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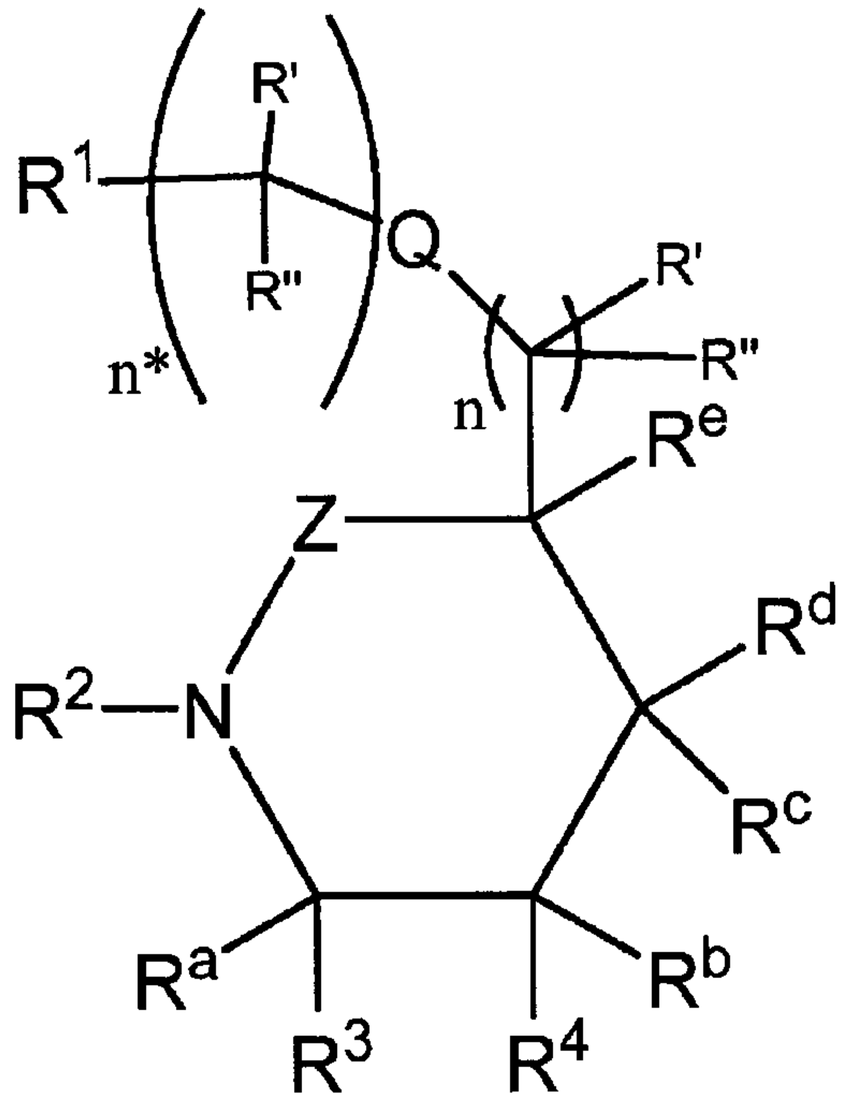
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(54) Titre : DERIVES DE LA PIPERIDINONE EN TANT QU'INHIBITEURS DE MDM2 POUR LE TRAITEMENT DU CANCER

(54) Title: PIPERIDINONE DERIVATIVES AS MDM2 INHIBITORS FOR THE TREATMENT OF CANCER

(I)



(57) Abrégé/Abstract:
The present invention provides MDM2 inhibitor compounds of Formula (I), wherein the variables are defined above, which compounds are useful as therapeutic agents, particularly for the treatment of cancers. The present invention also relates to pharmaceutical compositions that contain an MDM2 inhibitor.

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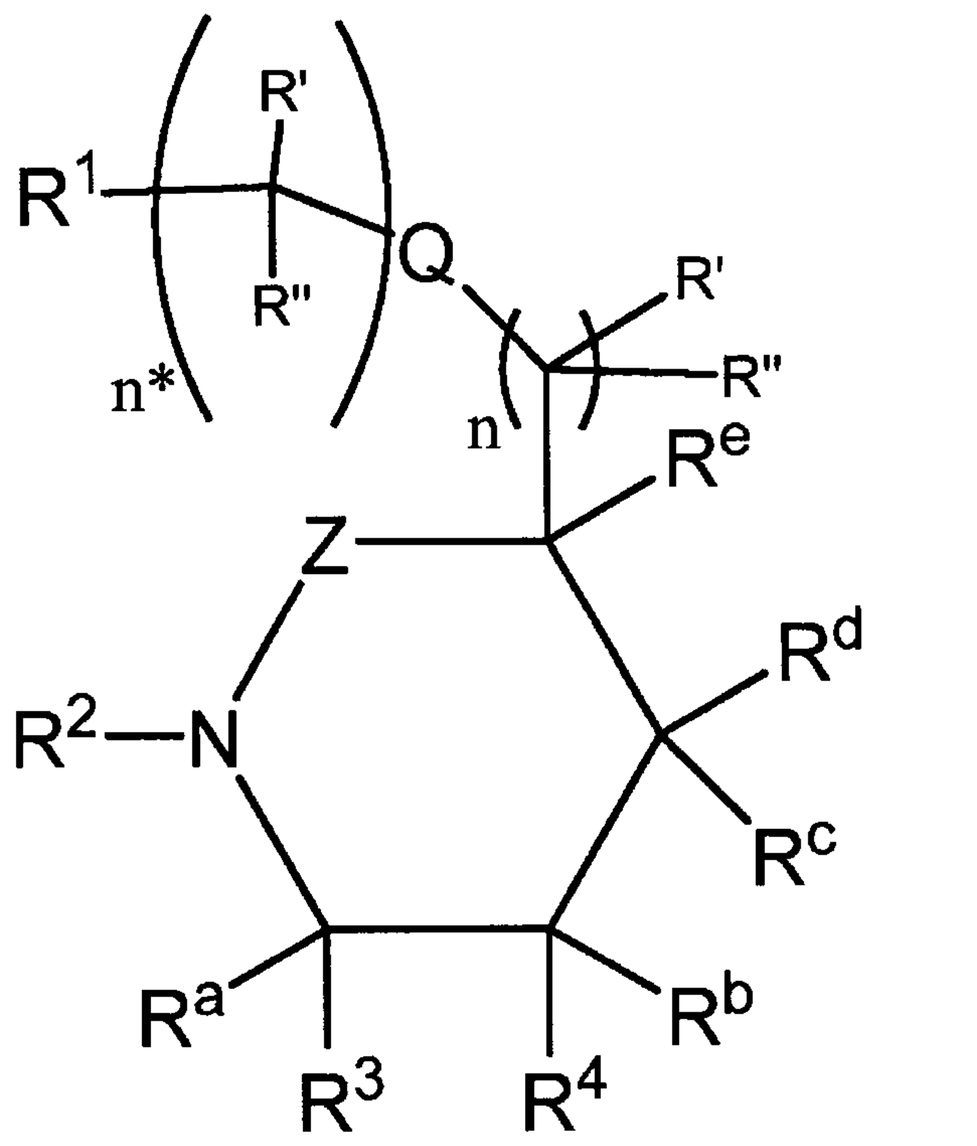
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ABSTRACT

The present invention provides MDM2 inhibitor compounds of Formula (I), wherein the variables are defined above, which compounds are useful as therapeutic agents, particularly for the treatment of cancers. The present invention also relates to pharmaceutical compositions that contain an MDM2 inhibitor.

(I)



PIPERIDINONE DERIVATIVES AS MDM2 INHIBITORS FOR THE TREATMENT OF CANCER

This application is a division of Canadian Patent Application No. 2,799,972, filed June 3, 2011.

FIELD OF THE INVENTION

The present invention relates to compounds that are MDM2 inhibitors that are useful as therapeutic agents, particularly for the treatment of cancers. The invention also relates to pharmaceutical compositions that contain an MDM2 inhibitor.

BACKGROUND OF THE INVENTION

p53 is a tumor suppressor and transcription factor that responds to cellular stress by activating the transcription of numerous genes involved in cell cycle arrest, apoptosis, senescence, and DNA repair. Unlike normal cells, which have infrequent cause for p53 activation, tumor cells are under constant cellular stress from various insults including hypoxia and pro-apoptotic oncogene activation. Thus, there is a strong selective advantage for inactivation of the p53 pathway in tumors, and it has been proposed that eliminating p53 function may be a prerequisite for tumor survival. In support of this notion, three groups of investigators have used mouse models to demonstrate that absence of p53 function is a continuous requirement for the maintenance of established tumors. When the investigators restored p53 function to tumors with inactivated p53, the tumors regressed.

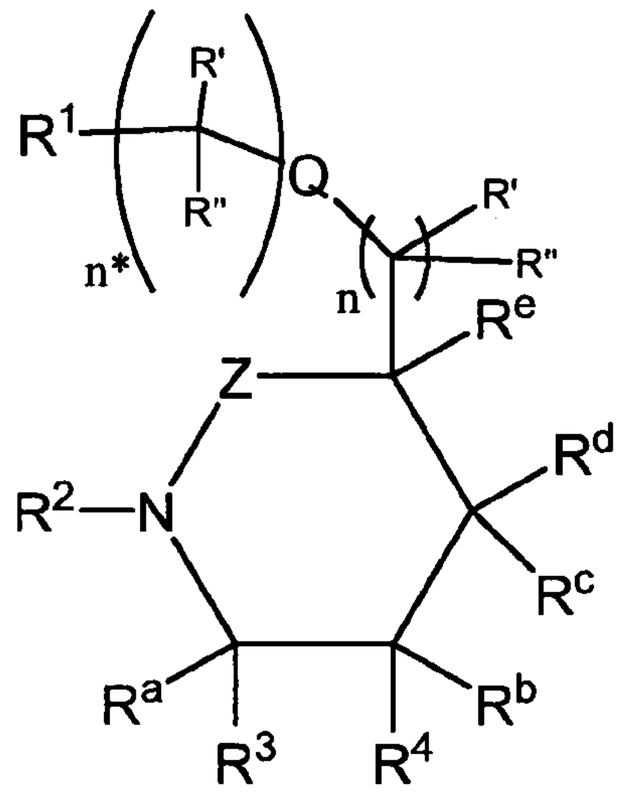
p53 is inactivated by mutation and/or loss in 50% of solid tumors and 10% of liquid tumors. Other key members of the p53 pathway are also genetically or epigenetically altered in cancer. MDM2, an oncoprotein, inhibits p53 function, and it is activated by gene amplification at incidence rates that are reported to be as high as 10%. MDM2, in turn, is inhibited by another tumor suppressor, p14ARF. It has been suggested that alterations downstream of p53 may be responsible for at least partially inactivating the p53 pathway in $p53^{WT}$ tumors (p53 wildtype). In support of this concept, some $p53^{WT}$ tumors appear to exhibit reduced apoptotic capacity, although their capacity to undergo cell cycle arrest remains intact. One cancer treatment strategy involves the use of small molecules that bind MDM2 and neutralize its interaction with p53. MDM2 inhibits p53 activity by three mechanisms: 1) acting as an E3 ubiquitin ligase to promote p53 degradation; 2) binding to and blocking the p53 transcriptional activation domain; and 3) exporting p53 from the nucleus to the cytoplasm. All three of these mechanisms would be blocked by neutralizing the MDM2-p53 interaction. In particular, this therapeutic strategy could be applied to tumors that are $p53^{WT}$, and studies with small molecule MDM2 inhibitors have yielded promising reductions in tumor growth both in

vitro and in vivo. Further, in patients with p53-inactivated tumors, stabilization of wildtype p53 in normal tissues by MDM2 inhibition might allow selective protection of normal tissues from mitotic poisons.

The present invention relates to compounds capable of inhibiting the interaction between p53 and MDM2 and activating p53 downstream effector genes. As such, compounds of the present invention would be useful in the treatment of cancers, bacterial infections, viral infections, ulcers and inflammation. In particular, the compounds of the present invention are useful to treat solid tumors such as: breast, colon, lung and prostate tumors; and liquid tumors such as lymphomas and leukemias. As used herein, MDM2 means a human MDM2 protein and p53 means a human p53 protein. It is noted that human MDM2 can also be referred to as HDM2 or hMDM2.

SUMMARY OF THE INVENTION

The present invention relates to piperidinone derivatives of Formula I.



I

enantiomers, diastereomers and pharmaceutically acceptable salts thereof,

wherein

Q is a bond or optionally can be selected from O, NR^7 and $S(O)_v$, when n* is an integer from 1 to 6,

Z is C=O or $S(=O)_2$

R^a is at each occurrence independently selected from H, $(C_1\text{-}C_3)$alkyl, (halo)$(C_1\text{-}C_3)$alkyl, (hydroxy)$(C_1\text{-}C_3)$alkyl, (alkoxy)$(C_1\text{-}C_3)$alkyl, or cyano;

R^b is H, halo, $(C_1\text{-}C_3)$alkyl, (halo)$(C_1\text{-}C_3)$alkyl, (hydroxy)$(C_1\text{-}C_3)$alkyl, (alkoxy)$(C_1\text{-}C_3)$alkyl, or cyano;

R^c and R^d are independently H, halo, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, (halo)$(C_1\text{-}C_3)$alkyl, (halo)$(C_1\text{-}C_3)$alkoxy, (alkoxy)$(C_1\text{-}C_3)$alkyl, (hydroxy)$(C_1\text{-}C_3)$alkyl;

or R^c and R^d may optionally combine to form a spiro-cycloalkyl or heterocyclo ring system;

R^e is (a) H, or halo; or

(b) $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_3\text{-}C_8)$heterocyclo, cyano, halogen, hydroxyl, -OR^5, NR^7R^8, heterocycloalkyl, any of which may be optionally substituted with 1 or more R^x groups as allowed by valence.

or R^e and any one of the R' or R" groups may optionally combine to form a spiro-cycloalkyl or heterocyclo ring system;

or R^d and any one of the R' or R" groups may optionally combine to form a fused cycloalkyl or heterocyclo ring system;

or R^d and R^e may optionally combine to form a fused cycloalkyl or heterocyclo ring system;

R' and R" at each occurrence, respectively, are independently H, halo, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, (halo)$(C_1\text{-}C_3)$alkyl, (halo)$(C_1\text{-}C_3)$alkoxy, (alkoxy)$(C_1\text{-}C_3)$alkyl, (hydroxy)$(C_1\text{-}C_3)$alkyl, -S-$(C_1\text{-}C_3)$alkyl, C(O)$(C_1\text{-}C_3)$alkyl, -NR^7R^8, or hydroxyl

or R' and R" bound to the same carbon atom may optionally combine to form =O;

or R' and R" bound to the same carbon atom may optionally combine to form a spiro-fused cycloalkyl or heterocyclo ring system

R^1 is

(a) –COOH, $-C(O)OR^{10}$, –C(O)NHOH, $-C(O)NH\text{-}NH_2$, $-C(O)NHS(O)_2R^{10}$, $-S(O)_2NHC(O)R^{10}$, $-S(O)_2NR^7R^8$, $-NR^7C(O)R^{10}$, $-NR^7C(O)OR^5$, $-C(O)NR^7R^8$, $-NR^7S(O)_2R^{10}$, or $-NR^7C(O)\,NR^7R^8$, $-S(O)_vR^{10}$, or CN;

(b) heteroaryl or heterocyclo either of which may be optionally independently substituted with one or more R^x groups as allowed by valence;

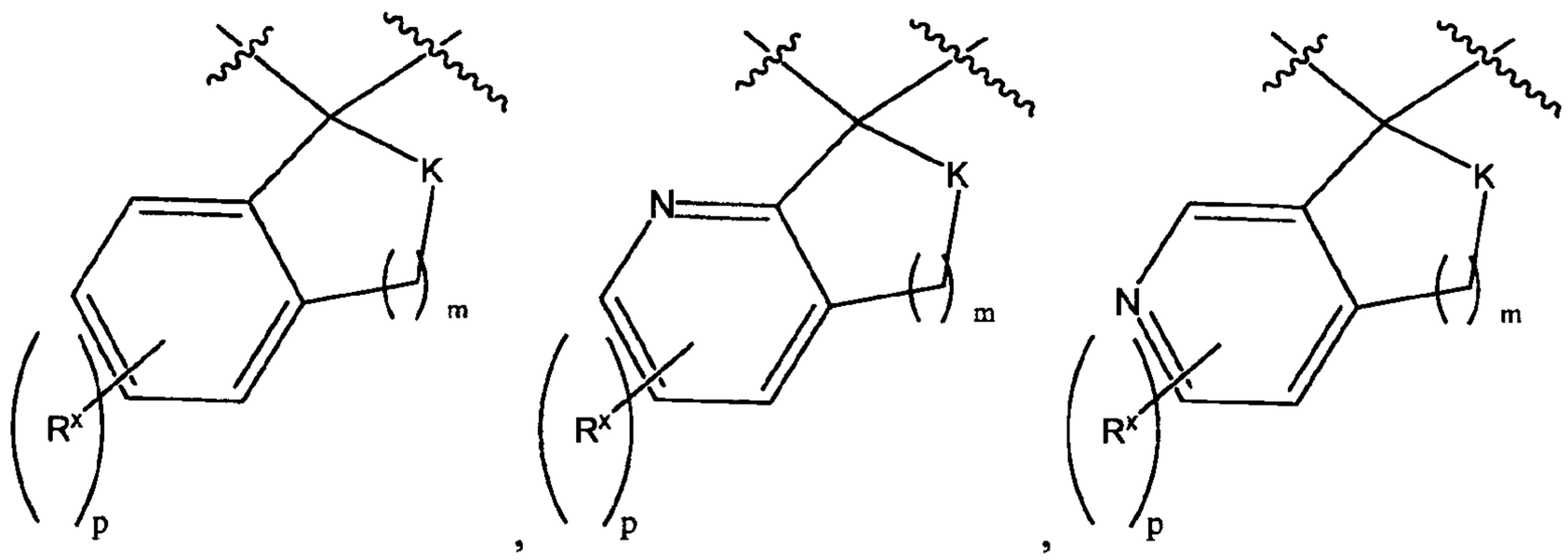
R^2 is

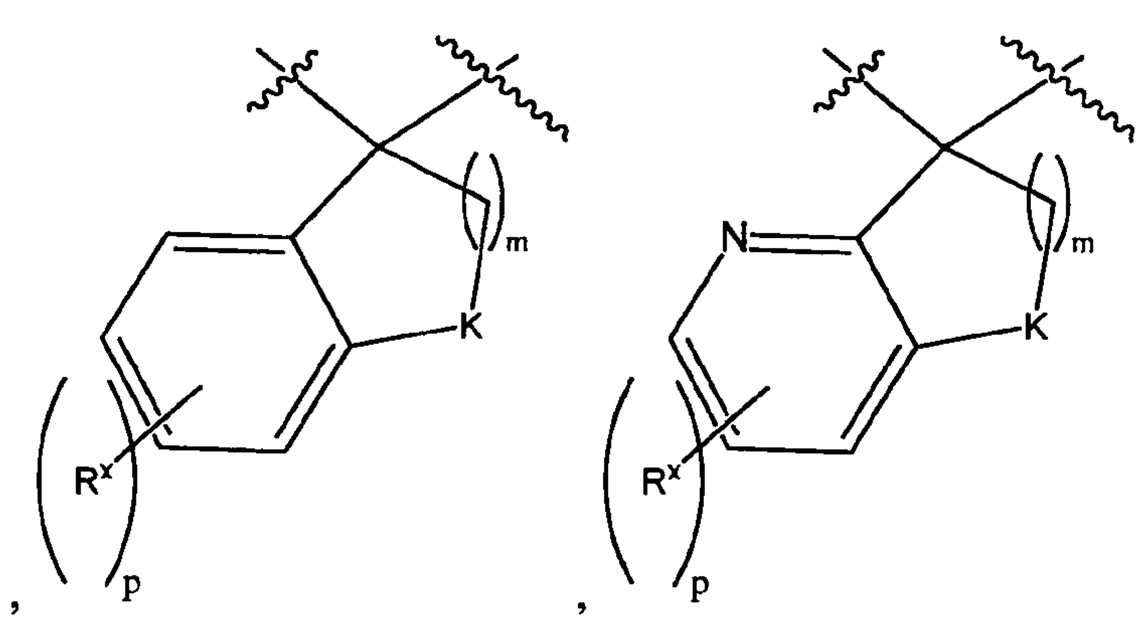
(a) $-NR^7R^8$, $NR^7C(O)OR^{10}$, $NR^7C(O)NR^7R^{10}$, or $-C(R^a)R^5R^6$;

(b) aryl, heteroaryl, cycloalkyl, or heterocyclo any of which may be optionally independently substituted with one or more R^x groups as allowed by valence;

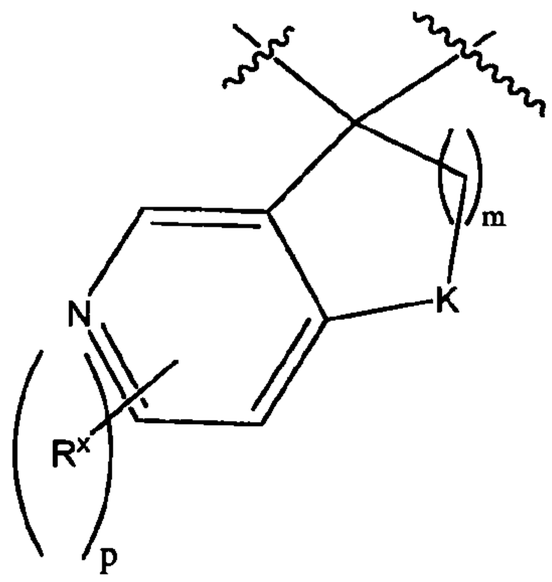
R^3 and R^4 are independently aryl or heteroaryl, either of which may be optionally independently substituted with one or more R^x groups as allowed by valence;

or either R^3 and R^a together with the ring carbon atom to which they are both bonded, or R^4 and R^b together with the ring carbon atom to which they are both bonded may optionally combine to form a spiro-fused bicyclic ring system selected from





or



wherein K is –O-, -NR^7-, or –C(=O)NR^7-,

R^5, and R^6 at each occurrence, respectively, are independently selected from

(a) H and CN; or

(b) -(alkylene)$_t$ –OH, -(alkylene)$_t$ –OR^9, -(alkylene)$_t$ –SR^9, -(alkylene)$_t$ –$NR^{10}R^{11}$, -(alkylene)$_t$-C(O)R^9, -(alkylene)$_t$ –C(O)OR^9, -(alkylene)$_t$ –OC(O)R^9, -(alkylene)$_t$ –$S(O)_vR^9$, -(alkylene)$_t$-$NHS(O)_2R^{10}$, -(alkylene)$_t$-$N(R^{11})S(O)_2R^{10}$, -(alkylene)$_t$-

$-NR^{10}C(O)R^9$, $C(O)NR^{10}R^{11}$, $NR^{10}S(O)_2R^9$, $S(O)_2NR^{10}$, and $NR^{10}C(O)NR^{10}R^{11}$; or

(a) haloalkyl, haloalkoxy, C_{1-6}-alkyl, C_{2-6}alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, (C_{3-8}-cycloalkyl)(C_{1-3}alkyl), C_{4-8}-cycloalkenyl, aryl, aryl(C_{1-3}-alkyl) heteroaryl, heteroaryl(C_{1-3}-alkyl), heterocyclo and heterocyclo(C_{1-3}-alkyl) m any of which may be optionally independently substituted with one or more R^x groups as allowed by valence;

R^7, and R^8 at each occurrence, respectively, are independently selected from H, C_{1-6}-alkyl, halo(C_{1-6})-alkyl, cycloalkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocyclo(C_{1-10}alkyl), and (C_{3-8}-cycloalkyl)(C_{1-3}alkyl), any of which may be optionally substituted as allowed by valence with one or more R^x;

or R^7 and R^8 may combine to form a C_4-C_8-heterocyclo ring optionally substituted with one or more R^x;

R^9 is

haloalkyl, haloalkoxy, C_{1-6}-alkyl, C_{2-6}alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, (C_{3-8}-cycloalkyl)(C_{1-3}alkyl), C_{4-8}-cycloalkenyl, aryl, heteroaryl, and heterocyclo any of which may be optionally independently substituted with one or more R^x groups as allowed by valence;

R^{10} and R^{11} at each occurrence, respectively, are independently selected from alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally substituted as allowed by valence with one or more R^x;

or R^{10} and R^{11} may combine to form a heterocyclo ring optionally substituted with one or more R^x;

R^x at each occurrence is independently, deuterium, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-(alkylene)_t-OR^*$, $-(alkylene)_t-S(O)_vR^*$, $-(alkylene)_t-NR^+R^{++}$, $-(alkylene)_t-C(=O)R^*$, $-(alkylene)_t-C(=S)R^*$, $-(alkylene)_t-C(=O)OR^*$, $-(alkylene)_t-OC(=O)R^*$, $-(alkylene)_t-C(=S)OR^*$, $-(alkylene)_t-C(=O)NR^+R^{++}$, $-(alkylene)_t-C(=S)NR^+R^{++}$, $-(alkylene)_t-N(R^+)C(=O)NR^+R^{++}$, $-(alkylene)_t-N(R^+)C(=S)NR^+R^{++}$, $-(alkylene)_t-N(R^+)C(=O)R^*$, $-(alkylene)_t-N(R^+)C(=S)R^*$, $-(alkylene)_t-OC(=O)NR^+R^{++}$, $-(alkylene)_t-OC(=S)NR^+R^{++}$, $-(alkylene)_t-SO_2NR^+R^{++}$, $-(alkylene)_t-N(R^+)SO_2R^*$,

-(alkylene)$_t$-N(R^+)$SO_2NR^+R^{++}$, -(alkylene)$_t$-N(R^+)C(=O)OR^*,
-(alkylene)$_t$-N(R^+)C(=S)OR^*, or -(alkylene)$_t$-N(R^+)SO_2R^*;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more halo, cyano, oxo, -(alkylene)$_t$-OR^*, -(alkylene)$_t$-S(O)$_v$$R^*$, -(alkylene)$_t$-$NR^+R^{++}$, -(alkylene)$_t$-C(=O)$R^*$, -(alkylene)$_t$-C(=S)$R^*$, -(alkylene)$_t$-C(=O)$OR^*$, -(alkylene)$_t$-OC(=O)$R^*$, -(alkylene)$_t$-C(=S)$OR^*$, —(alkylene)$_t$-C(=O)$NR^+R^{++}$, -(alkylene)$_t$-C(=S)$NR^+R^{++}$, -(alkylene)$_t$-N($R^+$)C(=O)$NR^+R^{++}$, -(alkylene)$_t$-N($R^+$)C(=S)$NR^+R^{++}$, -(alkylene)$_t$-N($R^+$)C(=O)$R^*$, -(alkylene)$_t$-N($R^+$)C(=S)$R^*$, -(alkylene)$_t$-OC(=O)$NR^+R^{++}$, -(alkylene)$_t$-OC(=S)$NR^+R^{++}$, -(alkylene)$_t$-$SO_2NR^+R^{++}$, -(alkylene)$_t$-N($R^+$)$SO_2R^*$, -(alkylene)$_t$-N($R^+$)$SO_2NR^+R^{++}$, -(alkylene)$_t$-N($R^+$)C(=O)$OR^*$, -(alkylene)$_t$-N($R^+$)C(=S)$OR^*$, or -(alkylene)$_t$-N($R^+$)$SO_2R^*$;

R* is

haloalkyl, haloalkoxy, C_{1-6}-alkyl, C_{2-6}alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, aryl, heteroaryl, and heterocyclo

R^+ and R^{++} are independently H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl,

or R^+ and R^{++} bound to the same nitrogen atom may optionally combine to form a heterocyclo ring system;

m is 1, 2 or 3

n and n* are each independently selected from 0 and integers from 1 to 6;

p is 0, 1, 2 or 3;

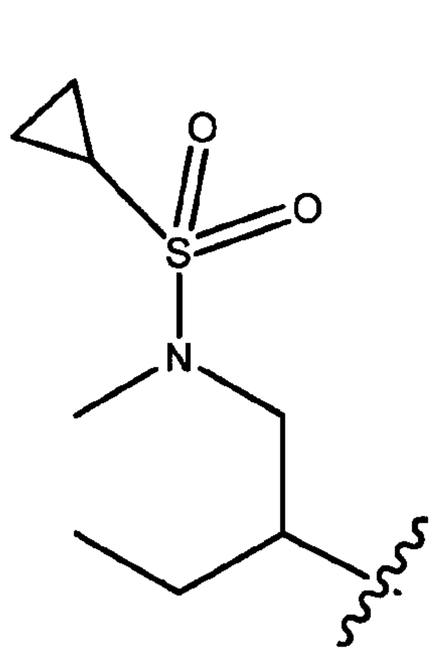
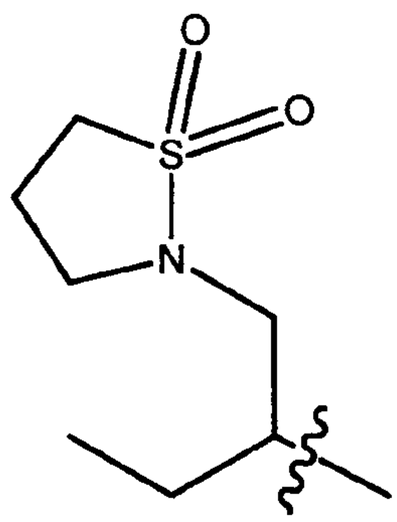
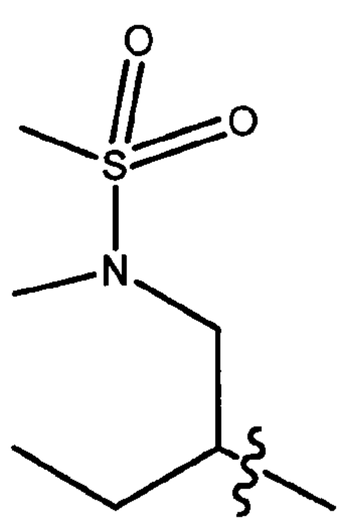
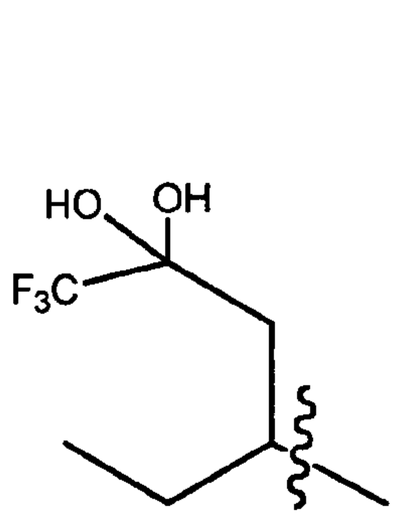
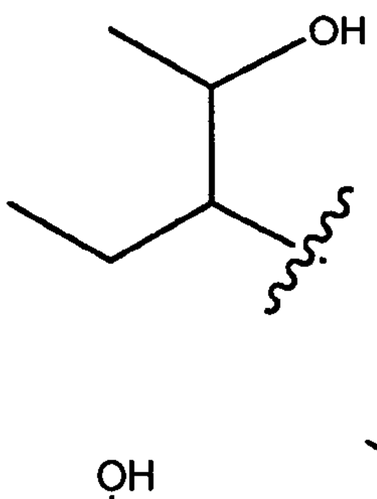
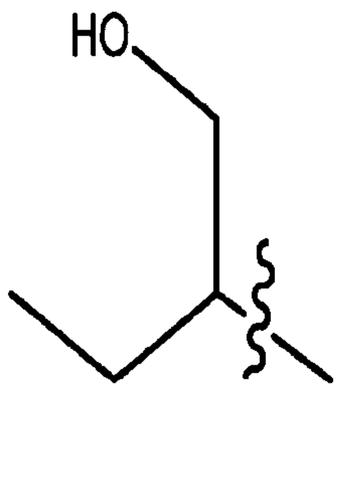
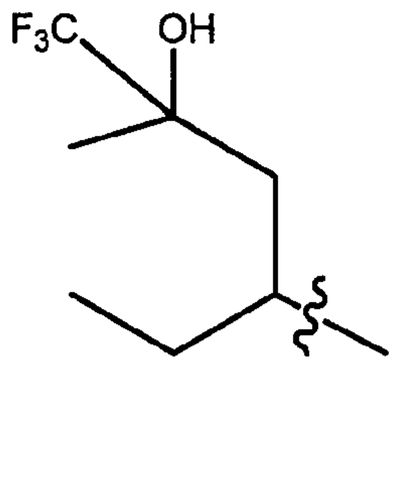
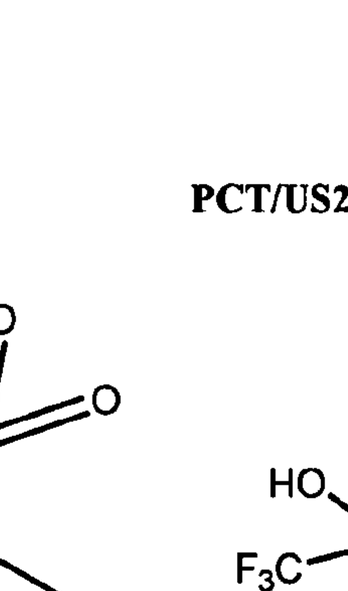
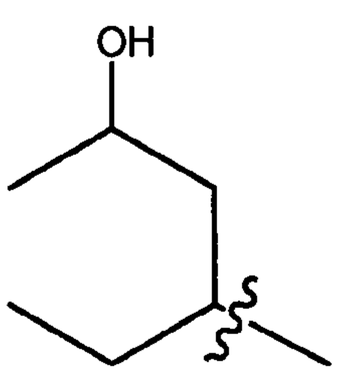
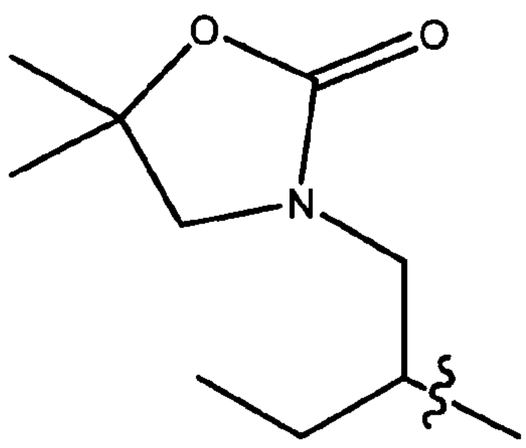
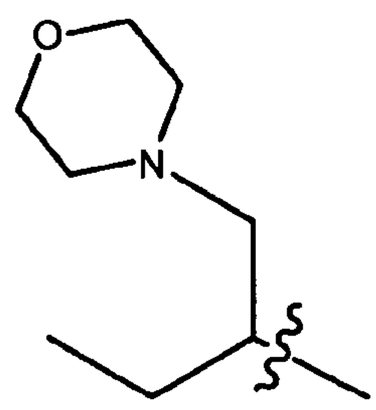
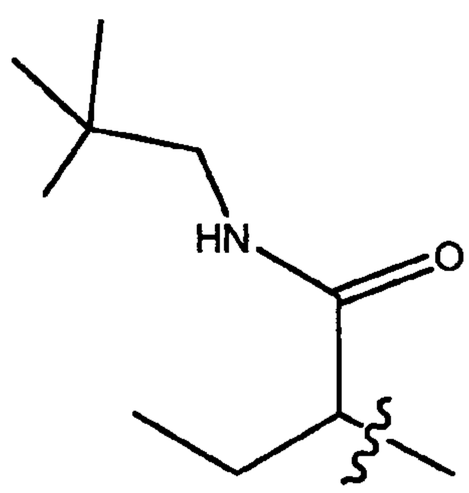
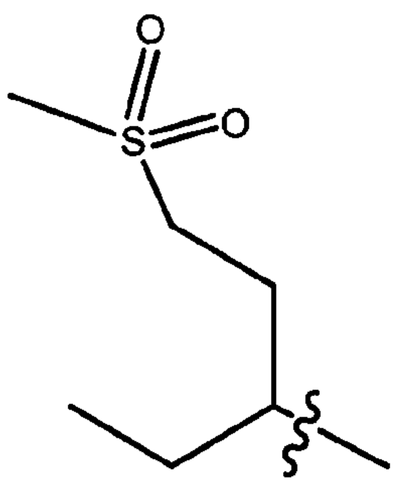
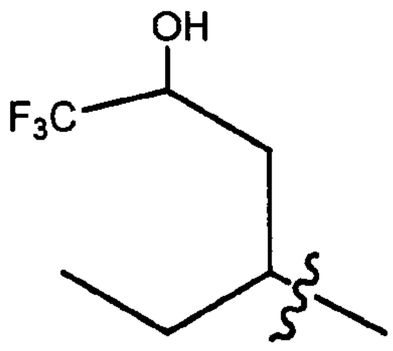
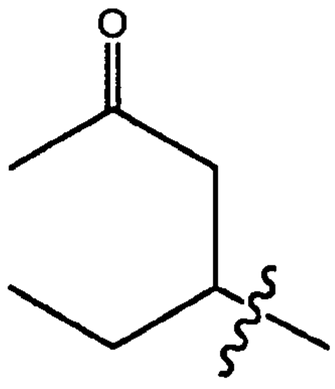
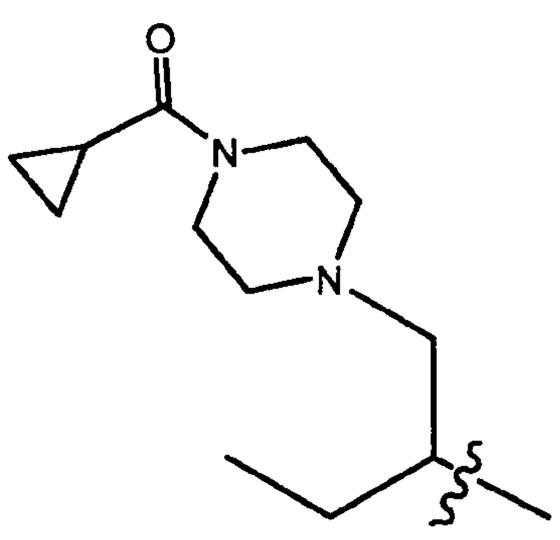
t at each occurrence is independently 0 or an integer from 1 to 6;

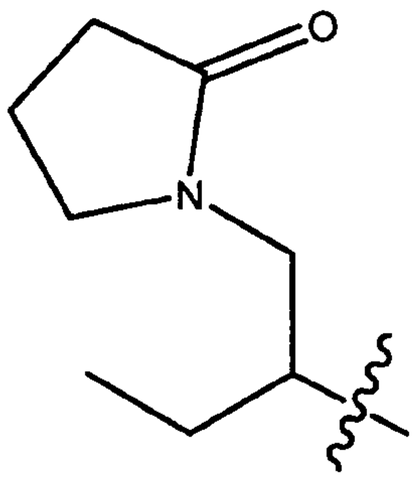
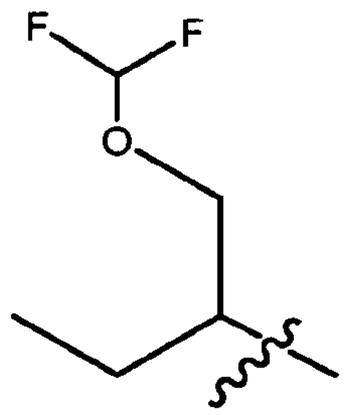
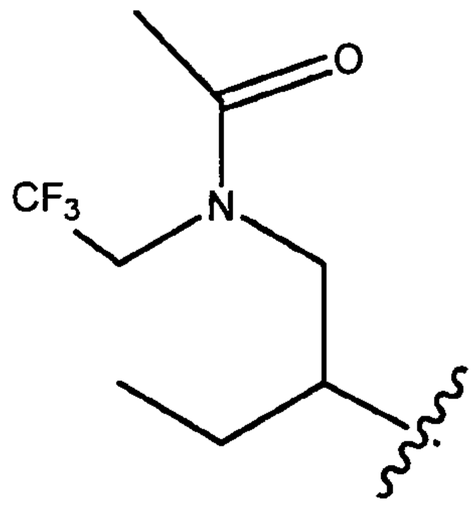
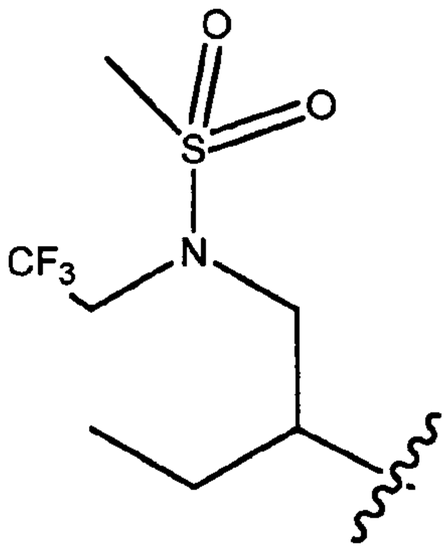
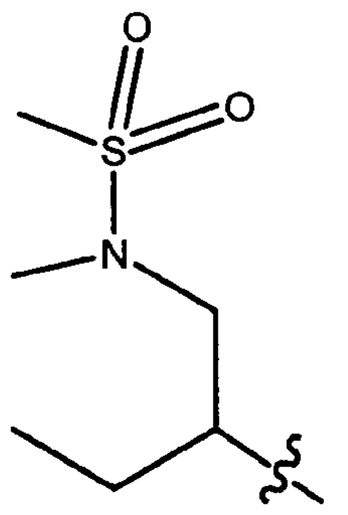
v at each occurrence is independently 0, 1 or 2;

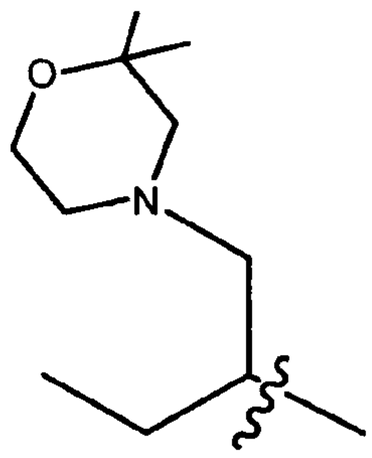
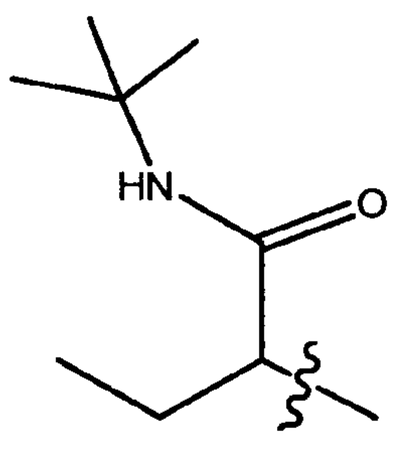
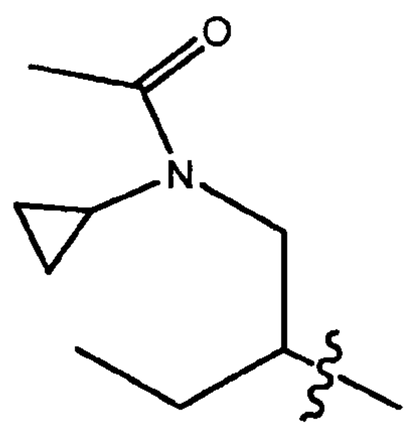
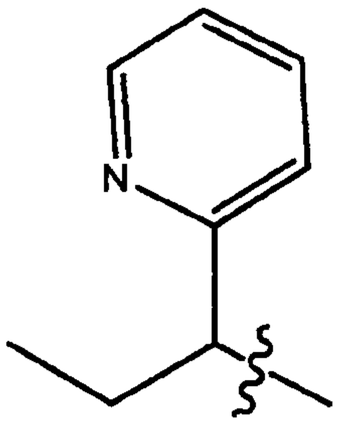
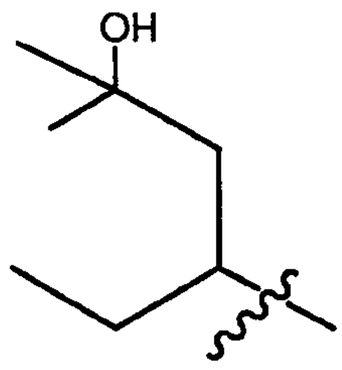
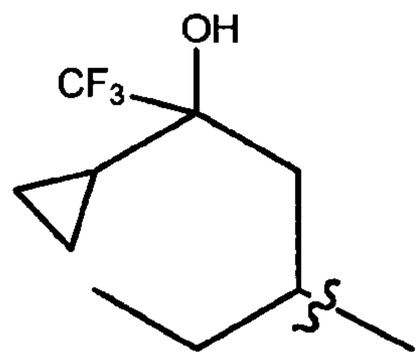
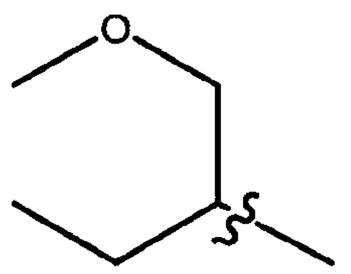
Preferred compounds within the scope of Formula I include compounds wherein R^2 is –$C(H)R^5R^6$ or –NR^7R^8, phenyl or pyridine, the phenyl or the pyridyl may be optionally substituted with one or more R^x as allowed by valence.

