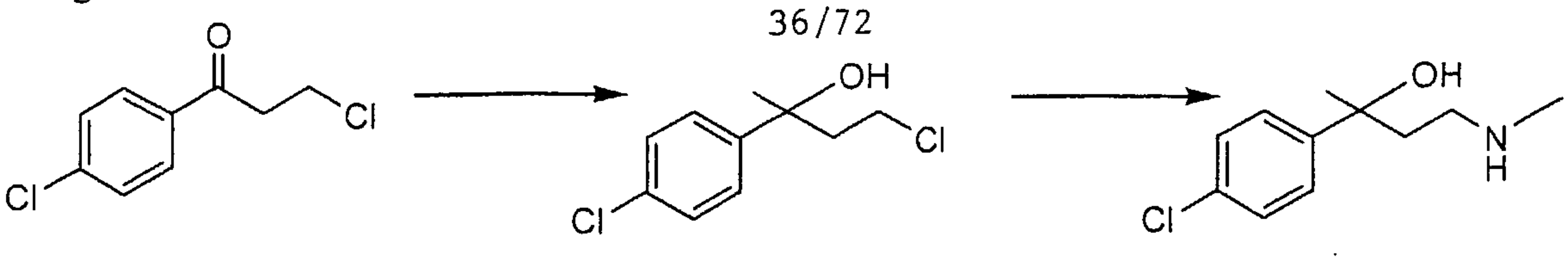


1 2

Fig. 9e

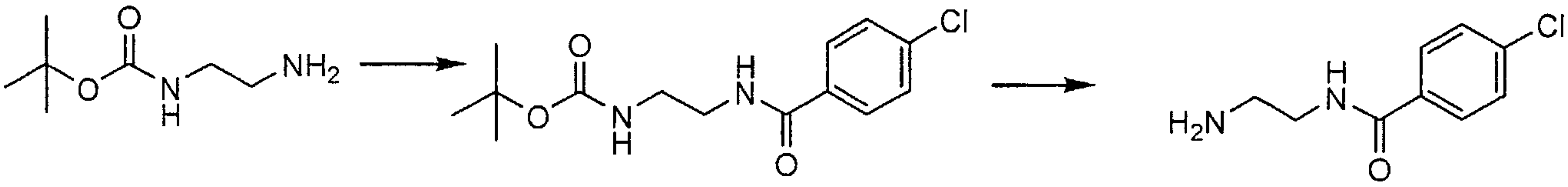
1 2

Fig. 10a



1 2 3

Fig. 10b



1 2 3

Fig. 10c

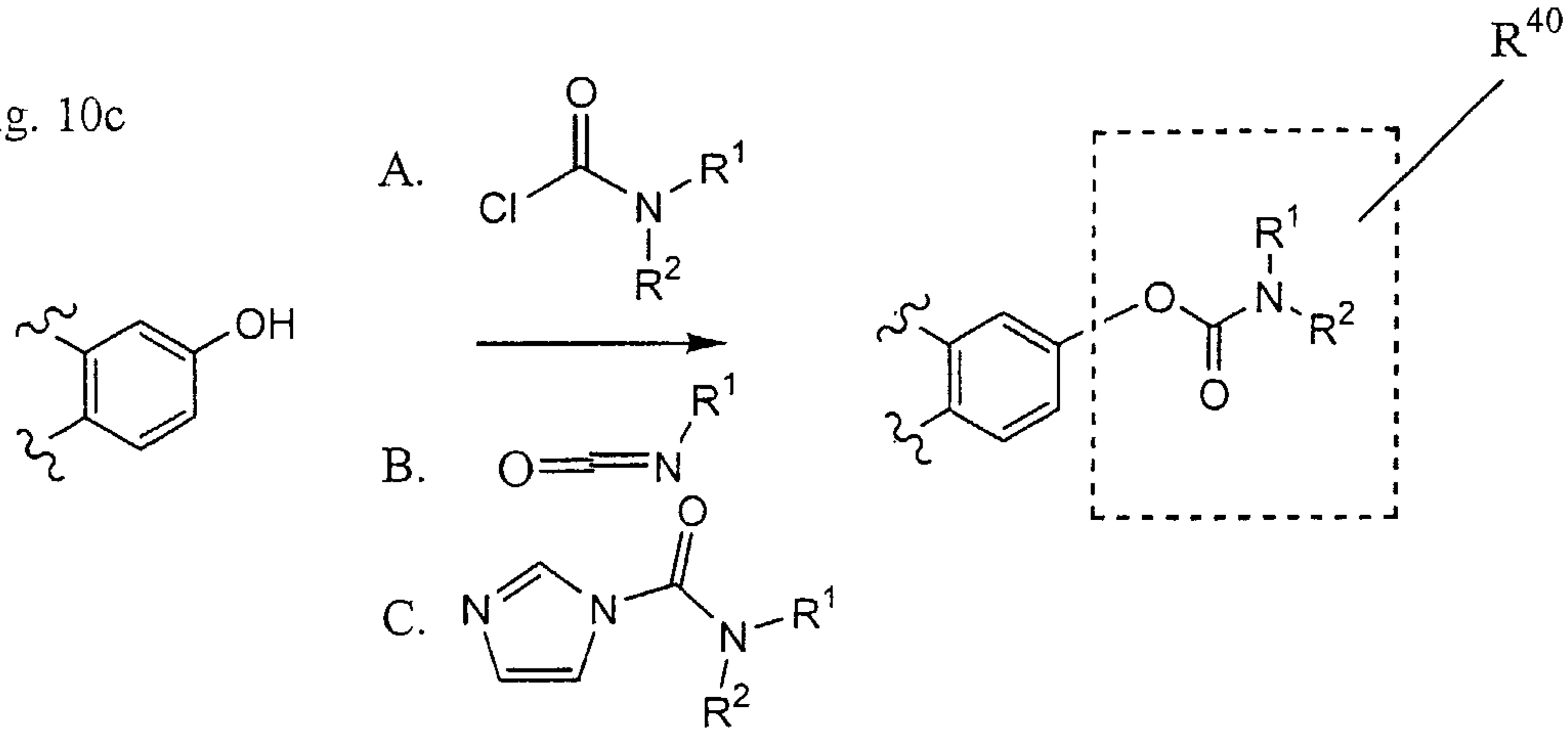
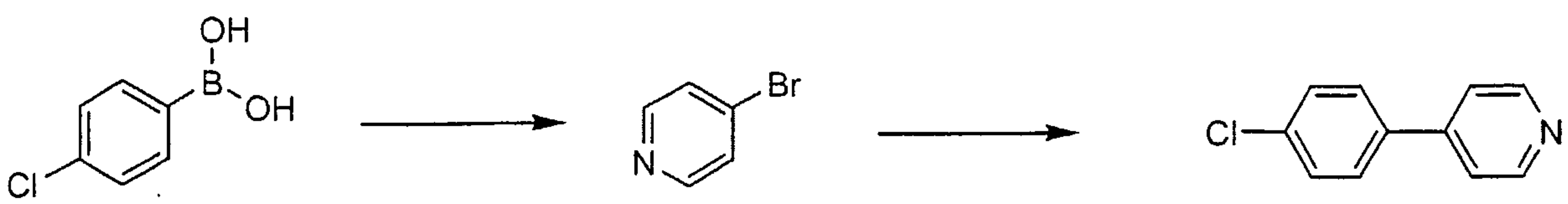
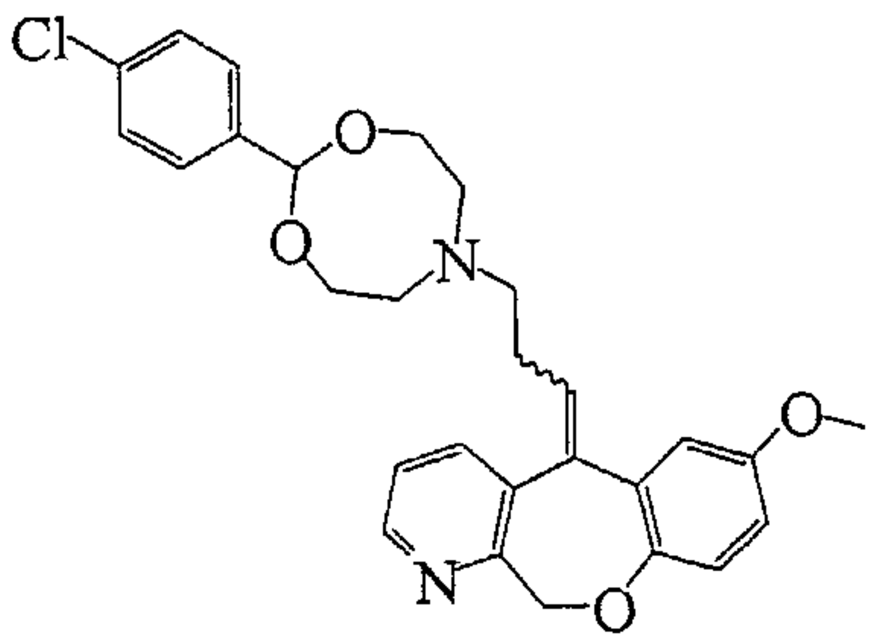
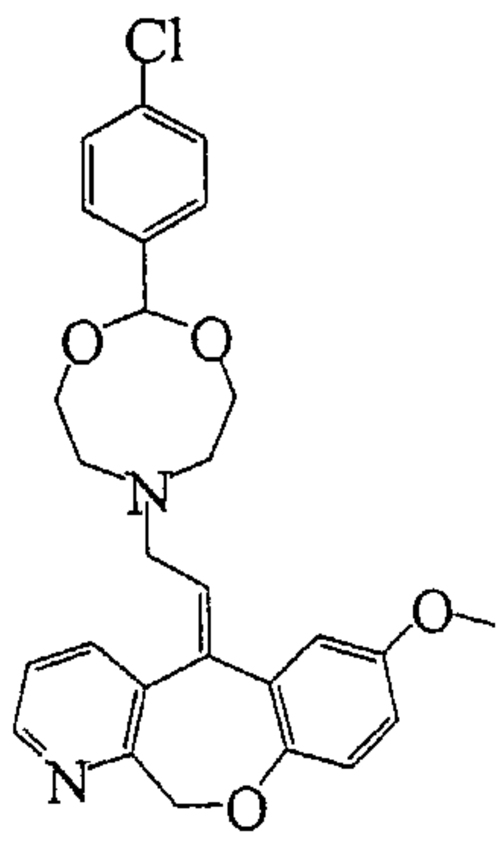


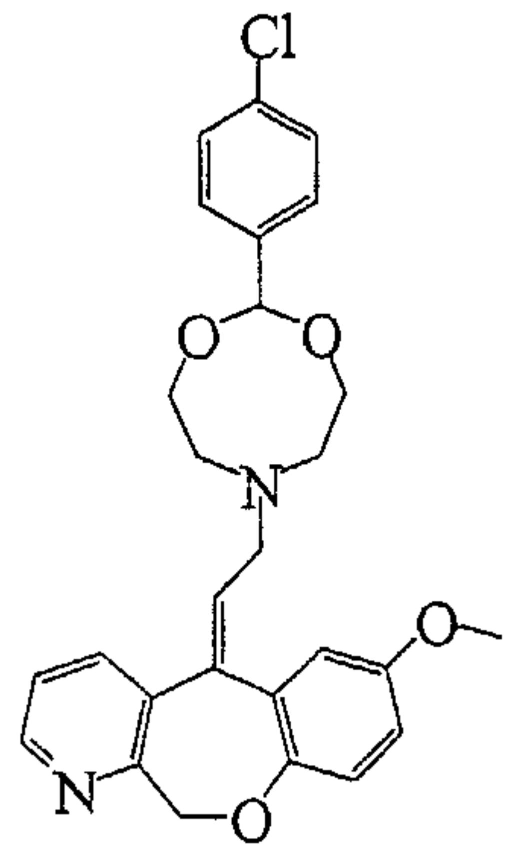
Fig. 10d

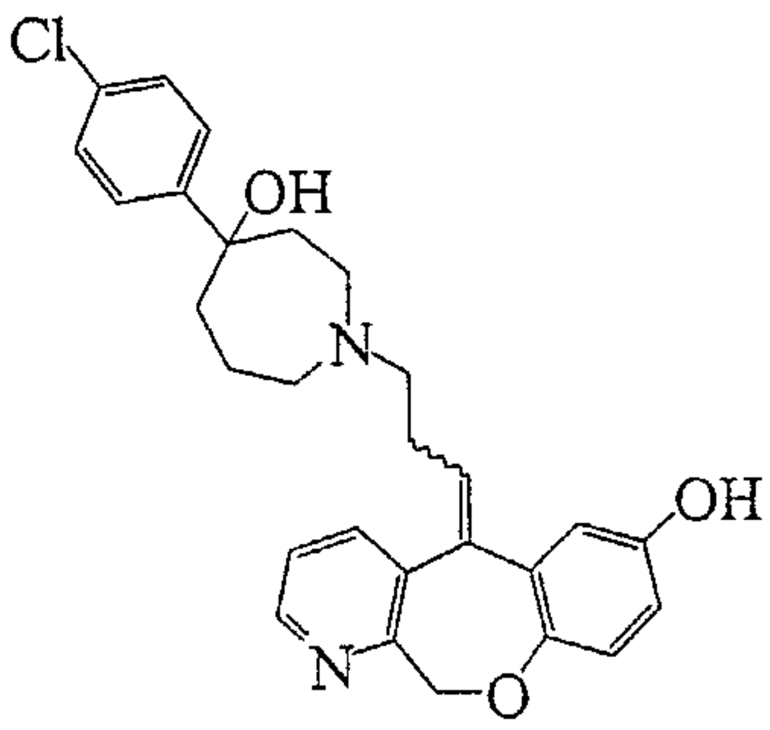


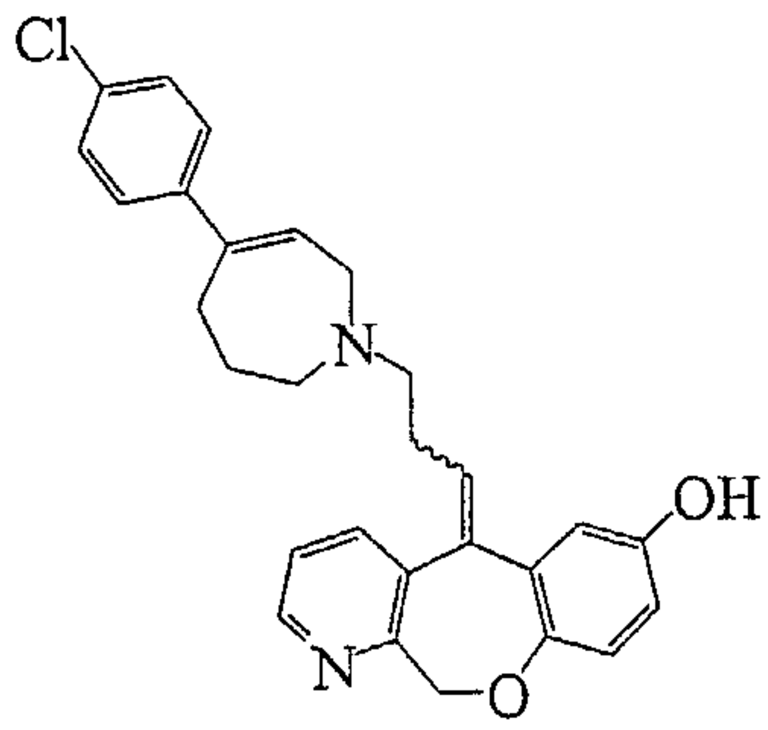
1 2 3

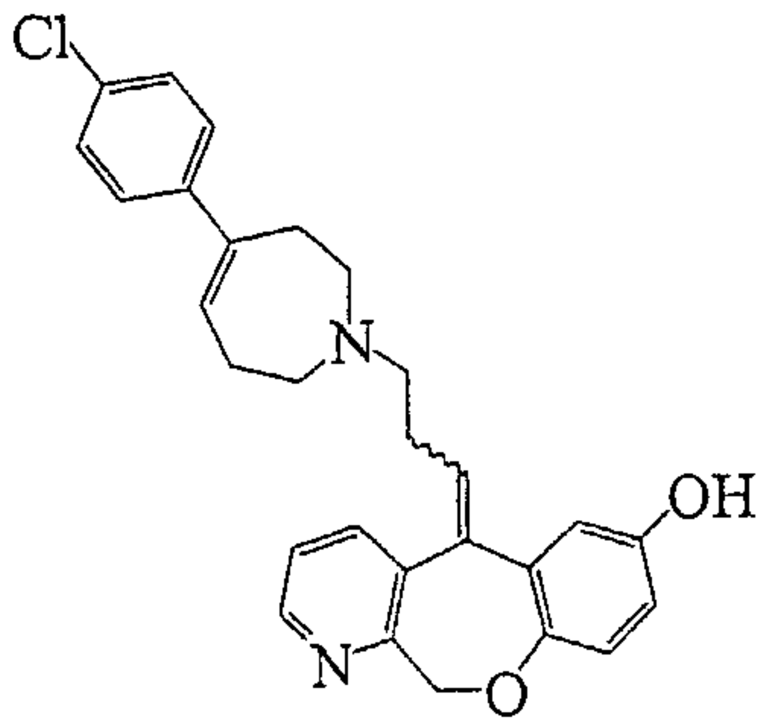

Example 249

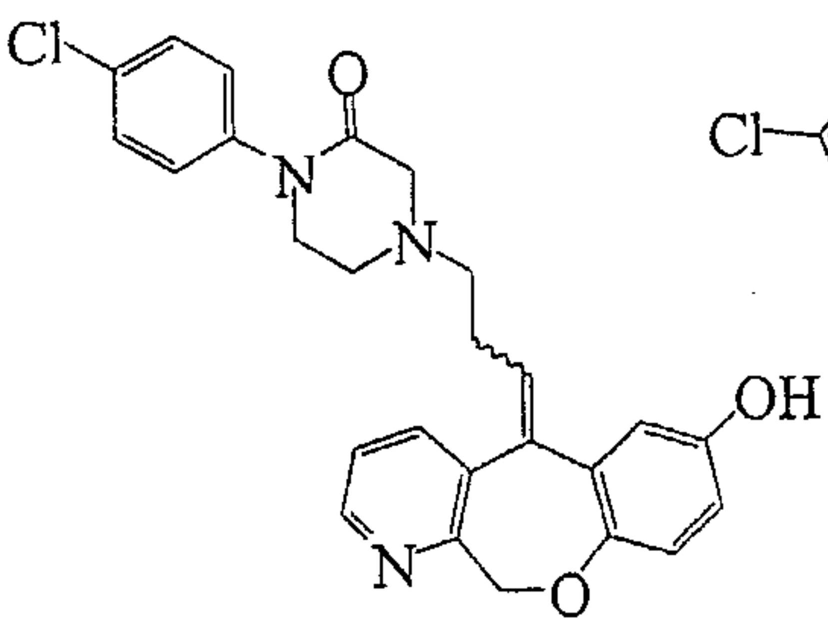

Example 250

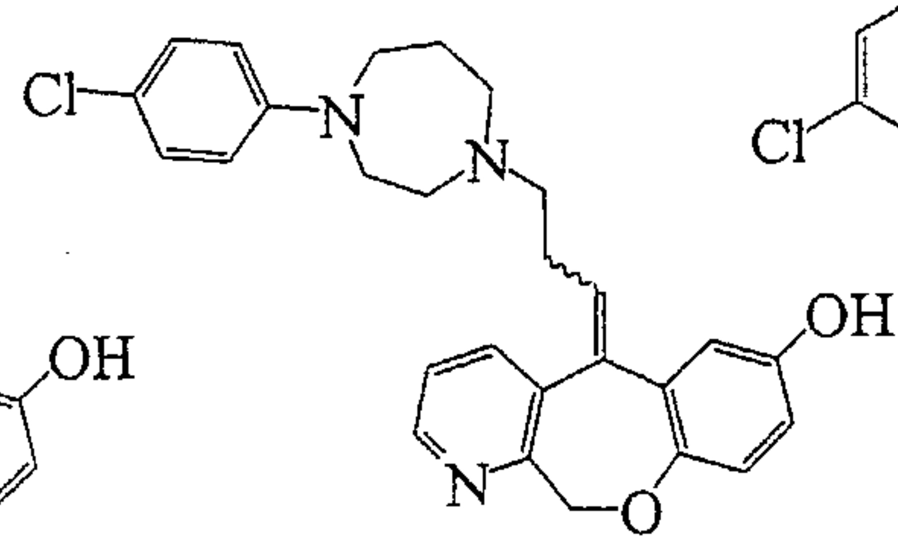

Example 251

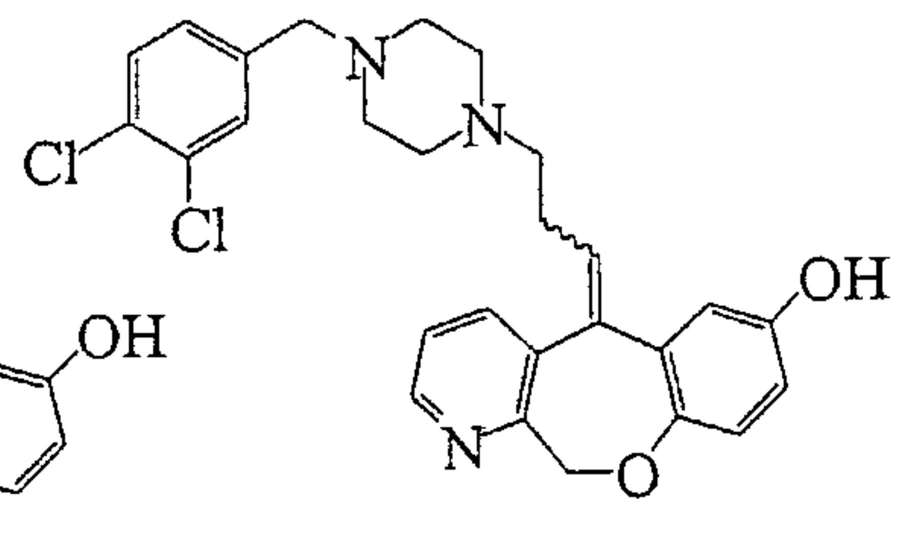

Example 252

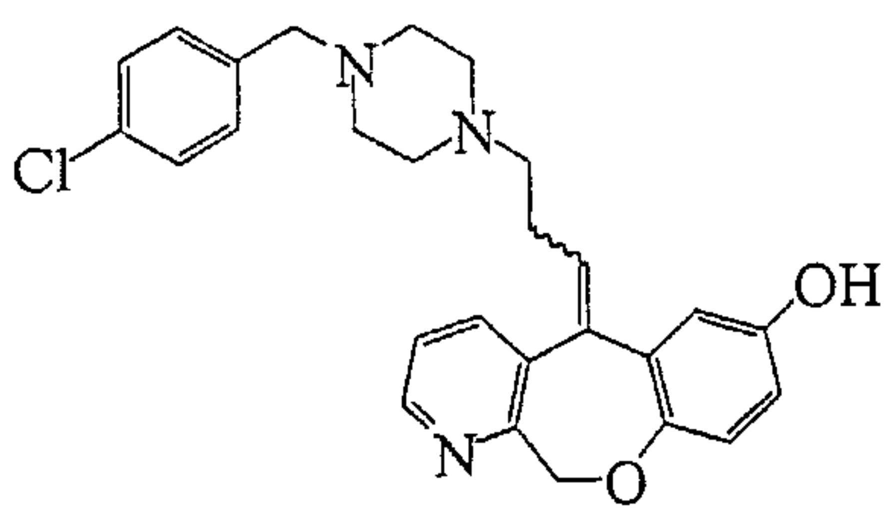

Example 253


Example 254


Example 255


Example 256


Example 257


Example 258

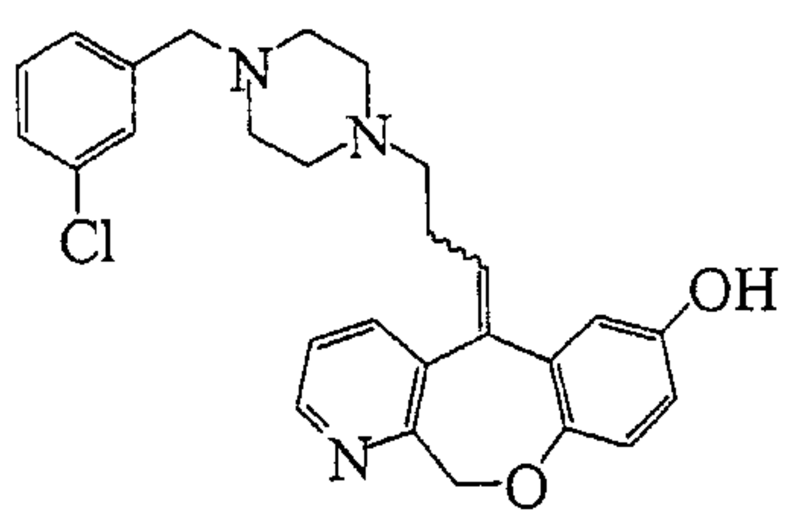
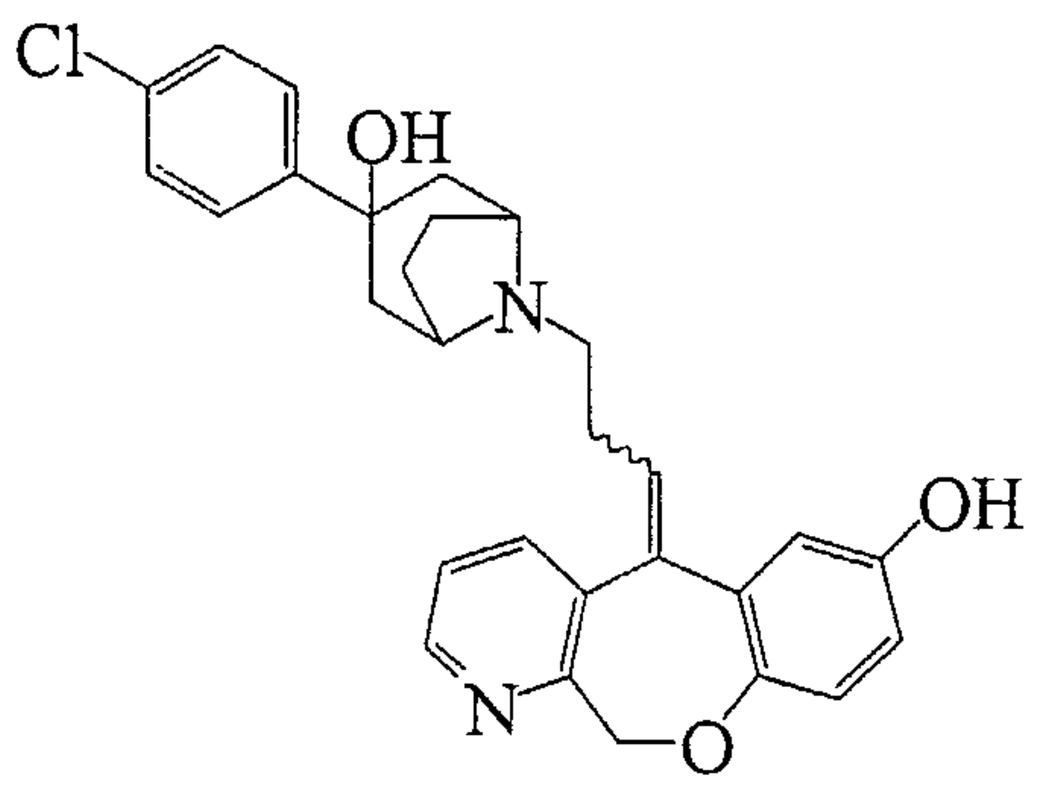
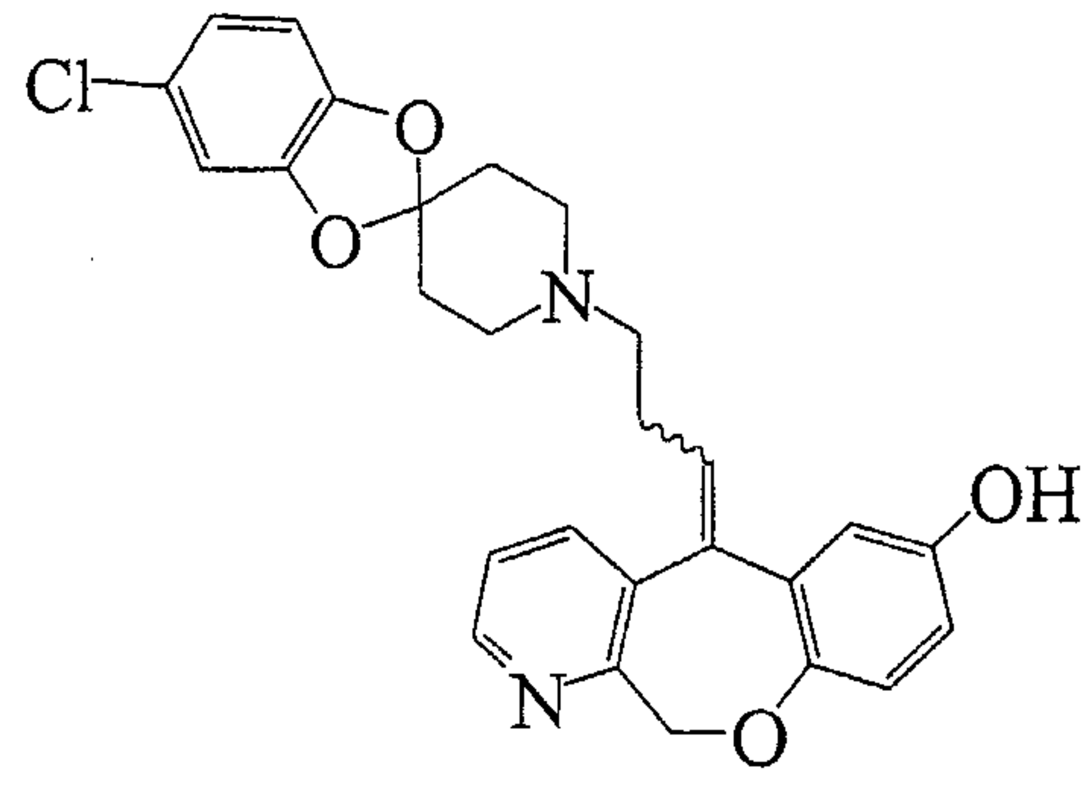

Example 259

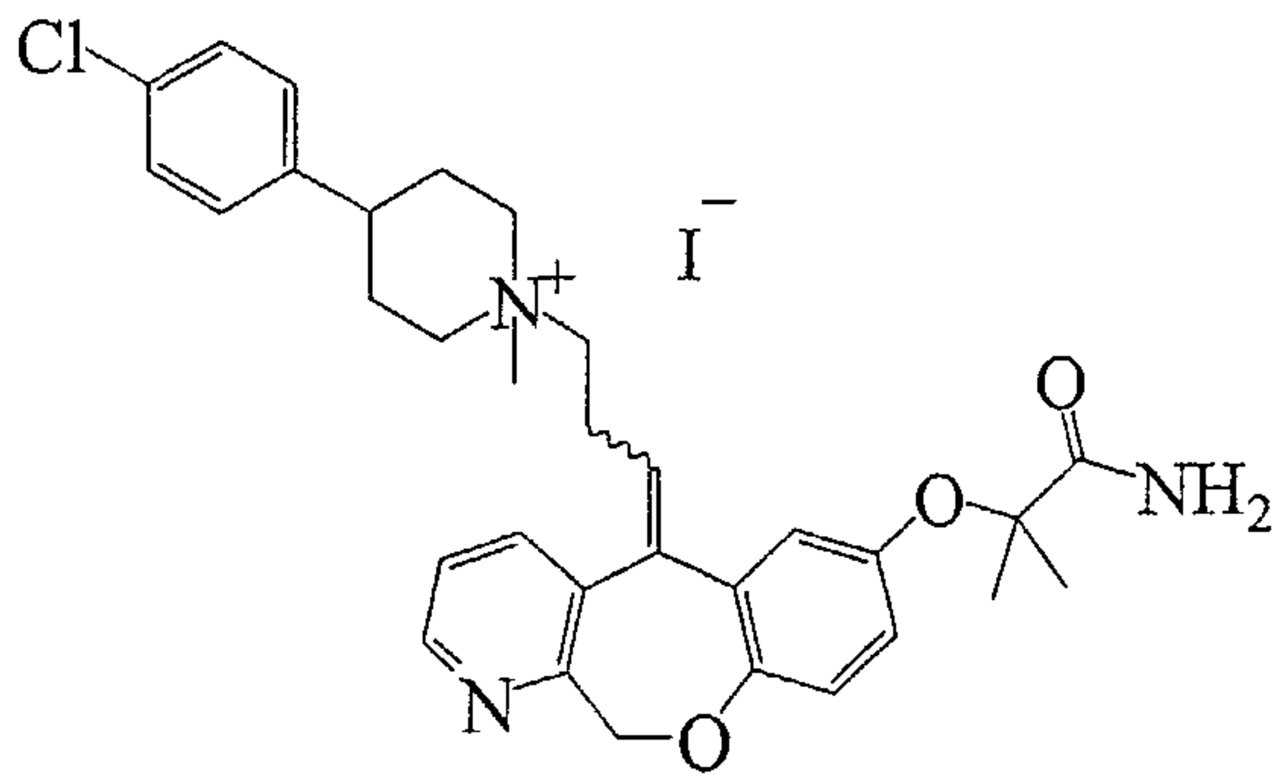
Figure 11A



Example 260

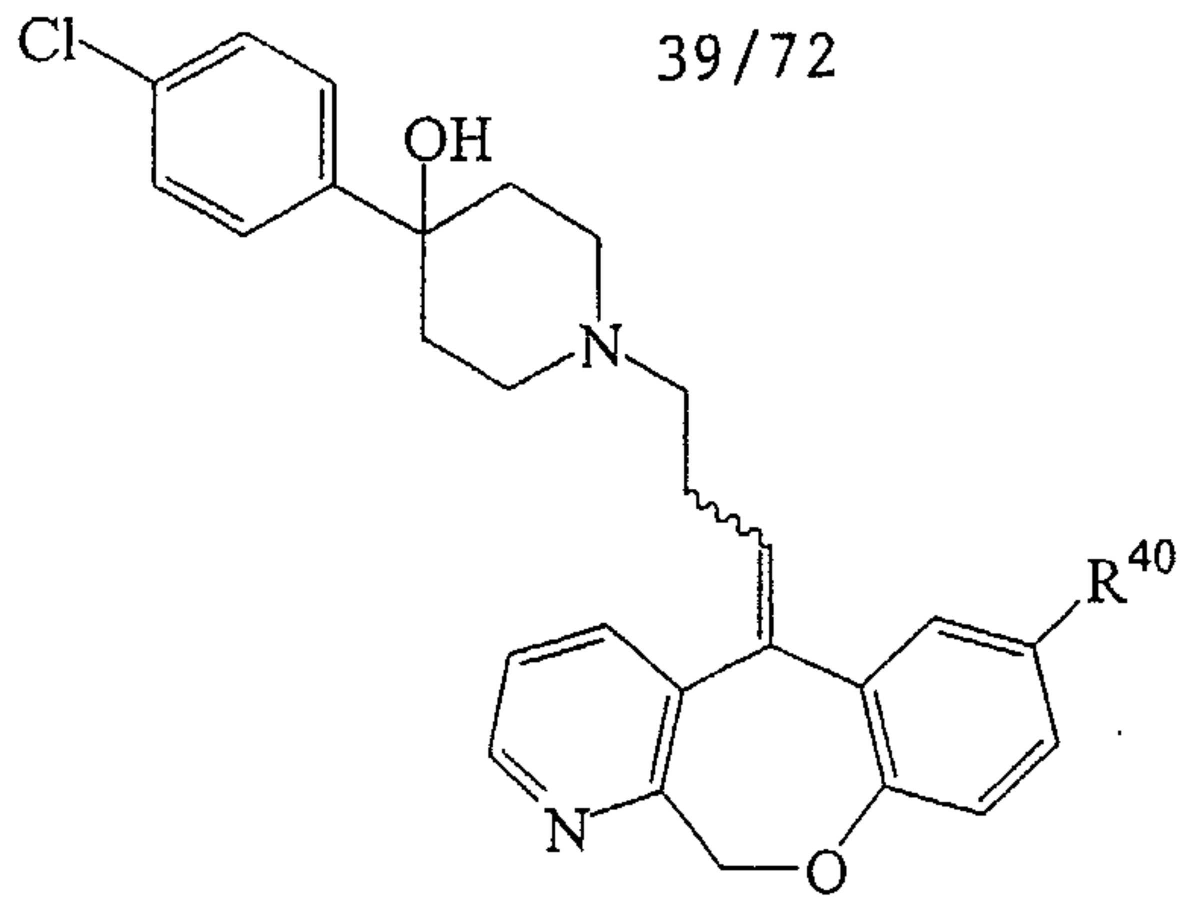


Example 261

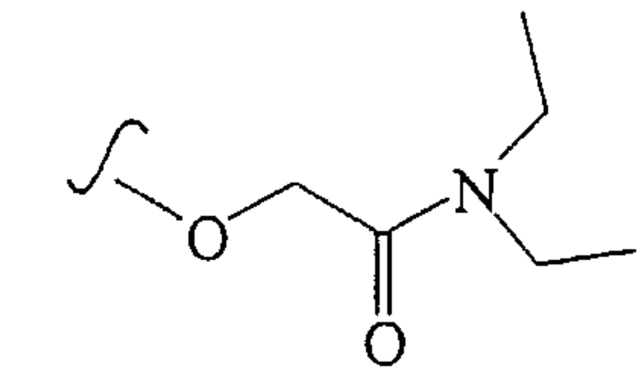


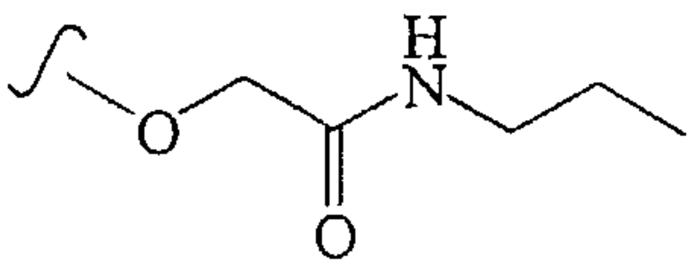
Example 262

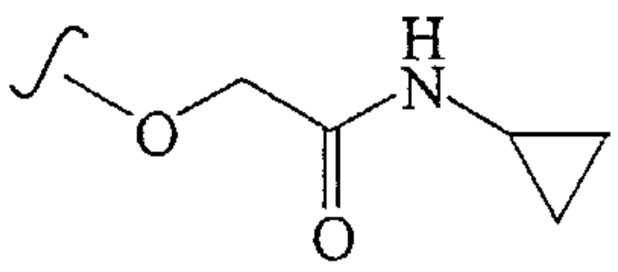
Figure 11B

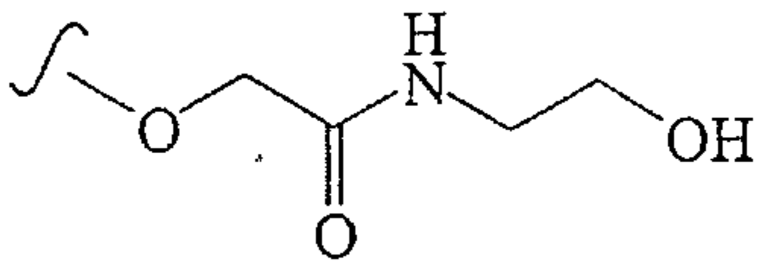


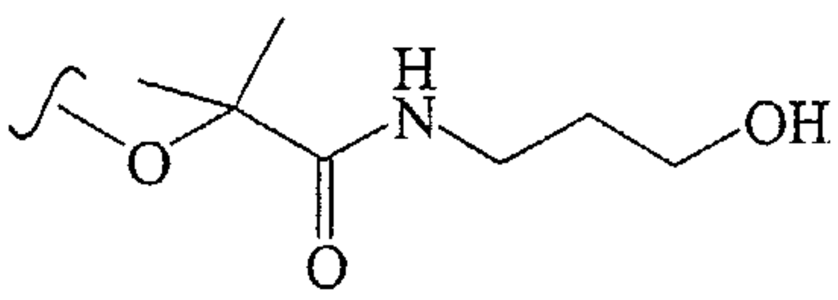
$\underline{R^{40}}$

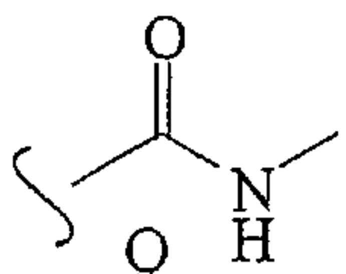
Example 263 

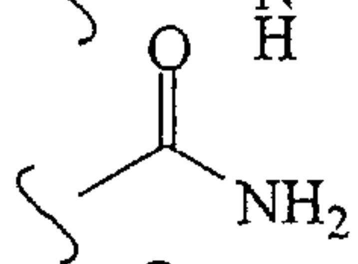
Example 264 

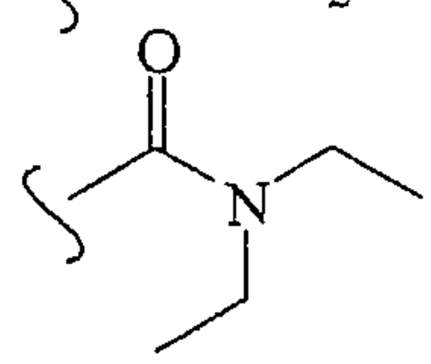
Example 265 

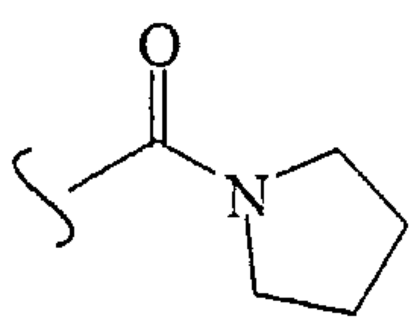
Example 266 

Example 267 

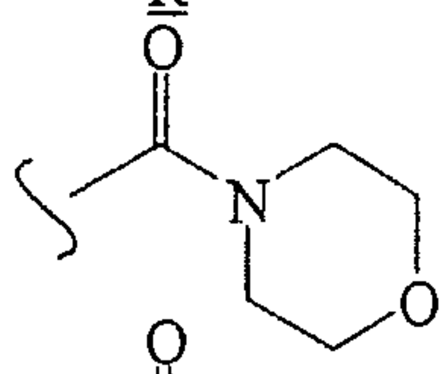
Example 268 

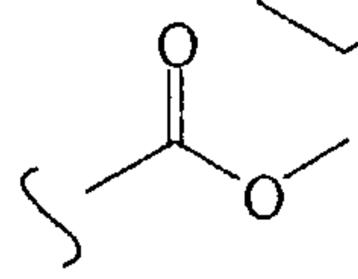
Example 269 

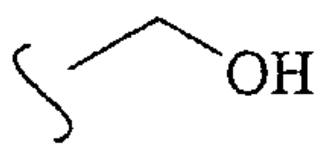
Example 270 

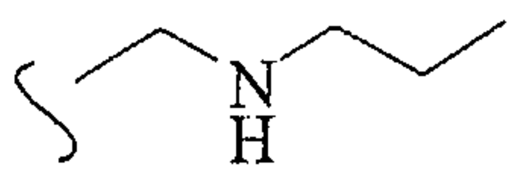
Example 271 

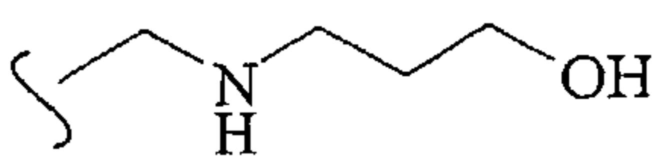
$\underline{R^{40}}$

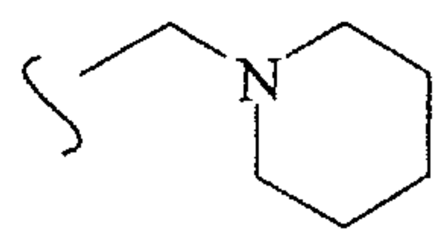
Example 272 

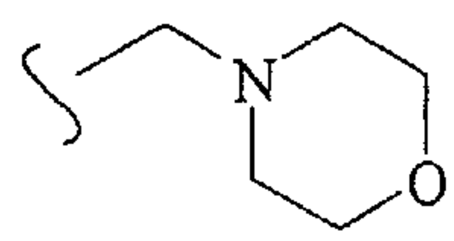
Example 273 

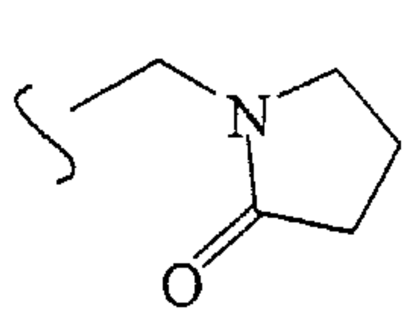
Example 274 

Example 275 

Example 276 

Example 277 

Example 278 

Example 279 

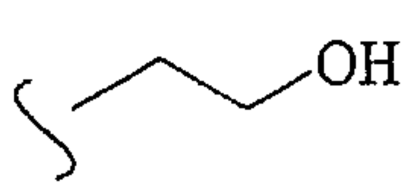
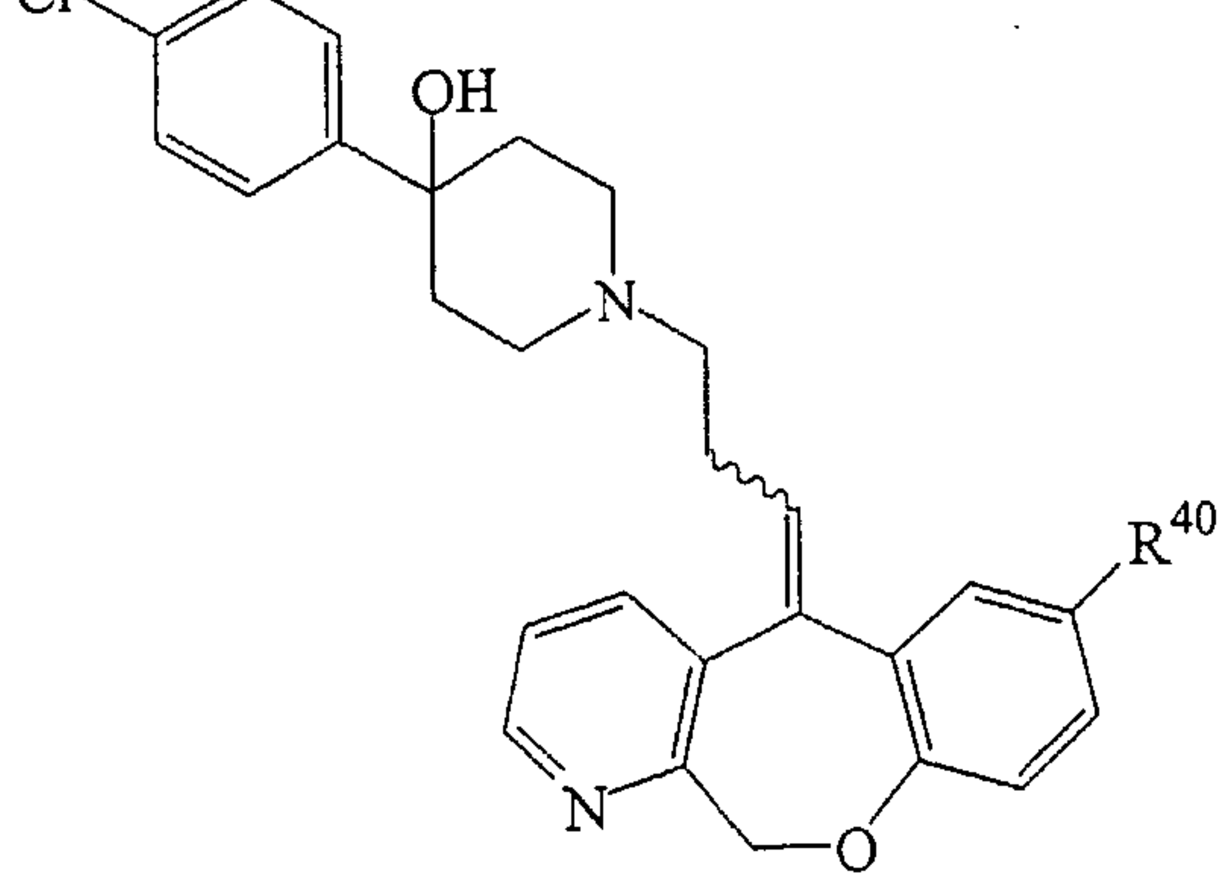
Example 280 

Figure 11C



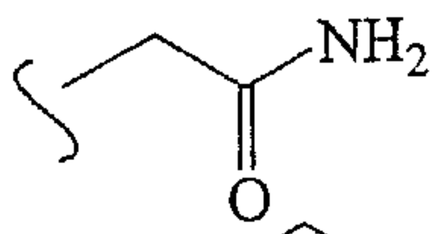
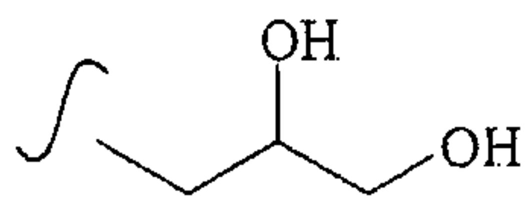
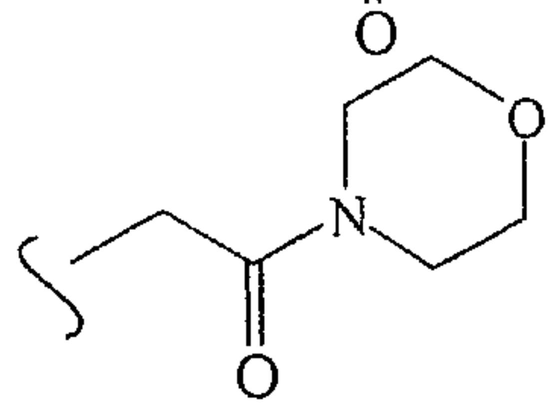
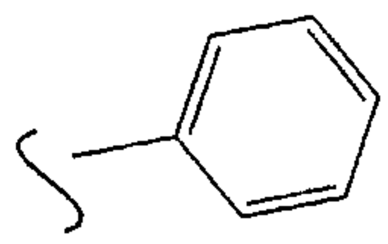
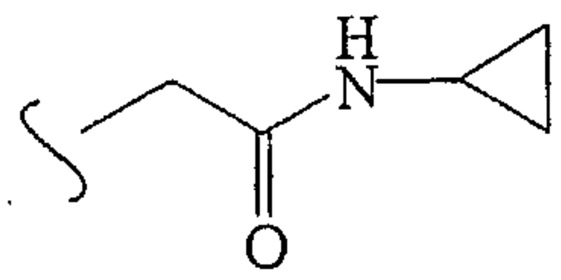
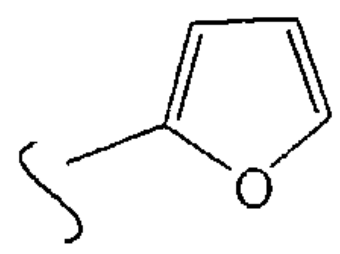
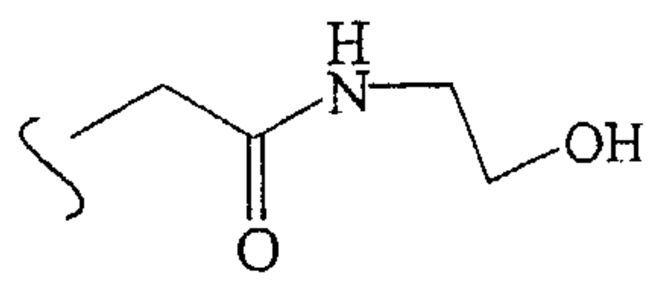
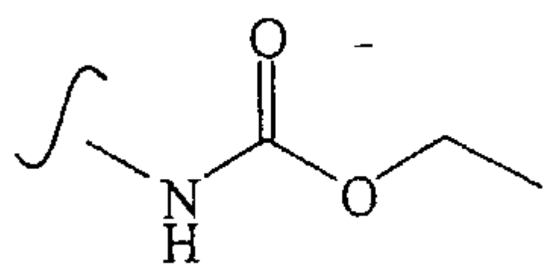
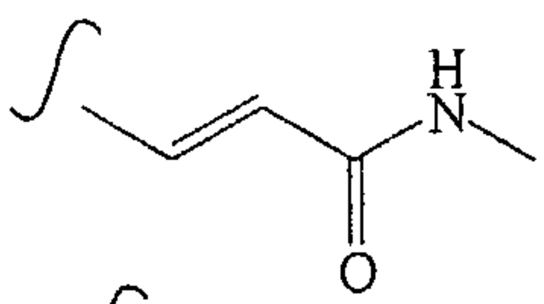
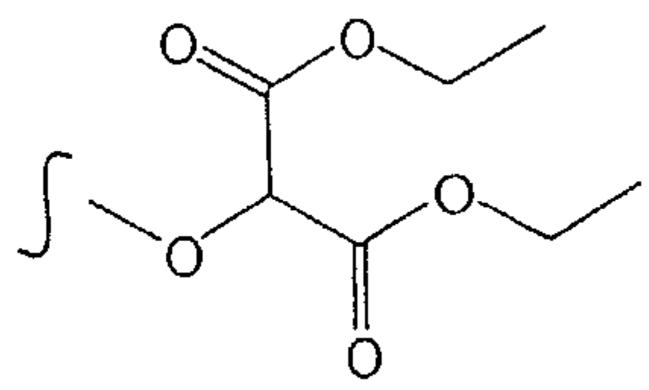
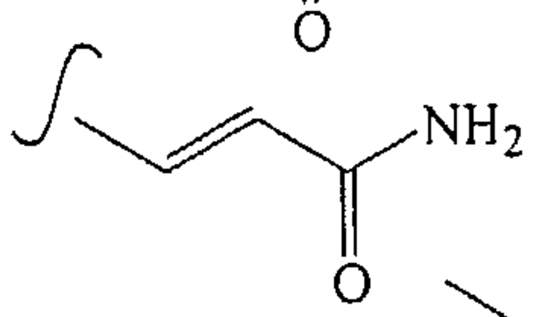
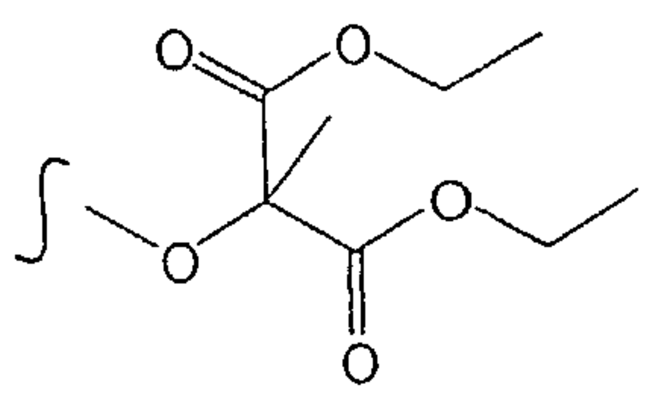
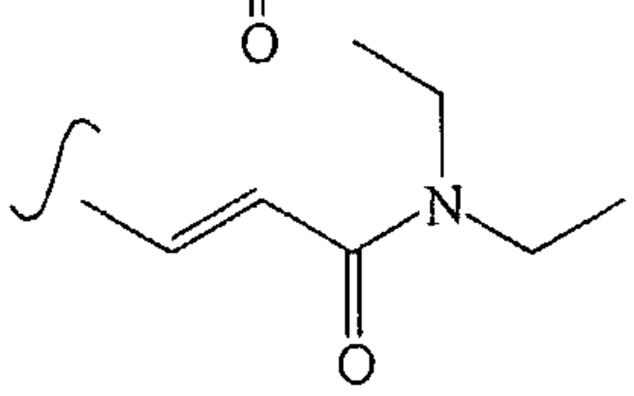
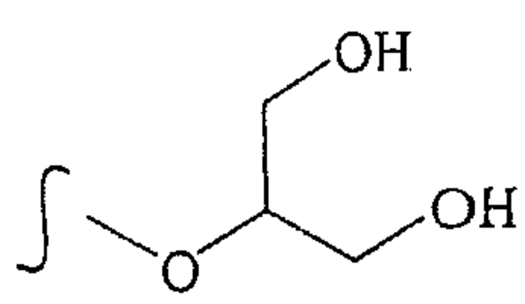
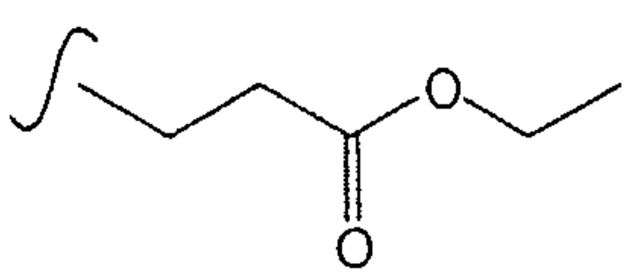
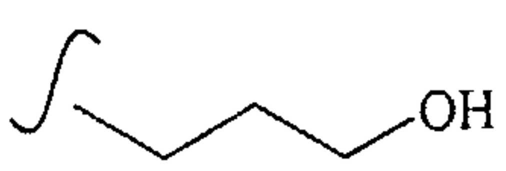
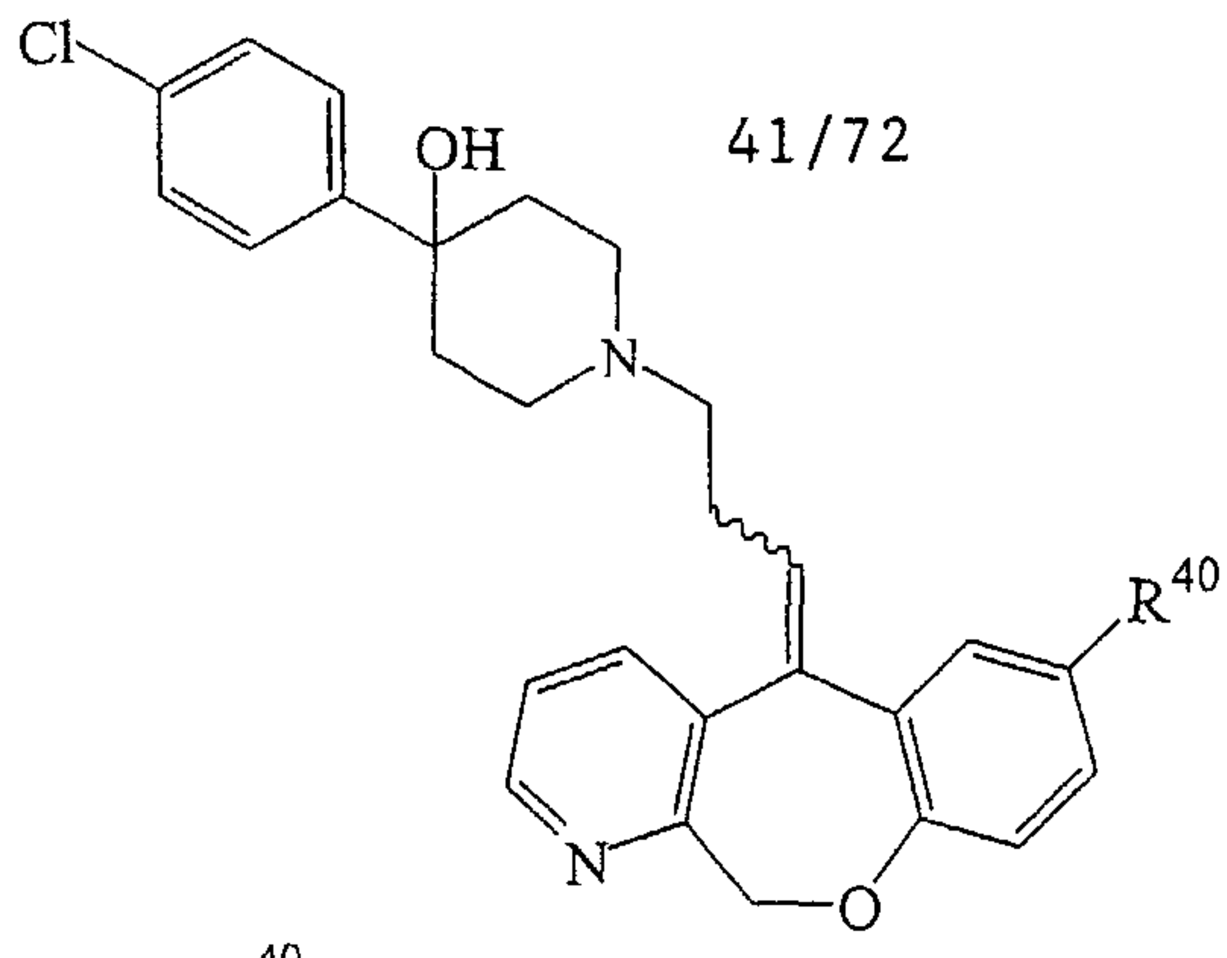
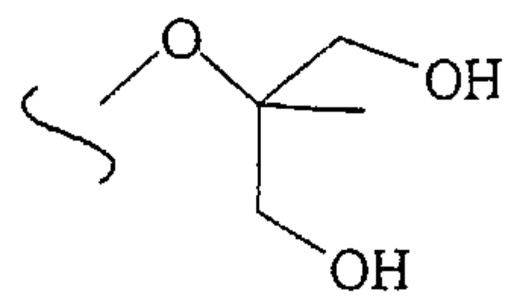
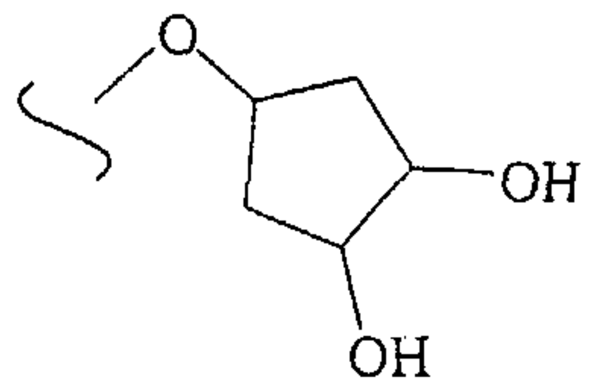
R40		R40	
Example 281		Example 290	
Example 282		Example 291	
Example 283		Example 292	
Example 284		Example 293	
Example 285		Example 294	
Example 286		Example 295	
Example 287		Example 296	
Example 288			
Example 289			

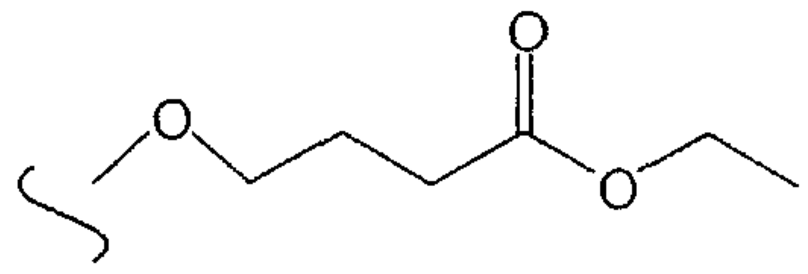
Figure 11D

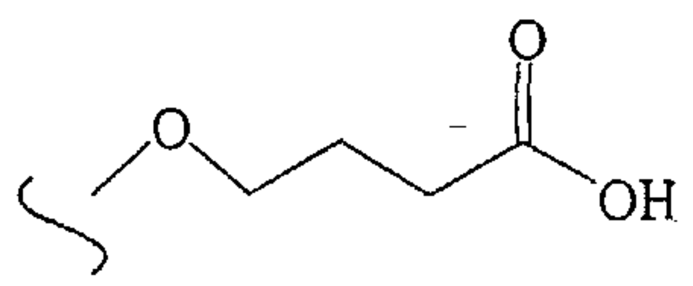


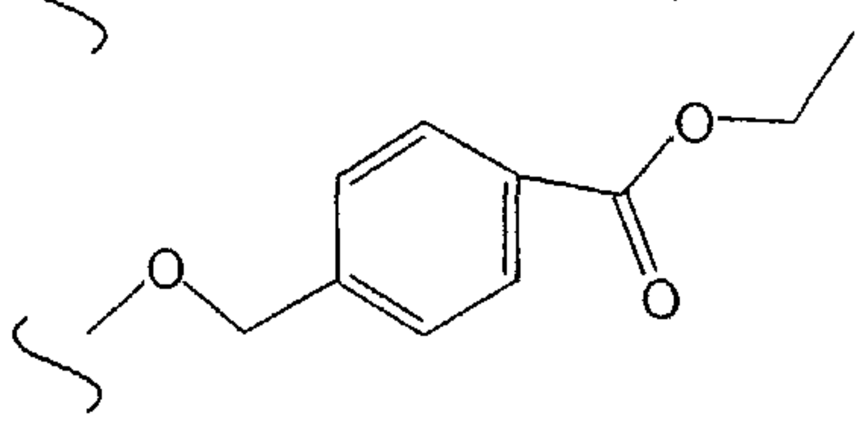
R40

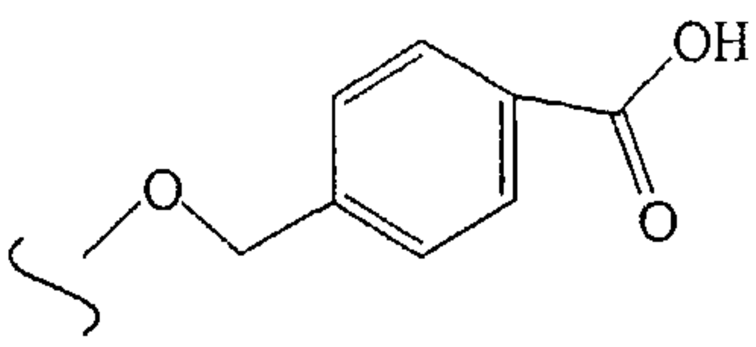
Example 297 

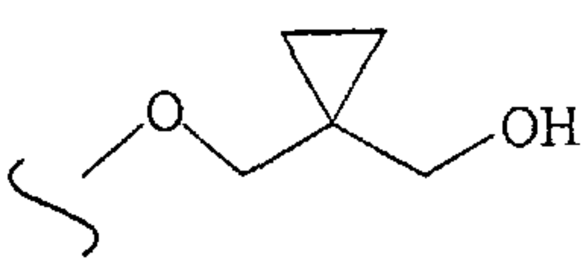
Example 298 

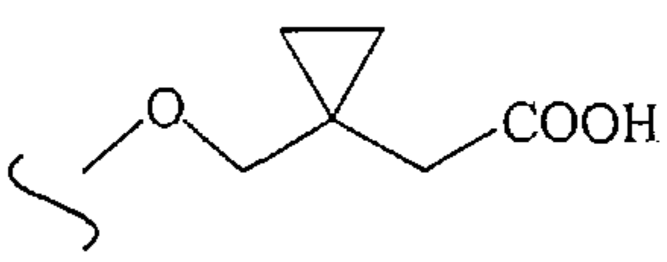
Example 299 

Example 300 

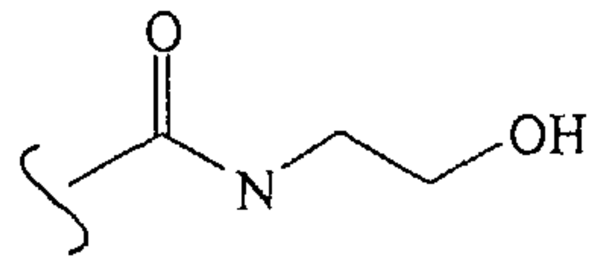
Example 301 

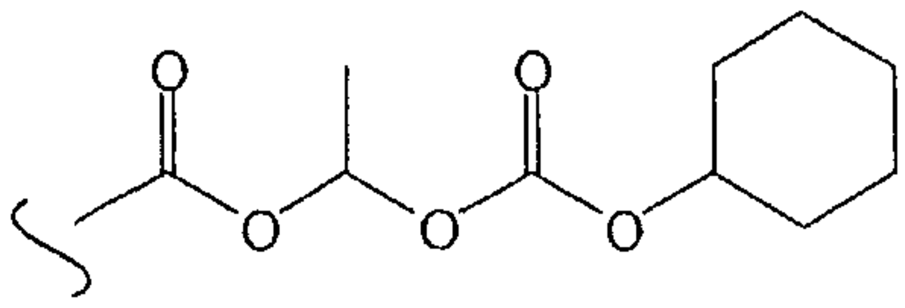
Example 302 

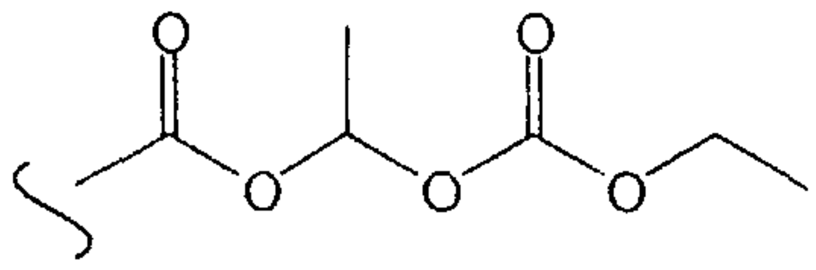
Example 303 

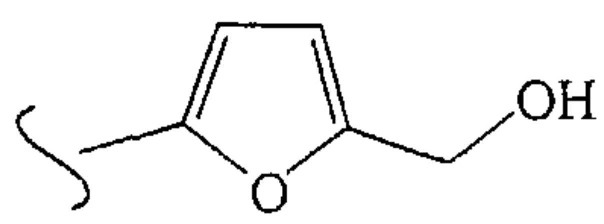
Example 304 

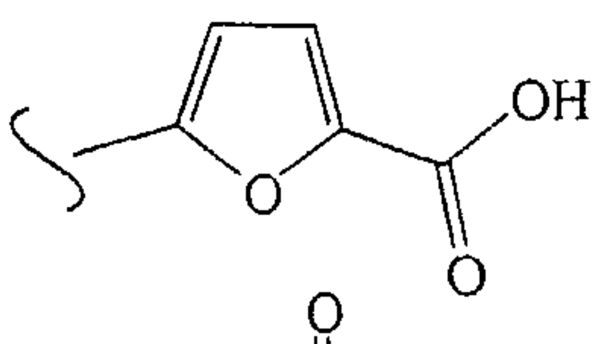
R40

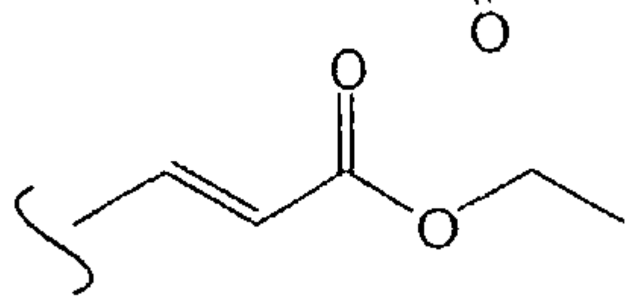
Example 305 

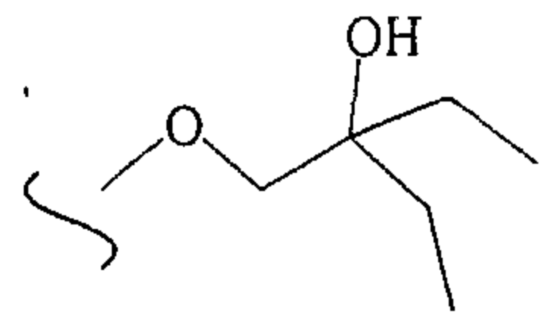
Example 306 

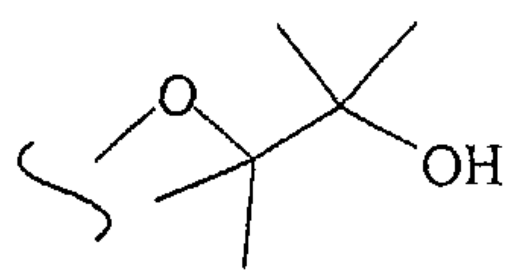
Example 307 

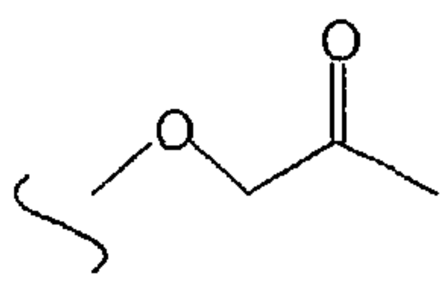
Example 308 

Example 309 

Example 310 

Example 311 

Example 312 

Example 313 

Example 314 -CHO

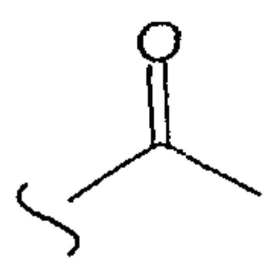
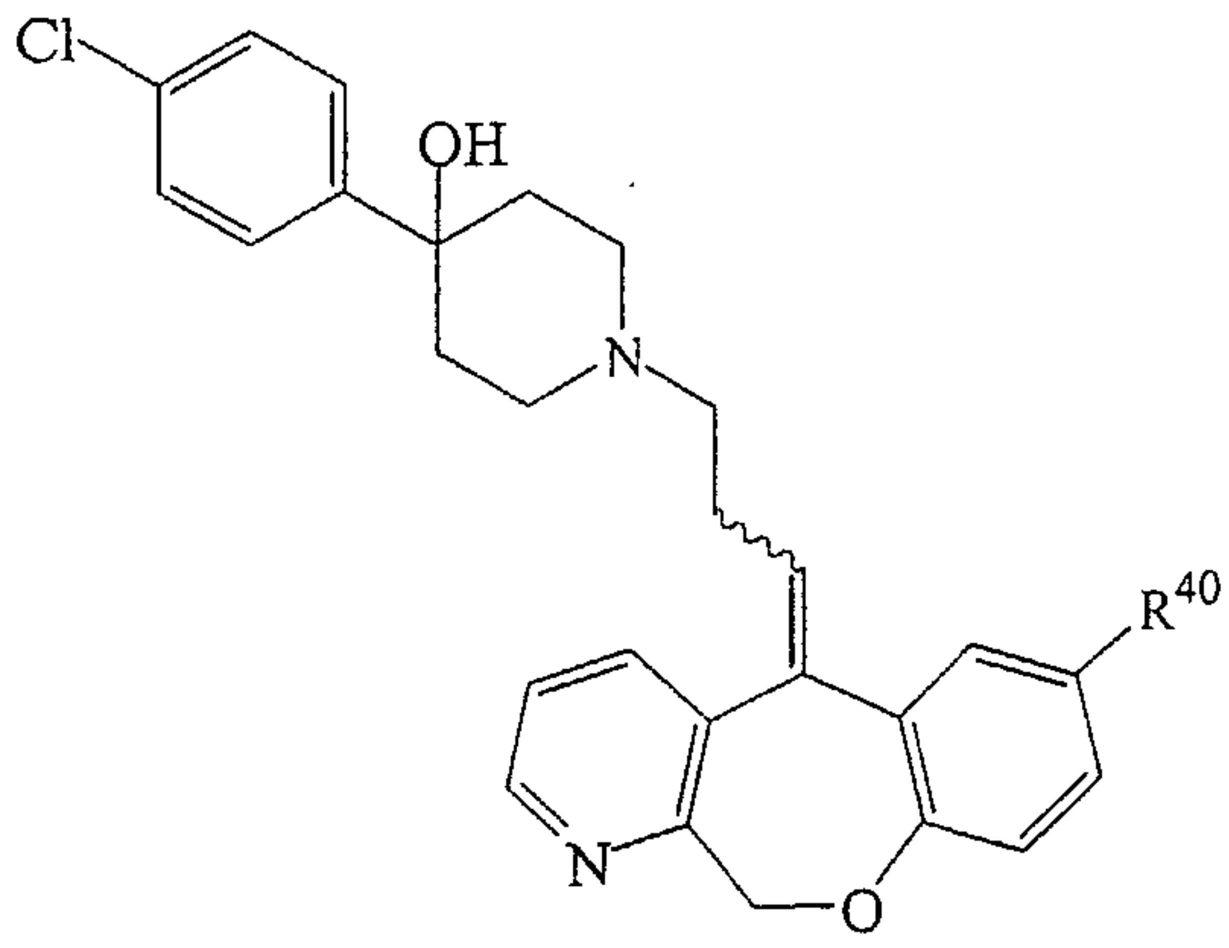
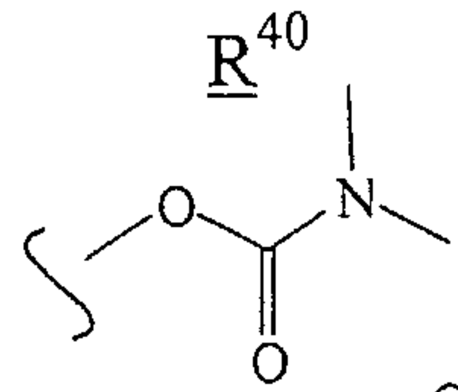
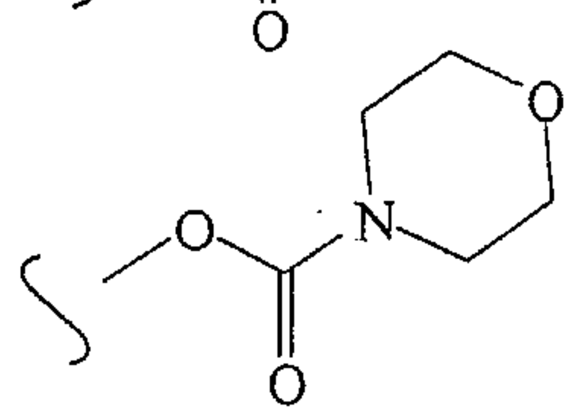
Example 315 