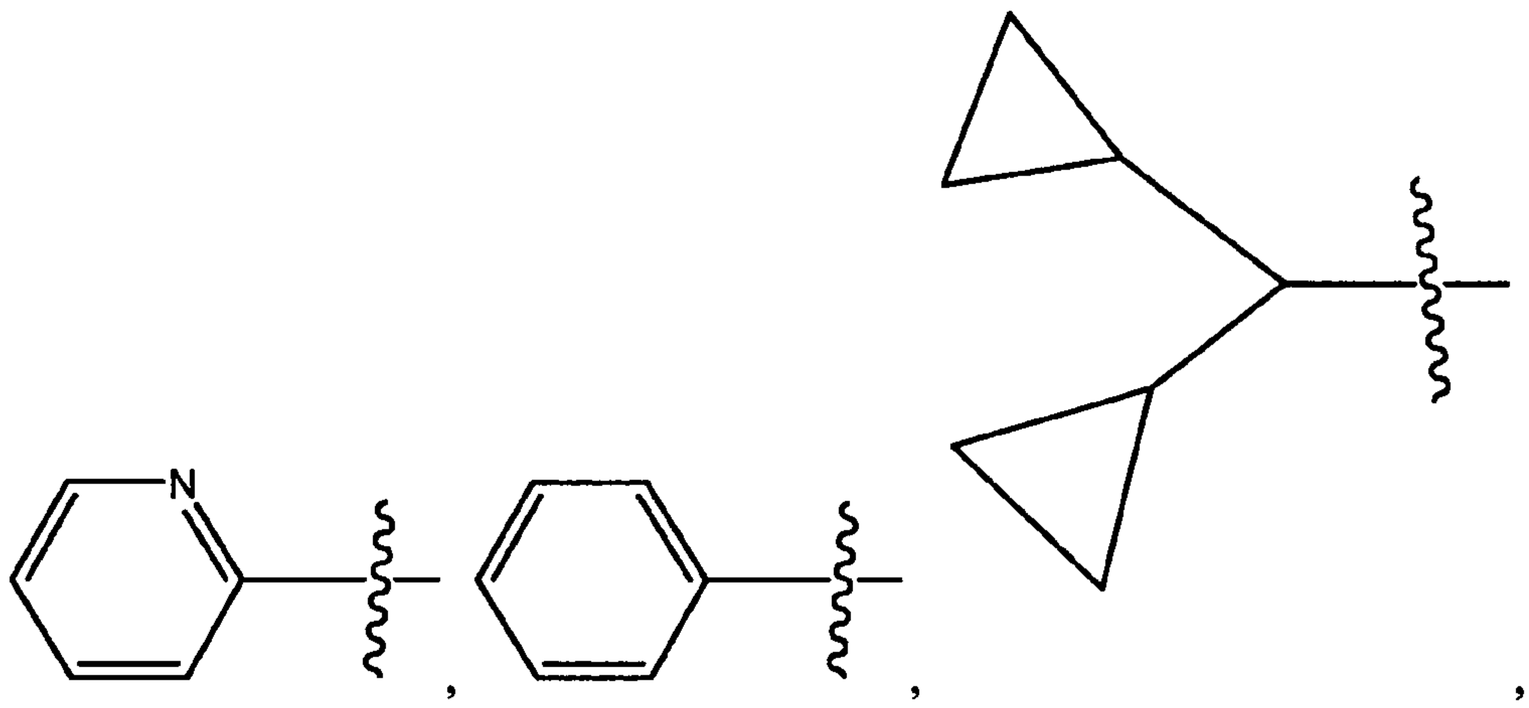
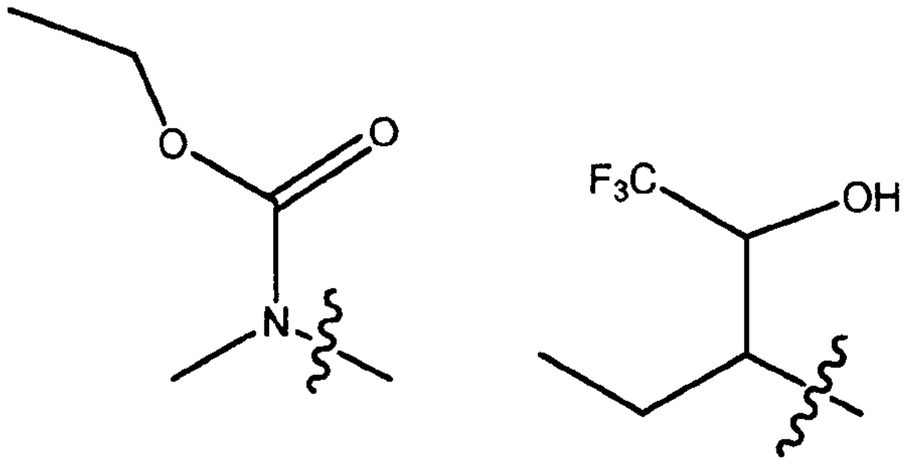
Preferred compounds within the scope of Formula I include compounds wherein R^2 is

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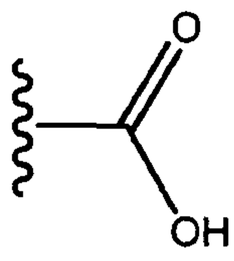






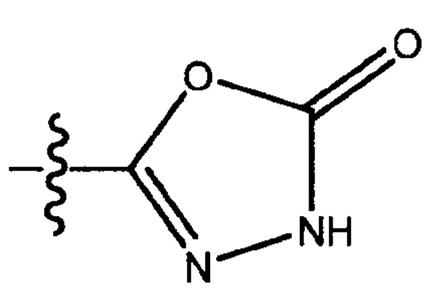
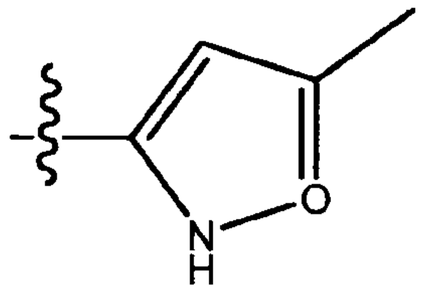
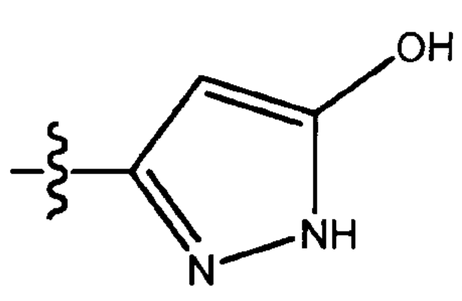
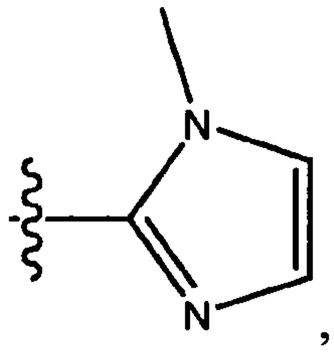
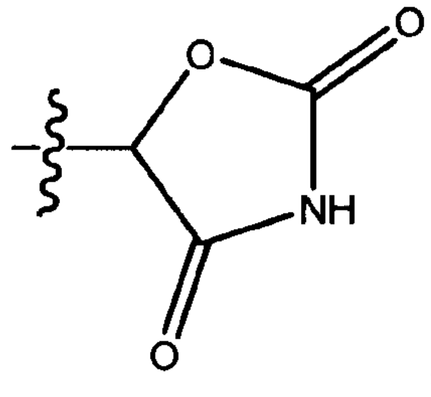
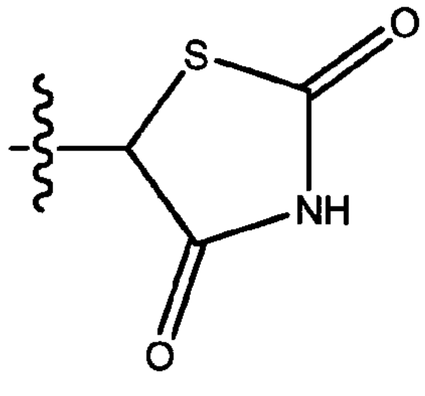
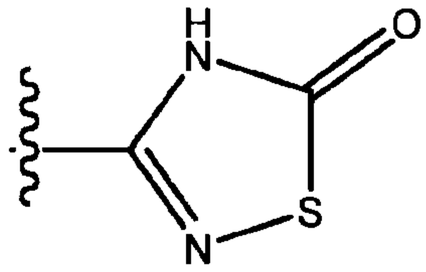
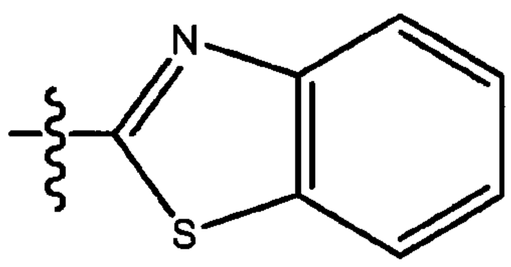
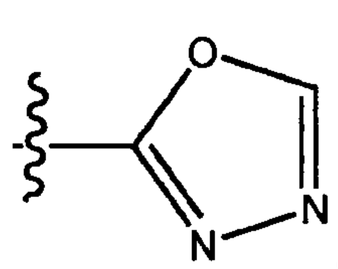
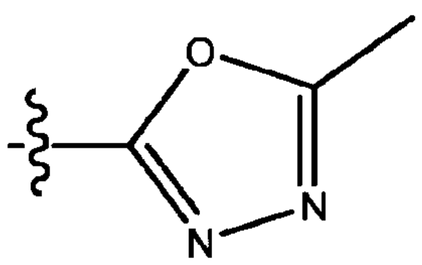
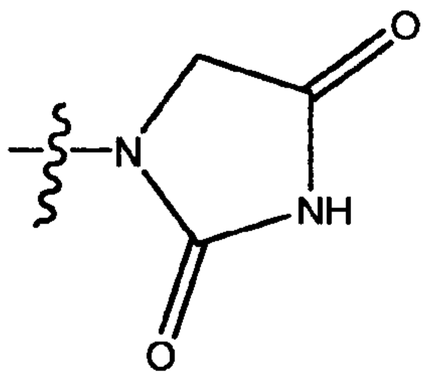
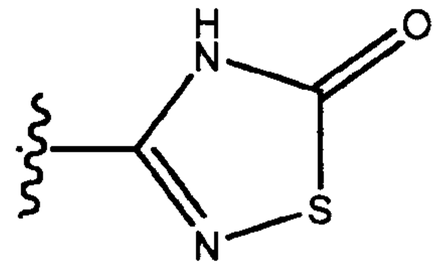
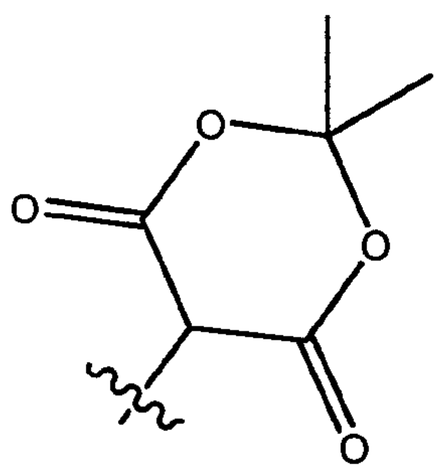
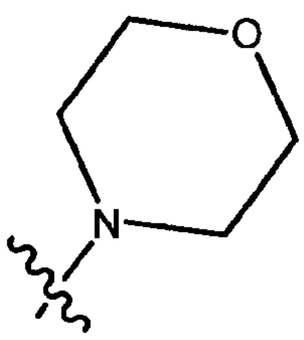
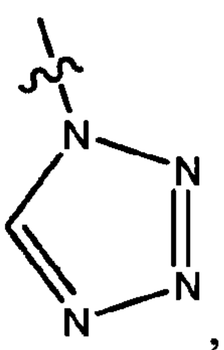
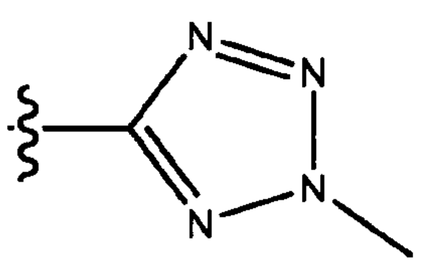
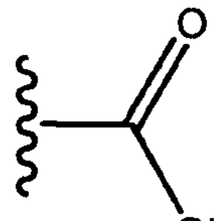








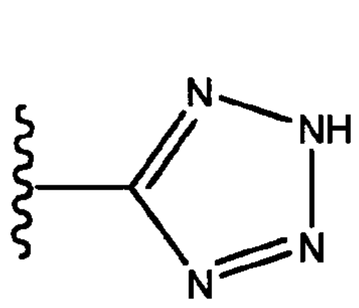
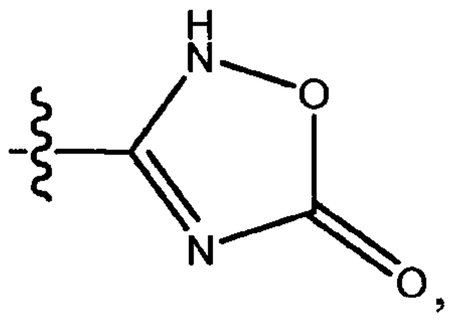
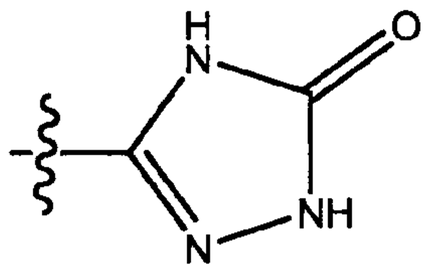
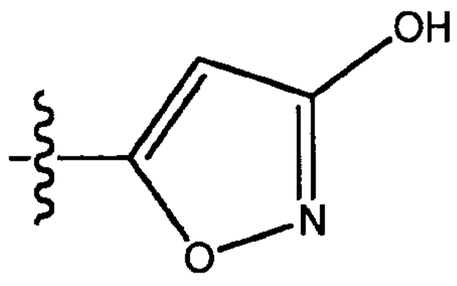
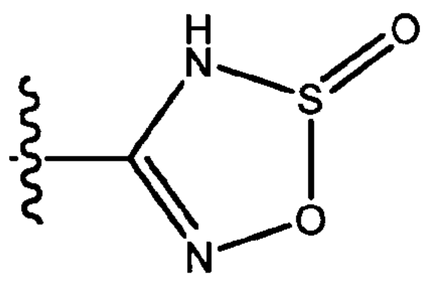
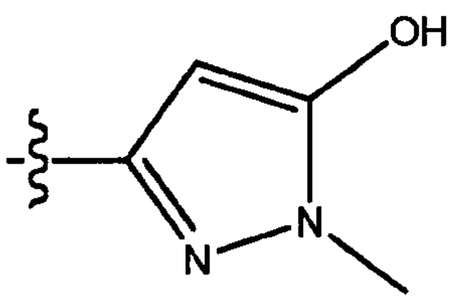
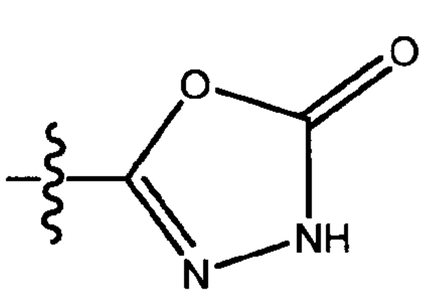
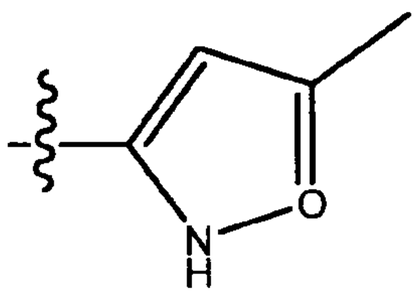
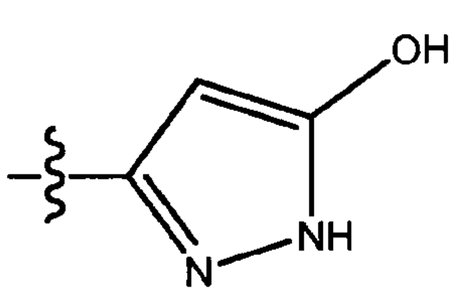
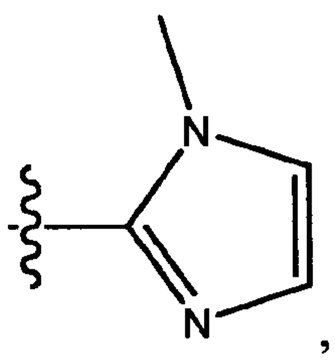
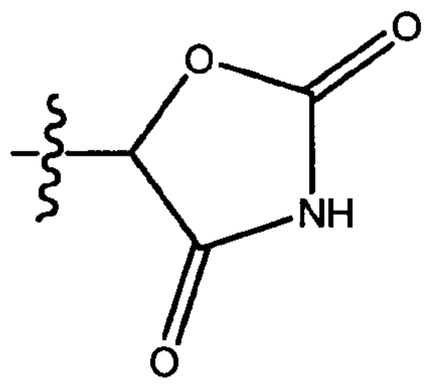
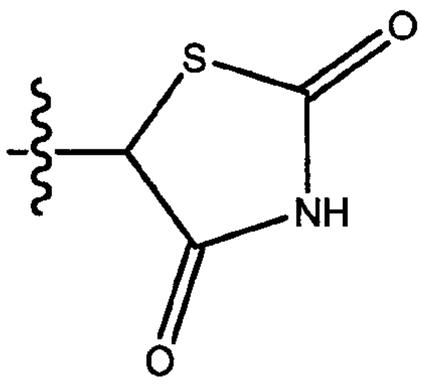
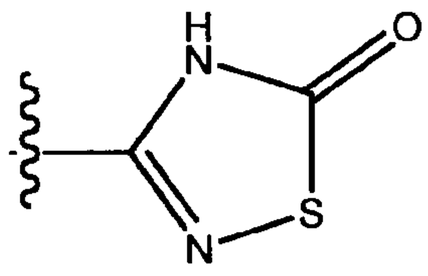



, and any of which may be optionally substituted with one or more R^x groups as allowed by valence.

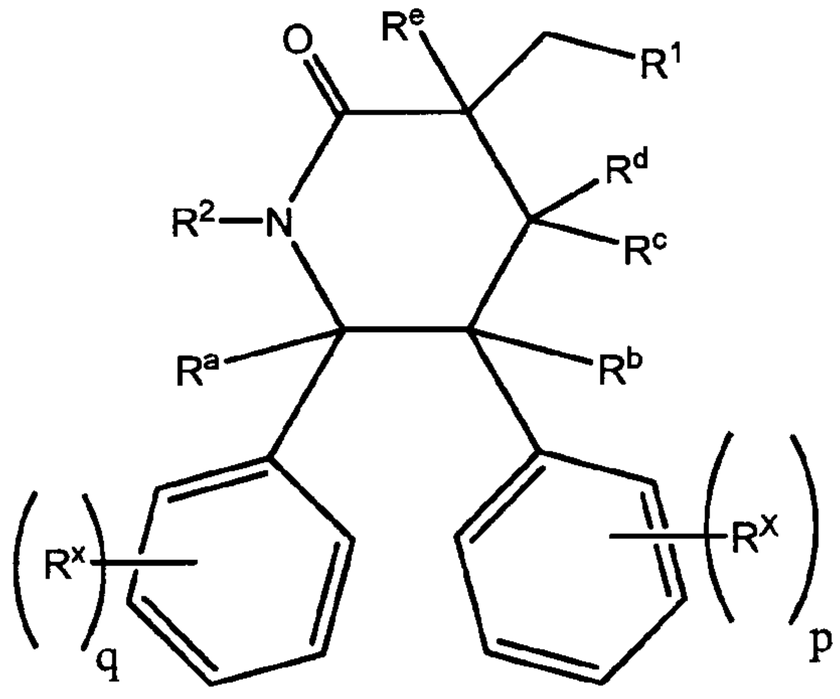
Preferred compounds within the scope of Formula I include compounds wherein R^1 is


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Preferred compounds within the scope of Formula I include compounds of Formula IA:

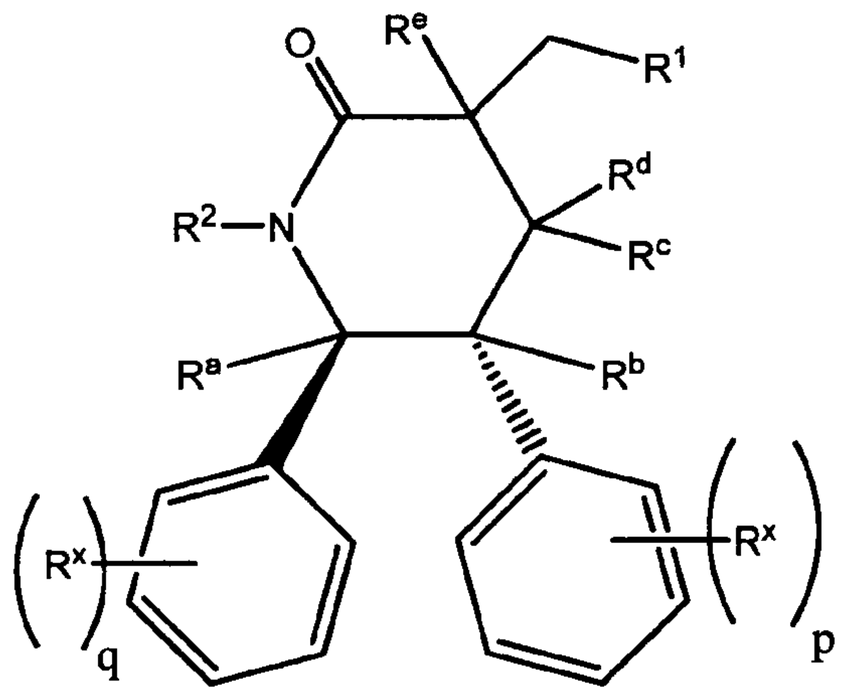


IA

enantiomers, diastereomers and pharmaceutically acceptable salts thereof

wherein q and p are each independently 0, 1, 2 or 3. Preferred compounds of Formula IA include compounds containing preferred R^1 and R^2 groups previously mentioned.

Preferred compounds within the scope of Formula I include compounds of Formula IB:

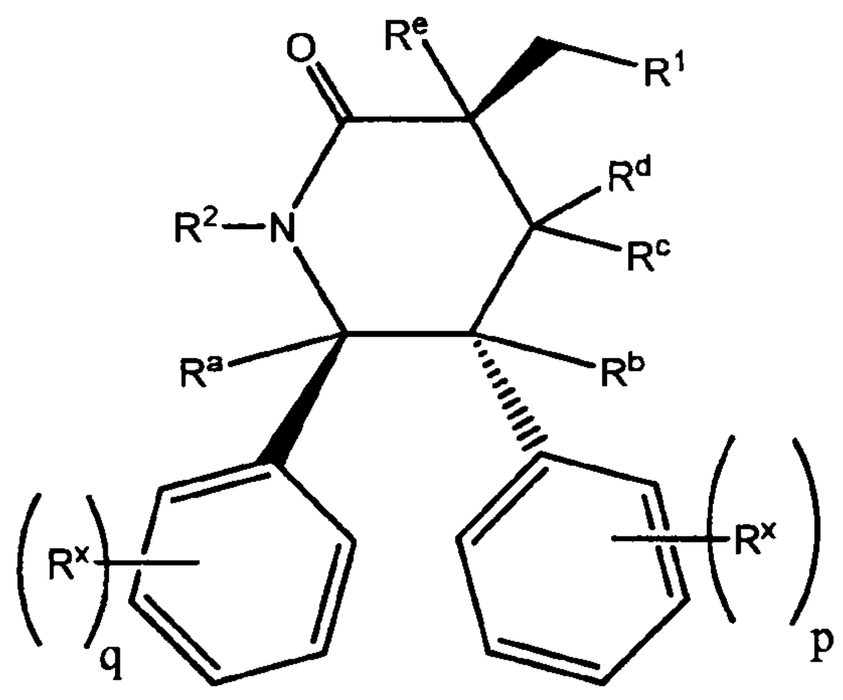


IB

enantiomers, diastereomers and pharmaceutically acceptable salts thereof

wherein q and p are each independently 0, 1, 2 or 3. Preferred compounds of Formula IB include compounds containing preferred R^1 and R^2 groups previously mentioned

Preferred compounds within the scope of formula I include compounds of Formula IC:

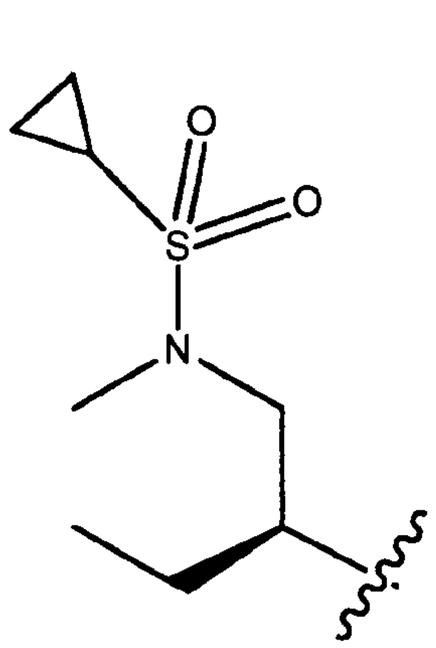
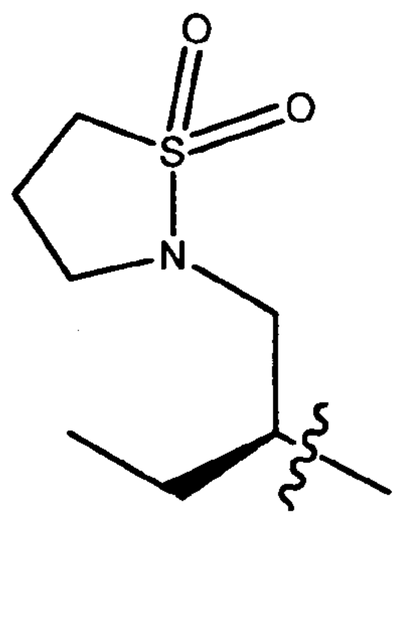
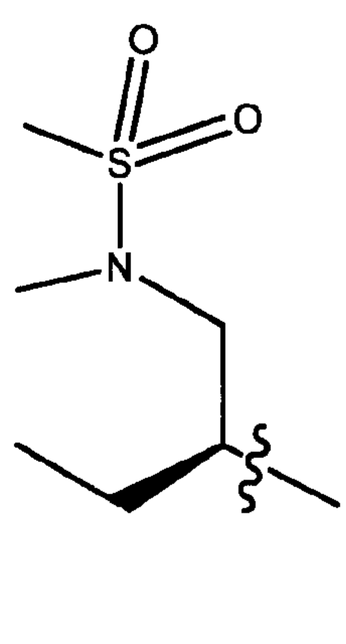
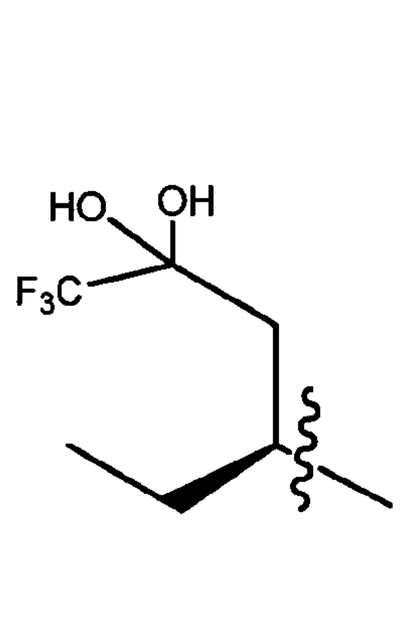
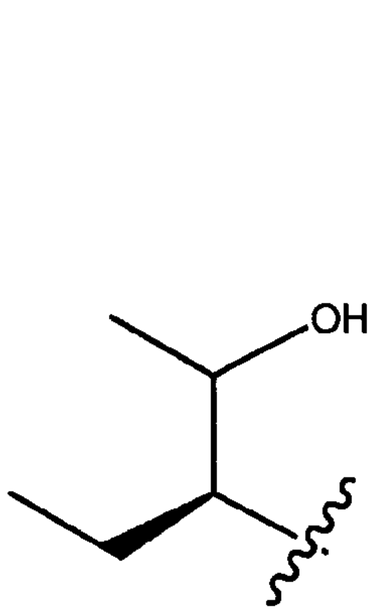
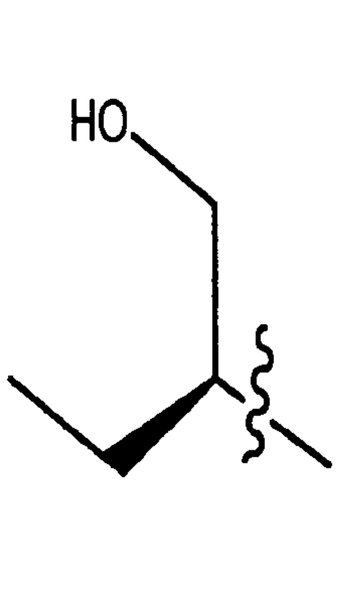
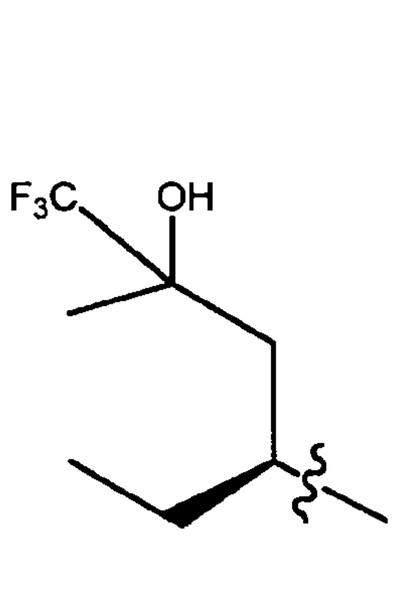
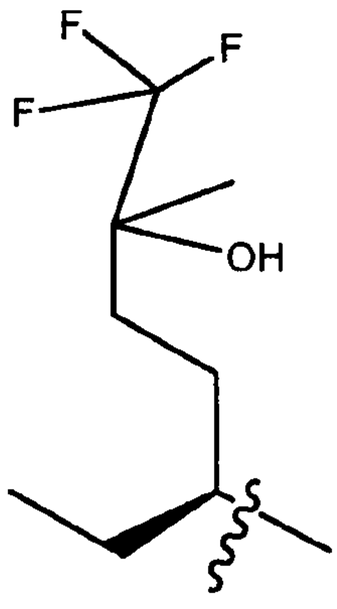
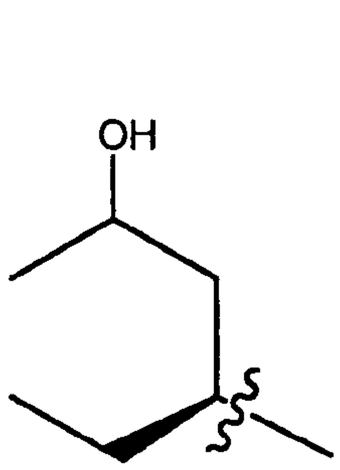
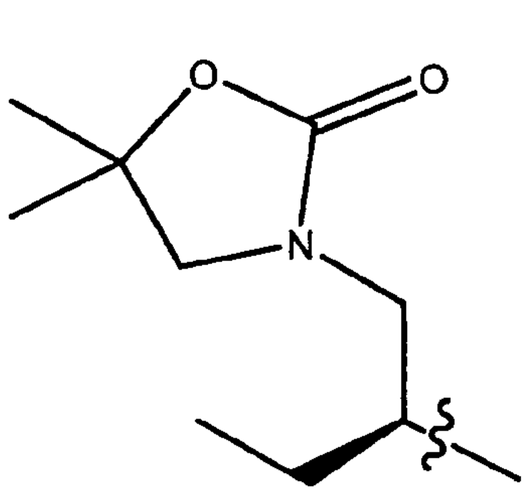
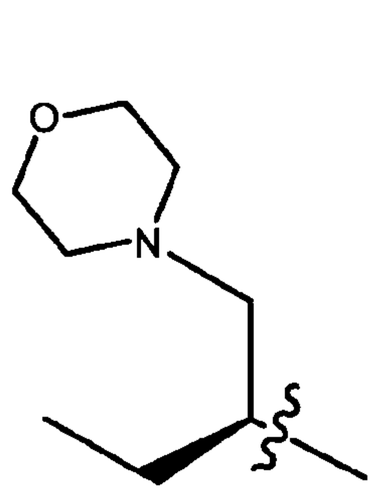
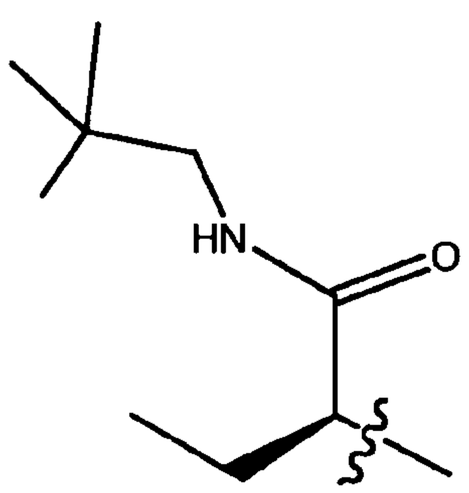
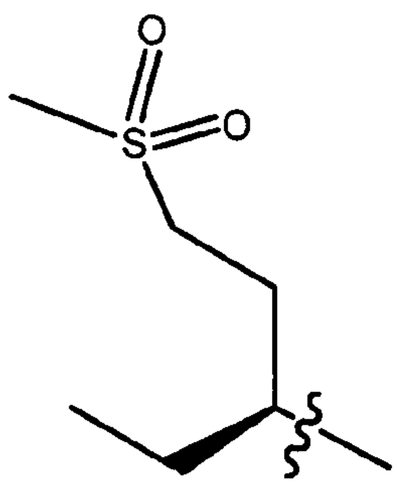
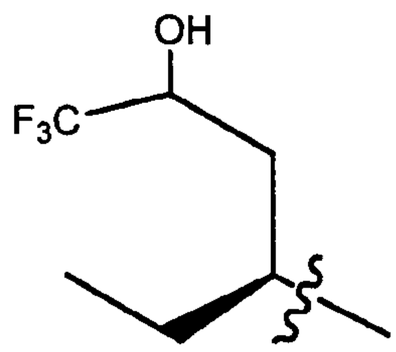
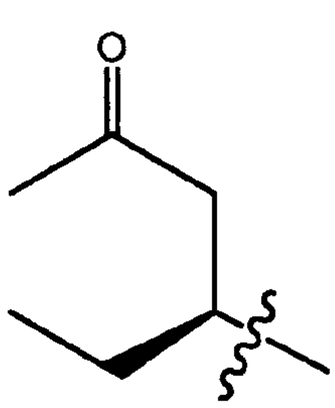
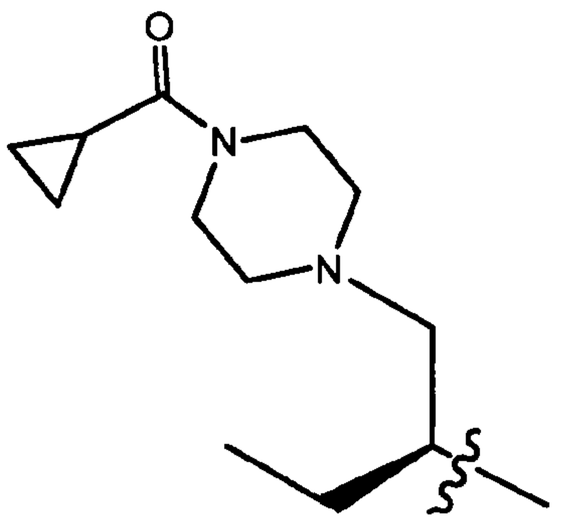