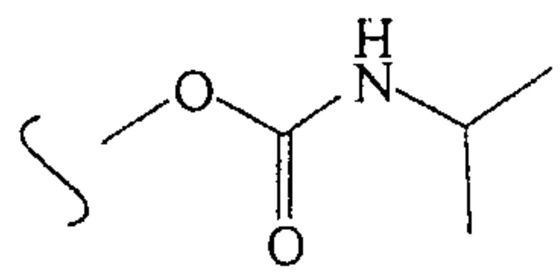
Figure 11E

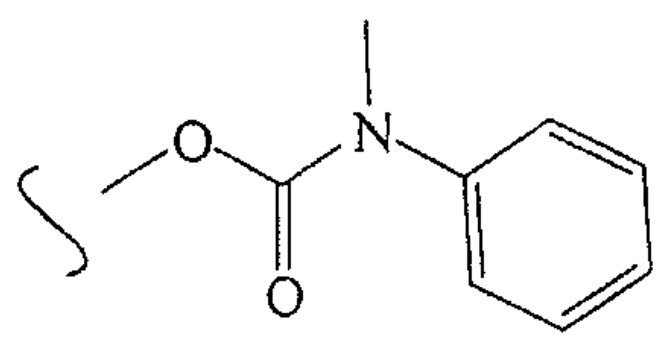


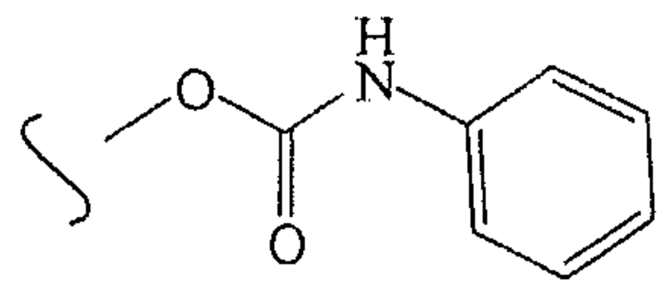
$\underline{R}^{40}$

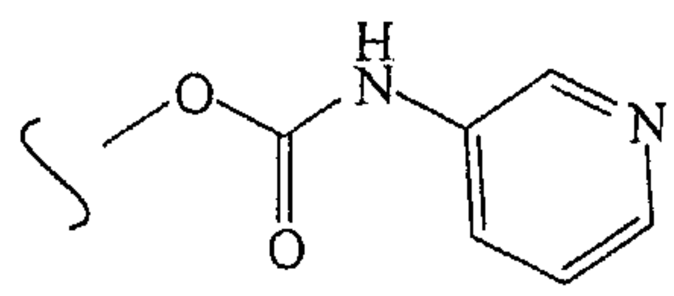
Example 316 

Example 317 

Example 318 

Example 319 

Example 320 

Example 321 

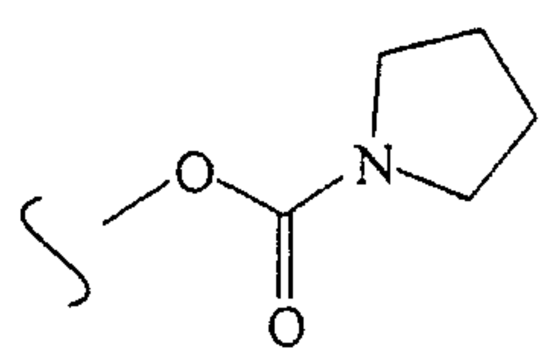
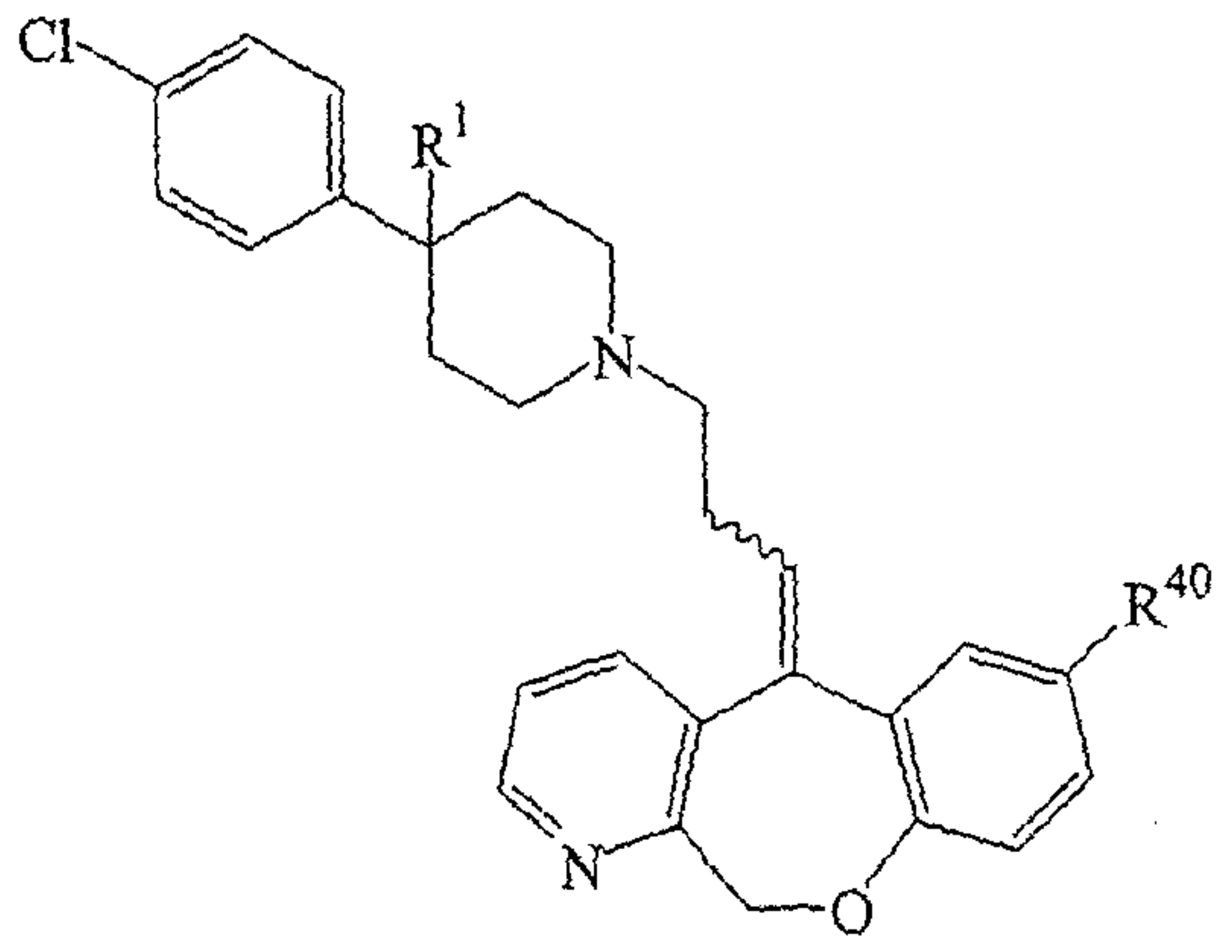
Example 322 

Figure 11F



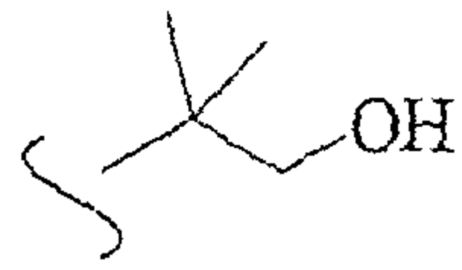
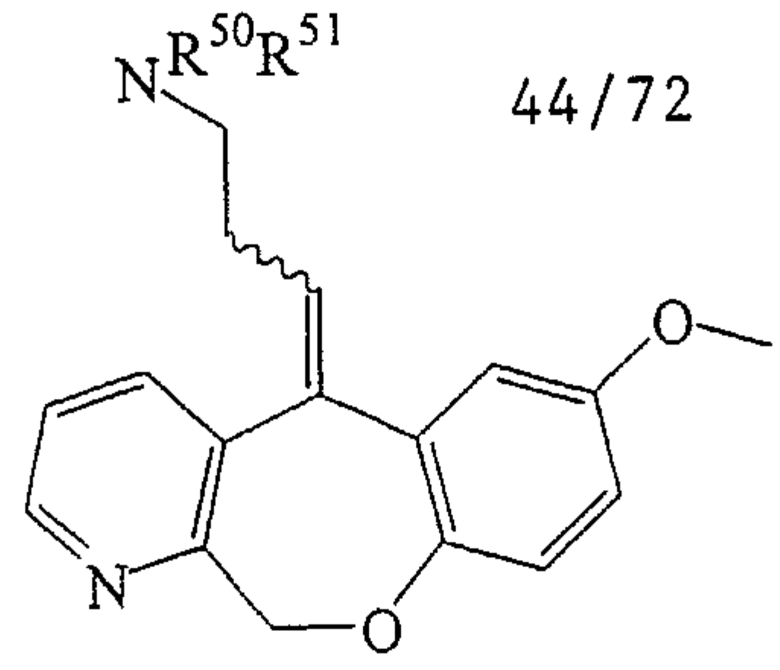
	$\underline{R}^1$	$\underline{R}^{40}$
Example 323	-CN	$-OCH_3$
Example 324	$-CH_2NH_2$	$-OCH_3$
Example 325	$-NH_2$	$-OCH_3$
Example 326	$-CH_3$	$-OCH_3$
Example 327	$-OCH_3$	$-OCH_3$
Example 328	-F	-OH
Example 329	$-CH_3$	-OH
Example 330	$-CH_3$	

Figure 11G



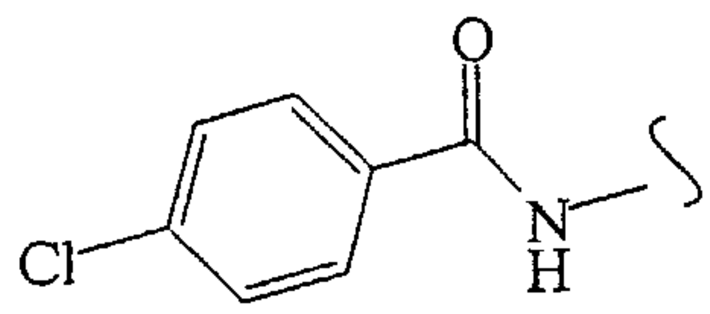
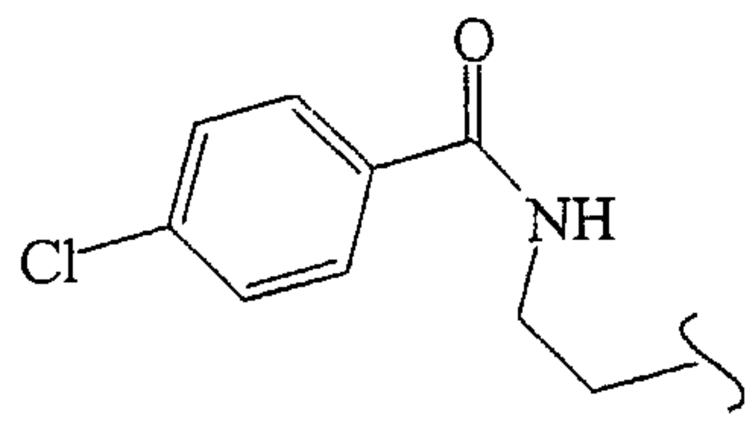
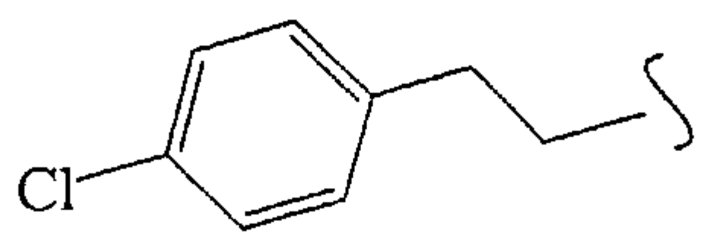
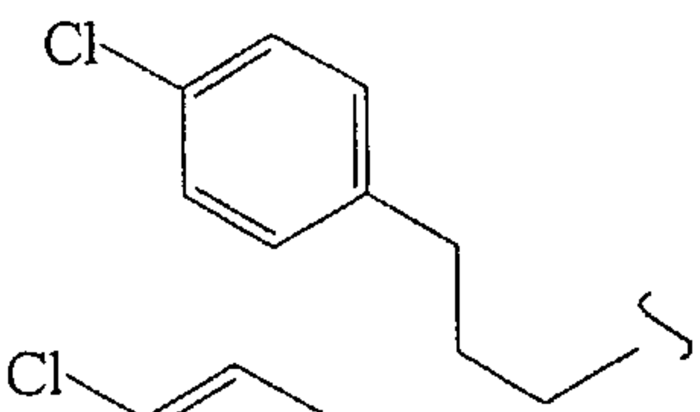
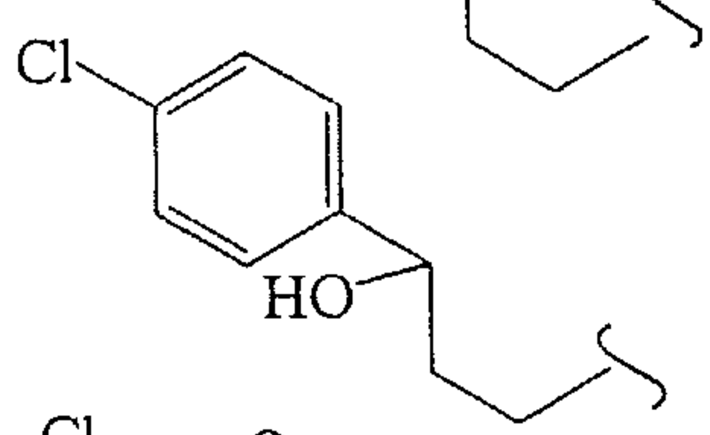
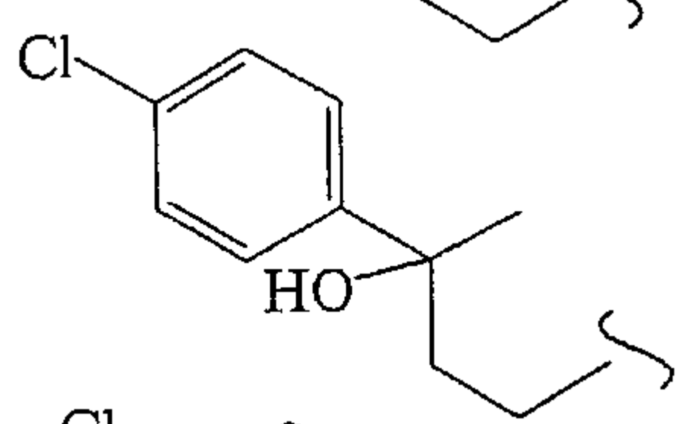
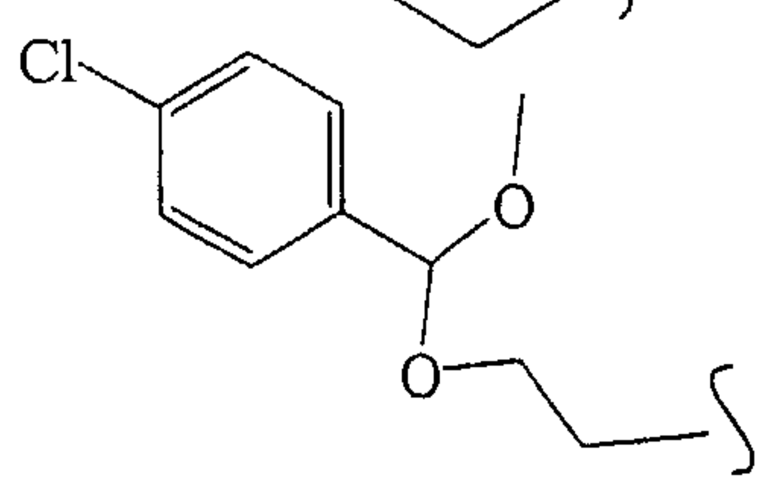
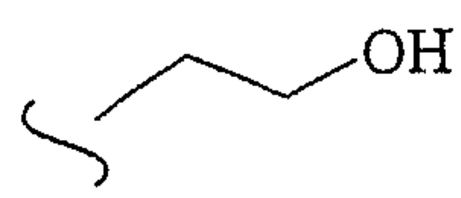
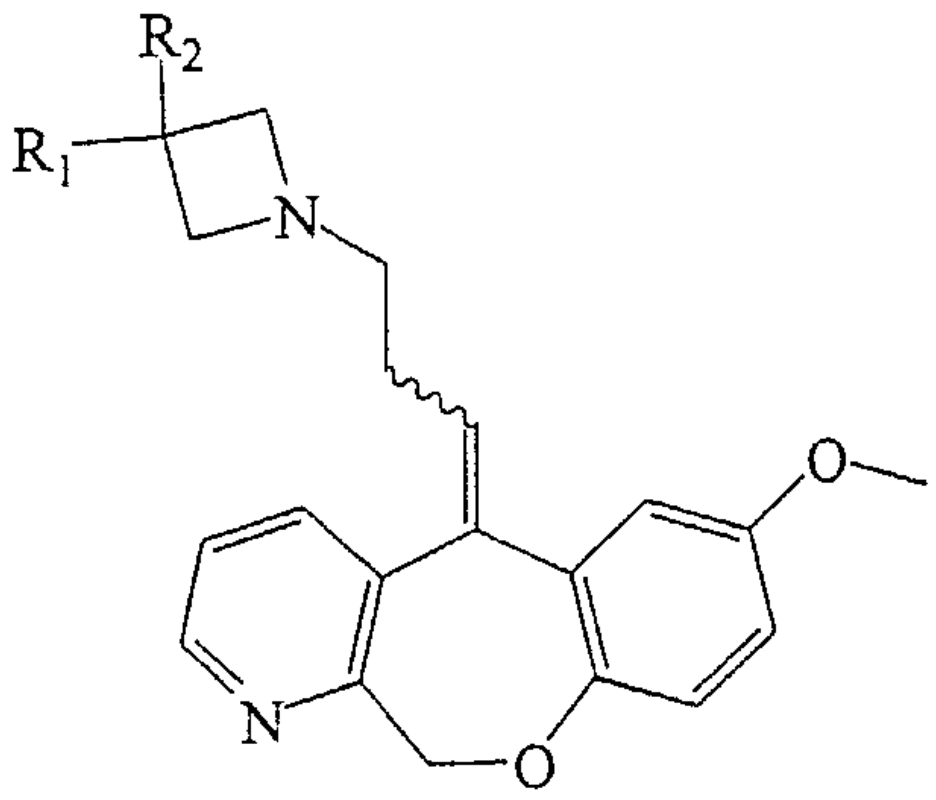
	$\underline{R}^{50}$	$\underline{R}^{51}$
Example 331		-H
Example 332		-H
Example 333		$-CH_3$
Example 334		$-CH_3$
Example 335		$-CH_3$
Example 336		$-CH_3$
Example 337		

Figure 11H



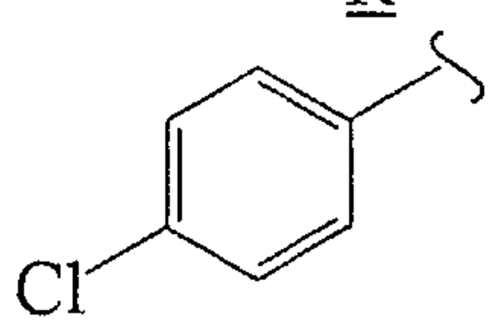
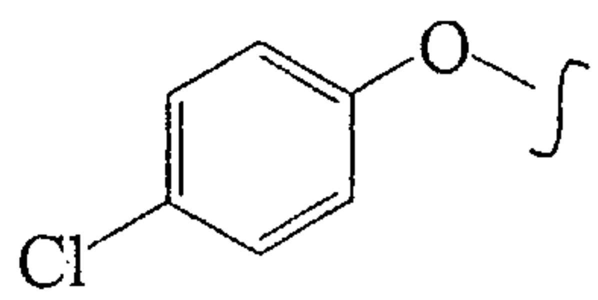
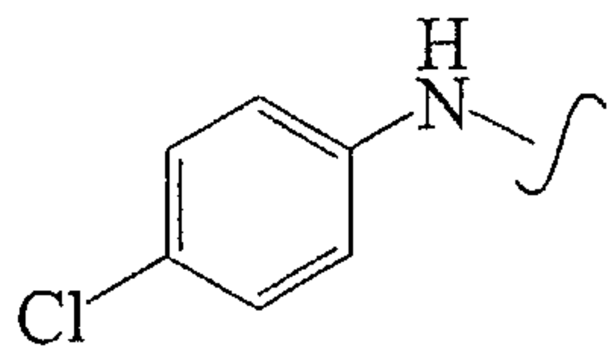
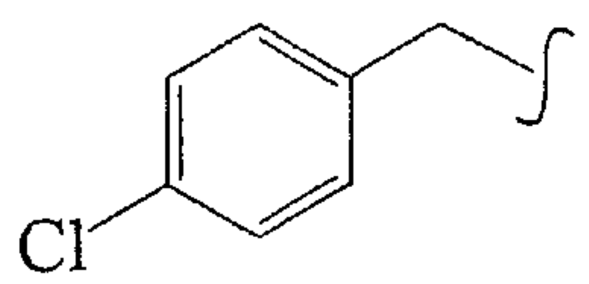
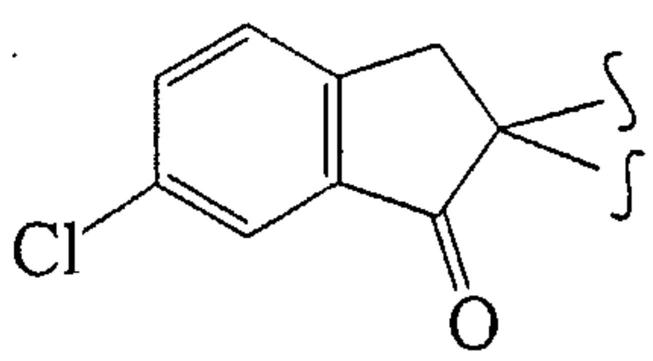
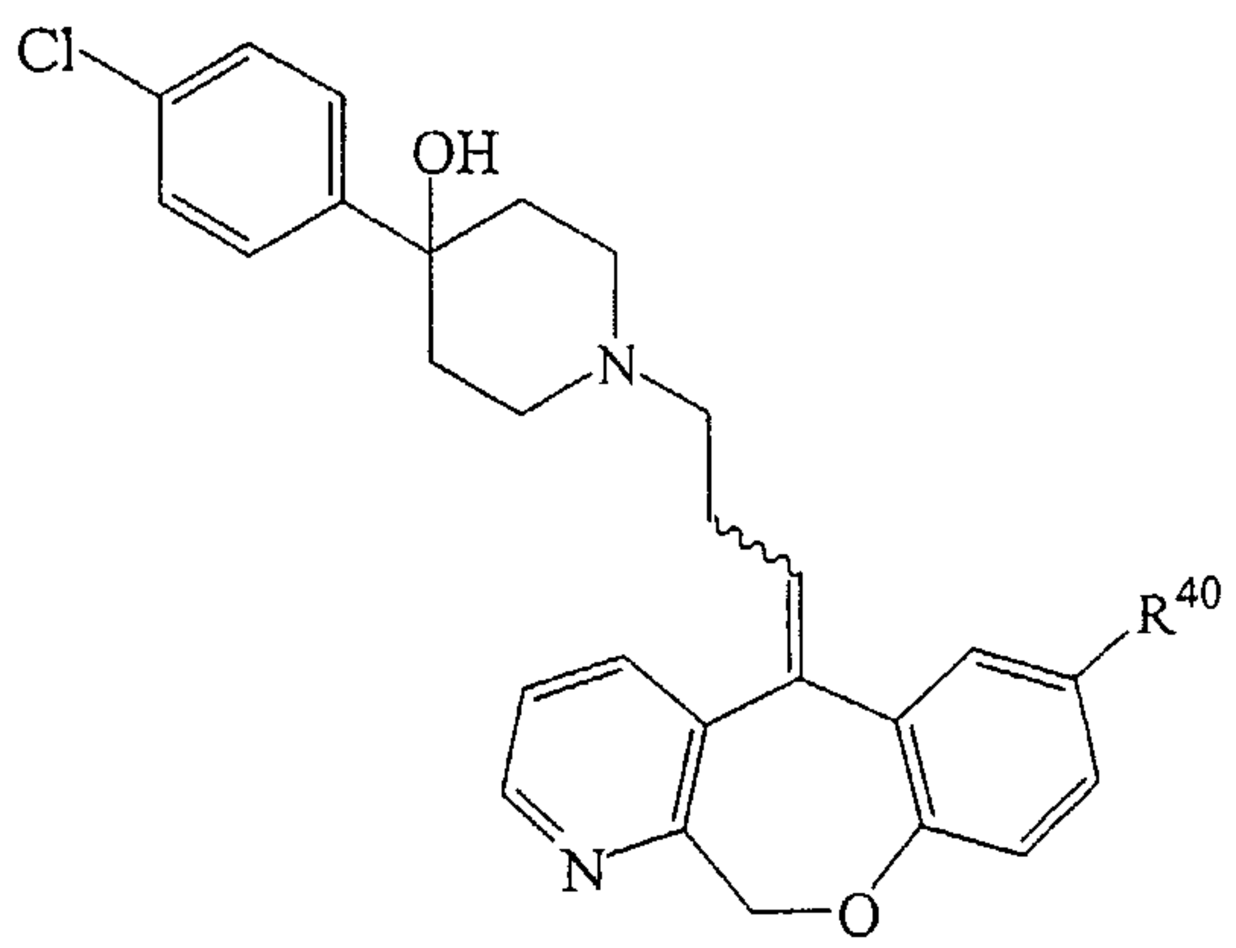
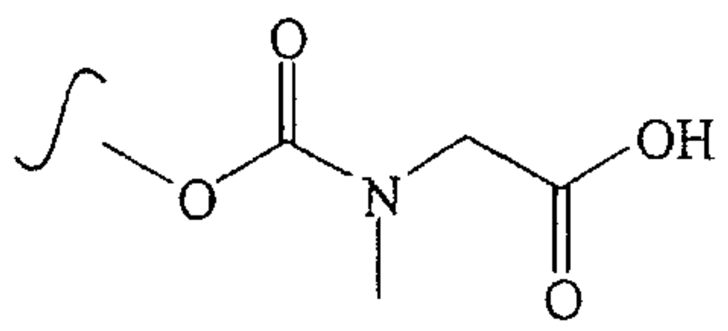
	R^1	R^2
Example 338	-OH	
Example 339	-H	
Example 340	-H	
Example 341	-OH	
Example 342		

Figure 11I



<u>R</u>^{40}

Example 343 

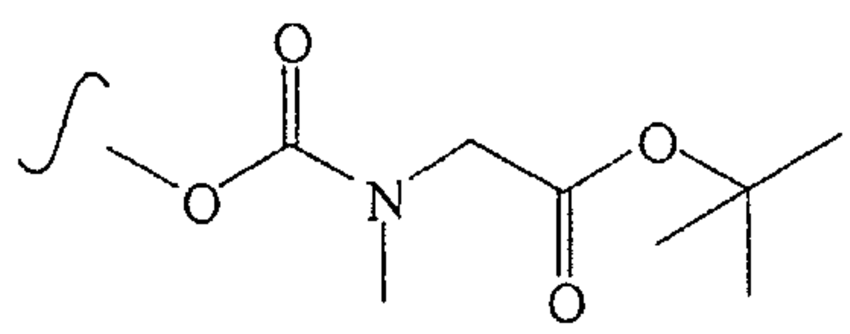
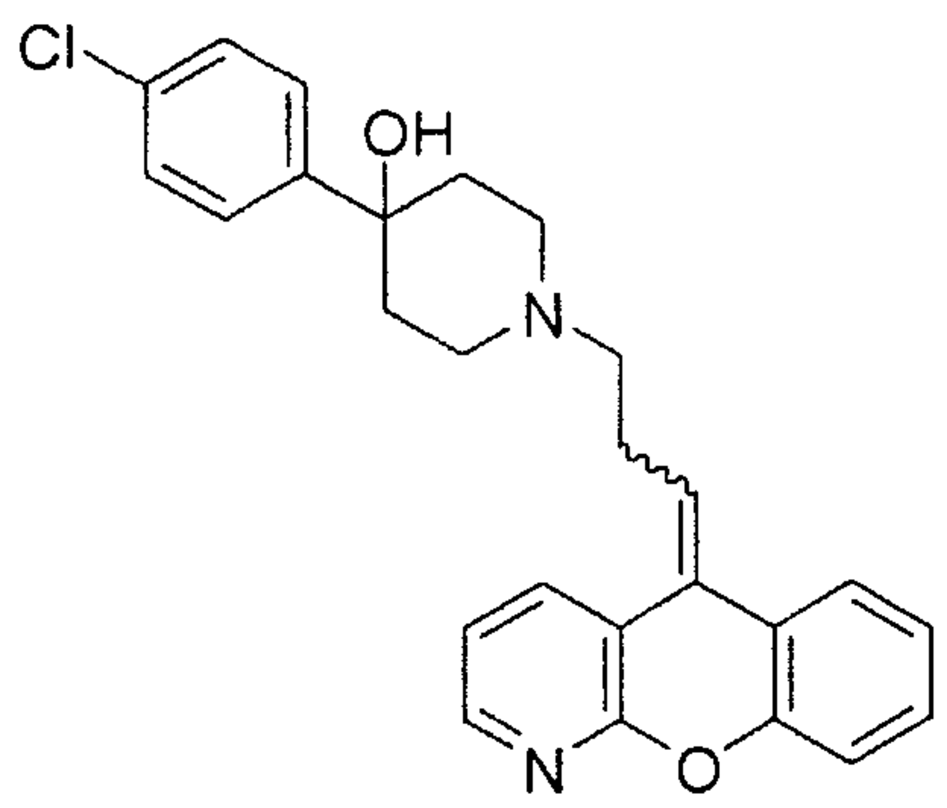
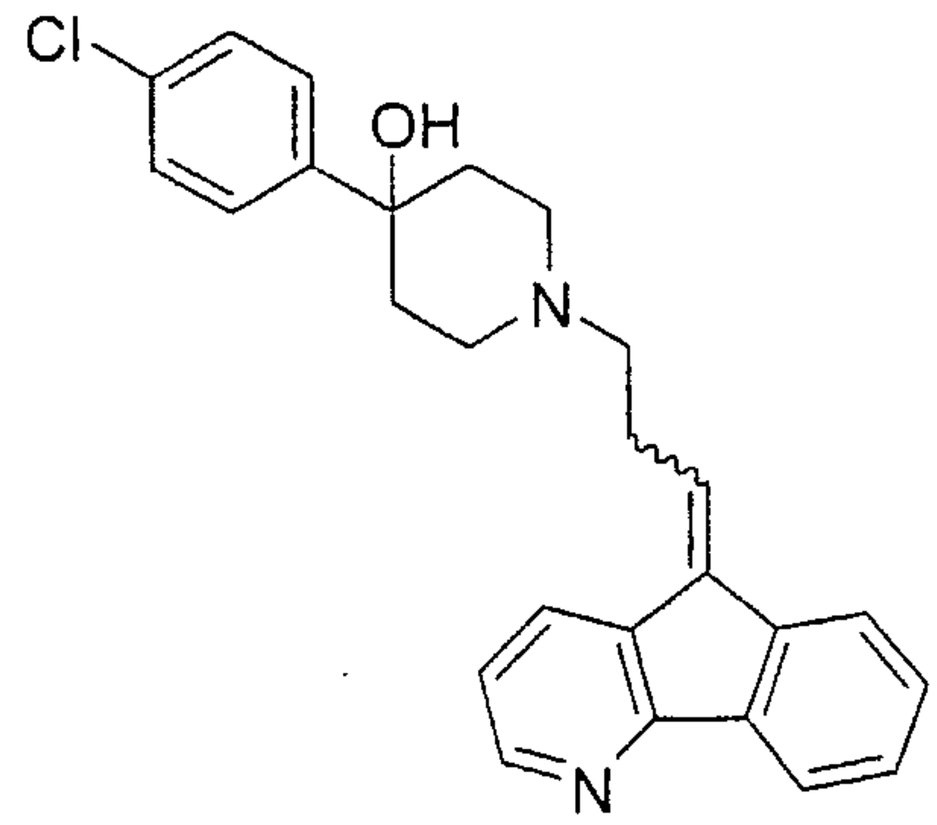
Example 344 

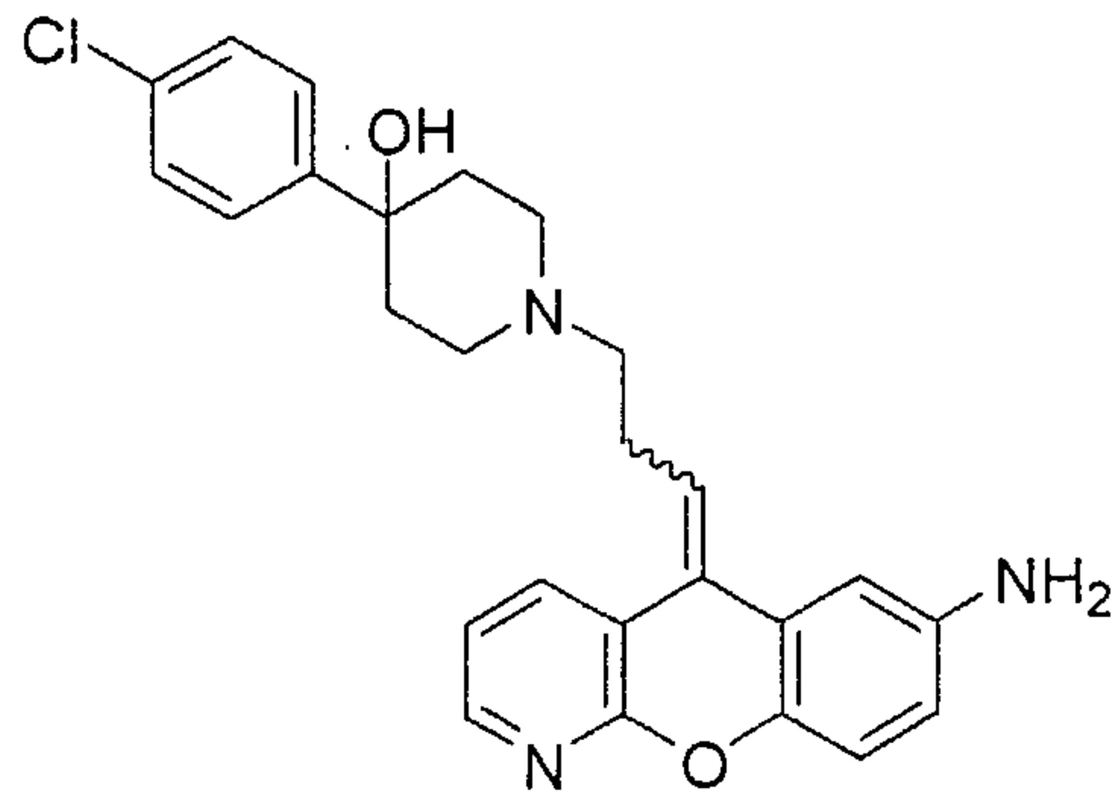
Figure 11J



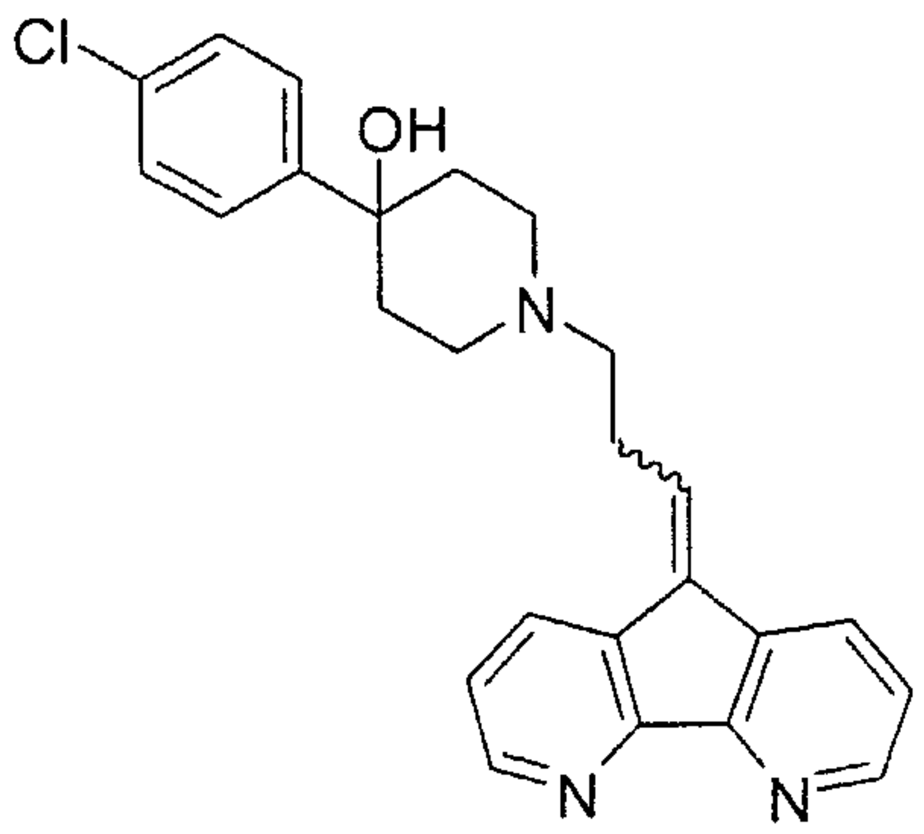
Example 345



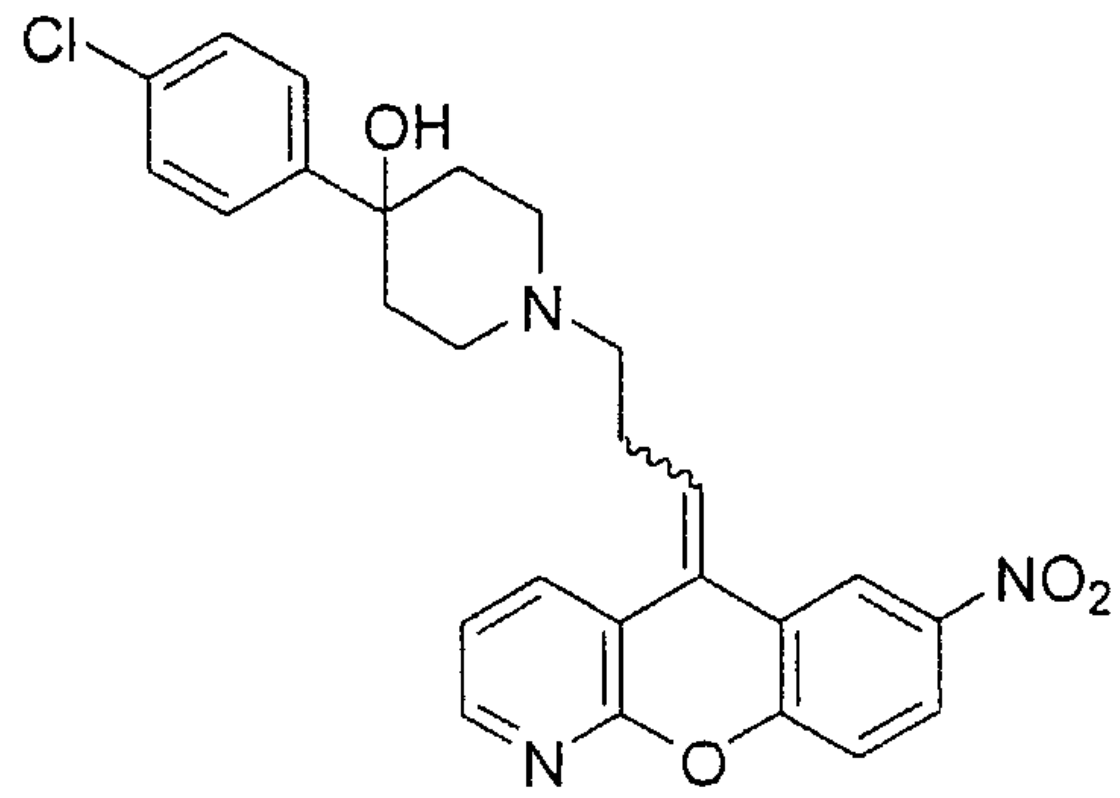
Example 346



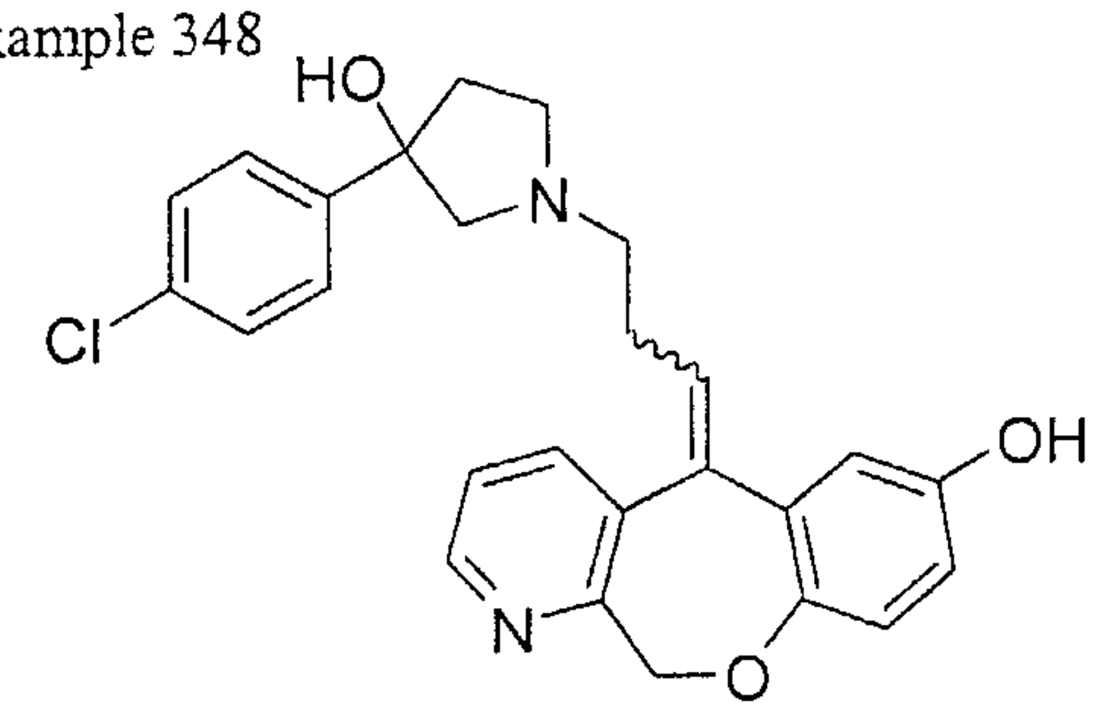
Example 347



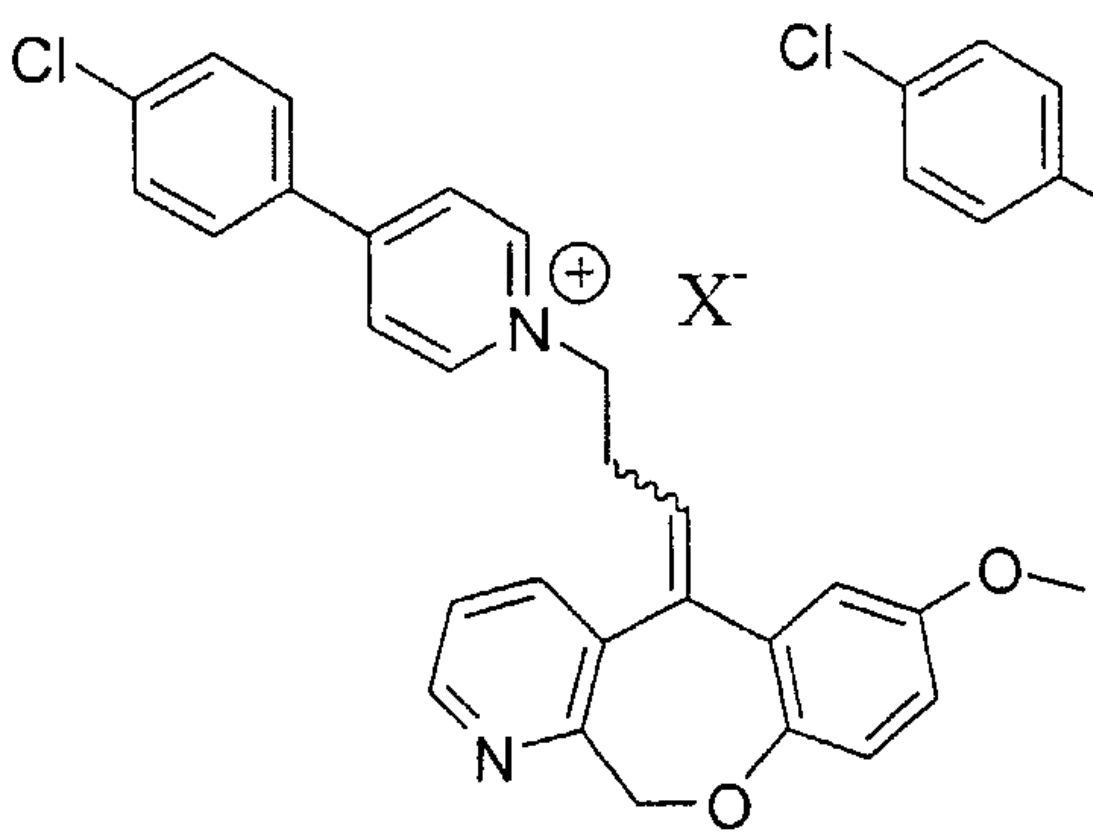
Example 348



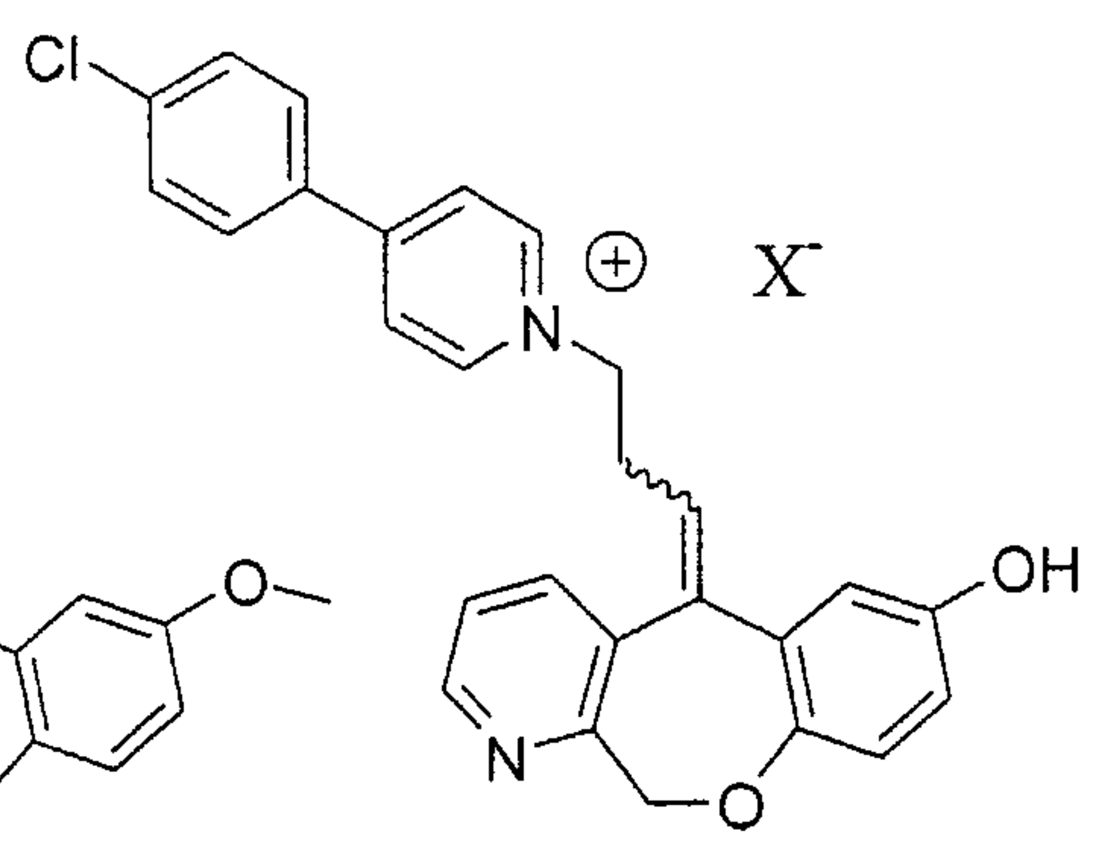
Example 349



Example 350

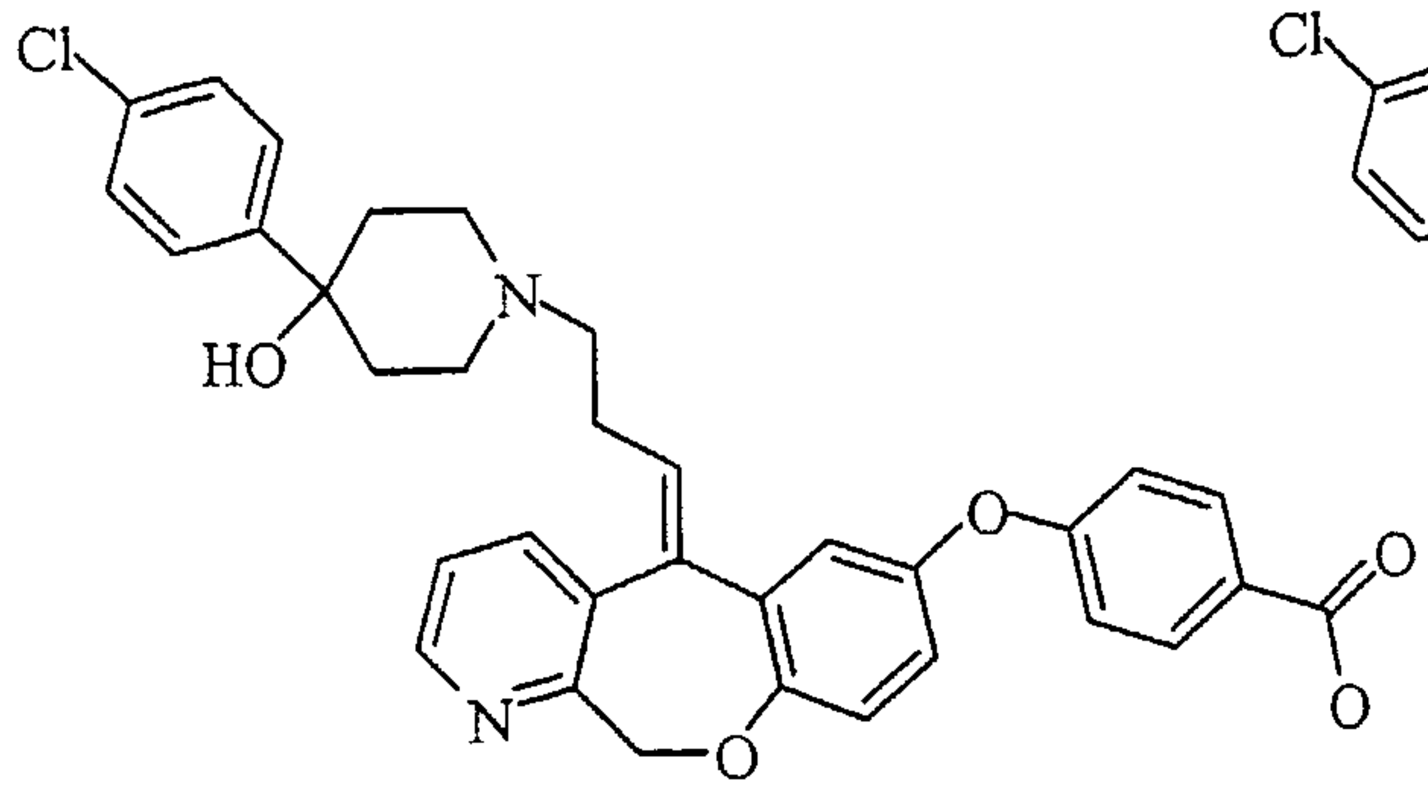


Example 351

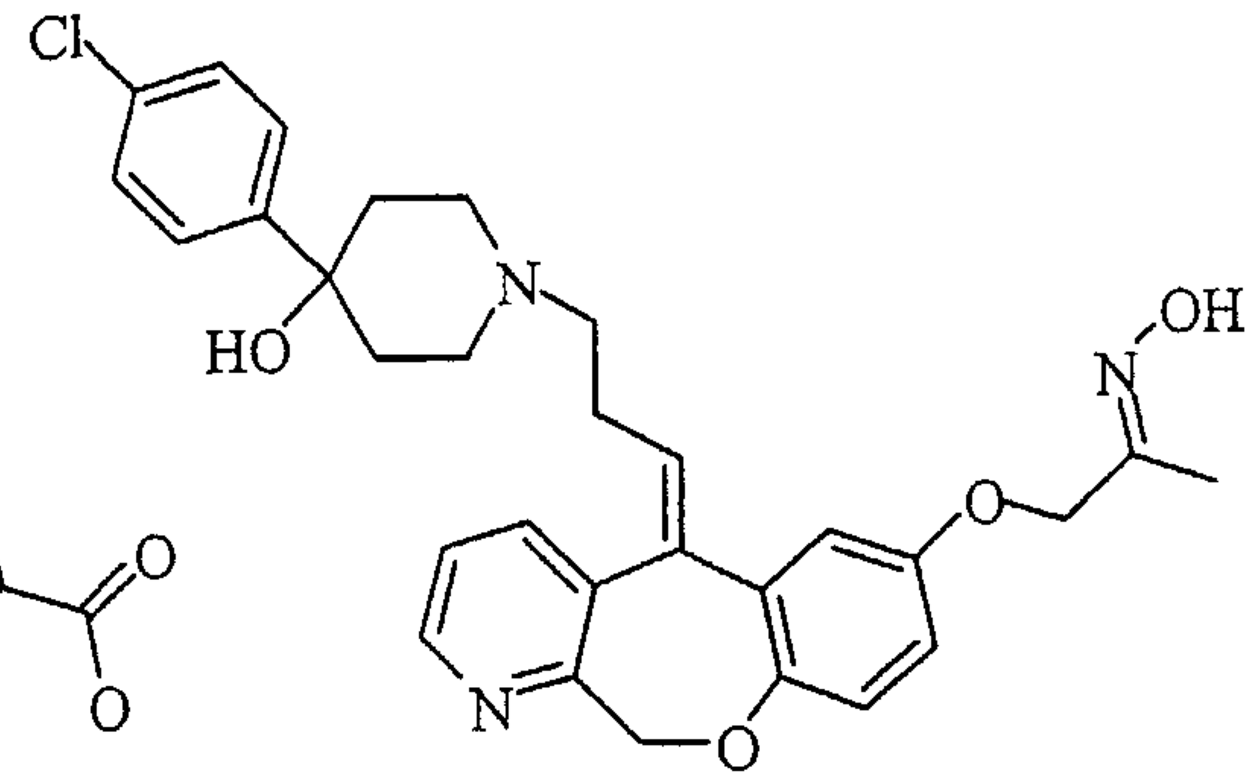


Example 352

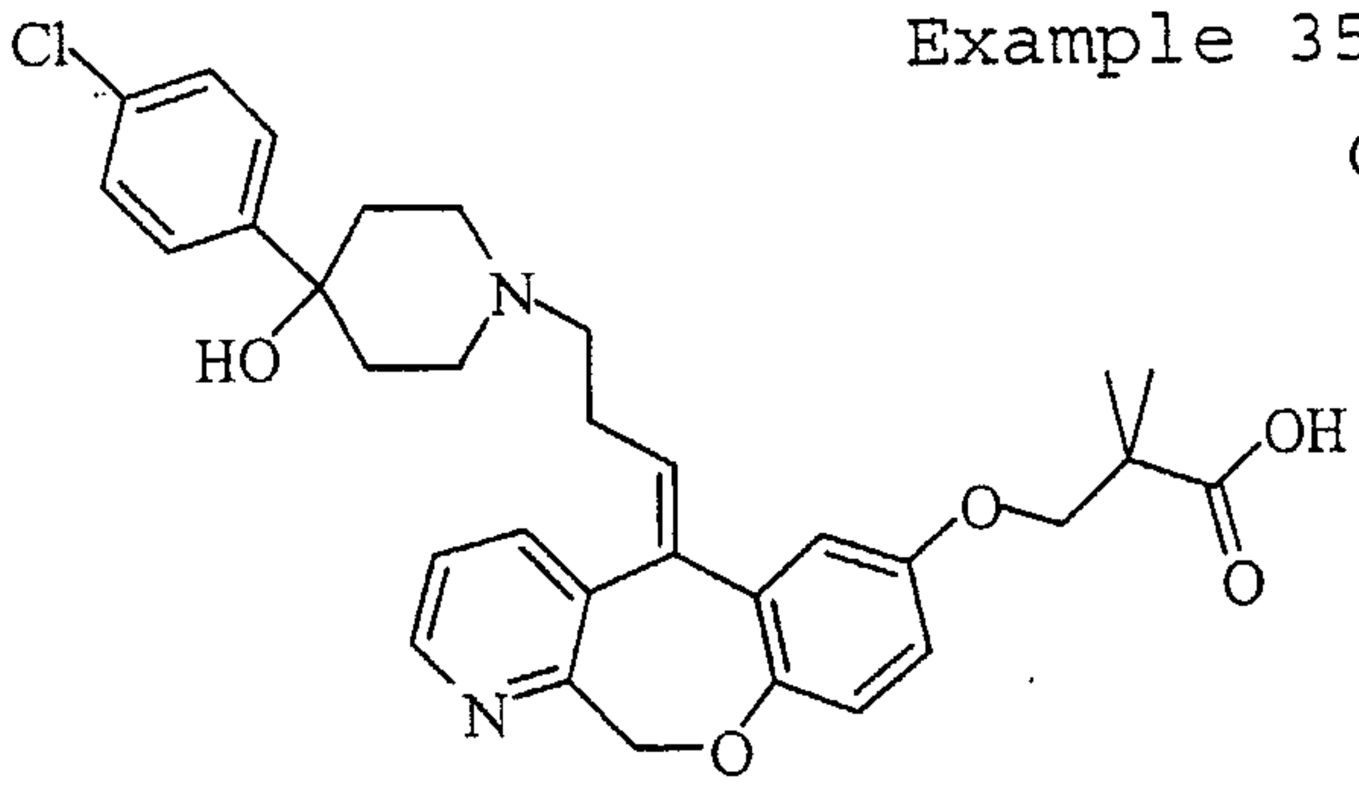
Figure 11K



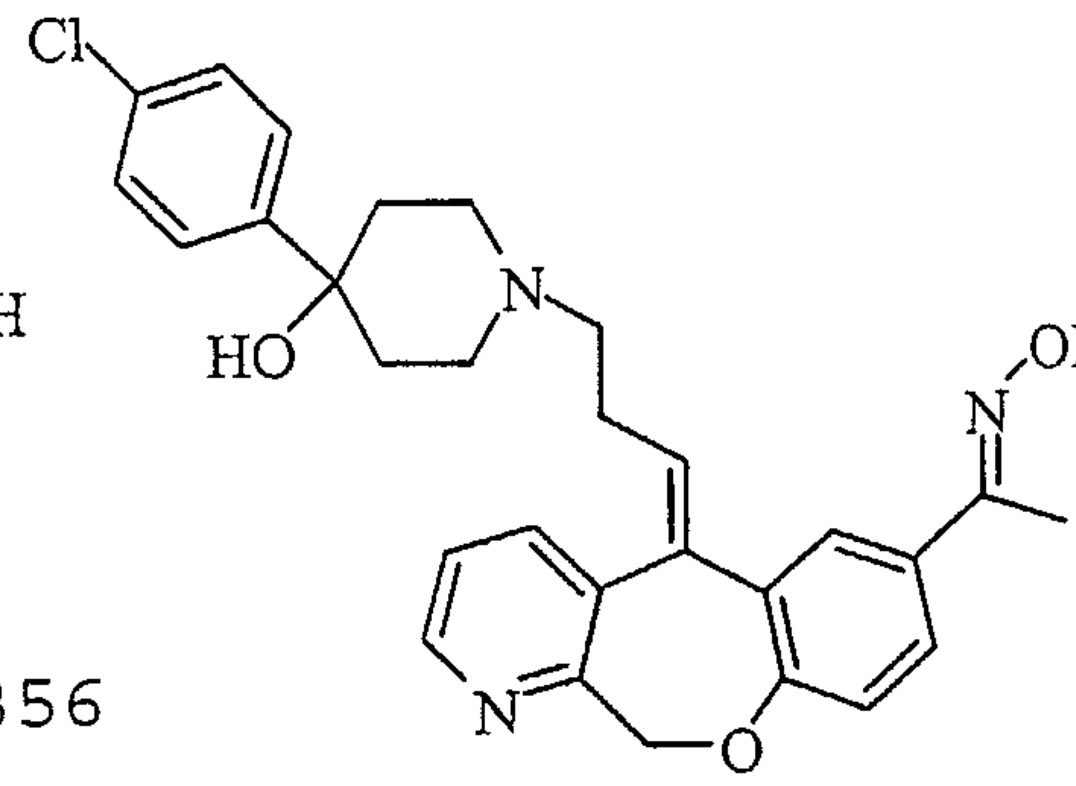
Example 354



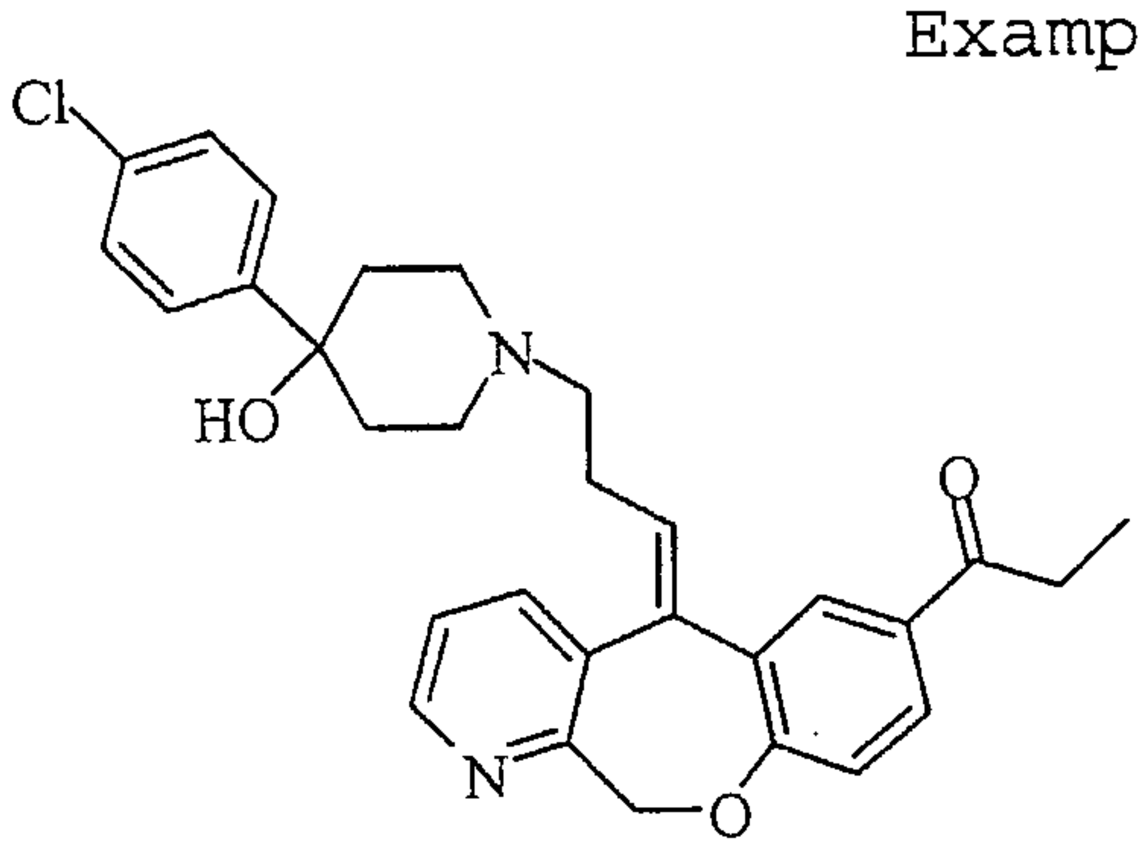
Example 355



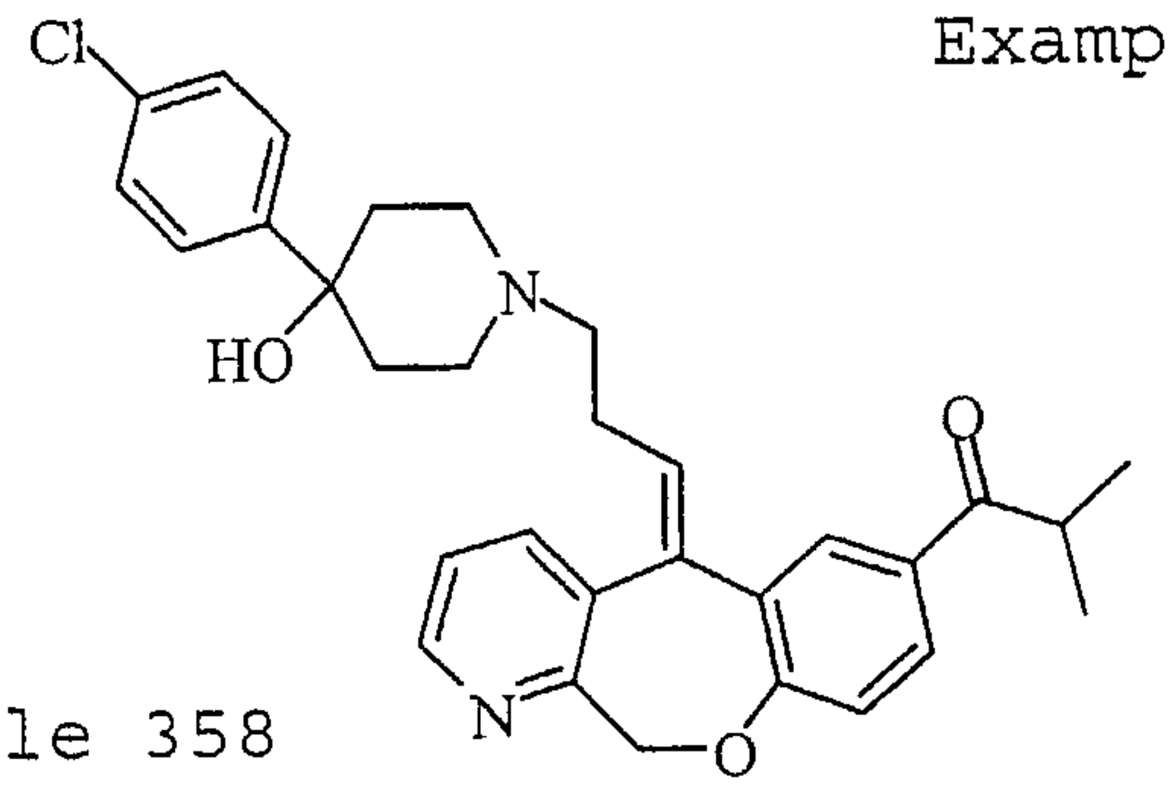
Example 356



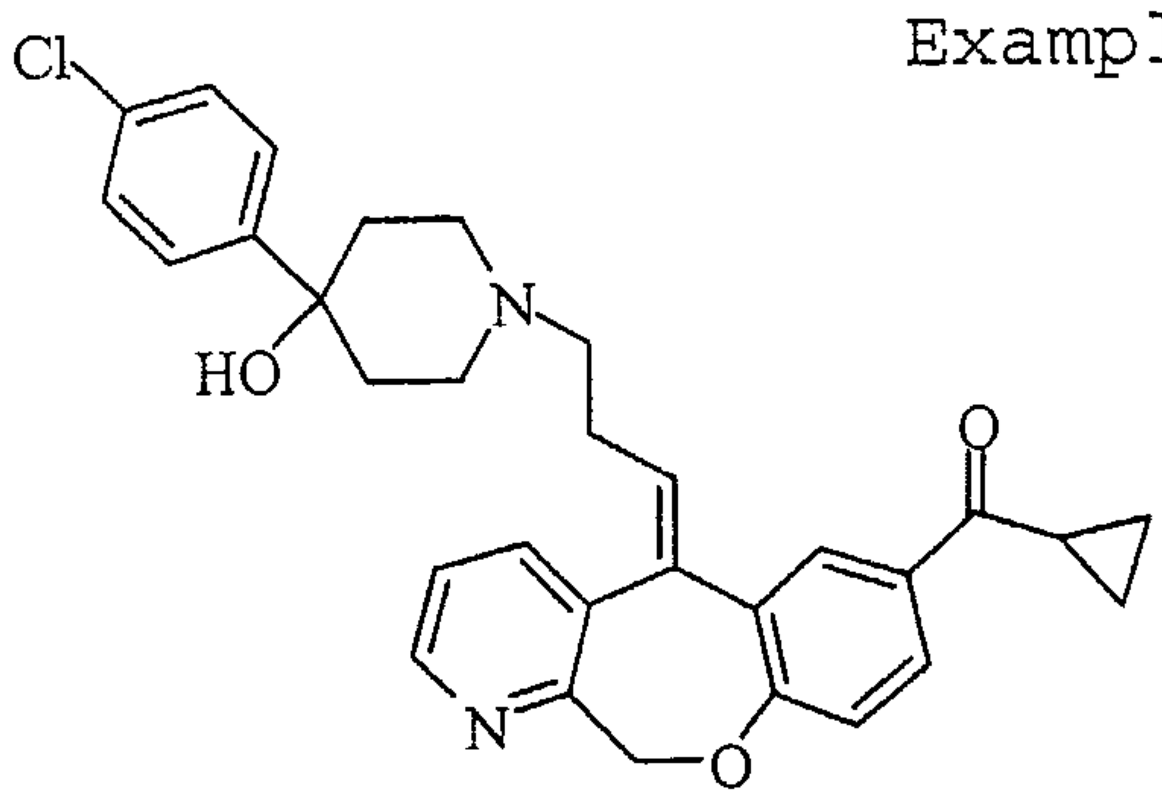
Example 357



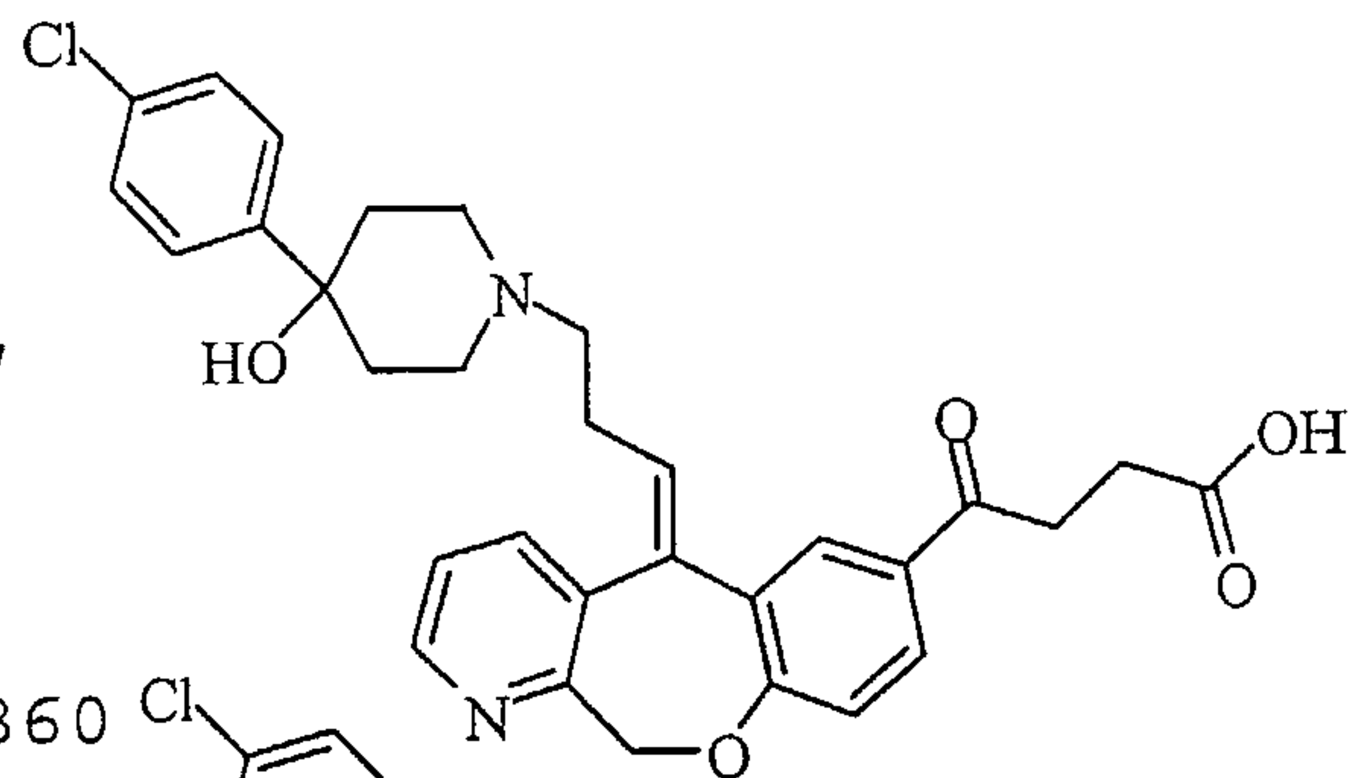
Example 358



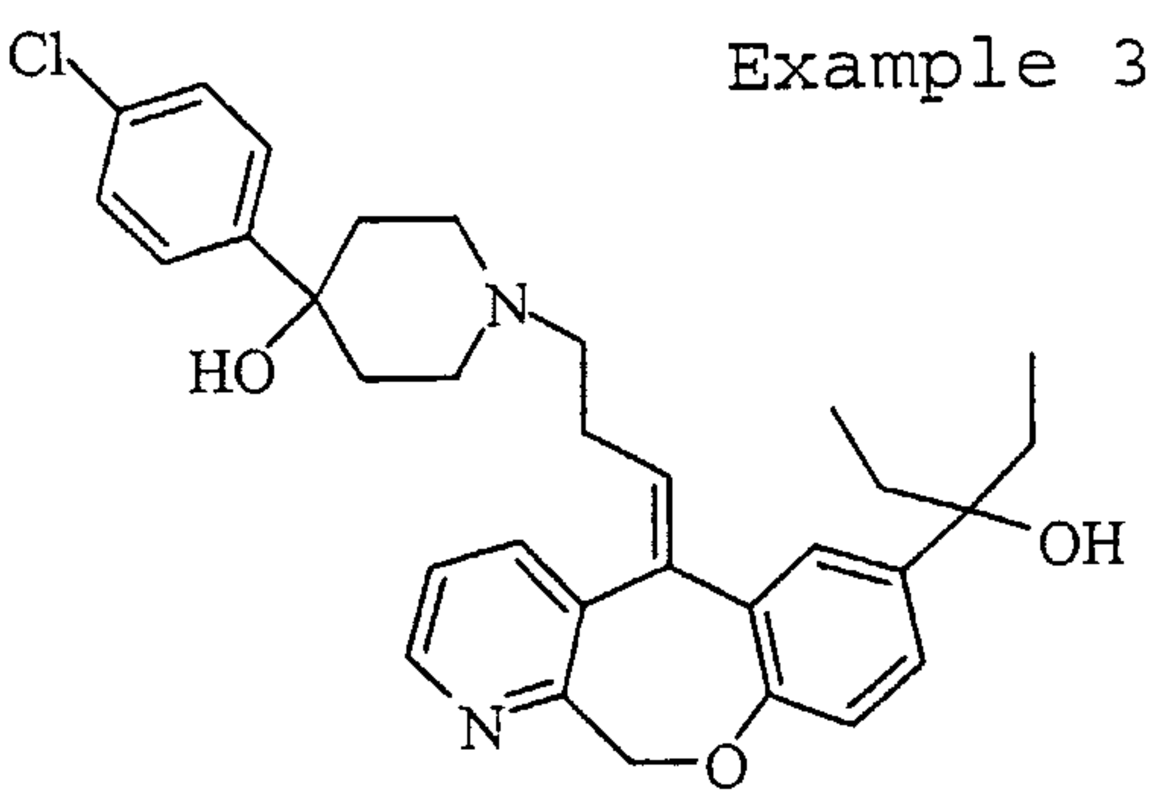
Example 359



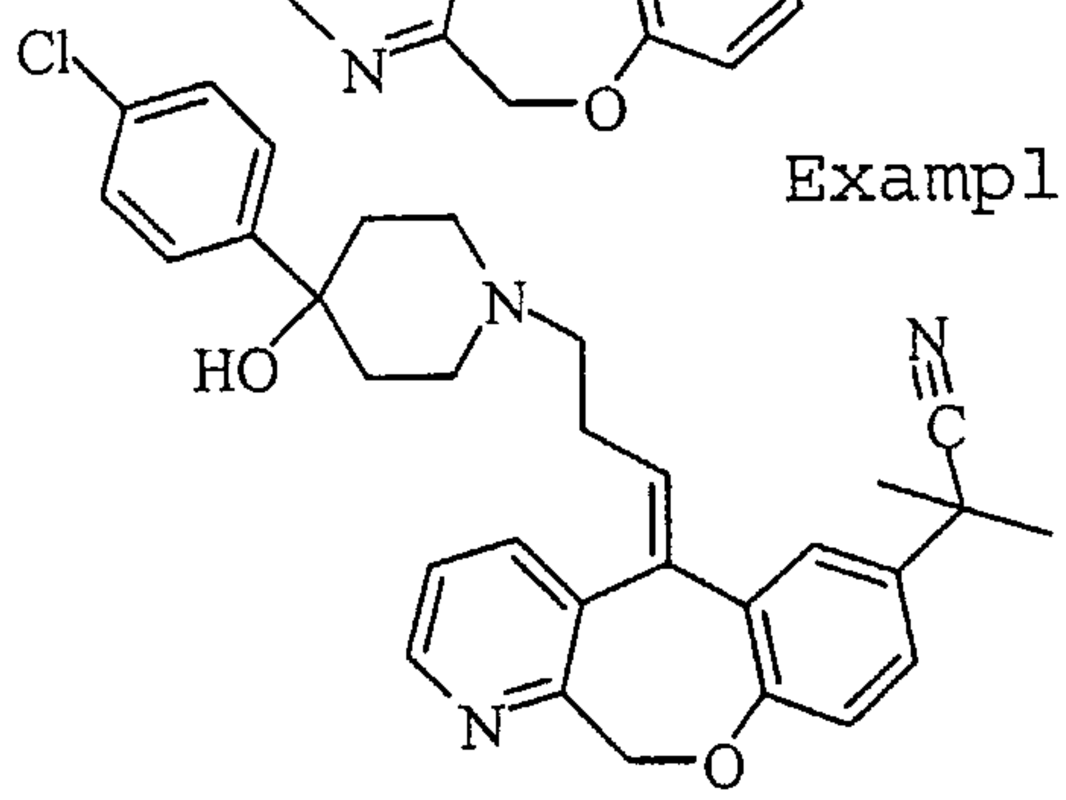
Example 360



Example 361

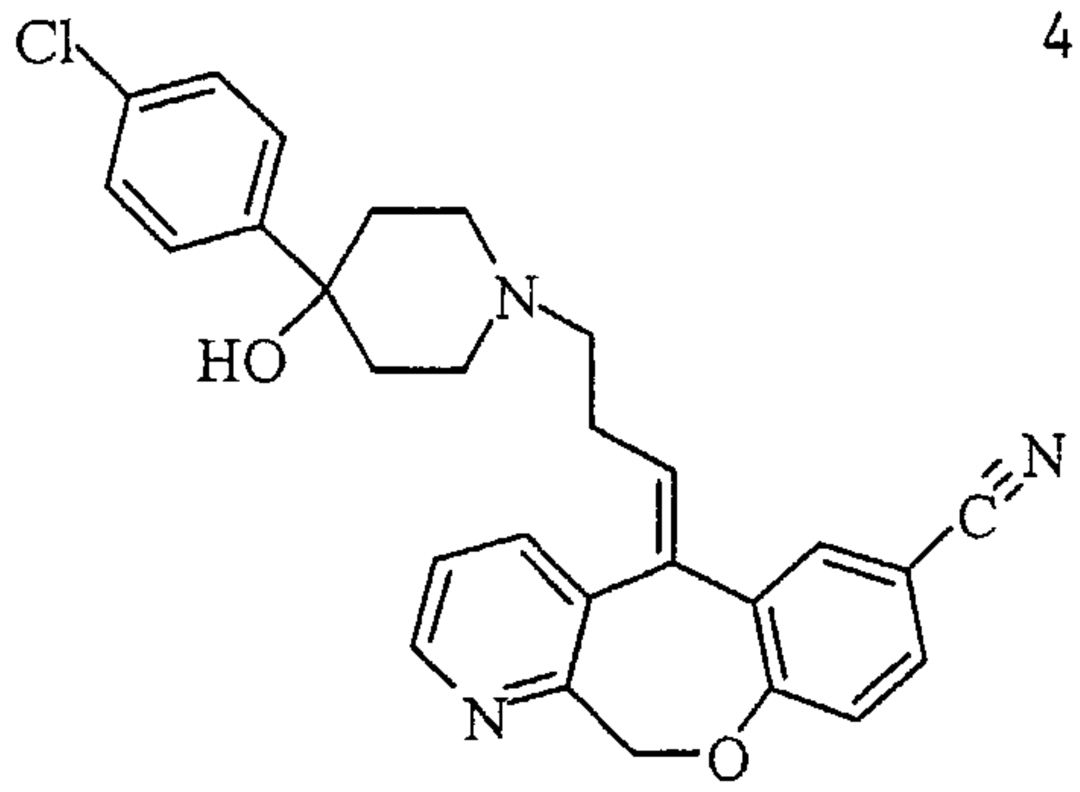


Example 362

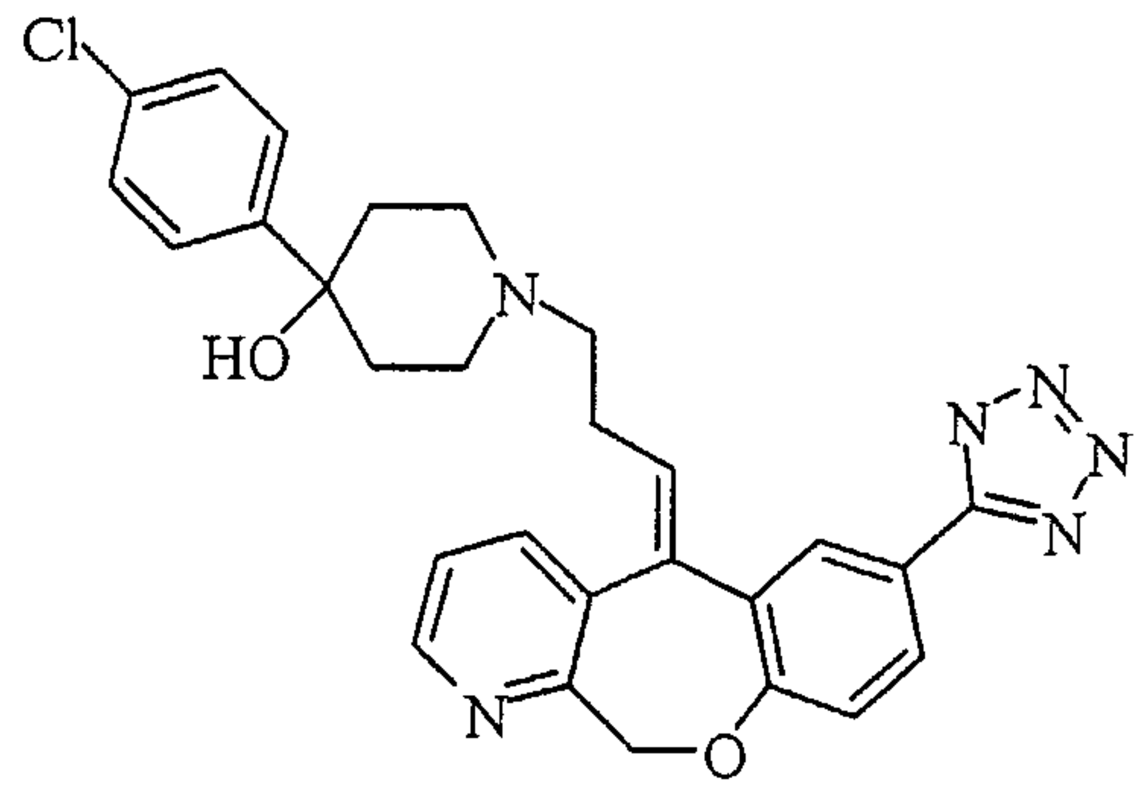


Example 363

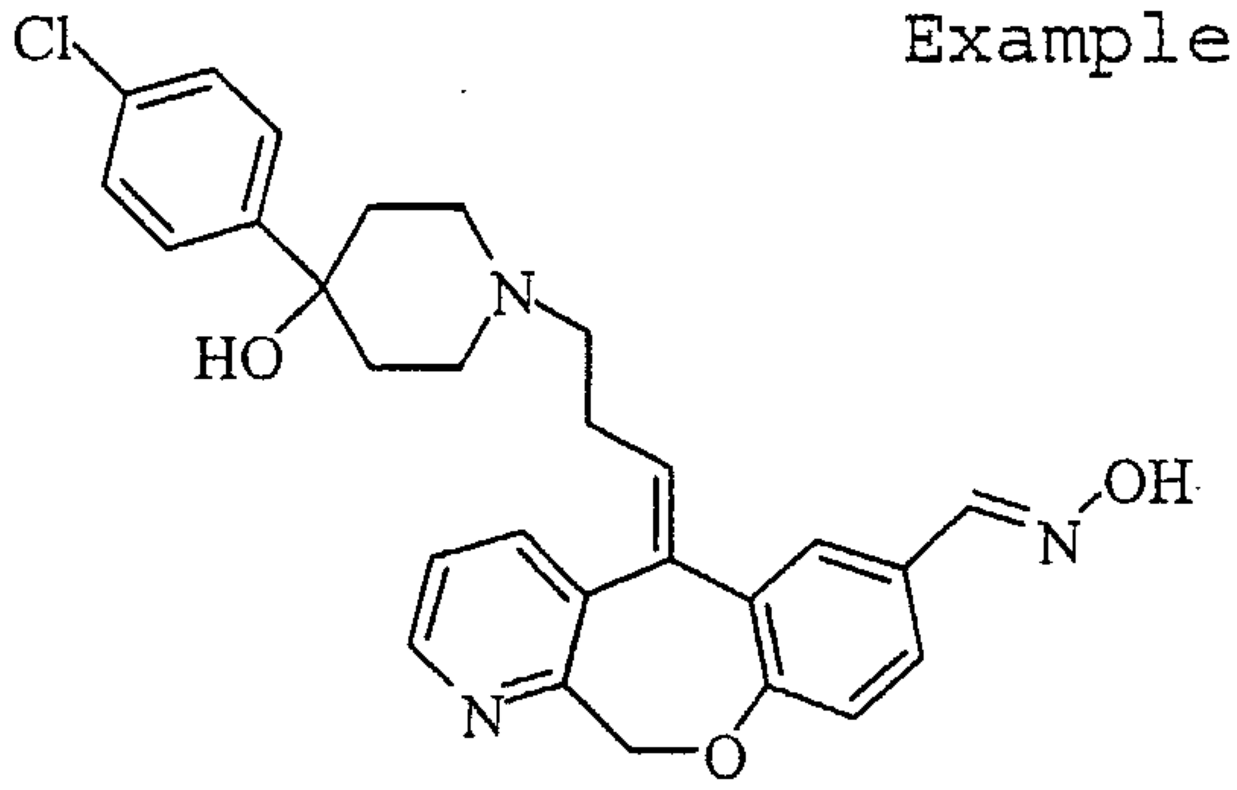
Figure 11L



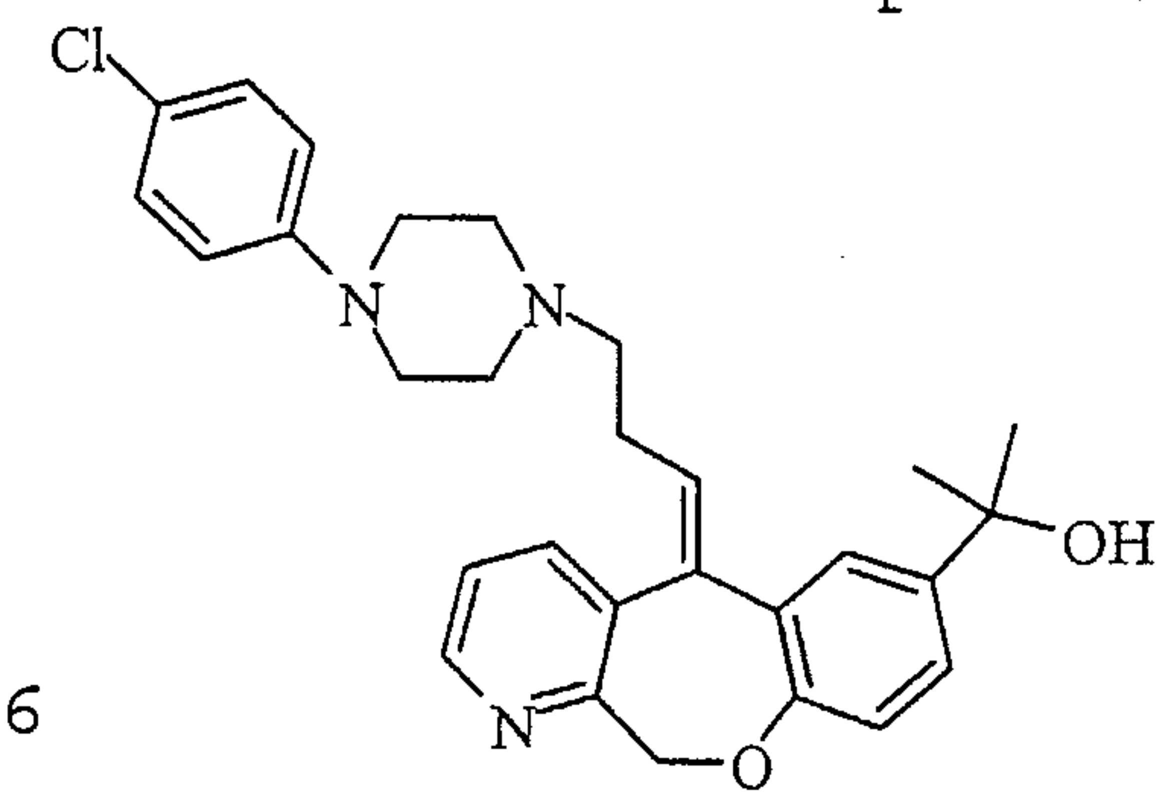
Example 364



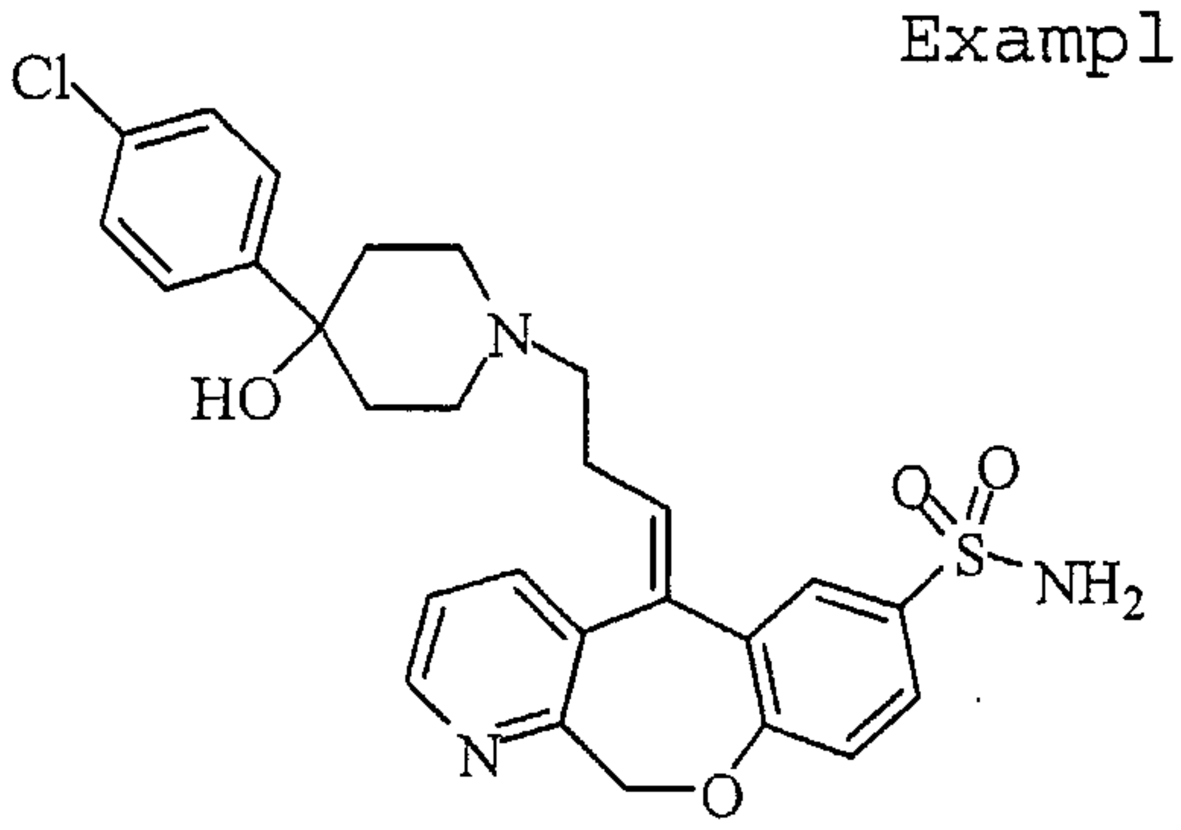
Example 365



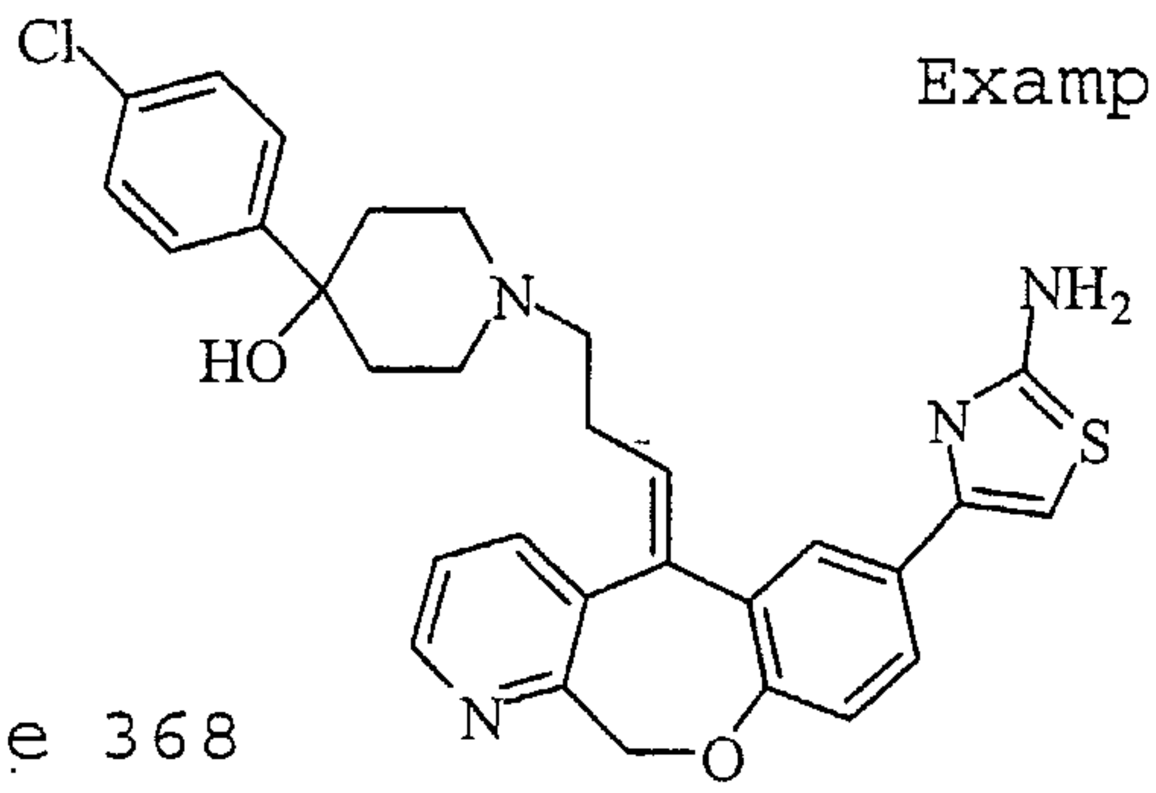
Example 366



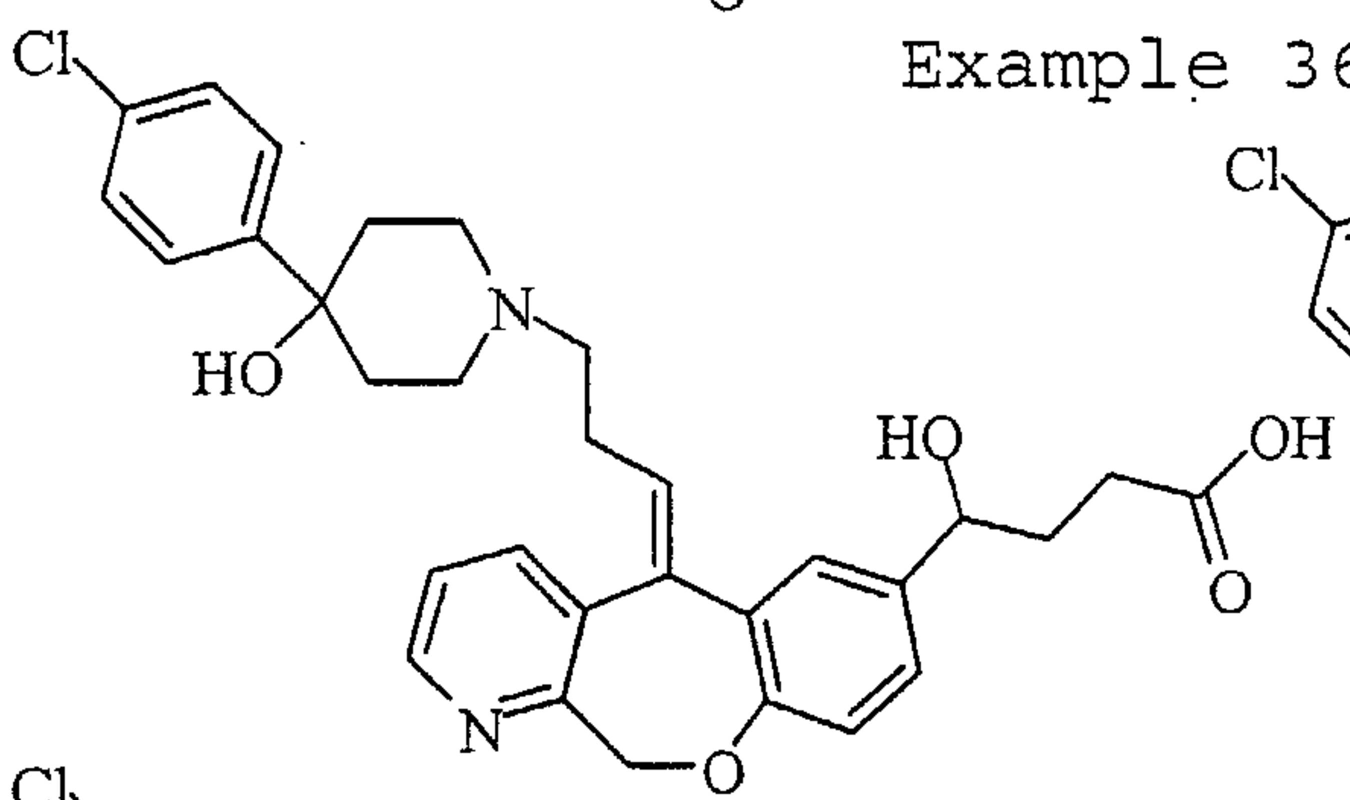
Example 367



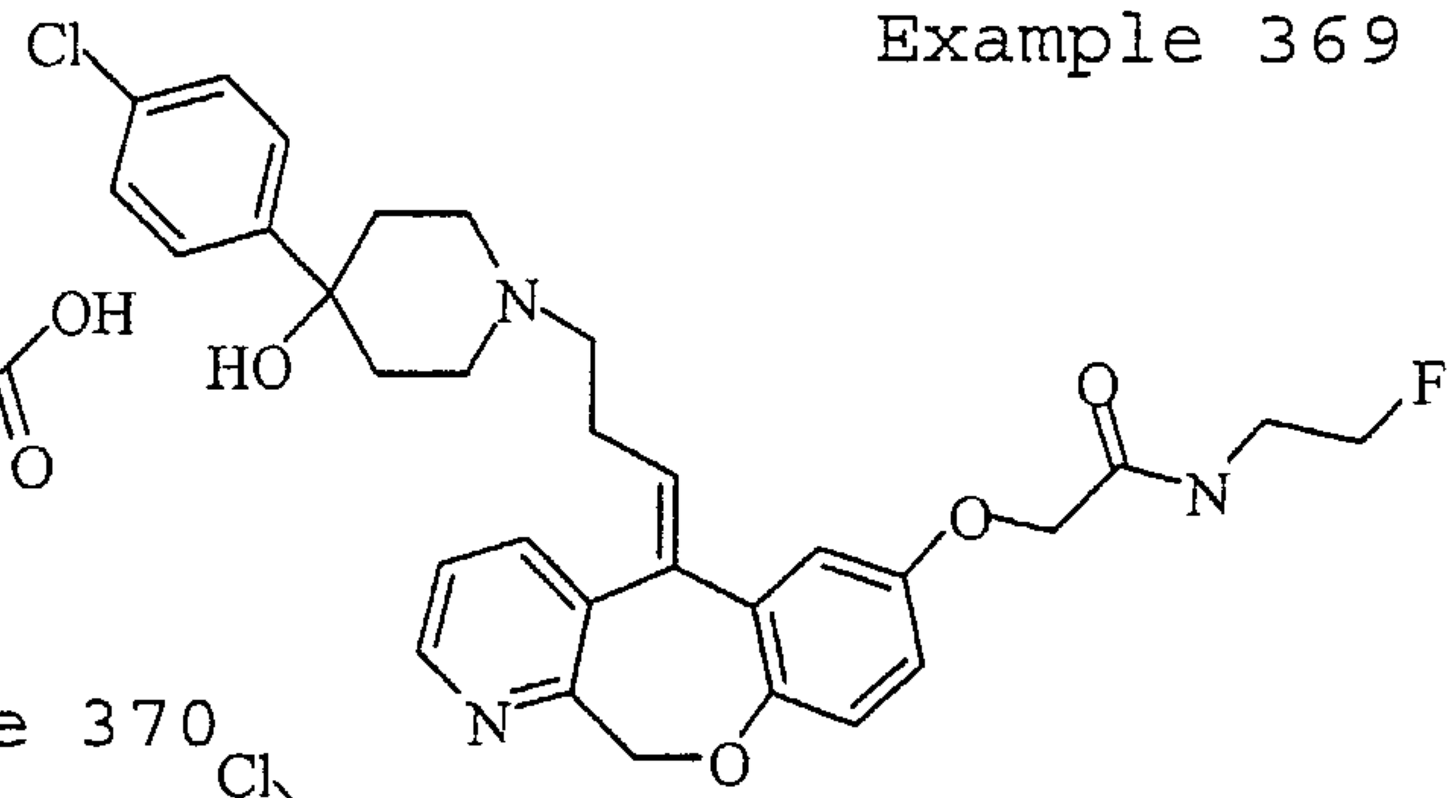
Example 368



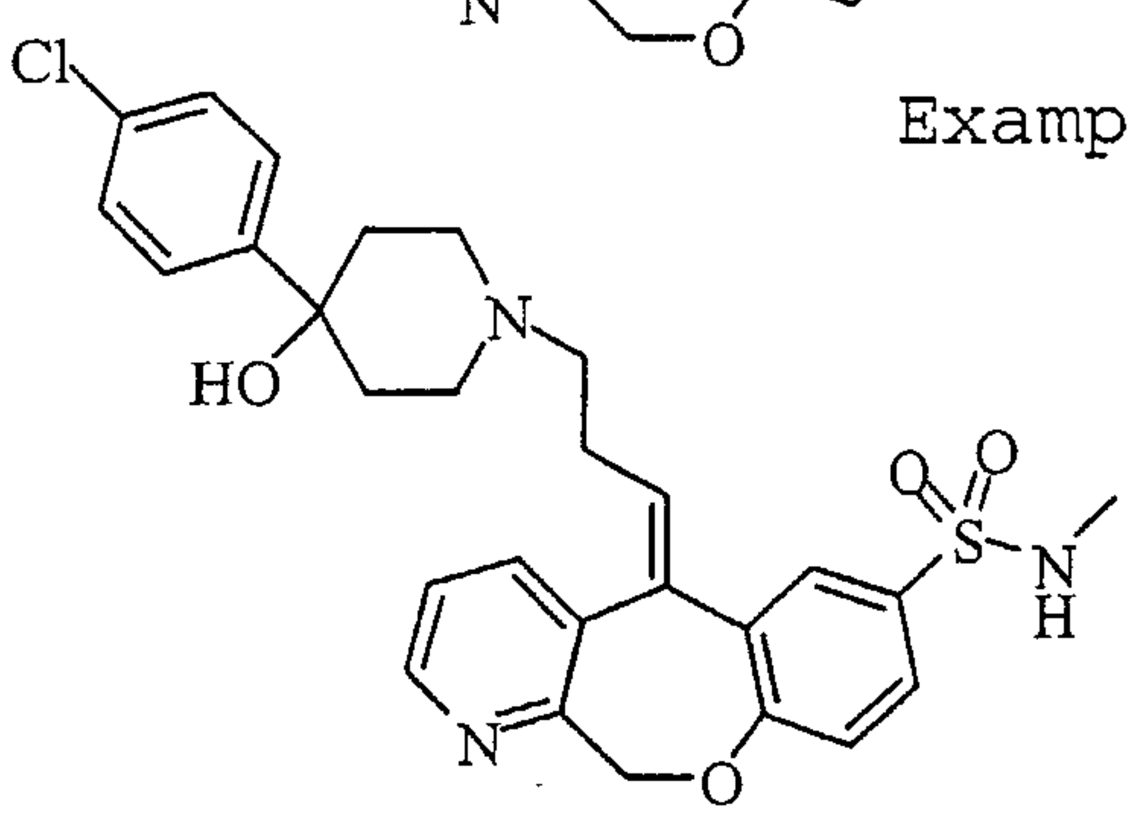
Example 369



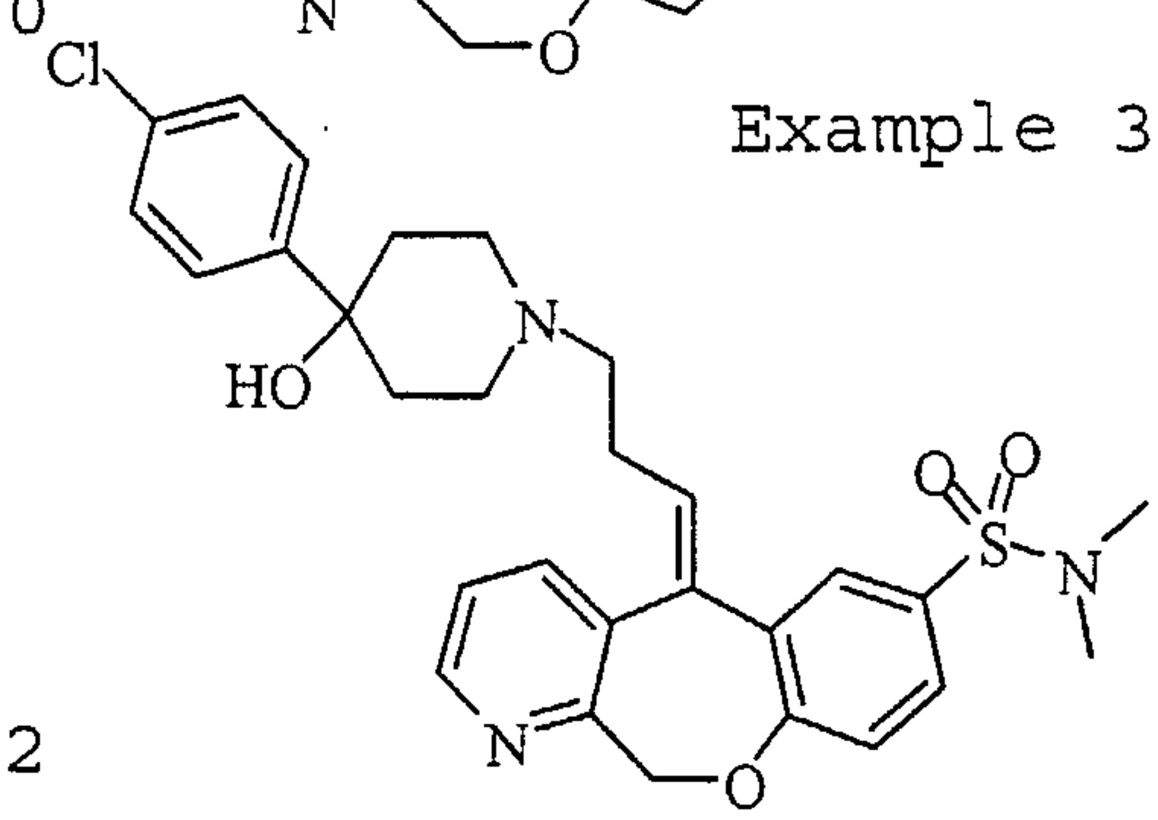
Example 370



Example 371

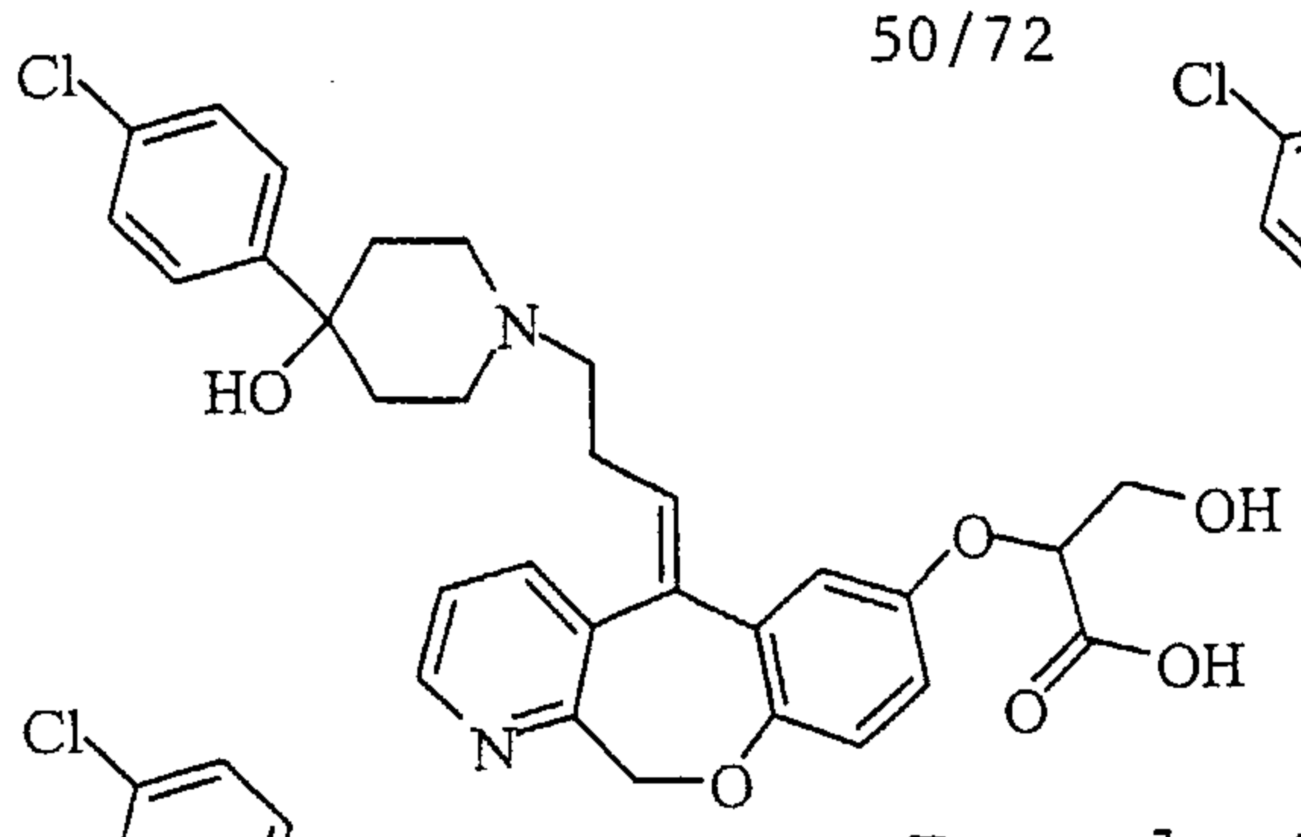


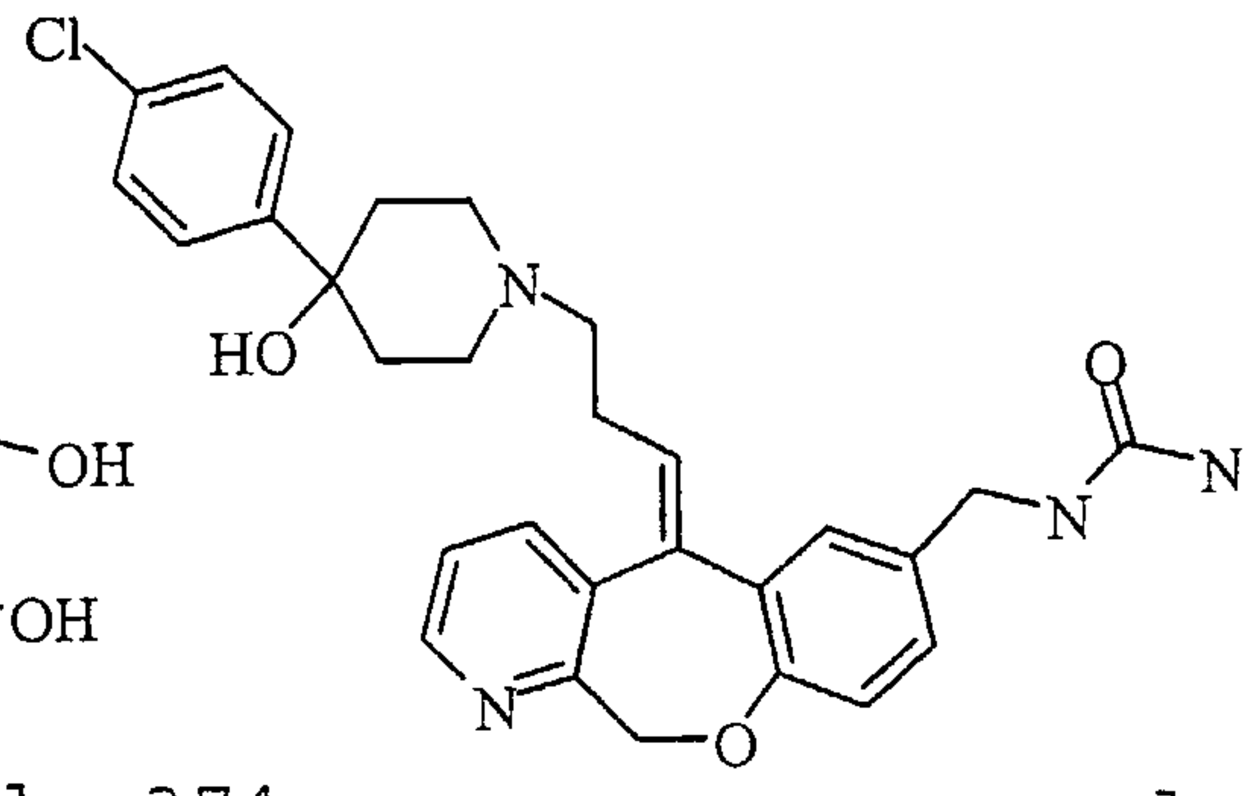
Example 372

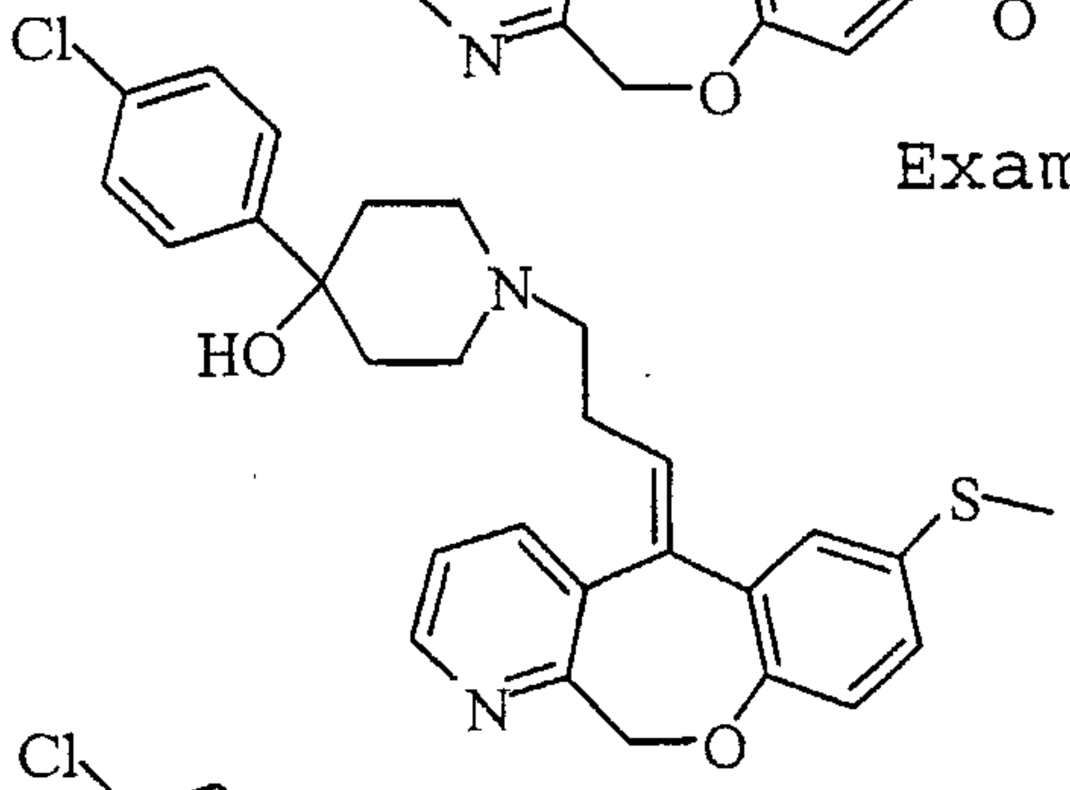


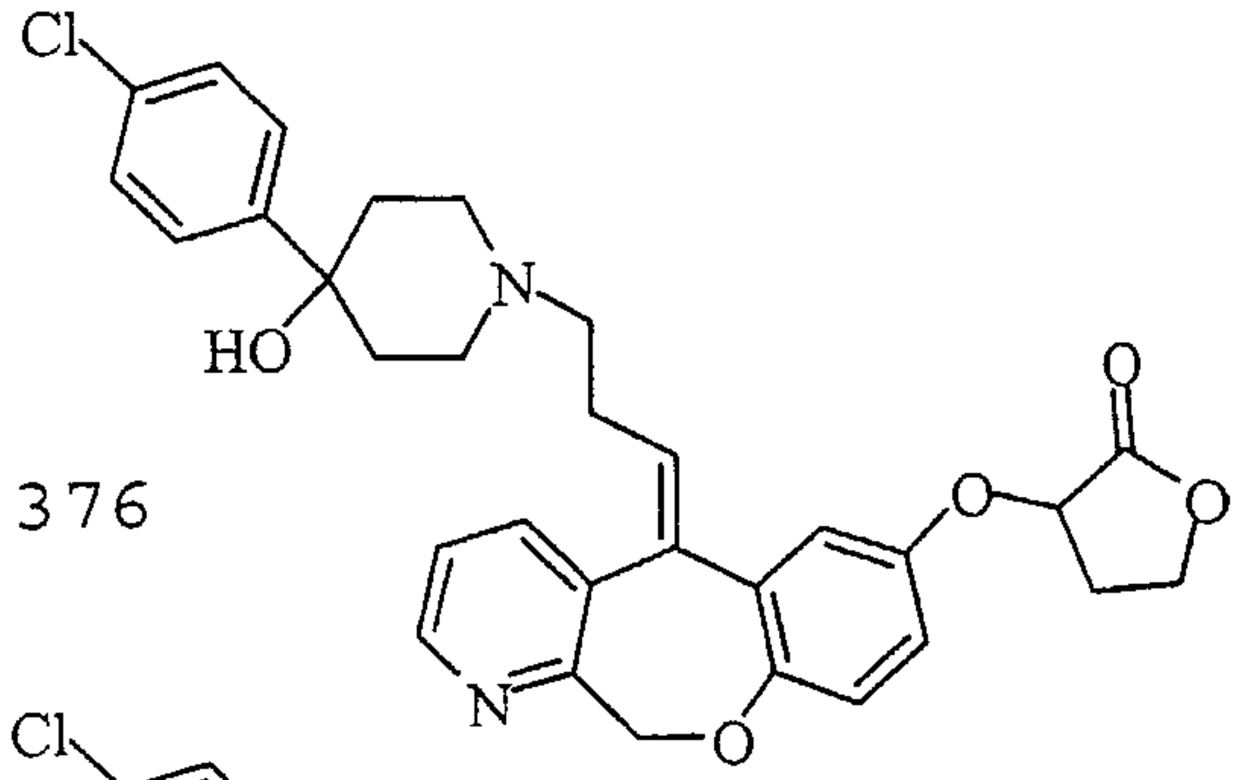
Example 373

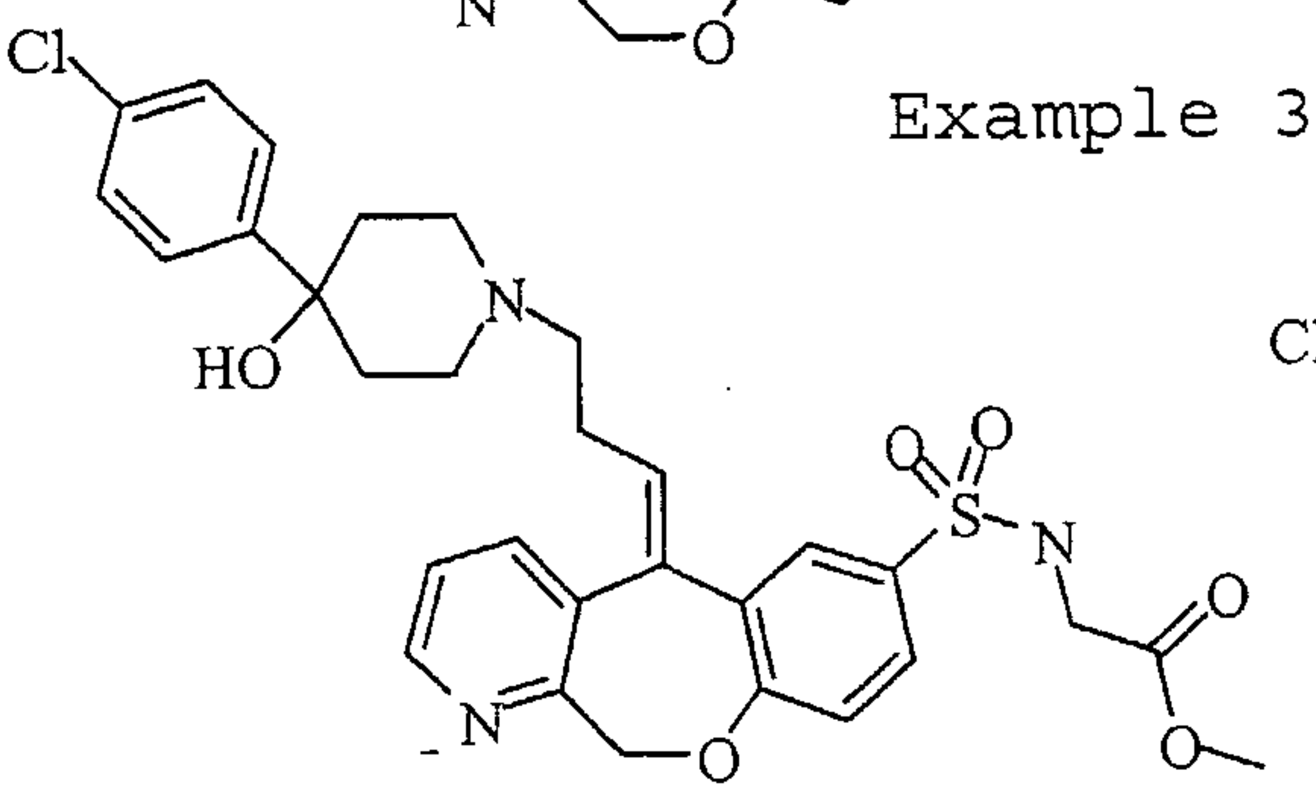
Figure 11M

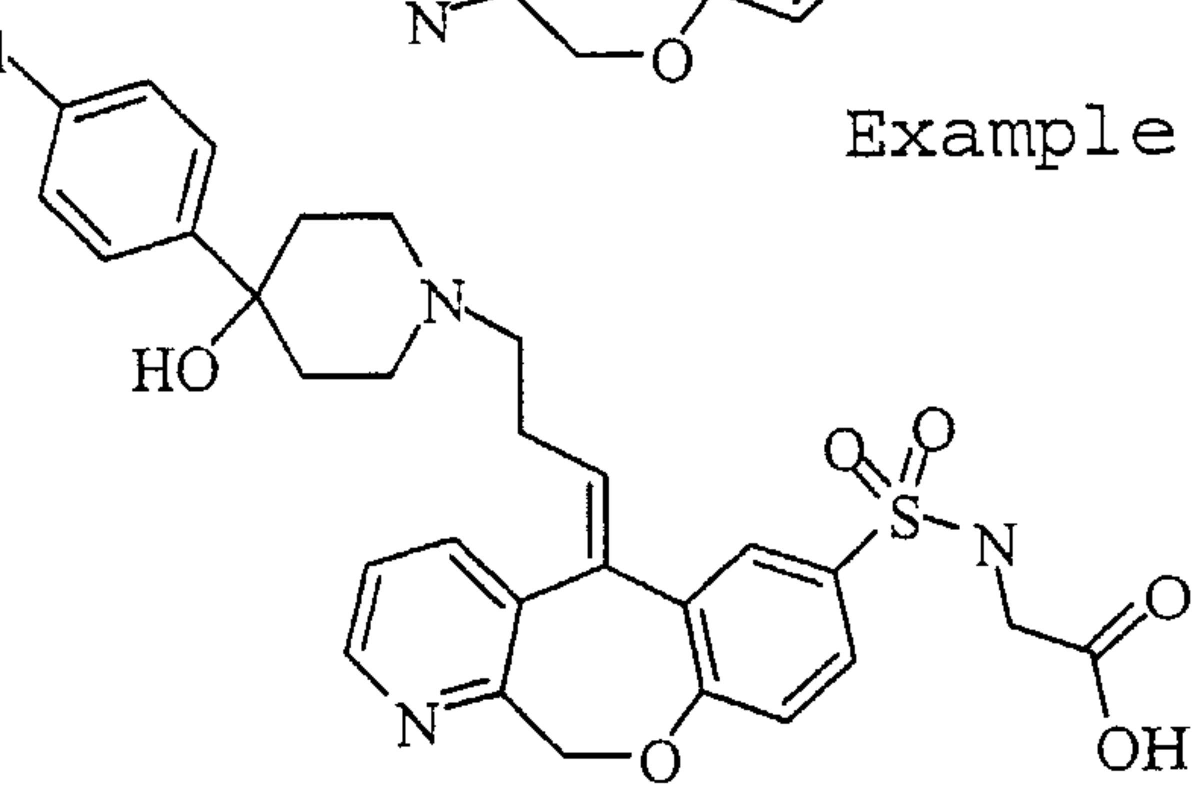

Example 374

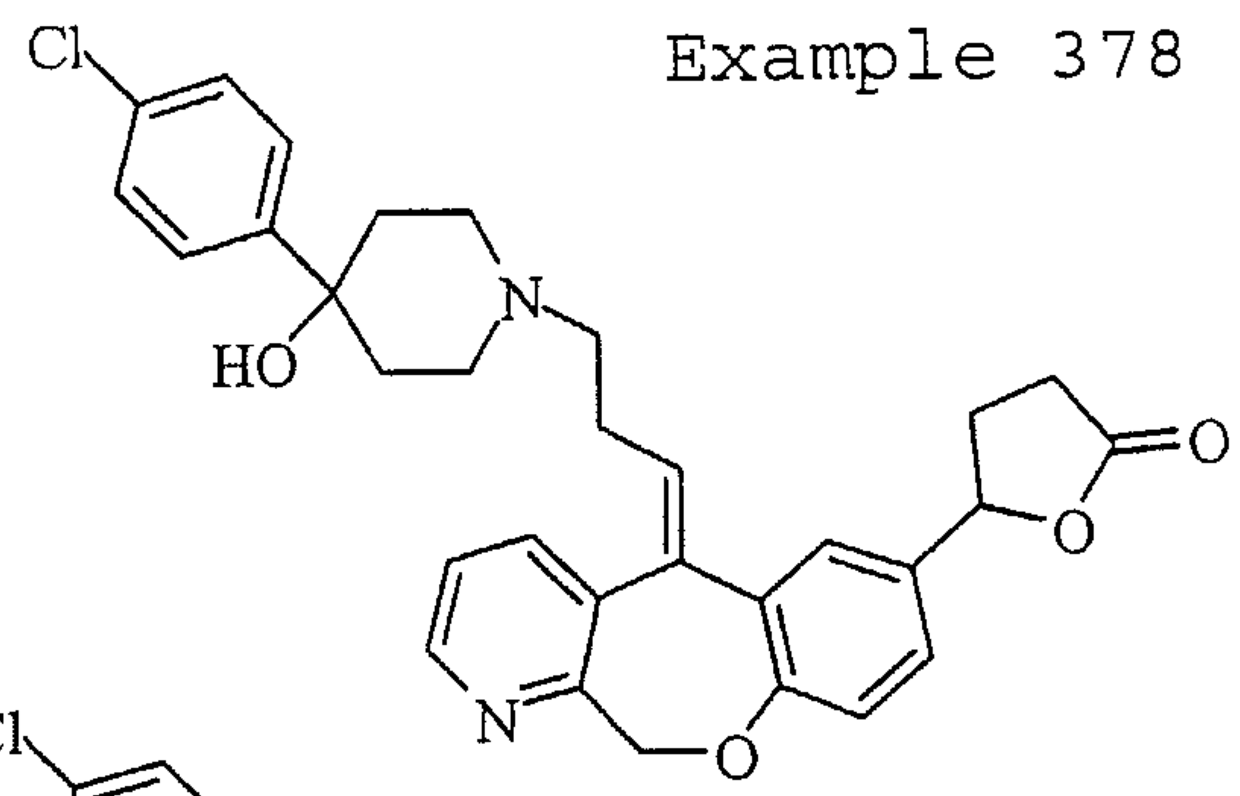

Example 375

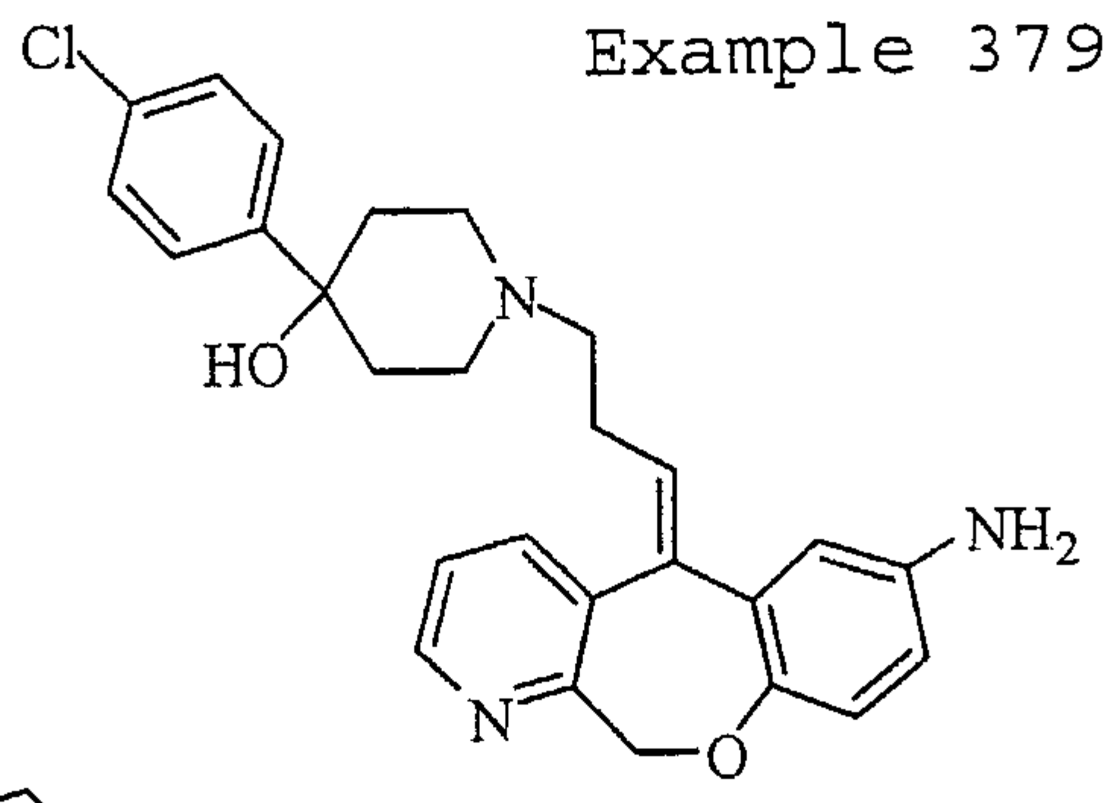

Example 376

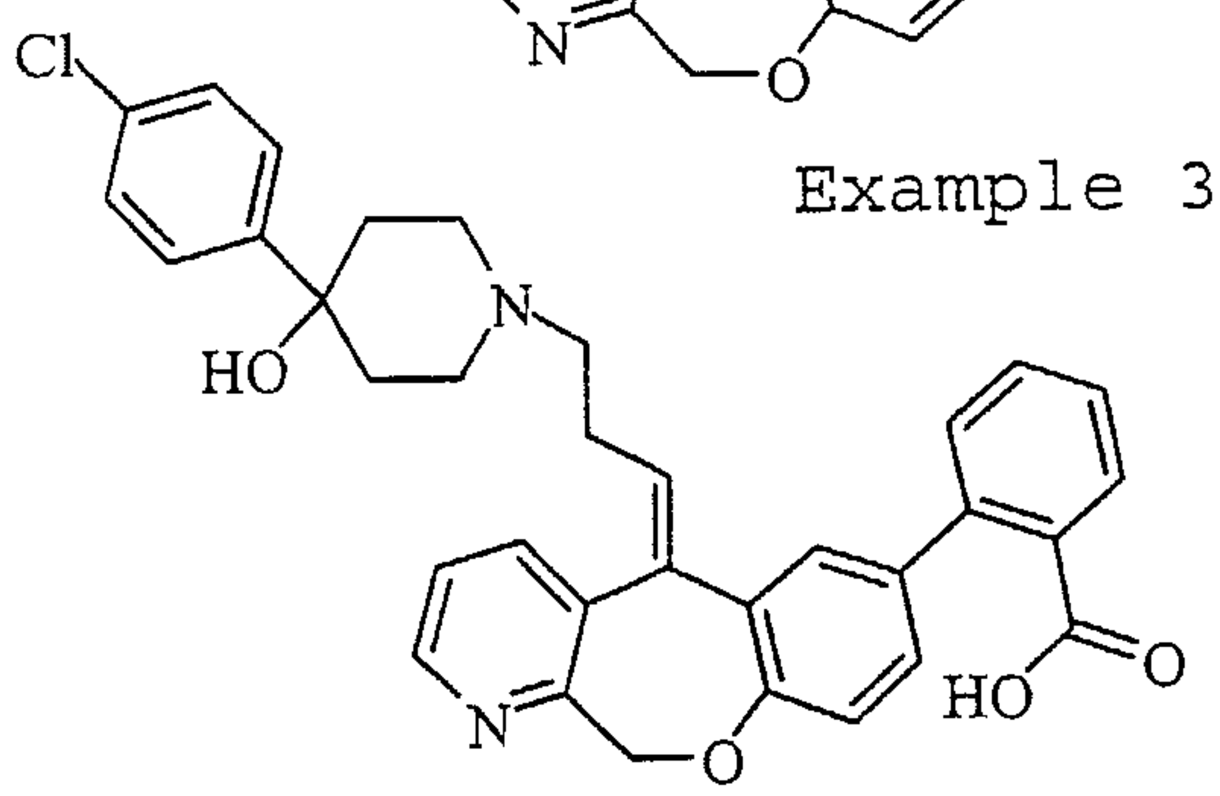

Example 377


Example 378


Example 379


Example 380


Example 381


Example 382

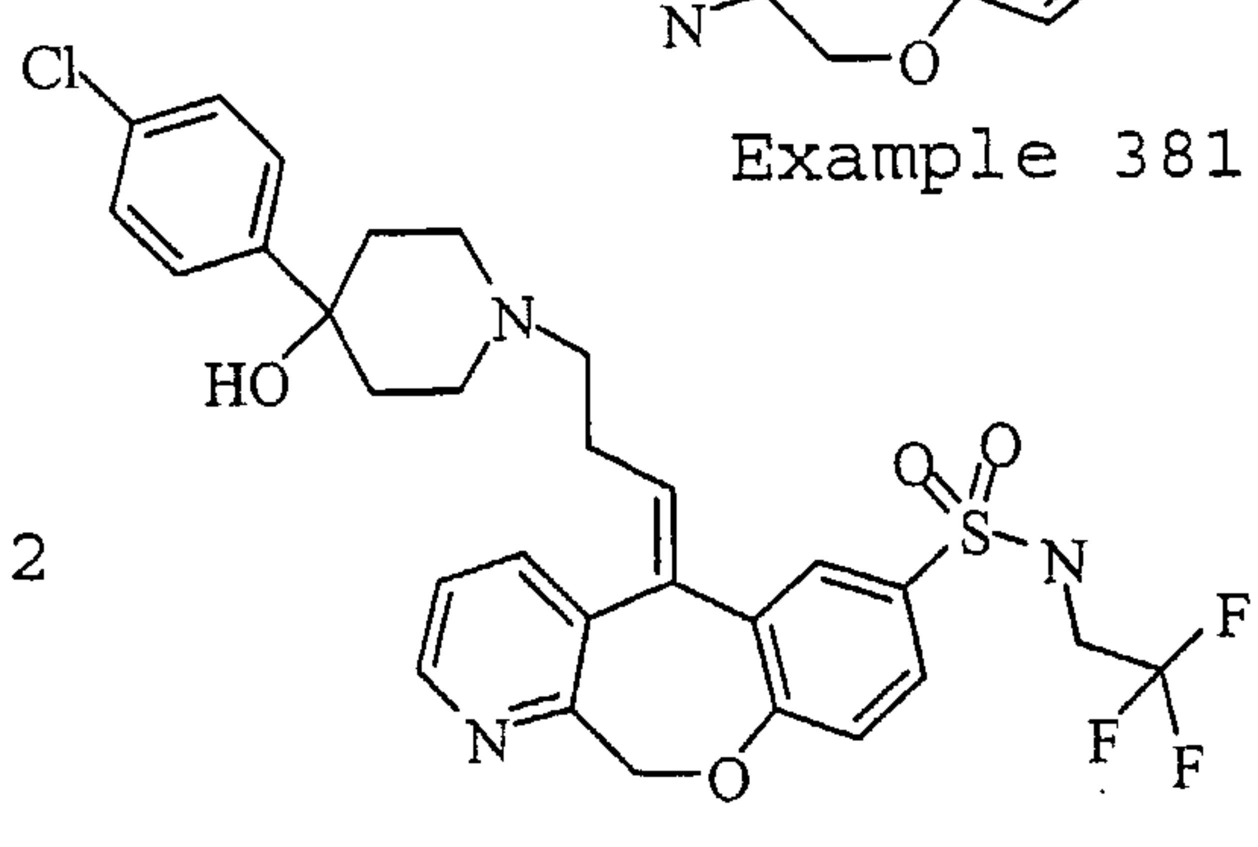
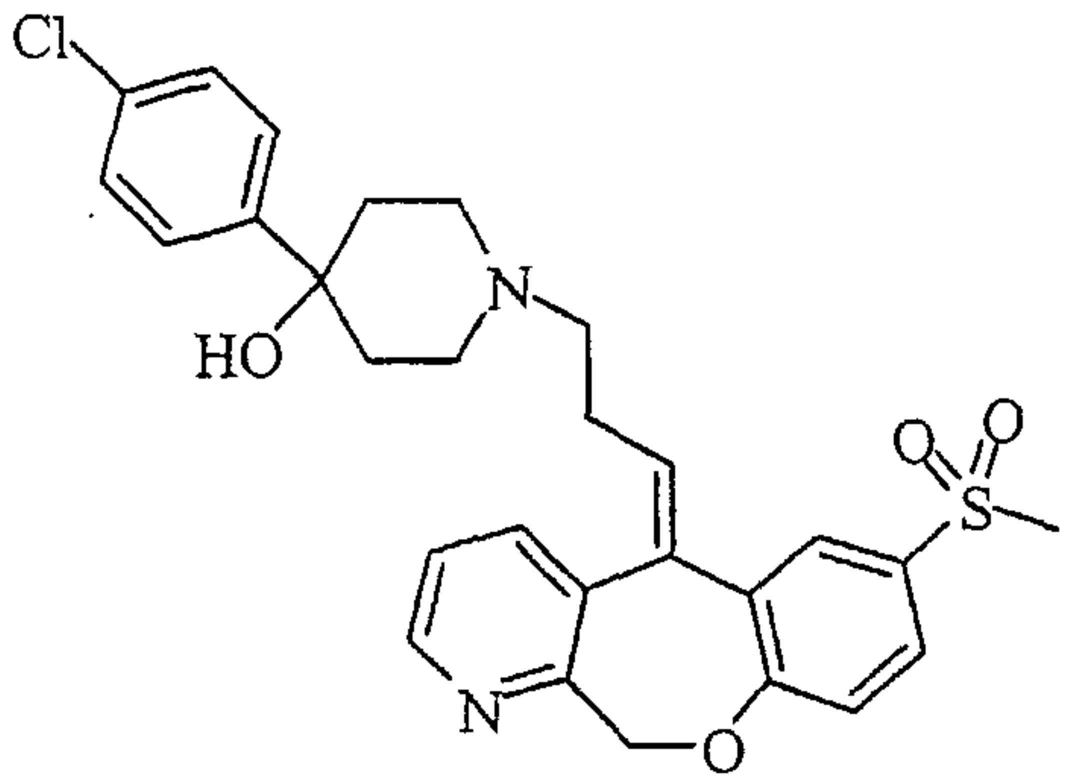
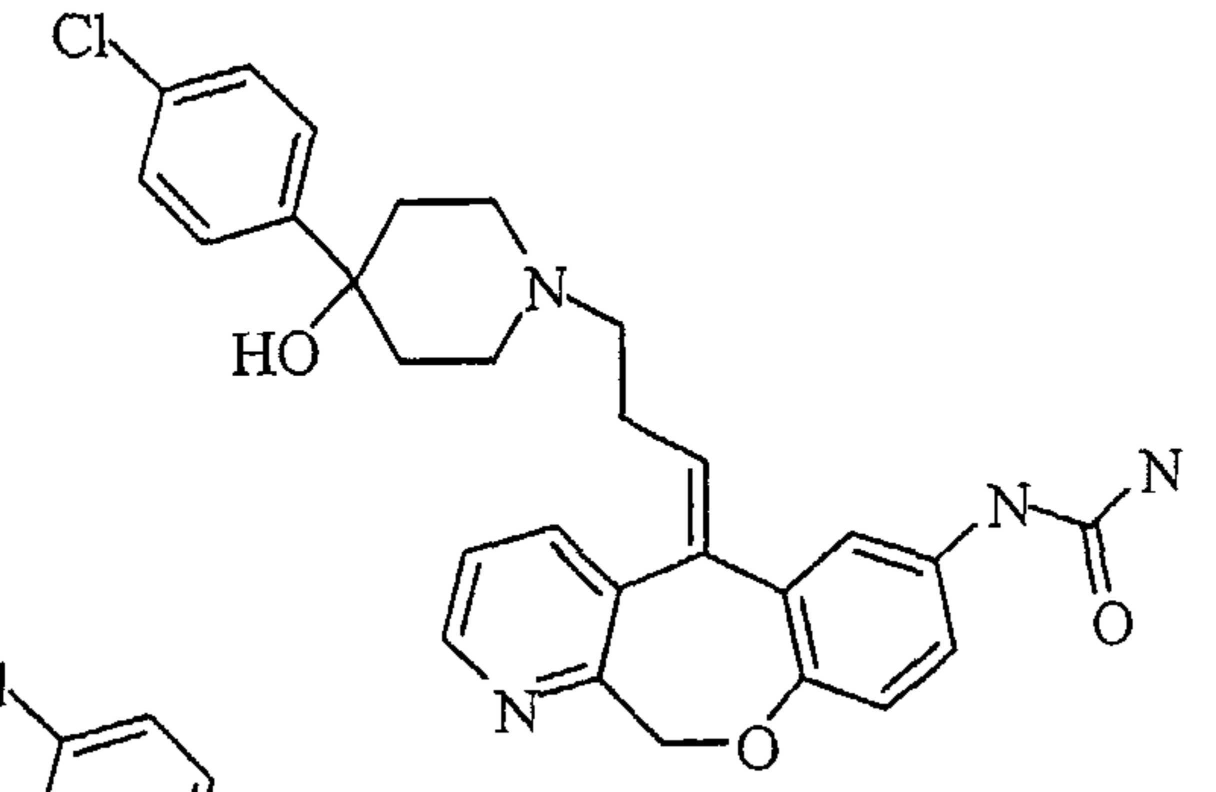