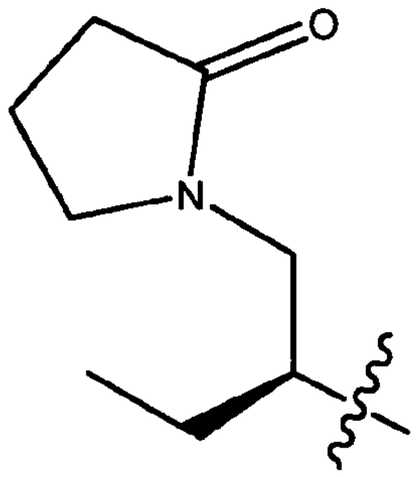
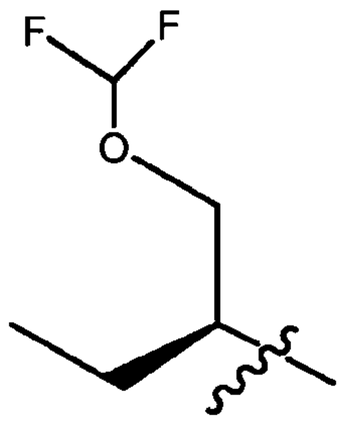
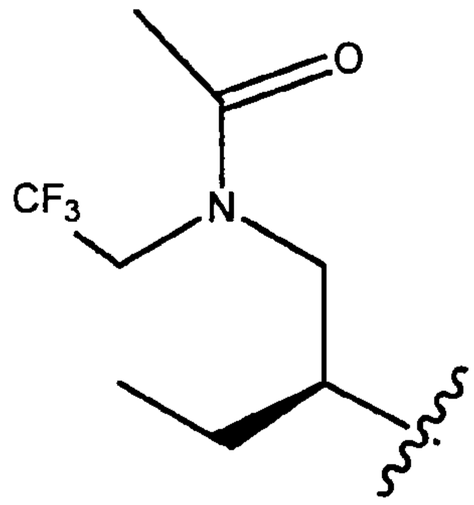
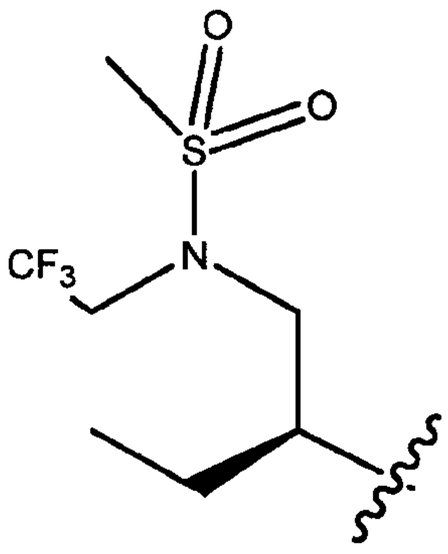
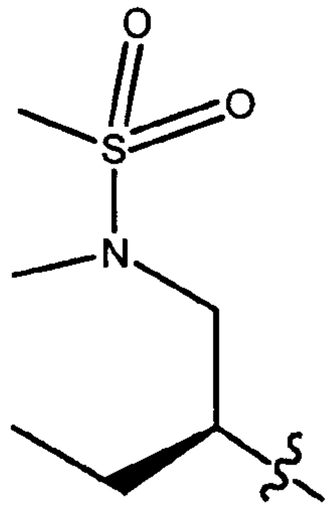
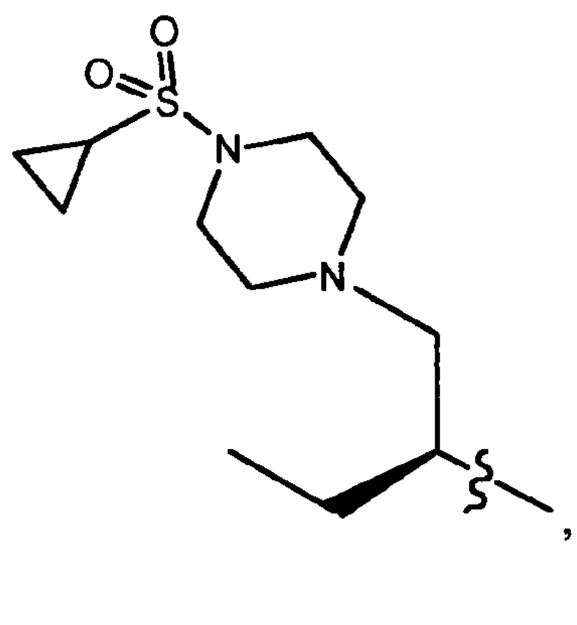
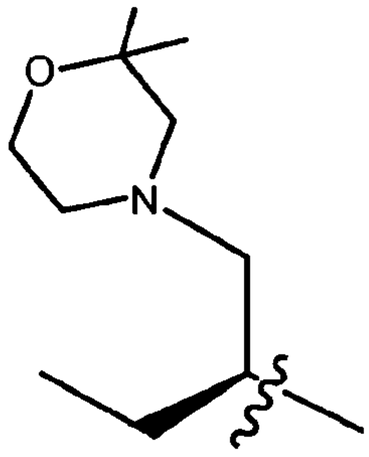
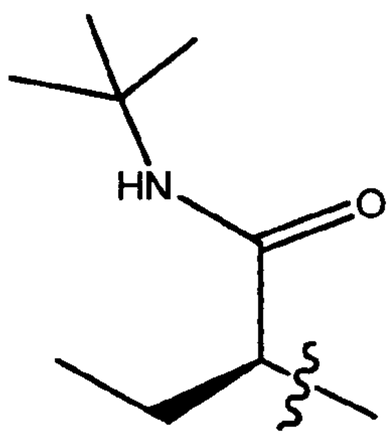
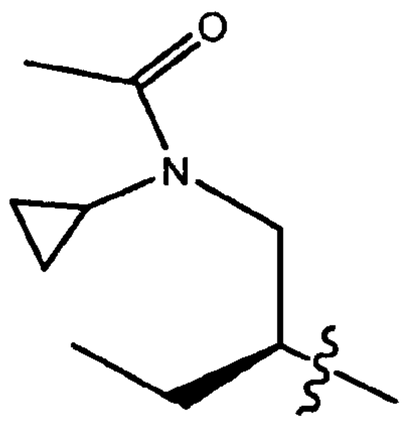
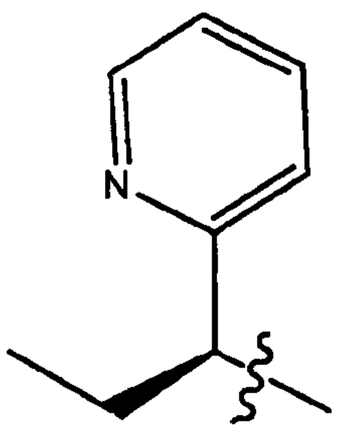
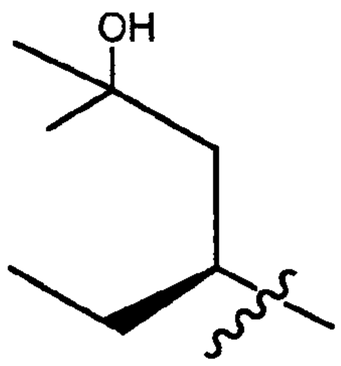
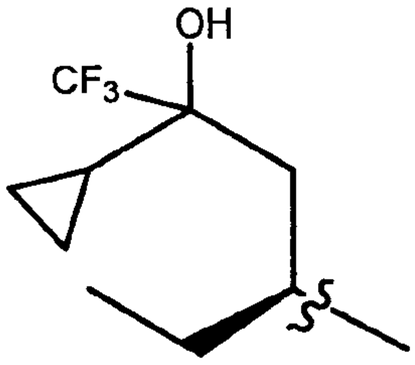
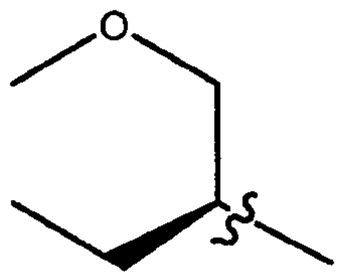
IC

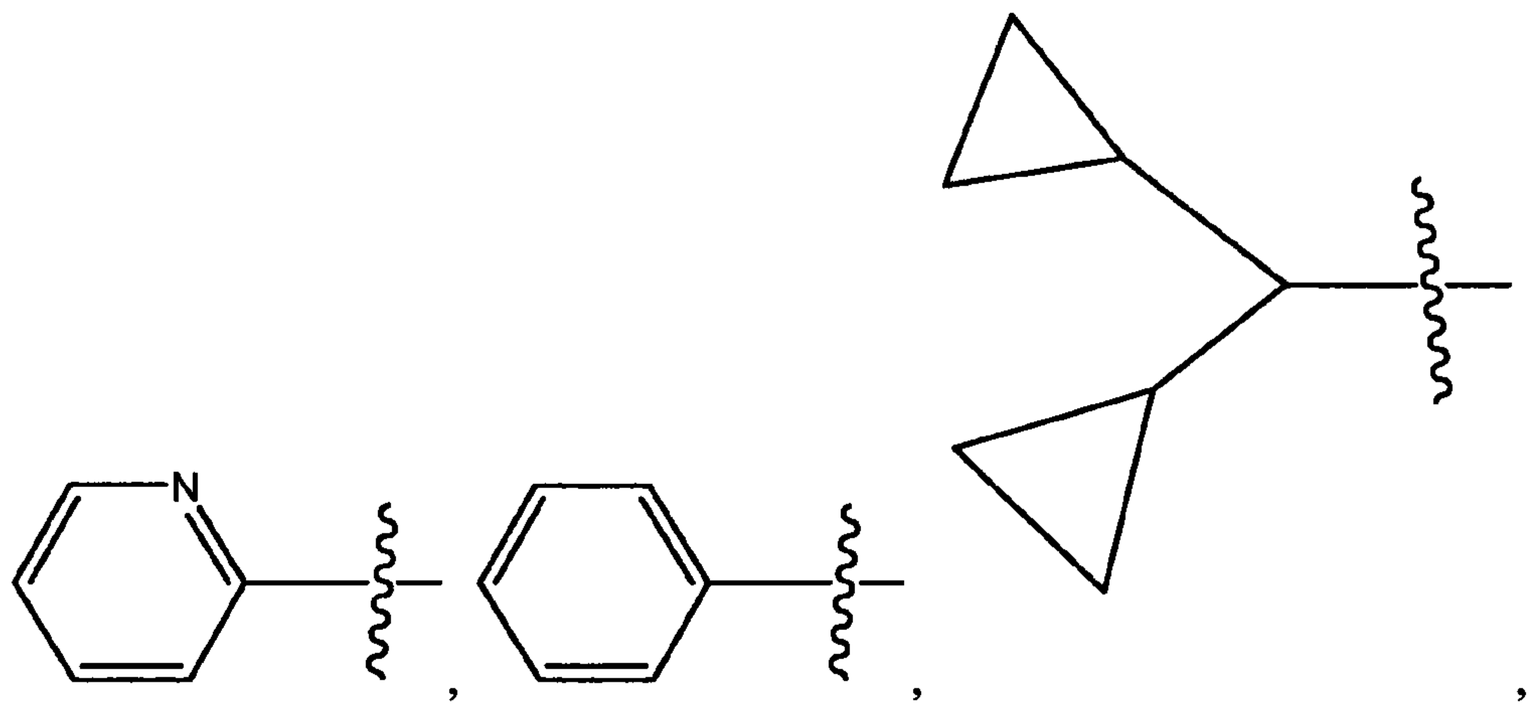
enantiomers, diastereomers and pharmaceutically acceptable salts thereof

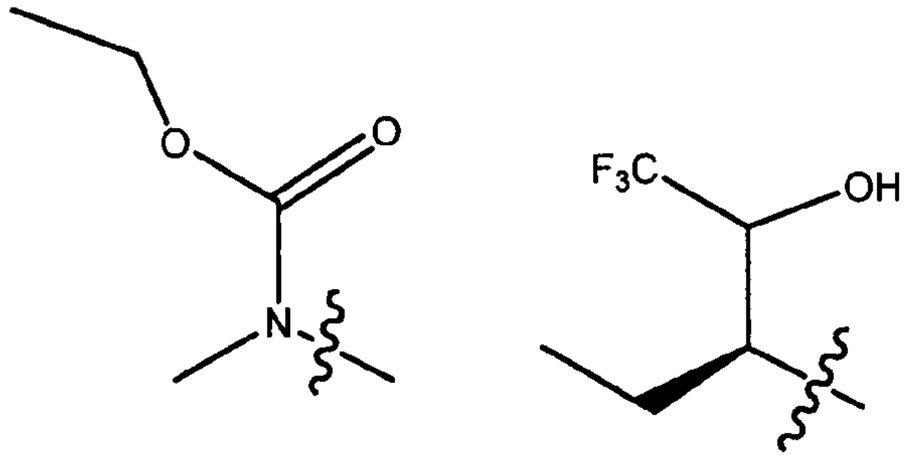
wherein q and p are each independently 0, 1, 2 or 3. Preferred compounds of Formula IC include compounds containing preferred R^1 and R^2 groups mentioned herein.

Preferred compounds within the scope of Formulae IA, IB and IC further include compounds wherein R^2 is selected from


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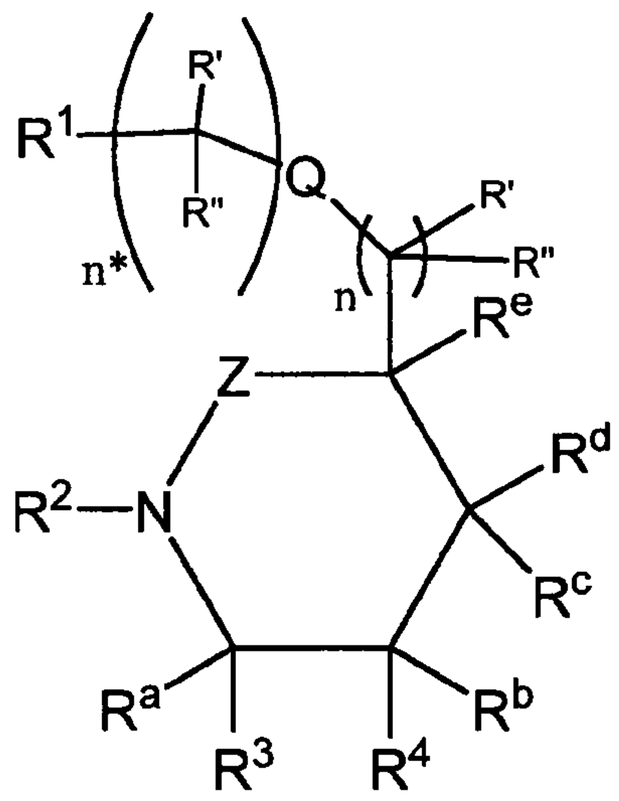


















, and any of which may be optionally substituted with one or more R^x groups as allowed by valence.

In another aspect, aspect A, the present invention provides compounds of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

Q is a bond or optionally can be selected from O, NR^7 or $S(O)_v$, when n* is an integer from 1 to 6;

Z is C=O or $S(=O)_2$;

R^a at each occurrence is independently selected from H, $(C_1\text{-}C_3)$alkyl, (halo)$(C_1\text{-}C_3)$alkyl, (hydroxy)$(C_1\text{-}C_3)$alkyl, (alkoxy)$(C_1\text{-}C_3)$alkyl, or cyano;

R^b is H, halo, $(C_1\text{-}C_3)$alkyl, (halo)$(C_1\text{-}C_3)$alkyl, (hydroxy)$(C_1\text{-}C_3)$alkyl, (alkoxy)$(C_1\text{-}C_3)$alkyl, or cyano;

R^c and R^d are independently selected from H, halo, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, (halo)$(C_1\text{-}C_3)$alkyl, (halo)$(C_1\text{-}C_3)$alkoxy, (alkoxy)$(C_1\text{-}C_3)$alkyl, or (hydroxy)$(C_1\text{-}C_3)$alkyl, or R^c and R^d may optionally combine to form a spiro-cycloalkyl or heterocyclo ring system;

R^e is

(a) H or halo; or

(b) $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_3\text{-}C_8)$heterocyclo, cyano, halogen, hydroxyl, $-OR^5$, NR^7R^8, or heterocycloalkyl, any of which may be optionally substituted with 1 or more R^x groups as allowed by valence, or R^e and any one of the R' or R" groups may optionally combine to form a spiro-cycloalkyl or heterocyclo ring system, or R^d and any one of the R' or R" groups may optionally combine to form a fused cycloalkyl or heterocyclo ring system, or R^d and R^e may optionally combine to form a fused cycloalkyl or heterocyclo ring system;

R' and R" at each occurrence, respectively, are independently H, halo, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, (halo)$(C_1\text{-}C_3)$alkyl, (halo)$(C_1\text{-}C_3)$alkoxy, (alkoxy)$(C_1\text{-}C_3)$alkyl, (hydroxy)$(C_1\text{-}C_3)$alkyl, -S-$(C_1\text{-}C_3)$alkyl, C(O)$(C_1\text{-}C_3)$alkyl, $-NR^7R^8$, or hydroxyl, or R' and R" bound to the same carbon atom may optionally combine to form =O, or R' and R" bound to the same carbon atom may optionally combine to form a spiro-fused cycloalkyl or heterocyclo ring system;

R^1 is

(a) $-COOH$, $-C(O)OR^{10}$, $-C(O)NHOH$, $-C(O)NH\text{-}NH_2$, $-C(O)NHS(O)_2R^{10}$, $-S(O)_2NHC(O)R^{10}$, $-S(O)_2NR^7R^8$, $-NR^7C(O)R^{10}$, $-NR^7C(O)OR^5$, $-C(O)NR^7R^8$, $-NR^7S(O)_2R^{10}$, '

$-NR^7C(O)NR^7R^8$, $-S(O)_vR^{10}$, hydroxylalkyl, -cyclopropyl-COOH, or CN; or

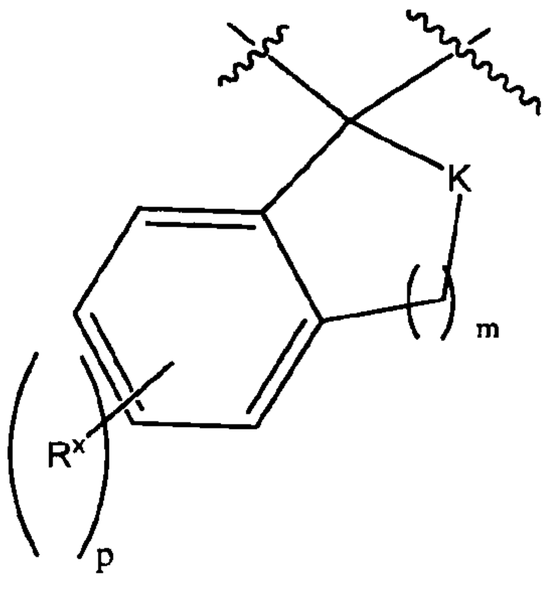
(b) heteroaryl or heterocyclo, either of which may be optionally independently substituted with one or more R^x groups as allowed by valence;

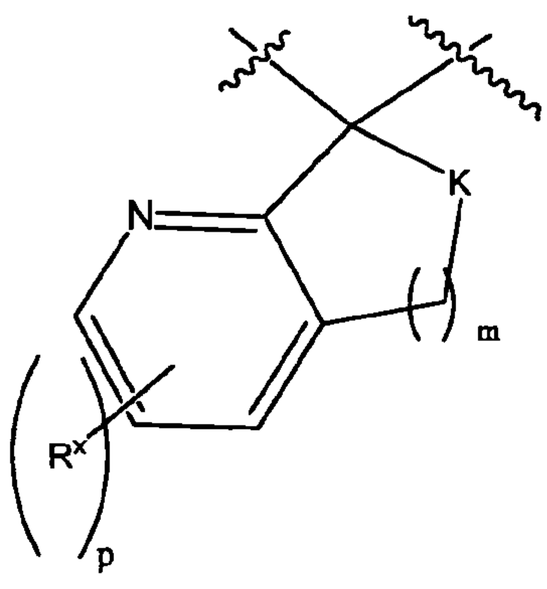
R^2 is

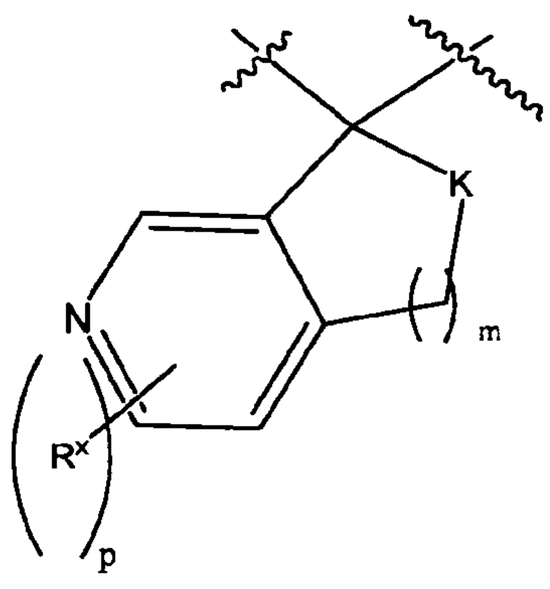
(a) $-NR^7R^8$, $NR^7C(O)OR^{10}$, $NR^7C(O)NR^7R^{10}$, or $-C(R^a)R^5R^6$; or

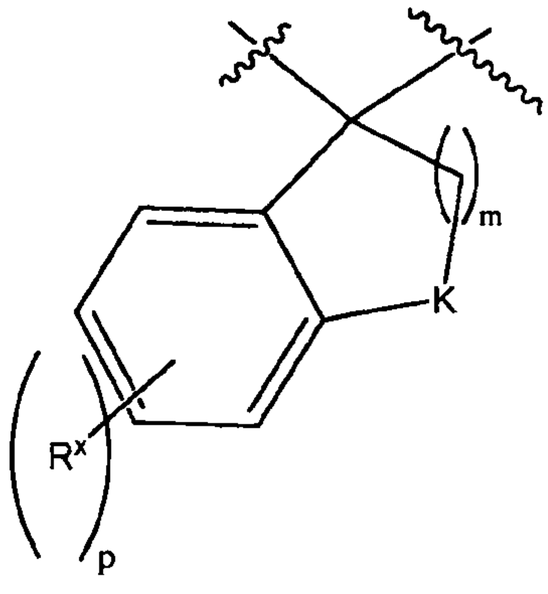
(b) aryl, heteroaryl, cycloalkyl, or heterocyclo, any of which may be optionally independently substituted with one or more R^x groups as allowed by valence;

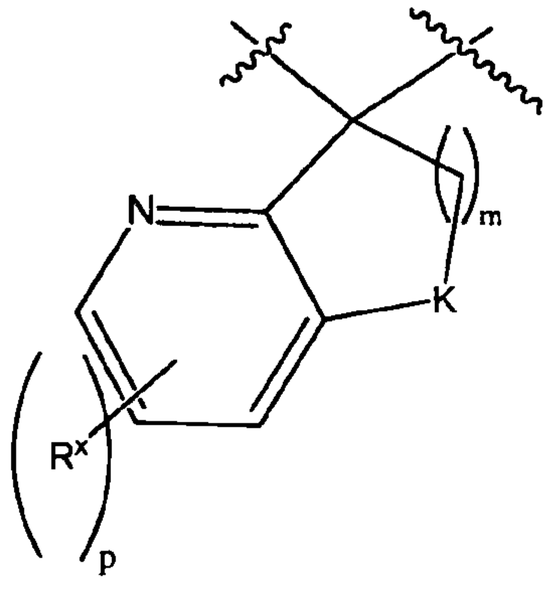
R^3 and R^4 are independently aryl or heteroaryl, either of which may be optionally independently substituted with one or more R^x groups as allowed by valence, or either R^3 and R^a together with the ring carbon atom to which they are both bonded, or R^4 and R^b together with the ring carbon atom to which they are both bonded may optionally combine to form a spiro-fused bicyclic ring system selected from

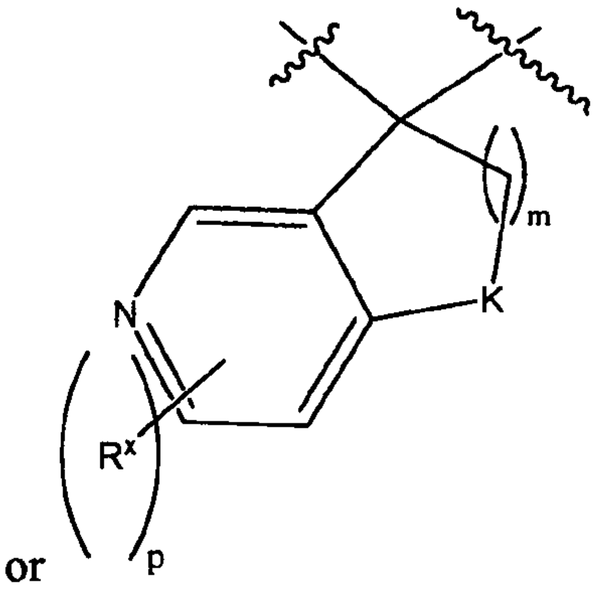


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or


wherein K is –O-, $-NR^7-$, or $-C(=O)NR^7-$;

R^5 and R^6 at each occurrence, respectively, are independently selected from

(a) H or CN;

(b) -(alkylene)$_t$ –OH, -(alkylene)$_t$ –OR^9, -(alkylene)$_t$ –SR^9, -(alkylene)$_t$ –NR^{10}R^{11}, -(alkylene)$_t$-C(O)R^9, -(alkylene)$_t$ –C(O)OR^9, -(alkylene)$_t$ –OC(O)R^9, -(alkylene)$_t$ –S(O)$_v$R^9, -(alkylene)$_t$-NHS(O)$_2$R^{10}, -(alkylene)$_t$-N(R^{11})S(O)$_2$R^{10}, -(alkylene)$_t$-S(O)$_2$NR^{10}R^{11}, –NR^{10}C(O)R^9, -C(O)NR^{10}R^{11}, -NR^{10}S(O)$_2$R^9, S(O)$_2$NR^{10}, or NR^{10}C(O)NR^{10}R^{11}; or

(c) haloalkyl, haloalkoxy, C$_{1-6}$-alkyl, C$_{2-6}$alkenyl, C$_{2-6}$-alkynyl, C$_{3-8}$-cycloalkyl, (C$_{3-8}$-cycloalkyl)(C$_{1-3}$alkyl), C$_{4-8}$-cycloalkenyl, aryl, aryl(C$_{1-3}$-alkyl), heteroaryl, heteroaryl(C$_{1-3}$-alkyl), heterocyclo or heterocyclo(C$_{1-3}$-alkyl), any of which may be optionally independently substituted with one or more R^x groups as allowed by valence;

R^7 and R^8 at each occurrence, respectively, are independently selected from H, cyano, -O C$_{1-6}$-alkyl, C$_{1-6}$-alkyl, halo(C$_{1-6}$)-alkyl, cycloalkyl, C$_{2-6}$-alkenyl, C$_{2-6}$-alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocyclo(C$_{1-10}$alkyl), or (C$_{3-8}$-cycloalkyl)(C$_{1-3}$alkyl), any of which may be optionally substituted as allowed by valence with one or more R^x, or R^7 and R^8 may combine to form a C$_4$-C$_8$-heterocyclo ring optionally substituted with one or more R^x;

R^9 is haloalkyl, haloalkoxy, C$_{1-6}$-alkyl, C$_{2-6}$alkenyl, C$_{2-6}$-alkynyl, C$_{3-8}$-cycloalkyl, (C$_{3-8}$-cycloalkyl)(C$_{1-3}$alkyl), C$_{4-8}$-cycloalkenyl, aryl, heteroaryl, or heterocyclo, any of which may be optionally independently substituted with one or more R^x groups as allowed by valence;

R^{10} and R^{11} at each occurrence, respectively, are independently selected from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, or cycloalkylalkyl, any of which may be optionally substituted as allowed by valence with one or more R^x, or R^{10} and R^{11} may combine to form a heterocyclo ring optionally substituted with one or more R^x;

R^x at each occurrence is independently, deuterium, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, -(alkylene)$_t$-OR*, -(alkylene)$_t$-S(O)$_v$R*, -(alkylene)$_t$-NR$^+$R^{++}, -(alkylene)$_t$-C(=O)R*, -(alkylene)$_t$-C(=S)R*, -(alkylene)$_t$-C(=O)OR*, -(alkylene)$_t$-OC(=O)R*, -(alkylene)$_t$-C(=S)OR*, —(alkylene)$_t$-C(=O)NR$^+$R^{++}, -(alkylene)$_t$-C(=S)NR$^+$R^{++}, -(alkylene)$_t$-N(R$^+$)C(=O)NR$^+$R^{++},

-(alkylene)$_t$-N(R^+)C(=S)NR^+R^{++}, -(alkylene)$_t$-N(R^+)C(=O)R^*, -(alkylene)$_t$-N(R^+)C(=S)R^*, -(alkylene)$_t$-OC(=O)NR^+R^{++}, -(alkylene)$_t$-OC(=S)NR^+R^{++}, -(alkylene)$_t$-SO_2NR^+R^{++}, -(alkylene)$_t$-N(R^+)SO_2R^*, -(alkylene)$_t$-N(R^+)SO_2NR^+R^{++}, -(alkylene)$_t$-N(R^+)C(=O)OR^*, -(alkylene)$_t$-N(R^+)C(=S)OR^*, or -(alkylene)$_t$-N(R^+)SO_2R^*, wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more halo, cyano, oxo, -(alkylene)$_t$-OR^*, -(alkylene)$_t$-S(O)$_v$$R^*$, -(alkylene)$_t$-N$R^+R^{++}$, -(alkylene)$_t$-C(=O)$R^*$, -(alkylene)$_t$-C(=S)$R^*$, -(alkylene)$_t$-C(=O)O$R^*$, -(alkylene)$_t$-OC(=O)$R^*$, -(alkylene)$_t$-C(=S)O$R^*$, —(alkylene)$_t$-C(=O)N$R^+R^{++}$, -(alkylene)$_t$-C(=S)N$R^+R^{++}$, -(alkylene)$_t$-N($R^+$)C(=O)N$R^+R^{++}$, -(alkylene)$_t$-N($R^+$)C(=S)N$R^+R^{++}$, -(alkylene)$_t$-N($R^+$)C(=O)$R^*$, -(alkylene)$_t$-N($R^+$)C(=S)$R^*$, -(alkylene)$_t$-OC(=O)N$R^+R^{++}$, -(alkylene)$_t$-OC(=S)N$R^+R^{++}$, -(alkylene)$_t$-$SO_2NR^+R^{++}$, -(alkylene)$_t$-N($R^+$)$SO_2R^*$, -(alkylene)$_t$-N($R^+$)$SO_2NR^+R^{++}$, -(alkylene)$_t$-N($R^+$)C(=O)O$R^*$, -(alkylene)$_t$-N($R^+$)C(=S)O$R^*$, or -(alkylene)$_t$-N($R^+$)$SO_2R^*$;

R* is H, haloalkyl, haloalkoxy, C_{1-6}-alkyl, C_{2-6}alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, aryl, heteroaryl, or heterocyclo;

R^+ and R^{++} are independently H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, or cycloalkylalkyl, or R^+ and R^{++} bound to the same nitrogen atom may optionally combine to form a heterocyclo ring system;

m is 1, 2 or 3;

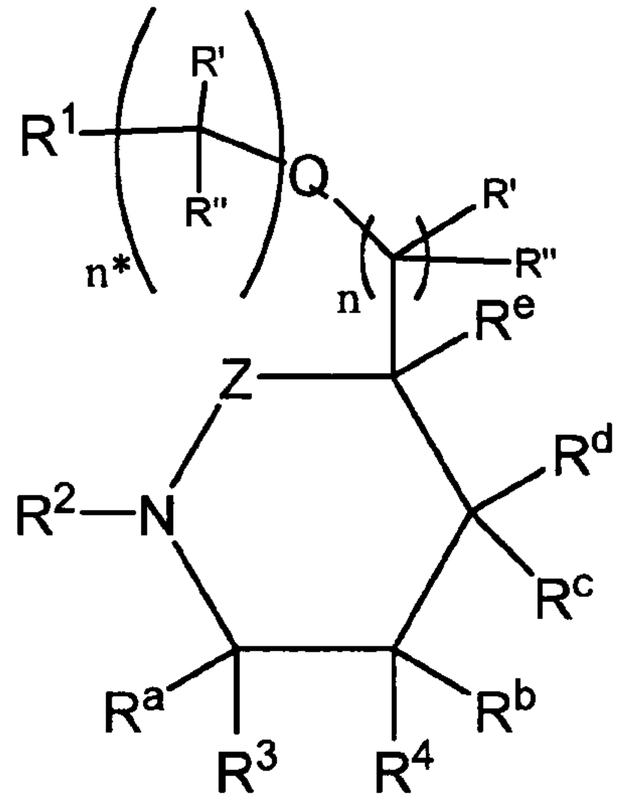
n and n* are each independently selected from 0 or an integer from 1 to 6;

p is 0, 1, 2 or 3;

t at each occurrence is independently 0 or an integer from 1 to 6; and

v at each occurrence is independently 0, 1 or 2.

In another aspect, aspect AA, the present invention provides compounds of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

Q is a bond or optionally can be selected from O, NR^7 or $S(O)_v$, when n* is an integer from 1 to 6;

Z is C=O or $S(=O)_2$;

R^a at each occurrence is independently selected from H, $(C_1\text{-}C_3)$alkyl, (halo)$(C_1\text{-}C_3)$alkyl, (hydroxy)$(C_1\text{-}C_3)$alkyl, (alkoxy)$(C_1\text{-}C_3)$alkyl, or cyano;

R^b is H, halo, $(C_1\text{-}C_3)$alkyl, (halo)$(C_1\text{-}C_3)$alkyl, (hydroxy)$(C_1\text{-}C_3)$alkyl, (alkoxy)$(C_1\text{-}C_3)$alkyl, or cyano;

R^c and R^d are independently selected from H, halo, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, (halo)$(C_1\text{-}C_3)$alkyl, (halo)$(C_1\text{-}C_3)$alkoxy, (alkoxy)$(C_1\text{-}C_3)$alkyl, or (hydroxy)$(C_1\text{-}C_3)$alkyl, or R^c and R^d may optionally combine to form a spiro-cycloalkyl or heterocyclo ring system;

R^e is

(a) H or halo; or

(b) $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_3\text{-}C_8)$heterocyclo, cyano, halogen, hydroxyl, $-OR^5$, NR^7R^8, or heterocycloalkyl, any of which may be optionally substituted with 1 or more R^x groups as allowed by valence, or R^e and any one of the R' or R" groups may

optionally combine to form a spiro-cycloalkyl or heterocyclo ring system, or R^d and any one of the R' or R" groups may optionally combine to form a fused cycloalkyl or heterocyclo ring system, or R^d and R^e may optionally combine to form a fused cycloalkyl or heterocyclo ring system;

R' and R" at each occurrence, respectively, are independently H, halo, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, (halo)$(C_1\text{-}C_3)$alkyl, (halo)$(C_1\text{-}C_3)$alkoxy, (alkoxy)$(C_1\text{-}C_3)$alkyl, (hydroxy)$(C_1\text{-}C_3)$alkyl, -S-$(C_1\text{-}C_3)$alkyl, C(O)$(C_1\text{-}C_3)$alkyl, $-NR^7R^8$, or hydroxyl, or R' and R" bound to the same carbon atom may optionally combine to form =O, or R' and R" bound to the same carbon atom may optionally combine to form a spiro-fused cycloalkyl or heterocyclo ring system;

R^1 is

(a) –COOH, $-C(O)OR^{10}$, –C(O)NHOH, $-C(O)NH\text{-}NH_2$, $-C(O)NHS(O)_2R^{10}$, $-S(O)_2NHC(O)R^{10}$, $-S(O)_2NR^7R^8$, $-NR^7C(O)R^{10}$, $-NR^7C(O)OR^5$, $-C(O)NR^7R^8$, $-NR^7S(O)_2R^{10}$, $-NR^7C(O)\,NR^7R^8$, $-S(O)_vR^{10}$, hydroxylalkyl, -cyclopropyl-COOH, or CN; or

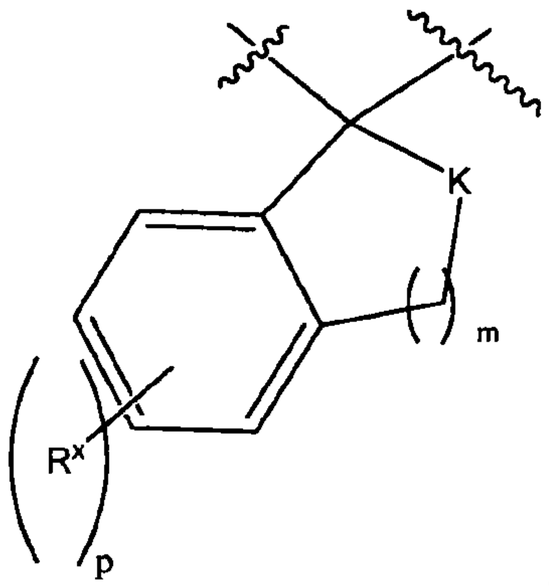
(b) heteroaryl or heterocyclo, either of which may be optionally independently substituted with one or more R^x groups as allowed by valence;

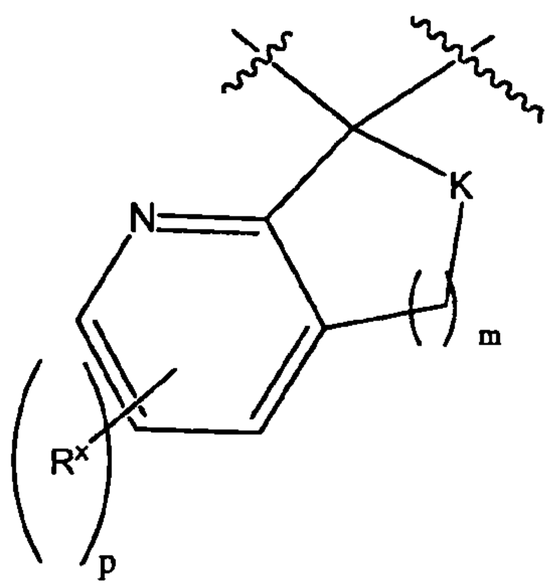
R^2 is

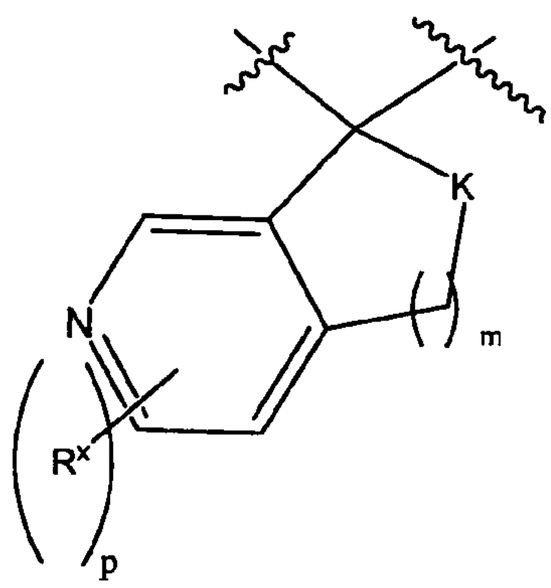
(a) $-NR^7R^8$, $NR^7C(O)OR^{10}$, $NR^7C(O)NR^7R^{10}$, or $-C(R^a)R^5R^6$; or

(b) aryl, heteroaryl, cycloalkyl, or heterocyclo, any of which may be optionally independently substituted with one or more R^x groups as allowed by valence;

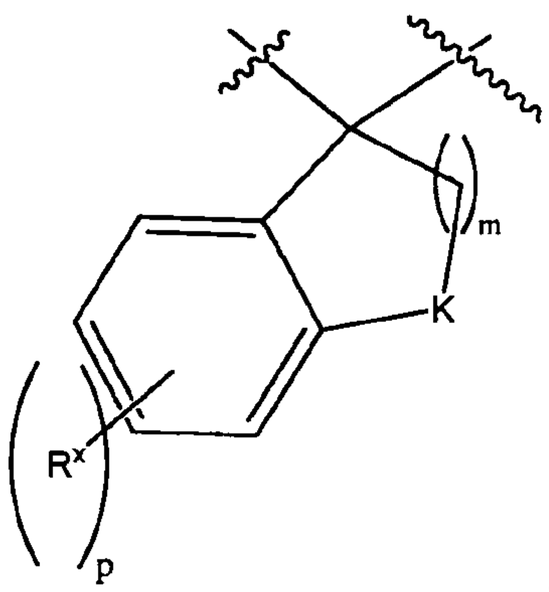
R^3 and R^4 are independently aryl or heteroaryl, either of which may be optionally independently substituted with one or more R^x groups as allowed by valence, or either R^3 and R^a together with the ring carbon atom to which they are both bonded, or R^4 and R^b together with the ring carbon atom to which they are both bonded may optionally combine to form a spiro-fused bicyclic ring system selected from

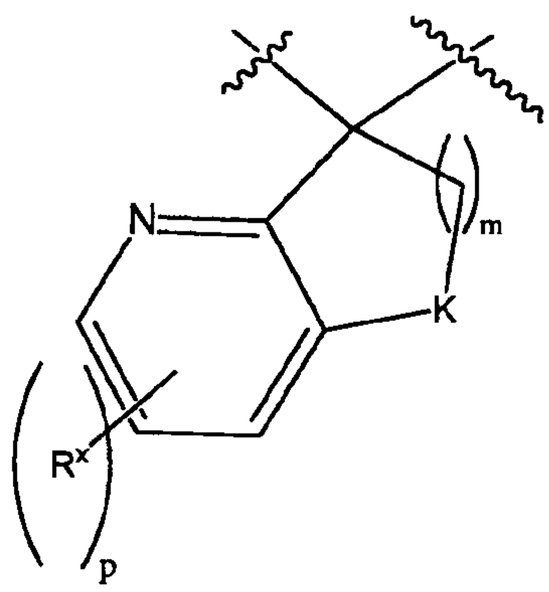


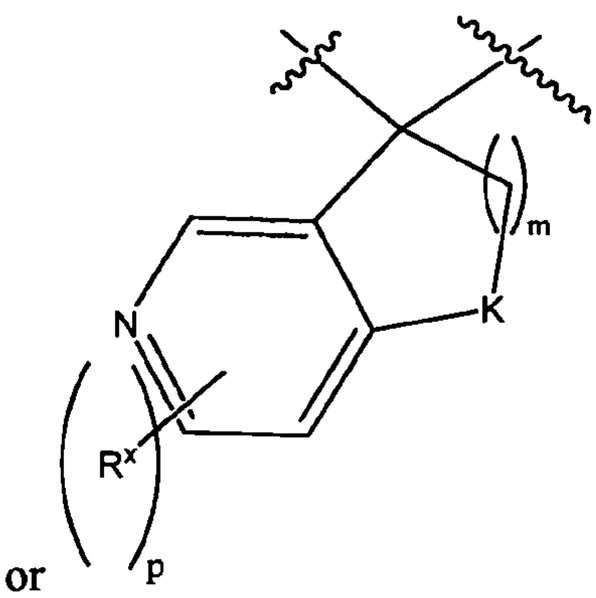
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or


wherein K is –O-, -NR^7-, or –C(=O)NR^7-;

R^5 and R^6 at each occurrence, respectively, are independently selected from

(a) H or CN;

(b) -(alkylene)$_t$ –OH, -(alkylene)$_t$ –OR^9, -(alkylene)$_t$ –SR^9, -(alkylene)$_t$ –$NR^{10}R^{11}$, -(alkylene)$_t$-$C(O)R^9$, -(alkylene)$_t$ –$C(O)OR^9$, -(alkylene)$_t$ –$OC(O)R^9$, -(alkylene)$_t$ –$S(O)_vR^9$, -(alkylene)$_t$-$NHS(O)_2R^{10}$, -(alkylene)$_t$-$N(R^{11})S(O)_2R^{10}$, -(alkylene)$_t$-$S(O)_2NR^{10}R^{11}$, -(alkylene)$_t$-$N(R^{11})S(O)_2NR^{10}R^{11}$, –$NR^{10}C(O)R^9$, -$C(O)NR^{10}R^{11}$, -$NR^{10}S(O)_2R^9$, $S(O)_2NR^{10}$, or $NR^{10}C(O)NR^{10}R^{11}$; or

(c) haloalkyl, haloalkoxy, C_{1-6}-alkyl, C_{2-6}alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, (C_{3-8}-cycloalkyl)(C_{1-3}alkyl), C_{4-8}-cycloalkenyl, aryl, aryl(C_{1-3}-alkyl), heteroaryl, heteroaryl(C_{1-3}-alkyl), heterocyclo or heterocyclo(C_{1-3}-alkyl), any of which may be optionally independently substituted with one or more R^x groups as allowed by valence;

R^7 and R^8 at each occurrence, respectively, are independently selected from H, cyano, -O C_{1-6}-alkyl, C_{1-6}-alkyl, halo(C_{1-6})-alkyl, cycloalkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocyclo(C_{1-10}alkyl), or (C_{3-8}-cycloalkyl)(C_{1-3}alkyl), any of which may be optionally substituted as allowed by valence with one or more

R^x, or R^7 and R^8 may combine to form a C_4-C_8-heterocyclo ring optionally substituted with one or more R^x;

R^9 is haloalkyl, haloalkoxy, C_{1-6}-alkyl, C_{2-6}alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, (C_{3-8}-cycloalkyl)(C_{1-3}alkyl), C_{4-8}-cycloalkenyl, aryl, heteroaryl, heterocyclo, or heterocycloalkyl, any of which may be optionally independently substituted with one or more R^x groups as allowed by valence;

R^{10} and R^{11} at each occurrence, respectively, are independently selected from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, or cycloalkylalkyl, any of which may be optionally substituted as allowed by valence with one or more R^x, or R^{10} and R^{11} may combine to form a heterocyclo ring optionally substituted with one or more R^x;

R^x at each occurrence is independently, deuterium, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, -(alkylene)$_t$-OR^*, -(alkylene)$_t$-$S(O)_vR^*$, -(alkylene)$_t$-NR^+R^{++}, -(alkylene)$_t$-$C(=O)R^*$, -(alkylene)$_t$-$C(=S)R^*$, -(alkylene)$_t$-$C(=O)OR^*$, -(alkylene)$_t$-$OC(=O)R^*$, -(alkylene)$_t$-$C(=S)OR^*$, —(alkylene)$_t$-$C(=O)NR^+R^{++}$, -(alkylene)$_t$-$C(=S)NR^+R^{++}$, -(alkylene)$_t$-$N(R^+)C(=O)NR^+R^{++}$, -(alkylene)$_t$-$N(R^+)C(=S)NR^+R^{++}$, -(alkylene)$_t$-$N(R^+)C(=O)R^*$, -(alkylene)$_t$-$N(R^+)C(=S)R^*$, -(alkylene)$_t$-$OC(=O)NR^+R^{++}$, -(alkylene)$_t$-$OC(=S)NR^+R^{++}$, -(alkylene)$_t$-$SO_2NR^+R^{++}$, -(alkylene)$_t$-$N(R^+)SO_2R^*$, -(alkylene)$_t$-$N(R^+)SO_2NR^+R^{++}$, -(alkylene)$_t$-$N(R^+)C(=O)OR^*$, -(alkylene)$_t$-$N(R^+)C(=S)OR^*$, or -(alkylene)$_t$-$N(R^+)SO_2R^*$, wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more halo, cyano, oxo, -(alkylene)$_t$-OR^*, -(alkylene)$_t$-$S(O)_vR^*$, -(alkylene)$_t$-NR^+R^{++}, -(alkylene)$_t$-$C(=O)R^*$, -(alkylene)$_t$-$C(=S)R^*$, -(alkylene)$_t$-$C(=O)OR^*$, -(alkylene)$_t$-$OC(=O)R^*$, -(alkylene)$_t$-$C(=S)OR^*$, —(alkylene)$_t$-$C(=O)NR^+R^{++}$, -(alkylene)$_t$-$C(=S)NR^+R^{++}$, -(alkylene)$_t$-$N(R^+)C(=O)NR^+R^{++}$, -(alkylene)$_t$-$N(R^+)C(=S)NR^+R^{++}$, -(alkylene)$_t$-$N(R^+)C(=O)R^*$, -(alkylene)$_t$-$N(R^+)C(=S)R^*$, -(alkylene)$_t$-$OC(=O)NR^+R^{++}$, -(alkylene)$_t$-$OC(=S)NR^+R^{++}$, -(alkylene)$_t$-$SO_2NR^+R^{++}$, -(alkylene)$_t$-$N(R^+)SO_2R^*$, -(alkylene)$_t$-$N(R^+)SO_2NR^+R^{++}$, -(alkylene)$_t$-$N(R^+)C(=O)OR^*$, -(alkylene)$_t$-$N(R^+)C(=S)OR^*$, or -(alkylene)$_t$-$N(R^+)SO_2R^*$;

R* is H, haloalkyl, haloalkoxy, C_{1-6}-alkyl, C_{2-6}alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, aryl, heteroaryl, or heterocyclo;

R^+ and R^{++} are independently H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, or cycloalkylalkyl, or R^+ and R^{++} bound to the same nitrogen atom may optionally combine to form a heterocyclo ring system;

m is 1, 2 or 3;

n and n* are each independently selected from 0 or an integer from 1 to 6;

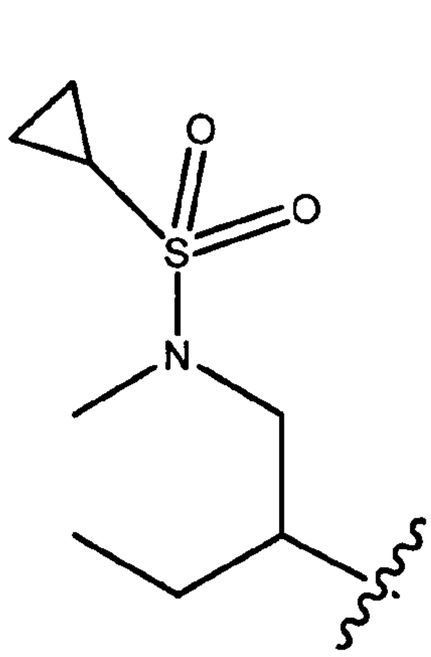
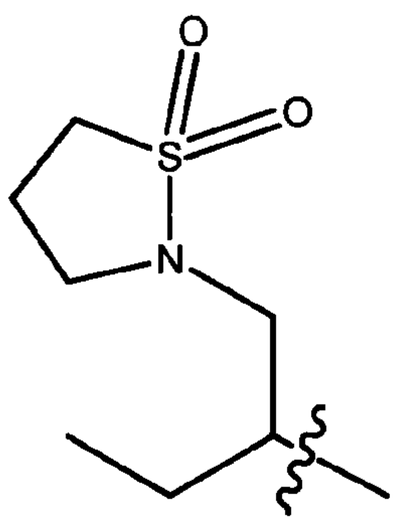
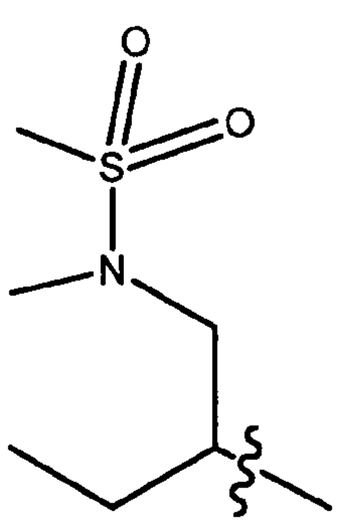
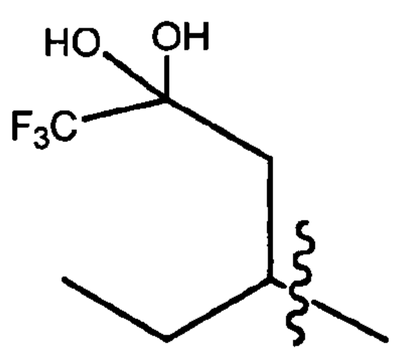
p is 0, 1, 2 or 3;

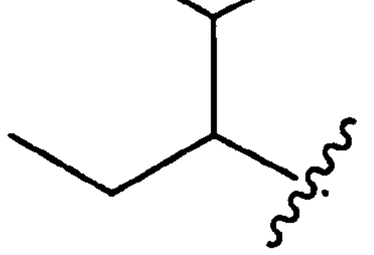
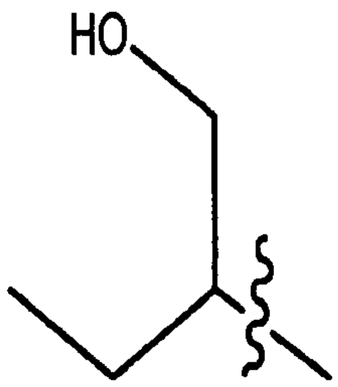
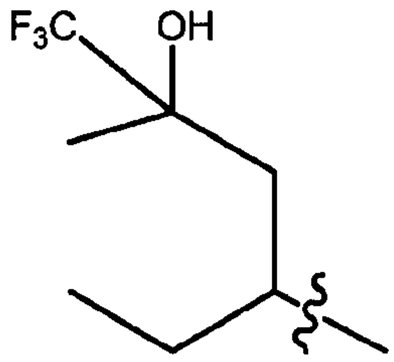
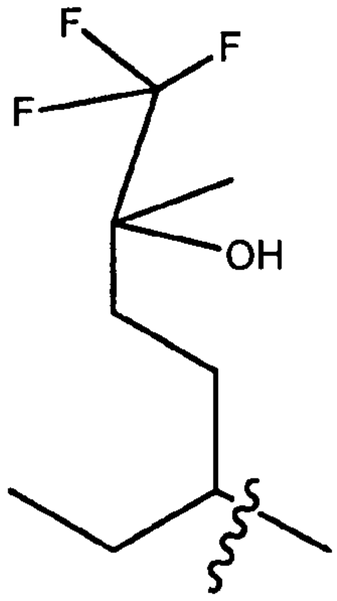
t at each occurrence is independently 0 or an integer from 1 to 6; and

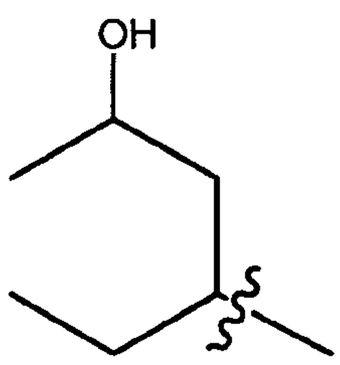
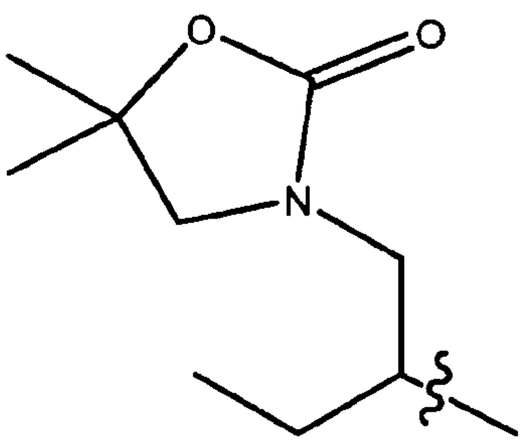
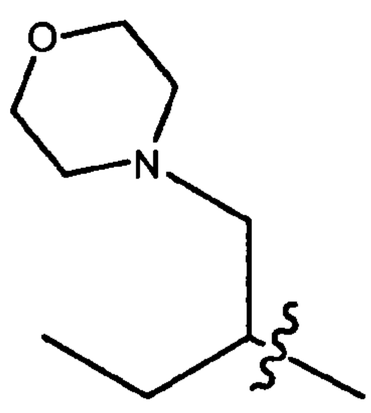
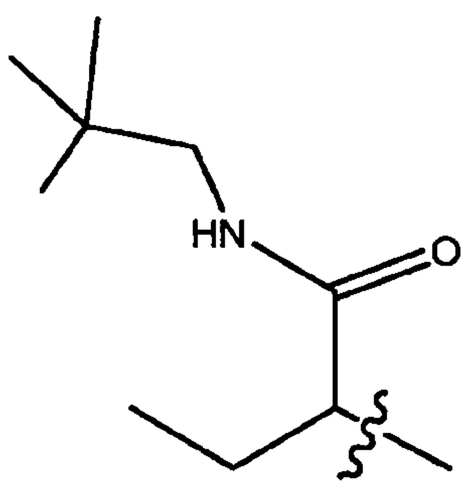
v at each occurrence is independently 0, 1 or 2.

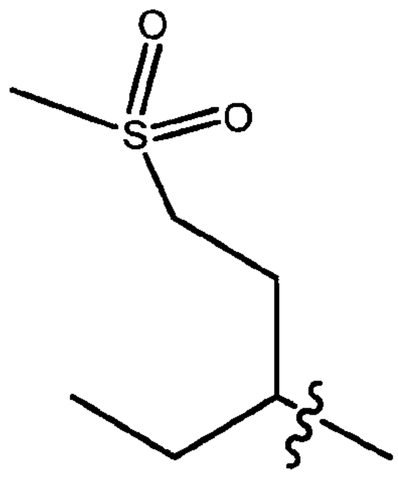
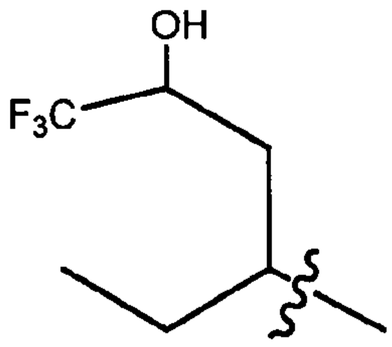
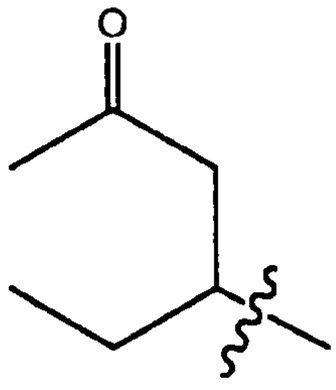
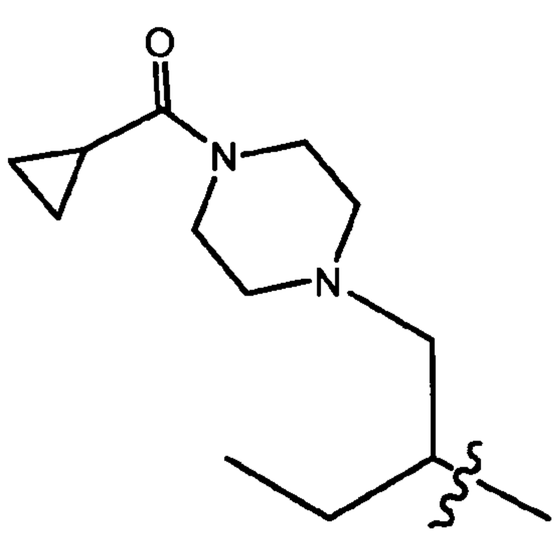
In another embodiment, embodiment 2, of the compounds of Aspect A or AA, or the pharmaceutically acceptable salts thereof, R^2 is $-C(H)R^5R^6$, $-NR^7R^8$, phenyl or pyridine, wherein the phenyl or the pyridyl may be optionally substituted with one or more R^x as allowed by valence.

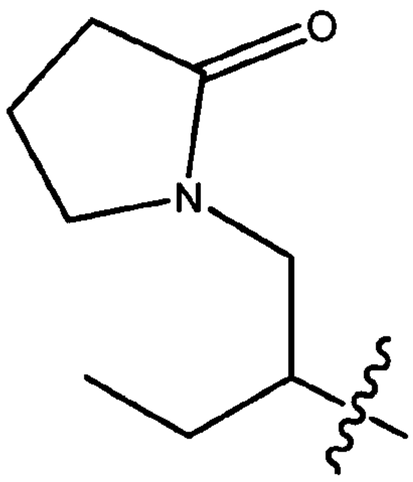
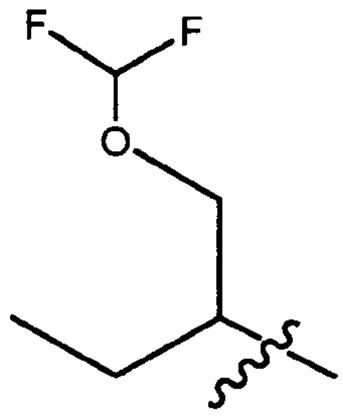
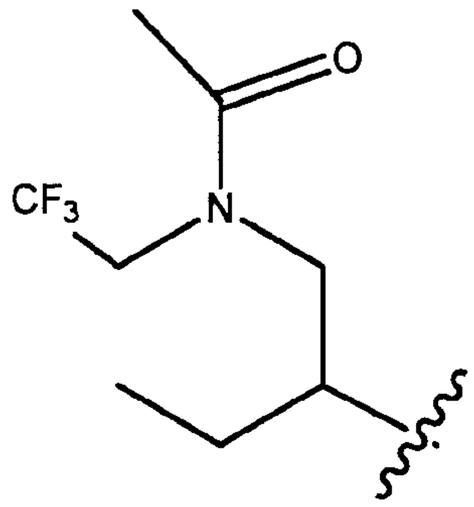
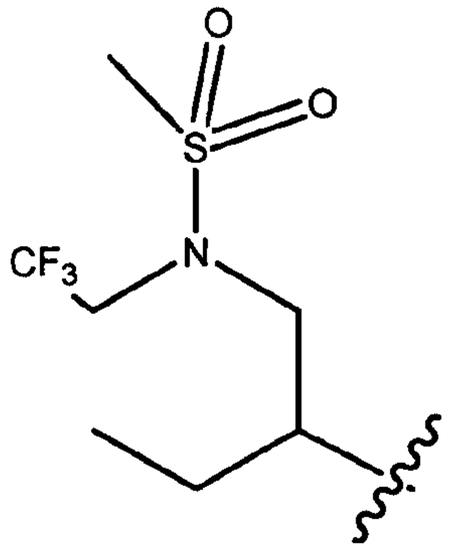
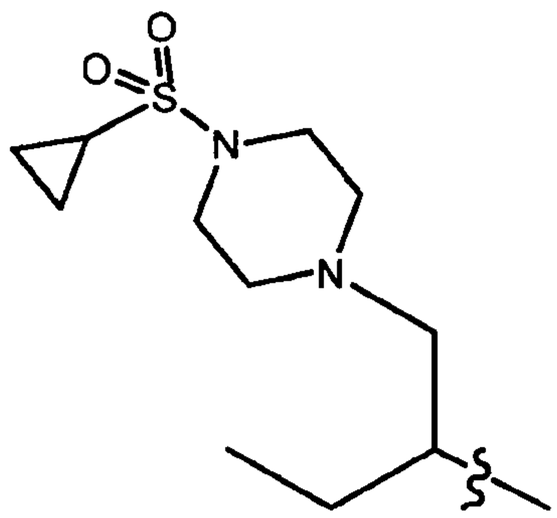
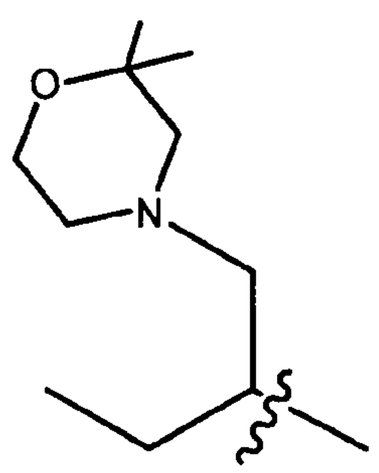
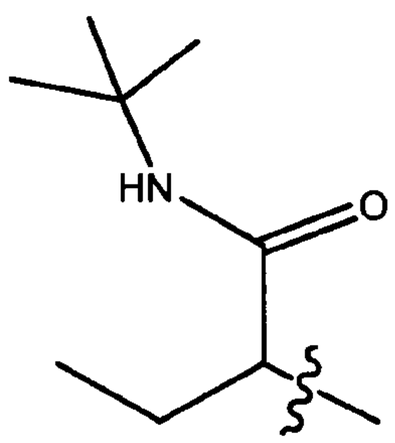
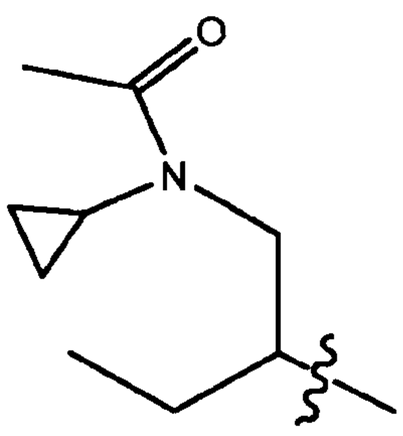
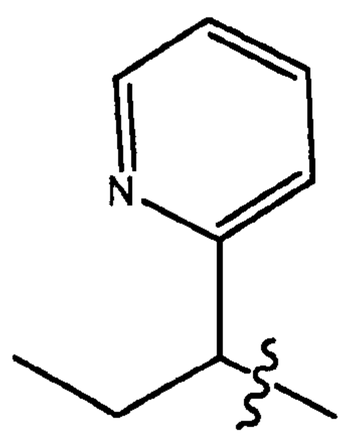
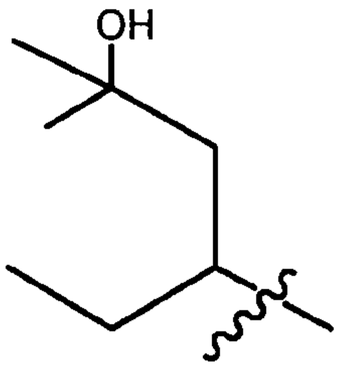
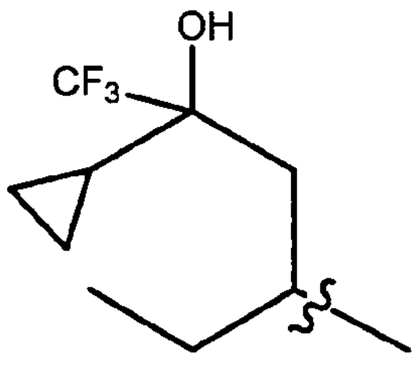
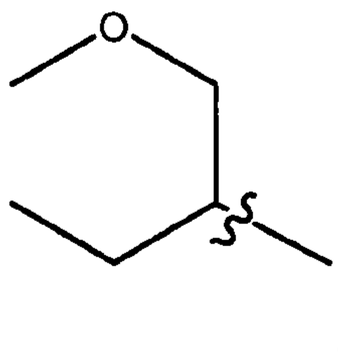
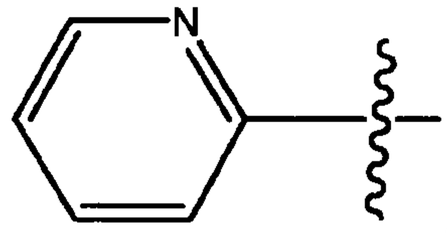
In another embodiment, embodiment 3, of the compounds of Aspect A or AA, or the pharmaceutically acceptable salts thereof, R^2 is selected from

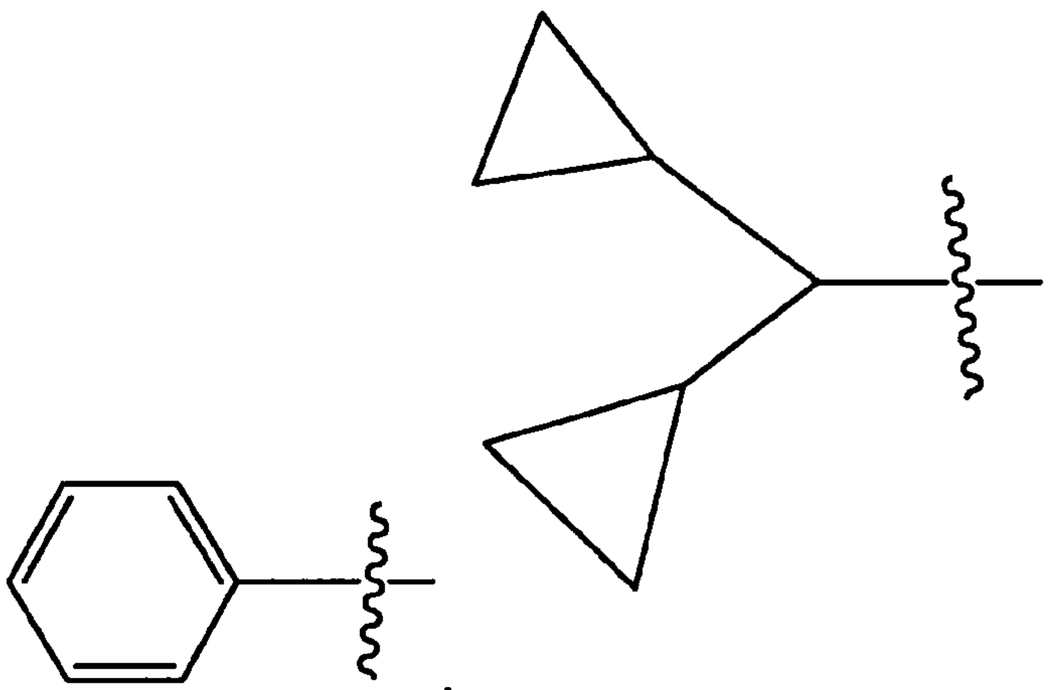

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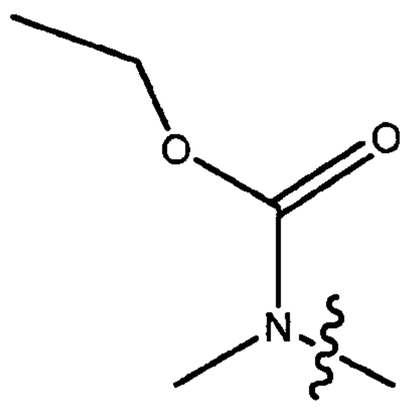
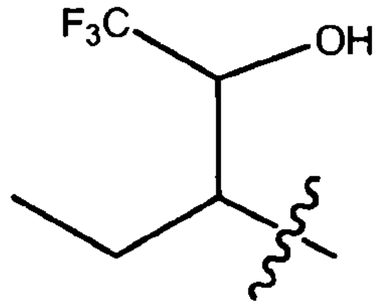

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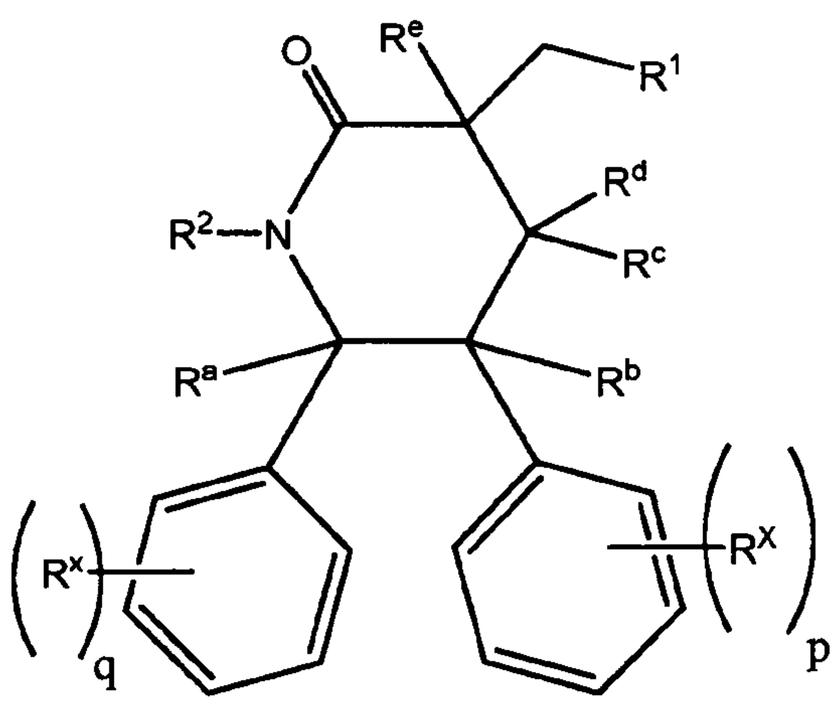

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, , , or , any of which may be optionally substituted with one or more R^x groups as allowed by valence.

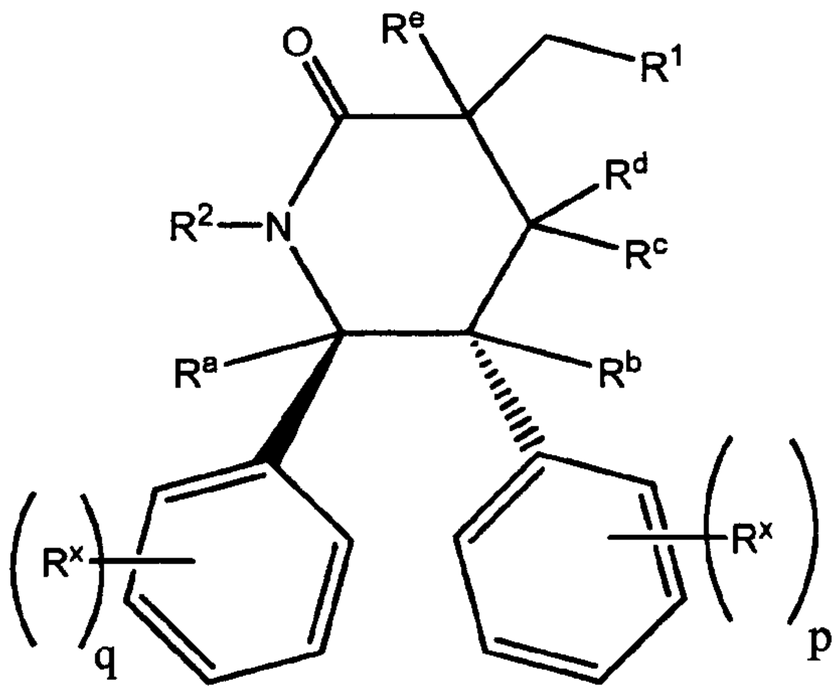
In another embodiment, embodiment 4, the compounds of Aspect A or AA have the structure of Formula IA



IA

or the pharmaceutically acceptable salts thereof, wherein q and p are each independently 0, 1, 2 or 3.

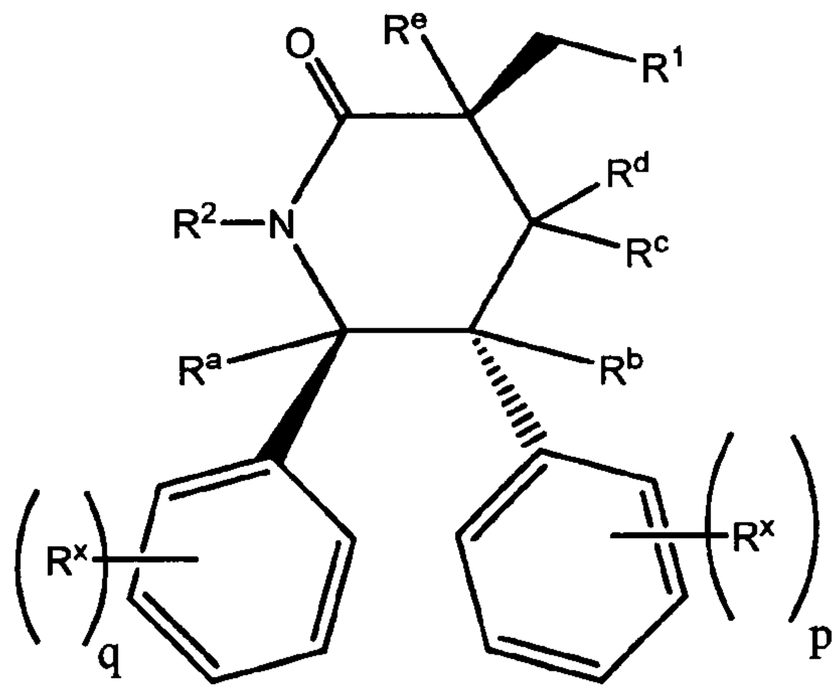
In another embodiment, embodiment 5, the compounds of Aspect A or AA have the structure of Formula IB



IB

or the pharmaceutically acceptable salts thereof, wherein q and p are each independently 0, 1, 2 or 3.