Example 383

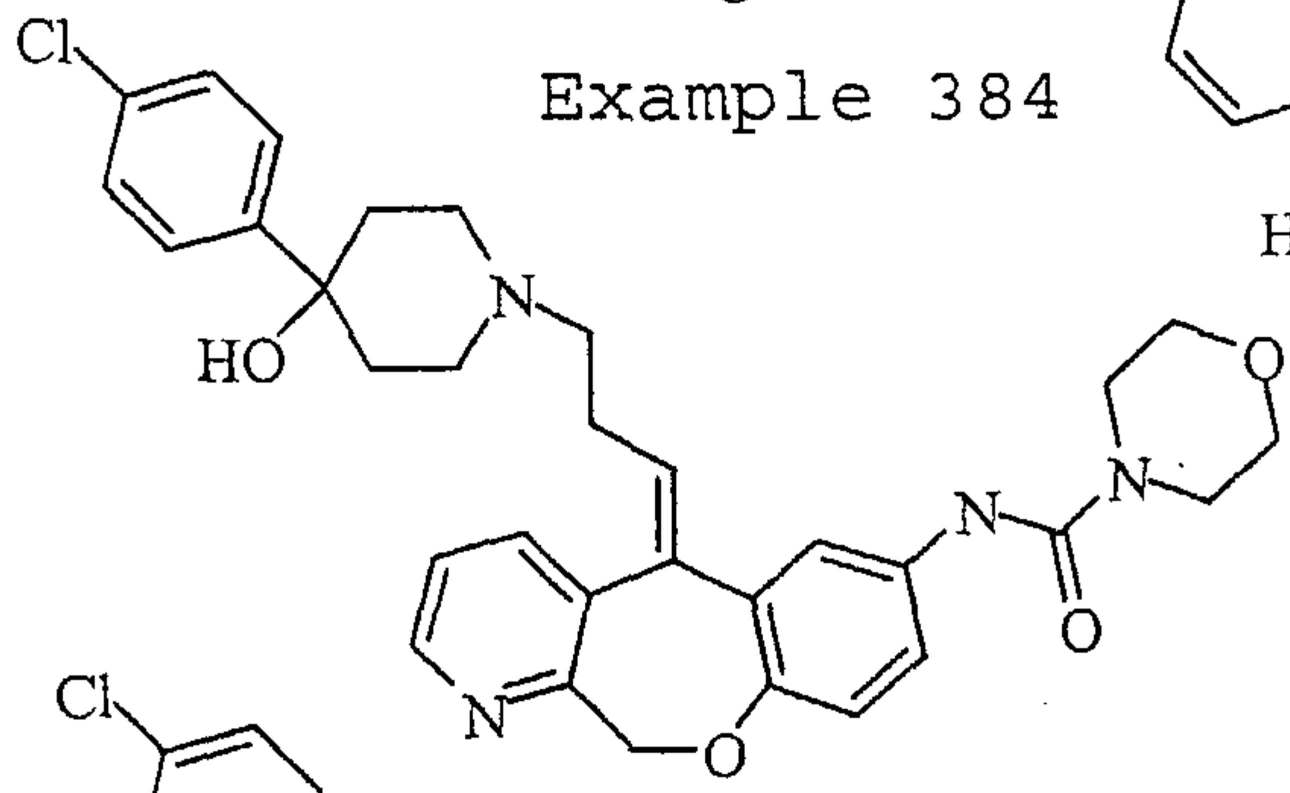
Figure 11N



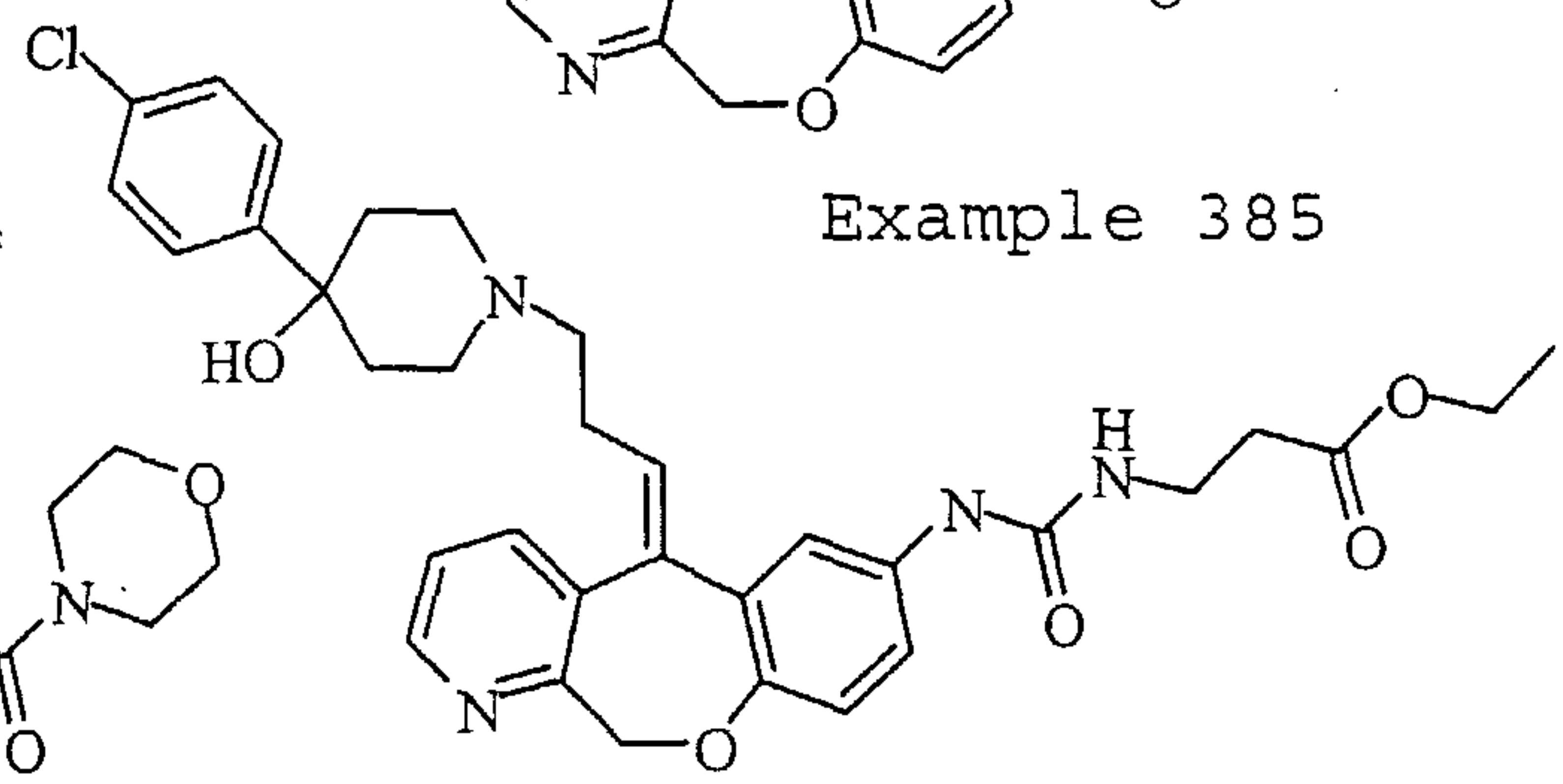
Example 384



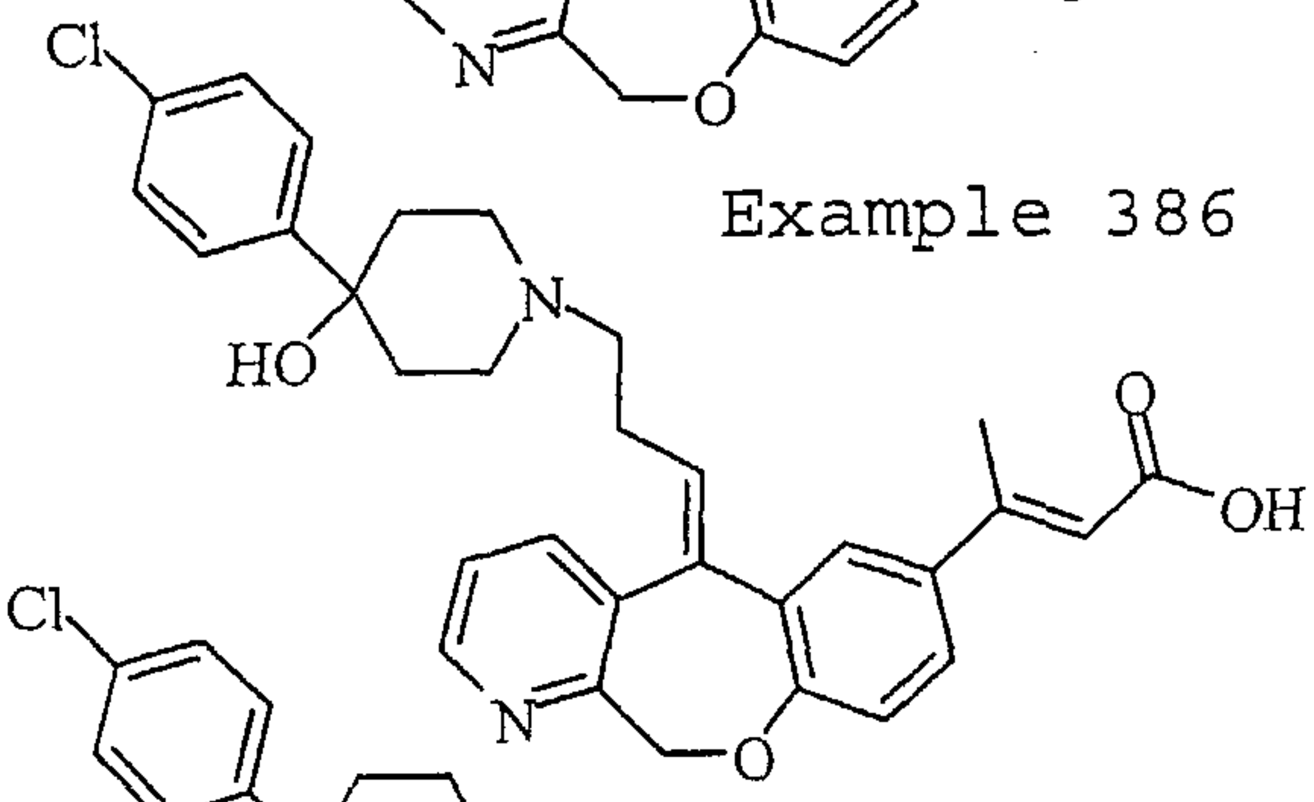
Example 385



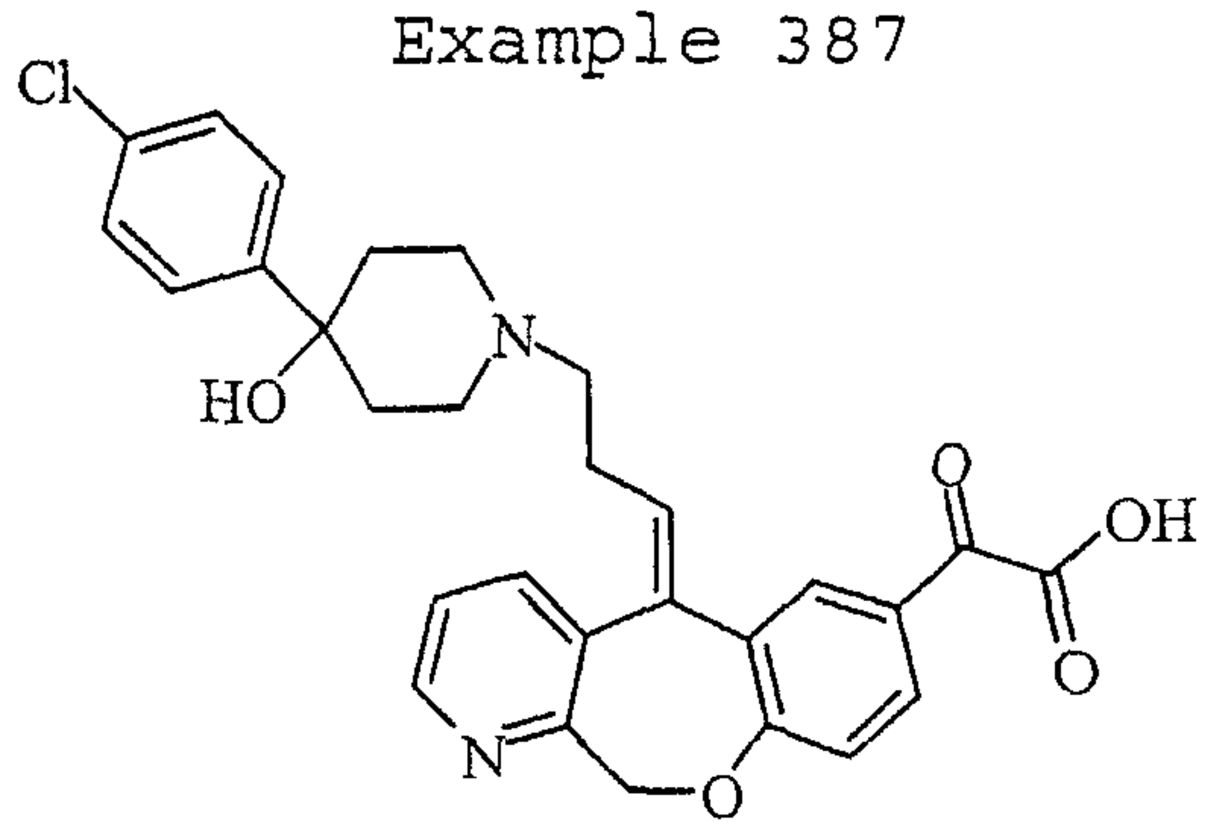
Example 386



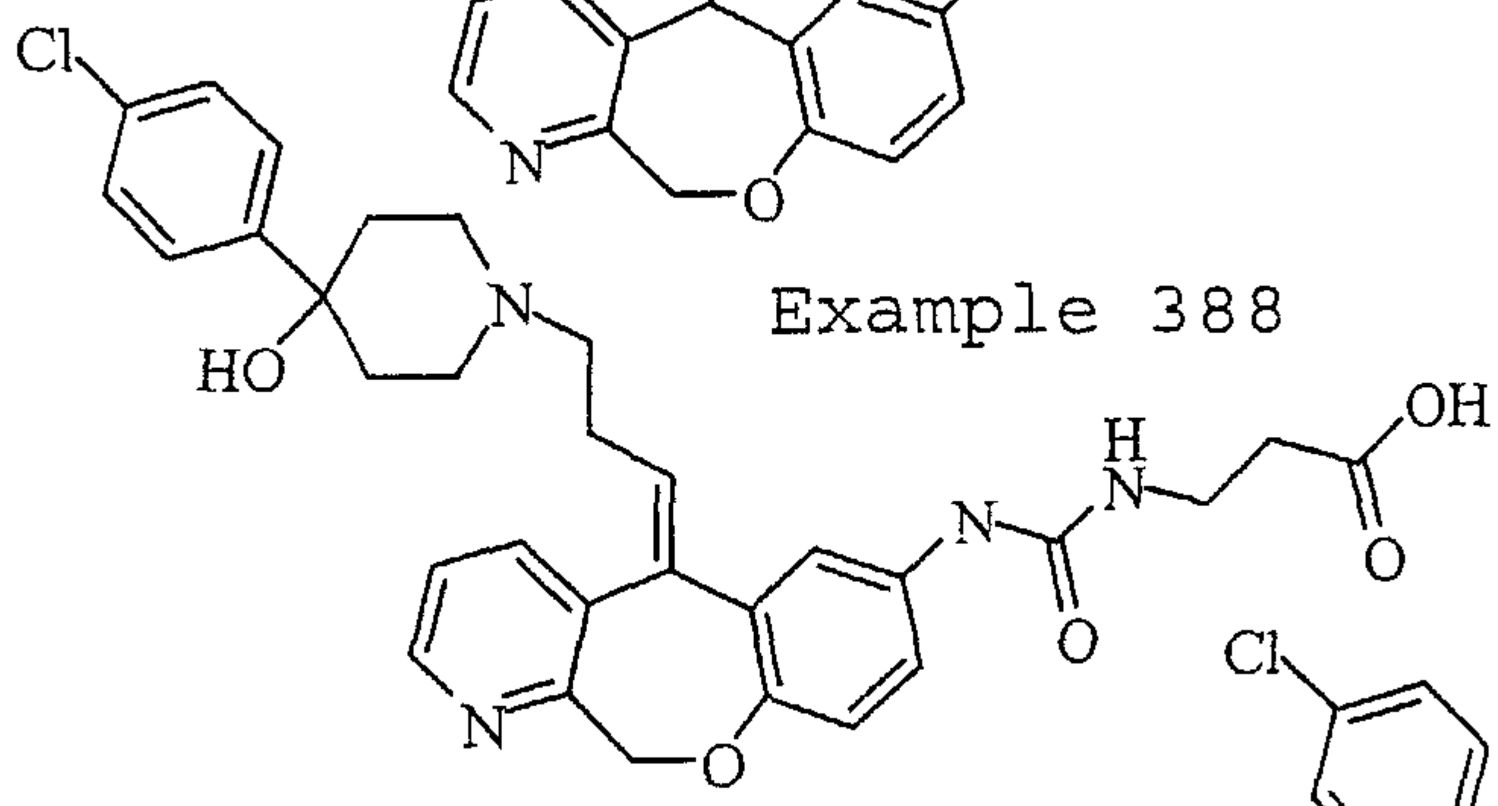
Example 387



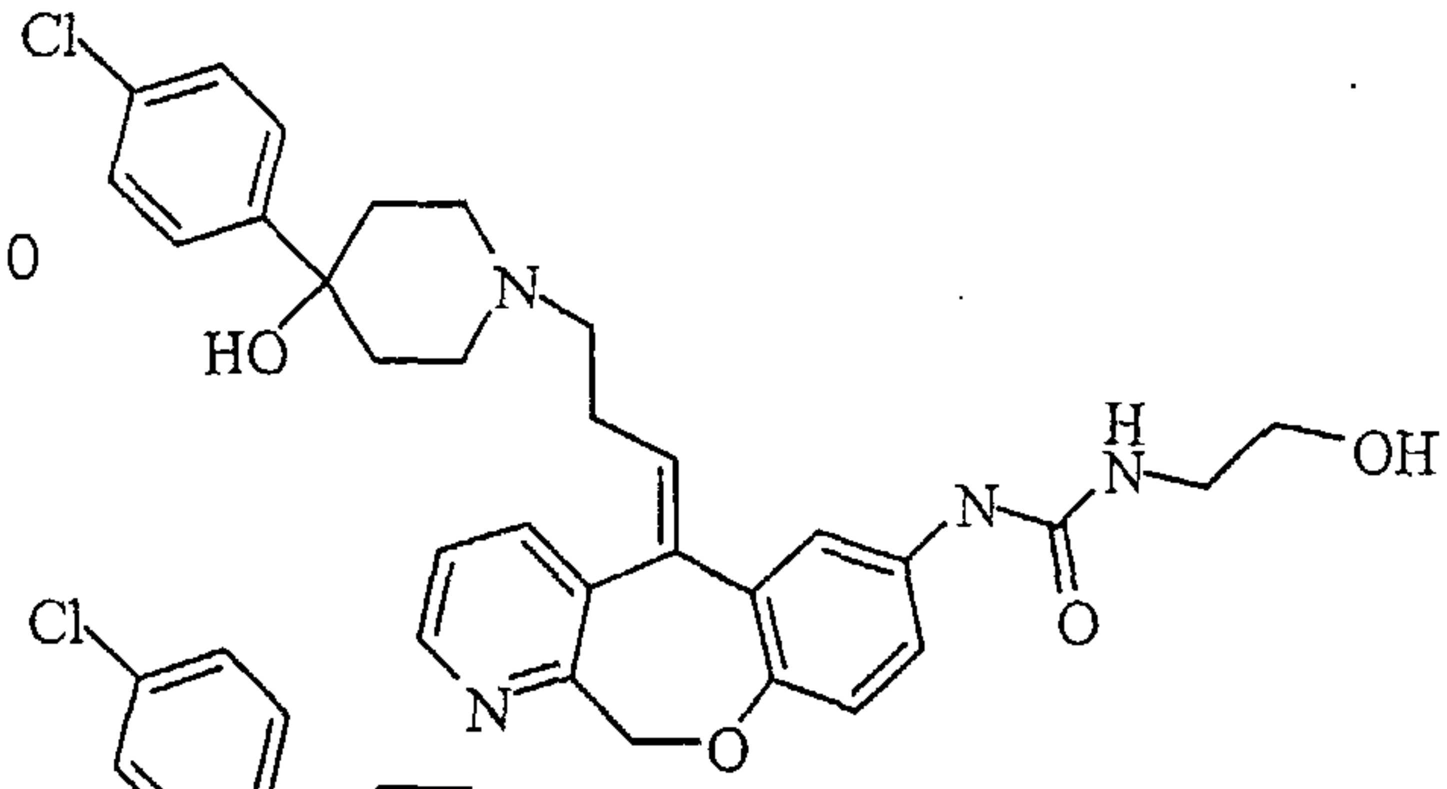
Example 388



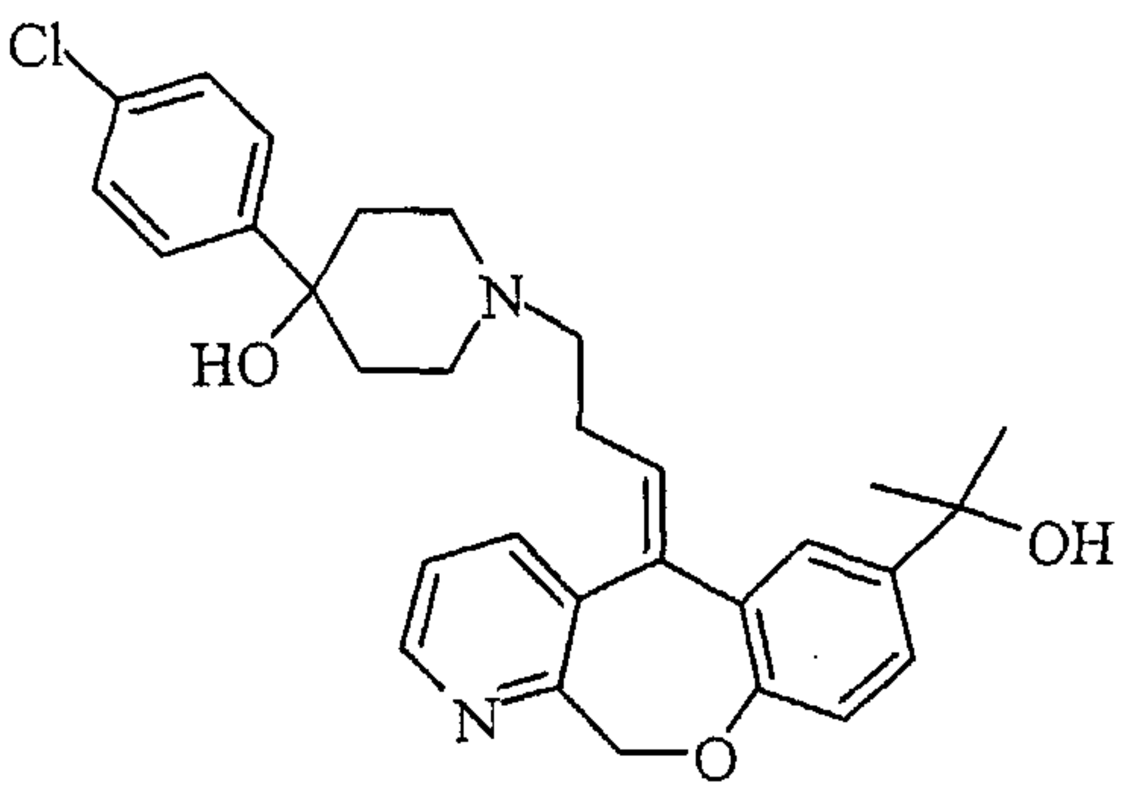
Example 389



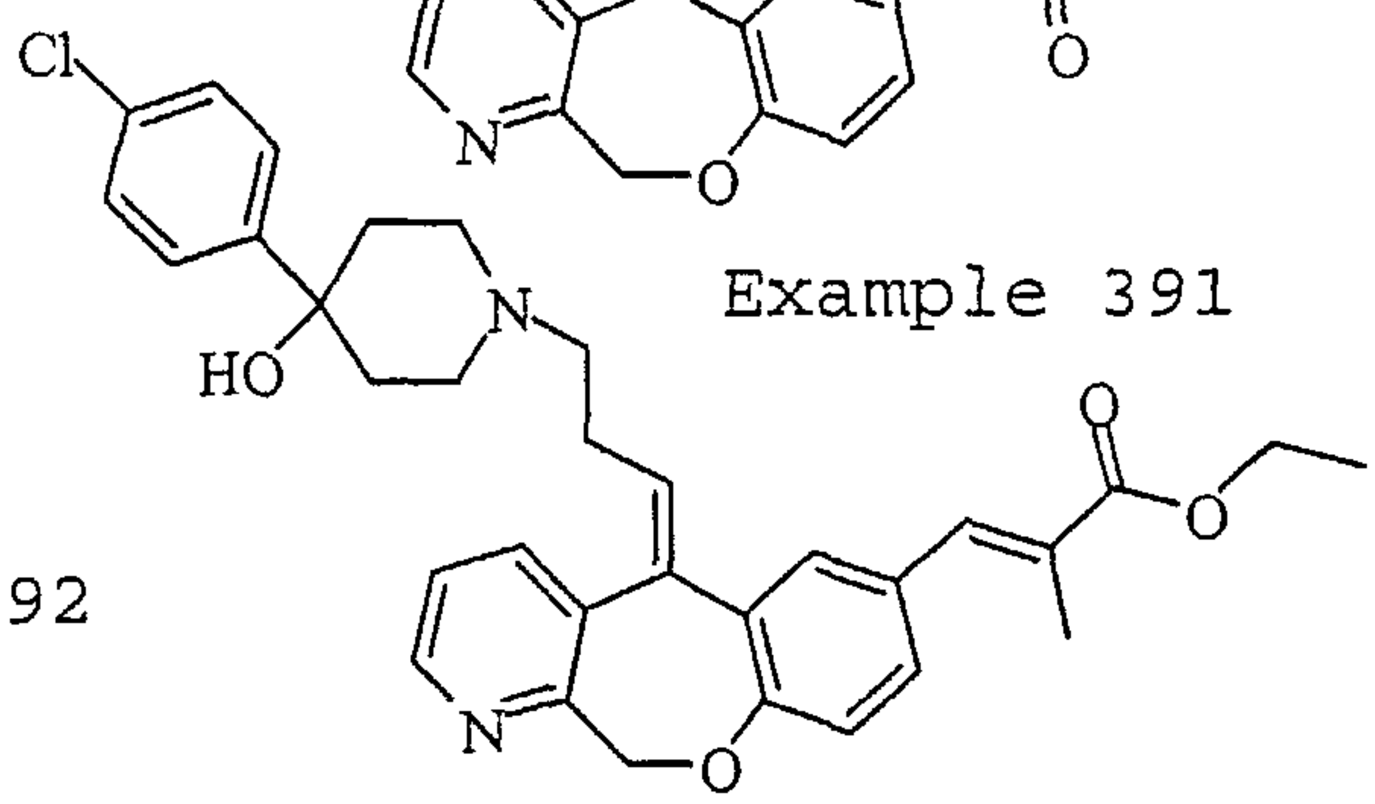
Example 390



Example 391

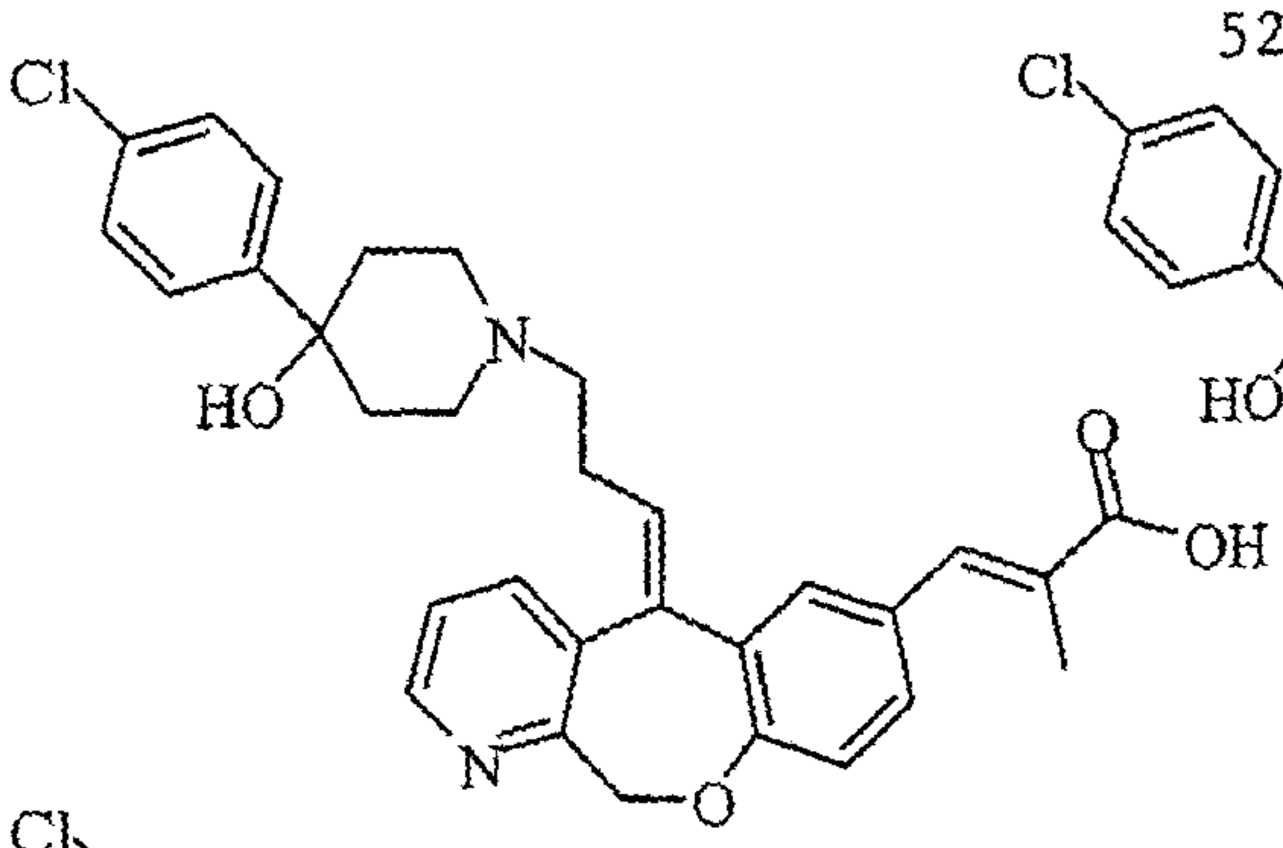


Example 392

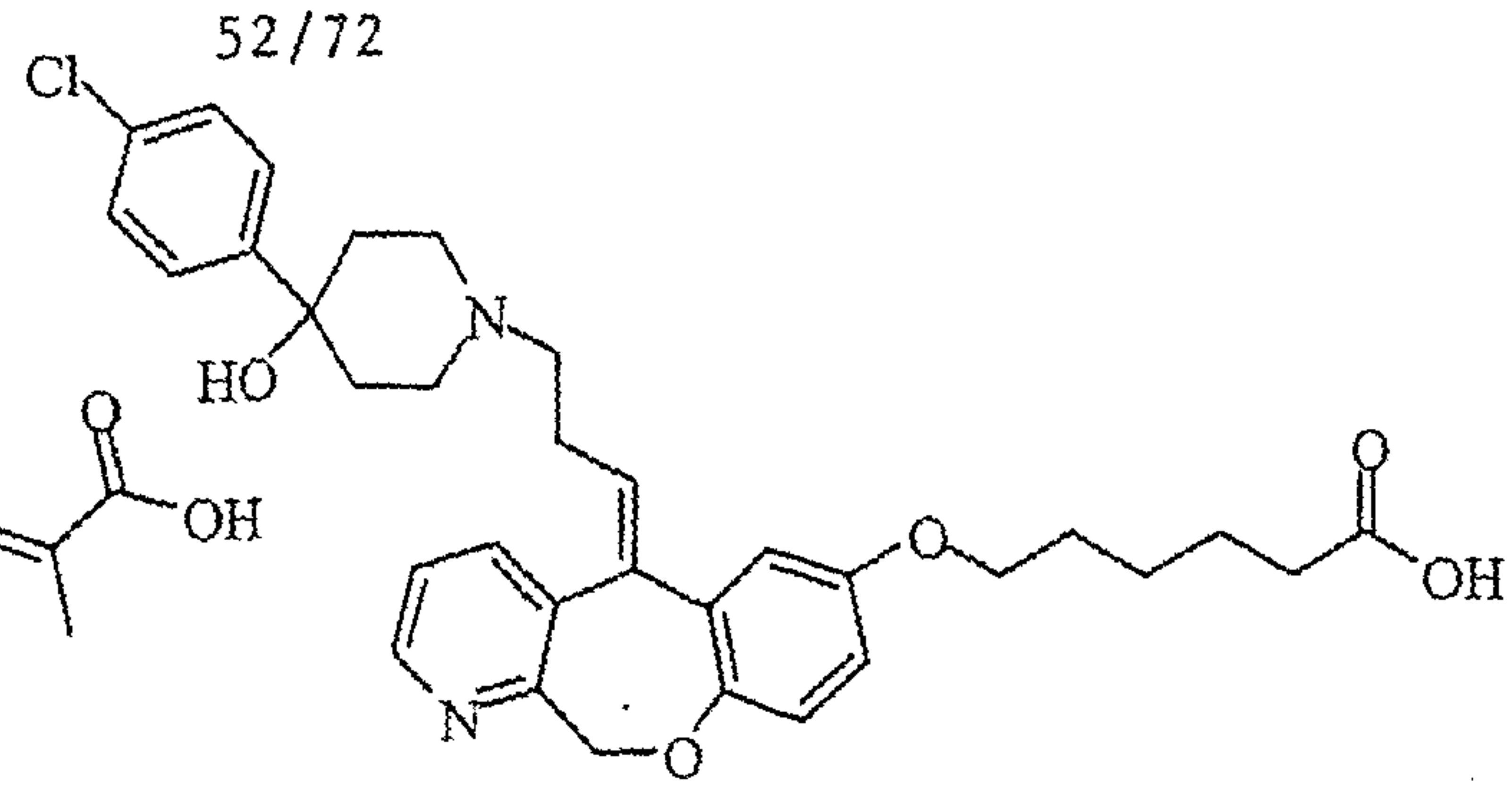


Example 393

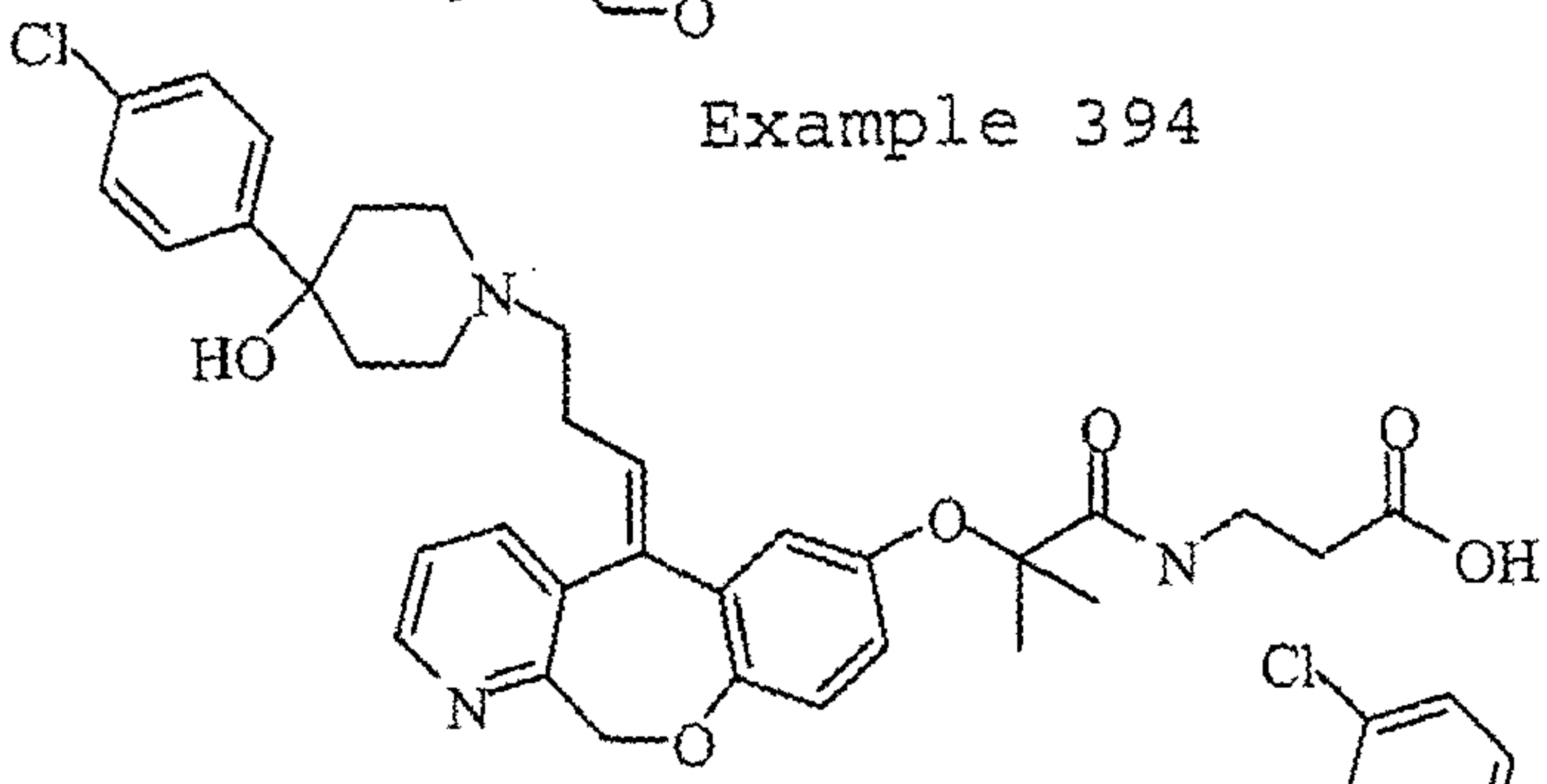
Figure 11O



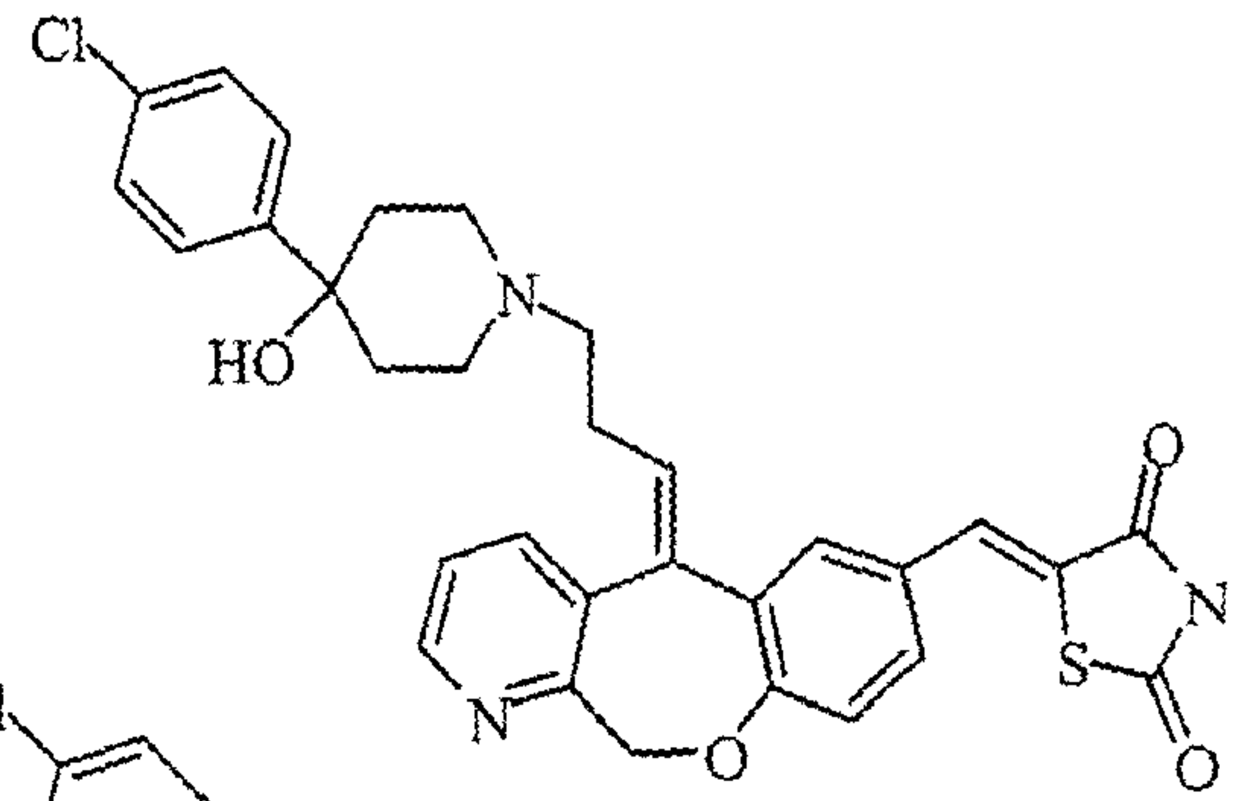
Example 394



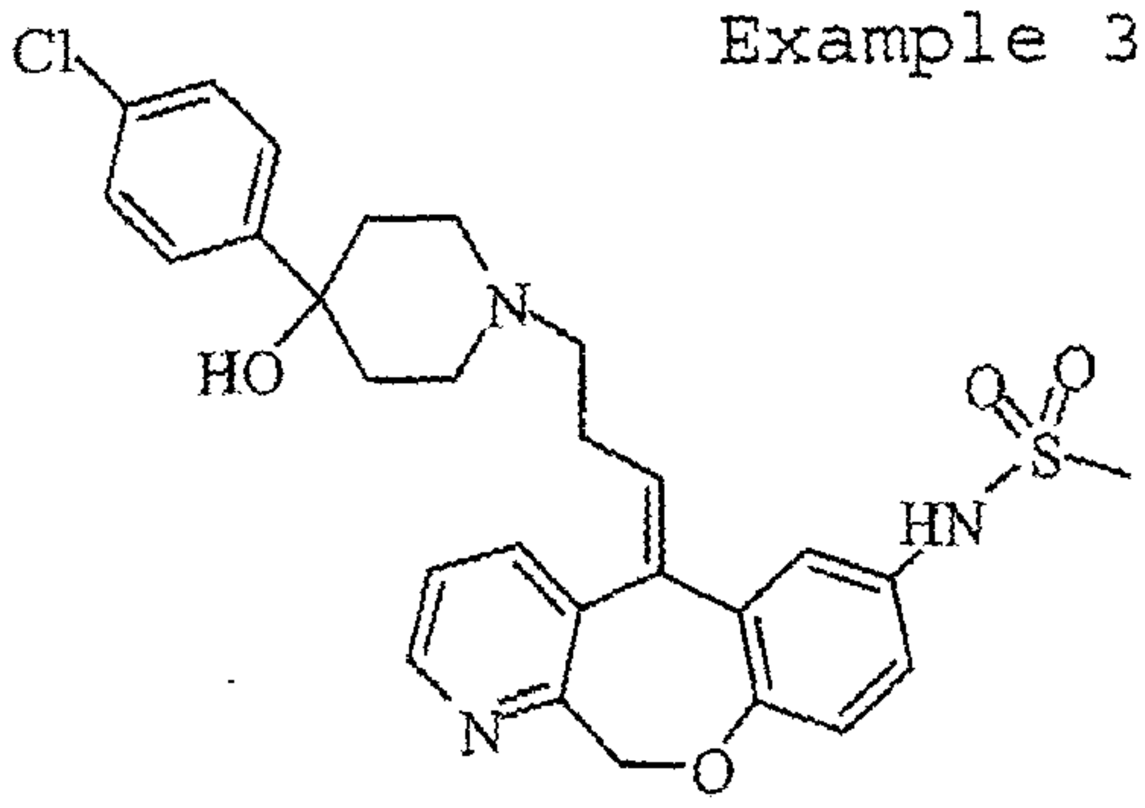
Example 395



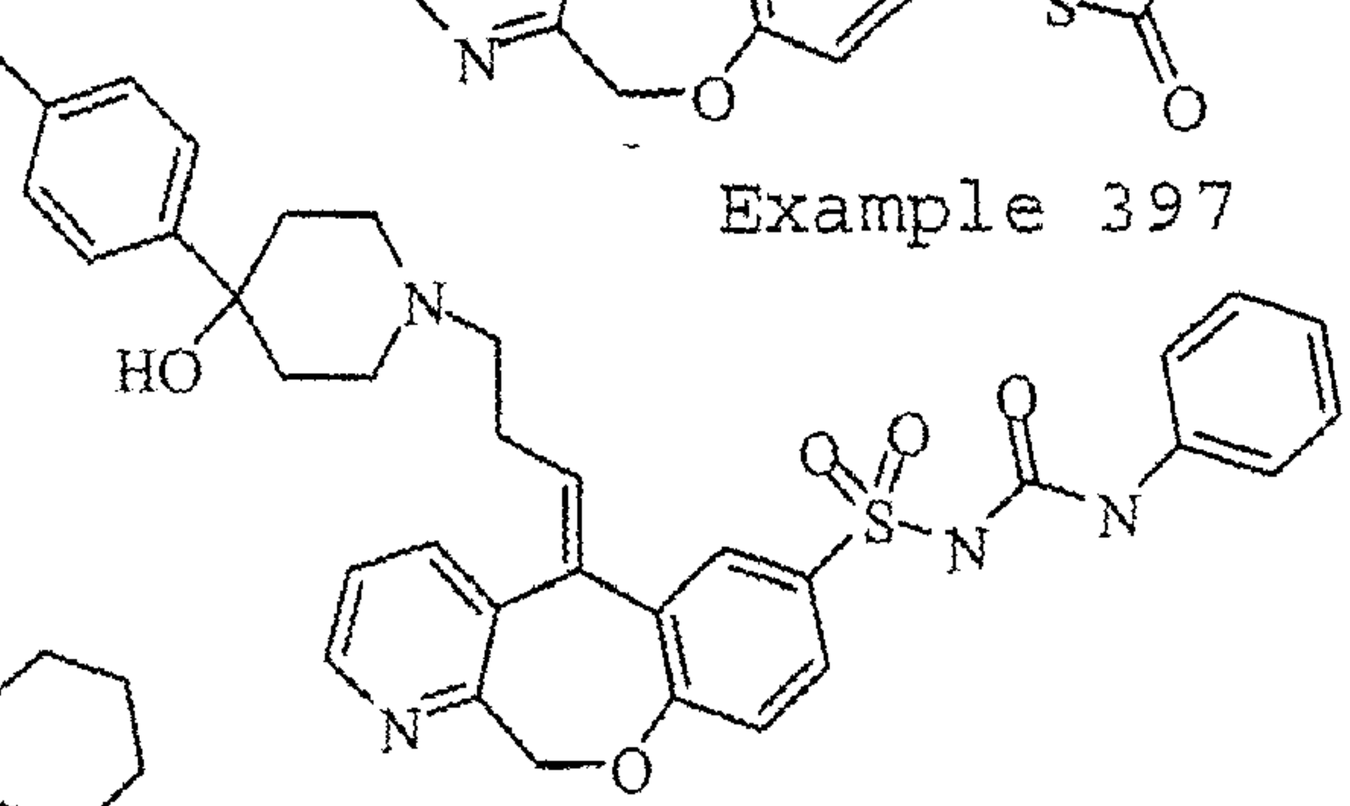
Example 396



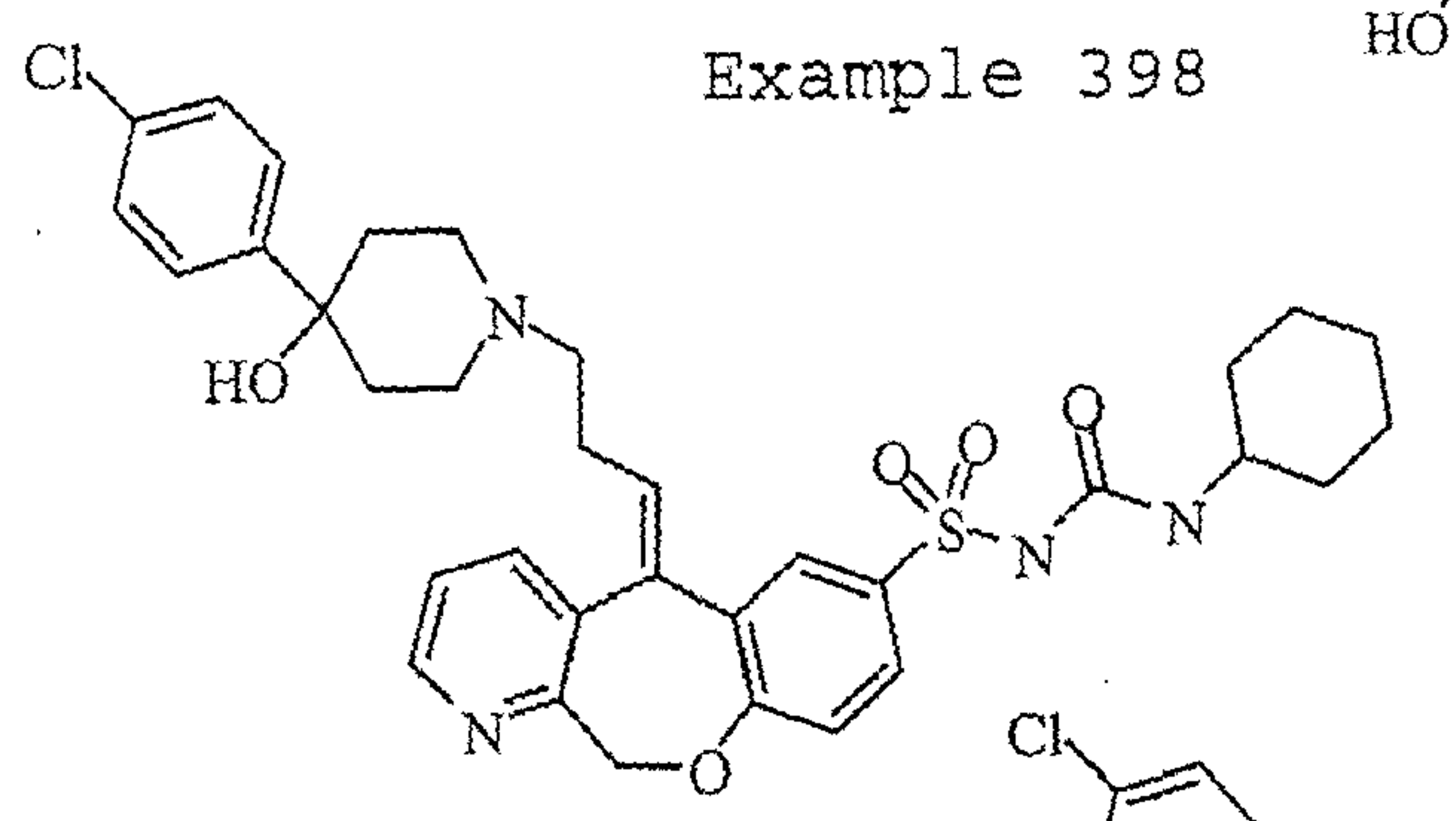
Example 397



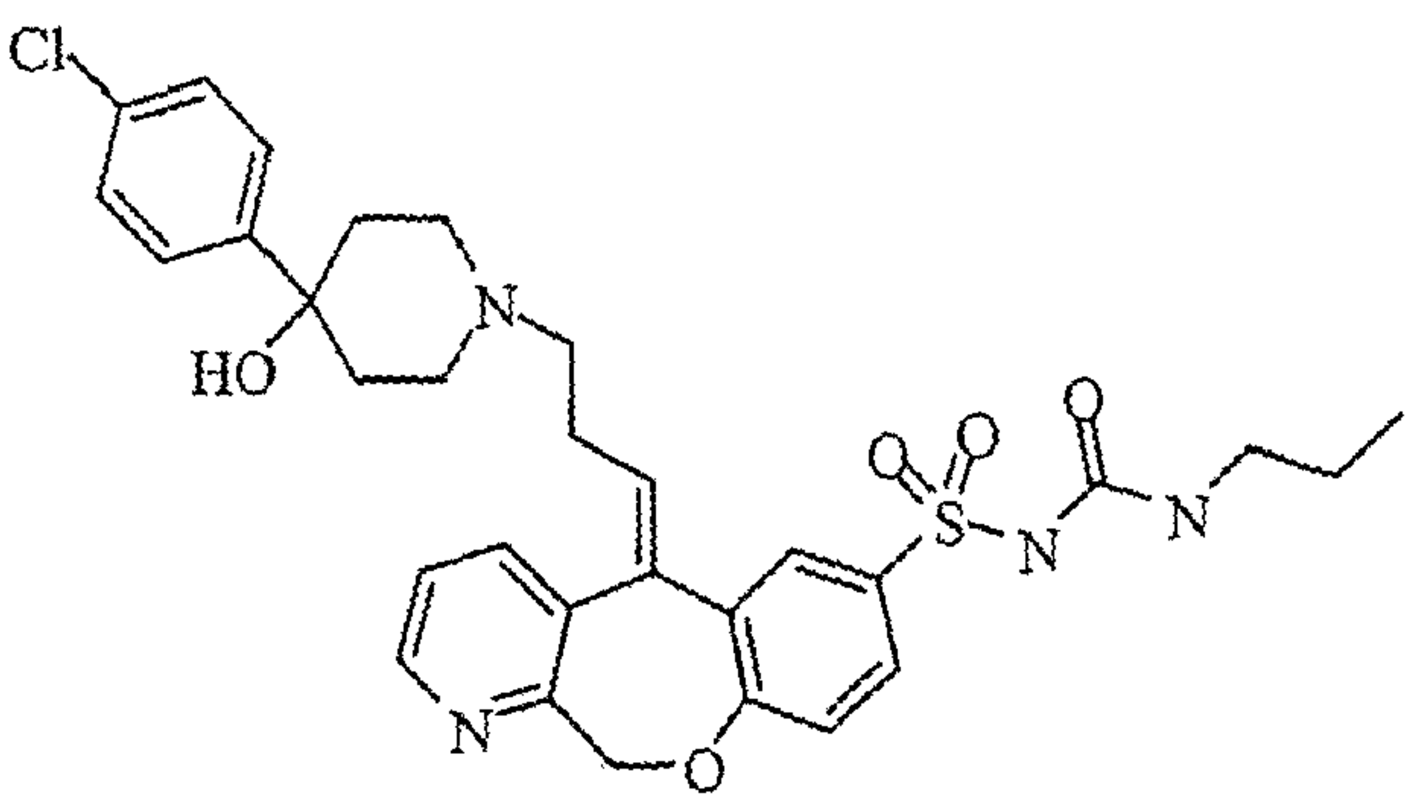
Example 398



Example 399

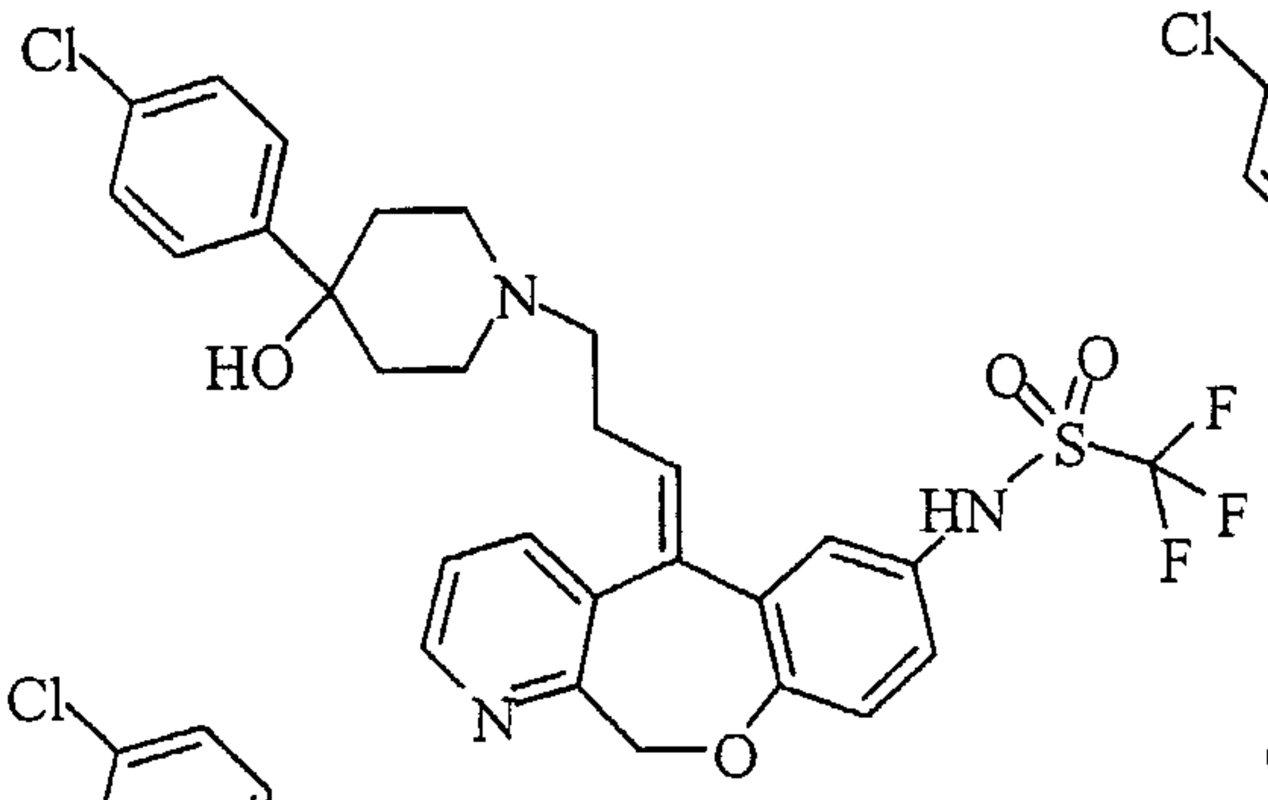


Example 400

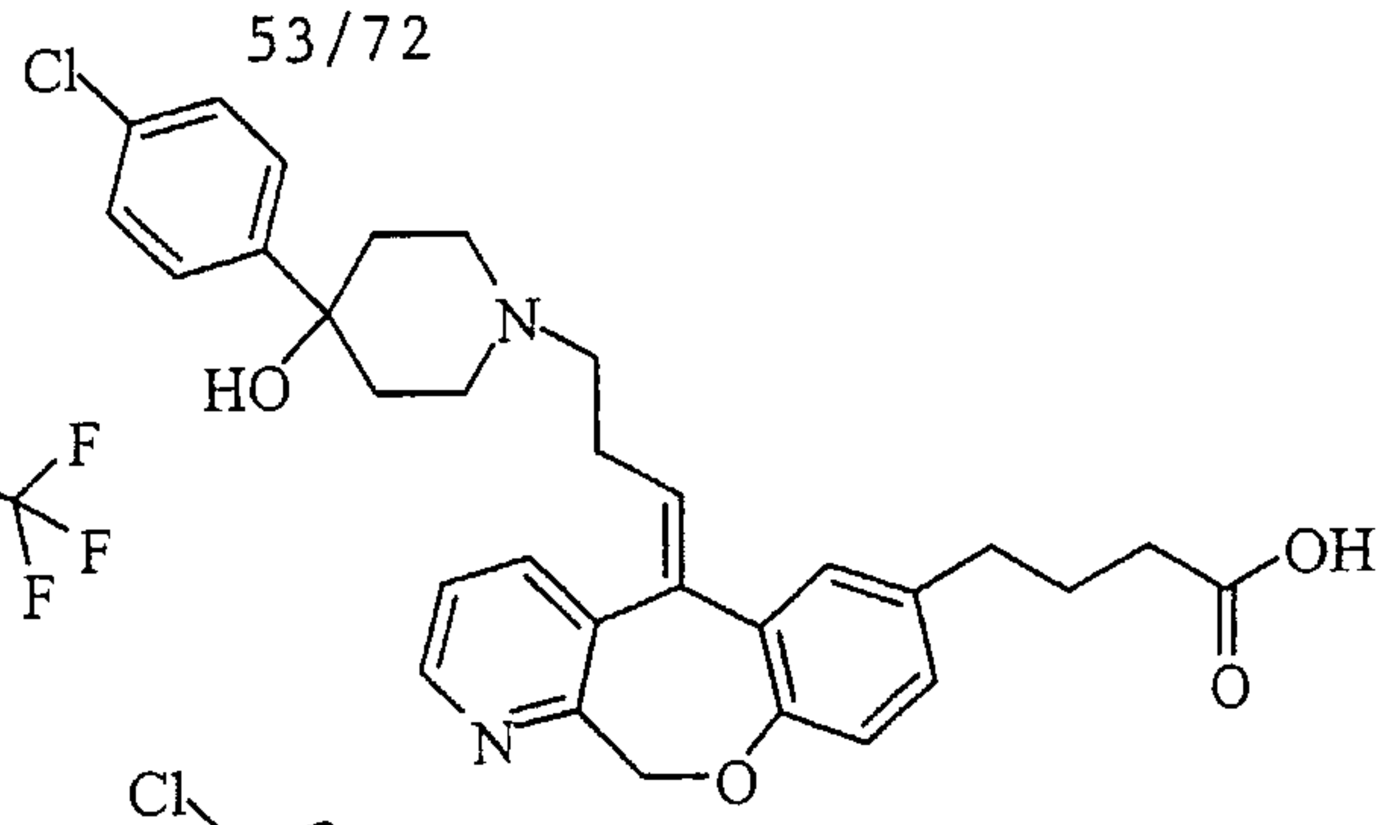


Example 401

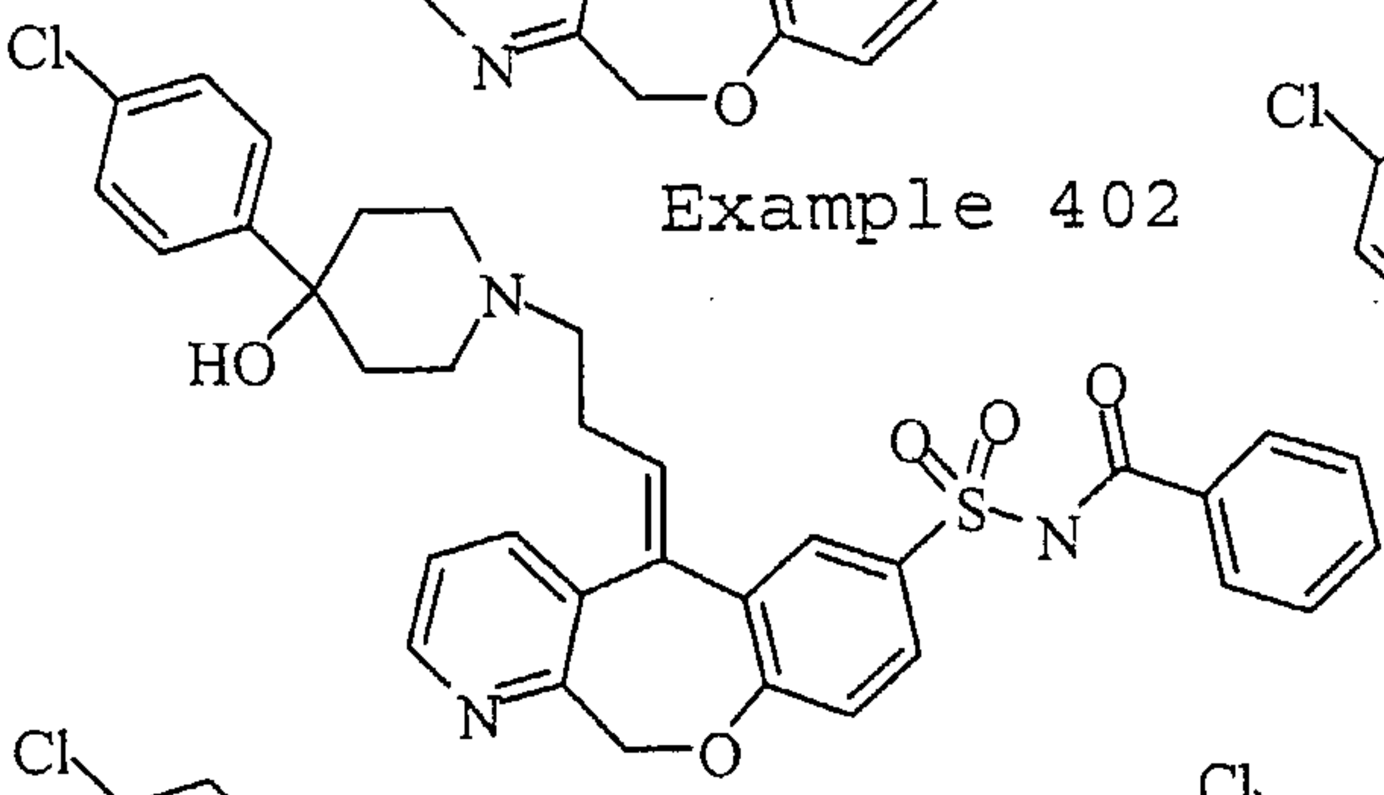
Figure 11P



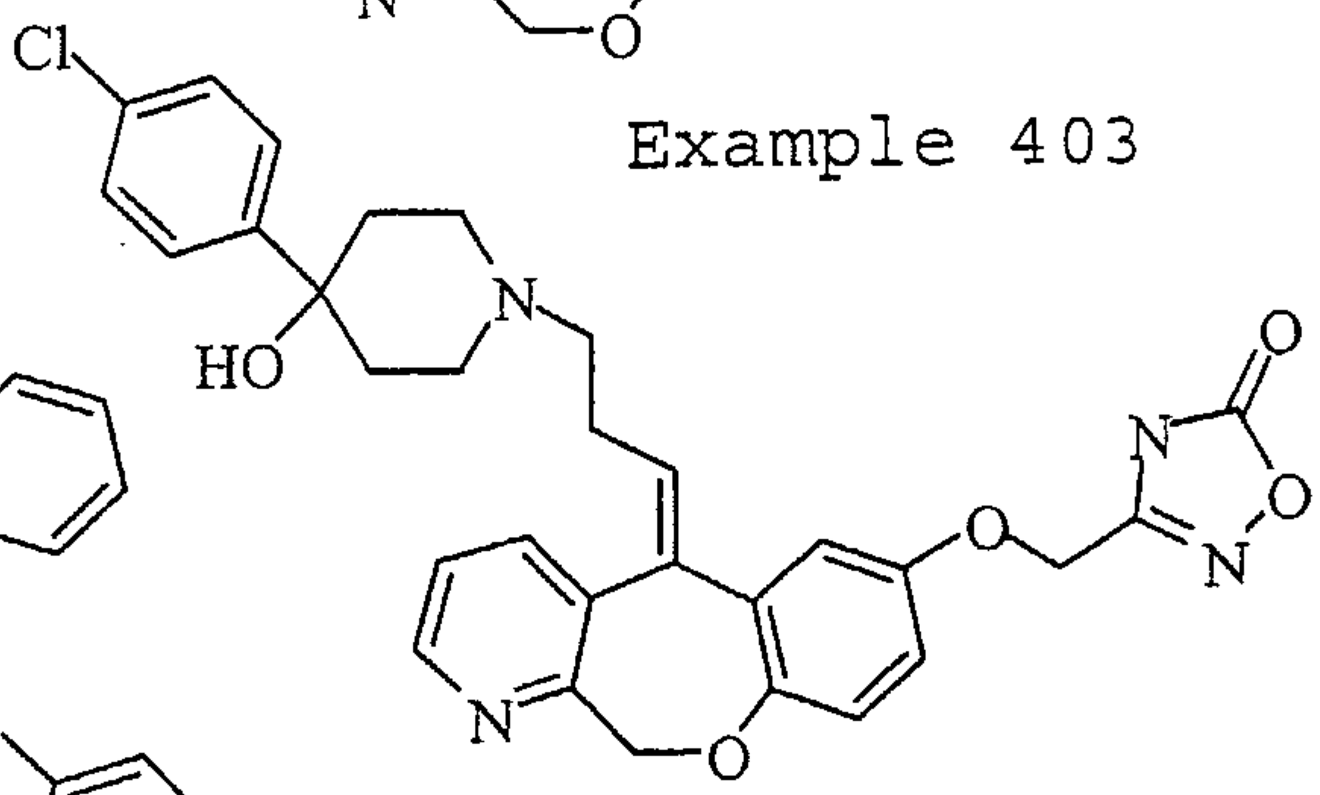
Example 402



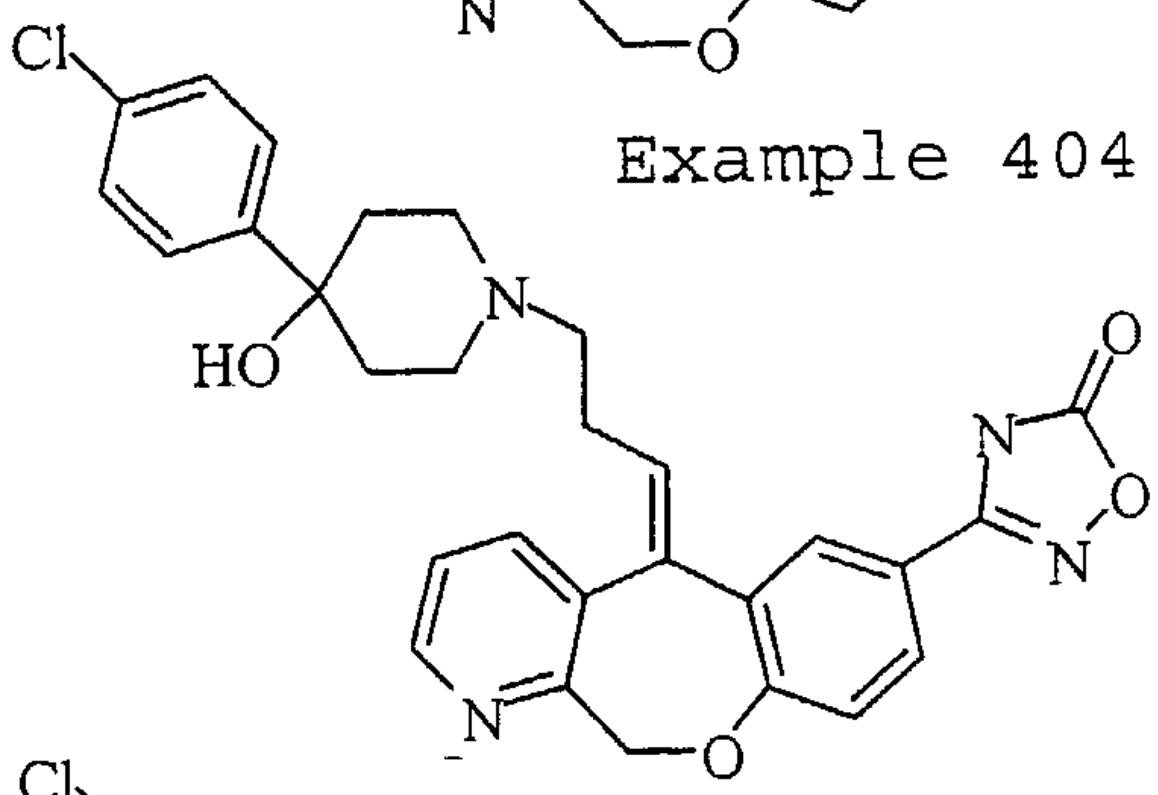
Example 403



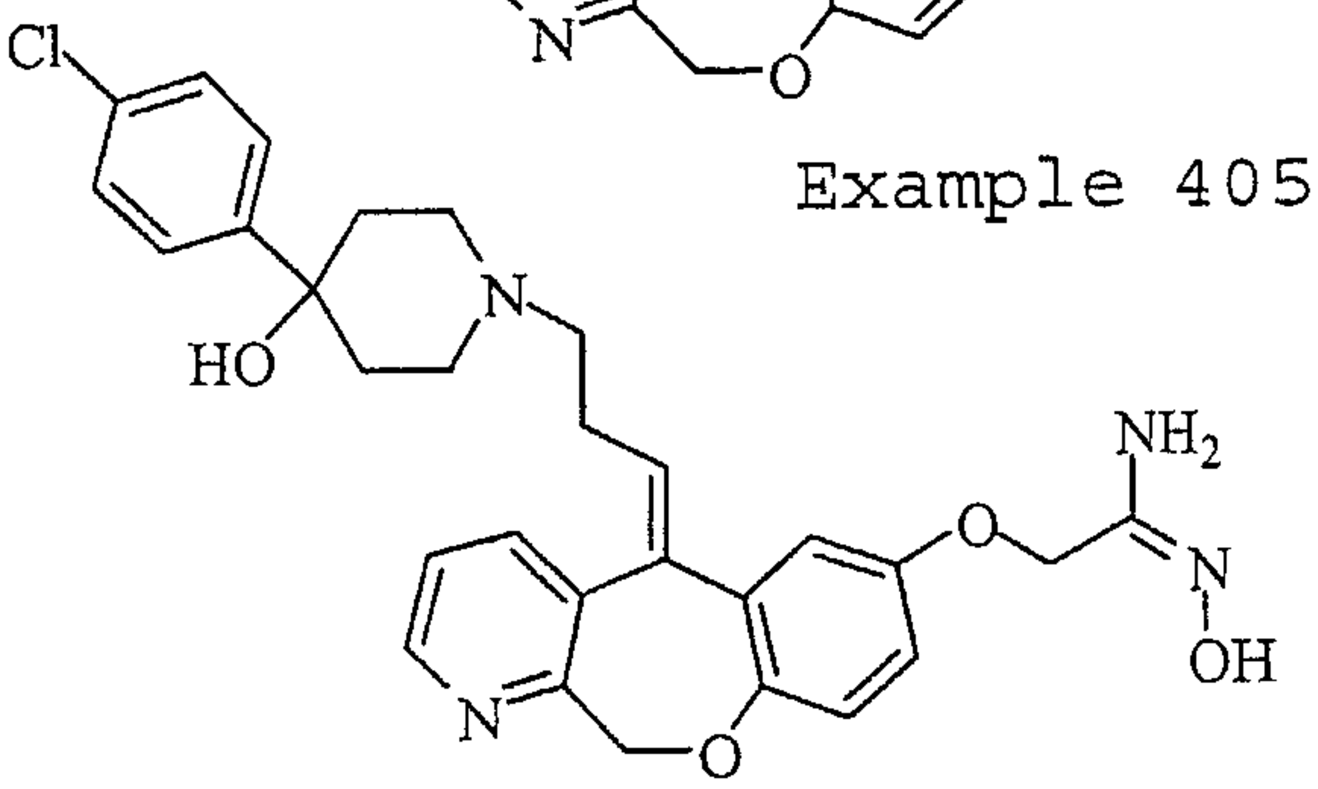
Example 404



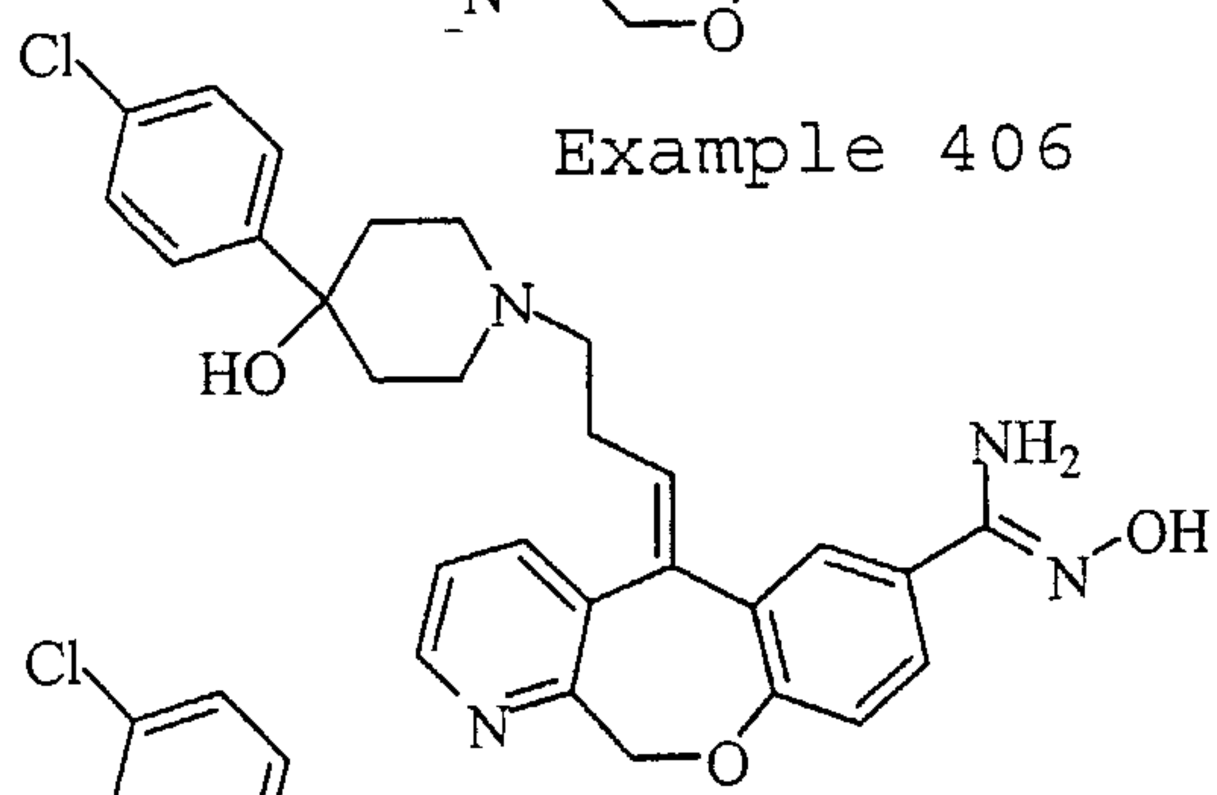
Example 405