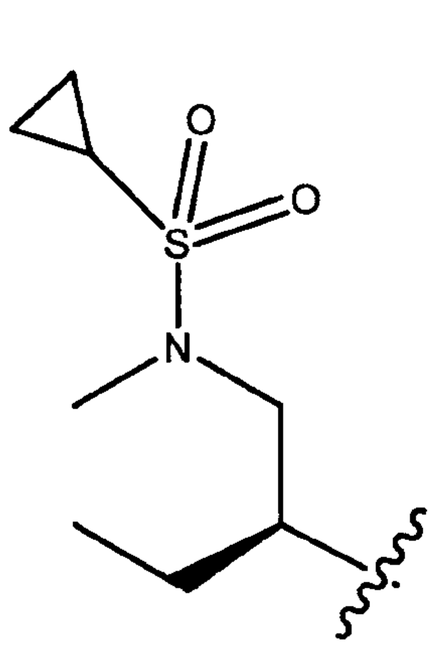
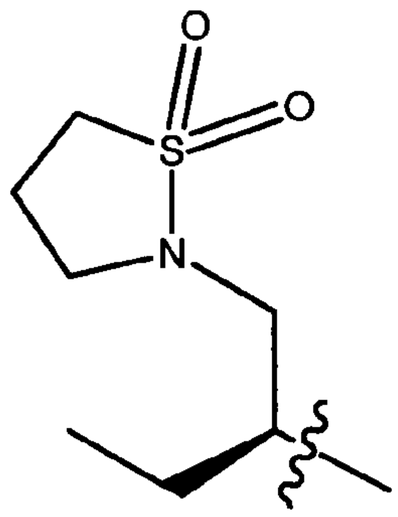
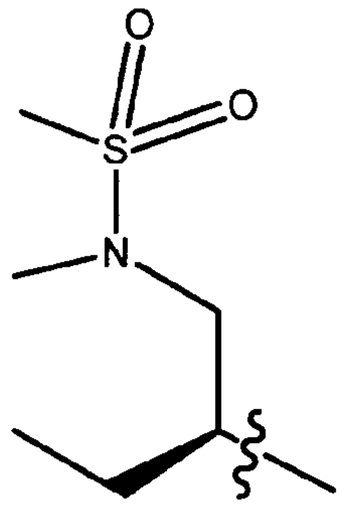
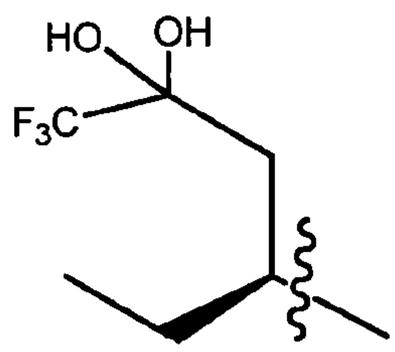
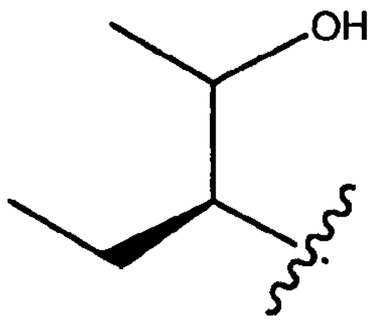
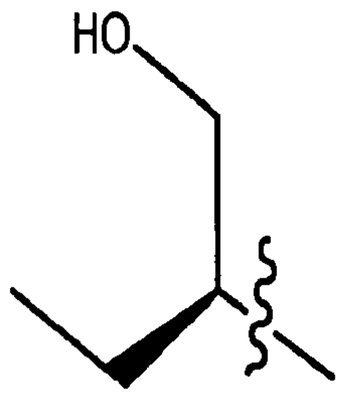
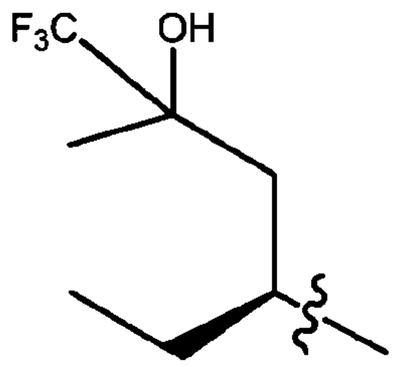
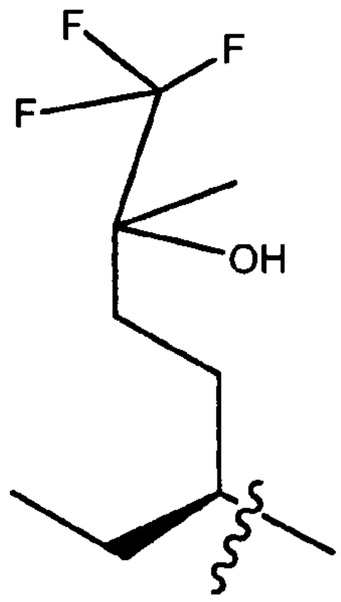
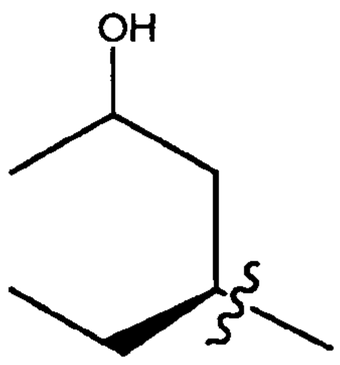
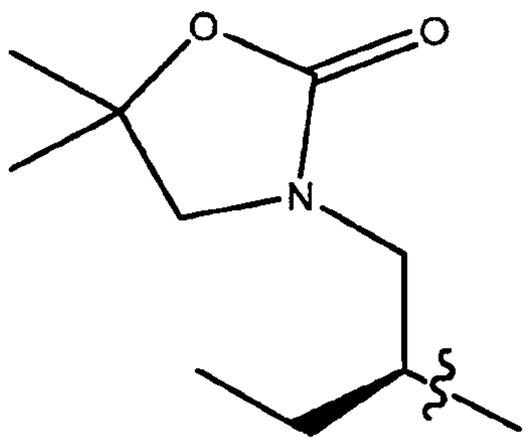
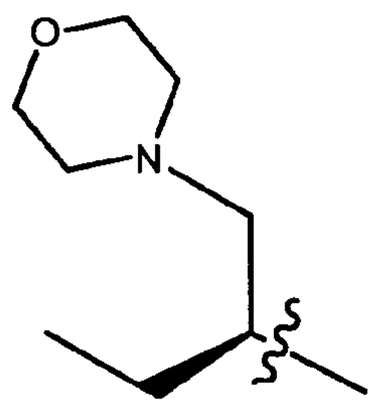
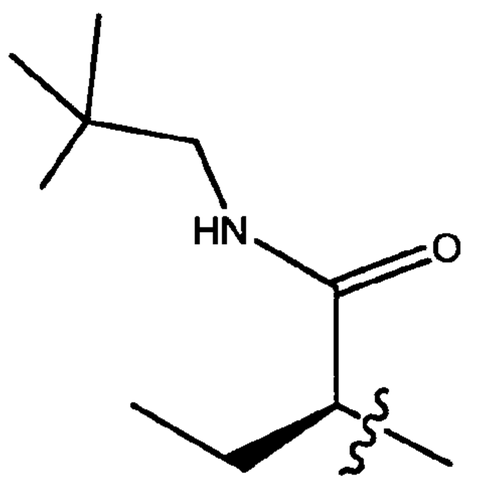
In another embodiment, embodiment 6, the compounds of Aspect A or AA have the structure of Formula IC

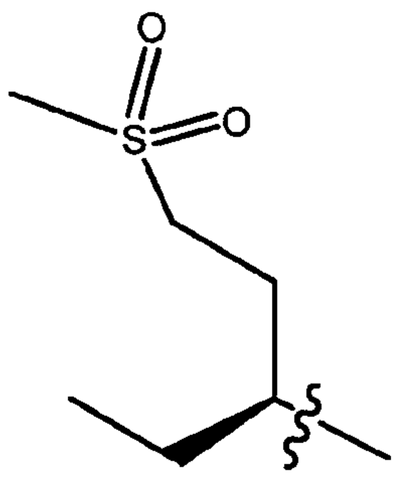
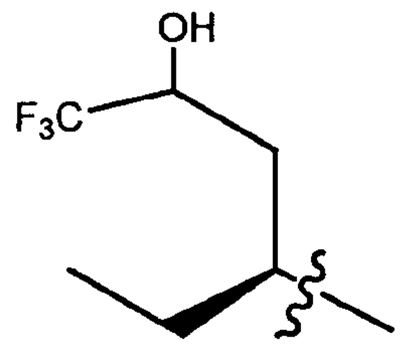
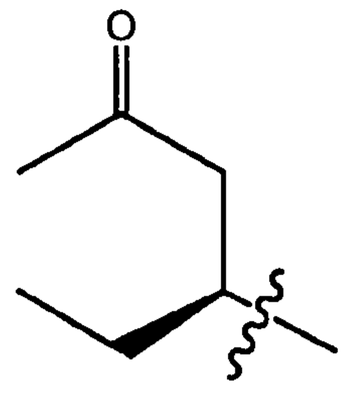
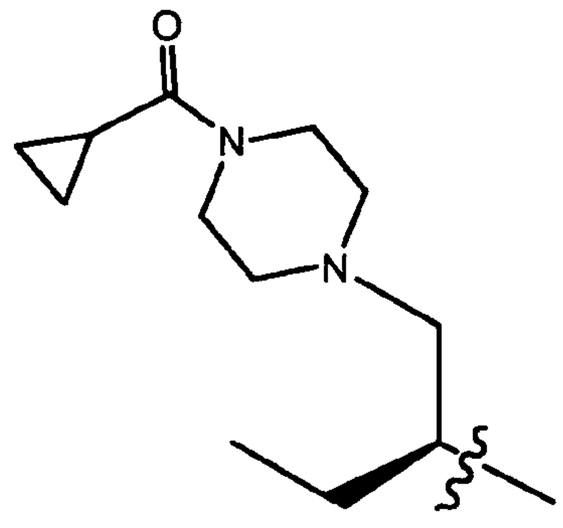
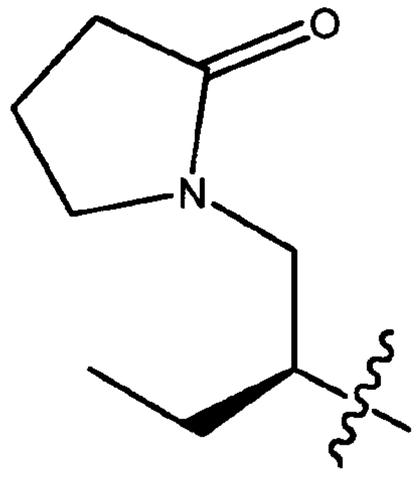
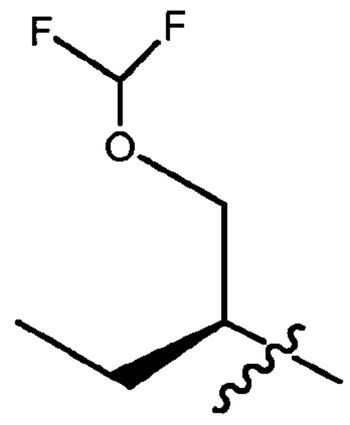
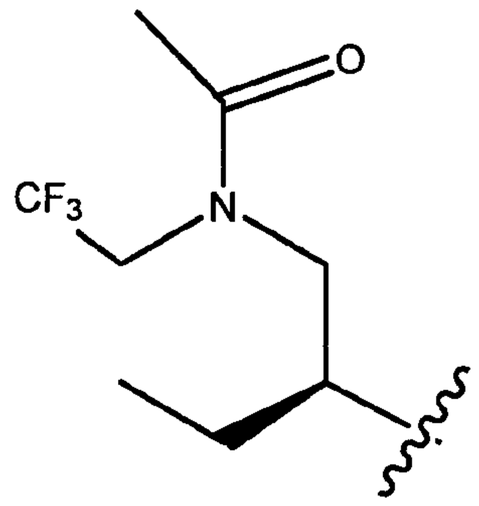
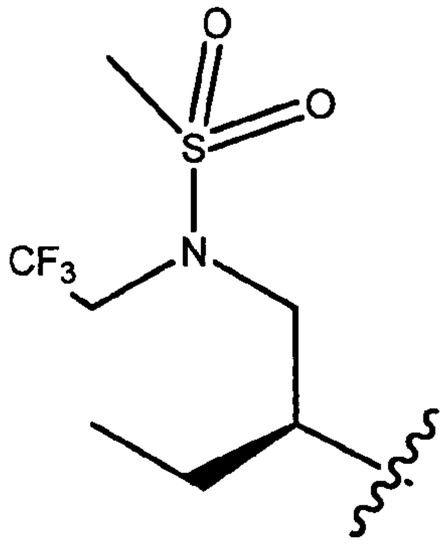
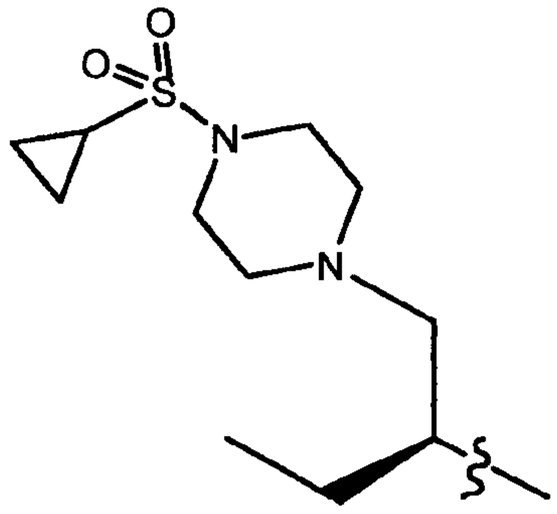
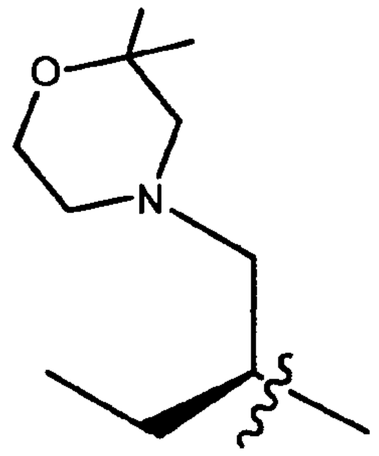
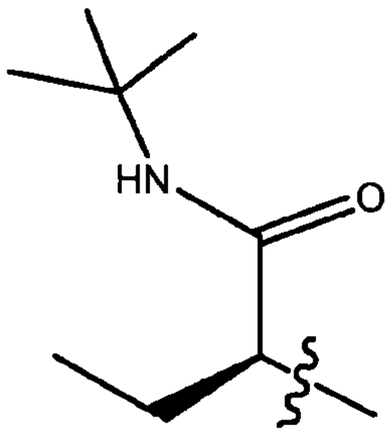
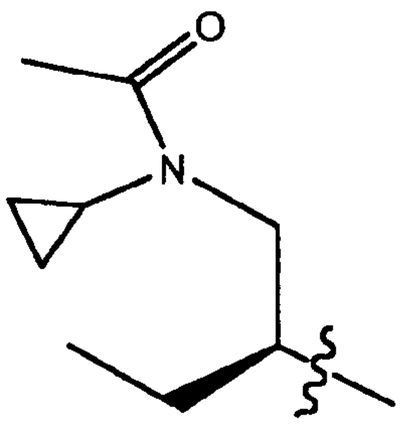
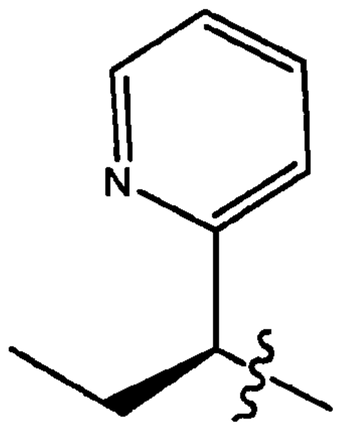


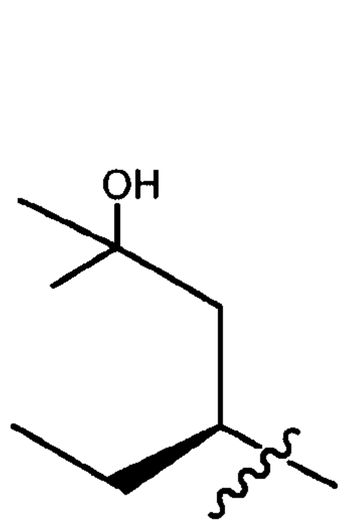
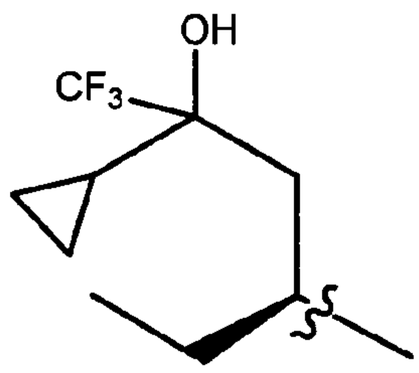
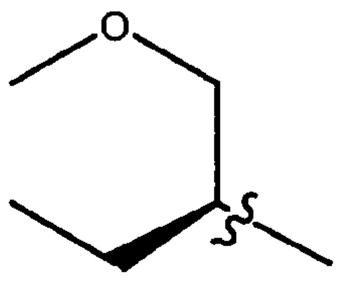
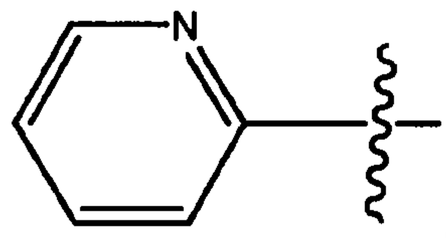
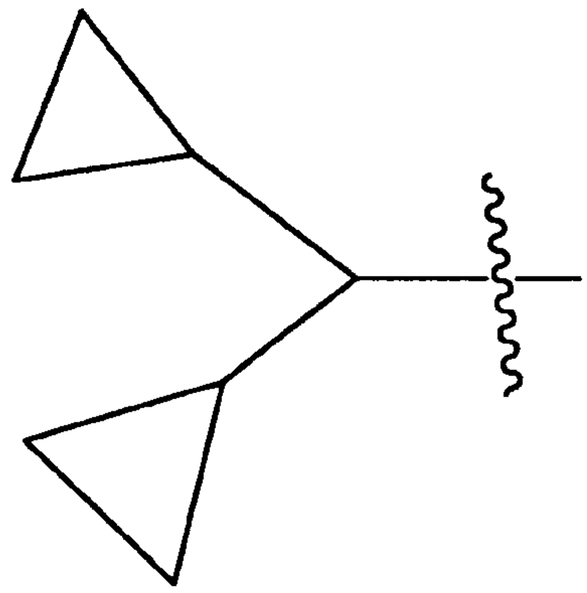
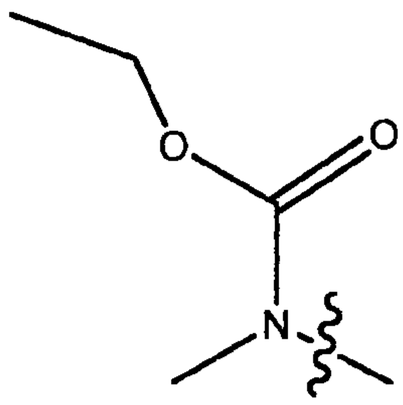
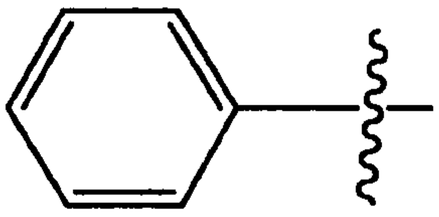
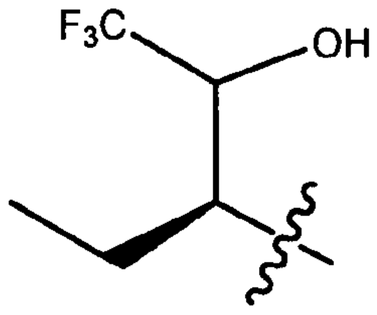
IC

or the pharmaceutically acceptable salts thereof, wherein q and p are each independently 0, 1, 2 or 3.

In another aspect of embodiment 6 (embodiment 7), or the pharmaceutically acceptable salts thereof, R^2 is selected from


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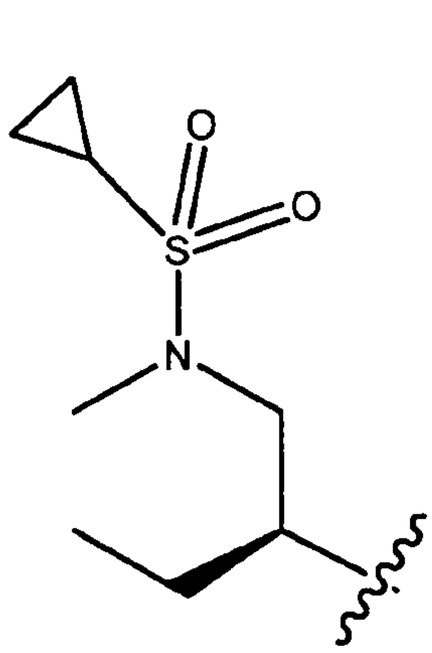
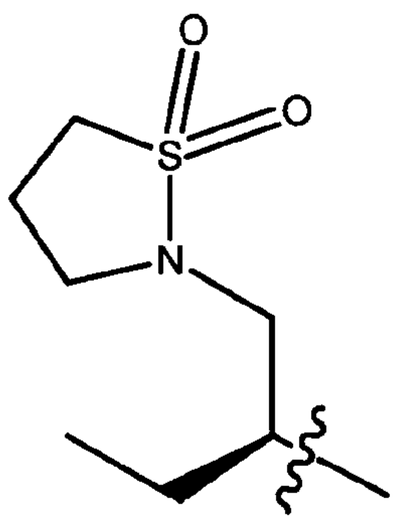
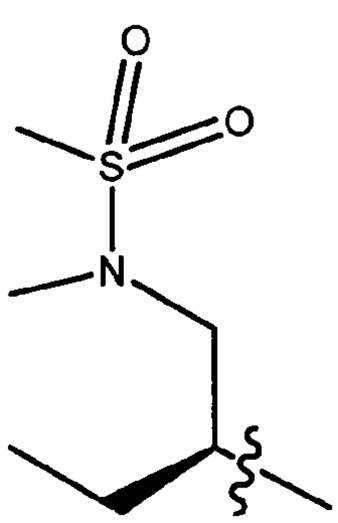
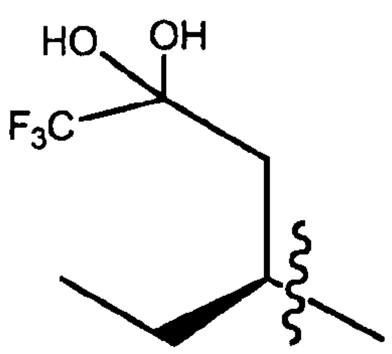
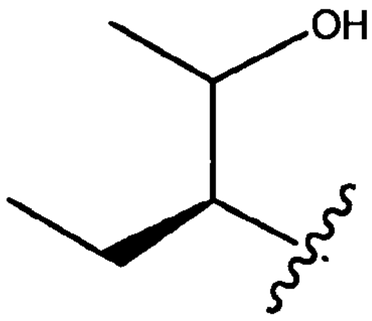
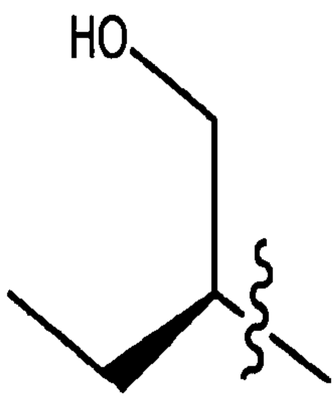
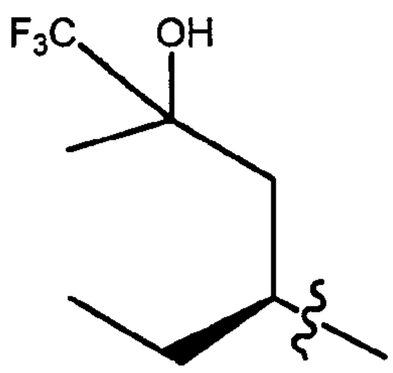
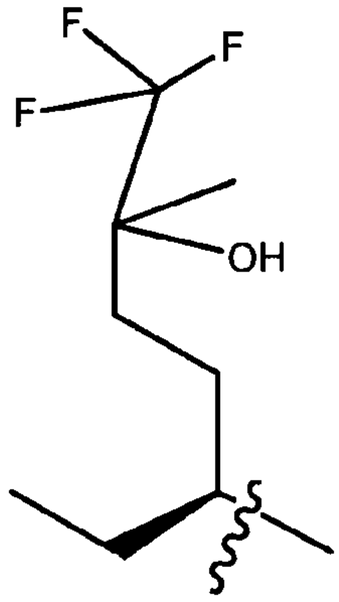
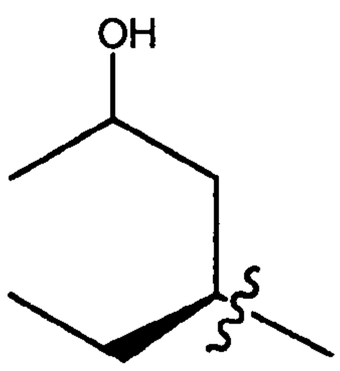
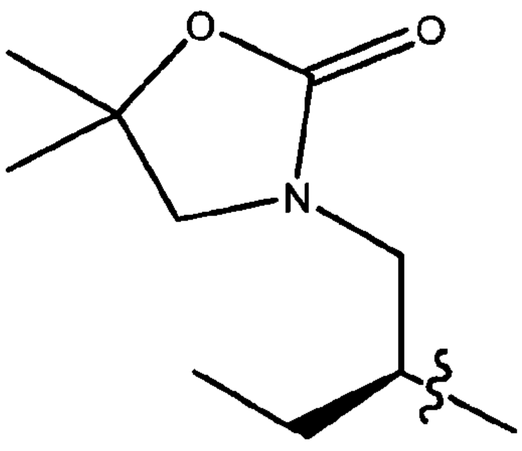
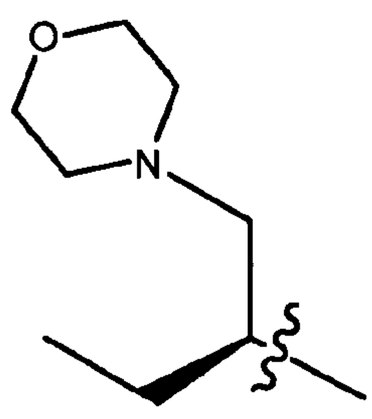
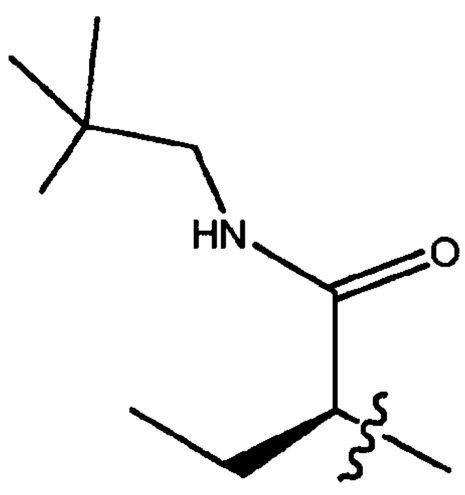
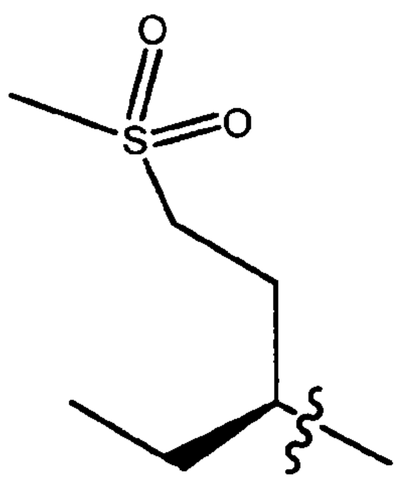
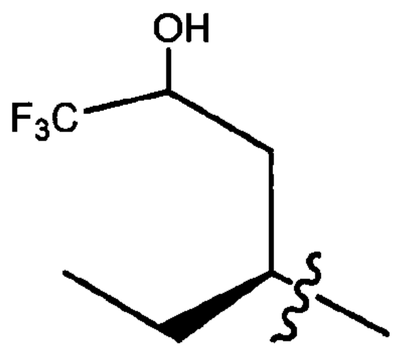
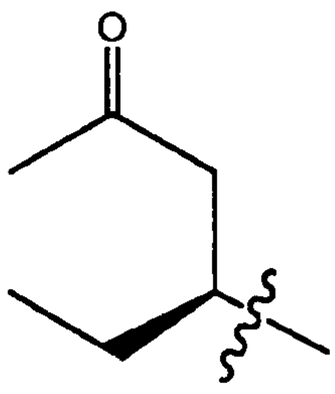
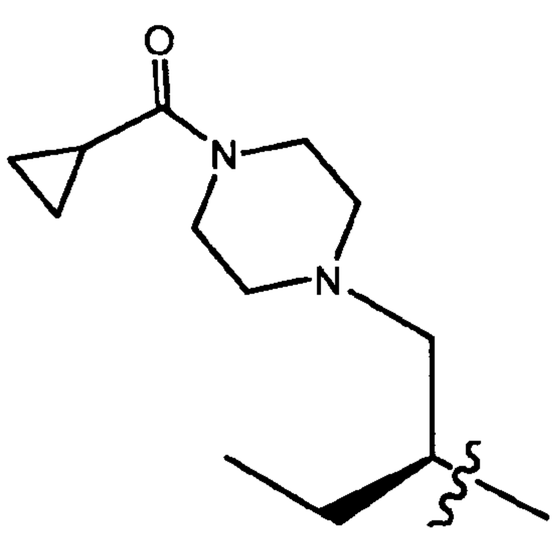














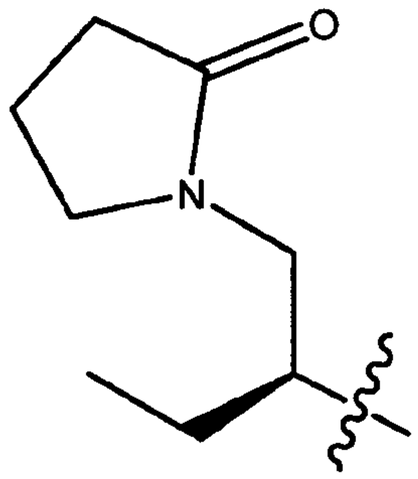
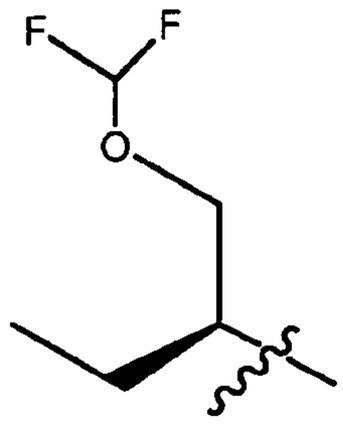
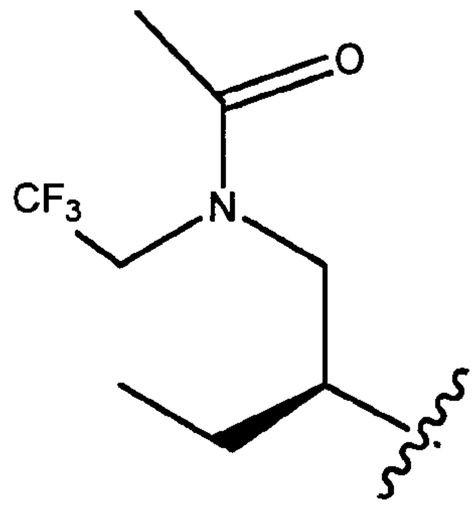
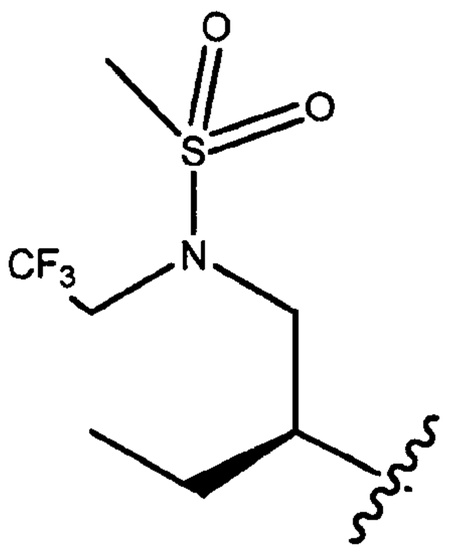
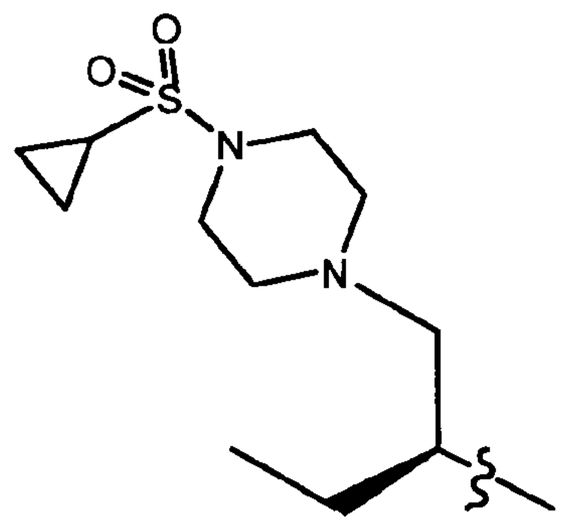
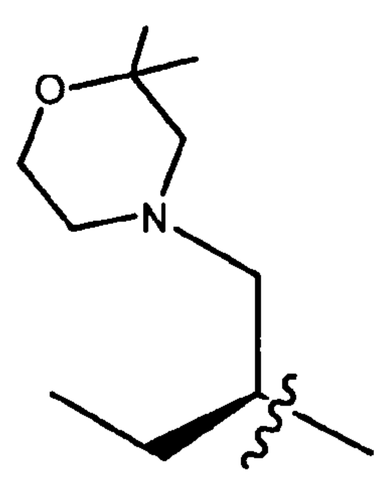
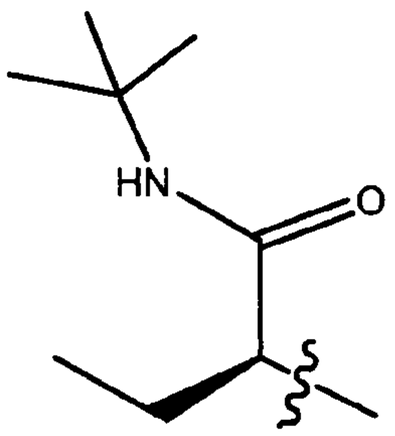
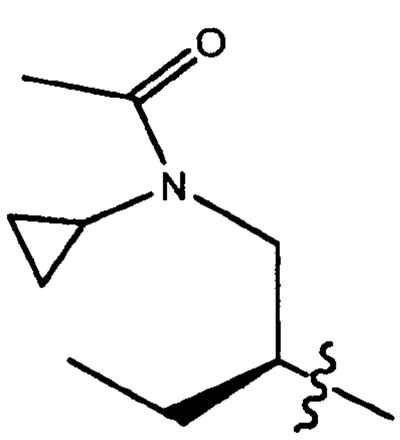
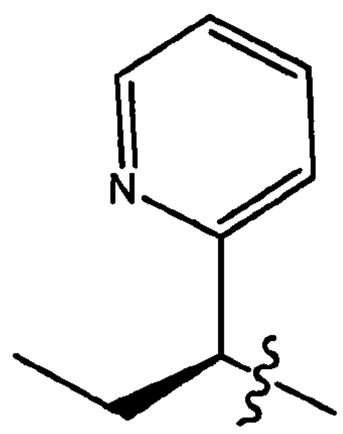
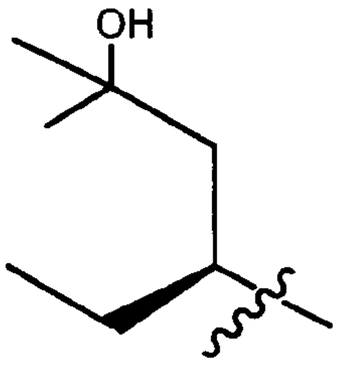
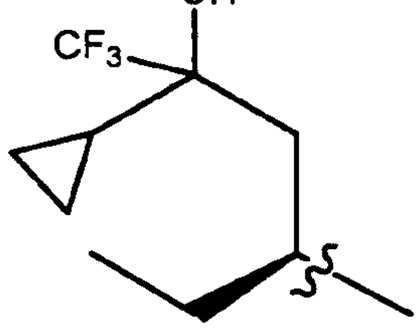
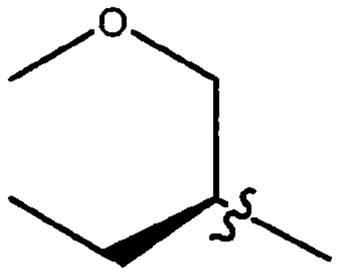
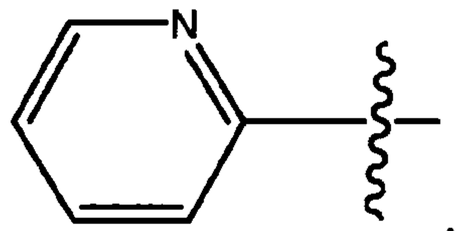









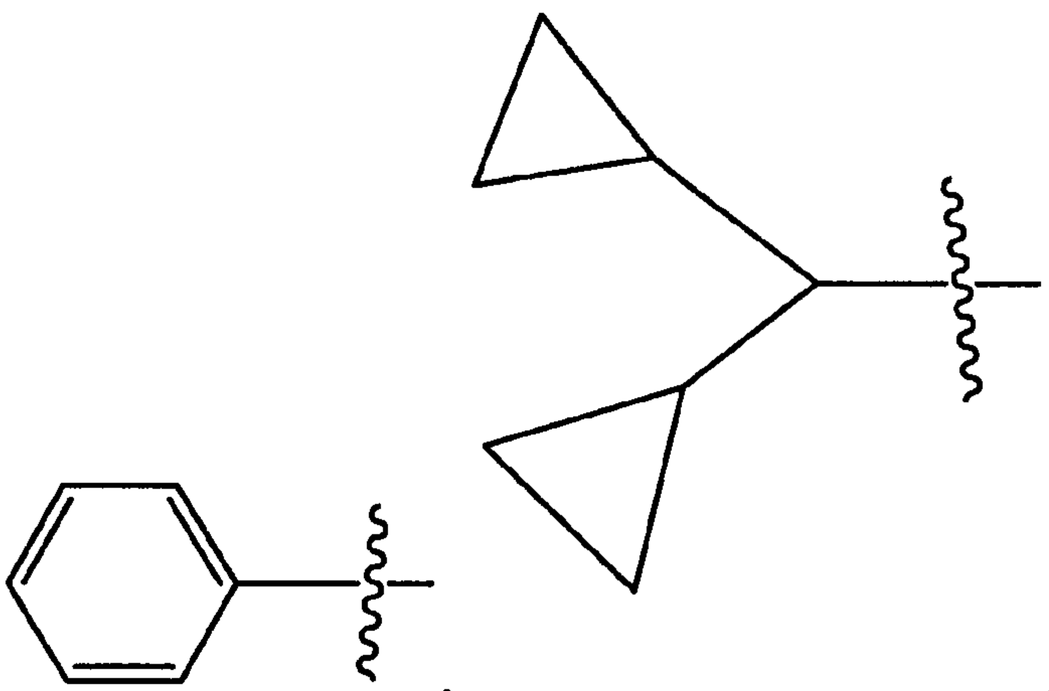
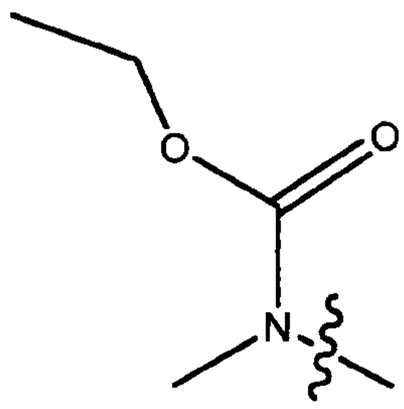
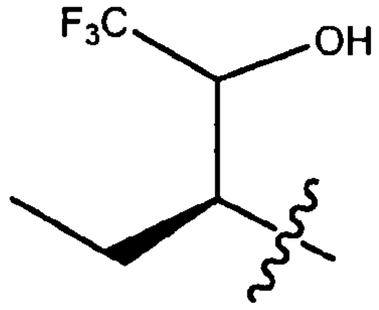
, any of which may be optionally substituted with one or more R^x groups as allowed by valence.

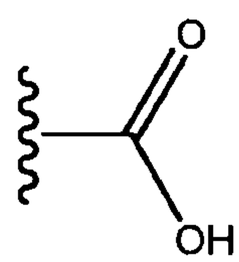
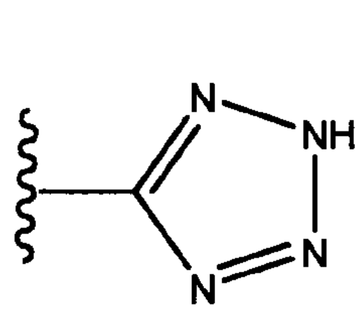
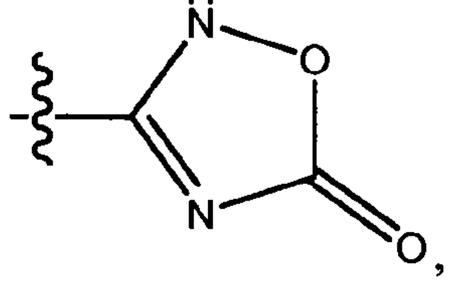
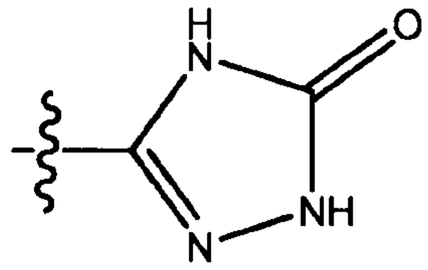
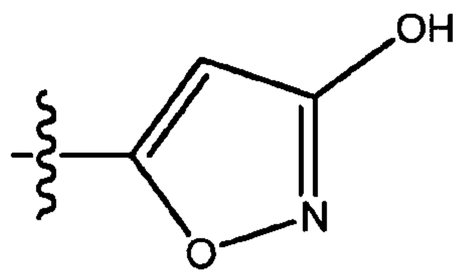
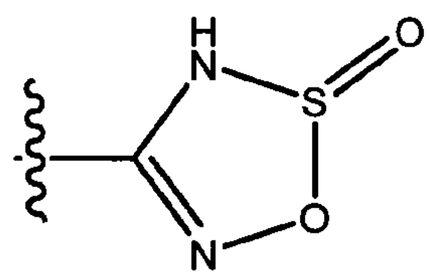
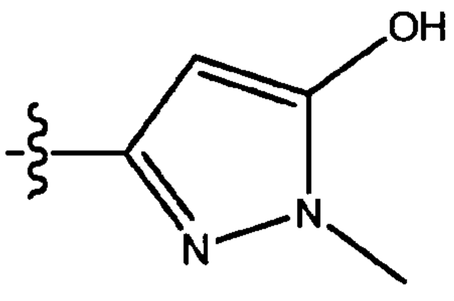
In another aspect of embodiment 6 (embodiment 8) or the pharmaceutically acceptable salts thereof,

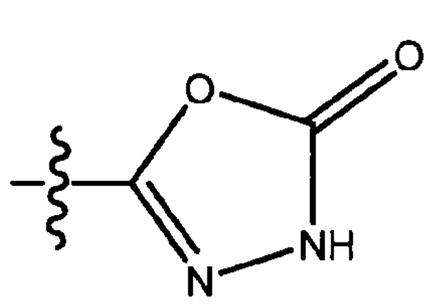
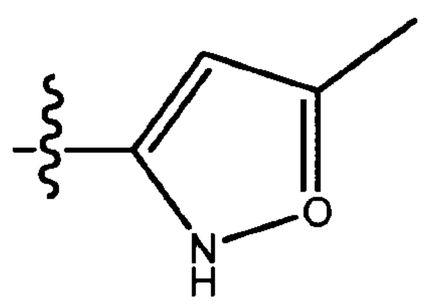
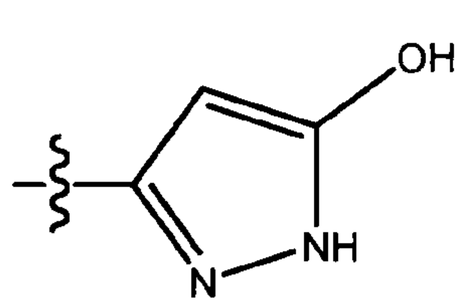
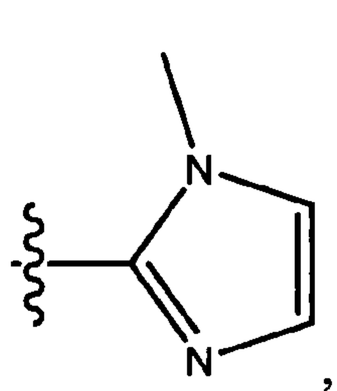
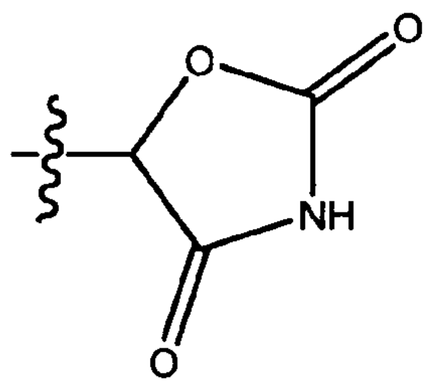
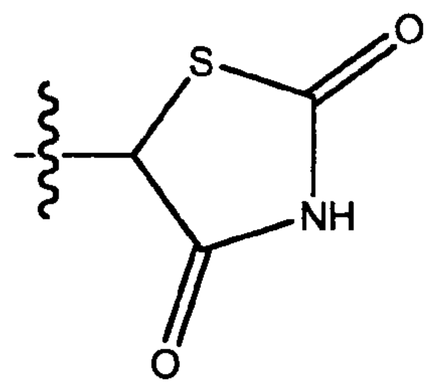
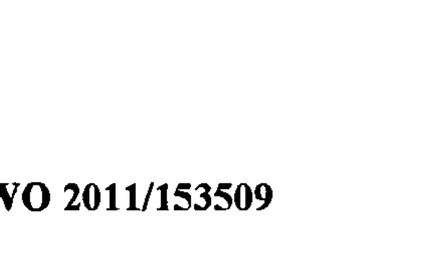
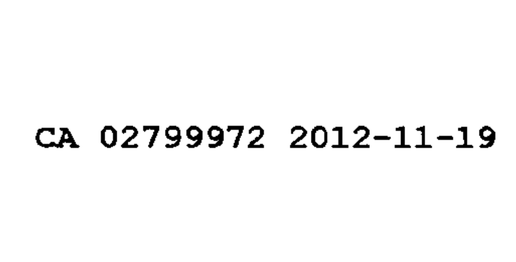
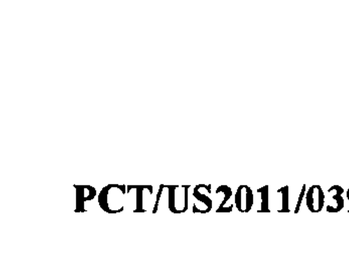
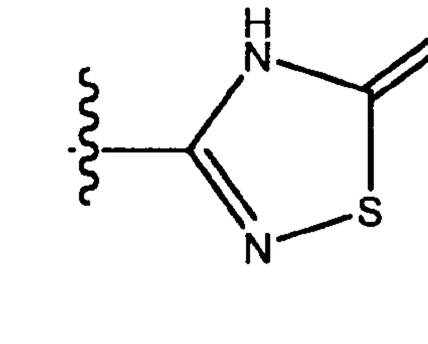
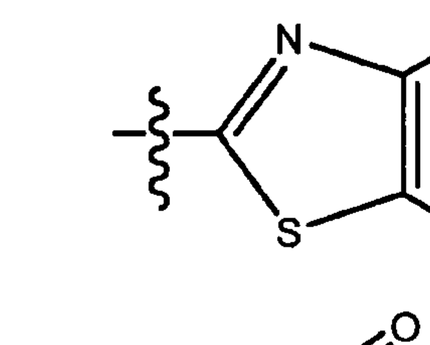
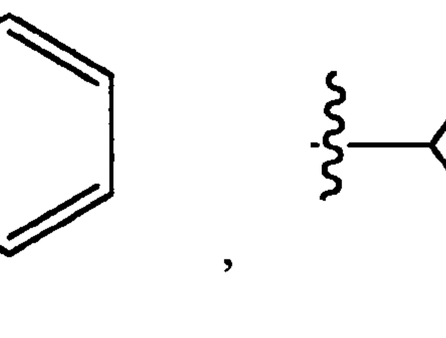
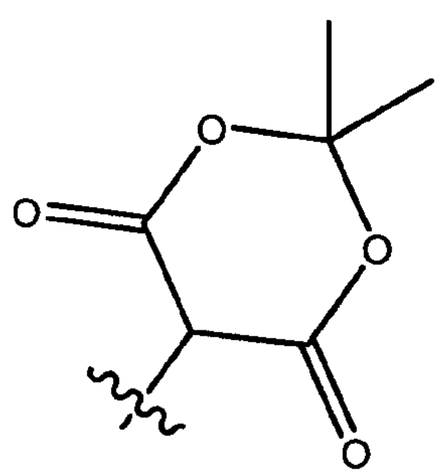
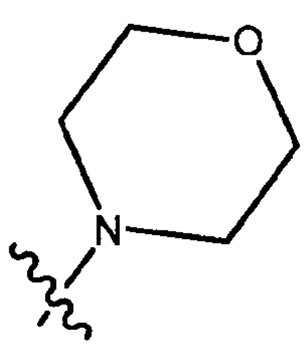
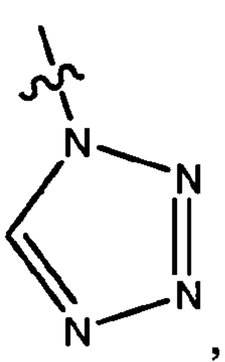
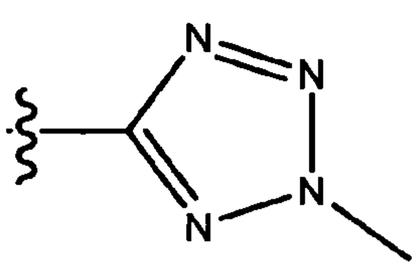
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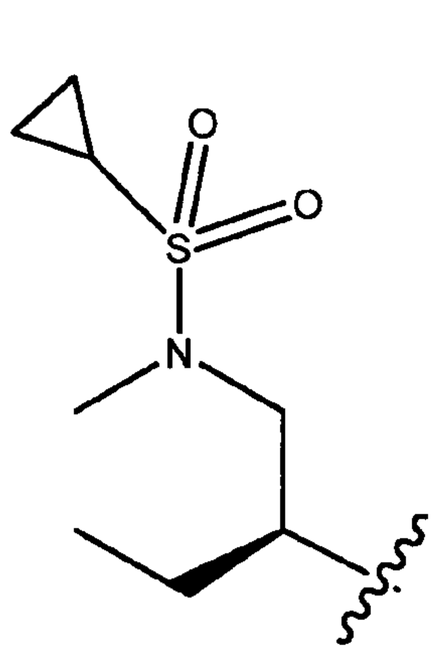
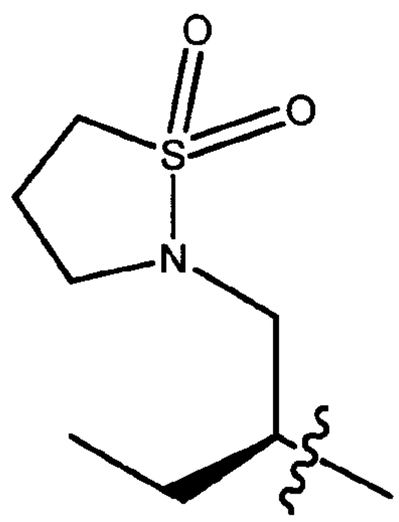
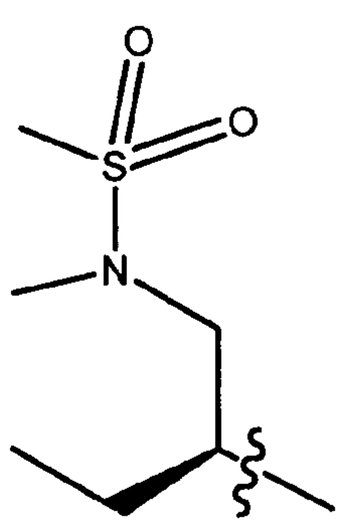
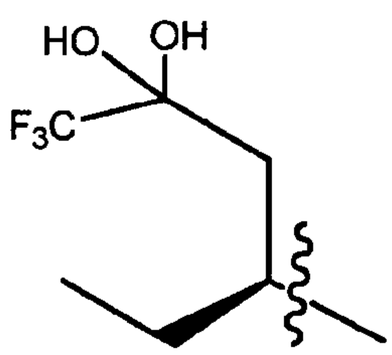
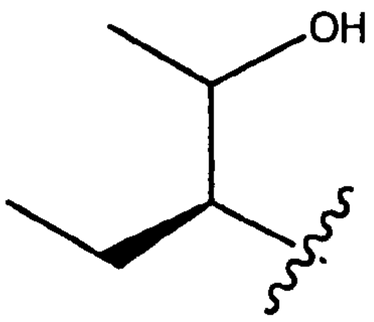
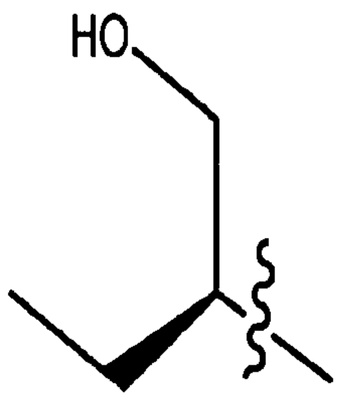
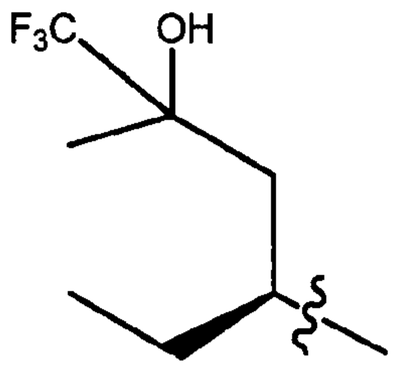
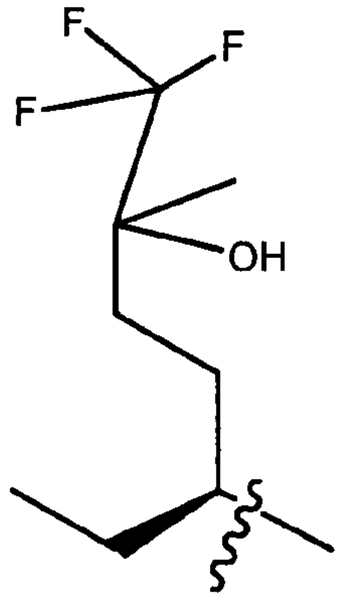
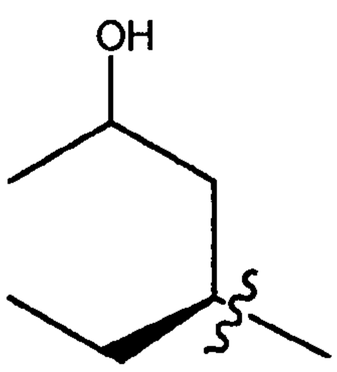
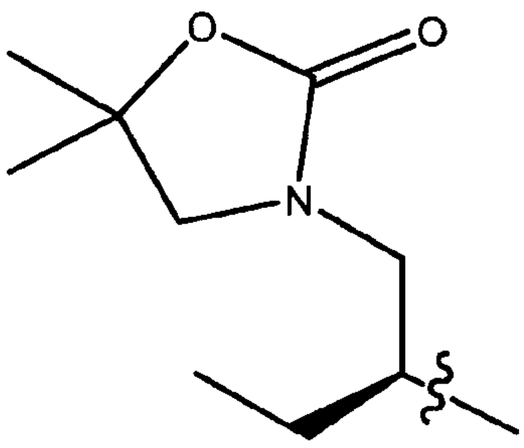
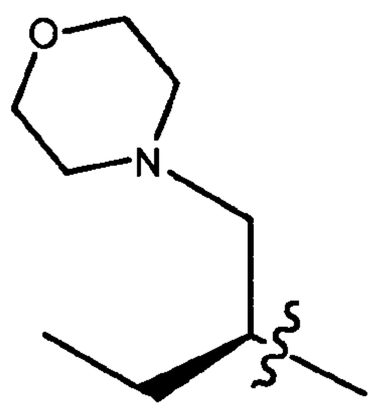
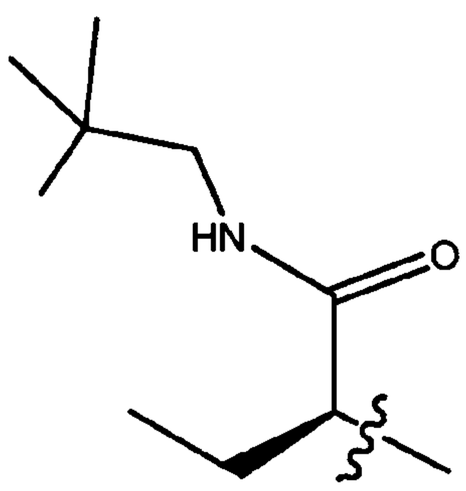
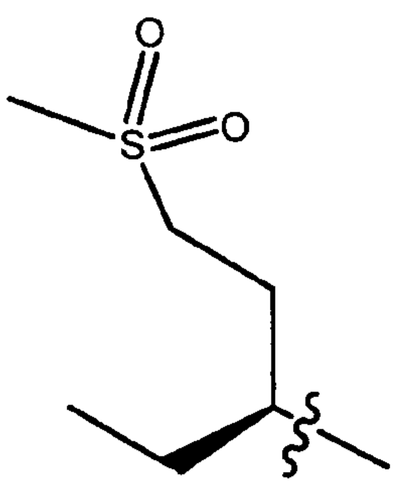
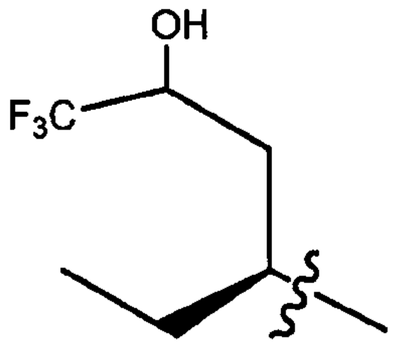
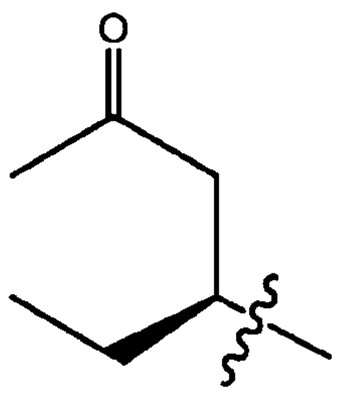
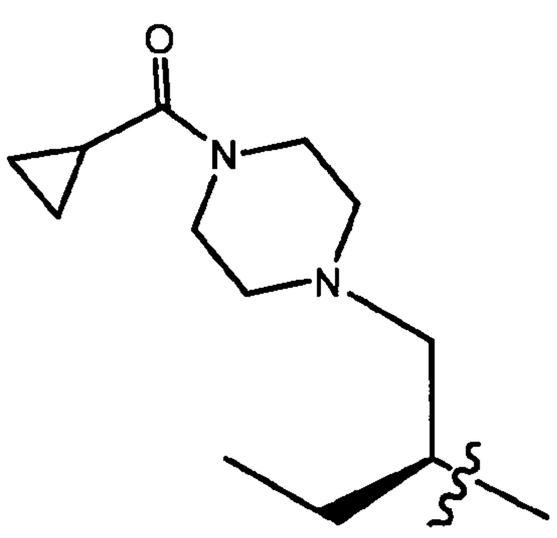
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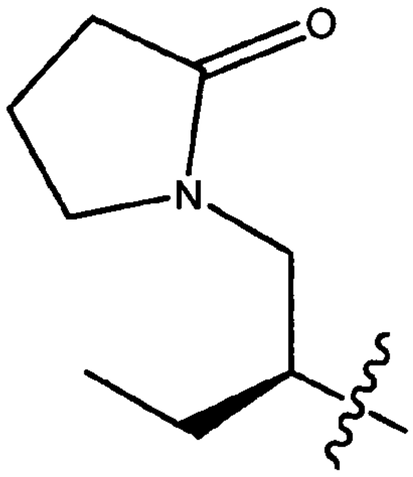
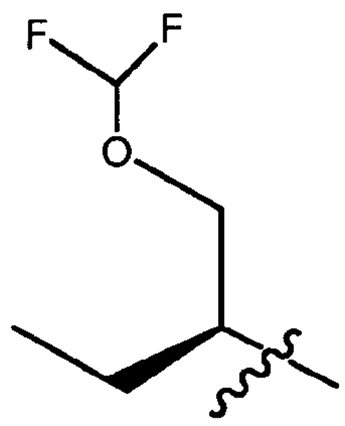
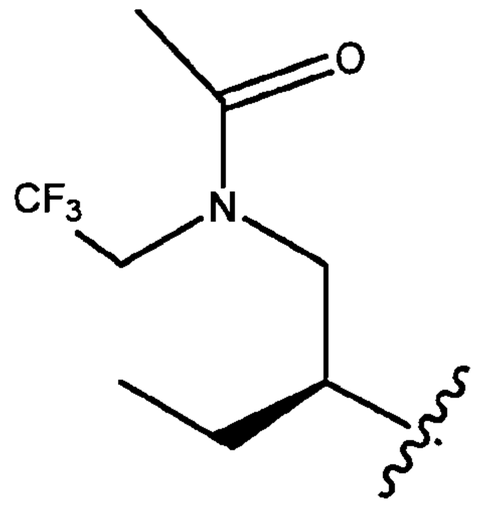
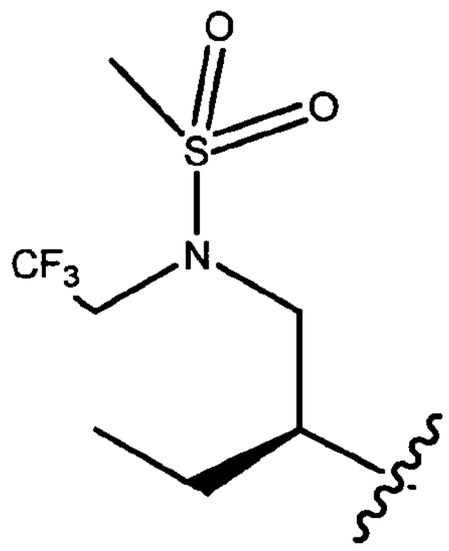
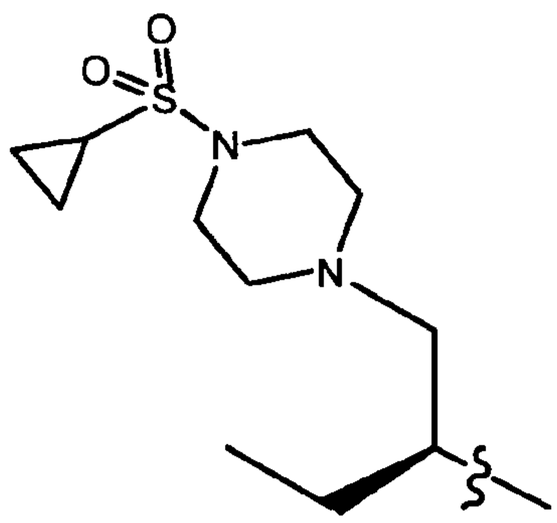
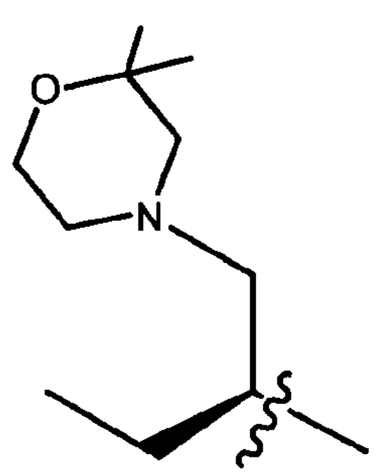
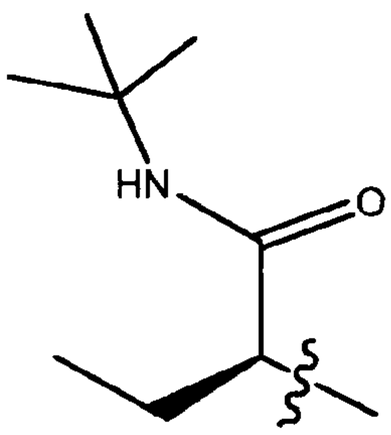
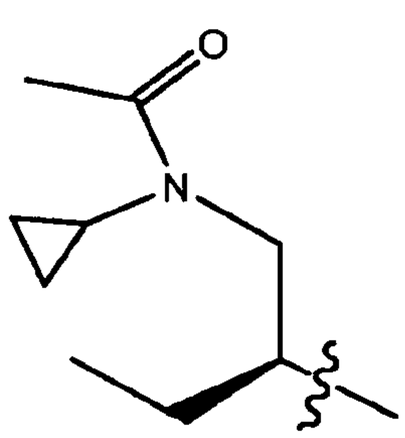
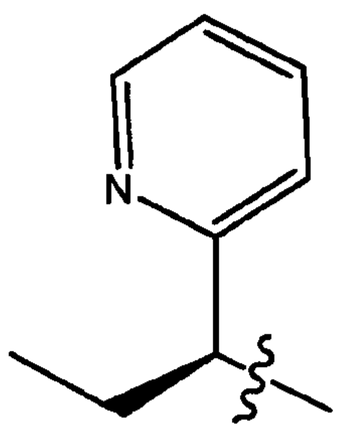
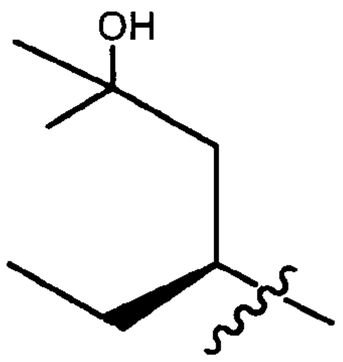
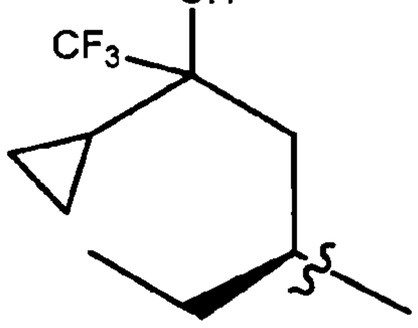
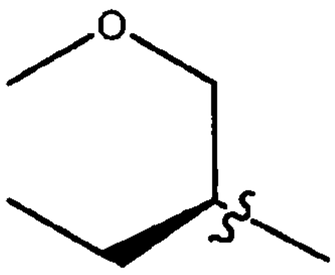
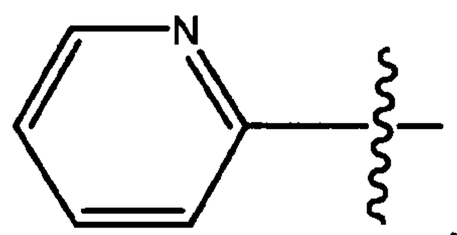

















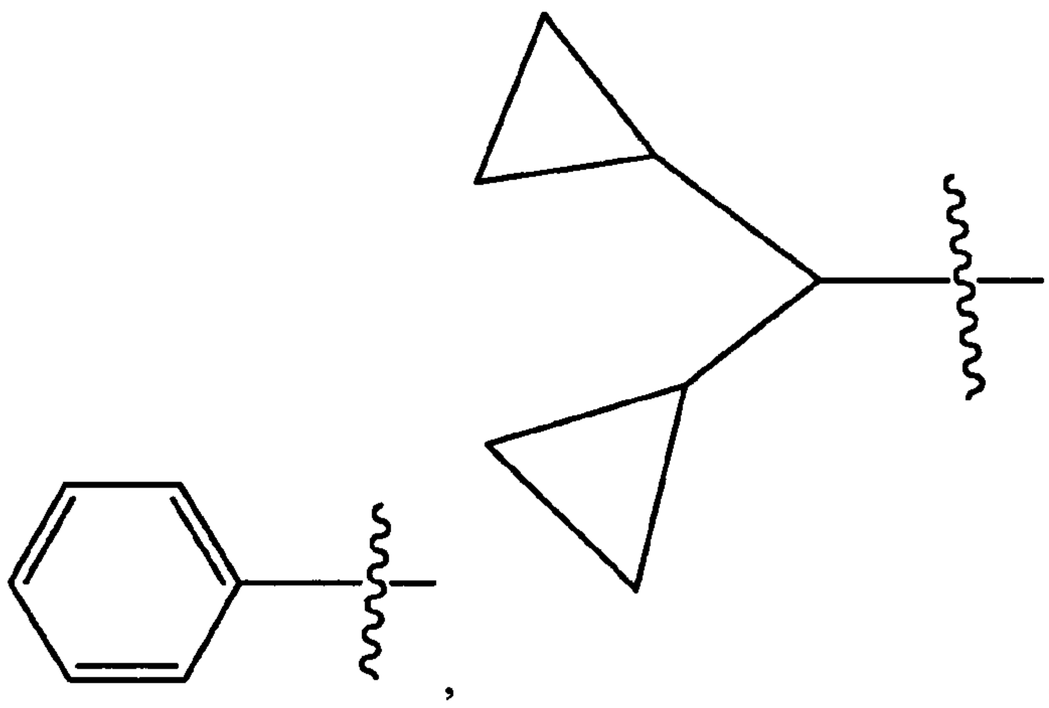
H_2O

In another aspect of embodiment 6 (embodiment 9), or the pharmaceutically acceptable salts thereof,

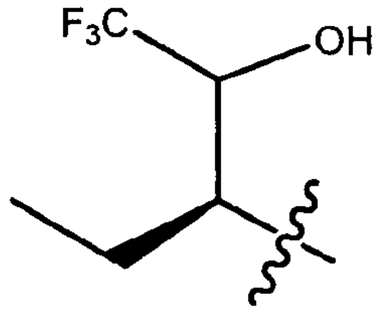
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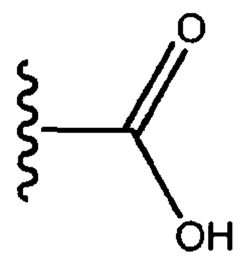


, , , or

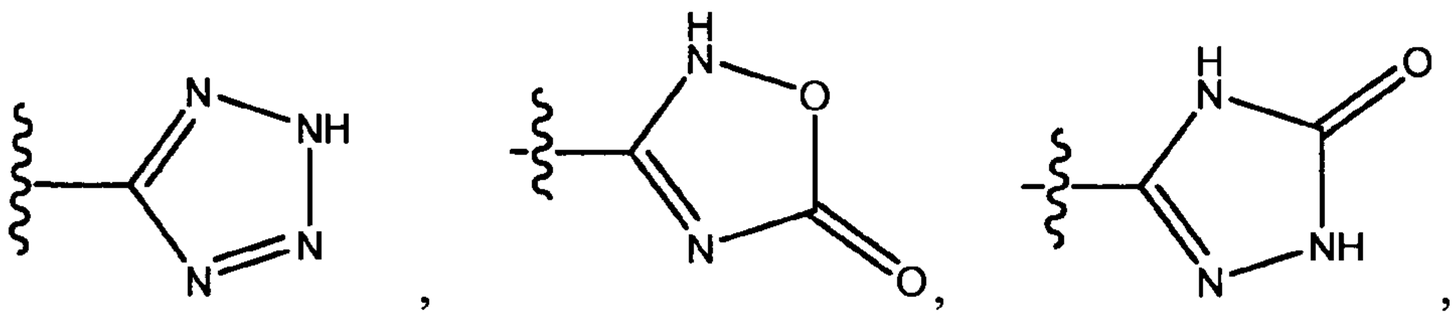


, any of which may be optionally substituted with one or more R^x groups as allowed by valence; and

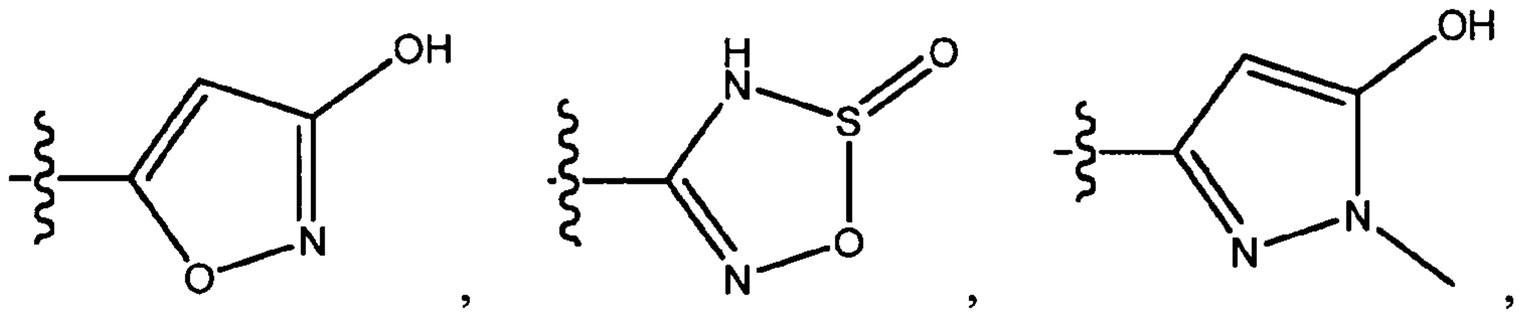
R^1 is



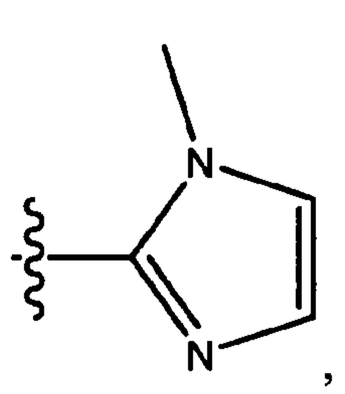
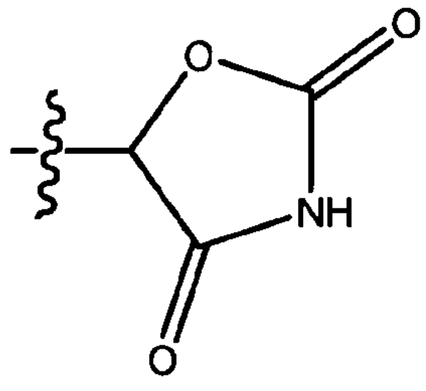
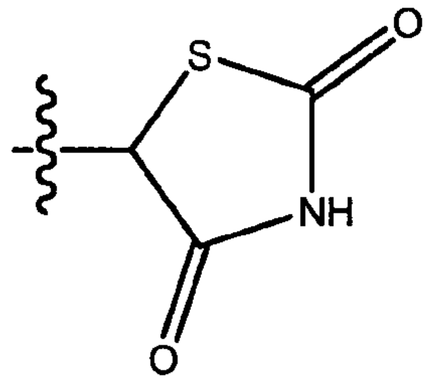
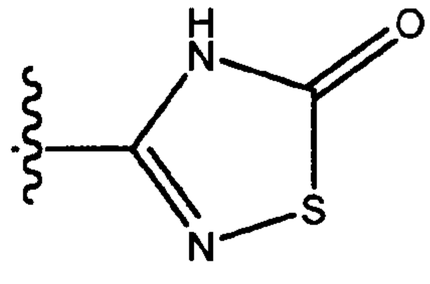
, or a heteroaryl or heterocycle selected from



, , ,

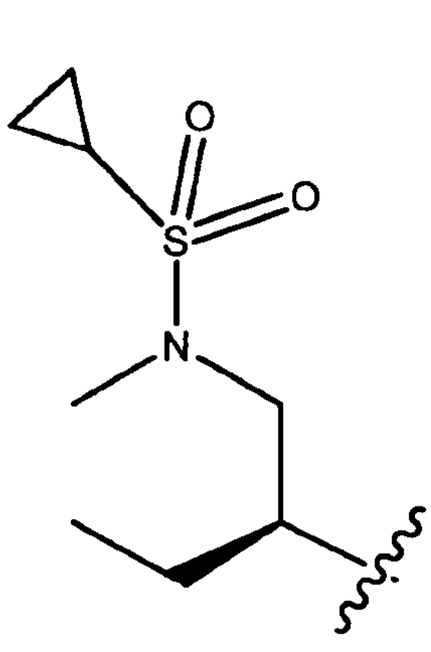
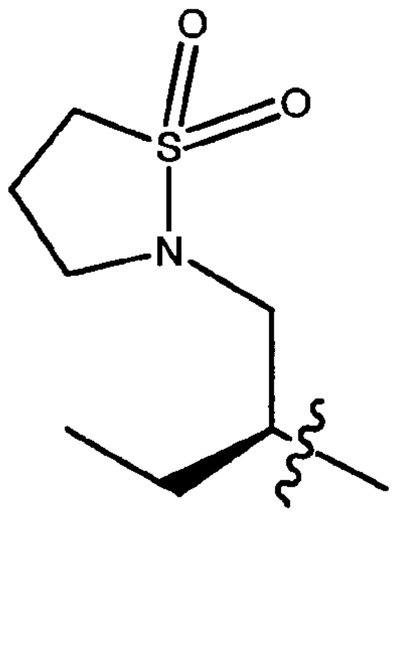
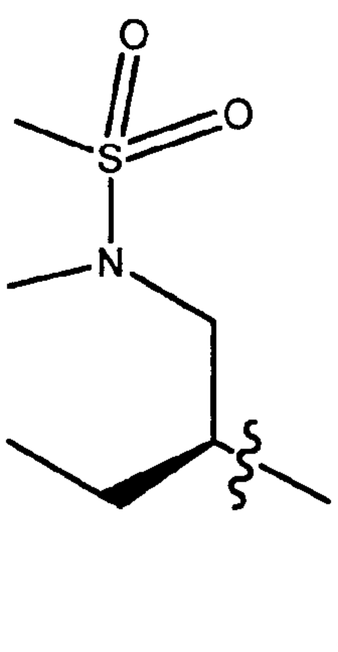
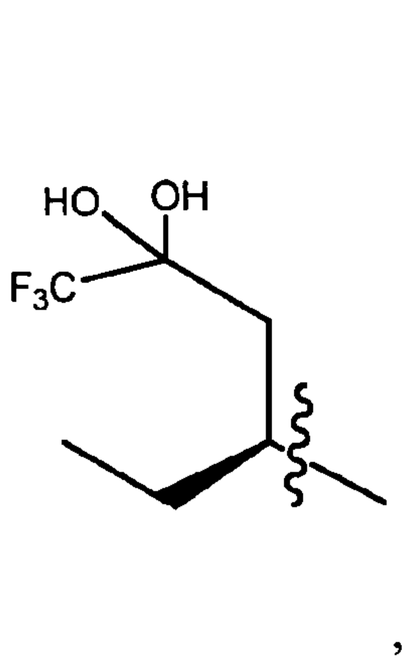
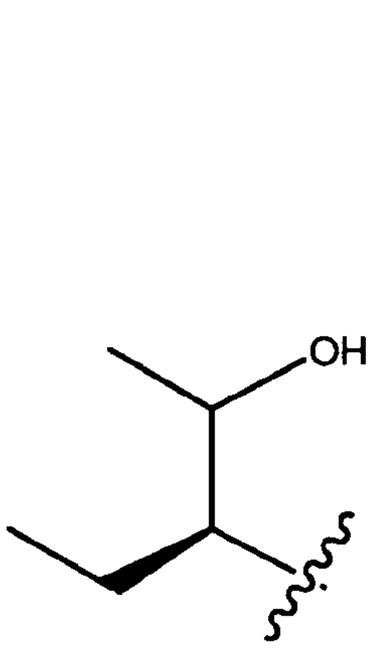
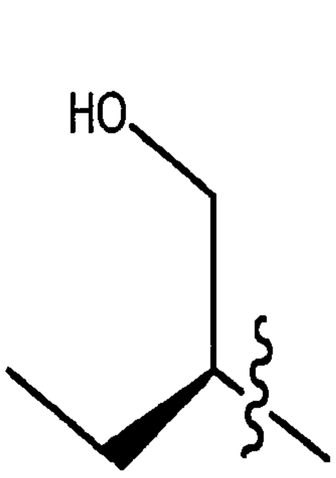
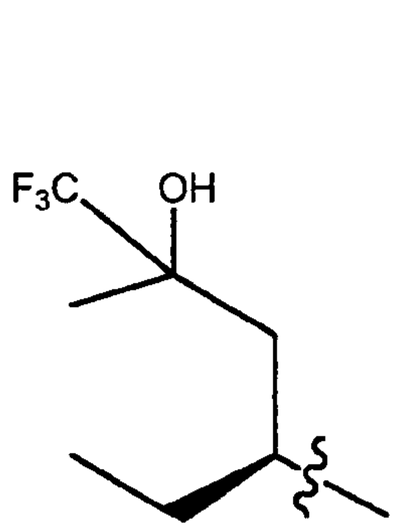
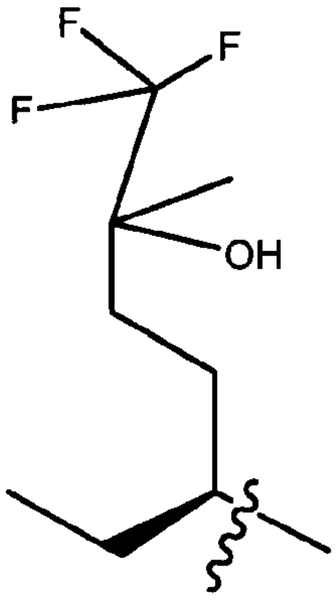


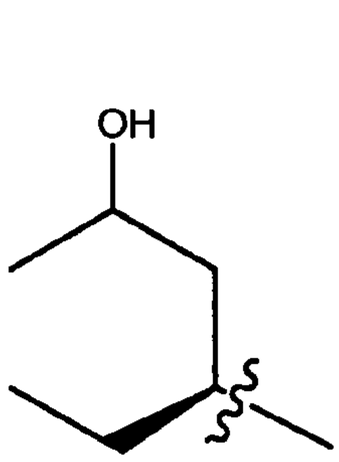
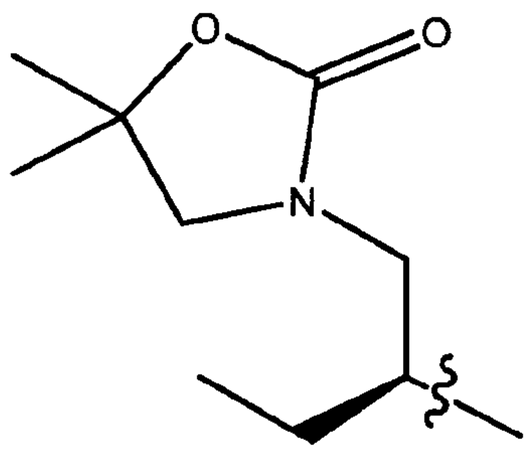
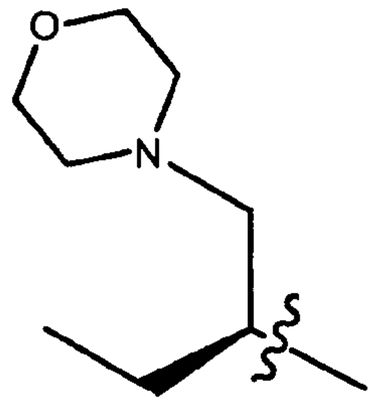
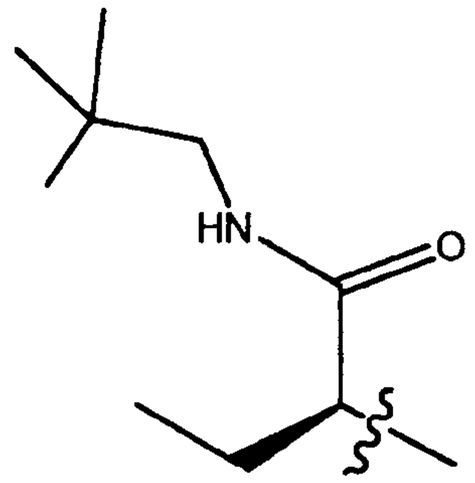
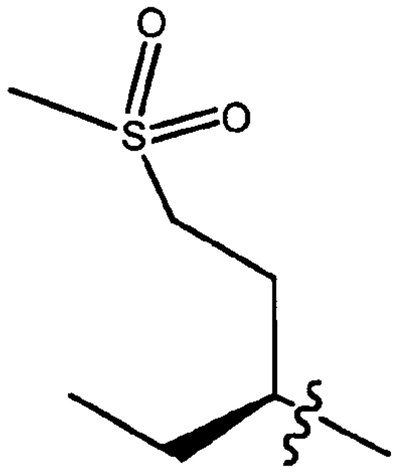
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or