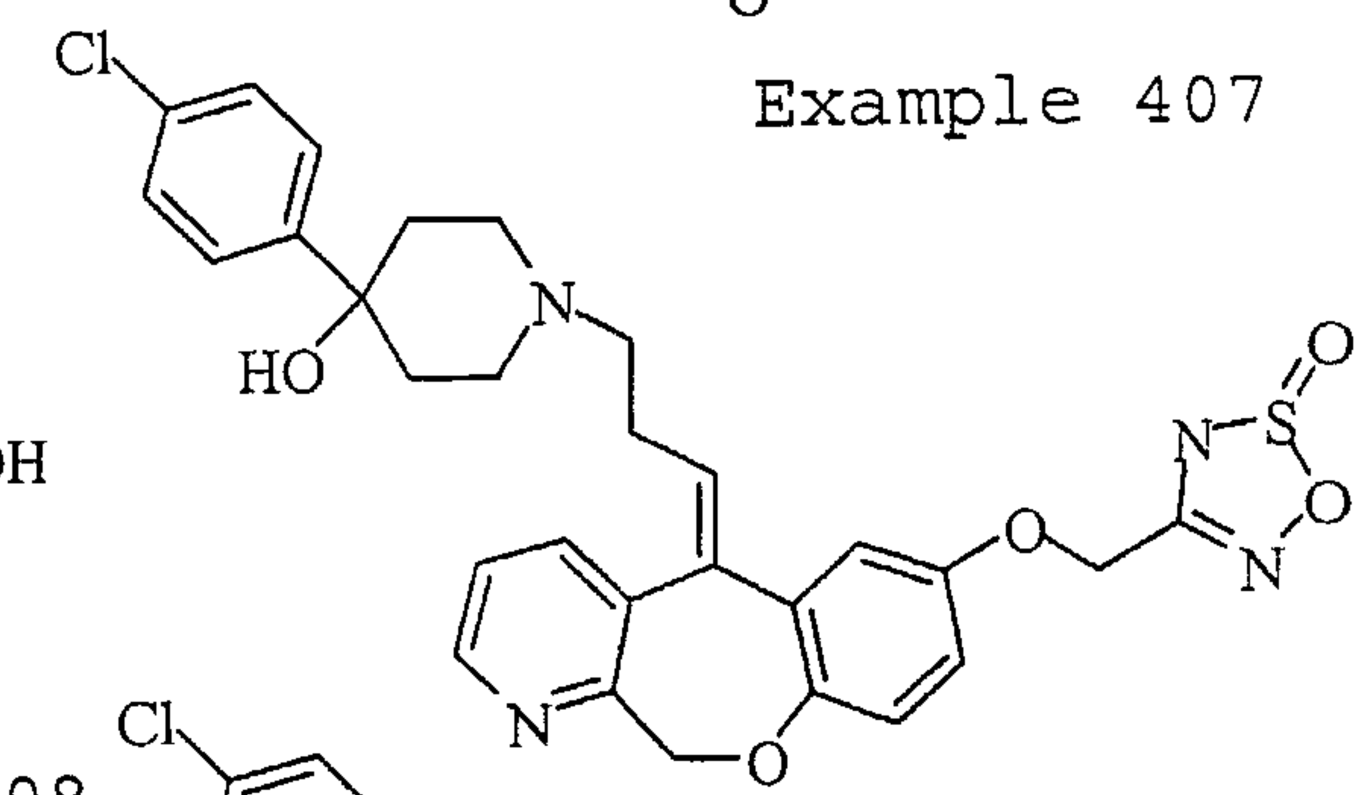
Example 406



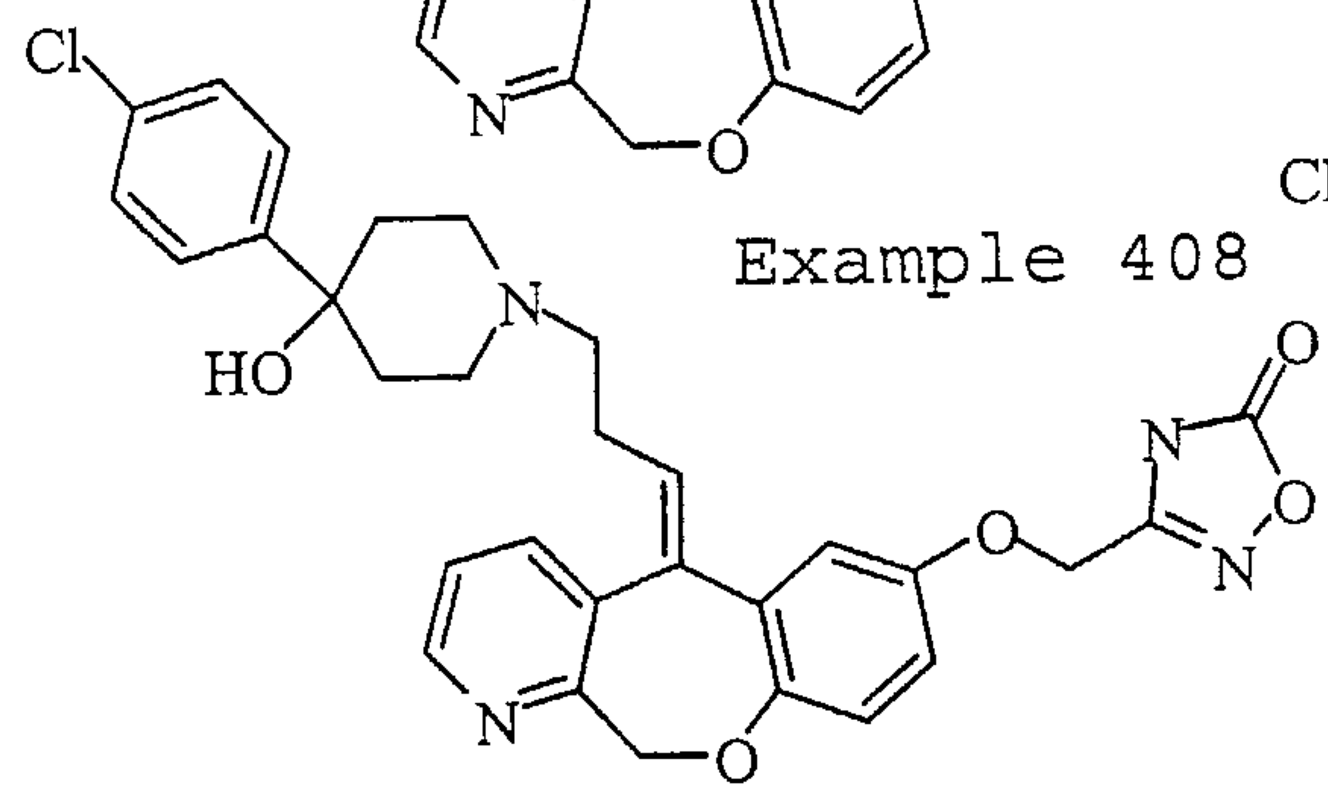
Example 407



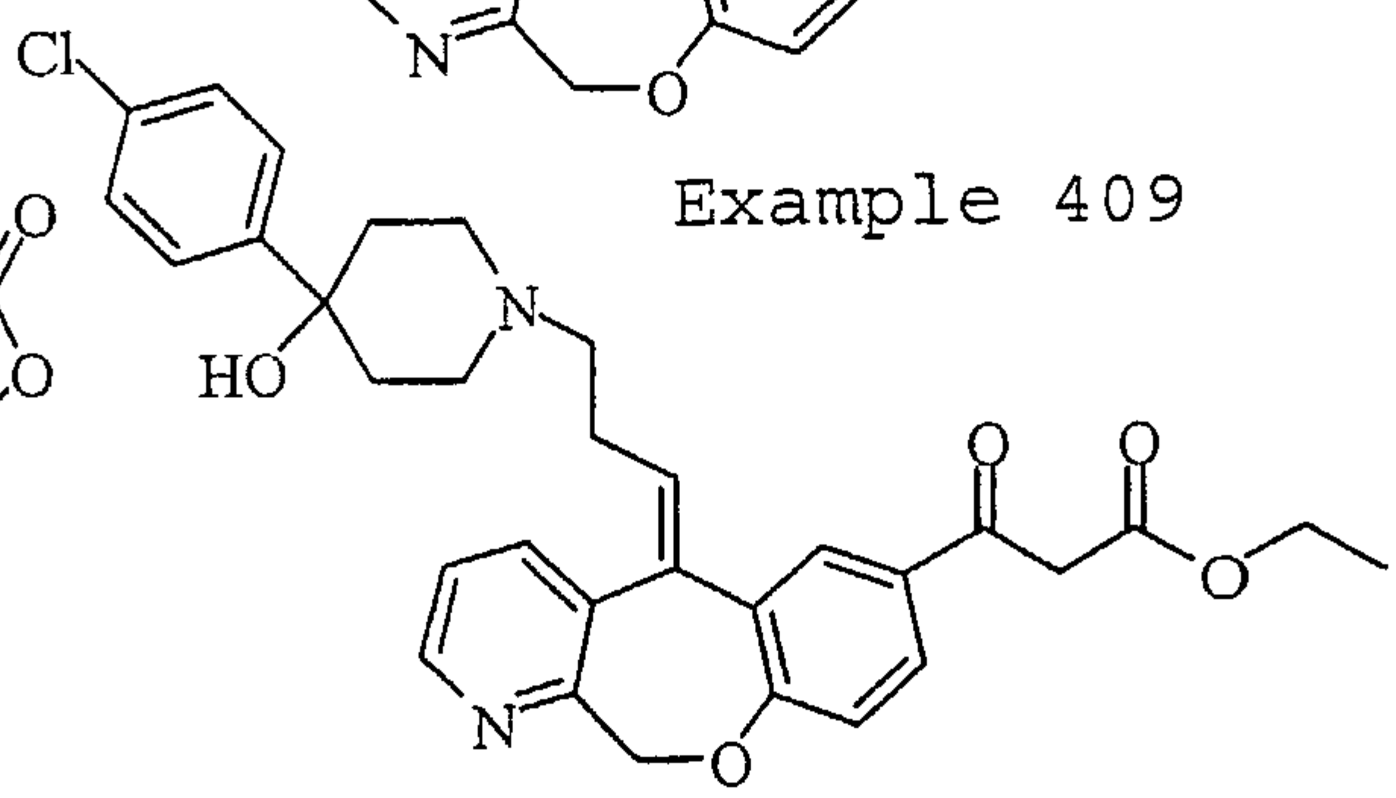
Example 408



Example 409

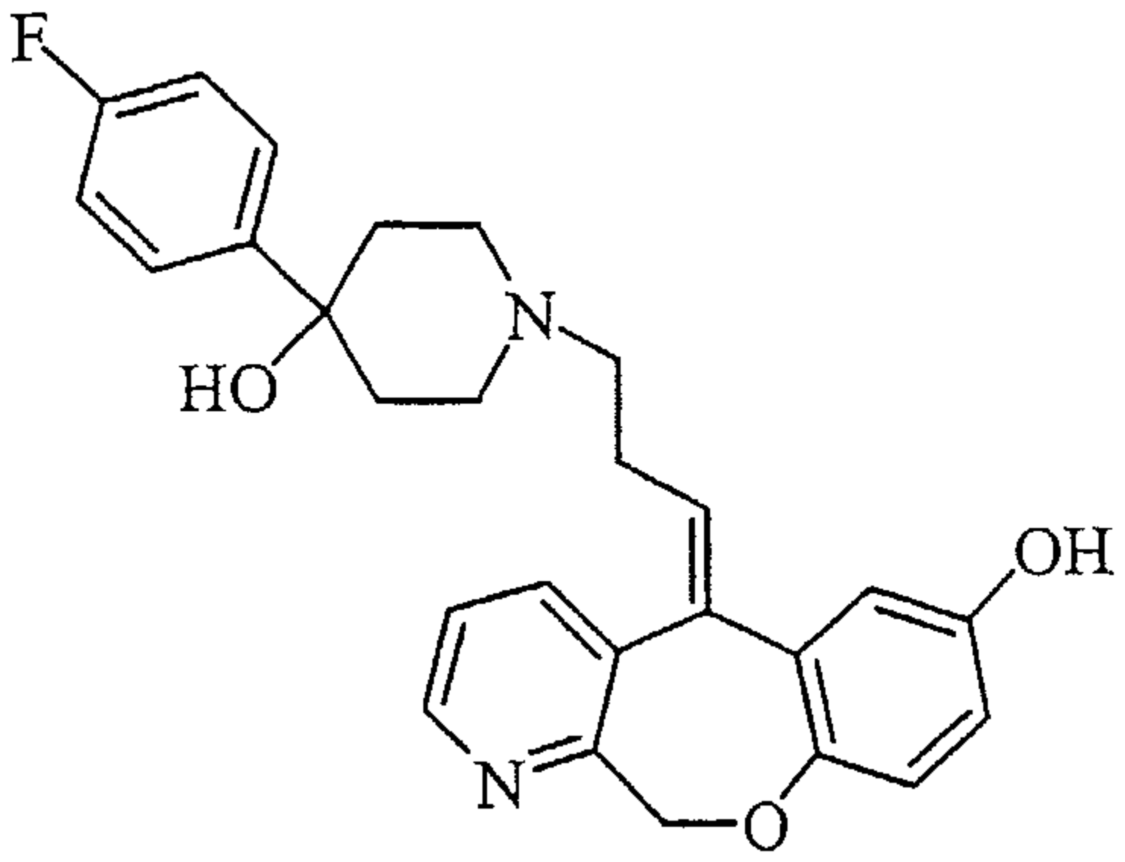


Example 410

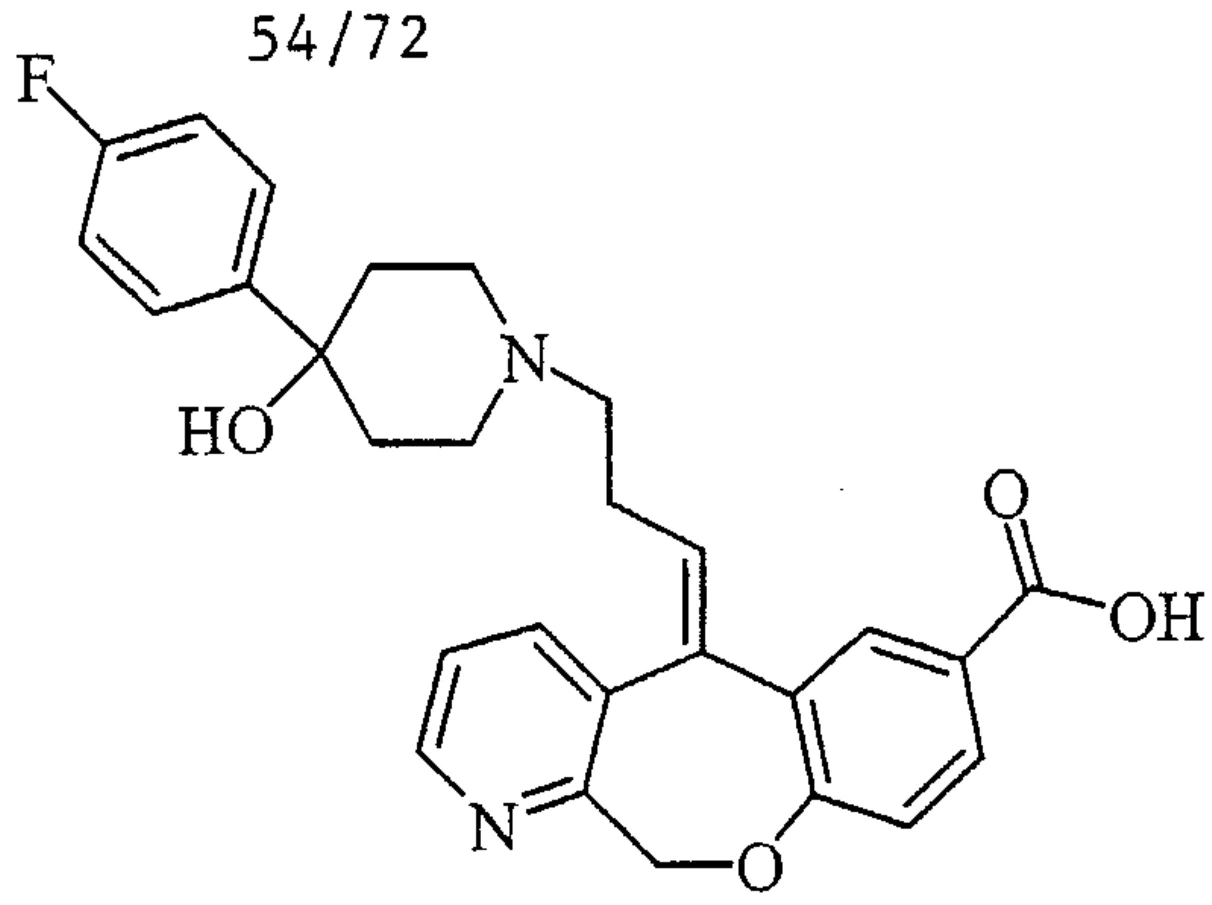


Example 411

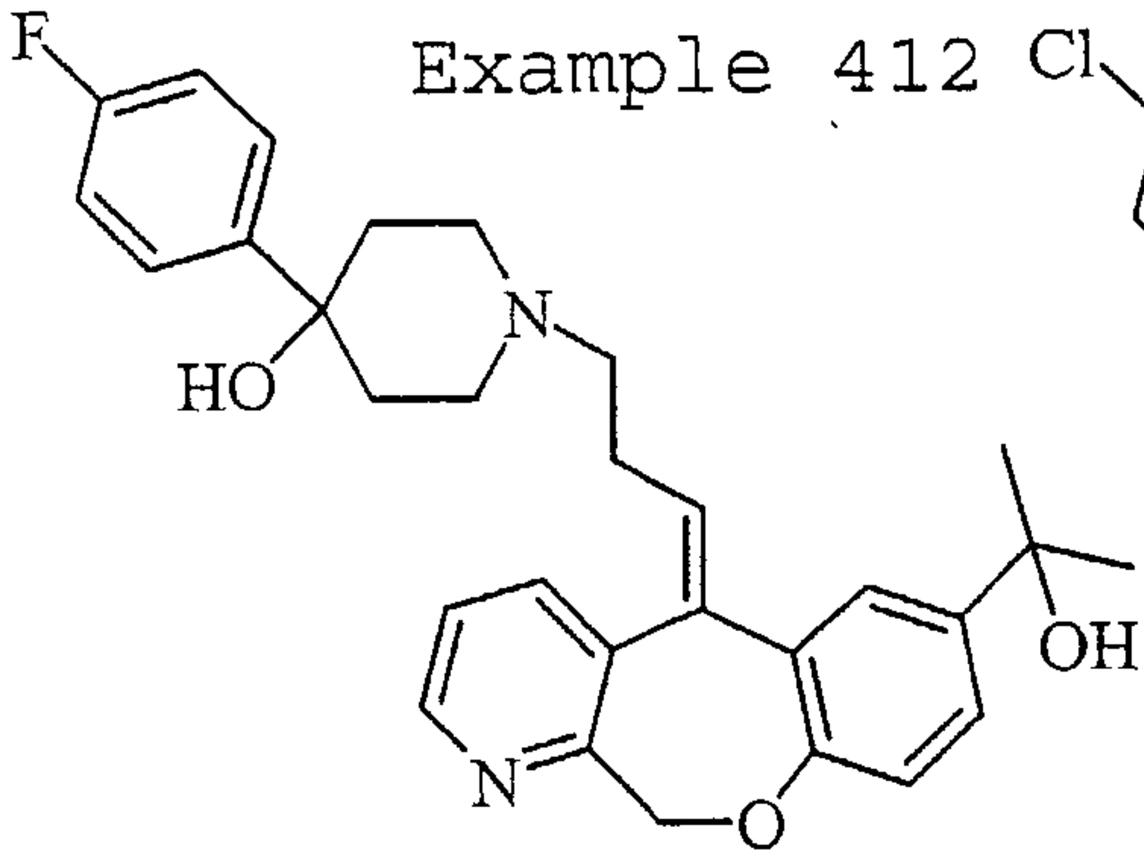
Figure 11Q



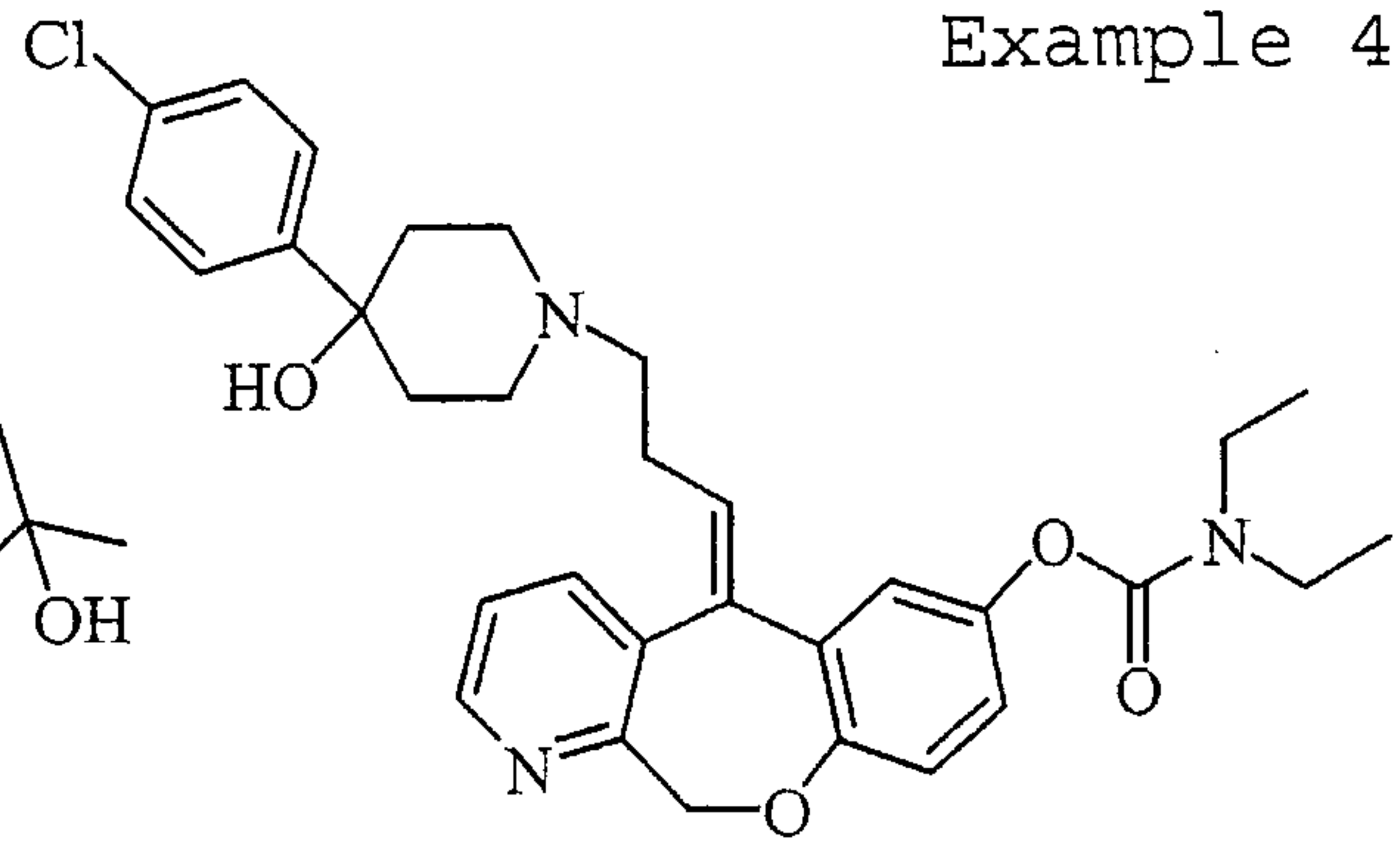
Example 412



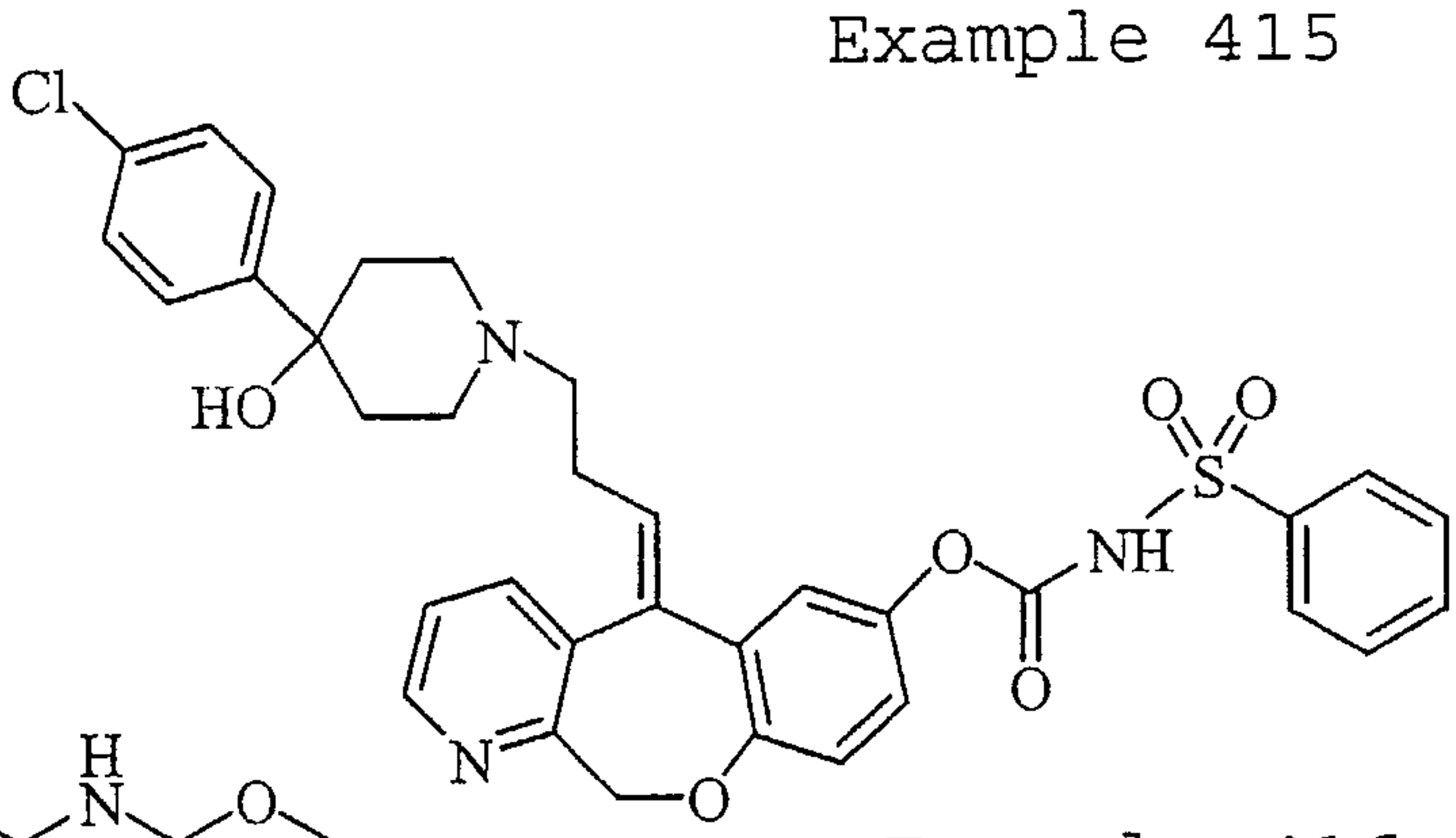
Example 413



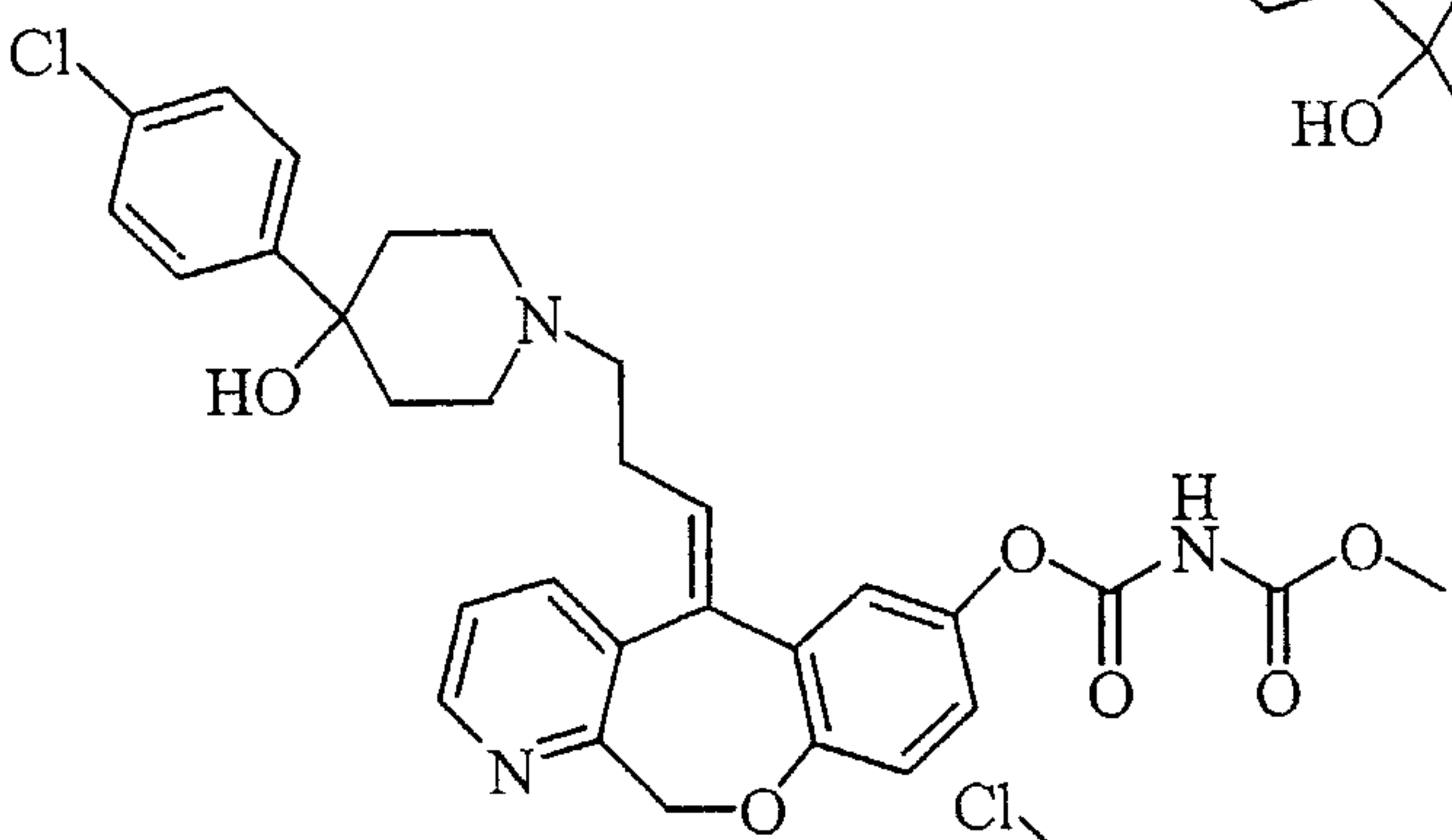
Example 414



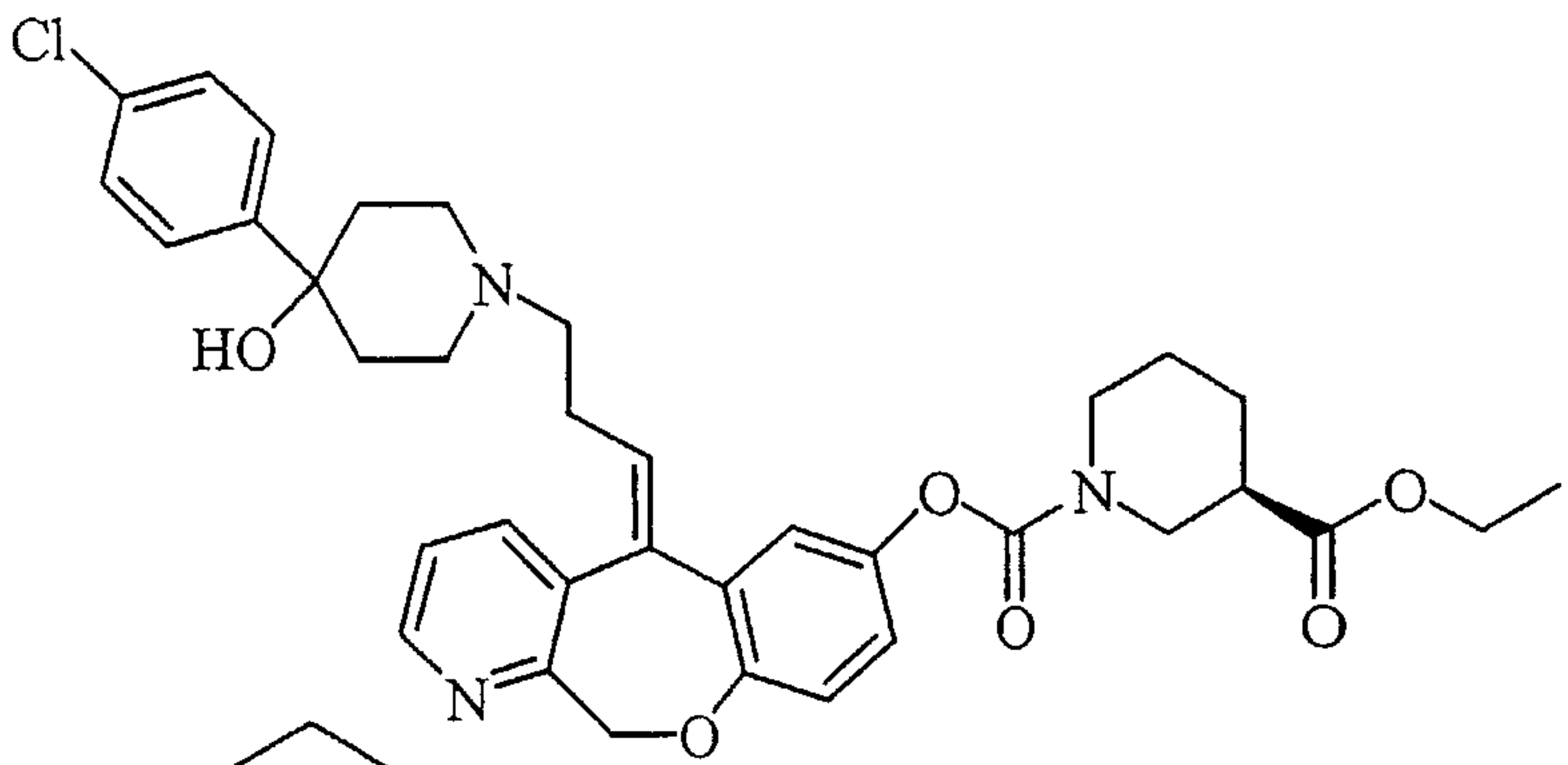
Example 415



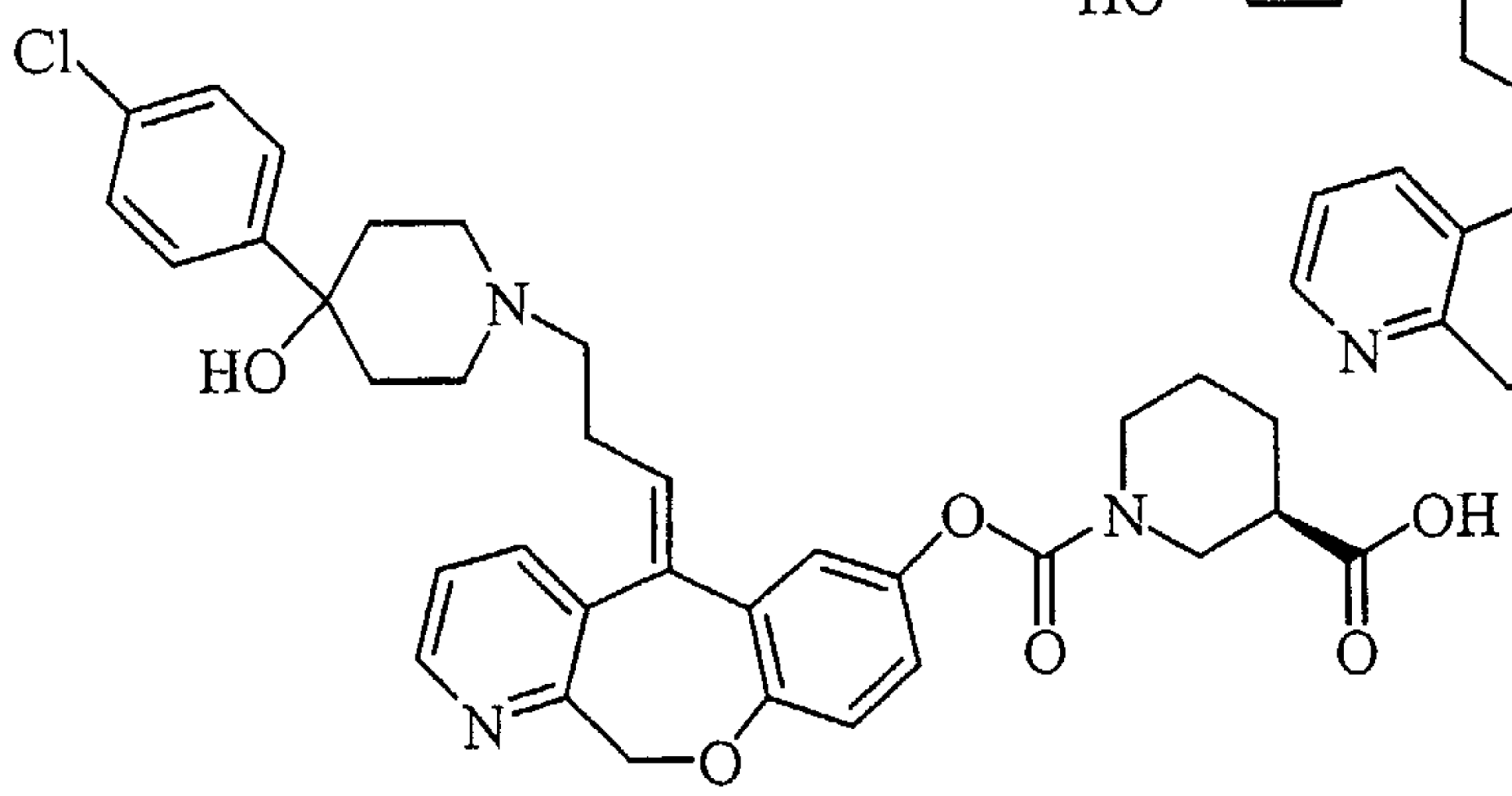
Example 416



Example 417

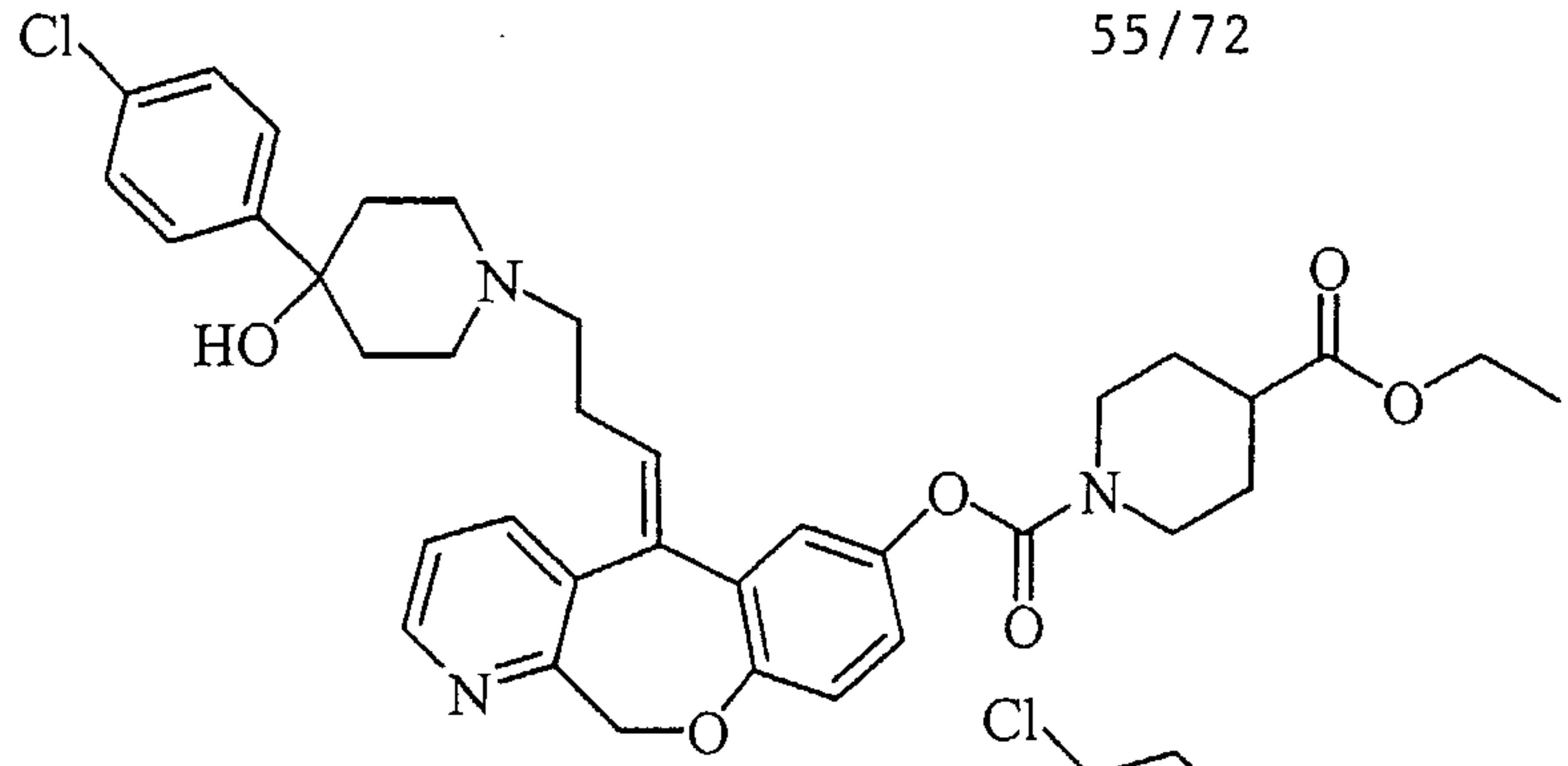


Example 418

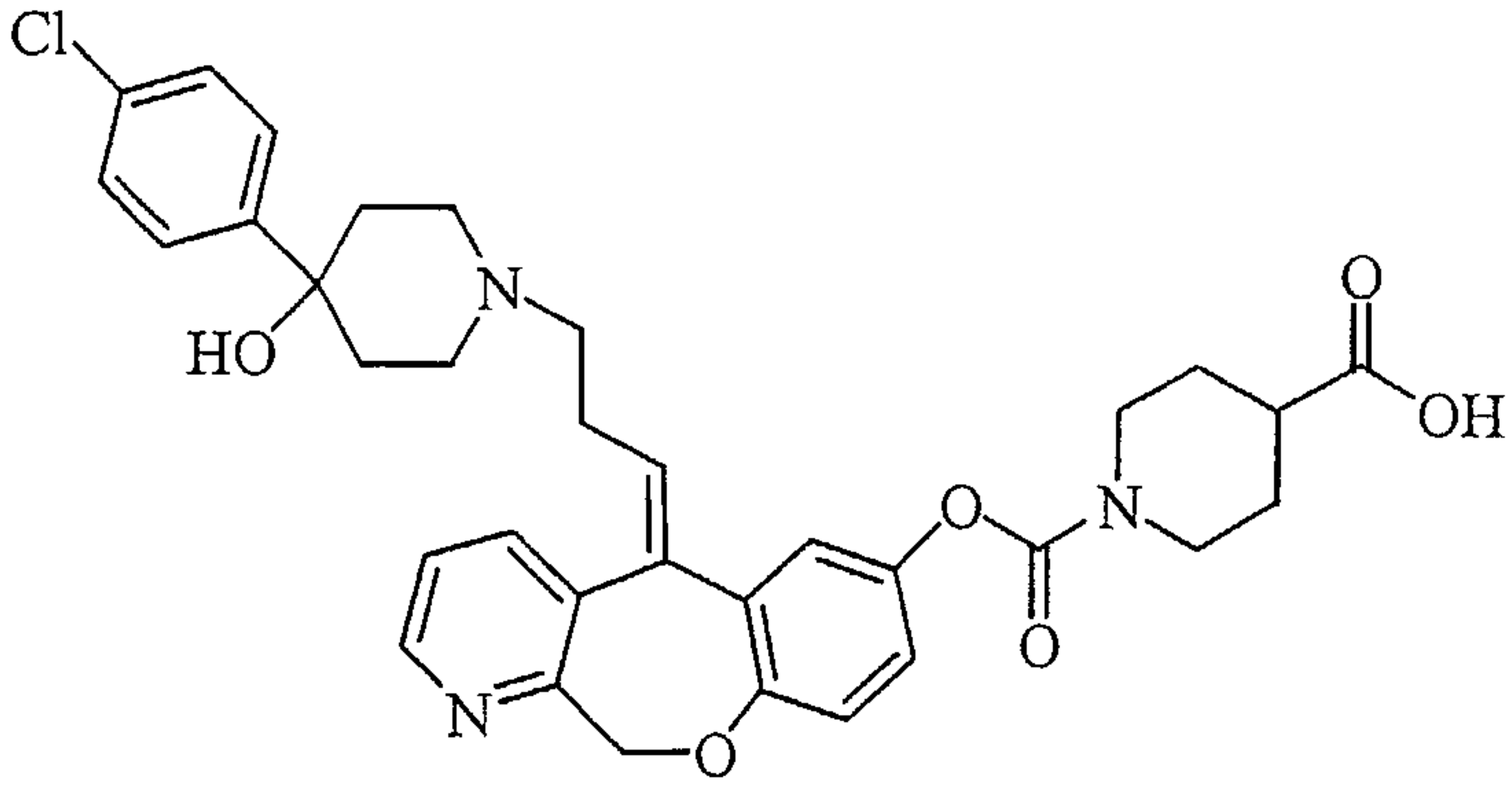


Example 419

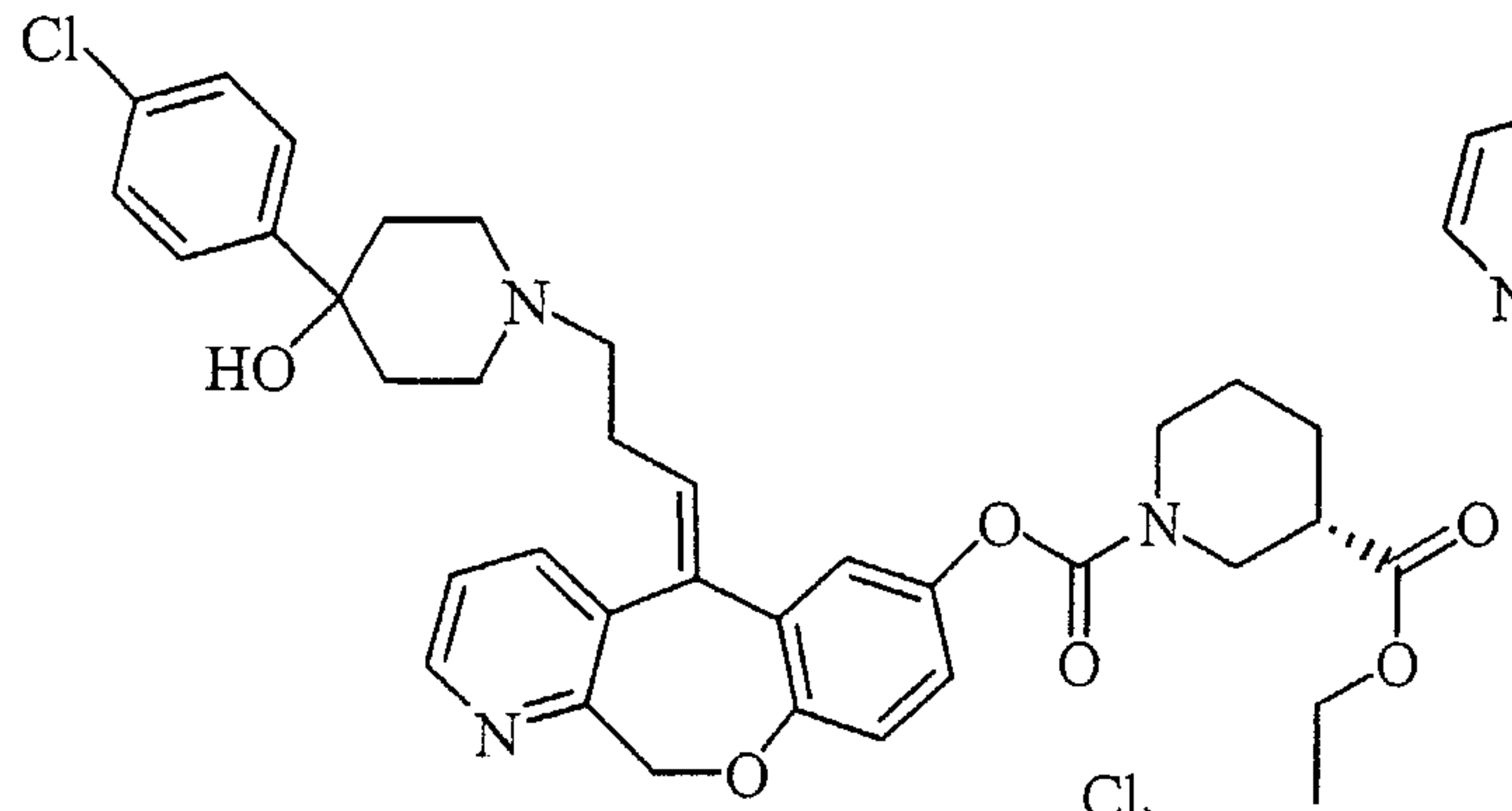
Figure 11R



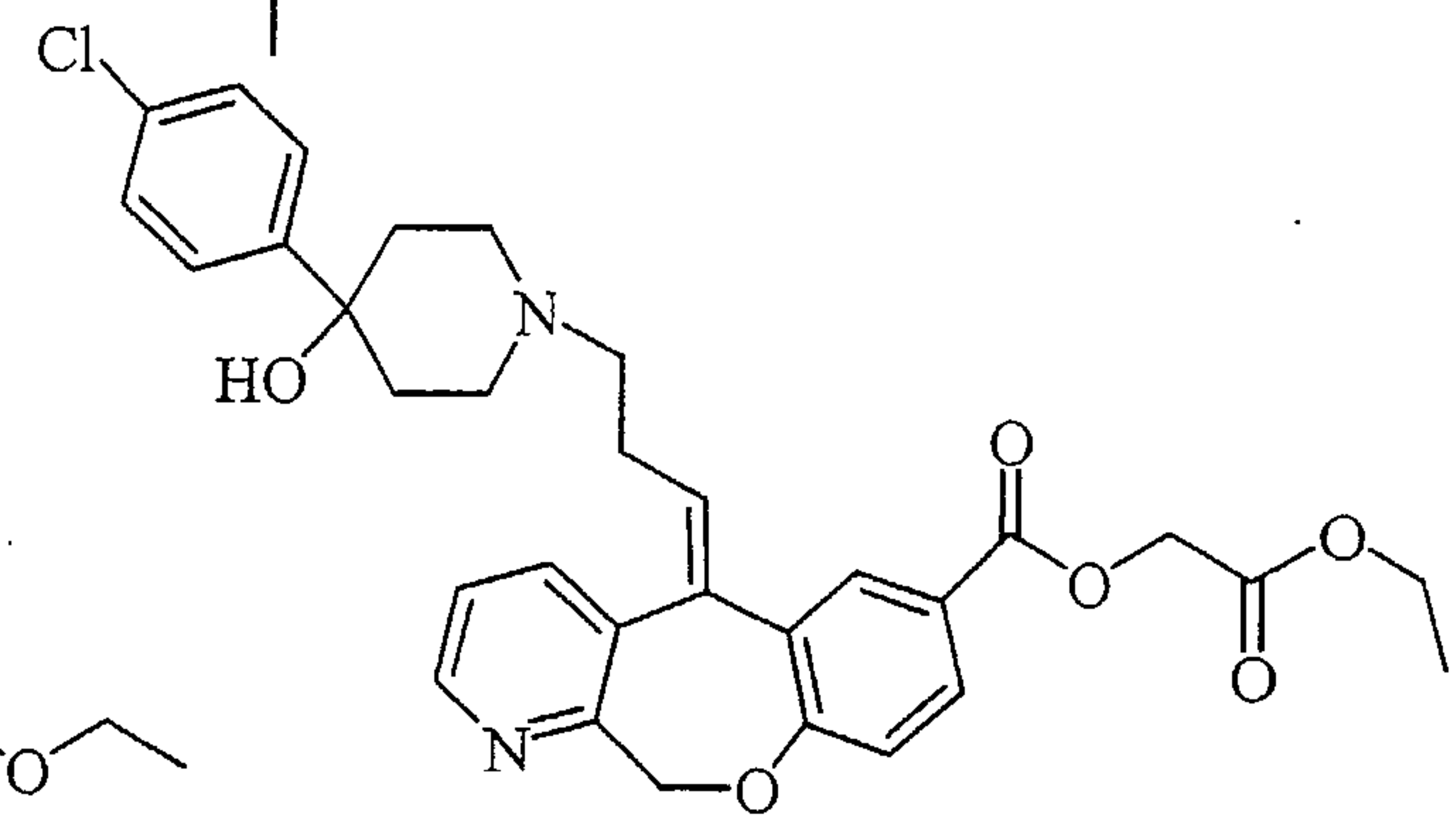
Example 420



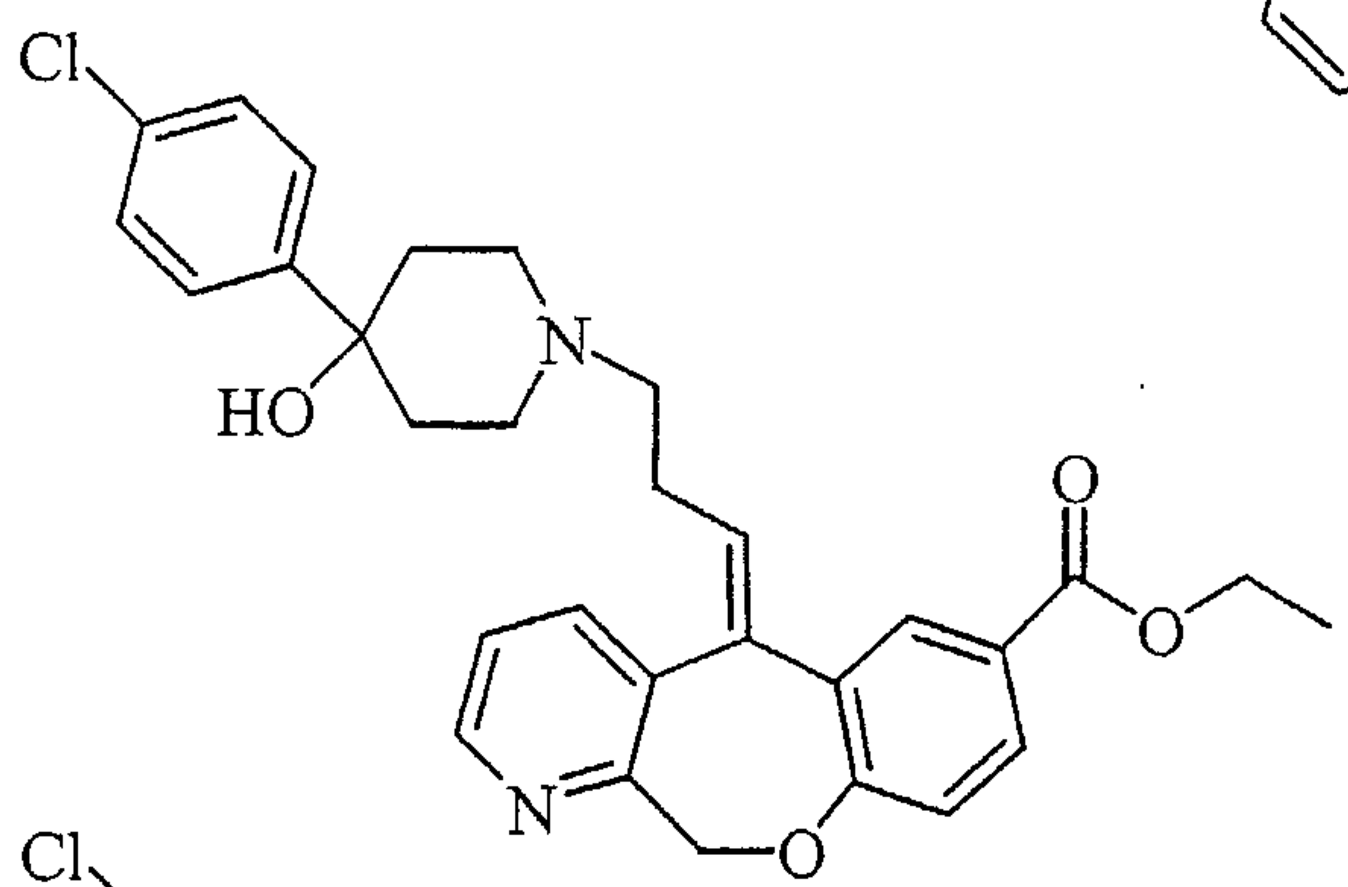
Example 421



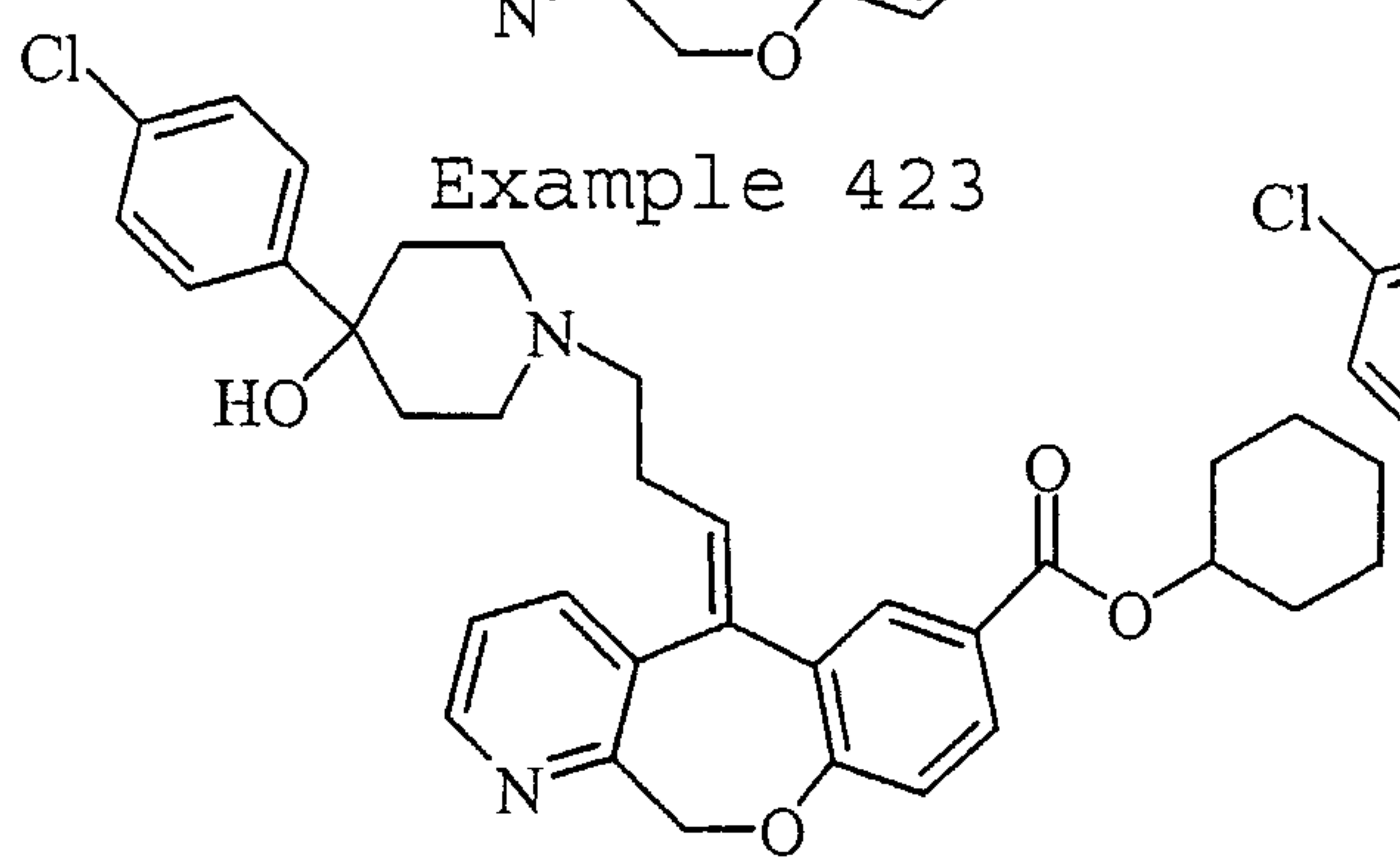
Example 422



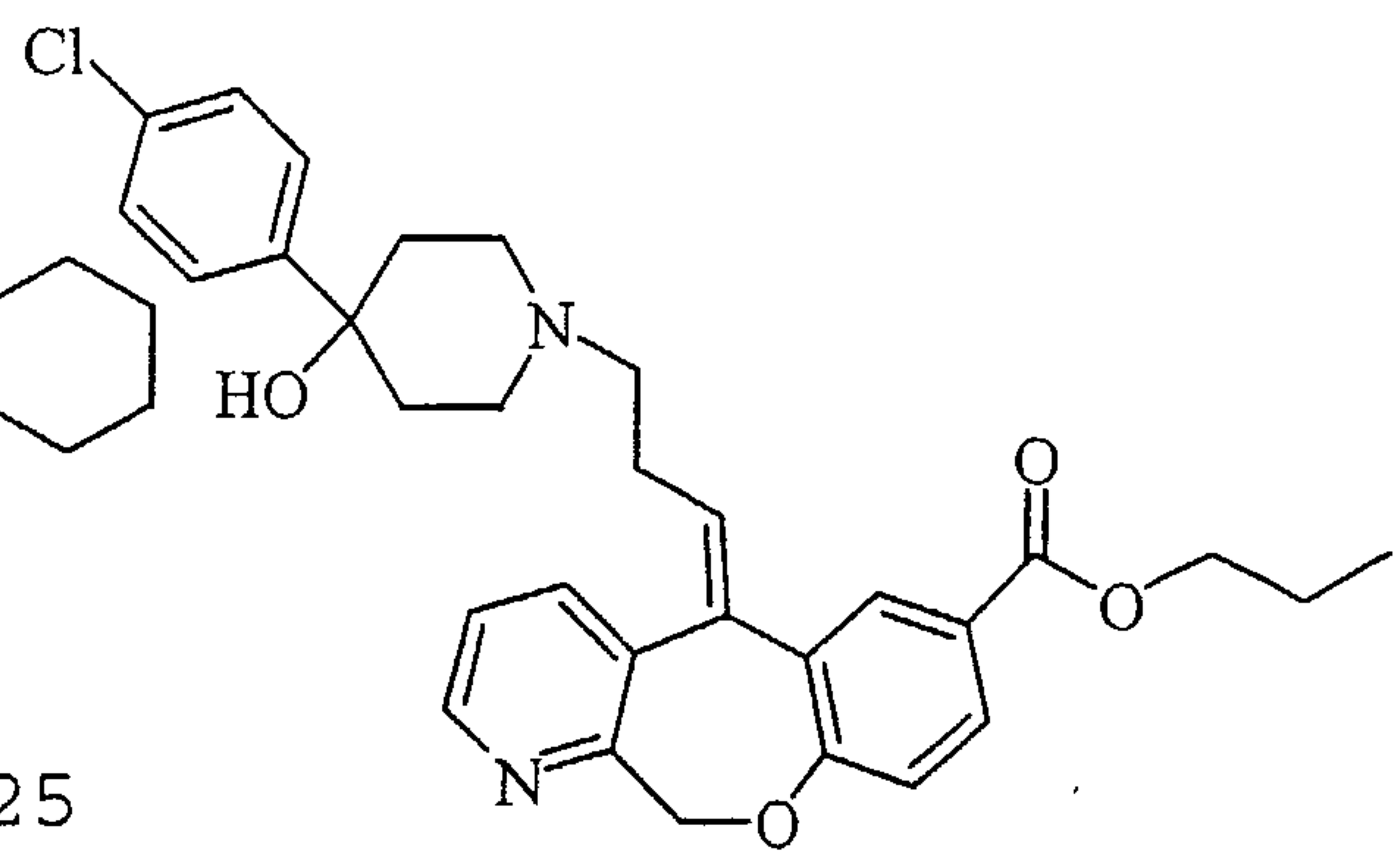
Example 424



Example 423

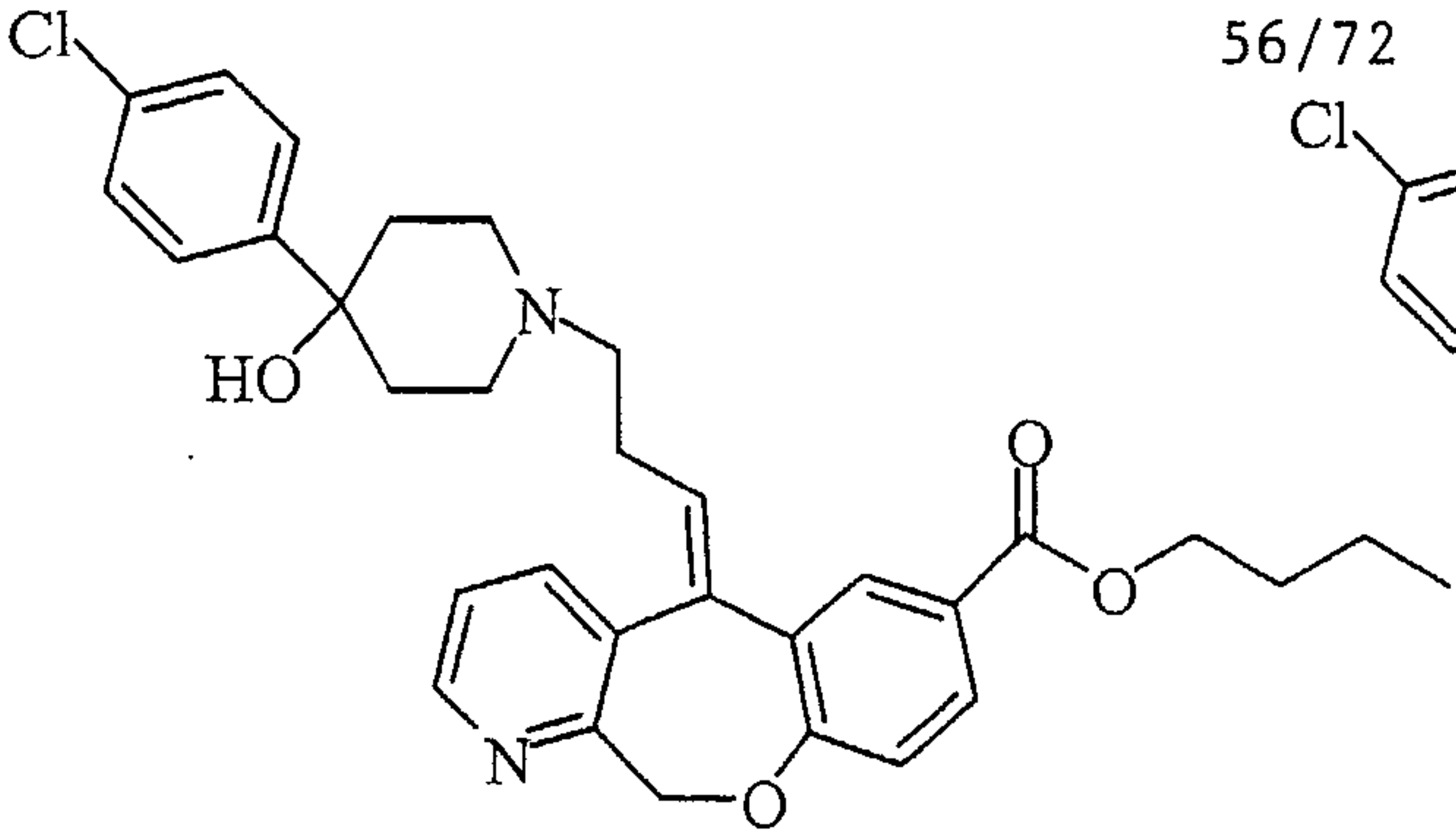


Example 425

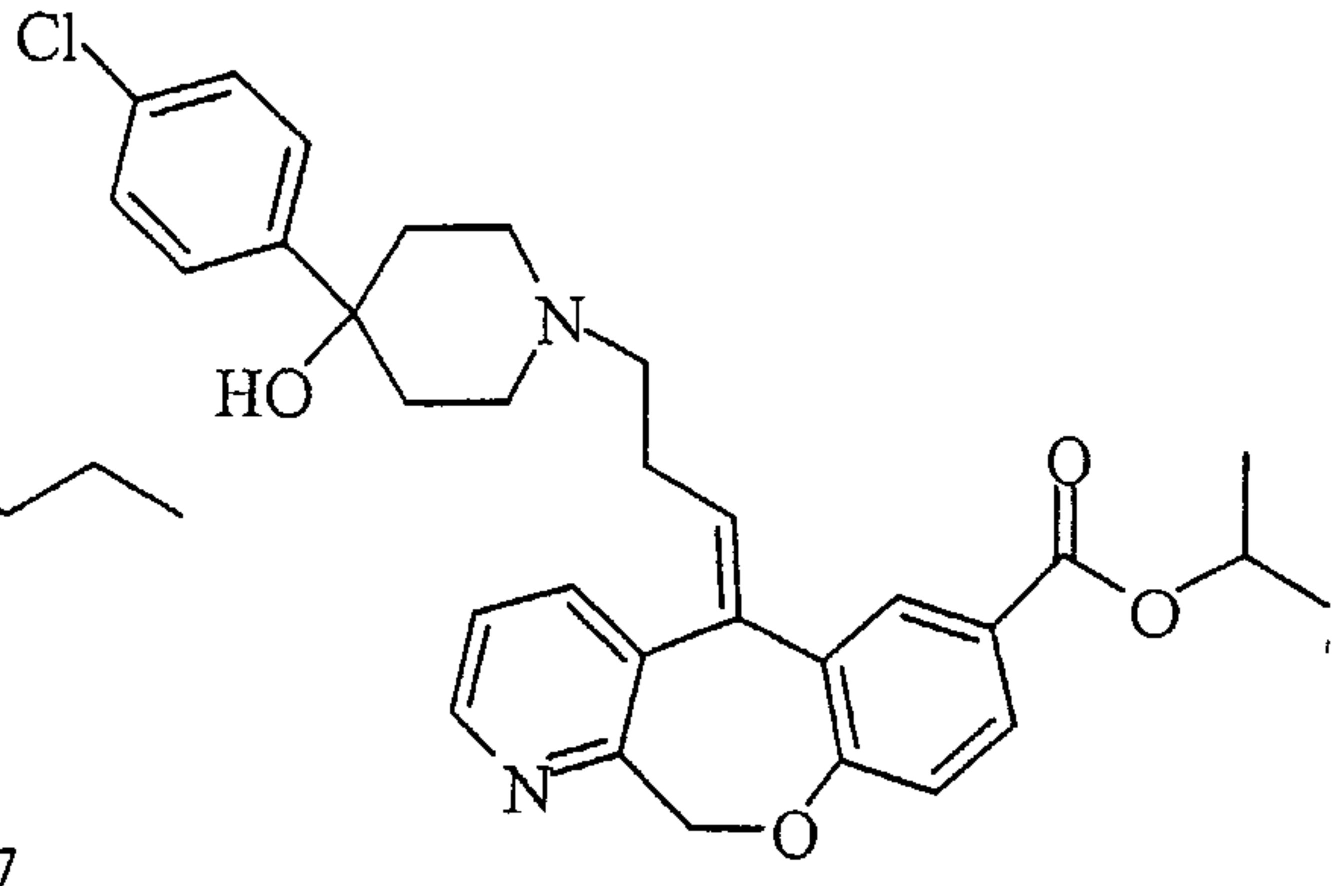


Example 426

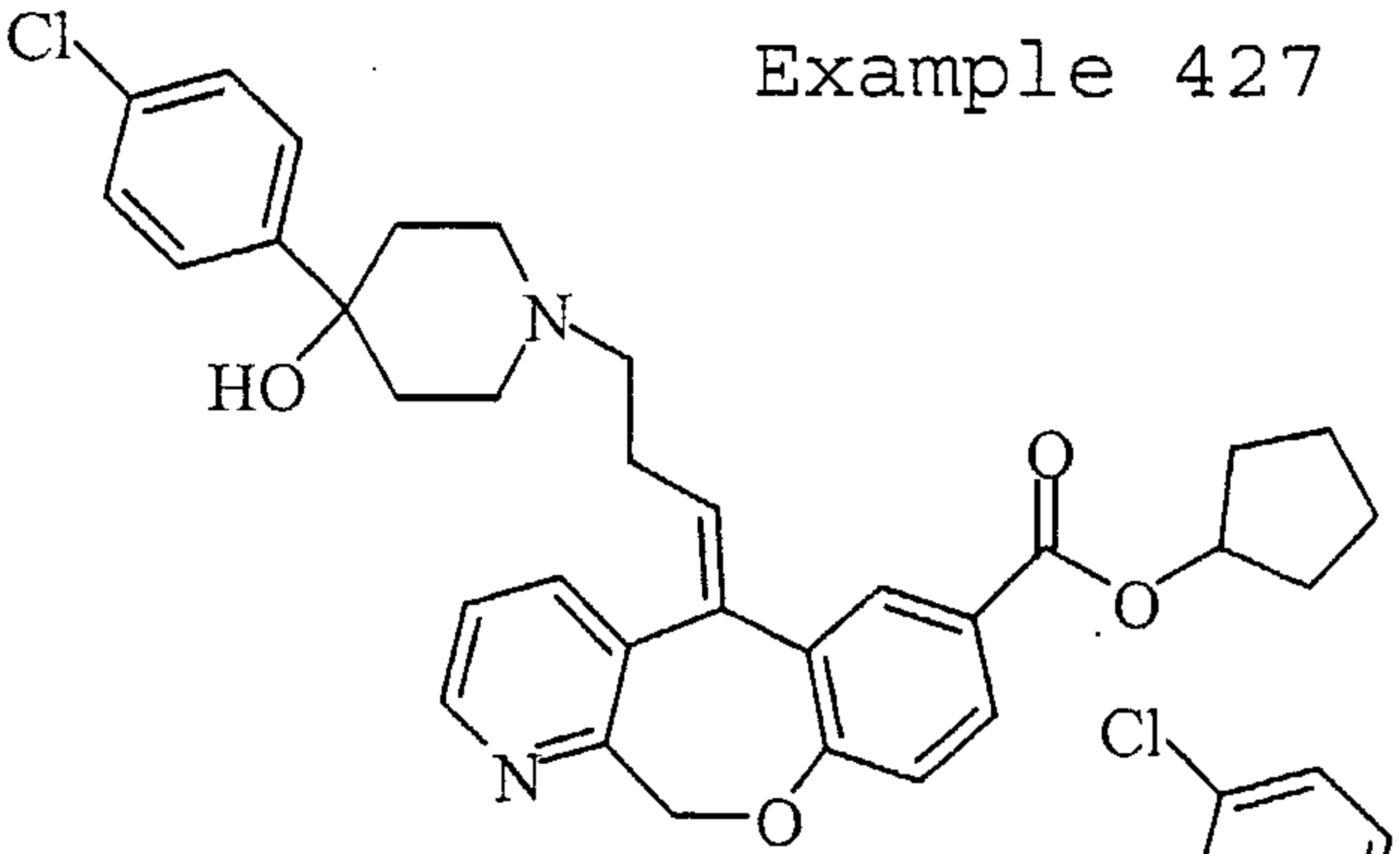
Figure 11S



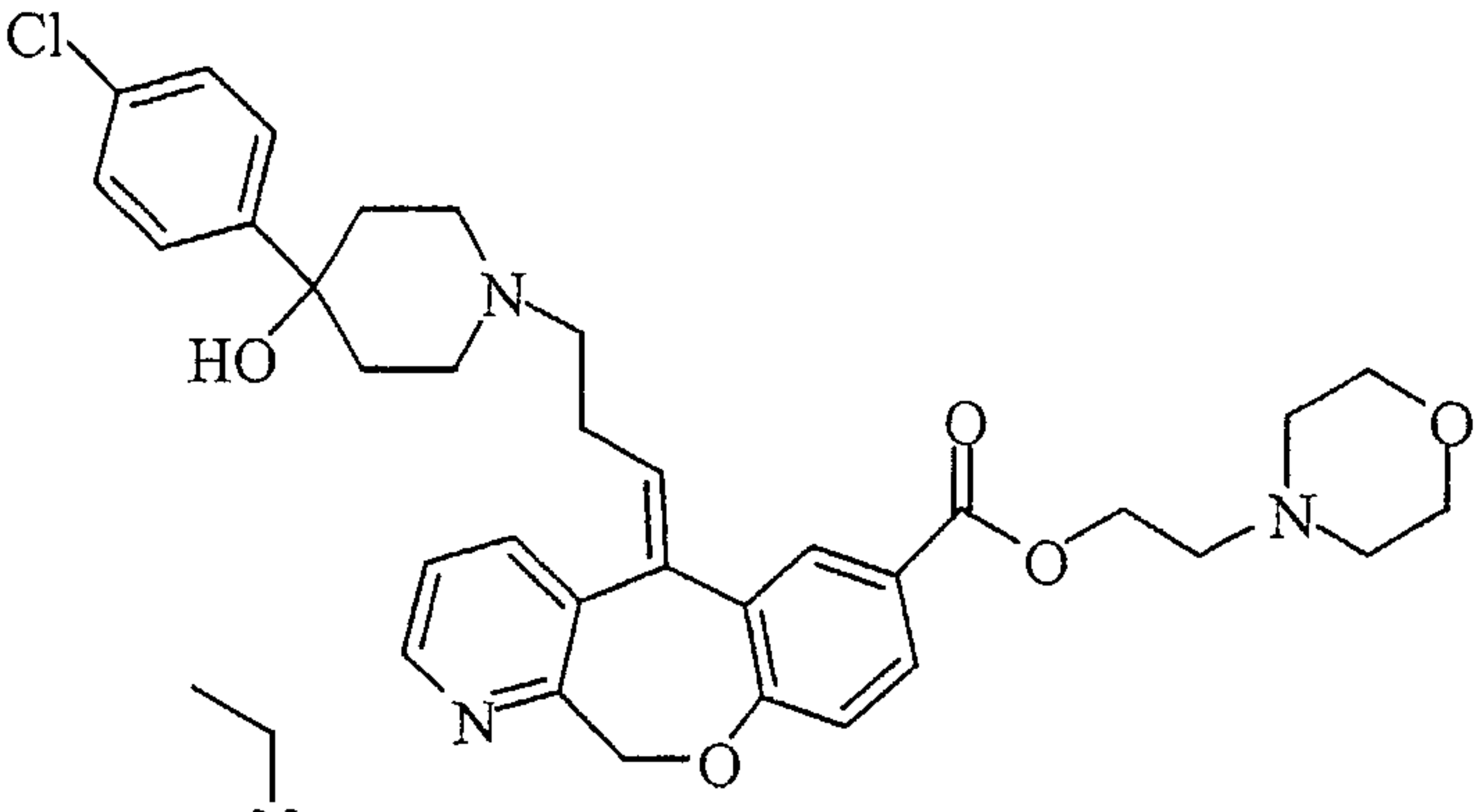
Example 427



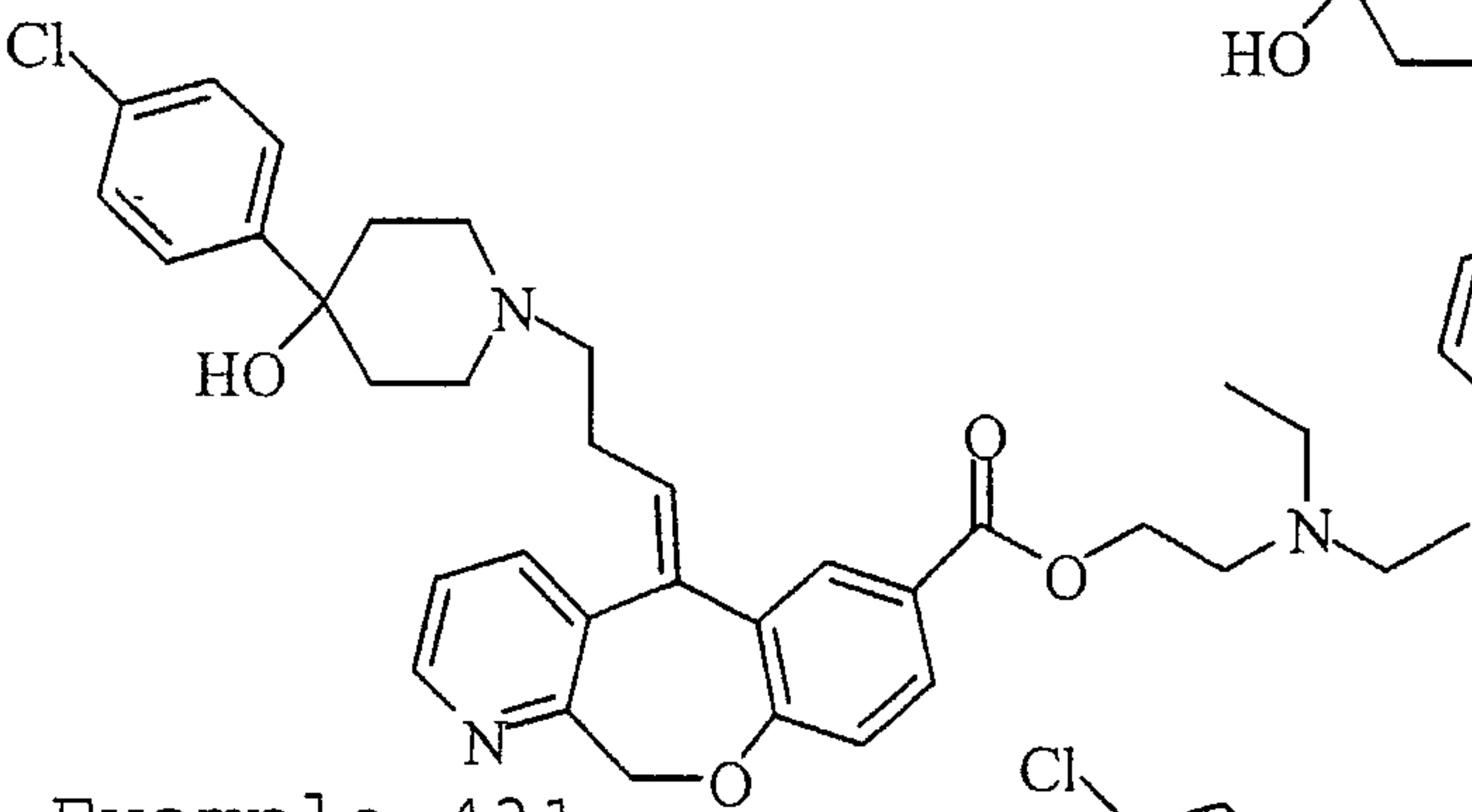