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In another aspect of embodiment 6 (embodiment 10), or the pharmaceutically acceptable salts thereof,

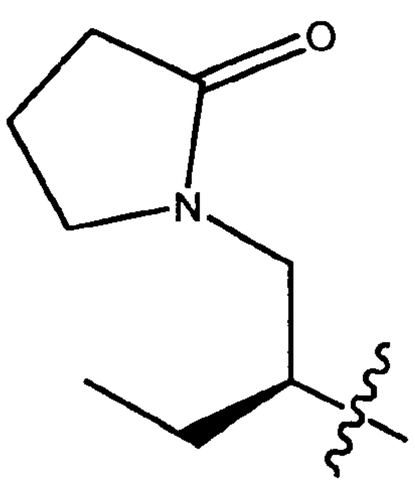
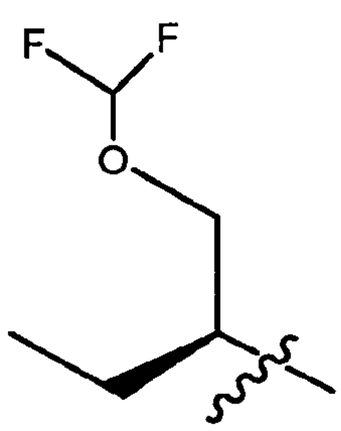
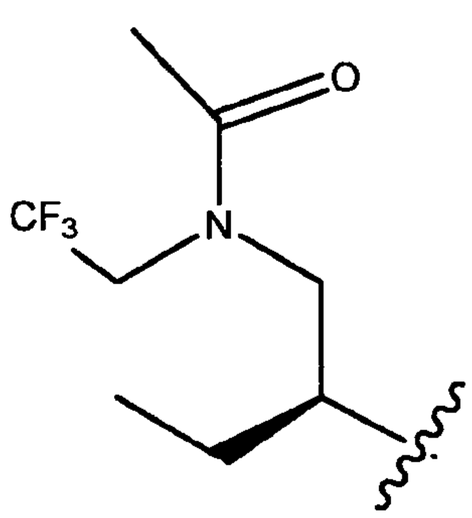
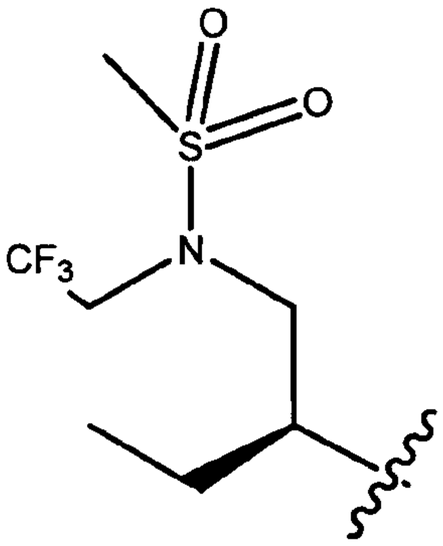
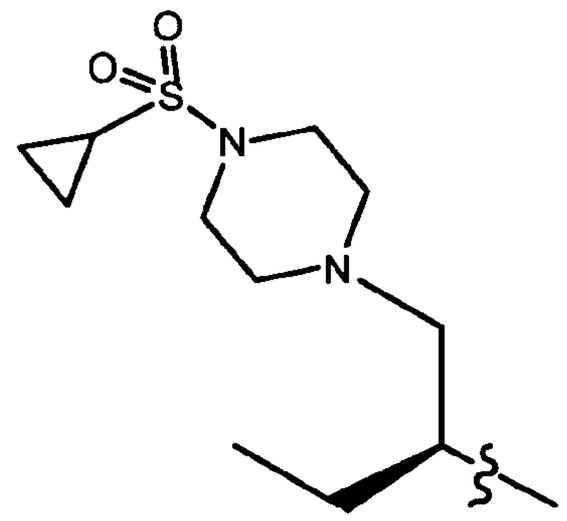
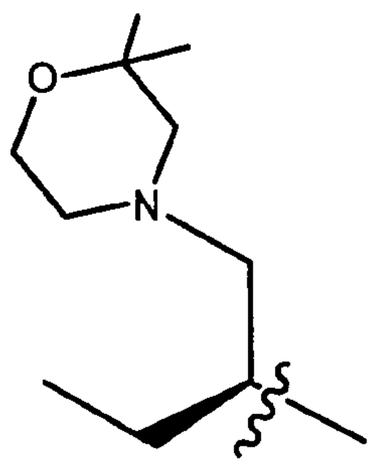
R^2 is selected from

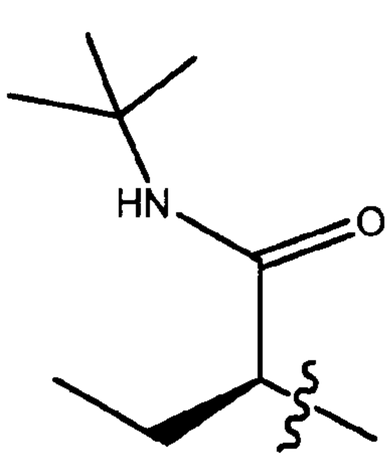
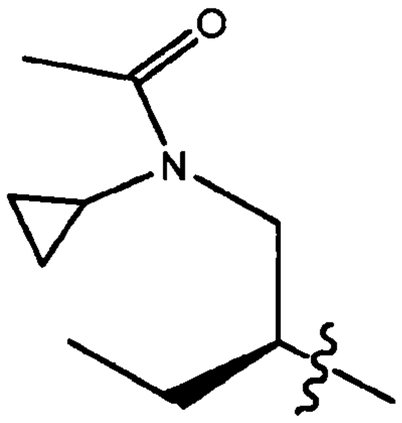
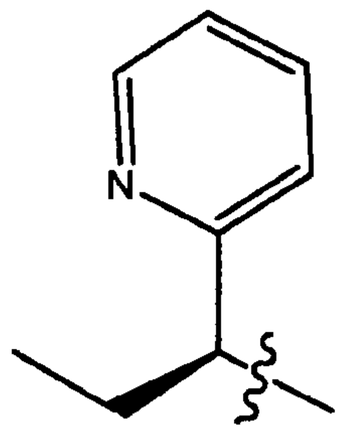
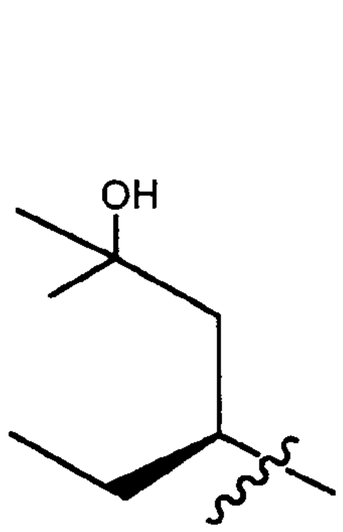
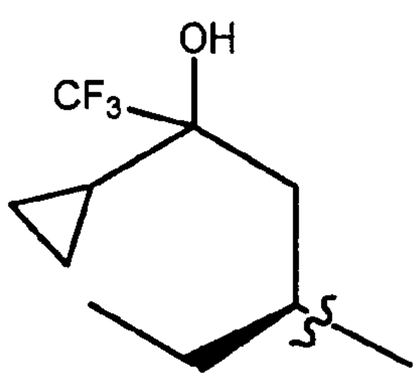
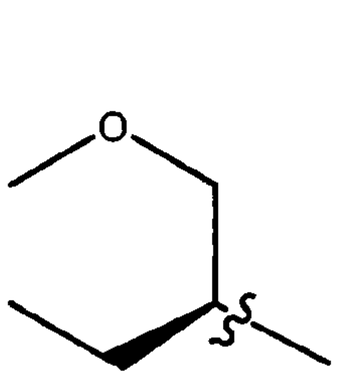
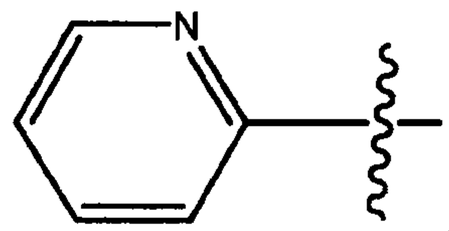
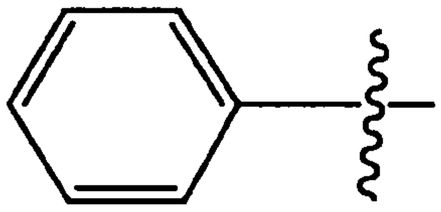
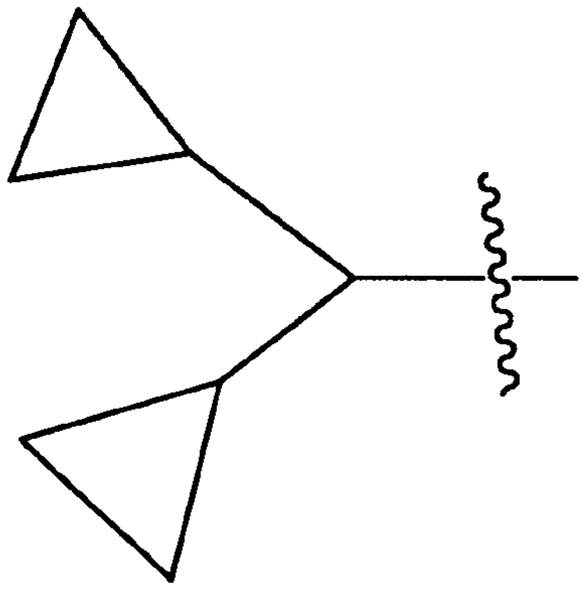
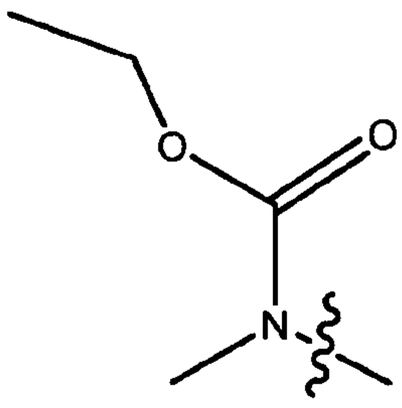
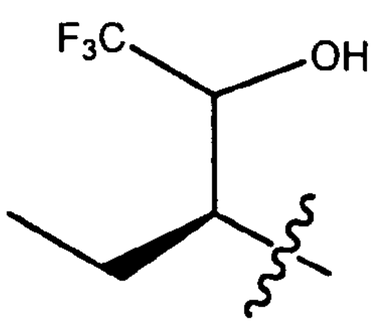

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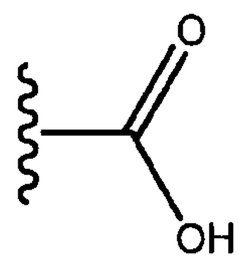
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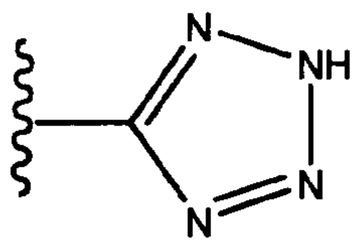












, any of which may be optionally substituted with one or more R^x groups as allowed by valence; and

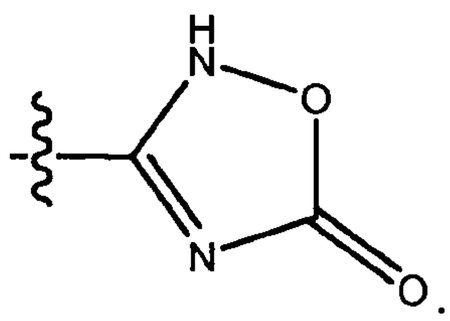
R^1 is



, or a heteroaryl or heterocycle selected from

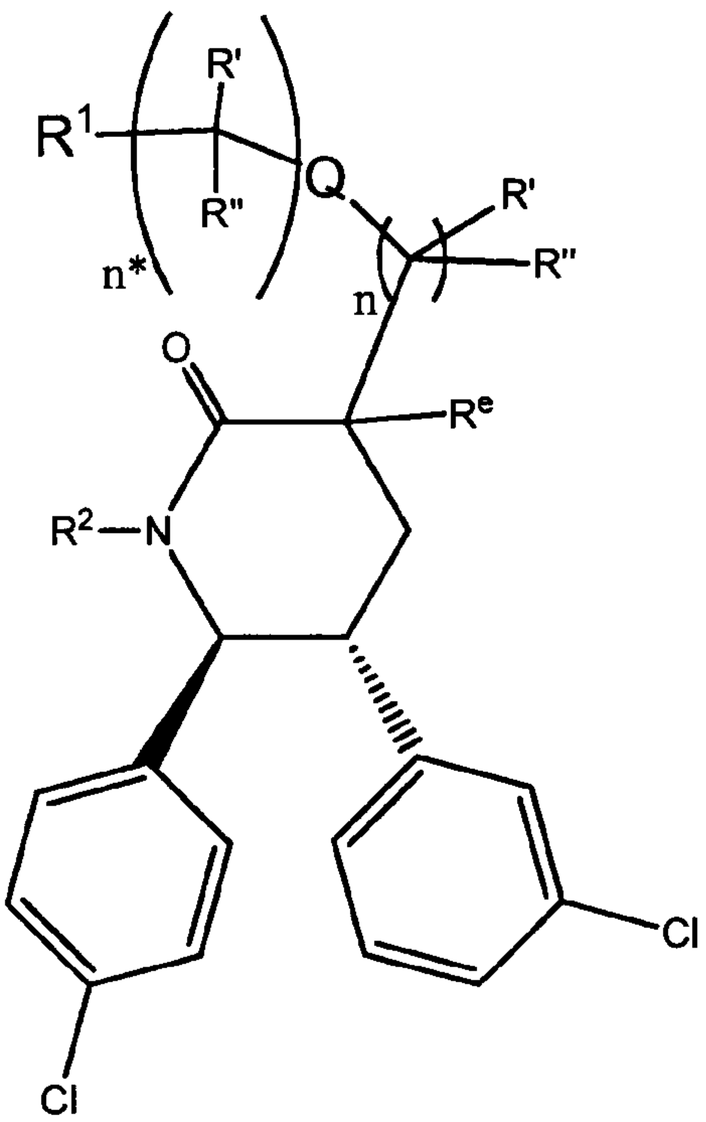


or



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In another embodiment, embodiment 11, the compounds of Aspect A have the structure of Formula ID

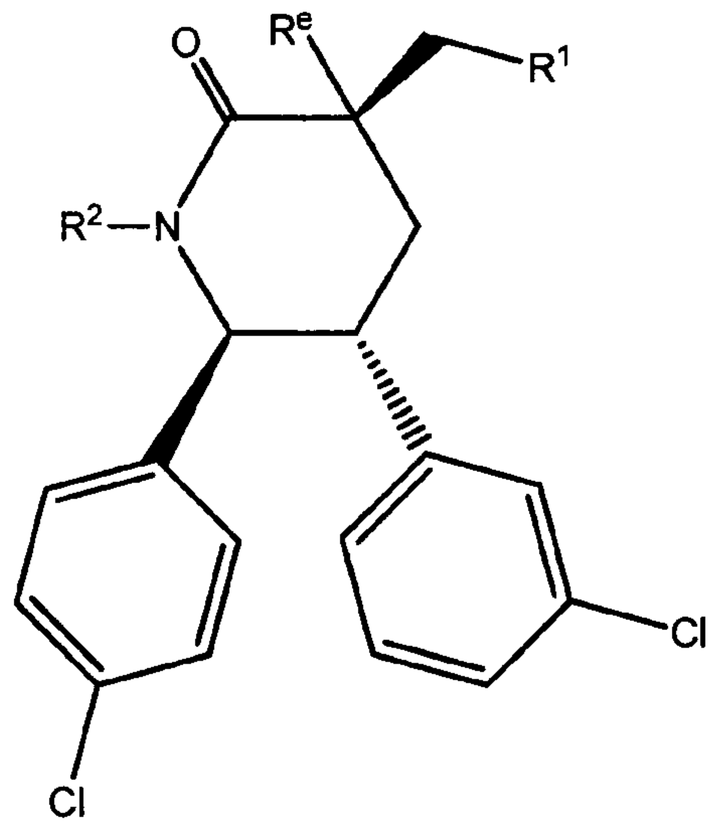


ID

or a pharmaceutically acceptable salt thereof.

In another aspect of embodiment 11 (embodiment 12), or the pharmaceutically acceptable salts thereof, Re is H or methyl or ethyl.

In another embodiment, embodiment 13, the compounds of Aspect A have the structure of Formula IE

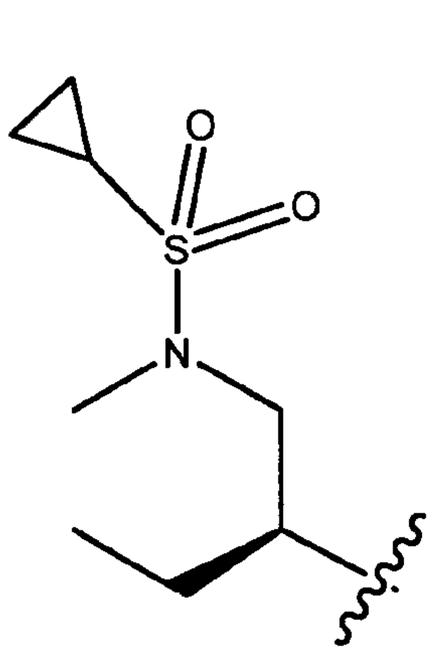
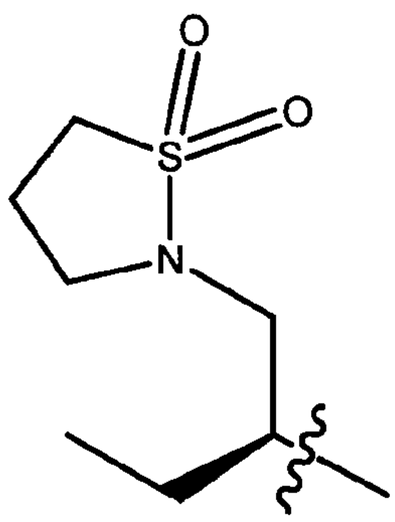
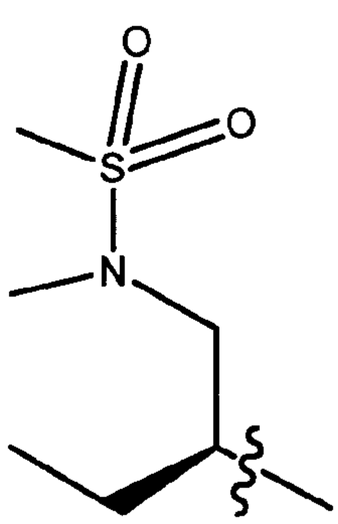
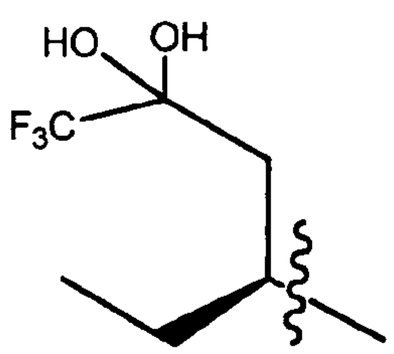


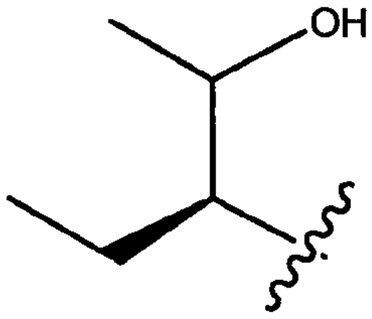
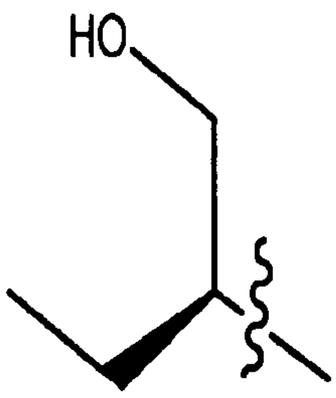
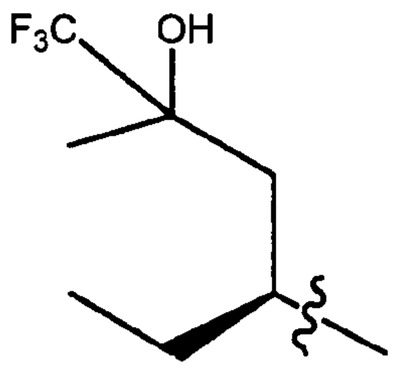
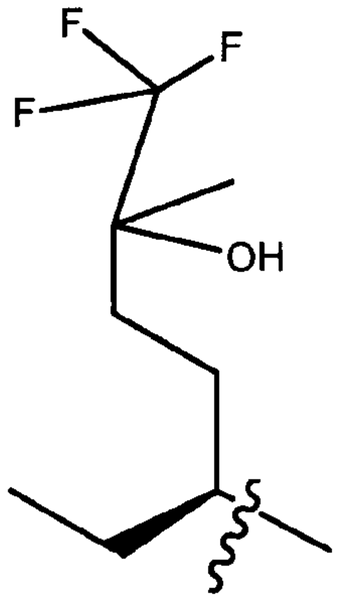
or the pharmaceutically acceptable salts thereof.

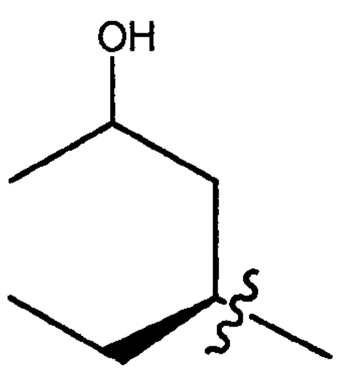
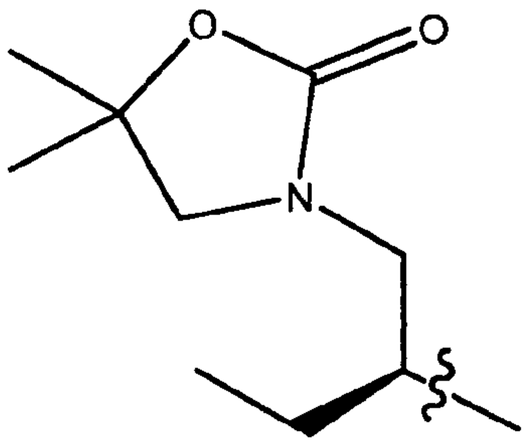
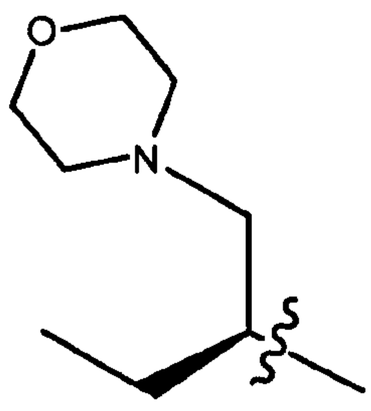
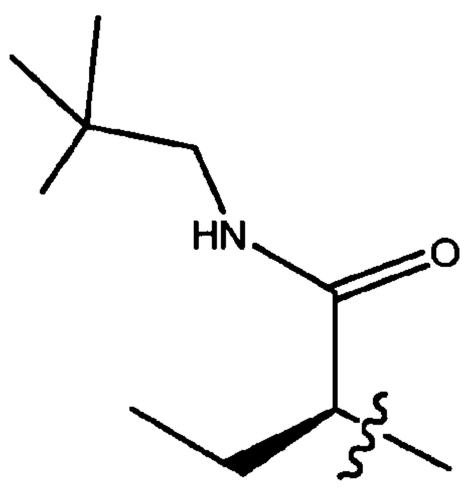
In another aspect of embodiment 13 (embodiment 14), or the pharmaceutically acceptable salts thereof, Re is H or methyl or ethyl.

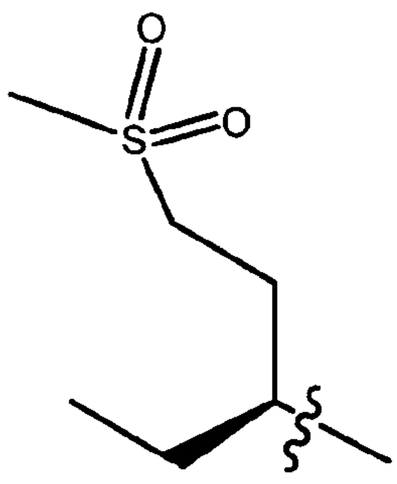
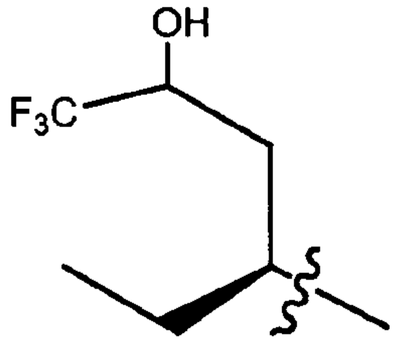
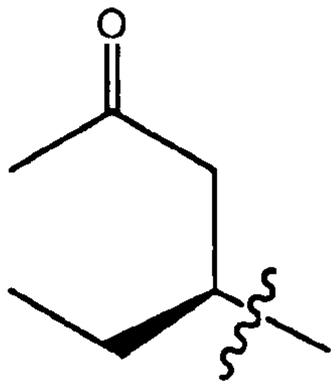
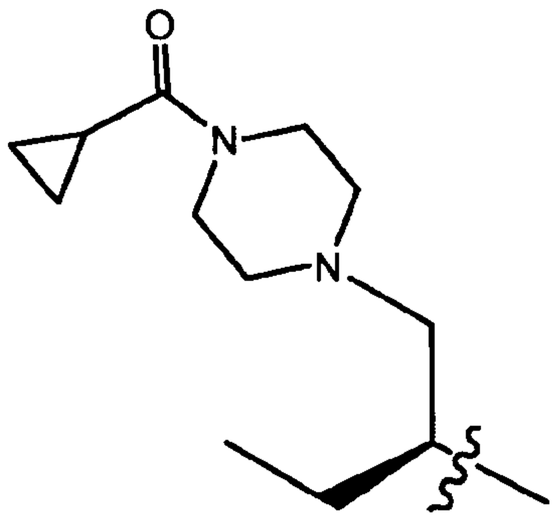
In another aspect of embodiment 13 (embodiment 15), or the pharmaceutically acceptable salts thereof, wherein

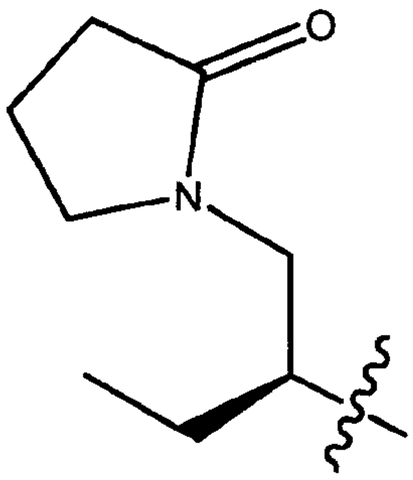
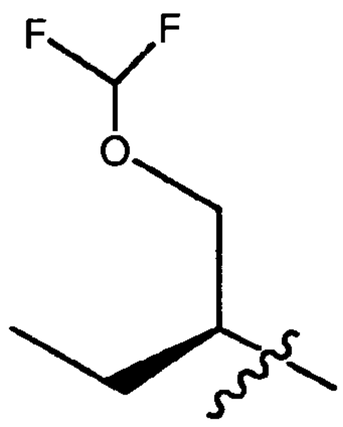
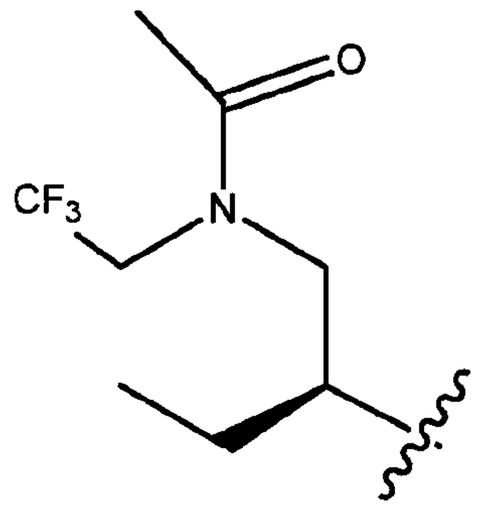
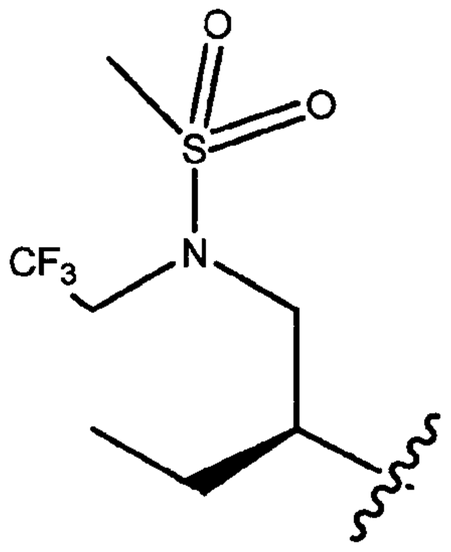
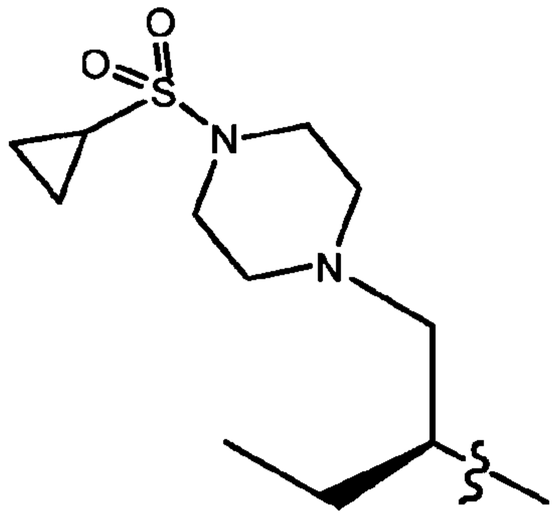
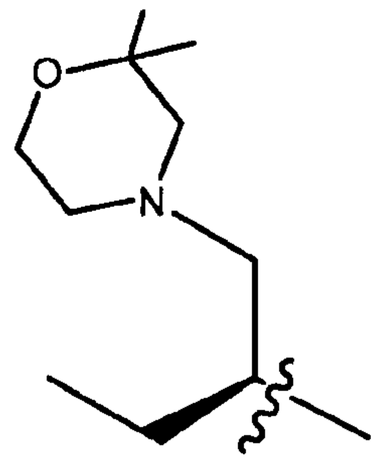
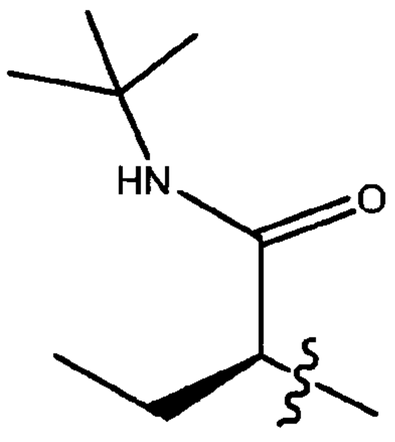
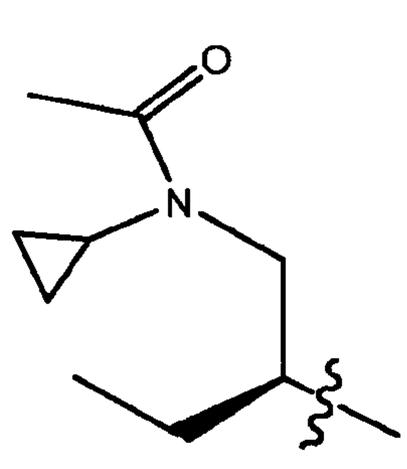
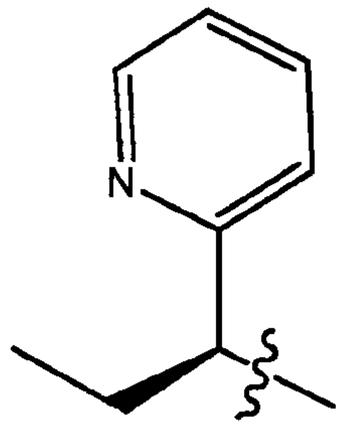
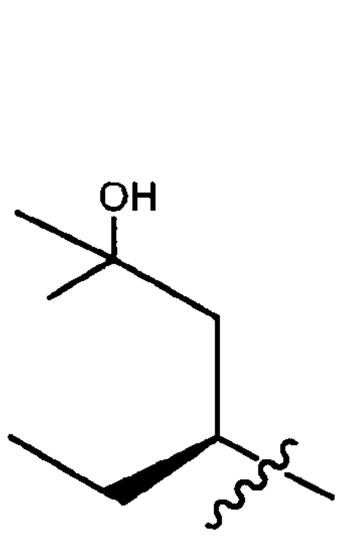
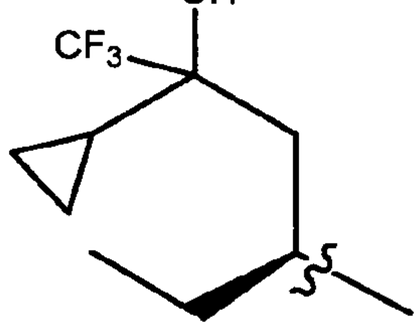
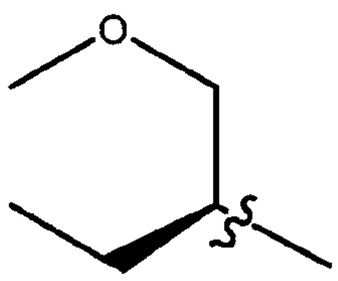
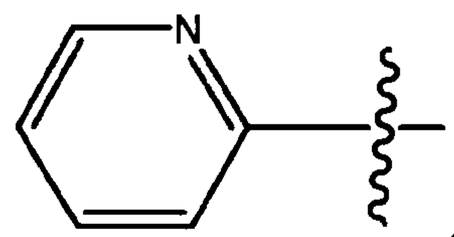
R^2 is selected from

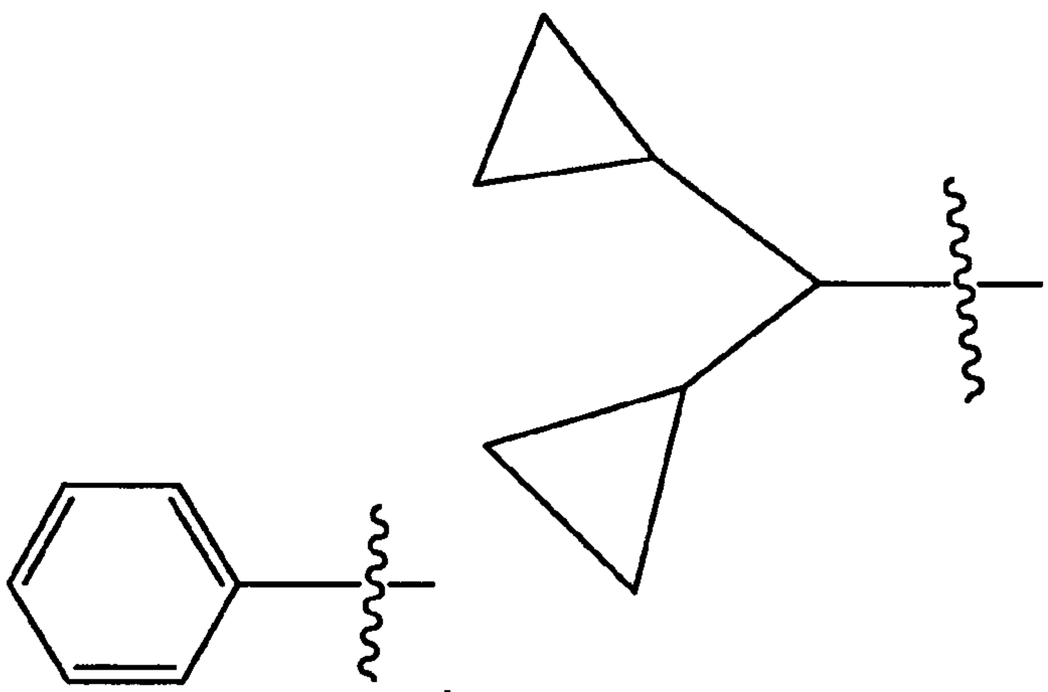
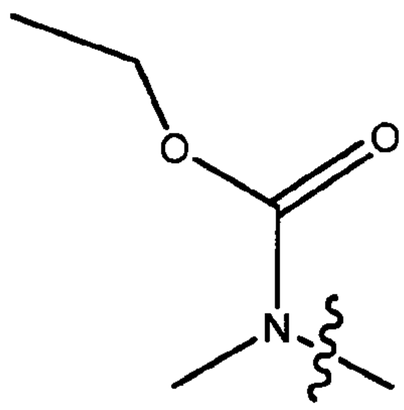
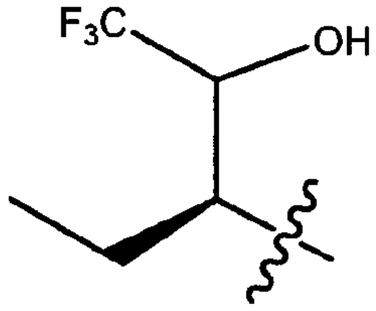

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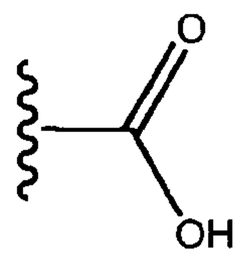
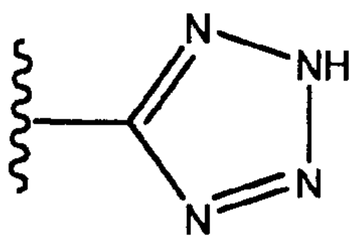
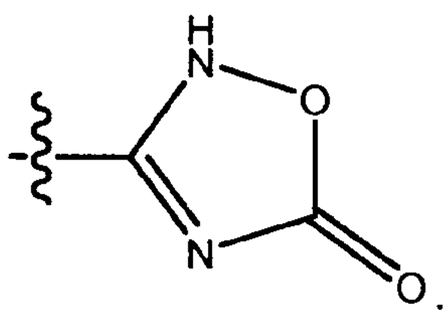

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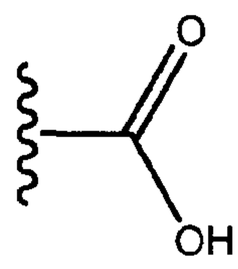
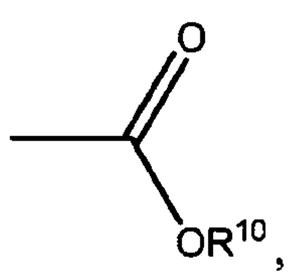

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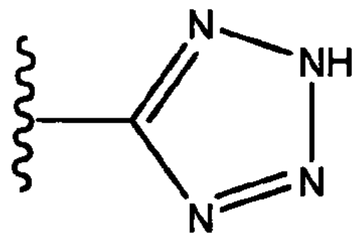
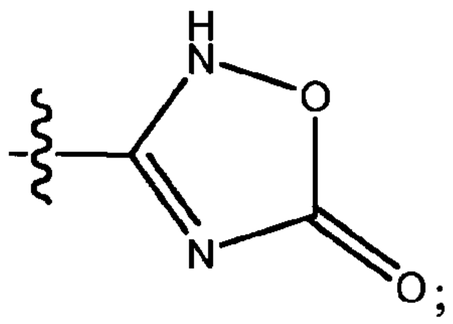

, , , or , any of which may be optionally substituted with one or more R^x groups as allowed by valence; and

R^1 is , or a heteroaryl or heterocycle selected from  or .