Example 428



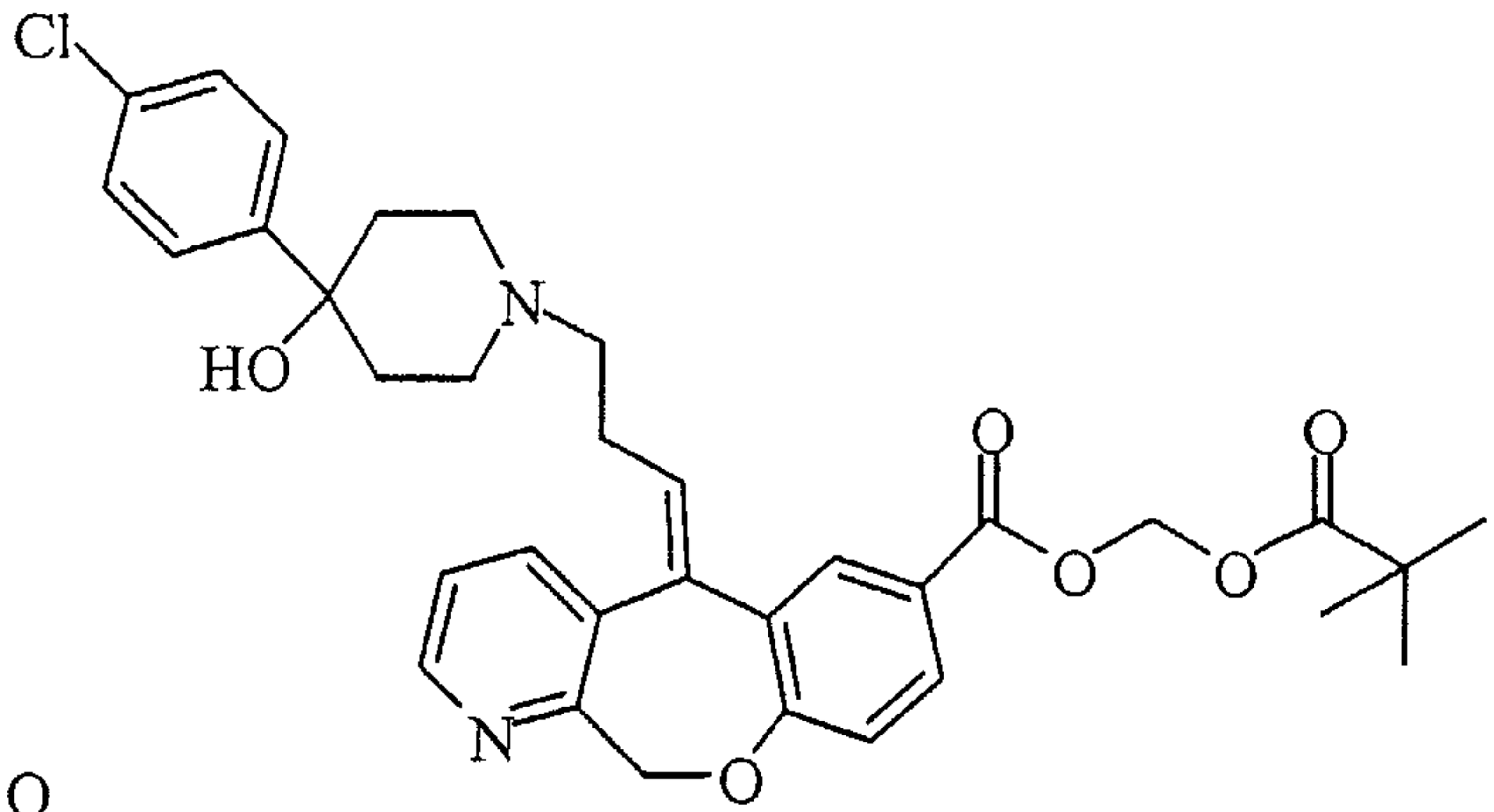
Example 429



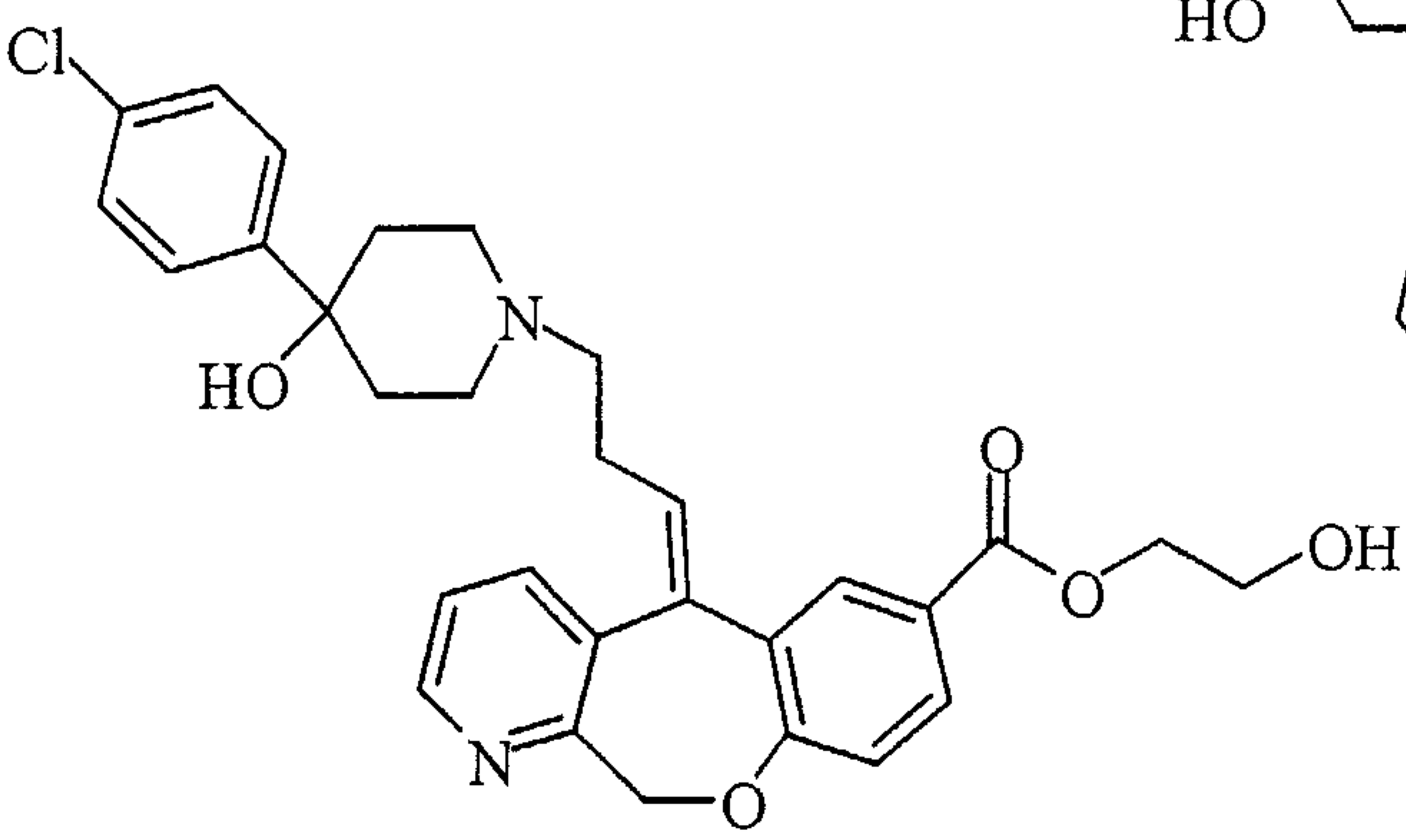
Example 430



Example 431



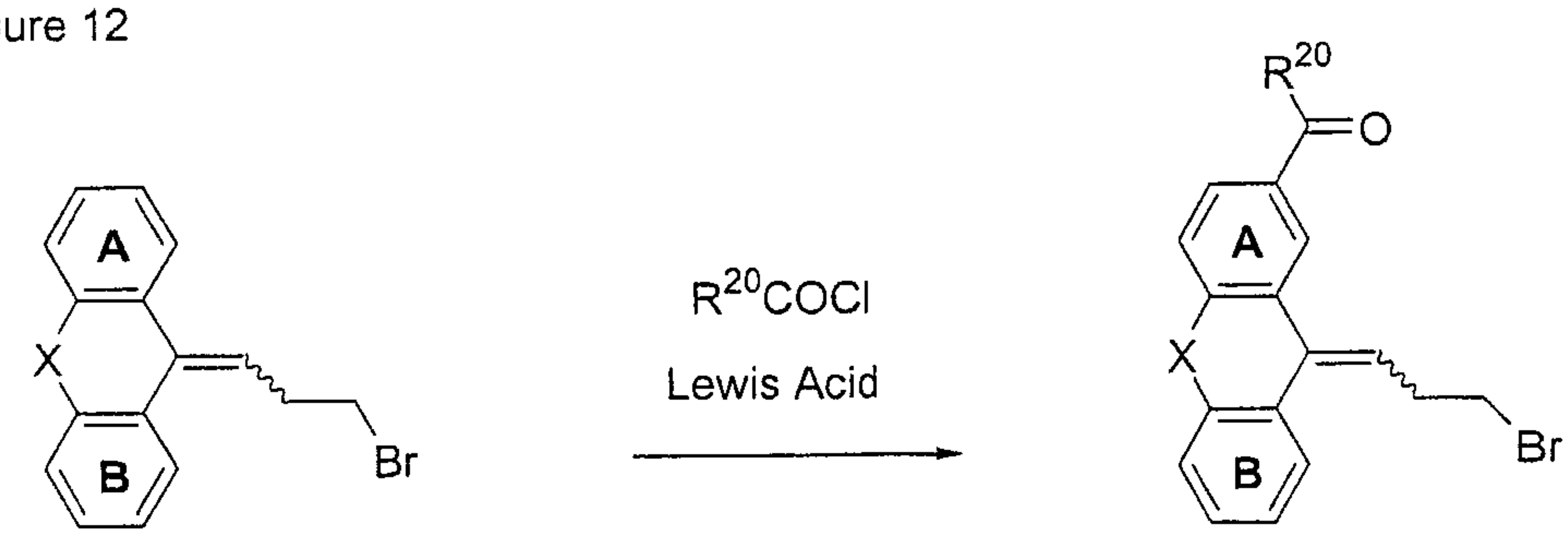
Example 432



Example 433

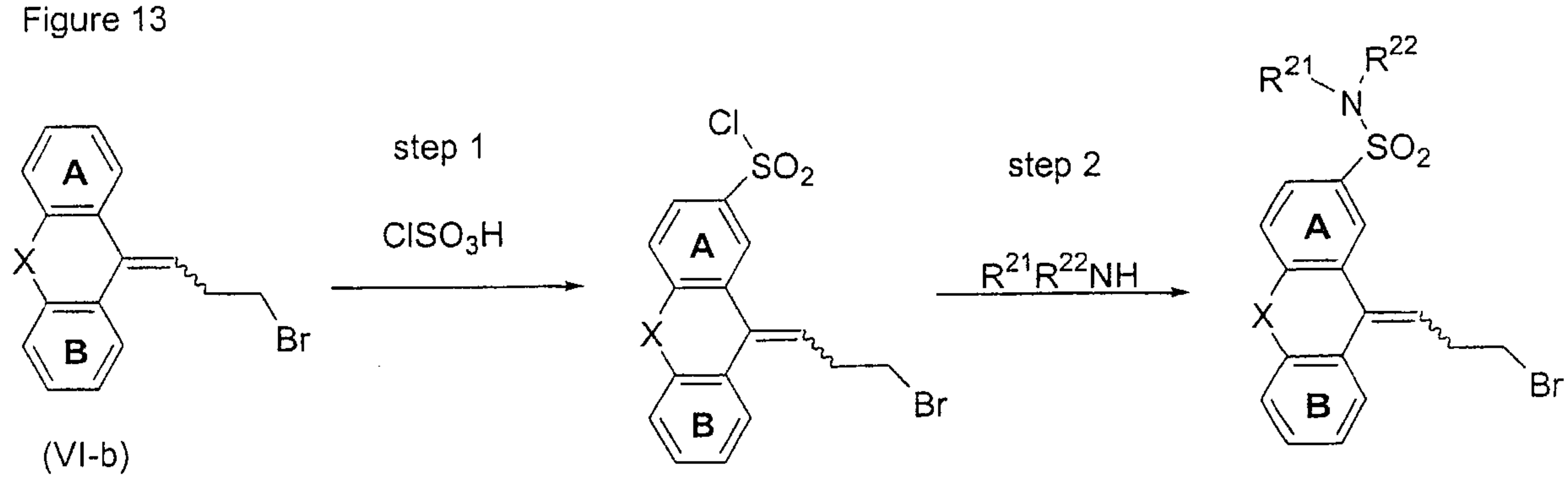
Figure 11T

Figure 12

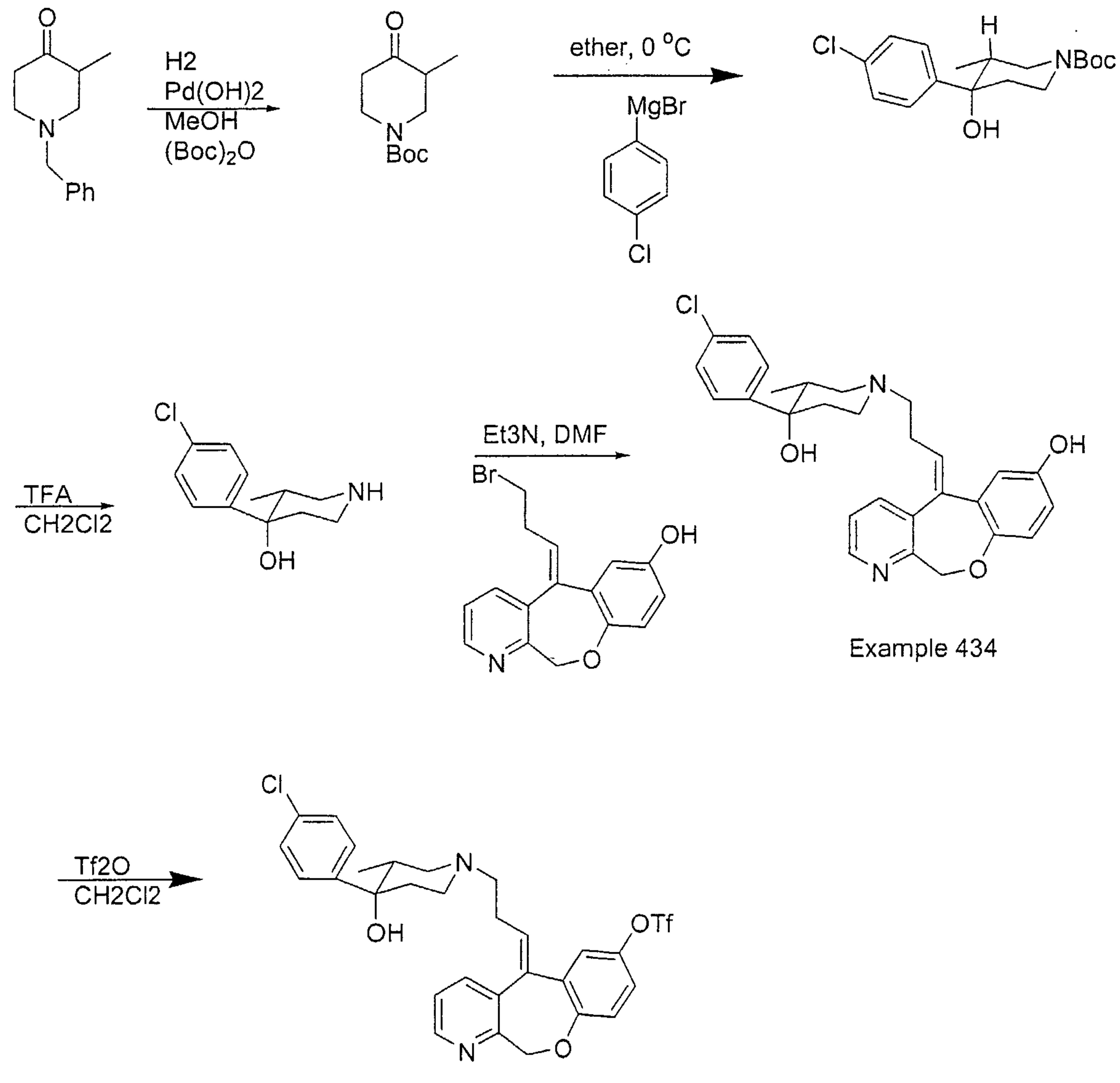


(VI-b) (VI-c)

Figure 13



(VI-b) (VI-d) (VI-e)



Example 435

Figure 14

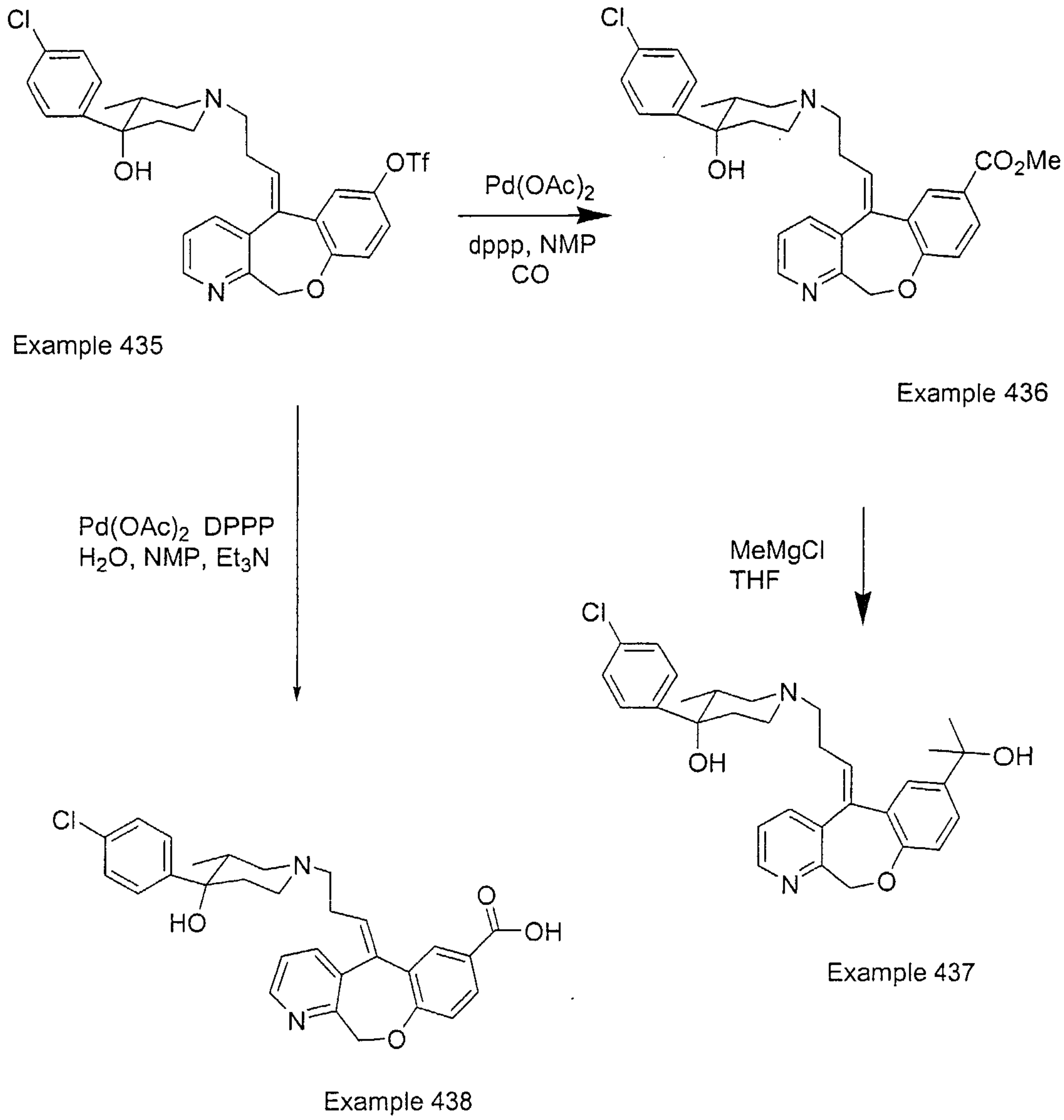

Cl
N
OH
OTf
N
O
Example 435
Pd(OAc)2
dppp, NMP
CO
CO2Me
Example 436
MeMgCl
THF
OH
Example 437
Pd(OAc)2 DPPP
H2O, NMP, Et3N
HO
OH
Example 438

Figure 15

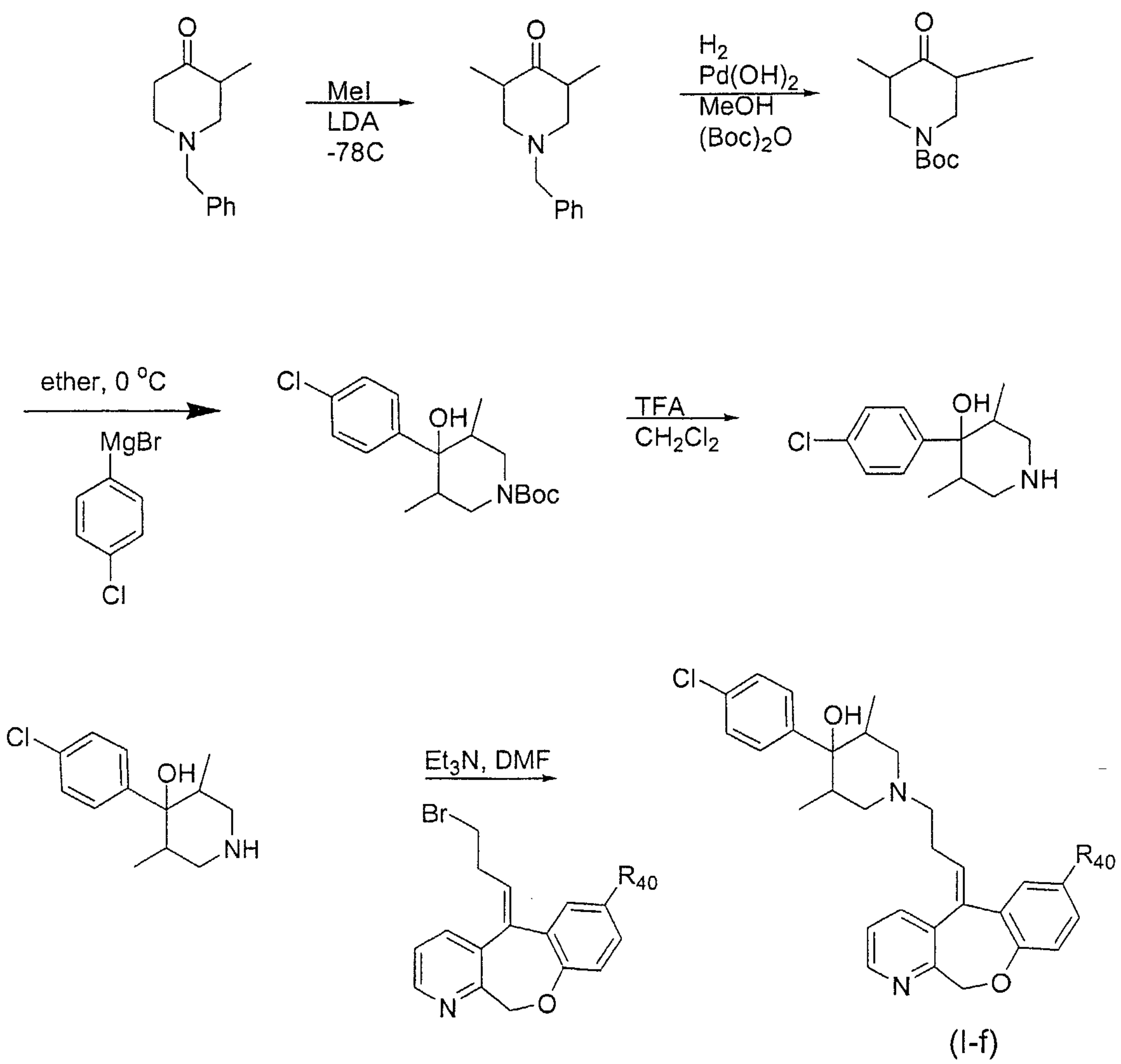

O
N
Ph
MeI
LDA
-78C
H2
Pd(OH)2
MeOH
(Boc)2O
Boc
ether, 0 °C
MgBr
Cl
OH
NBoc
TFA
CH2Cl2
NH
Et3N, DMF
Br
R40
(I-f)

Figure 16

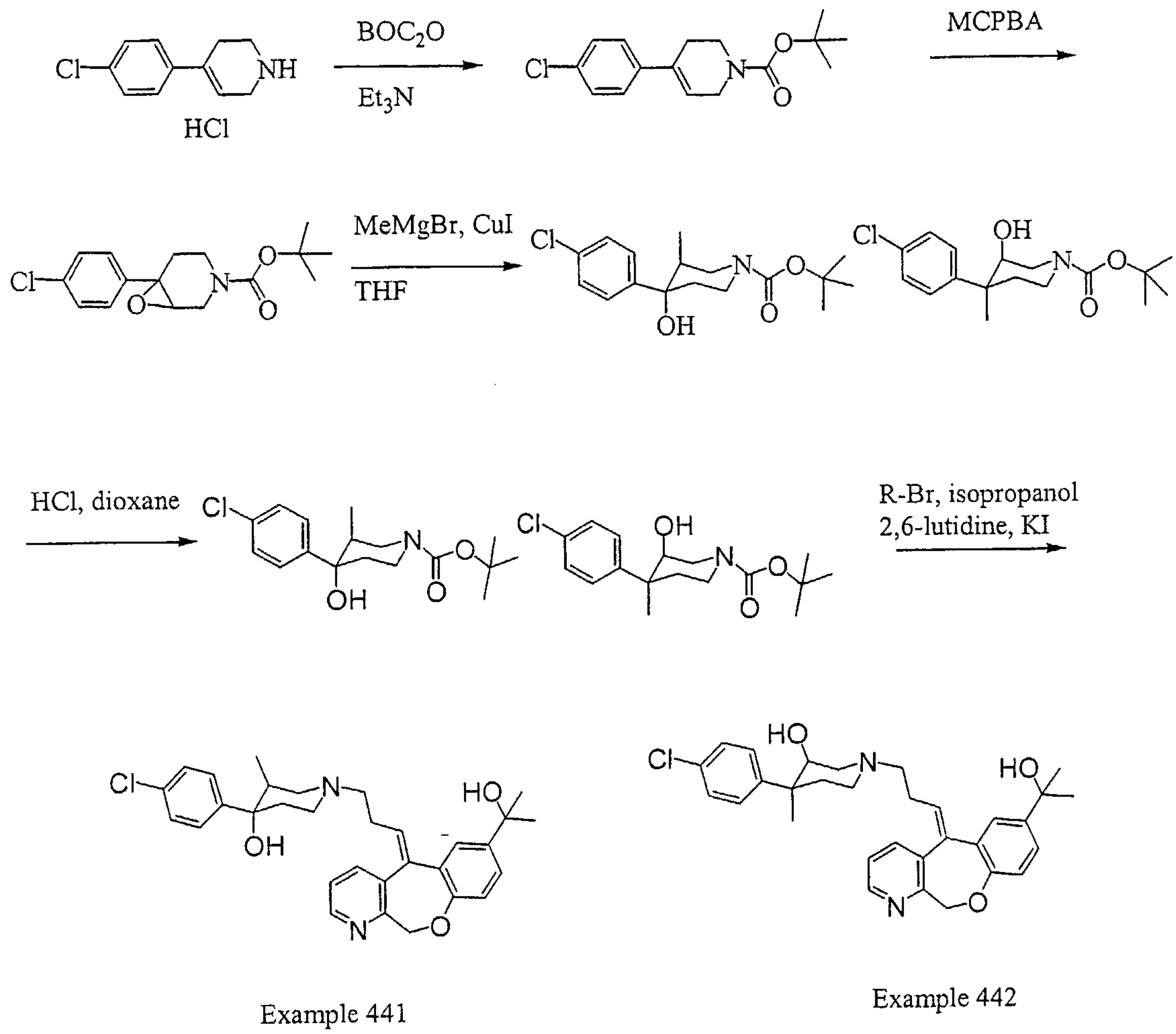
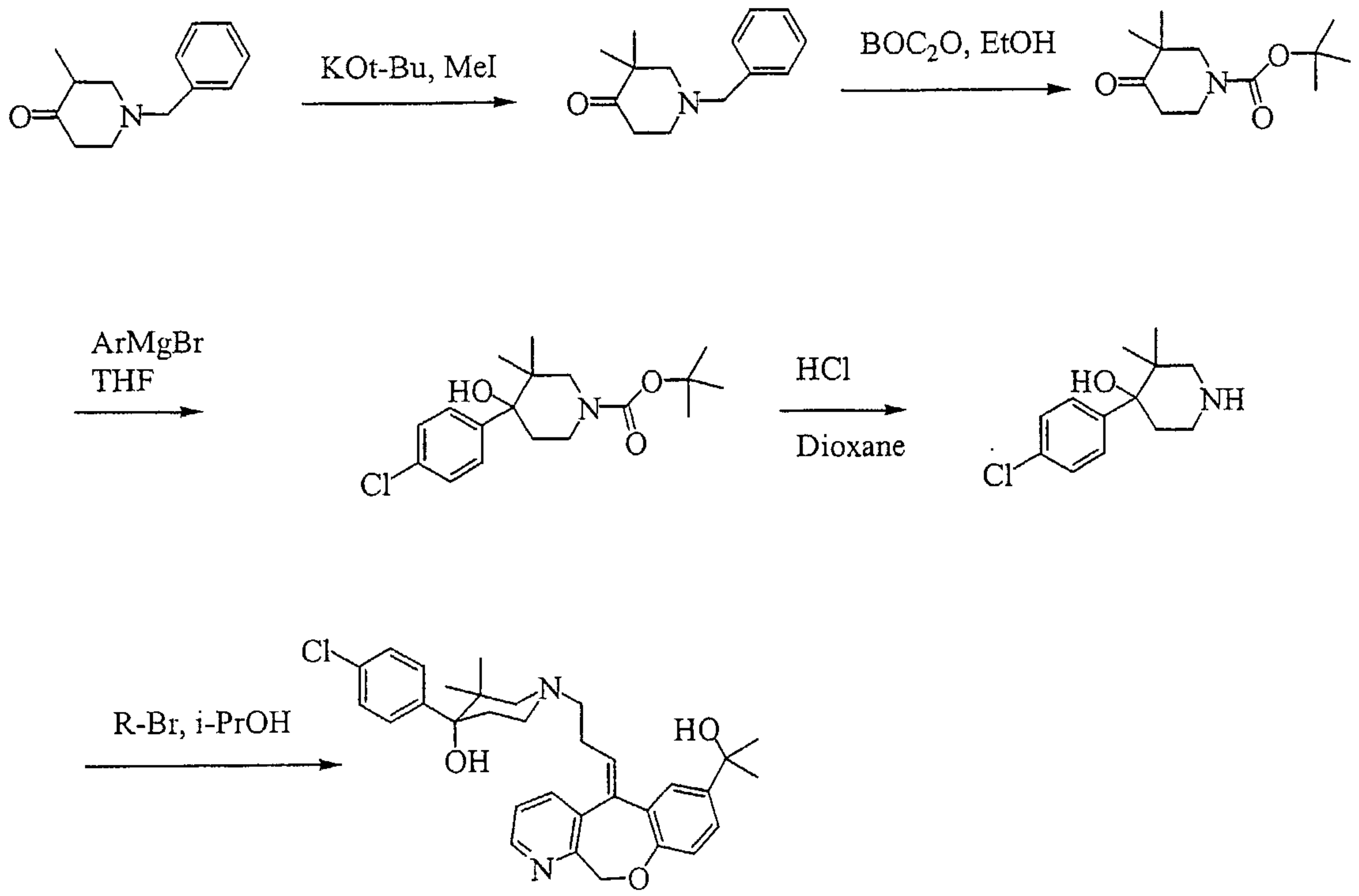

BOC$_2$O
Et$_3$N
HCl
MCPBA
MeMgBr, CuI
THF
HCl, dioxane
R-Br, isopropanol
2,6-lutidine, KI
Example 441
Example 442

Figure 17



Example 443

Figure 18

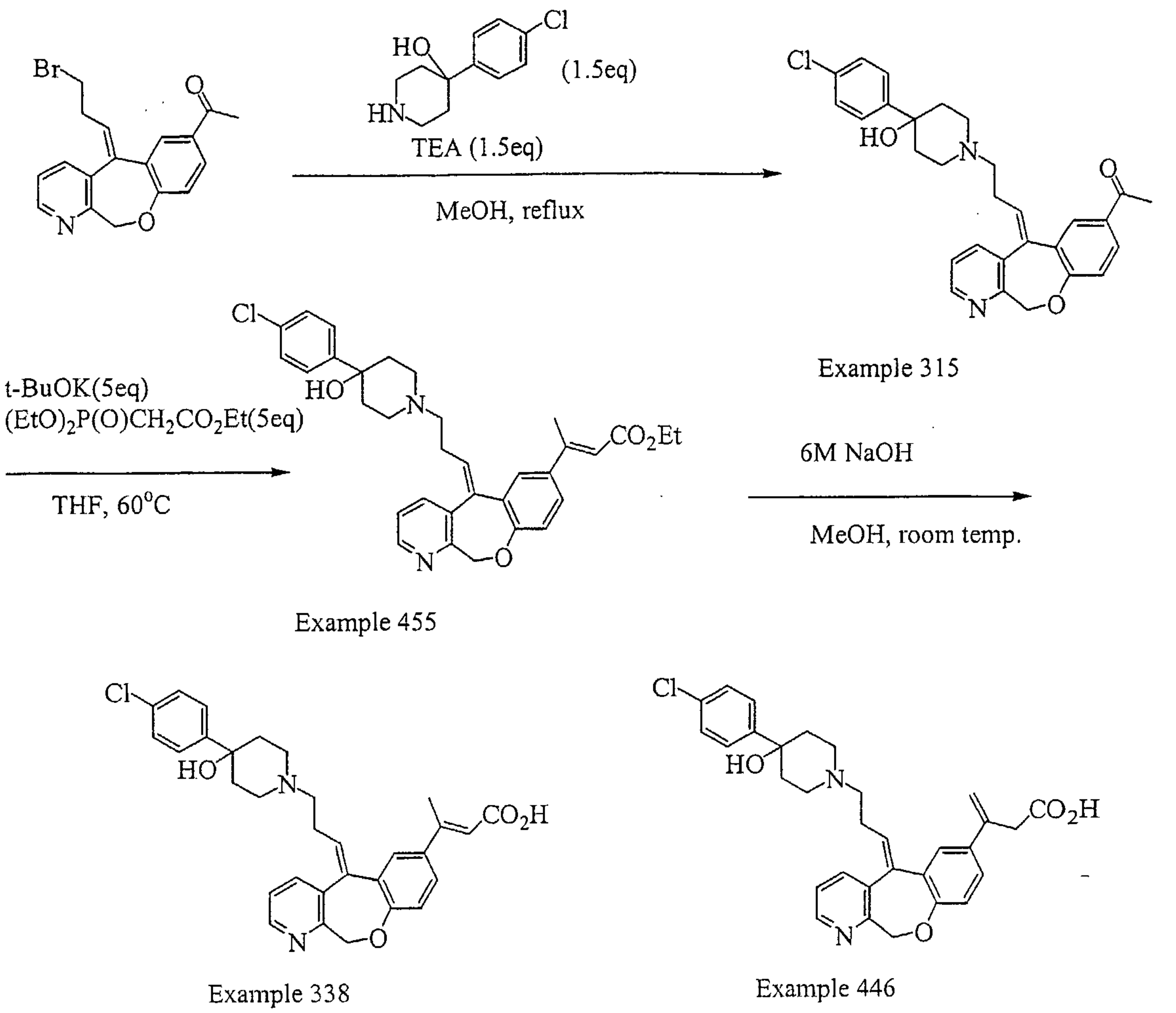
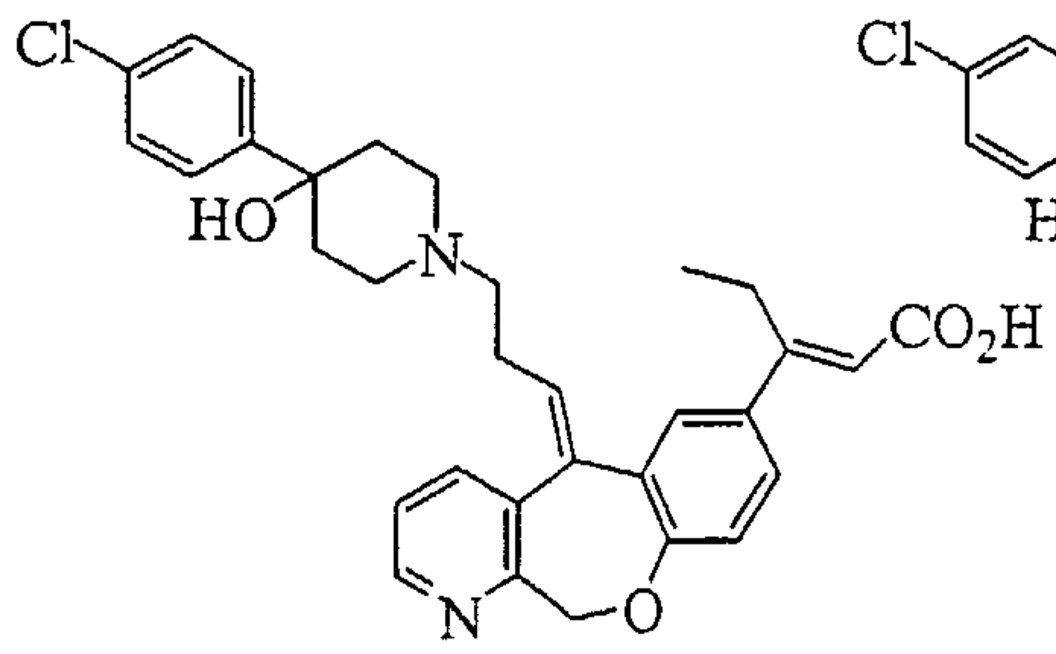
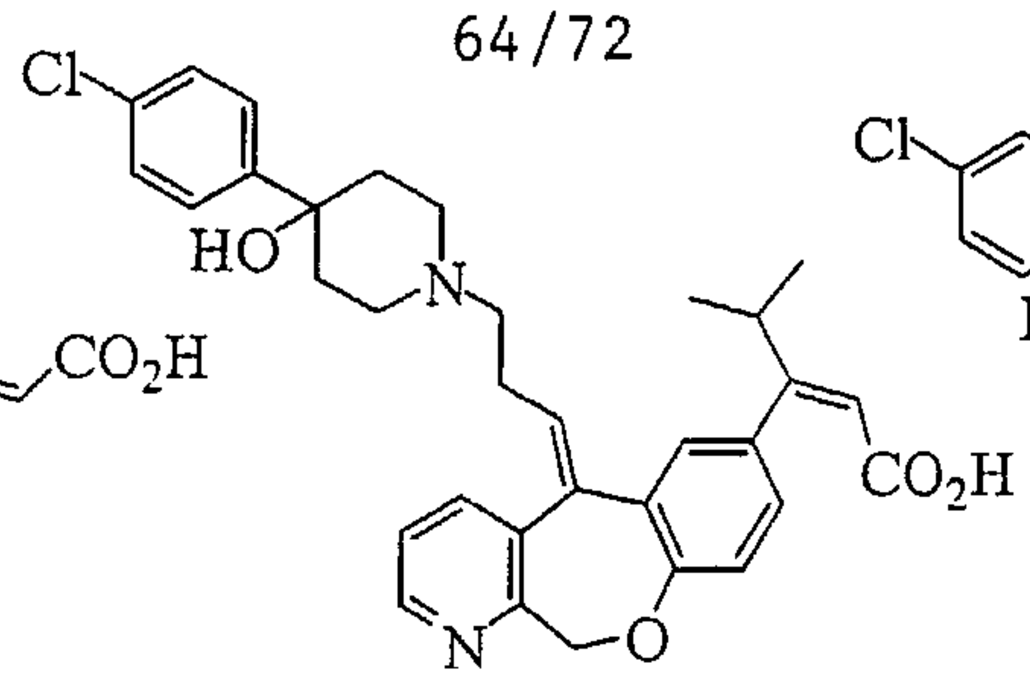

HO
HN
Cl
(1.5eq)
TEA (1.5eq)
MeOH, reflux
Br
O
N
O
Cl
HO
N
Example 315
t-BuOK(5eq)
(EtO)$_2$P(O)CH$_2$CO$_2$Et(5eq)
THF, 60°C
CO$_2$Et
Example 455
6M NaOH
MeOH, room temp.
CO$_2$H
Example 338
Example 446

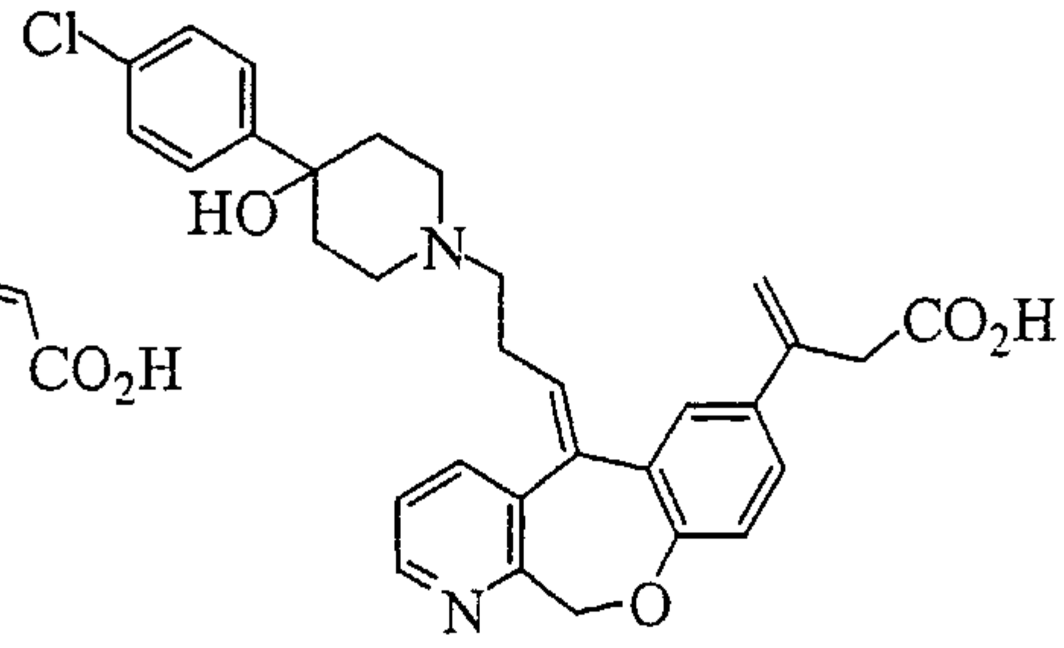
Figure 19



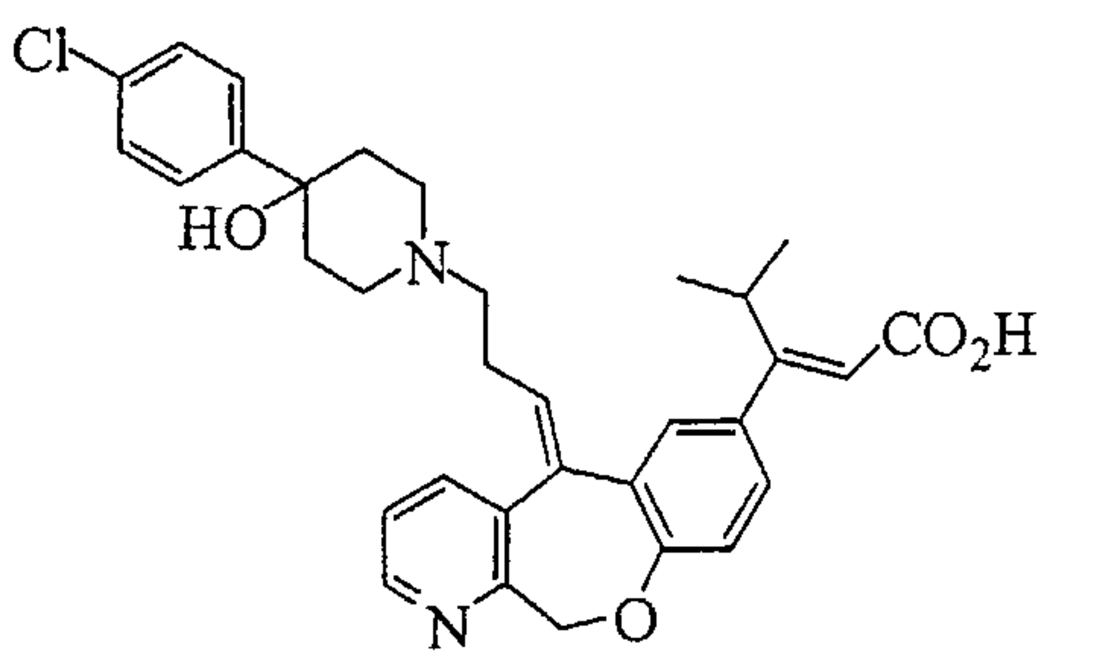
Example 444



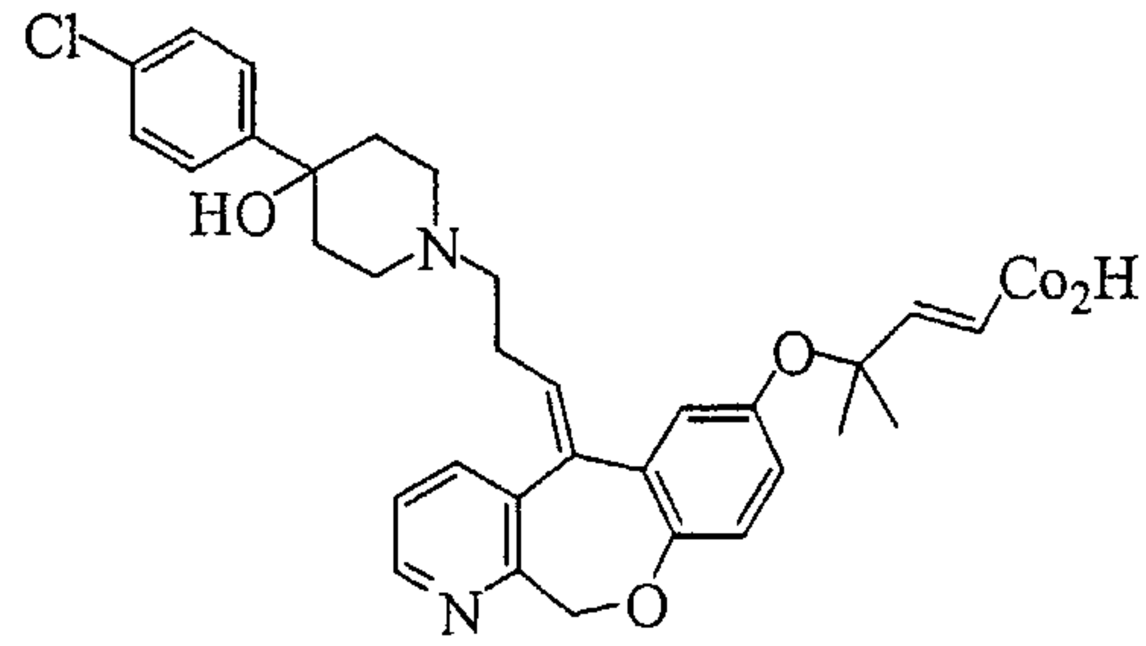
Example 445



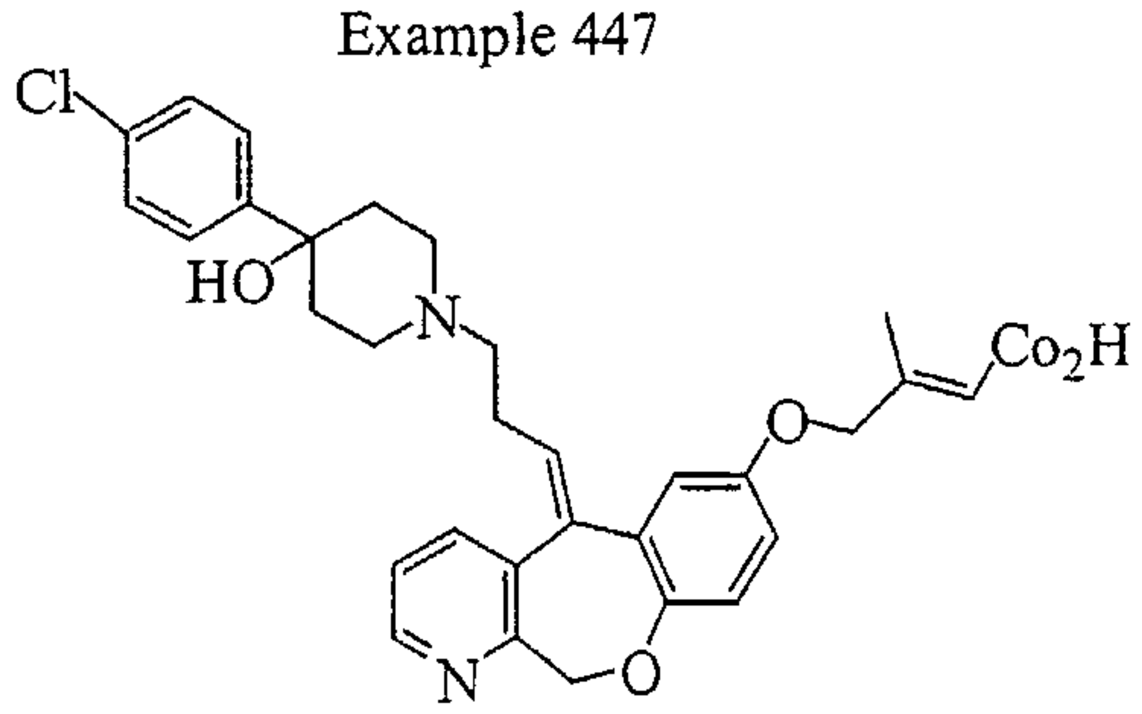
Example 446



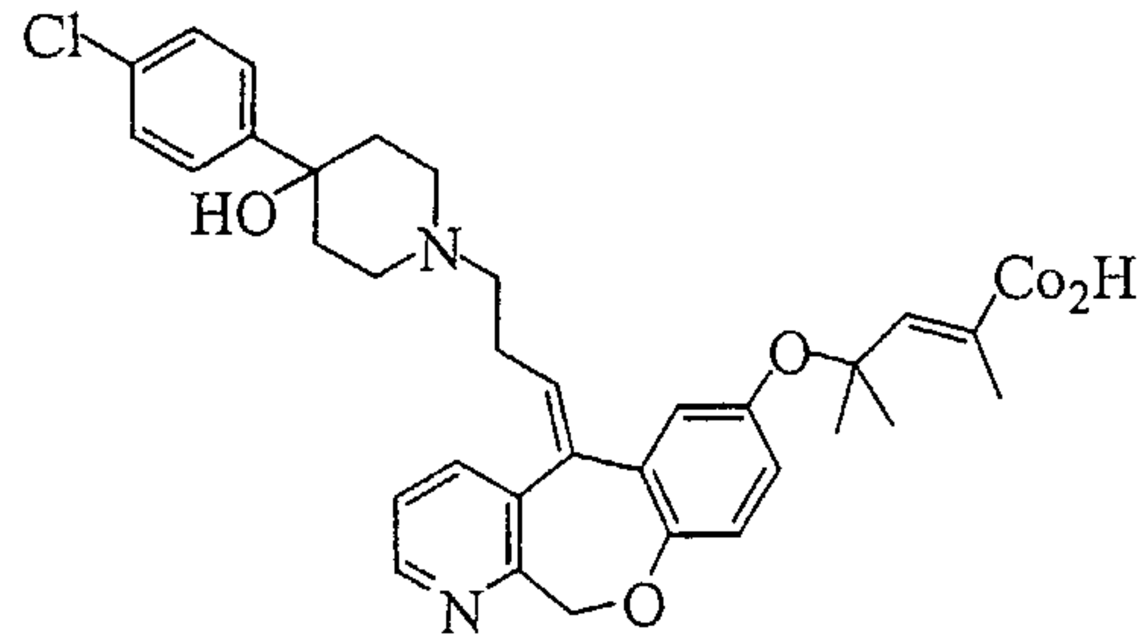
Example 447



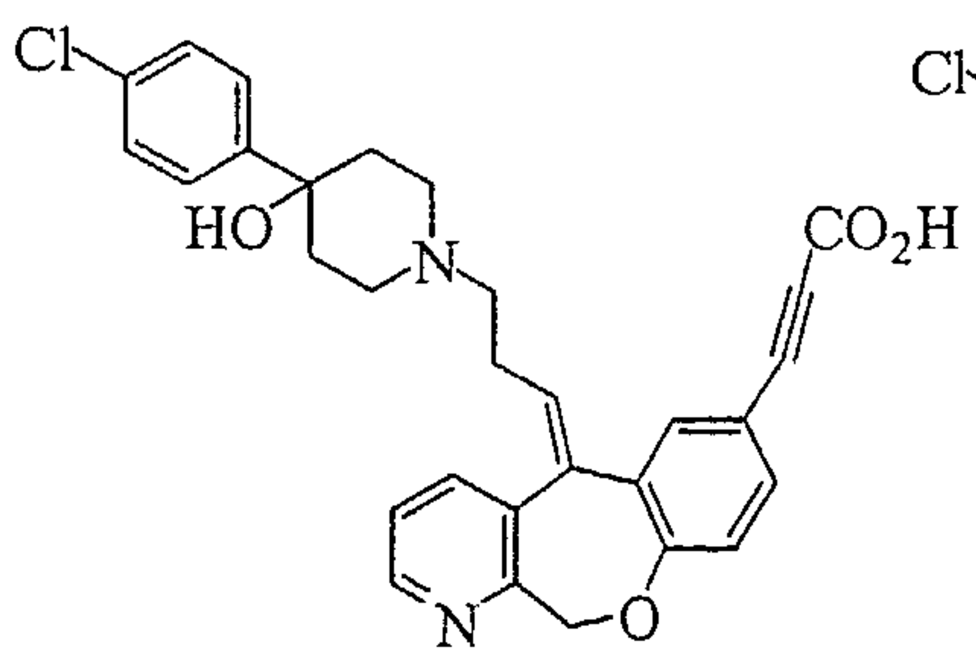
Example 448



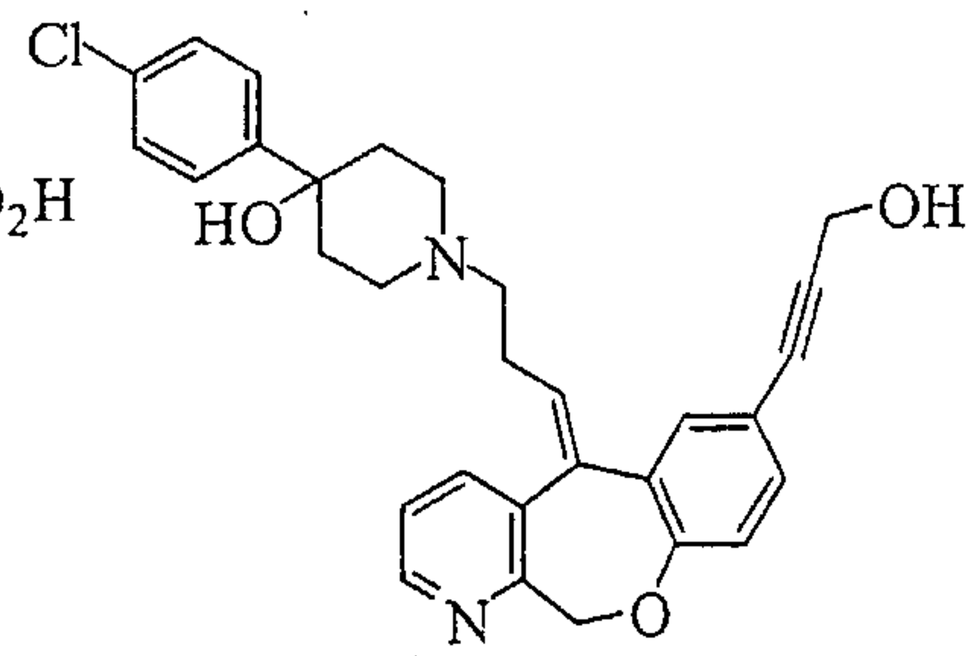
Example 449



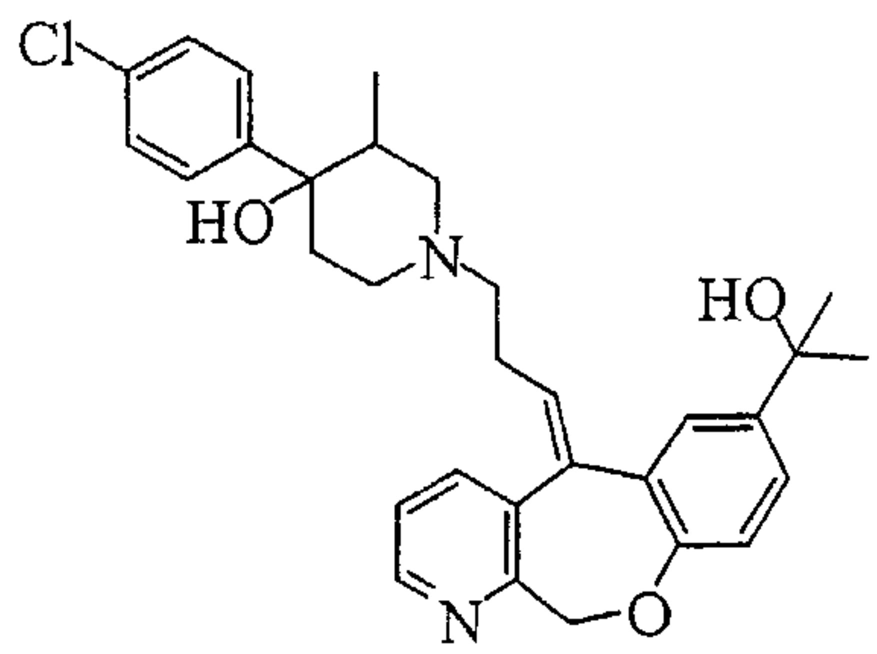
Example 450



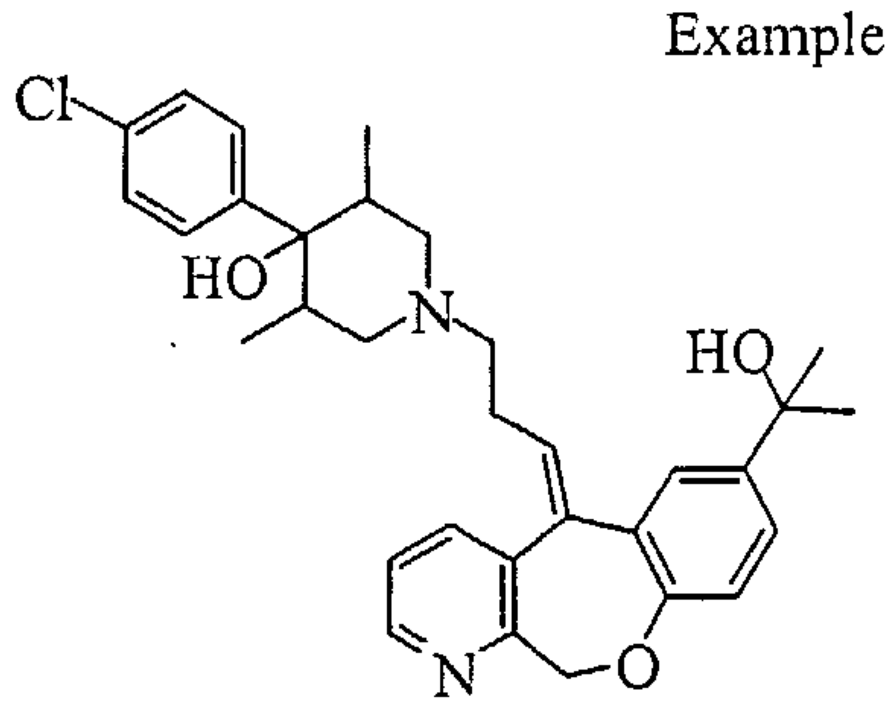
Example 451



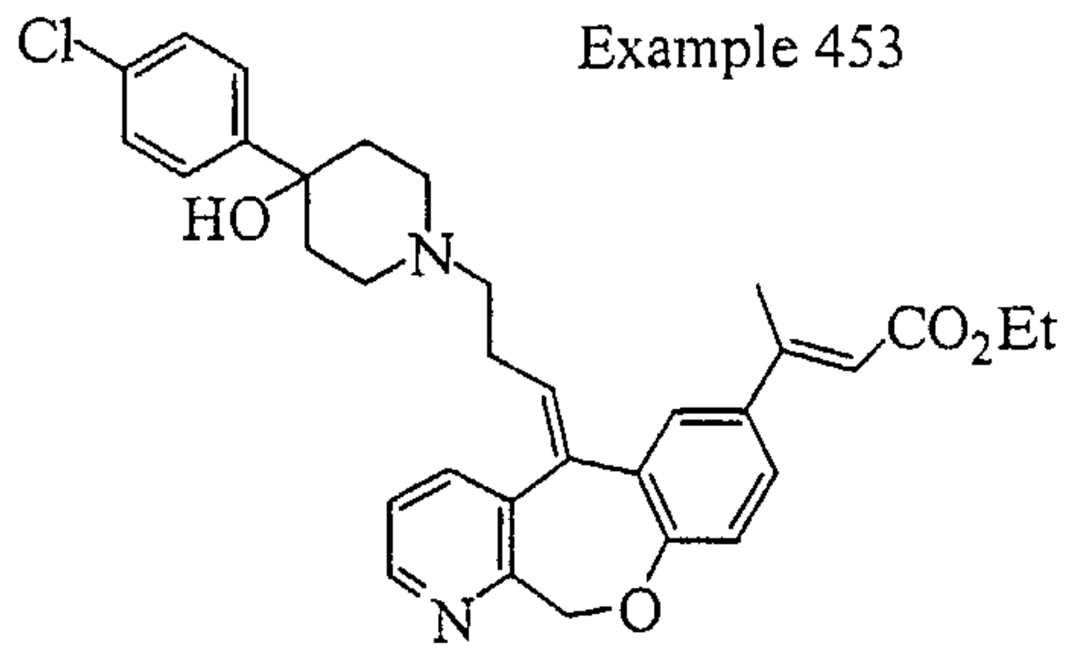
Example 452



Example 453

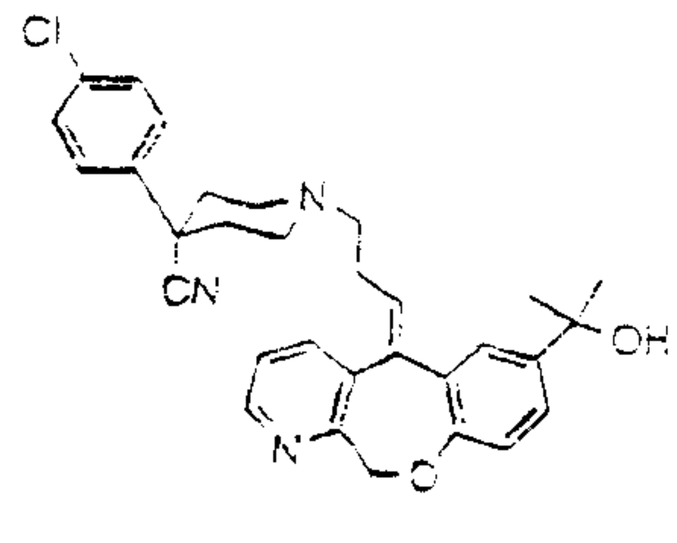


Example 454

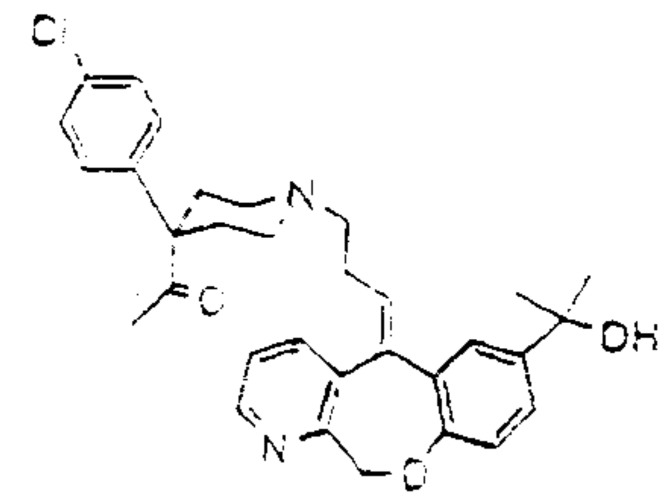


Example 455

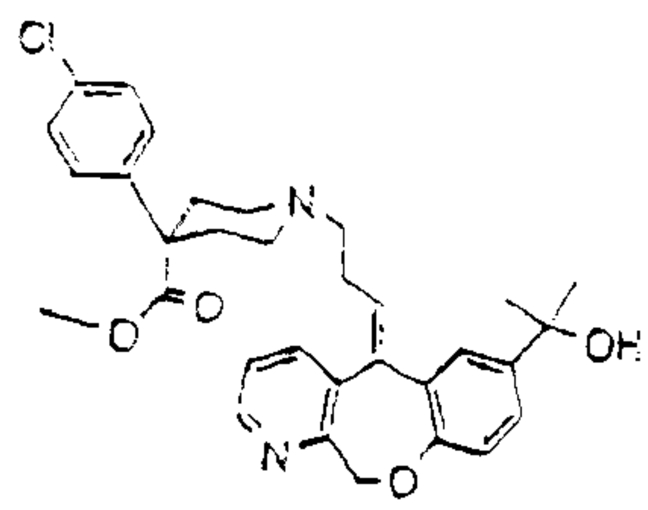
Figure 20



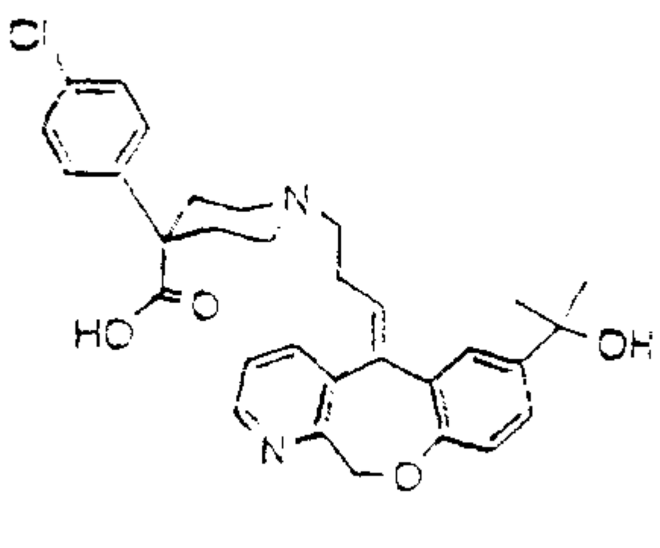
Example 456



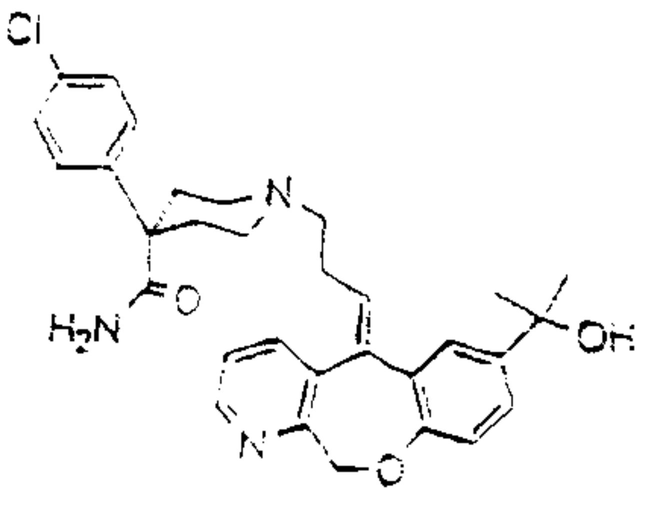
Example 457



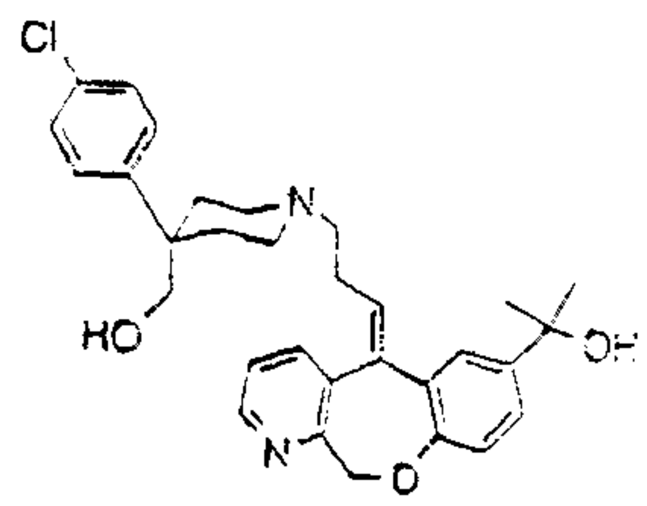
Example 458



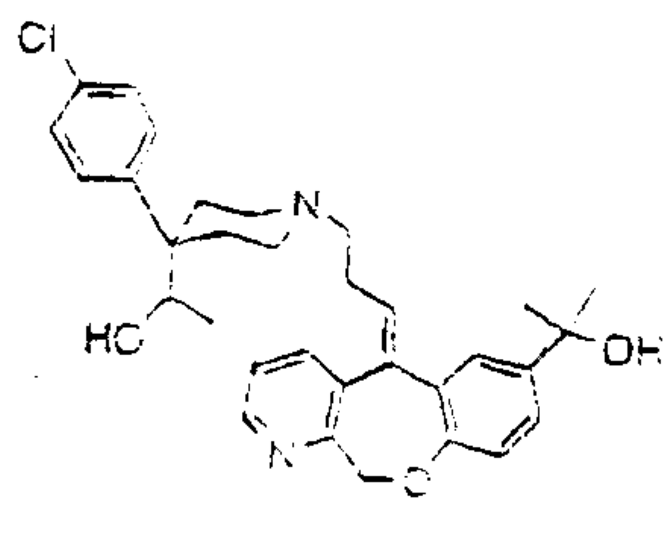
Example 459



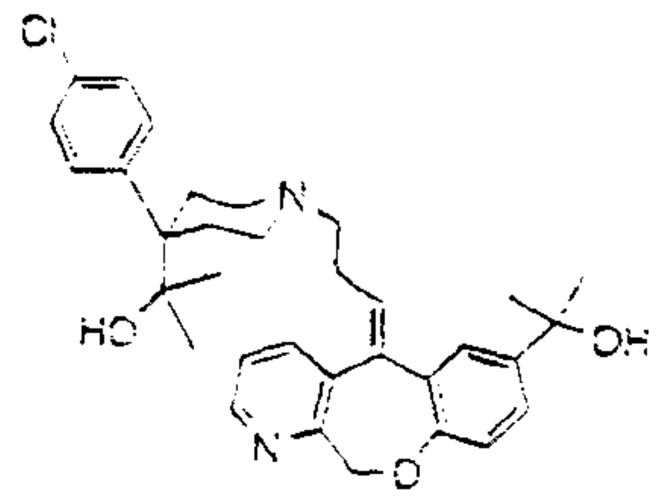
Example 460



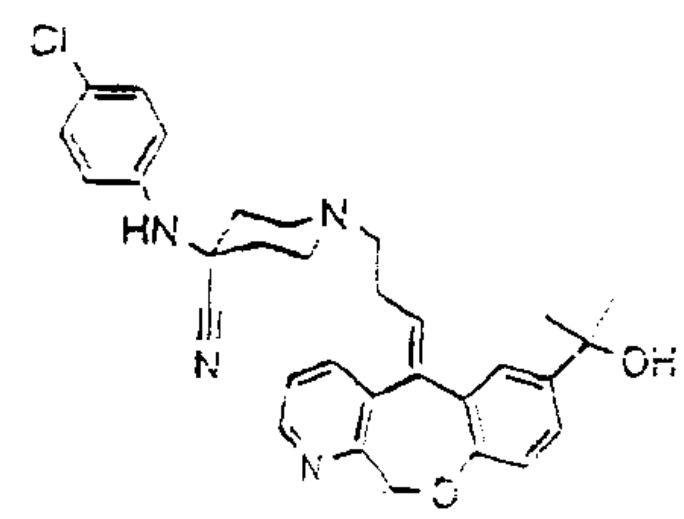
Example 561



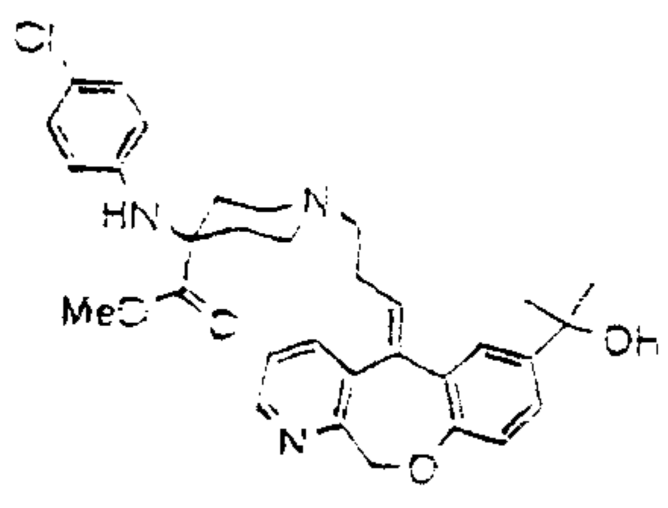
Example 462



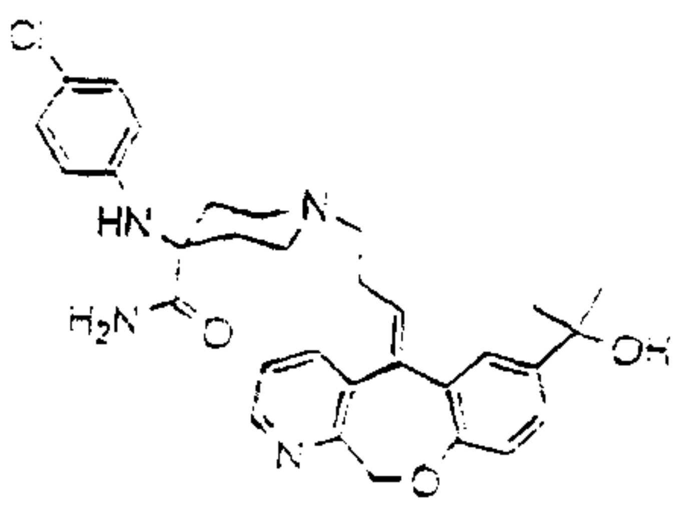
Example 463



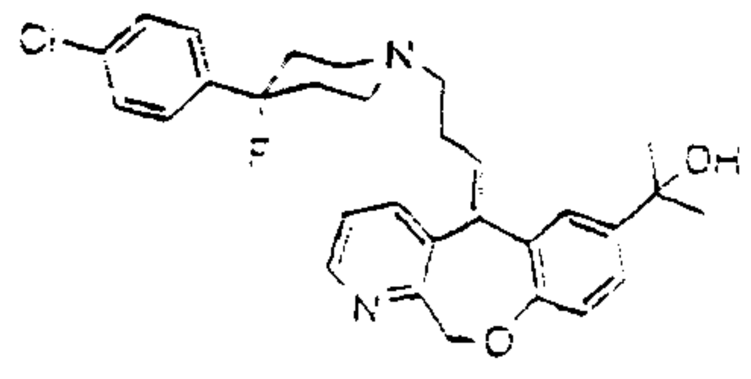
Example 464



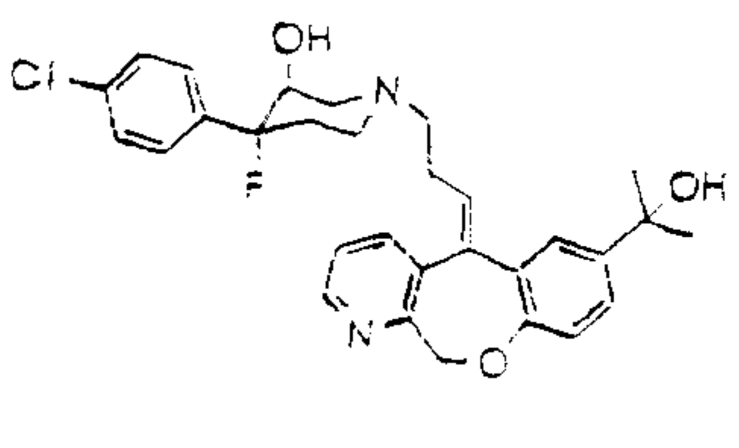
Example 465



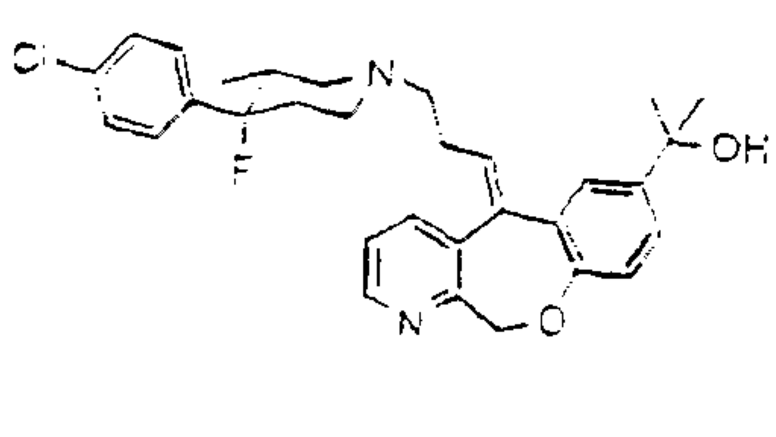
Example 466



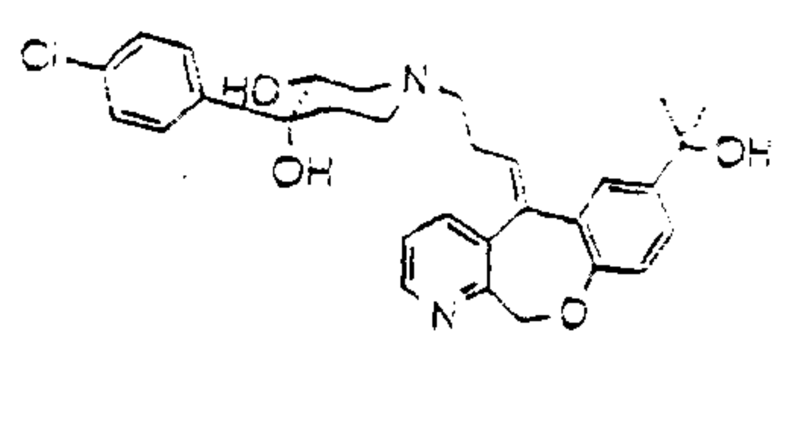
Example 467



Example 468

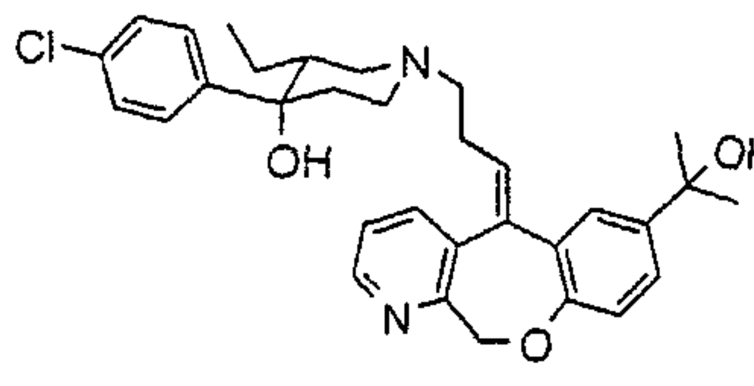


Example 469

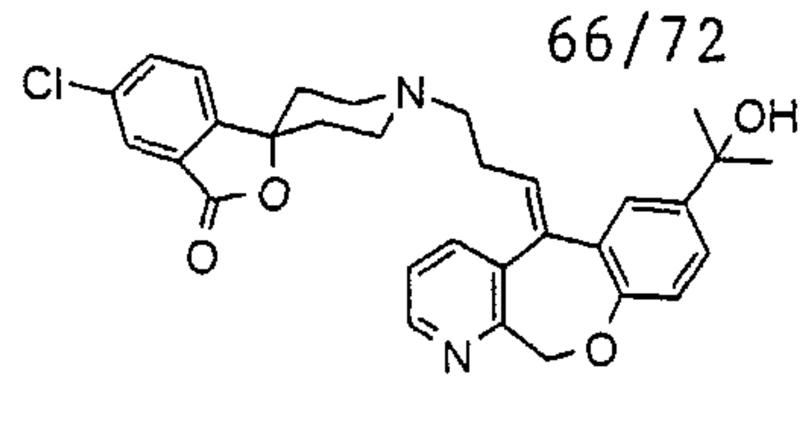


Example 470

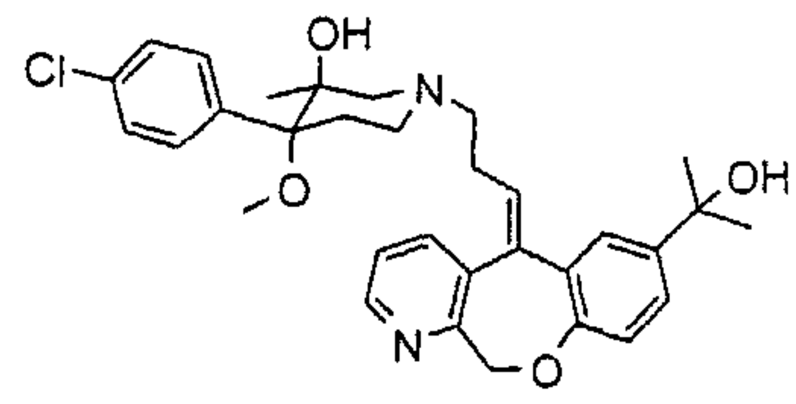
Figure 21



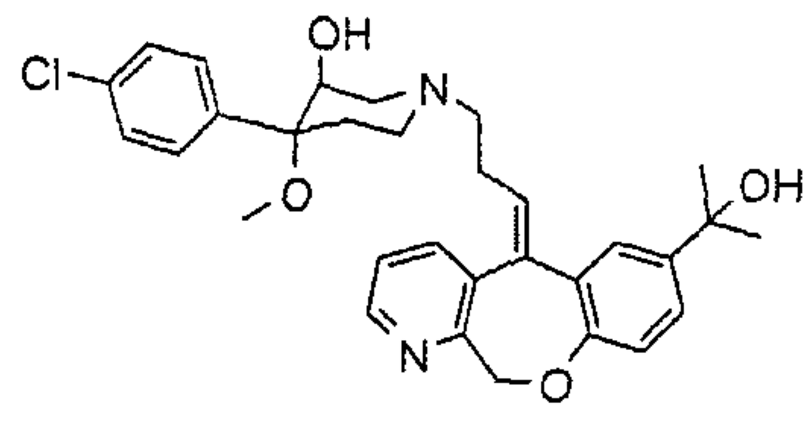
Example 471



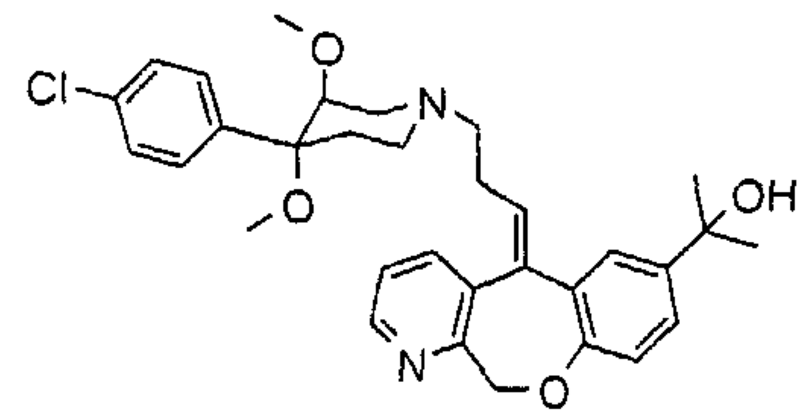
Example 472



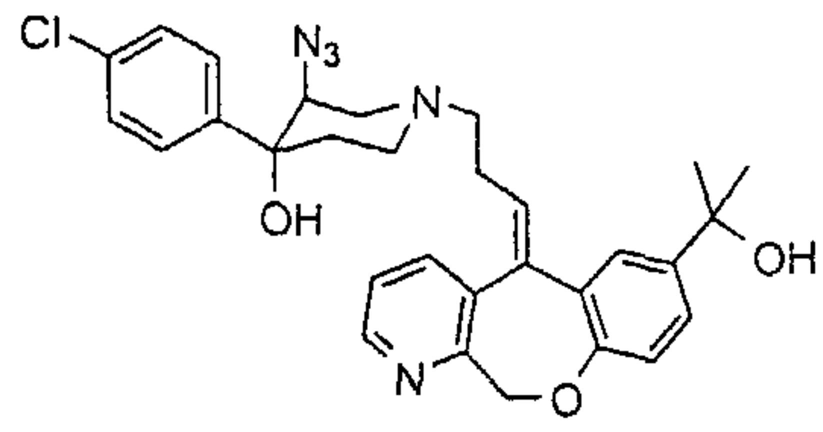
Example 473



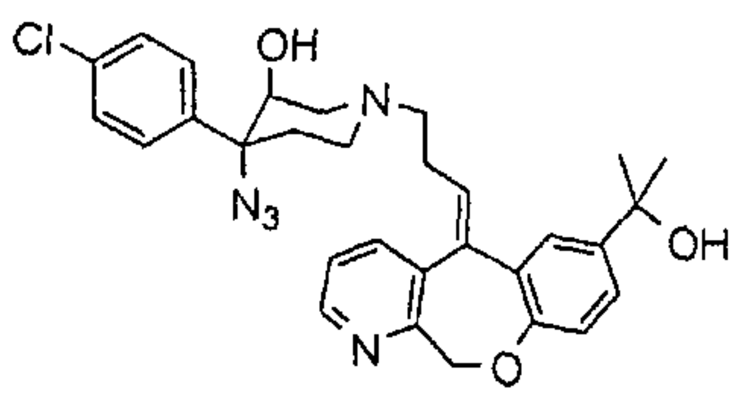
Example 474



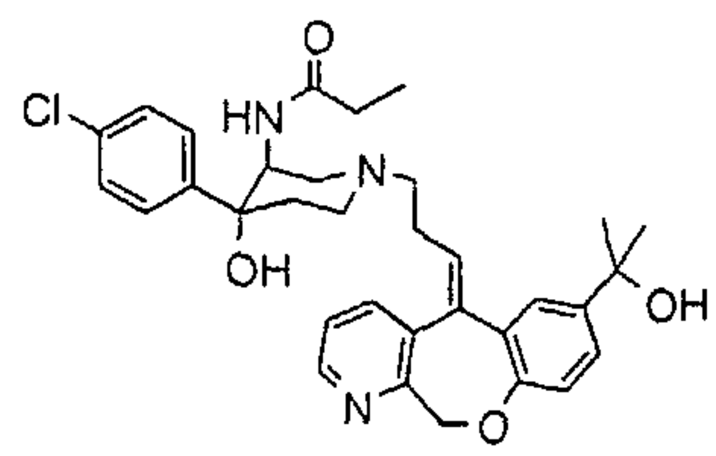
Example 475



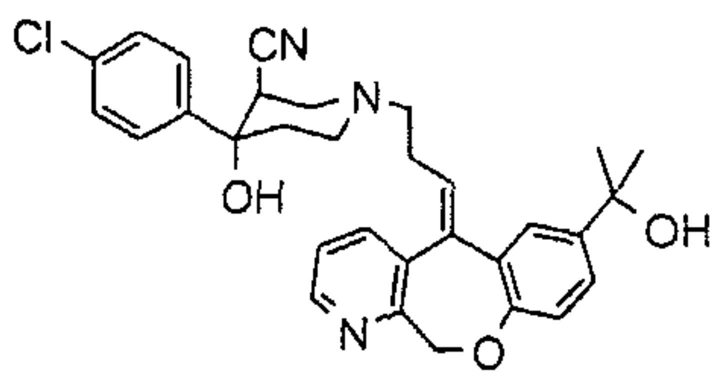
Example 476



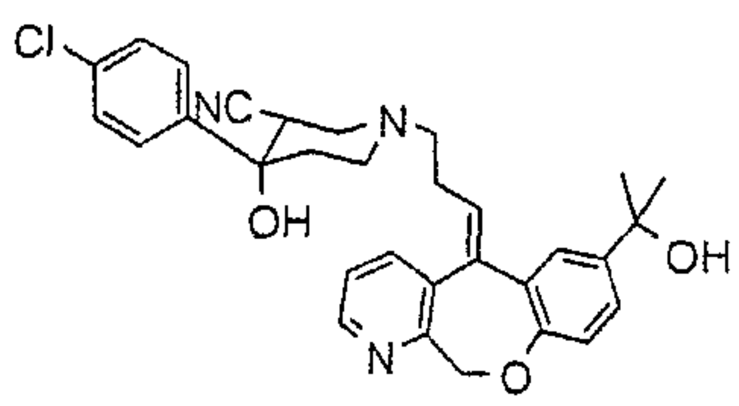
Example 477



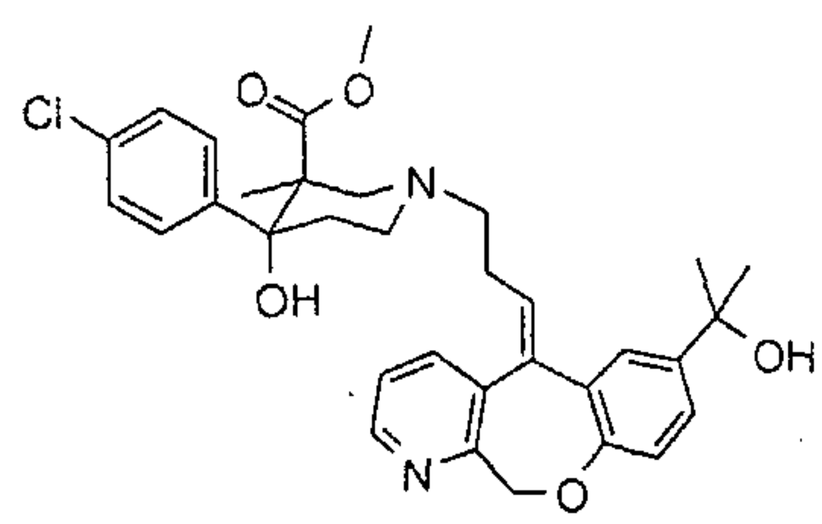
Example 478



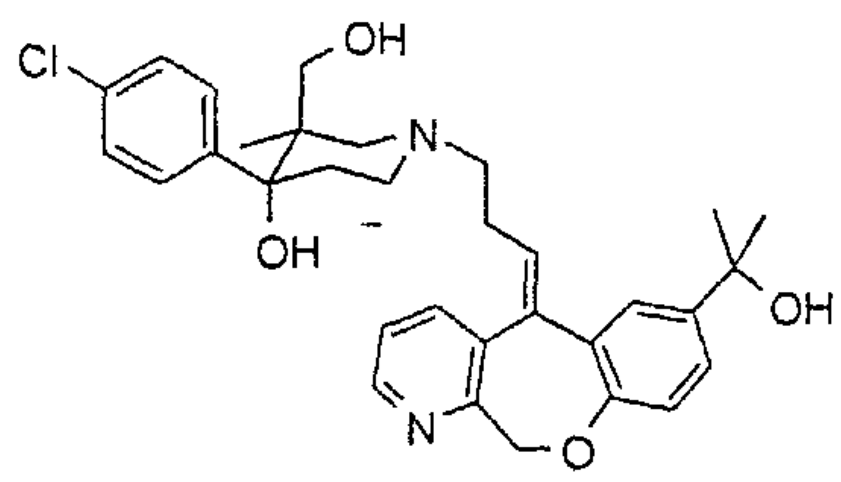
Example 479



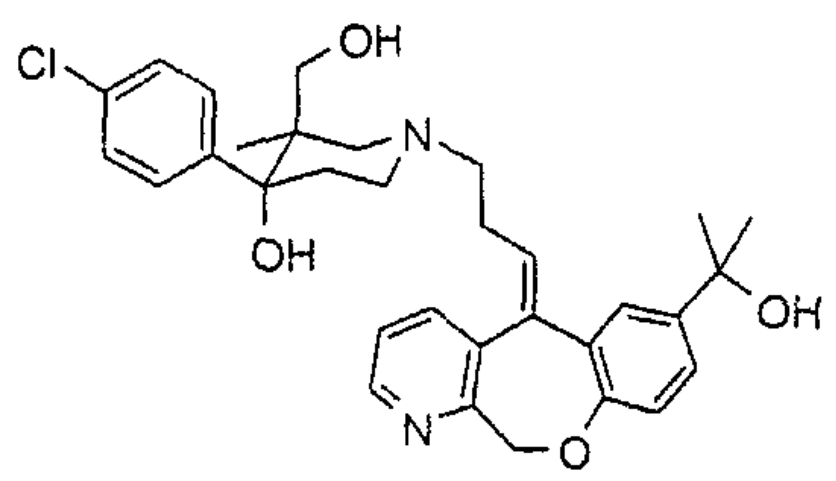
Example 480



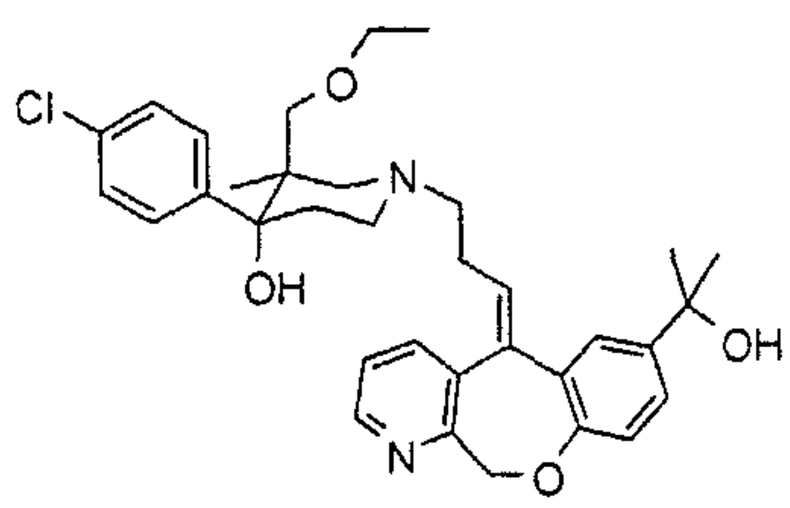
Example 481



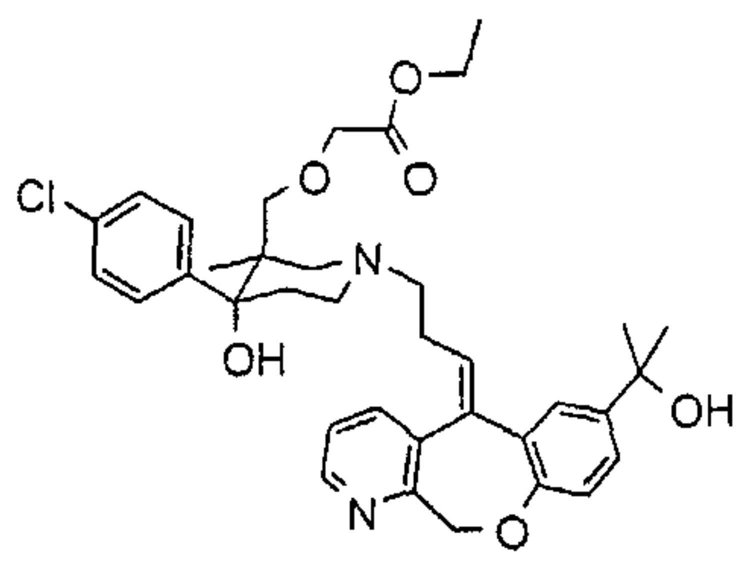
Example 482
(racemic)



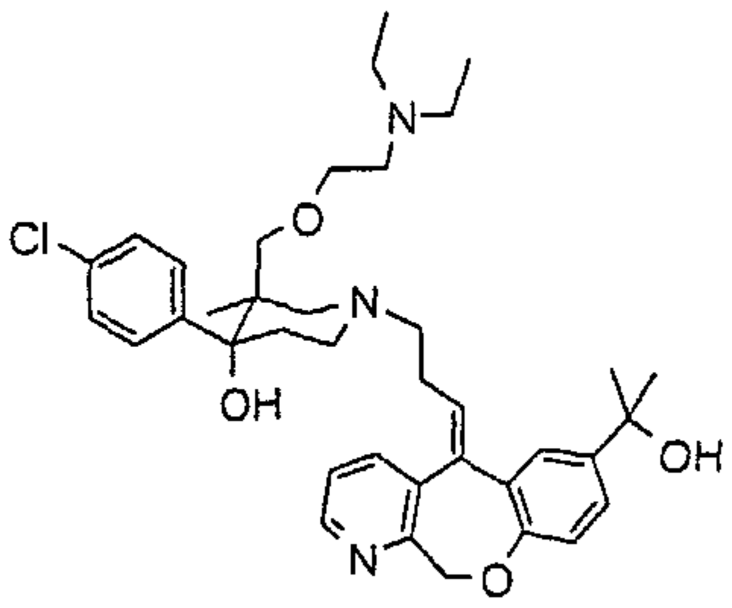
Example 483-1 (chiral)
Example 483-2 (chiral)



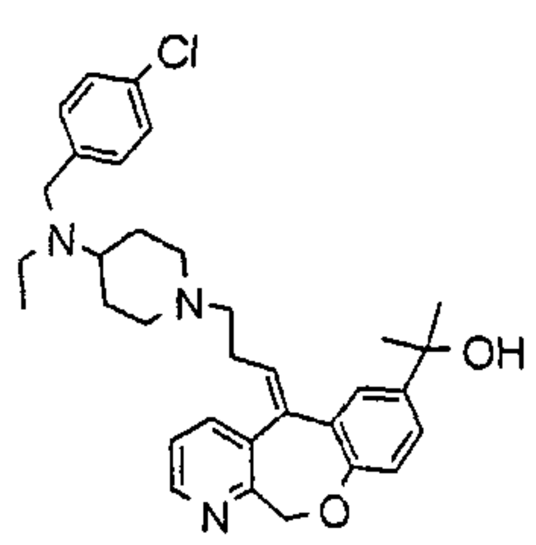
Example 484



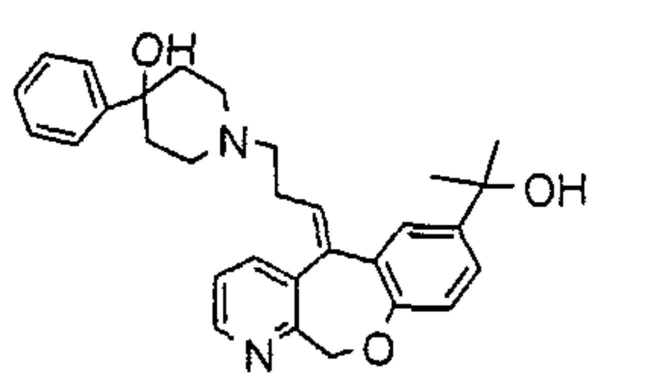
Example 485



Example 486

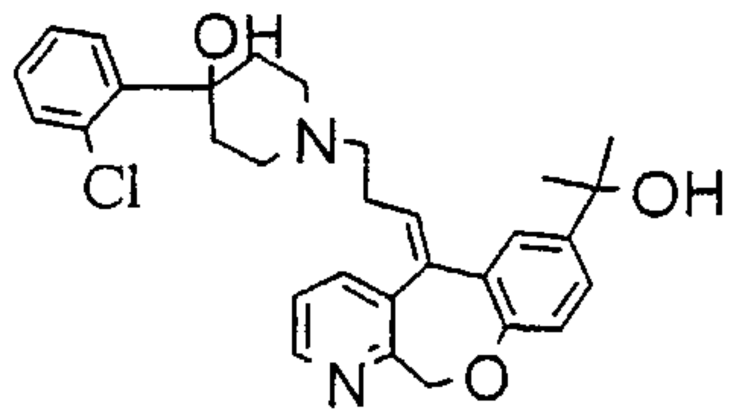


Example 487

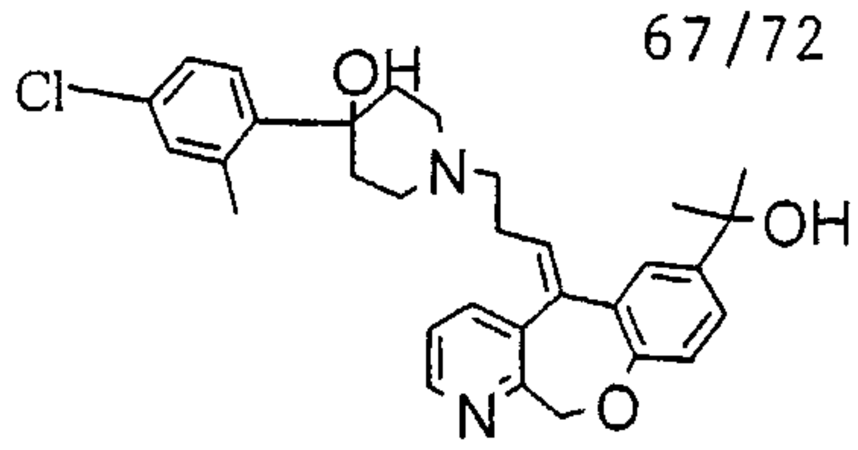


Example 488

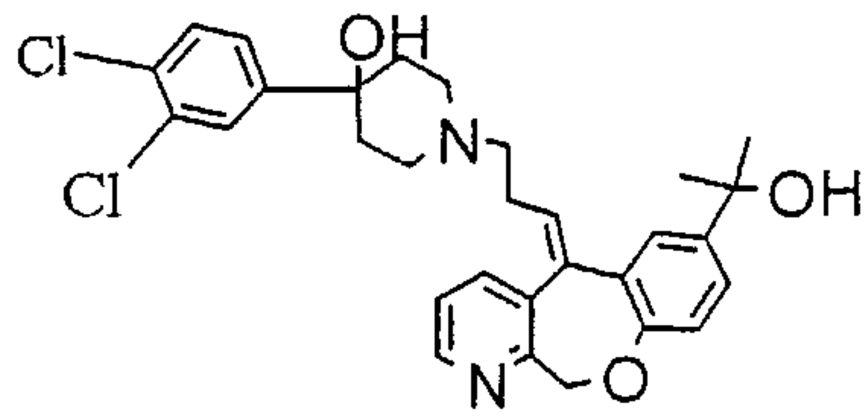
Figure 22



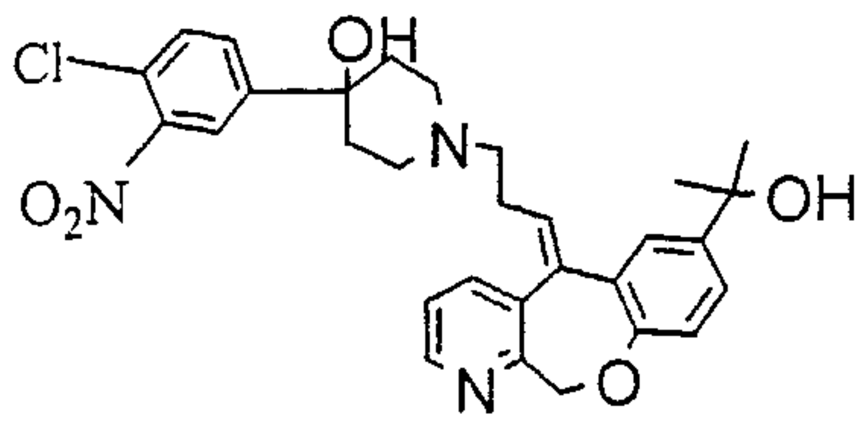
Example 489



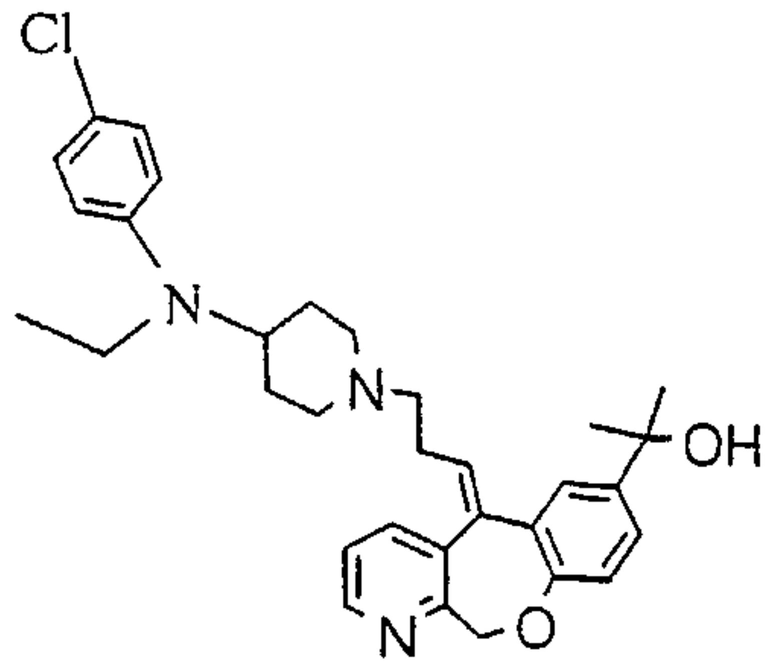
Example 490



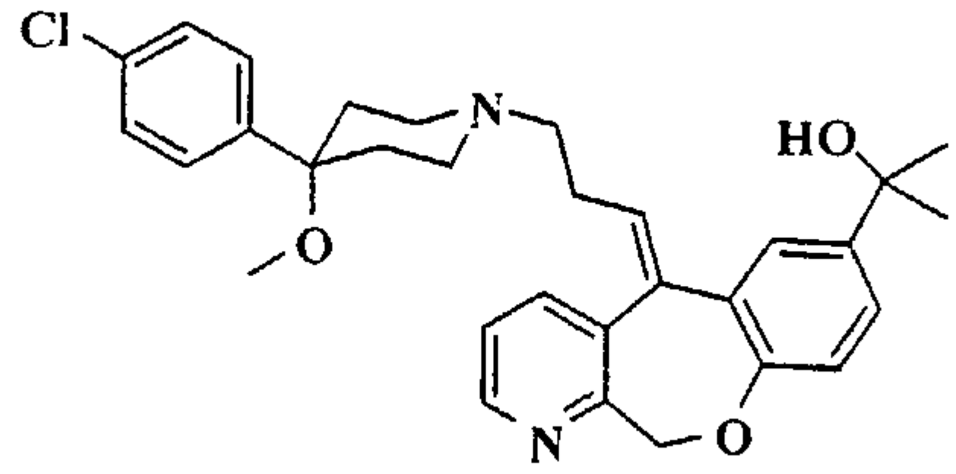
Example 491



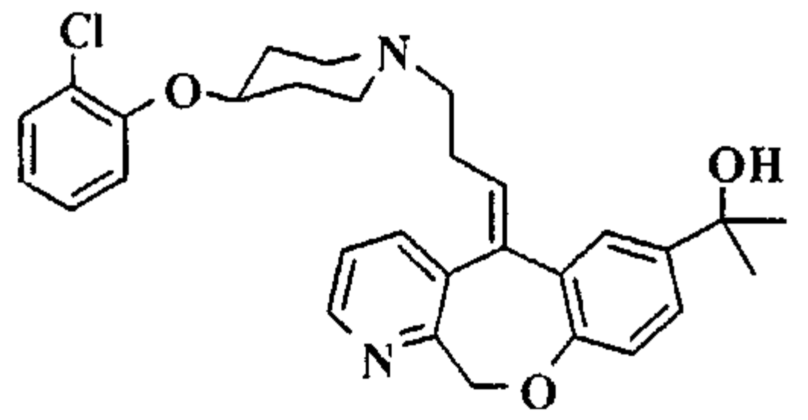
Example 492



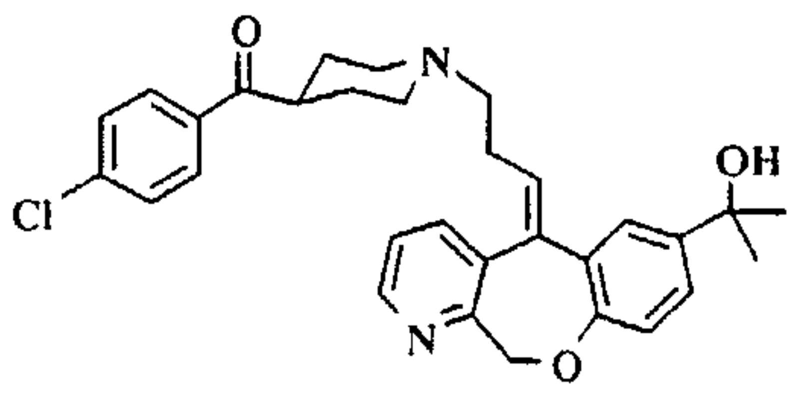
Example 493



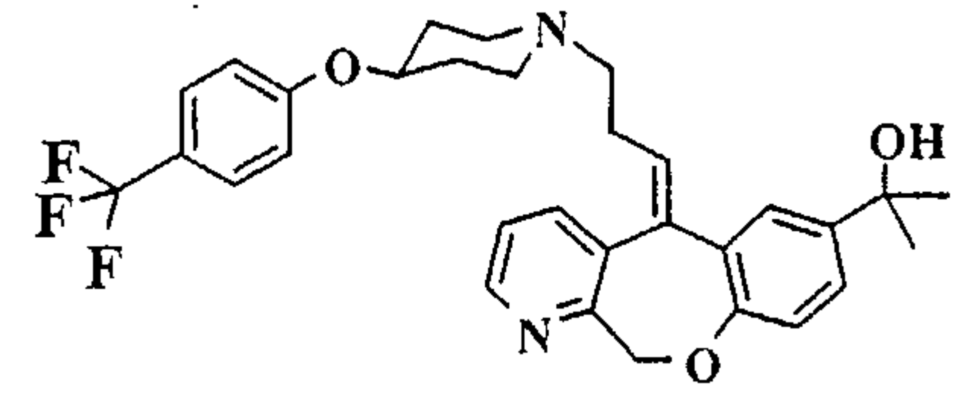
Example 494



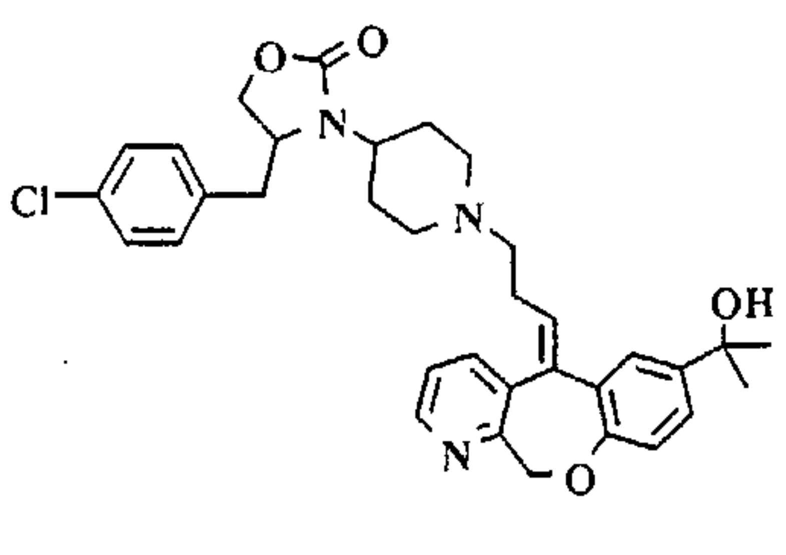
Example 495



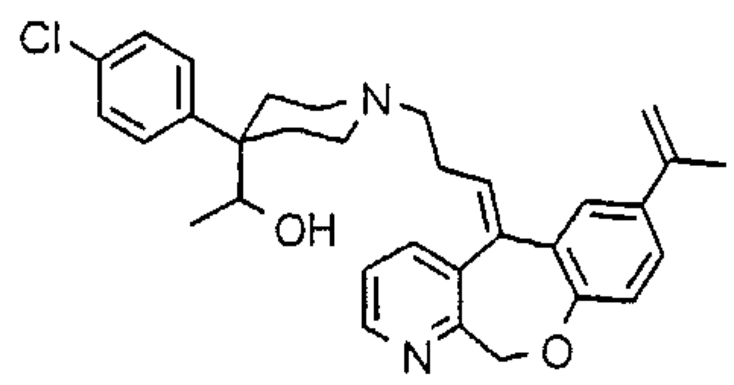
Example 496



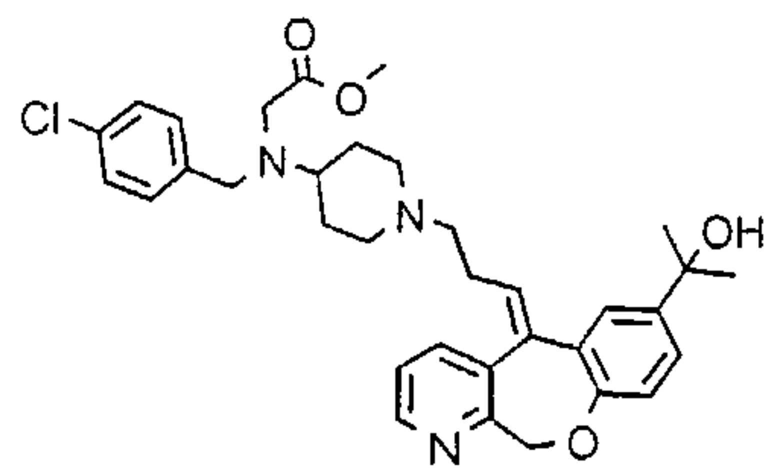
Example 497



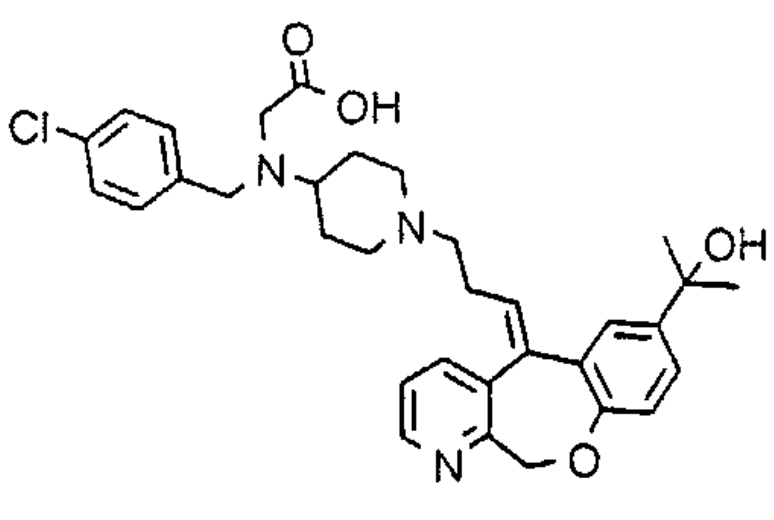
Example 498



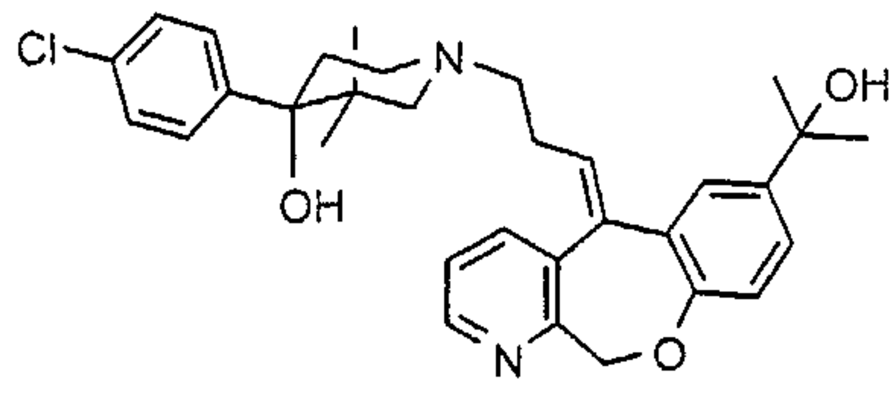
Example 499



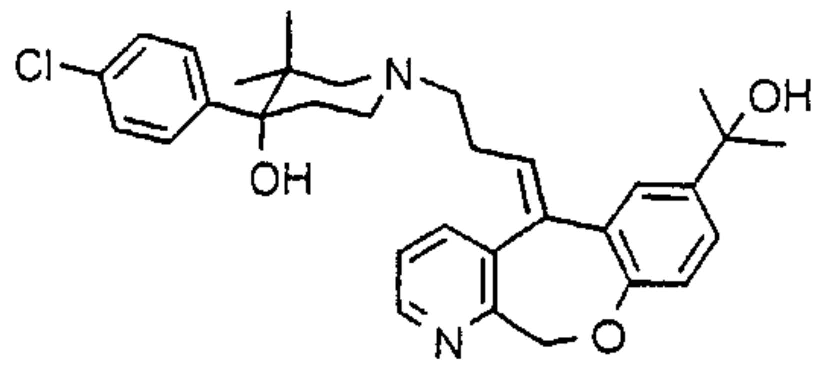
Example 500



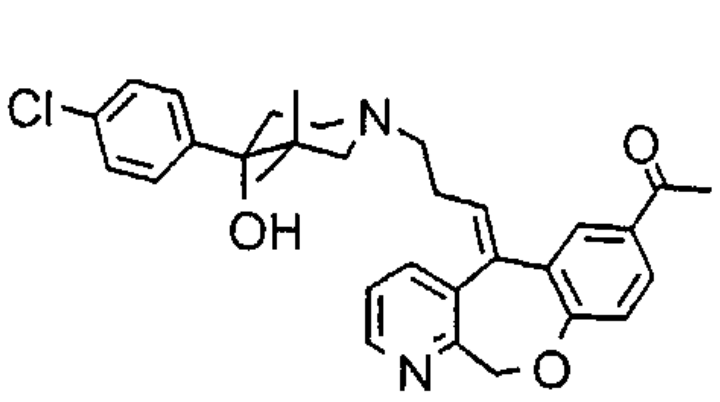
Example 501



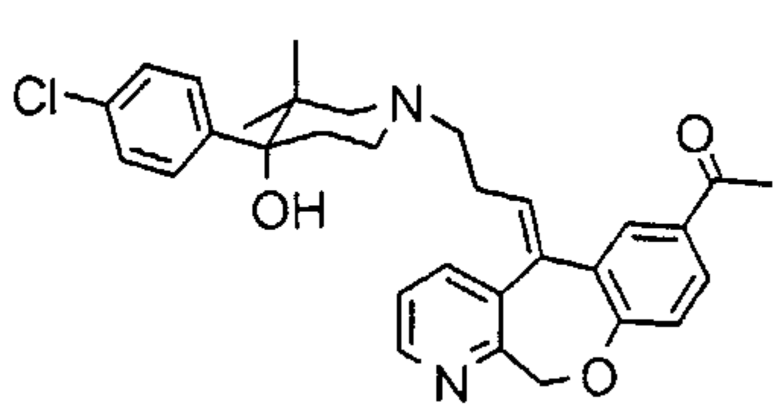
Example 502



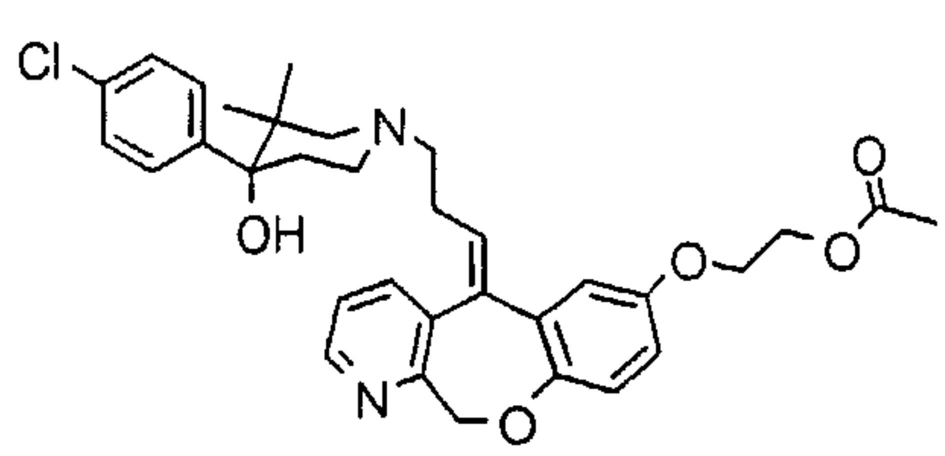
Example503



Example 504

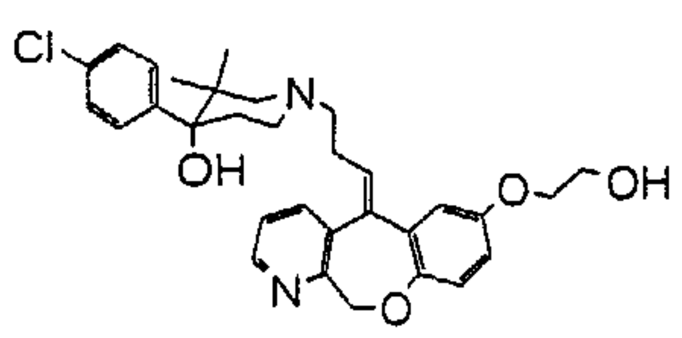


Example 505

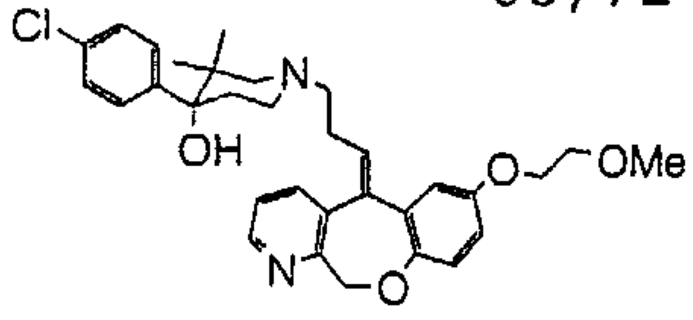


Example 506

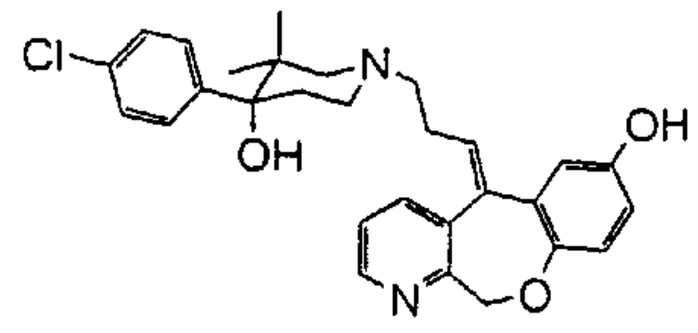
Figure 23



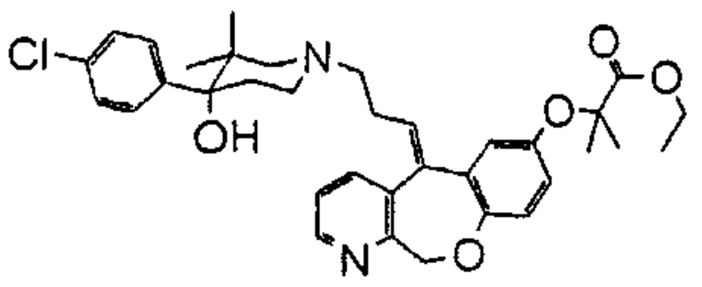
Example 507



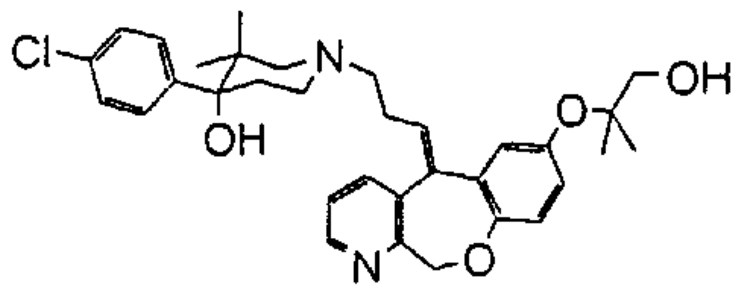
Example 508



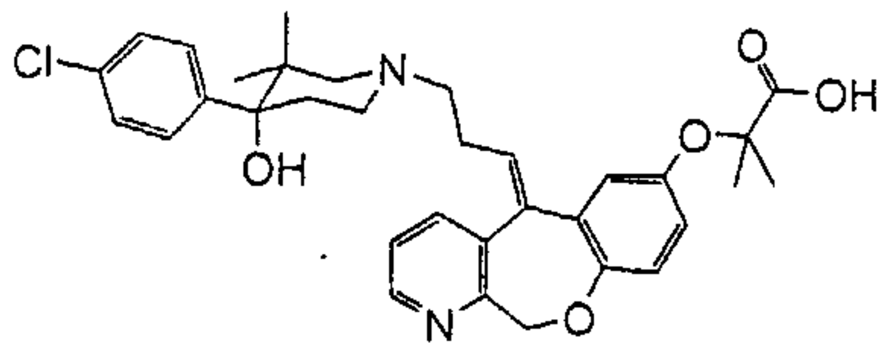
Example 509



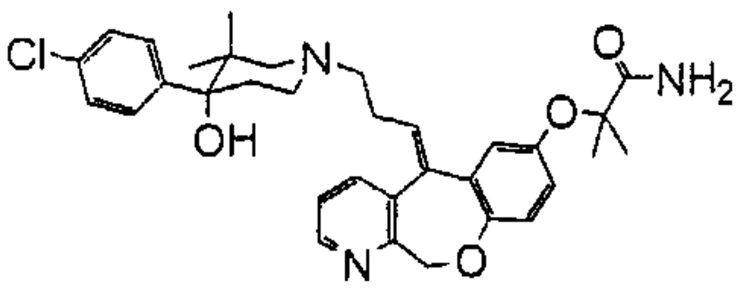
Example 510



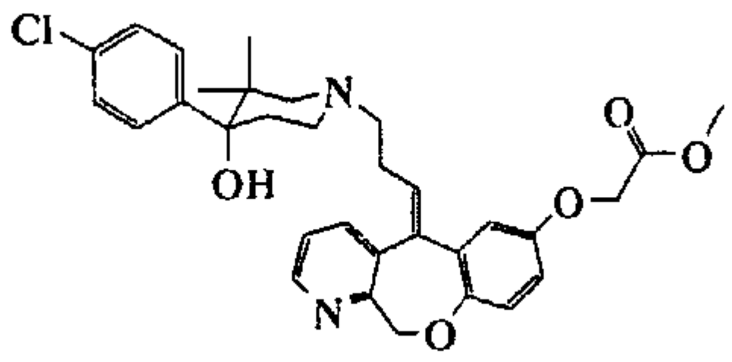
Example 511



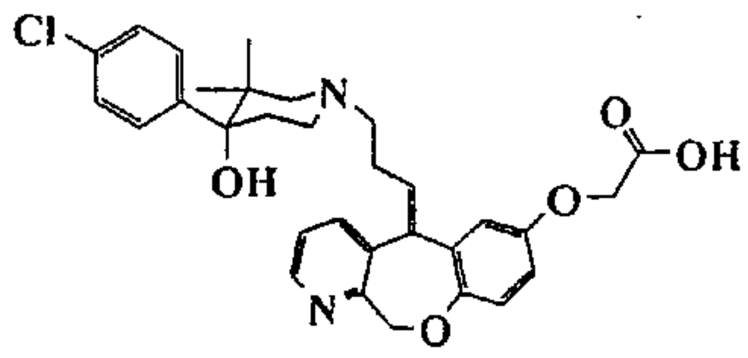
Example 512



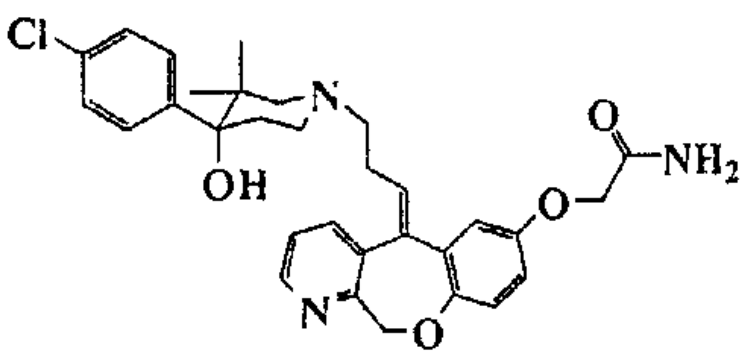
Example 513



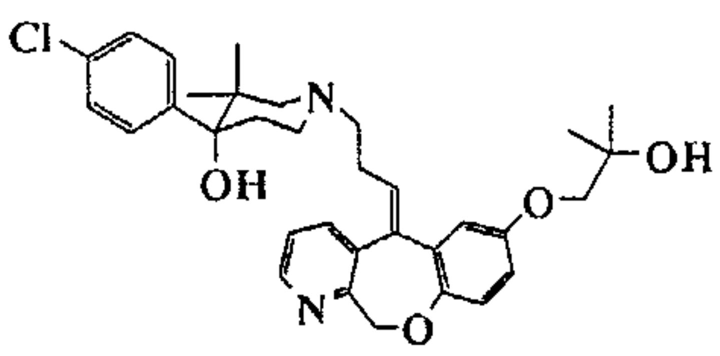
Example 514



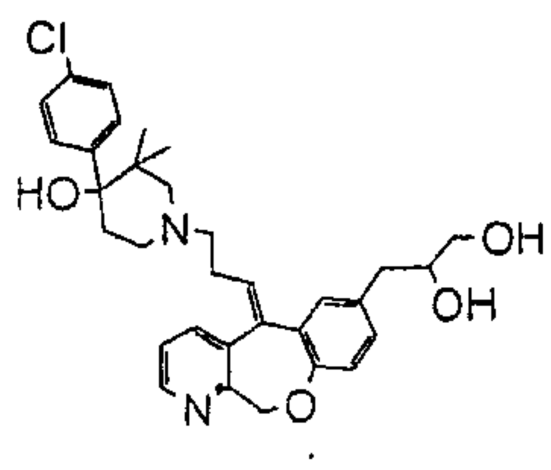
Example 515



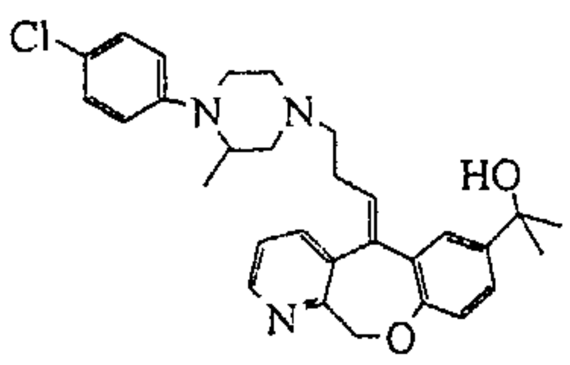
Example 516



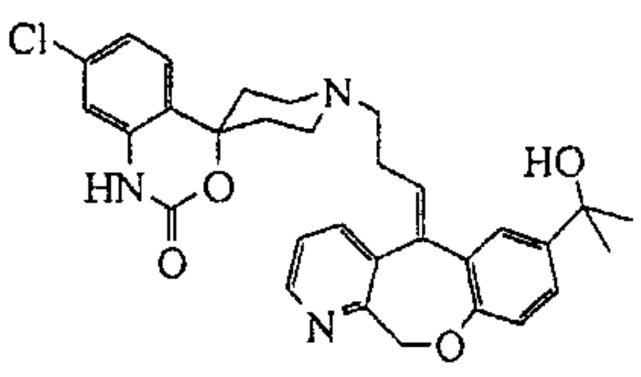
Example 517



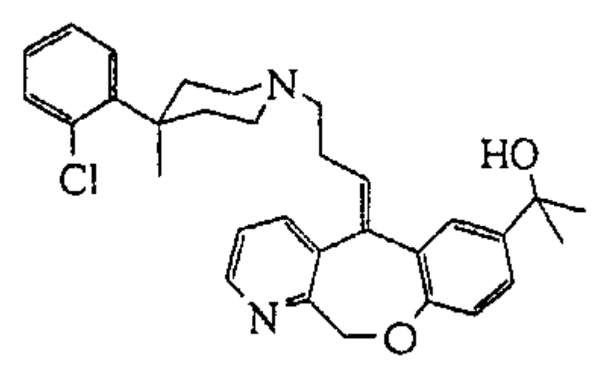
Example 518



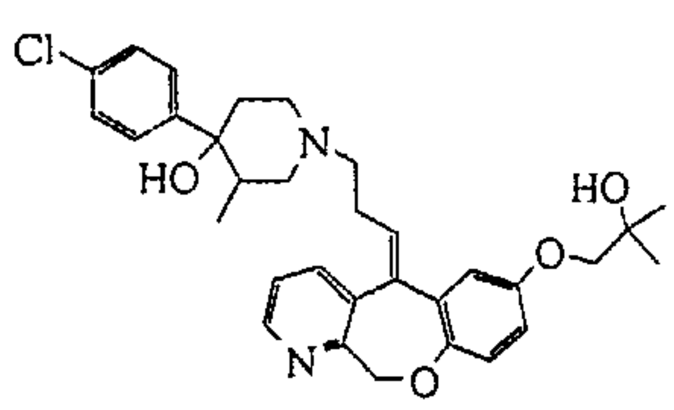
Example 519



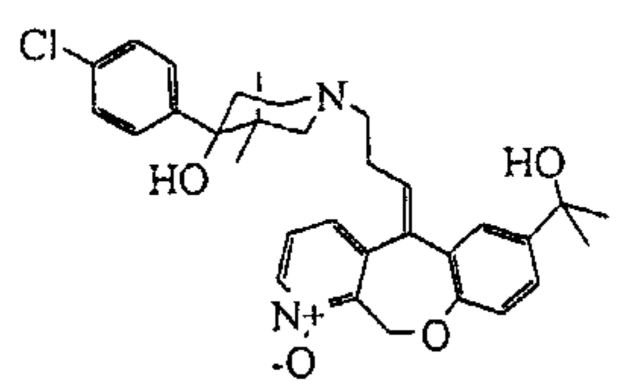
Example 520



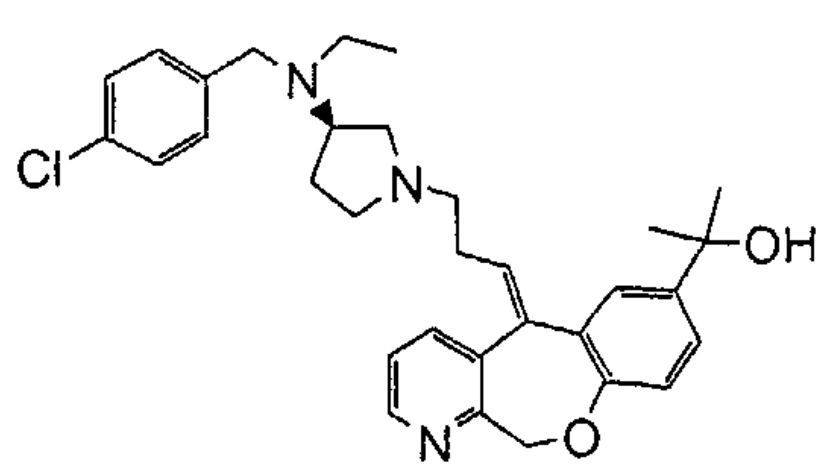
Example 521



Example 522

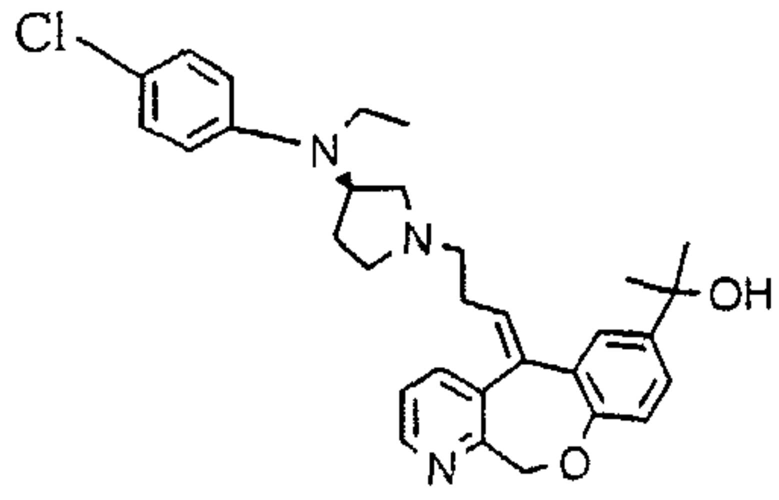


Example 523

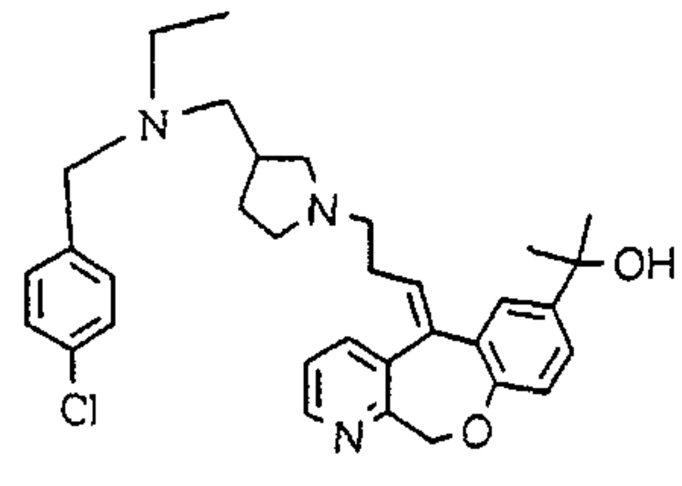


Example 524

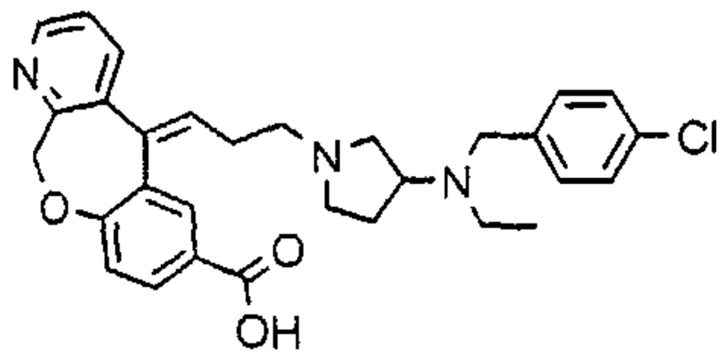
Figure 24



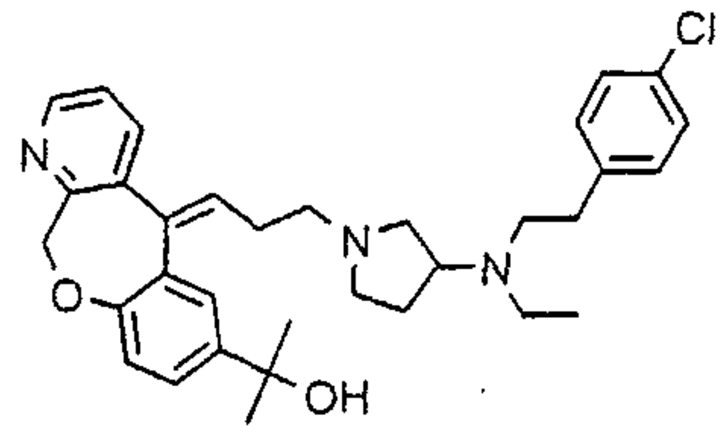
Example 525



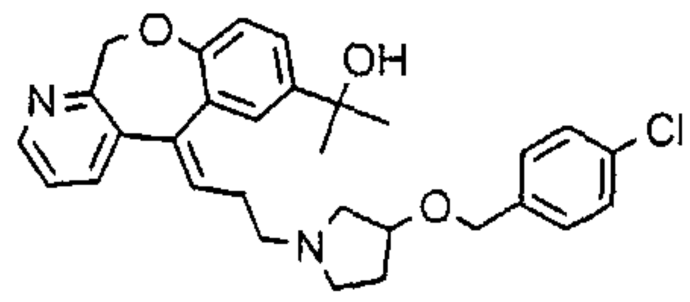
Example 526



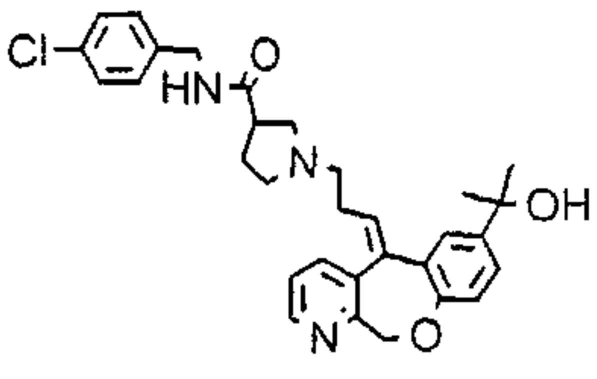
Example 527



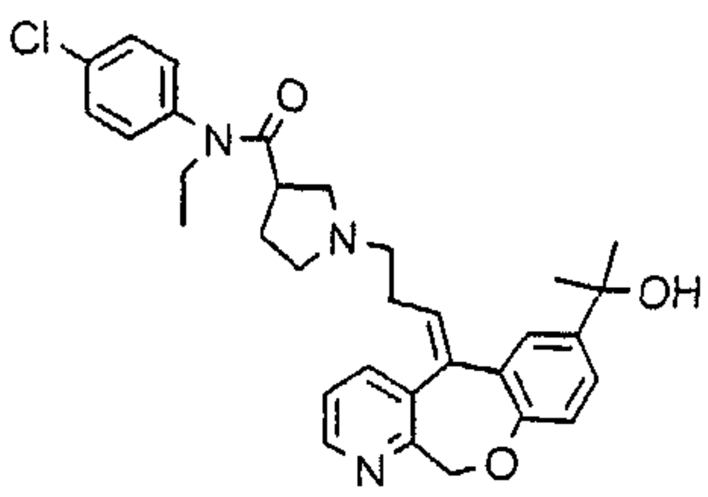
Example 528



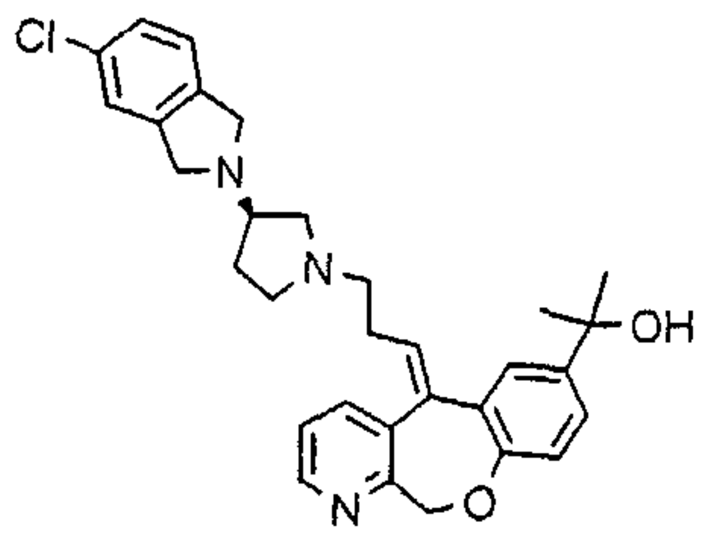
Example 529



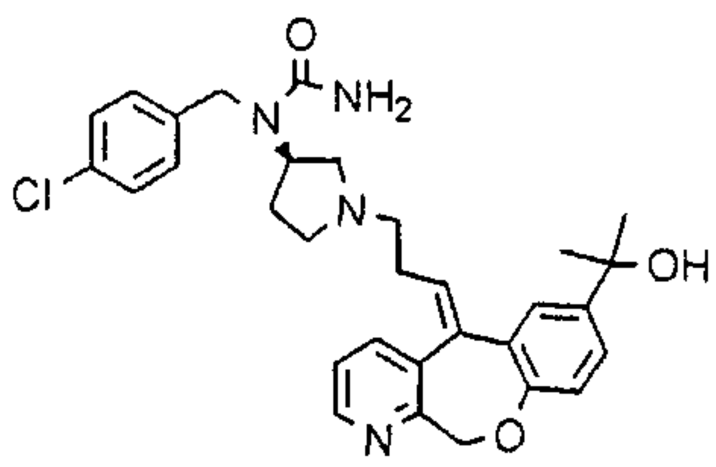
Example 530



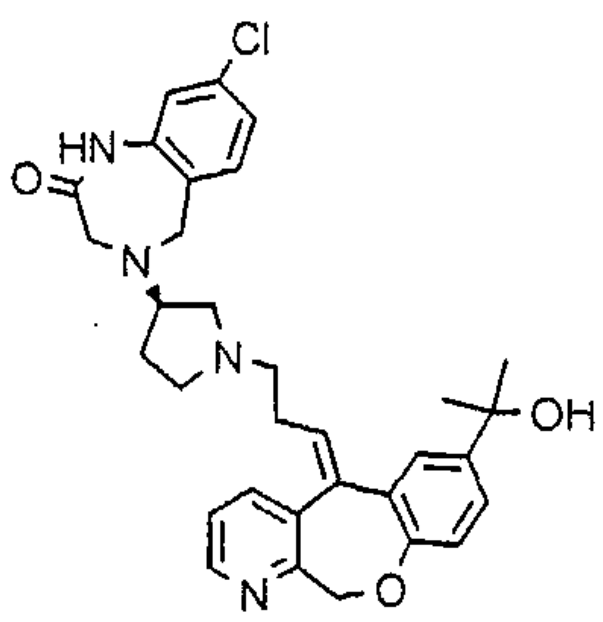
Example 531



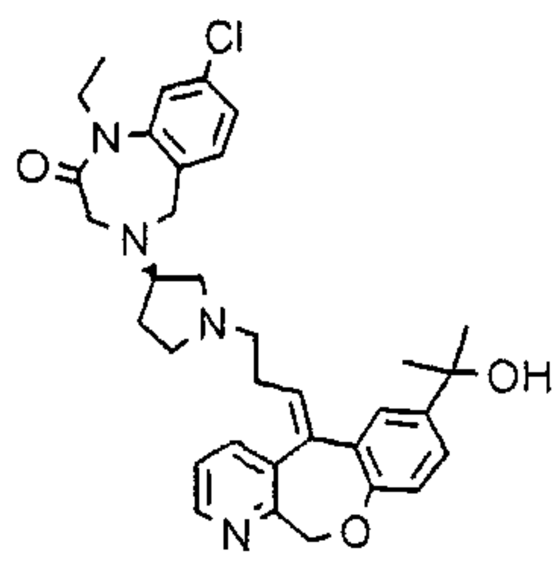
Example 532



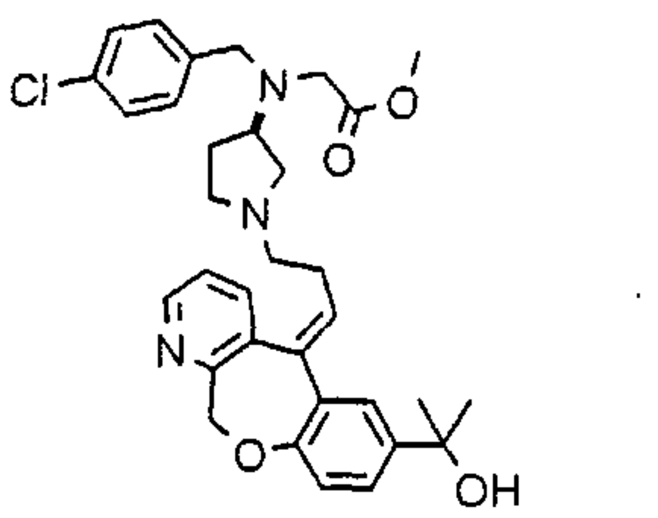
Example 533



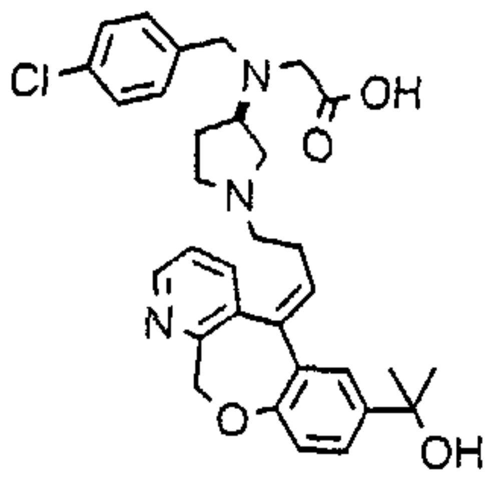
Example 534



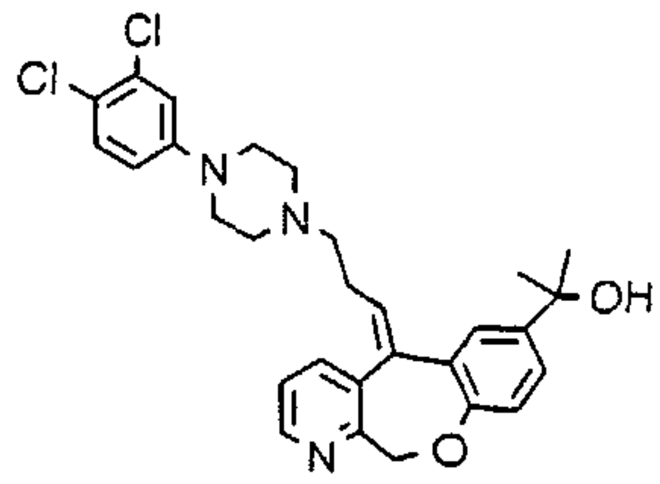
Example 535



Example 536

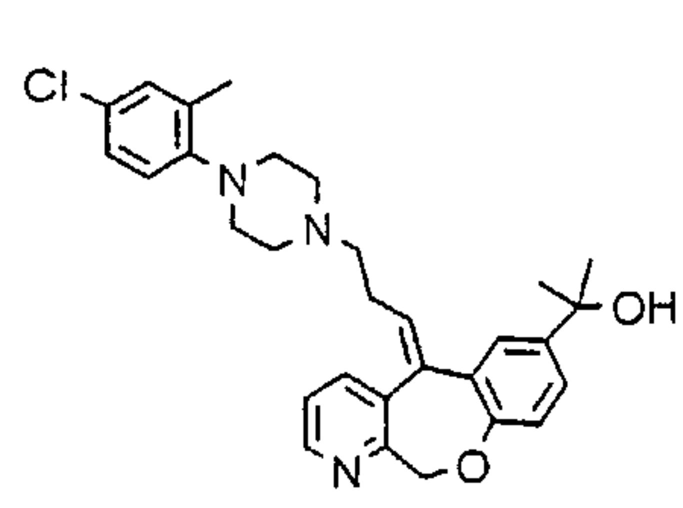


Example 537

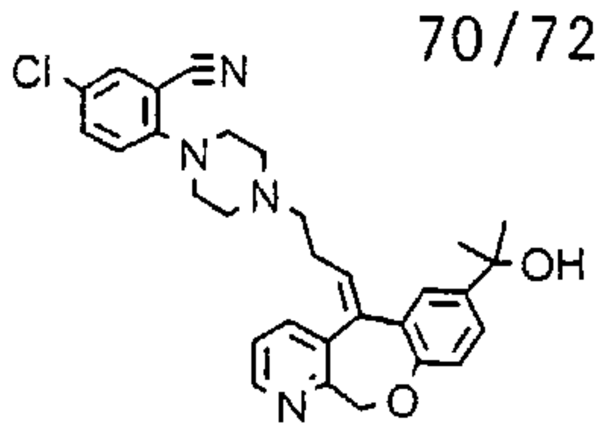


Example 538

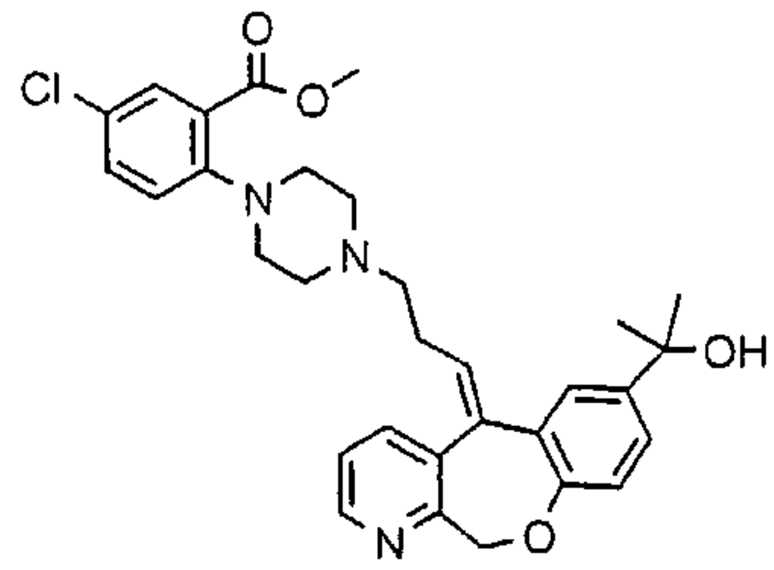
Figure 25



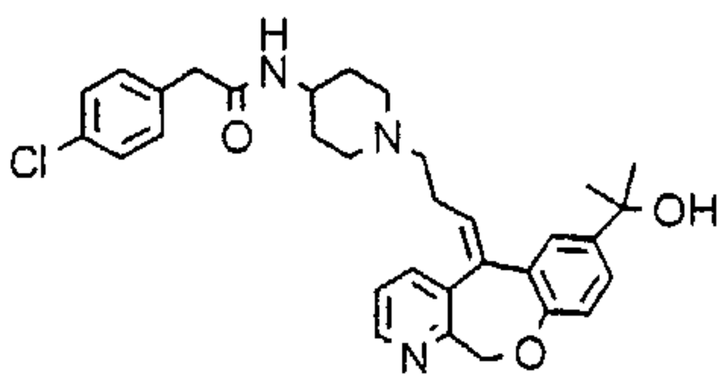
Example 539



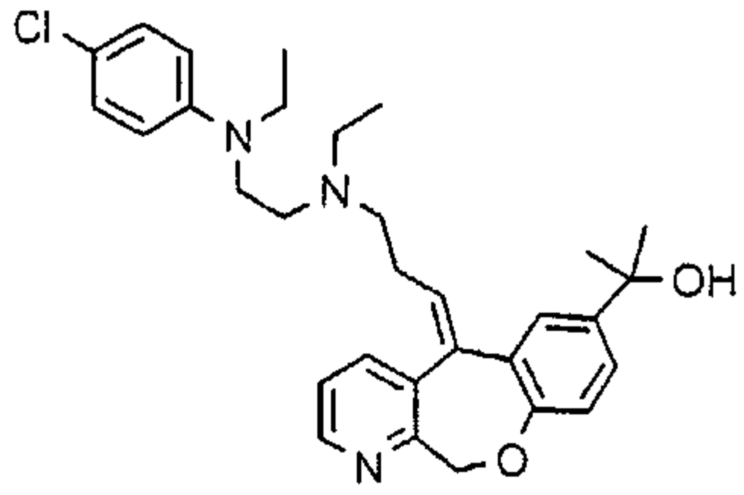
Example 540



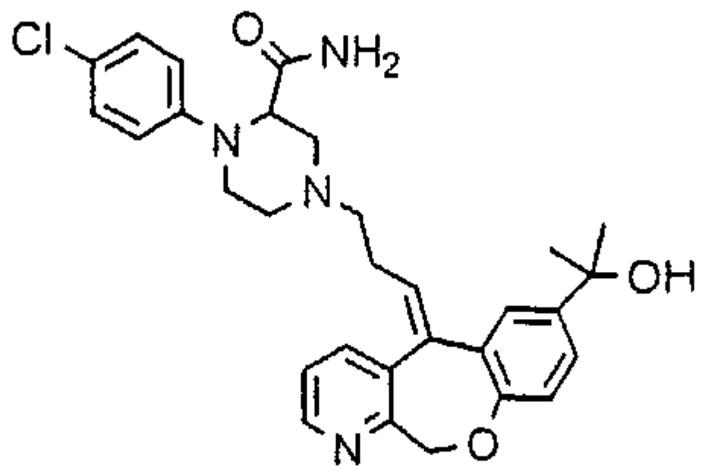
Example 541



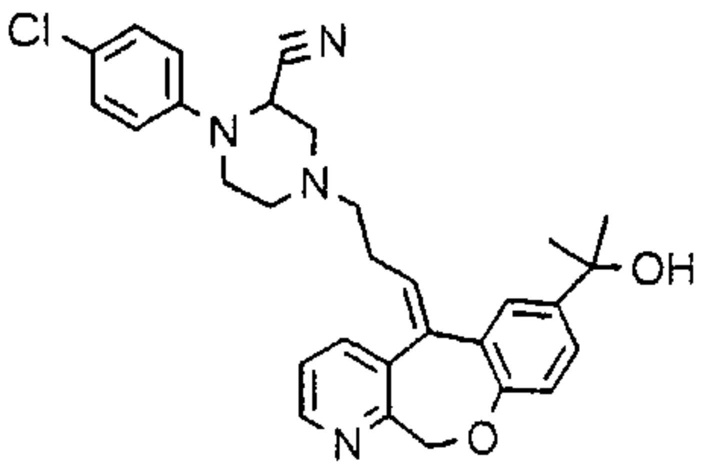
Example 542



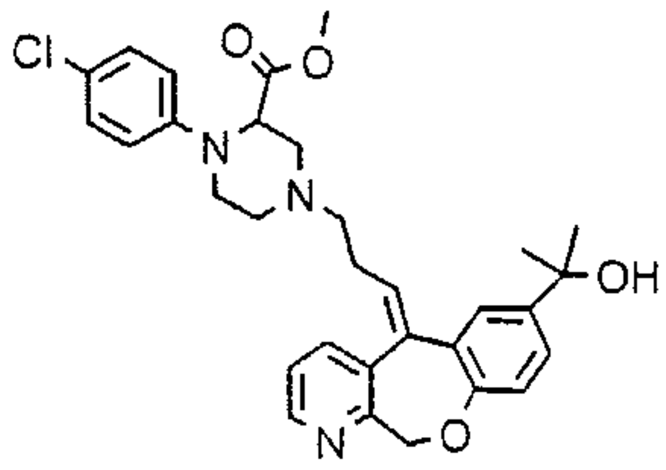
Example 543



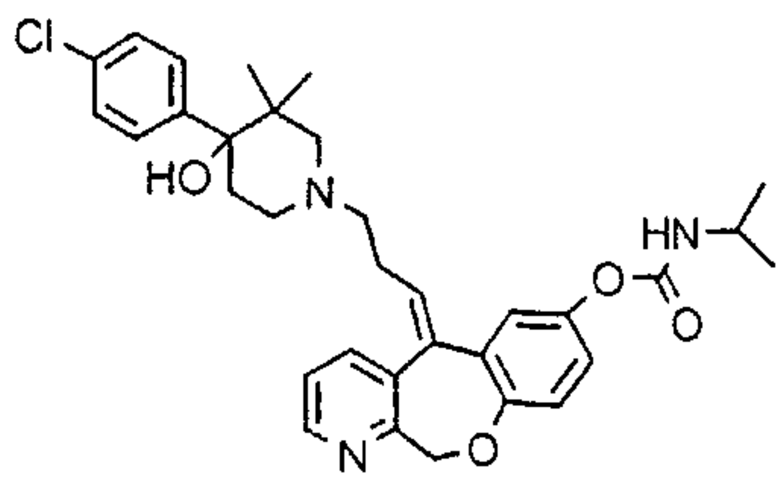
Example544



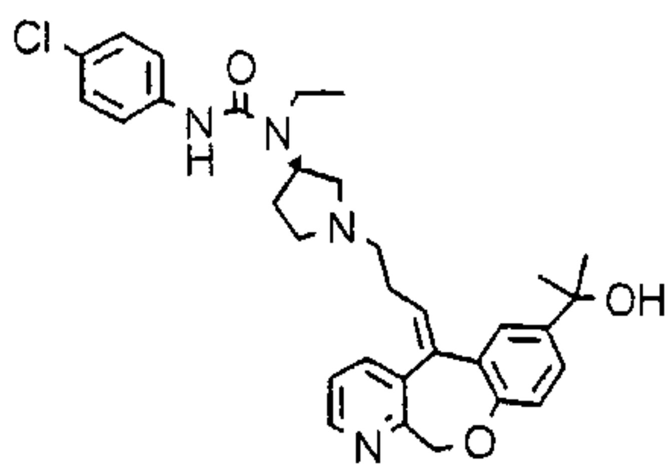
Example 545



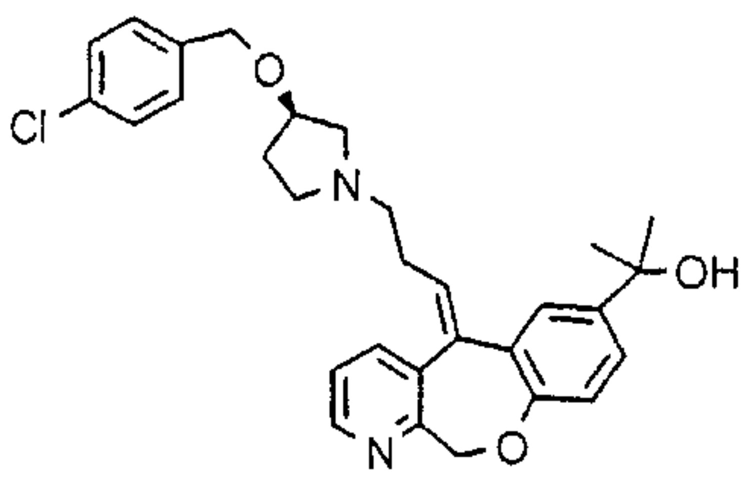
Example 546



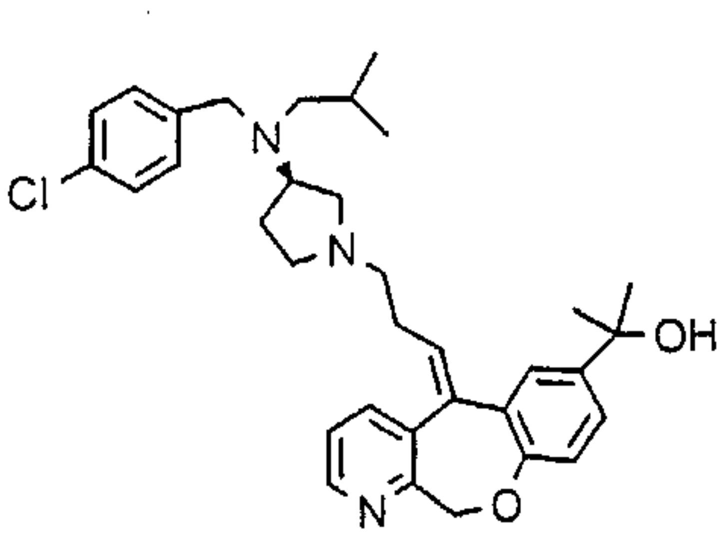
Example 547



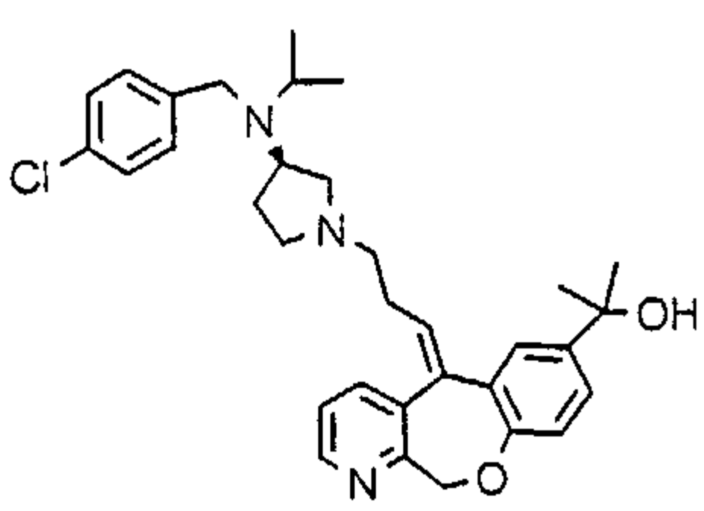
Example 548



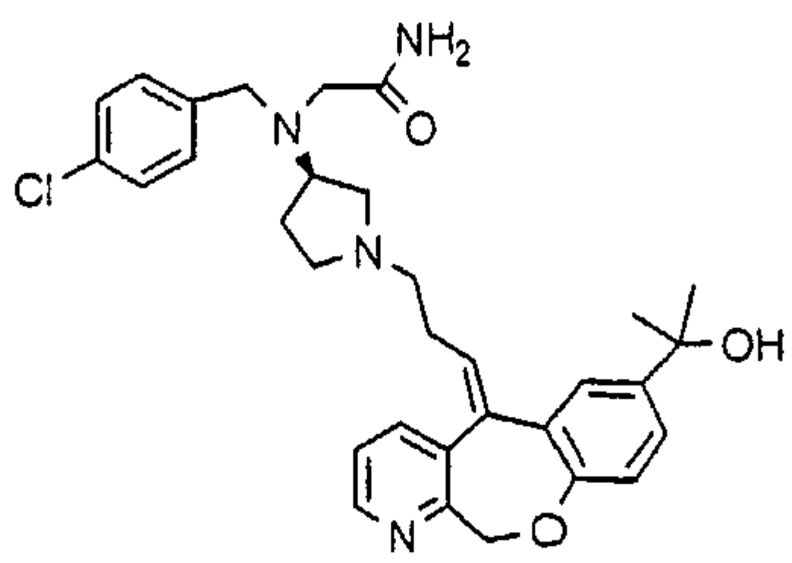
Example549



Example 550

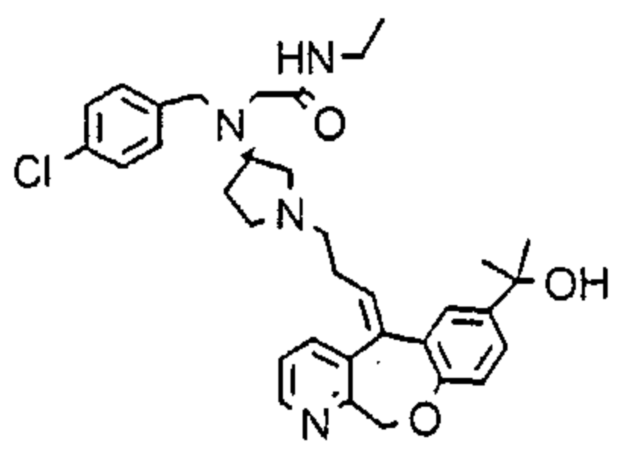


Example 551

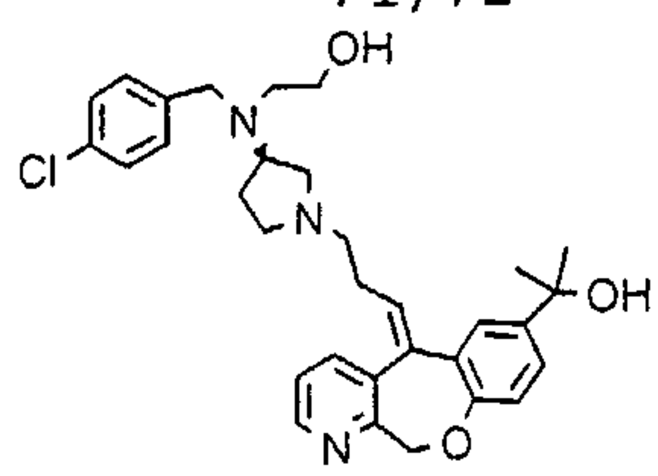


Example 552

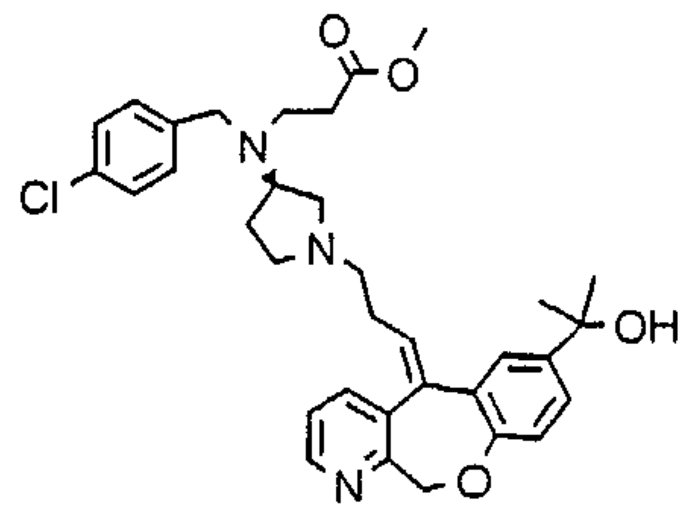
Figure 26



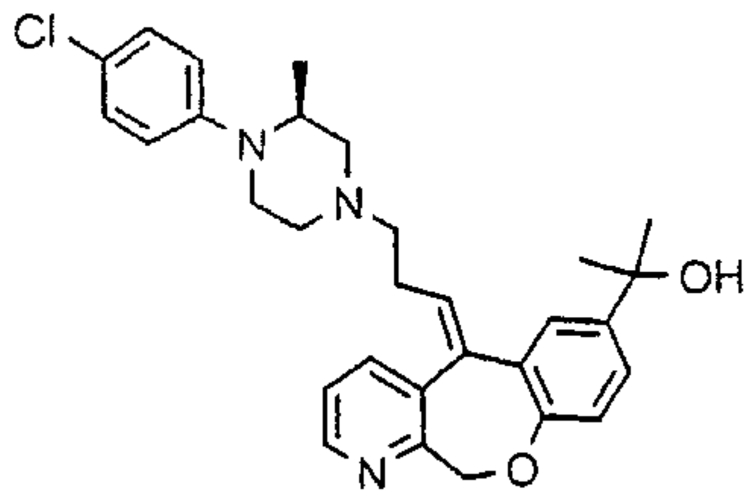
Example 553



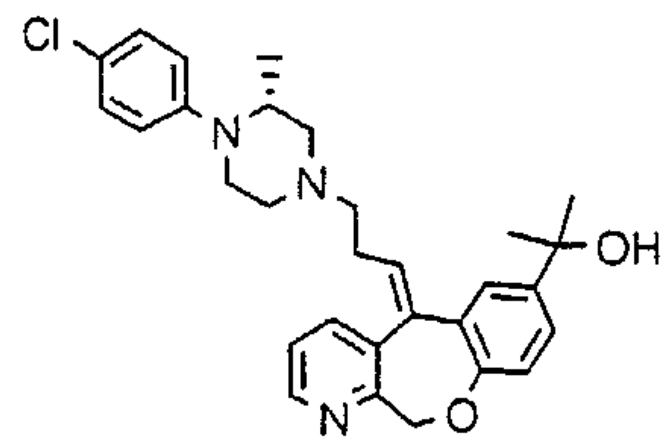
Example 554



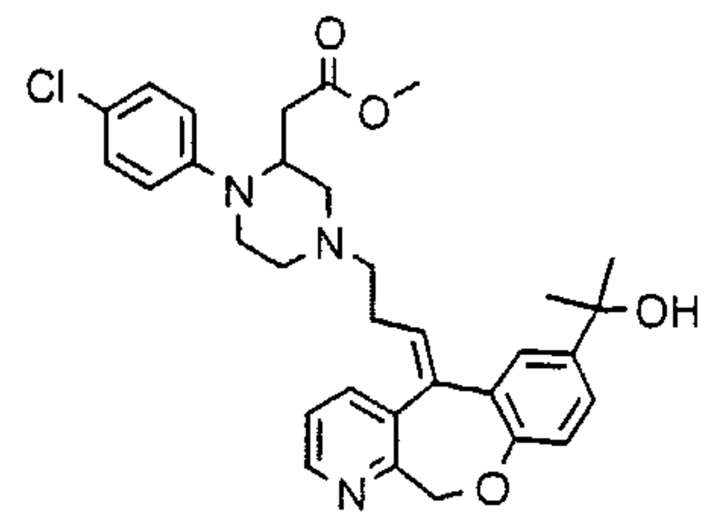
Example 555



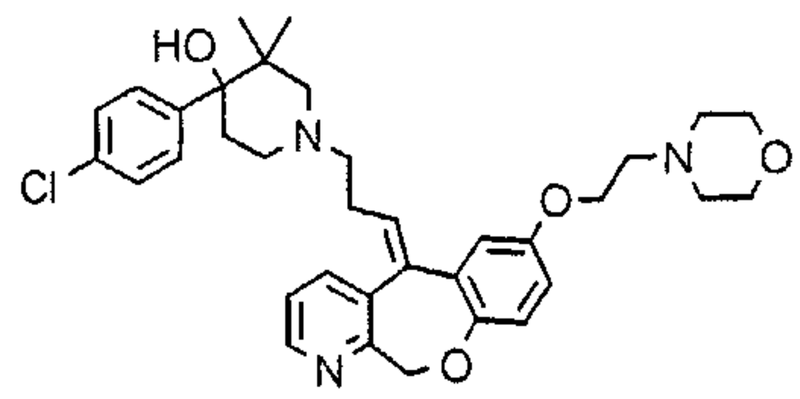
Example 556



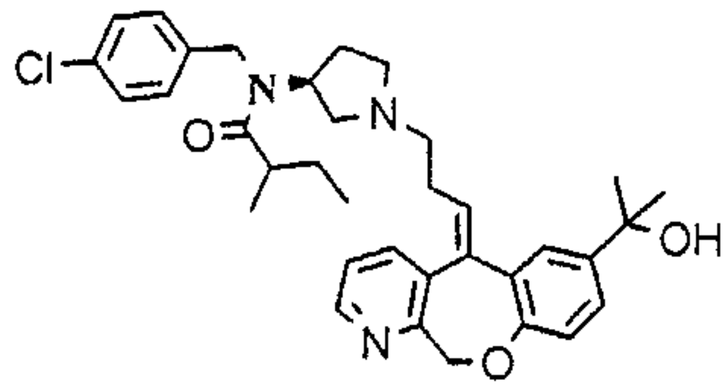
Example 557



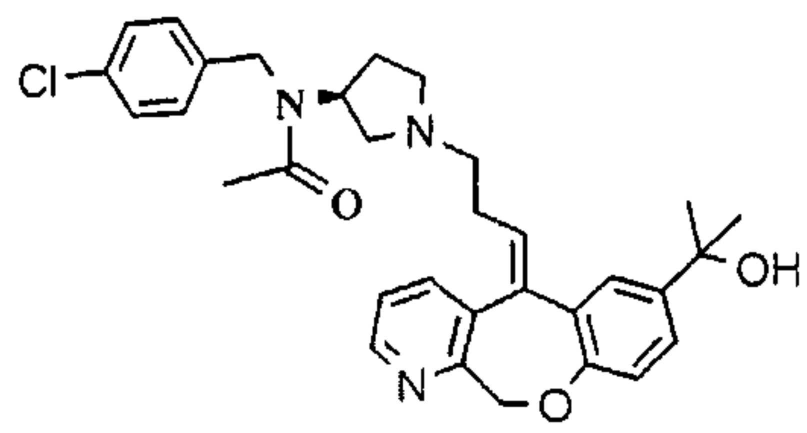
Example 558



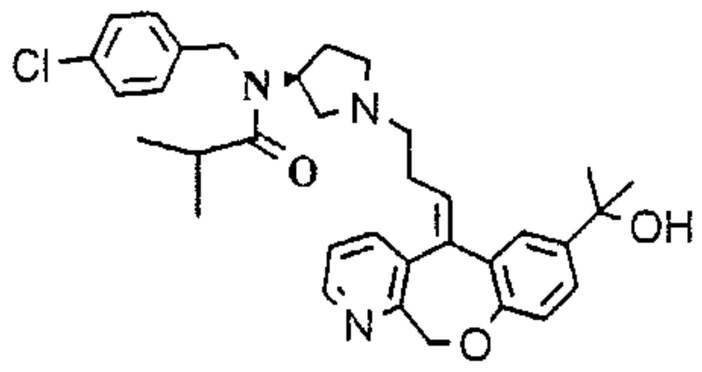
Example 559



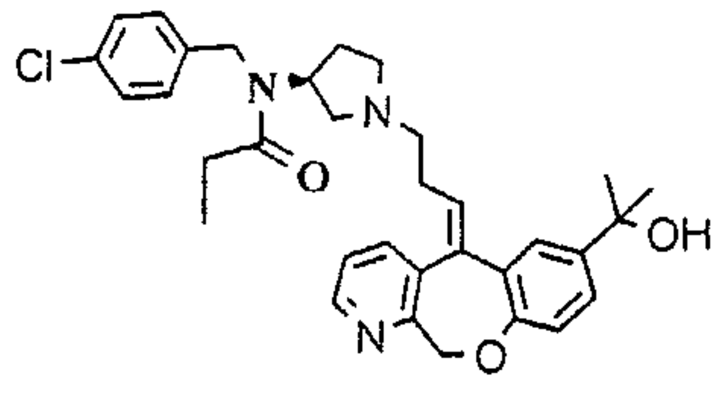
Example560



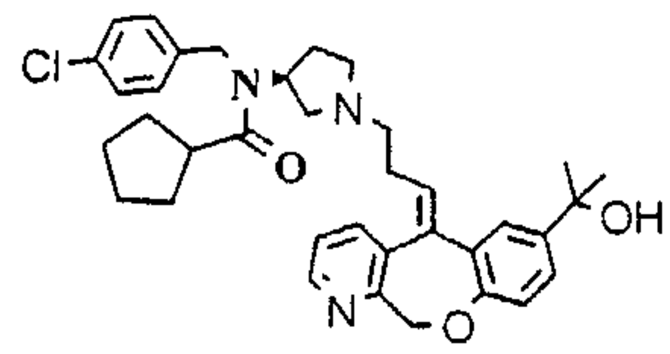
Example 561



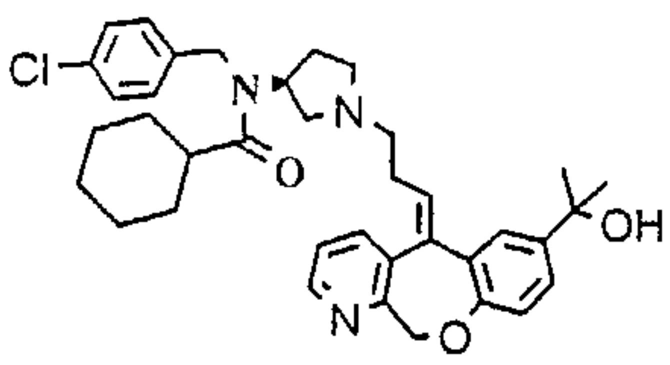
Example 562



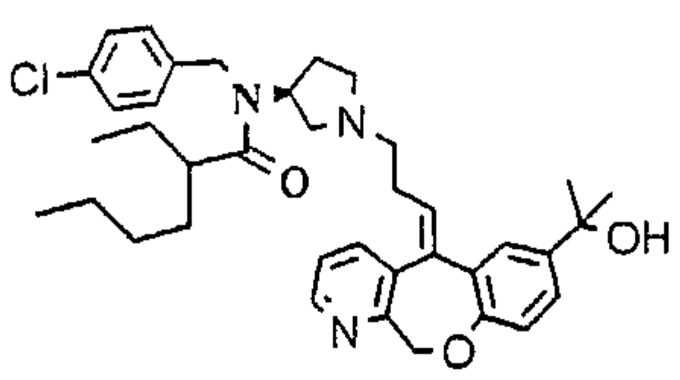
Example 563



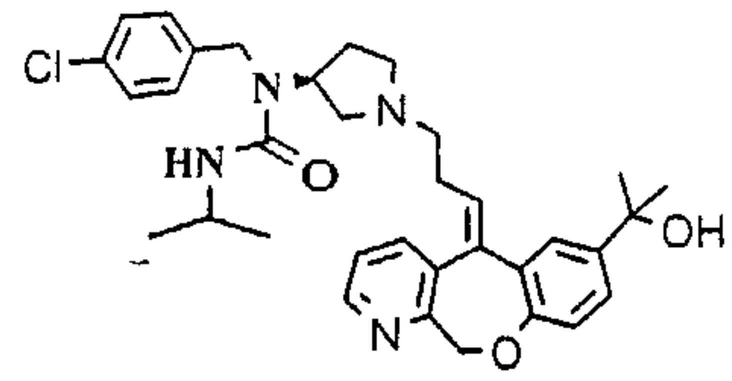
Example 564



Example 565

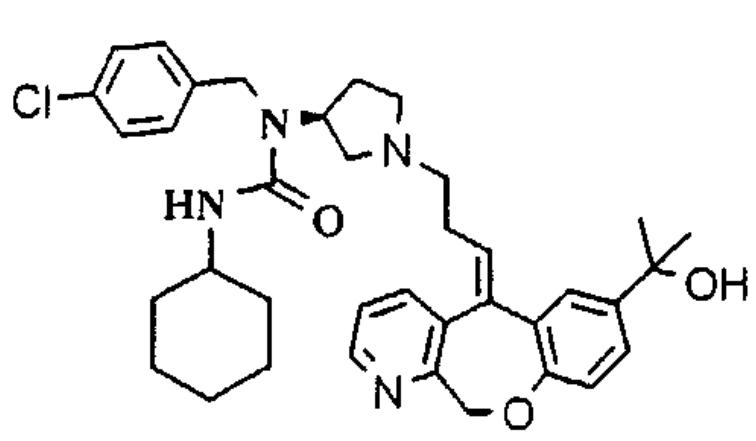


Example 566

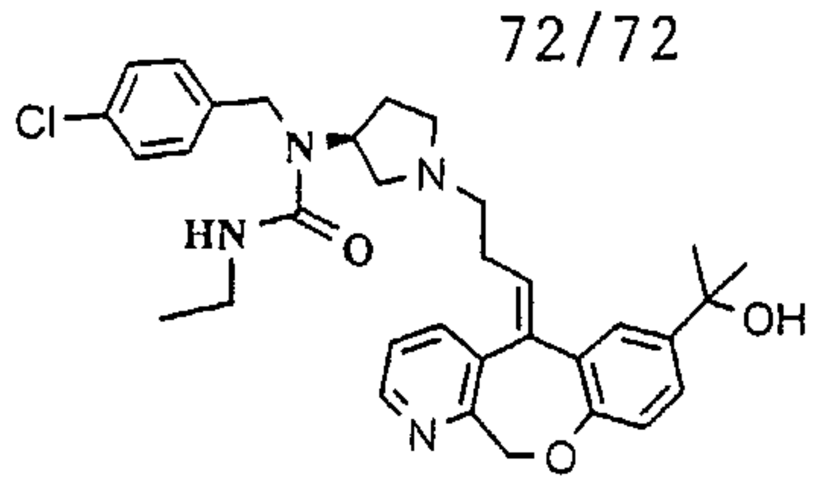


Example 567

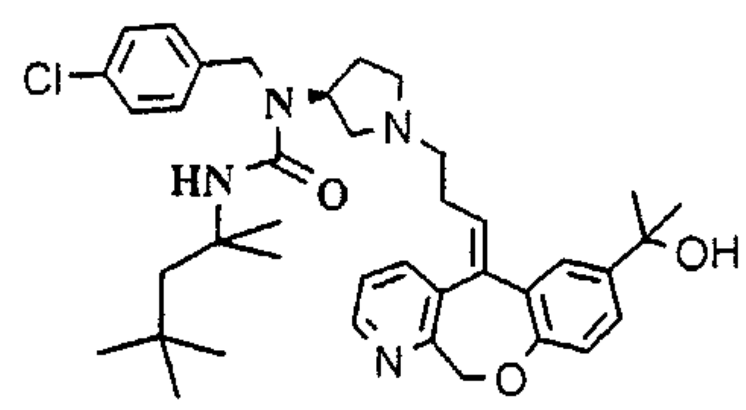
Figure 27



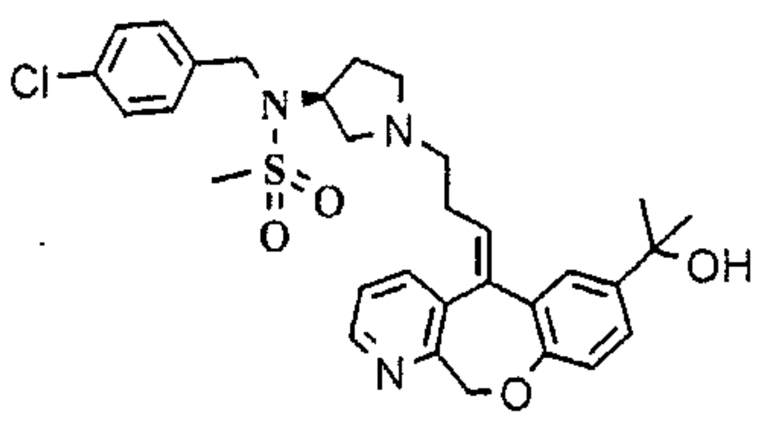
Example 568



Example 569



Example 570



Example 571

Figure 28