In another aspect of embodiment 13 (embodiment 16), or a pharmaceutically acceptable salt thereof,

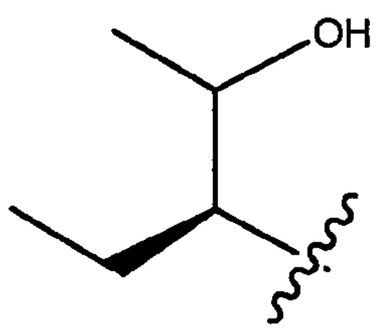
R^1 is , or ,

or a heteroaryl or heterocycle selected from

or

R^2 is

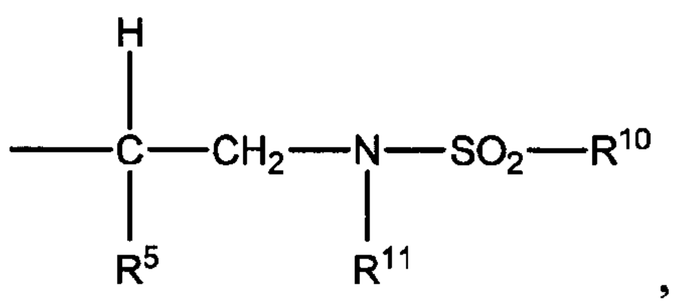
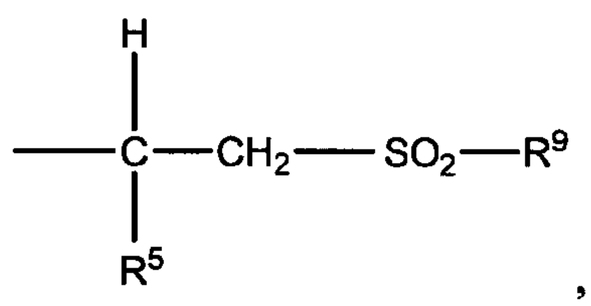
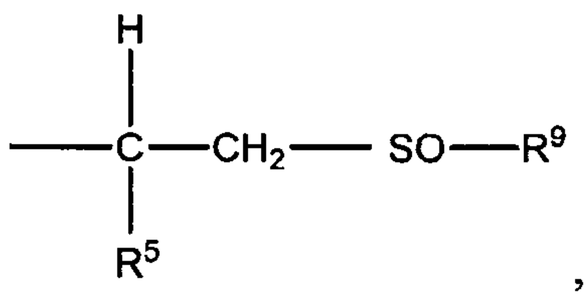
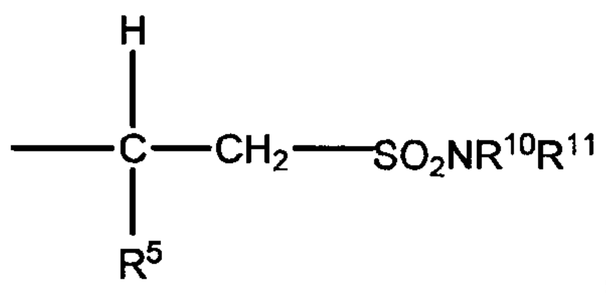
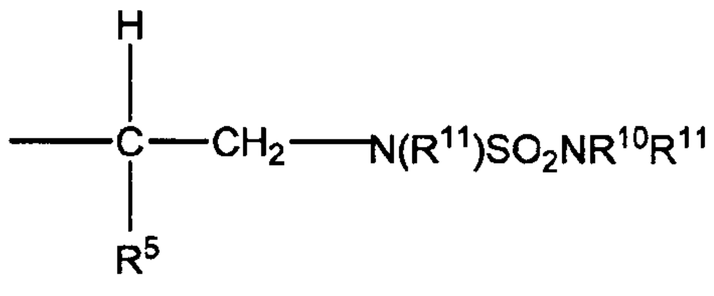


; and

R^e is methyl.

In another aspect of embodiment 13(embodiment 17), or a pharmaceutically acceptable salt thereof,:

R^2 is

;

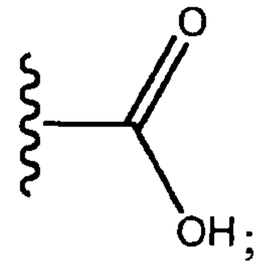
R^5 is cyclopropyl, or $C_{1\text{-}6}$alkyl;

R^9 is haloalkyl, haloalkoxy, $C_{1\text{-}6}$-alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$-alkynyl, $C_{3\text{-}8}$-cycloalkyl, ($C_{3\text{-}8}$-cycloalkyl)($C_{1\text{-}3}$alkyl), $C_{4\text{-}8}$-cycloalkenyl, aryl, heteroaryl, or heterocycloalkyl, or R^9 is haloalkyl, haloalkoxy, $C_{1\text{-}6}$-alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$-alkynyl, $C_{3\text{-}8}$-cycloalkyl, ($C_{3\text{-}8}$-cycloalkyl)($C_{1\text{-}3}$alkyl), $C_{4\text{-}8}$-cycloalkenyl, aryl, heteroaryl, or heterocyclo, any of which may be optionally independently substituted with one or more R^x groups as allowed by valence; and

R^{10} and R^{11} at each occurrence, respectively, are independently selected from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, or cycloalkylalkyl, any of which may be optionally substituted as allowed by valence with one or more R^x, or R^{10} and R^{11} may combine to form a heterocyclo ring optionally substituted with one or more R^x.

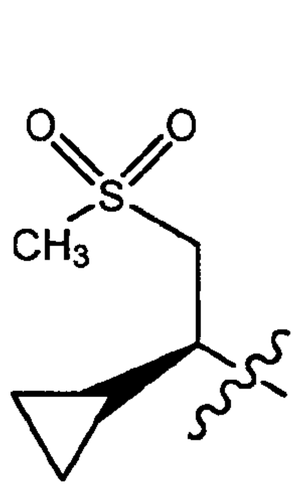
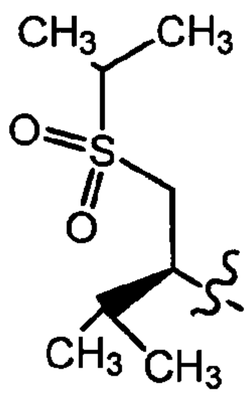
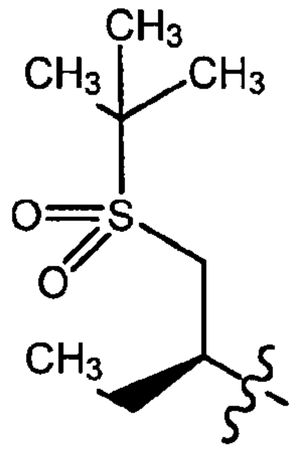
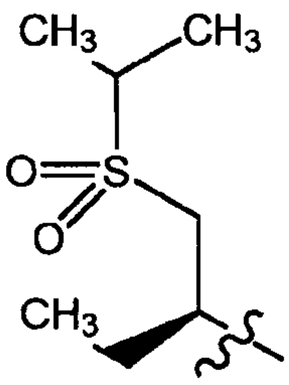
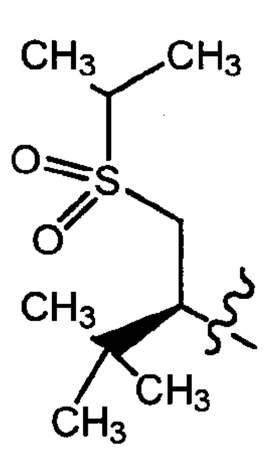
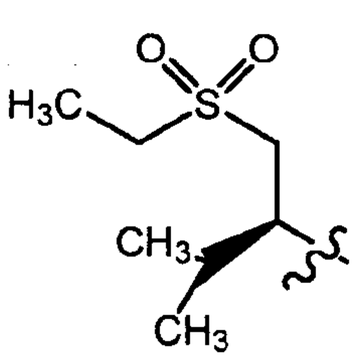
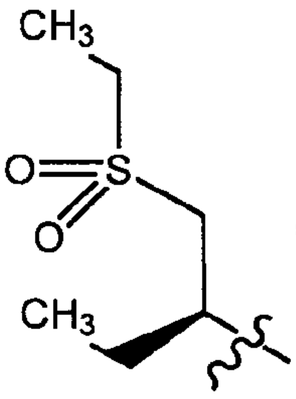
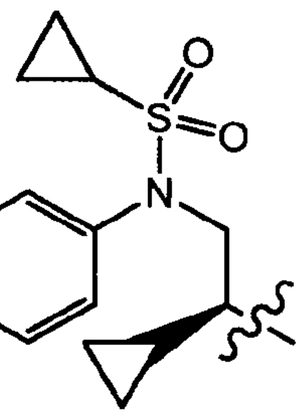
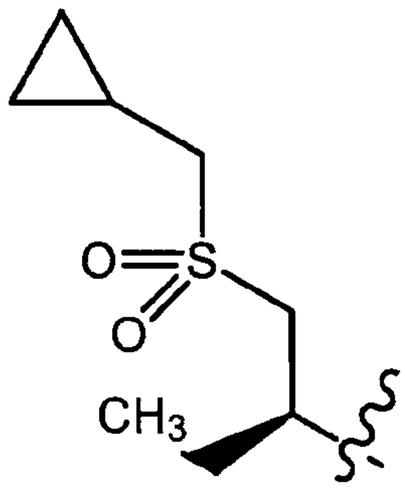
In another aspect of embodiment 13 (embodiment 18), or a pharmaceutically acceptable salt thereof,

R^1 is



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R^2 is


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, or

;

and R^e is methyl.

In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, selected from:

2-((3R,5R,6S)-1-((S)-1-tert-butoxy-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-1-((S)-1-tert-butoxy-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-ethoxy-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-ethoxy-4-methyl-1-oxopentan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-ethoxy-1-oxopentan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5S,6R)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-ethoxy-1-oxopentan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-2-tert-Butoxy-1-cyclopropyl-2-oxoethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-hydroxybutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-hydroxyethyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-methoxybutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(2-methoxyethoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-((1-cyanocyclopropyl)methoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-methoxybutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(2-methoxyethoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-1-((1-carbamoylcyclopropyl)methoxy)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid (isomer 1);

2-((3S,5R,6S)-1-((S)-1-((1-carbamoylcyclopropyl)methoxy)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid (isomer 2);

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(2-hydroxy-2-methylpropoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((3S)-1,1,1-trifluoro-2-hydroxypentan-3-yl)piperidin-3-yl)acetic acid (isomer 1);

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((3S)-1,1,1-trifluoro-2-hydroxypentan-3-yl)piperidin-3-yl)acetic acid (isomer 2);

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(ethylamino)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((S)-1-(2,2,2-trifluoroethylamino)butan-2-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((S)-1-(pyrrolidin-1-yl)butan-2-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((S)-1-(2-oxopyrrolidin-1-yl)butan-2-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1,1-dioxidothiomorpholino)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((S)-1-(thiazol-2-ylamino)butan-2-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-1-acetamidobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(methylsulfonamido) butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyanopentan-3-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(methylsulfonyl)pentan-3-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((S)-1-(pyridin-2-yl)pentan-3-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(ethylamino)-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-(ethylamino)-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(5-methyl-1,3,4-oxadiazol-2-yl)propyl)-2-oxopiperidin-3-yl)acetic;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclobutylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2-ethylbutyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopentylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((2,2-dimethylcyclopentyl)methyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclohexylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-propylpiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclobutylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isobutyl-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopentylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid;

Methyl 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetate;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetamide;

Ethyl 2-(2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetamido)acetate;

2-(2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetamido)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetohydrazide;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)-N-hydroxyacetamide;

(S)-Ethyl 2-((2S,3R,5R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-5-(2-(methylsulfonamido)-2-oxoethyl)-6-oxopiperidin-1-yl)butanoate;

(S)-Ethyl 2-((2S,3R,5R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-5-(2-((3-morpholinopropyl)amino)-2-oxoethyl)-6-oxopiperidin-1-yl)butanoate;

(3R,5R,6S)-3-((1H-Tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one;

(3R,5R,6S)-3-((1,3,4-oxadiazol-2-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one;

(3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)piperidin-2-one;

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)-N-(methylsulfonyl)acetamide;

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetamide;

(3S,5R,6S)-3-((1H-tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one;

(3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-((5-methylisoxazol-3-yl)methyl)piperidin-2-one;

2-((2'S,3'R,5'R)-6-chloro-3'-(3-chlorophenyl)-1'-(cyclopropylmethyl)-2,6'-dioxospiro[indoline-3,2'-piperidine]-5'-yl)acetic acid;

2-((2'R,3'S,5'S)-6-chloro-3'-(3-chlorophenyl)-1'-(cyclopropylmethyl)-2,6'-dioxospiro[indoline-3,2'-piperidine]-5'-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(5-chlorothiophen-2-yl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(5-chlorothiophen-2-yl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-ethoxy-1-oxobutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-1-tert-butoxy-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((R)-1-tert-butoxy-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethoxy)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid ;

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3-(2-(pyrrolidin-1-yl)ethyl)piperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-(2-morpholinoethyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-cyclobutyl-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-cyclopentyl-3-methyl-2-oxopiperidin-3-yl)acetic acid;

(3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-((5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)-1-(pentan-3-yl)piperidin-2-one;

5-(((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)methyl)-1,3,4-oxadiazol-2(3H)-one;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)-N-(trifluoromethylsulfonyl)acetamide;

(3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-((3-hydroxy-1H-pyrazol-5-yl)methyl)-3-methyl-1-(pentan-3-yl)piperidin-2-one;

(3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-((3-hydroxyisoxazol-5-yl)methyl)-3-methyl-1-(pentan-3-yl)piperidin-2-one;

5-(((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)methyl)oxazolidine-2,4-dione;

3-(((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)methyl)-1,2,4-oxadiazol-5(4H)-one;

3-(((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methyl-2-oxopiperidin-3-yl)methyl)-1,2,4-oxadiazol-5(4H)-one;

3-(((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)methyl)-1,2,4-thiadiazol-5(4H)-one;

3-(((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methyl-2-oxopiperidin-3-yl)methyl)-1,2,4-thiadiazol-5(4H)-one;

(3R,5R,6S)-3-((1H-Tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methylpiperidin-2-one;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid;

(3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-(methylsulfonylmethyl)-1-(pentan-3-yl)piperidin-2-one;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(2,2,2-trifluoroethylamino)butan-2-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(2,2-dimethylmorpholino)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((2S)-1-(2,6-dimethylmorpholino)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(4-(cyclopropylsulfonyl)piperazin-1-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(4-(methylsulfonyl)piperazin-1-yl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-1-(4-acetylpiperazin-1-yl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(4-(cyclopropanecarbonyl)piperazin-1-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
3-(((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)methyl)-1,2,4-oxadiazol-5(4H)-one;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(5,5-dimethyl-2-oxooxazolidin-3-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-1-((S)-1-(tert-butylamino)-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((1S,2R,3S)-2,3-dihydroxycyclopentyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((1R,2R,3S)-2,3-dihydroxycyclopentyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,3'S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1'-(2,2,2-trifluoroethyl)-1,3'-bipiperidin-3-yl)acetic acid;
2-((3R,3'R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1'-(2,2,2-trifluoroethyl)-1,3'-bipiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((1S,3S)-3-hydroxycyclopentyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((1S,3R)-3-hydroxycyclopentyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-tetrahydro-2H-pyran-3-yl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((R)-tetrahydro-2H-pyran-3-yl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pyrazin-2-yl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-methyl-1H-pyrazol-4-yl)-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pyrimidin-4-yl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2-chloropyrimidin-4-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pyrimidin-2-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(3-methylpyridin-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(4-methylpyridin-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(dicyclopropylmethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3S, 5R, 6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(dicyclopropylmethyl)-3-methyl-2-oxopiperidin-3-yl) acetic acid;

((3S,4R,6R)-4-(3-chlorophenyl)-3-(4-chlorophenyl)-1,1-dioxido-2-(2-propanyl)-1,2-thiazinan-6-yl)acetic acid;

((3S,4R,6S)-4-(3-chlorophenyl)-3-(4-chlorophenyl)-1,1-dioxido-2-(2-propanyl)-1,2-thiazinan-6-yl)acetic acid;

((3S,4R,6R)-4-(3-chlorophenyl)-3-(4-chlorophenyl)-6-methyl-1,1-dioxido-2-(2-propanyl)-1,2-thiazinan-6-yl)acetic acid;

((3S,4R,6S)-4-(3-chlorophenyl)-3-(4-chlorophenyl)-6-methyl-1,1-dioxido-2-(2-propanyl)-1,2-thiazinan-6-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(5-chloropyridin-2-yl)-3-methyl-1-((S)-1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-Chlorophenyl)-6-(5-chloropyridin-2-yl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(5-chloropyridin-2-yl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-Chlorophenyl)-6-(5-chloropyridin-2-yl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-1-tert-butoxy-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(5-chloropyridin-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid; or

2-((3R,5S,6S)-1-((S)-1-tert-butoxy-1-oxobutan-2-yl)-6-(4-chlorophenyl)-5-(4-chloropyridin-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.

In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, selected from:

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;
2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)propanoic acid;
(S)-*tert*-butyl 2-((3R,5R,6S)-3-((1H-tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoate;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(methylsulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-5-oxohexan-3-yl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-5-hydroxy-5-methylhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((3S,5S)-6,6,6-trifluoro-5-hydroxy-5-methylhexan-3-yl)piperidin-3-yl)acetic acid (isomer 1);
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((3S,5R)-6,6,6-trifluoro-5-hydroxy-5-methylhexan-3-yl)piperidin-3-yl)acetic acid (isomer 2);
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylmethylsulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((3S)-5-cyclopropyl-6,6,6-trifluoro-5-hydroxyhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-6-hydroxy-6-methylheptan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-6,6,6-trifluoro-5,5-dihydroxyhexan-3-yl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((3S)-7,7,7-trifluoro-6-hydroxy-6-methylheptan-3-yl)piperidin-3-yl)acetic acid (isomer 1);
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((3S)-7,7,7-trifluoro-6-hydroxy-6-methylheptan-3-yl)piperidin-3-yl)acetic acid (isomer 2);
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-7-hydroxy-7-methyloctan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(N-cyclopropylmethylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((3S)-6,6,6-trifluoro-5-hydroxyhexan-3-yl)piperidin-3-yl)acetic acid (isomer 1);

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((3S)-6,6,6-trifluoro-5-hydroxyhexan-3-yl)piperidin-3-yl)acetic acid (isomer 2);

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((3S)-5-hydroxyhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid (isomer 1);

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((3S)-5-hydroxyhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid (isomer 2);

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(N-(2,2,2-trifluoroethyl)methylsulfonamido)butan-2-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1,1-dioxidoisothiazolidin-2-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((3S,4R)-5-hydroxy-4,5-dimethylhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((3S,4S)-5-hydroxy-4,5-dimethylhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-5-cyano-5-methylhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-2-oxopentan-3-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((2S,3S)-2-hydroxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((2S,3S)-2-methoxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((2R,3S)-2-hydroxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((2S,3R)-2-hydroxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((2R,3R)-2-hydroxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-2-hydroxy-2-methylpentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((3S,4S)-4-hydroxyhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((3S,4R)-4-hydroxyhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-methoxybutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(3S)-1,1,1-trifluoro-2-hydroxy-2-methylpentan-3-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetamide;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-(methylsulfonyl)acetamide;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-(3-hydroxypropyl)acetamide;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-(2-hydroxyethyl)acetamide;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-hydroxyacetamide;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-methoxyacetamide;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-((R)-2,3-dihydroxypropyl)acetamide;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-((S)-2,3-dihydroxypropyl)acetamide;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-cyanoacetamide;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-(2-(dimethylamino)ethyl)acetamide;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-(3,4-dihydroxybutyl)acetamide;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropanesulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

(S)-2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)propanoic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(3S)-2-(cyclopropanesulfonamido)pentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid (isomer 1);

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(3S)-2-(cyclopropanesulfonamido)pentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid (isomer 2);

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((2R,3S)-2-(1-methylethylsulfonamido)pentan-3-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(neopentylamino)-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(N-(2,2,2-trifluoroethyl)acetamido)butan-2-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1,1-dimethylethylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(N,2-dimethylpropan-2-ylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1-methylethylsulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(N-ethylpropan-2-ylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-hydroxybutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(trifluoromethylsulfonamido)butan-2-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(4-chlorophenylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(4-methylphenylsulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(2-chlorophenylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(2-methylphenylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(4-methoxyphenylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(phenylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1-methylcyclopropanesulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1,1-dioxidobenzo[d]isothiazol-2(3H)-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(3,3-dimethyl-1,1-dioxidobenzo[d]isothiazol-2(3H)-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(pyridine-3-sulfonamido)butan-2-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(4-cyanophenylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(3-cyanophenylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(pyridine-2-sulfonamido)butan-2-yl)piperidin-3-yl)acetic acid.

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(N,1-dimethylcyclopropanesulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

3-((3S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)propanoic acid;

3-((3R,5S,6R)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)propanoic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methoxy-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-6-methyl-4-oxoheptan-3-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(ethylsulfonyl)pentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)pentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethylsulfonyl)pentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(2-oxopyrrolidin-1-yl)butan-2-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-1-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-((S)-3-methylmorpholino)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-((R)-3-methylmorpholino)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(thiomorpholino-1,1-dioxide)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(3,3-difluoroazetidin-1-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((2S)-1-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(3,3-dimethylmorpholino)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(3-hydroxy-3-(trifluoromethyl)azetidin-1-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(methyl(oxetan-3-yl)amino)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(2-oxooxazolidin-3-yl)butan-2-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(2-oxopyridin-1(2H)-yl)butan-2-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(2-oxo-5-(trifluoromethyl)pyridin-1(2H)-yl)butan-2-yl)piperidin-3-yl)acetic acid;

(3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(pyridin-3-yloxy)butan-2-yl)piperidin-2-one;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((1S)-1-(tetrahydrofuran-2-yl)propyl)piperidin-3-yl)acetic acid (isomer 1);

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((1S)-1-(tetrahydrofuran-2-yl)propyl)piperidin-3-yl)acetic acid (isomer 2);

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((1S)-1-5-oxotetrahydrofuran-2-yl)propyl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((1S)-1-(tetrahydro-2H-pyran-2-yl)propyl)piperidin-3-yl)acetic acid (isomer 1);

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((1S)-1-(tetrahydro-2H-pyran-2-yl)propyl)piperidin-3-yl)acetic acid (isomer 2);

2-((3R,5R,6S)-1-((R)-1-(benzo[d]thiazol-2-yl)propyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-1-(benzo[d]thiazol-2-yl)propyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(3-methylisoxazol-5-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((R)-1-(3-methylisoxazol-5-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(6-chloropyridin-2-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-(6-chloropyridin-2-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(pyridin-2-yl)propyl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((R)-1-(pyridin-2-yl)propyl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(pyridin-2-yl)butyl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((R)-1-(pyridin-2-yl)butyl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-2-cyclopropyl-1-(pyridin-2-yl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((R)-2-cyclopropyl-1-(pyridin-2-yl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(pyridin-3-yl)propyl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((R)-1-(pyridin-3-yl)propyl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(pyrazin-2-yl)propyl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((R)-1-(pyrazin-2-yl)propyl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(pyrimidin-2-yl)propyl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((R)-1-(pyrimidin-2-yl)propyl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(6-methylpyridin-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((R)-1-(6-methylpyridin-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(pyridin-4-yl)propyl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((R)-1-(pyridin-4-yl)propyl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(6-(trifluoromethyl)pyridin-2-yl)propyl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((R)-1-(6-(trifluoromethyl)pyridin-2-yl)propyl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-1-((S)-1-(6-bromopyridin-2-yl)propyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-1-((R)-1-(6-bromopyridin-2-yl)propyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(thiazol-2-yl)propyl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((R)-1-(thiazol-2-yl)propyl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(6-cyclopropylpyridin-2-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-(6-cyclopropylpyridin-2-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-3,3,3-trifluoro-1-(pyridin-2-yl)propyl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((R)-3,3,3-trifluoro-1-(pyridin-2-yl)propyl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-2-methyl-1-(pyridin-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((R)-2-methyl-1-(pyridin-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;

(3R,5R,6S)-3-((1H-tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(pentan-3-yl)piperidin-2-one;

(3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-((R)-2,3-dihydroxypropyl)-1-((2S,3S)-2-hydroxypentan-3-yl)-3-methylpiperidin-2-one;

(3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-((S)-2,3-dihydroxypropyl)-1-((2S,3S)-2-hydroxypentan-3-yl)-3-methylpiperidin-2-one;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-hydroxybutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)cyclopropanecarboxylic acid;

2-((3R,5R,6S)-1-((S)-2-(tert-Butoxy)-1-cyclopropyl-2-oxoethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-ethoxy-2-oxoethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-hydroxyethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((1S,2S)-1-cyclopropyl-2-hydroxybutyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((1S,2R)-1-cyclopropyl-2-hydroxybutyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-methylcyclopropanesulfonamido)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-2-(cyclopropanesulfonamido)-1-cyclopropylethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(ethylsulfonamido)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-methylcyclopropanesulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((1S,2R)-1-cyclopropyl-2-hydroxypropyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((1S,2S)-1-cyclopropyl-2-hydroxypropyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(1-methylethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-cyclopropyl-2-(N-methylcyclopropanesulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((2S,3S)-2-hydroxy-4-methylpentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-cyclopropyl(pyridin-2-yl)methyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid; or
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((R)-cyclopropyl(pyridin-2-yl)methyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.

In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, selected from:
2-(1-(1-tert-butoxy-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-ethoxy-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-ethoxy-4-methyl-1-oxopentan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-ethoxy-1-oxopentan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(1-(2-tert-Butoxy-1-cyclopropyl-2-oxoethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-hydroxybutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-hydroxyethyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(cyclopropylmethoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-methoxybutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(2-methoxyethoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-((1-cyanocyclopropyl)methoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(cyclopropylmethoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-methoxybutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(2-methoxyethoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(1-(1-((1-carbamoylcyclopropyl)methoxy)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(2-hydroxy-2-methylpropoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-(1,1,1-trifluoro-2-hydroxypentan-3-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(ethylamino)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-(1-(2,2,2-trifluoroethylamino)butan-2-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-(1-(pyrrolidin-1-yl)butan-2-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-(1-(2-oxopyrrolidin-1-yl)butan-2-yl)piperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(1,1-dioxidothiomorpholino)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-(1-(thiazol-2-ylamino)butan-2-yl)piperidin-3-yl)acetic acid;

2-(1-(1-acetamidobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(methylsulfonamido) butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyanopentan-3-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(methylsulfonyl)pentan-3-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-(1-(pyridin-2-yl)pentan-3-yl)piperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(ethylamino)-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(5-methyl-1,3,4-oxadiazol-2-yl)propyl)-2-oxopiperidin-3-yl)acetic;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclobutylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2-ethylbutyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopentylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((2,2-dimethylcyclopentyl)methyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclohexylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-propylpiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclobutylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isobutyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopentylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid;

Methyl 2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetate;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetamide;

Ethyl 2-(2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetamido)acetate;

2-(2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetamido)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetohydrazide;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)-N-hydroxyacetamide;

Ethyl 2-(3-(3-chlorophenyl)-2-(4-chlorophenyl)-5-(2-(methylsulfonamido)-2-oxoethyl)-6-oxopiperidin-1-yl)butanoate;

Ethyl 2-(3-(3-chlorophenyl)-2-(4-chlorophenyl)-5-(2-((3-morpholinopropyl)amino)-2-oxoethyl)-6-oxopiperidin-1-yl)butanoate;

3-((1H-Tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one;

3-((1,3,4-oxadiazol-2-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one;

5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)piperidin-2-one;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)-N-(methylsulfonyl)acetamide;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetamide.

3-((1H-tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one;

5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-((5-methylisoxazol-3-yl)methyl)piperidin-2-one;

2-(6-chloro-3'-(3-chlorophenyl)-1'-(cyclopropylmethyl)-2,6'-dioxospiro[indoline-3,2'-piperidine]-5'-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(5-chlorothiophen-2-yl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(5-chlorothiophen-2-yl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-ethoxy-1-oxobutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(1-(1-tert-butoxy-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(cyclopropylmethoxy)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid ;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3-(2-(pyrrolidin-1-yl)ethyl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-(2-morpholinoethyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-cyclobutyl-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-cyclopentyl-3-methyl-2-oxopiperidin-3-yl)acetic acid;

5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-((5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)-1-(pentan-3-yl)piperidin-2-one;

5-((5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)methyl)-1,3,4-oxadiazol-2(3H)-one;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)-N-(trifluoromethylsulfonyl)acetamide;

5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-((3-hydroxy-1H-pyrazol-5-yl)methyl)-3-methyl-1-(pentan-3-yl)piperidin-2-one;

5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-((3-hydroxyisoxazol-5-yl)methyl)-3-methyl-1-(pentan-3-yl)piperidin-2-one;

5-((5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)methyl)oxazolidine-2,4-dione;

3-((5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)methyl)-1,2,4-oxadiazol-5(4H)-one;

3-((5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methyl-2-oxopiperidin-3-yl)methyl)-1,2,4-oxadiazol-5(4H)-one;

3-((5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)methyl)-1,2,4-thiadiazol-5(4H)-one;

3-((5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methyl-2-oxopiperidin-3-yl)methyl)-1,2,4-thiadiazol-5(4H)-one;

3-((1H-Tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methylpiperidin-2-one;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid;

5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-(methylsulfonylmethyl)-1-(pentan-3-yl)piperidin-2-one;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(2,2,2-trifluoroethylamino)butan-2-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(2,2-dimethylmorpholino)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(2,6-dimethylmorpholino)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(4-(cyclopropylsulfonyl)piperazin-1-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(4-(methylsulfonyl)piperazin-1-yl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(1-(1-(4-acetylpiperazin-1-yl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(4-(cyclopropanecarbonyl)piperazin-1-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

3-((5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)methyl)-1,2,4-oxadiazol-5(4H)-one;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(5,5-dimethyl-2-oxooxazolidin-3-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(1-(1-(tert-butylamino)-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,3-dihydroxycyclopentyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1'-(2,2,2-trifluoroethyl)-1,3'-bipiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(3-hydroxycyclopentyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(tetrahydro-2H-pyran-3-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pyrazin-2-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-methyl-1H-pyrazol-4-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pyrimidin-4-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2-chloropyrimidin-4-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pyrimidin-2-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(3-methylpyridin-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(4-methylpyridin-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(dicyclopropylmethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

(4-(3-chlorophenyl)-3-(4-chlorophenyl)-1,1-dioxido-2-(2-propanyl)-1,2-thiazinan-6-yl)acetic acid;

(4-(3-chlorophenyl)-3-(4-chlorophenyl)-6-methyl-1,1-dioxido-2-(2-propanyl)-1,2-thiazinan-6-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(5-chloropyridin-2-yl)-3-methyl-1-(1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(5-chloropyridin-2-yl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid;

2-(1-(1-tert-butoxy-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(5-chloropyridin-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid; or

2-(1-(1-tert-butoxy-1-oxobutan-2-yl)-6-(4-chlorophenyl)-5-(4-chloropyridin-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.

In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, selected from:

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)propanoic acid;

tert-butyl 2-(3-((1H-tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoate;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(methylsulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(5-oxohexan-3-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(5-hydroxy-5-methylhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(6,6,6-trifluoro-5-hydroxy-5-methylhexan-3-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylmethylsulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(5-cyclopropyl-6,6,6-trifluoro-5-hydroxyhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(6-hydroxy-6-methylheptan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(6,6,6-trifluoro-5,5-dihydroxyhexan-3-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(7,7,7-trifluoro-6-hydroxy-6-methylheptan-3-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(7-hydroxy-7-methyloctan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(N-cyclopropylmethylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(6,6,6-trifluoro-5-hydroxyhexan-3-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(5-hydroxyhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(N-(2,2,2-trifluoroethyl)methylsulfonamido)butan-2-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(1,1-dioxidoisothiazolidin-2-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(5-hydroxy-4,5-dimethylhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(5-cyano-5-methylhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(2-oxopentan-3-yl)piperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-hydroxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-methoxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-hydroxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-hydroxy-2-methylpentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(4-hydroxyhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-methoxybutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1,1,1-trifluoro-2-hydroxy-2-methylpentan-3-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetamide;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-(methylsulfonyl)acetamide;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-(3-hydroxypropyl)acetamide;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-(2-hydroxyethyl)acetamide;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-hydroxyacetamide;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-methoxyacetamide;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-(2,3-dihydroxypropyl)acetamide;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-(2,3-dihydroxypropyl)acetamide;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-cyanoacetamide;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-(2-(dimethylamino)ethyl)acetamide;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)-N-(3,4-dihydroxybutyl)acetamide;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(cyclopropanesulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)propanoic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-(cyclopropanesulfonamido)pentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(2-(1-methylethylsulfonamido)pentan-3-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylcyclopropanesulfonamido)-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(neopentylamino)-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(N-(2,2,2-trifluoroethyl)acetamido)butan-2-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(1,1-dimethylethylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(N,2-dimethylpropan-2-ylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(1-methylethylsulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(N-ethylpropan-2-ylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-hydroxybutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(trifluoromethylsulfonamido)butan-2-yl)piperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(4-chlorophenylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(4-methylphenylsulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(2-chlorophenylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(2-methylphenylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(4-methoxyphenylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(phenylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(1-methylcyclopropanesulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(1,1-dioxidobenzo[d]isothiazol-2(3H)-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(3,3-dimethyl-1,1-dioxidobenzo[d]isothiazol-2(3H)-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(pyridine-3-sulfonamido)butan-2-yl)piperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(4-cyanophenylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(3-cyanophenylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(pyridine-2-sulfonamido)butan-2-yl)piperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(N,1-dimethylcyclopropanesulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

3-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)propanoic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methoxy-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(6-methyl-4-oxoheptan-3-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(ethylsulfonyl)pentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(isopropylsulfonyl)pentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(cyclopropylmethylsulfonyl)pentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(2-oxopyrrolidin-1-yl)butan-2-yl)piperidin-3-yl)acetic acid;

2-(1-(1-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(3-methylmorpholino)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(thiomorpholino-1,1-dioxide)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(3,3-difluoroazetidin-1-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(1-(1-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(3,3-dimethylmorpholino)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(3-hydroxy-3-(trifluoromethyl)azetidin-1-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(methyl(oxetan-3-yl)amino)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(2-oxooxazolidin-3-yl)butan-2-yl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(2-oxopyridin-1(2H)-yl)butan-2-yl)piperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(2-oxo-5-(trifluoromethyl)pyridin-1(2H)-yl)butan-2-yl)piperidin-3-yl)acetic acid;

3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(pyridin-3-yloxy)butan-2-yl)piperidin-2-one;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(tetrahydrofuran-2-yl)propyl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(5-oxotetrahydrofuran-2-yl)propyl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(tetrahydro-2H-pyran-2-yl)propyl)piperidin-3-yl)acetic acid;

2-(1-(1-(benzo[d]thiazol-2-yl)propyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(3-methylisoxazol-5-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(6-chloropyridin-2-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(pyridin-2-yl)propyl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(pyridin-2-yl)butyl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2-cyclopropyl-1-(pyridin-2-yl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(pyridin-3-yl)propyl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(pyrazin-2-yl)propyl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(pyrimidin-2-yl)propyl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(6-methylpyridin-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(pyridin-4-yl)propyl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(6-(trifluoromethyl)pyridin-2-yl)propyl)piperidin-3-yl)acetic acid;

2-(1-(1-(6-bromopyridin-2-yl)propyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(thiazol-2-yl)propyl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(6-cyclopropylpyridin-2-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(3,3,3-trifluoro-1-(pyridin-2-yl)propyl)piperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(2-methyl-1-(pyridin-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;

3-((1H-tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(pentan-3-yl)piperidin-2-one;

5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-(2,3-dihydroxypropyl)-1-(2-hydroxypentan-3-yl)-3-methylpiperidin-2-one;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-hydroxybutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)cyclopropanecarboxylic acid;

2-(1-(2-(tert-Butoxy)-1-cyclopropyl-2-oxoethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-ethoxy-2-oxoethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-hydroxyethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-hydroxybutyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-methylcyclopropanesulfonamido)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-(cyclopropanesulfonamido)-1-cyclopropylethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(ethylsulfonamido)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-methylcyclopropanesulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-hydroxypropyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(1-methylethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-methylcyclopropanesulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-hydroxy-4-methylpentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid; or
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropyl(pyridin-2-yl)methyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.

In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, selected from:
2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1,1-dioxidoisothiazolidin-2-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((2S,3S)-2-hydroxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((2R,3S)-2-hydroxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1,1-dimethylethylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(N,2-dimethylpropan-2-ylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(N,1-dimethylcyclopropanesulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-methylcyclopropanesulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((1S,2R)-1-cyclopropyl-2-hydroxypropyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid; or
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((1S,2S)-1-cyclopropyl-2-hydroxypropyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.

In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, selected from:
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(1,1-dioxidoisothiazolidin-2-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-hydroxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-hydroxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(1,1-dimethylethylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(N,2-dimethylpropan-2-ylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(N,1-dimethylcyclopropanesulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-methylcyclopropanesulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid; or
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-hydroxypropyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.

In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, selected from:
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(thiophene-2-sulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-methylthiophene-2-sulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-2-(5-chlorothiophene-2-sulfonamido)-1-cyclopropylethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-1-((S)-2-(5-Chloro-N-methylthiophene-2-sulfonamido)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-(difluoromethyl)-2-methylpropan-2-ylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-(difluoromethyl)ethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-(difluoromethyl)cyclopropanesulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

1-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-2-(cyclopropanesulfonamido)-1-cyclopropylethyl)-3-methyl-2-oxopiperidin-3-yl)cyclopropanecarboxylic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-(2-fluorophenyl)ethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-(2-fluorophenyl)methylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-phenylcyclopropanesulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-phenylethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(ethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-(3-fluorophenyl)ethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-2-(N-(2-cyanophenyl)methylsulfonamido)-1-cyclopropylethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(propylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-phenylmethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-2-(N-(3-cyanophenyl)methylsulfonamido)-1-cyclopropylethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-(pyridin-3-yl)methylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-(thiophen-2-ylmethyl)methylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-(3-methoxybenzyl)methylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(phenylmethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(pyridin-2-ylmethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(pyridin-3-ylmethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-(pyridin-2-yl)methylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(methylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-ethylmethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-isopropylmethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(1-methylethylsulfonamido)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-2-(cyclobutanesulfonamido)-1-cyclopropylethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-2-(cyclopentanesulfonamido)-1-cyclopropylethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-3-methyl-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropanesulfonamido)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(ethylsulfonamido)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclobutanesulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(N-ethylcyclobutanesulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(phenylsulfonyl)butan-2-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(methylsulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(propylsulfonyl)butan-2-yl)piperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isobutylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-((cyclopropylmethyl)sulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-((cyclobutylmethyl)sulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopentylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(oxetan-3-ylsulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(((3-methyloxetan-3-yl)methyl)sulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-((tetrahydro-2H-pyran-4-yl)sulfonyl)butan-2-yl)piperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-((2-hydroxy-2-methylpropyl)sulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-1-((S)-1-((R)-sec-butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-1-((S)-1-((S)-sec-butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-2-(cyclopentylsulfonyl)-1-cyclopropylethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(((3-methyloxetan-3-yl)methyl)sulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(phenylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(o-tolylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-2-((2-chlorophenyl)sulfonyl)-1-cyclopropylethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-2-((4-chlorophenyl)sulfonyl)-1-cyclopropylethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-((4-fluorophenyl)sulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(pyridin-4-ylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-2-((2-Chloro-4-fluorophenyl)sulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-((cyclopropylmethyl)sulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-((2,2,2-trifluoroethyl)sulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-((trifluoromethyl)sulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(phenylsulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-2-((2-chlorophenyl)sulfonyl)-1-cyclopropylethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-((2-fluorophenyl)sulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-((3-fluorophenyl)sulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-((4-fluorophenyl)sulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(propylsulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-2-(Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(isopentylsulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-2-(cyclopentylsulfonyl)-1-cyclopropylethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-2-(cyclohexylsulfonyl)-1-cyclopropylethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(methylsulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-3-methyl-1-((2,2,2-trifluoroethyl)sulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-1-(*tert*-Butylsulfonyl)-3-methylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-3-methyl-1-(methylsulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(ethylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-1-(tert-butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclobutylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-1-((S)-1-(ethylsulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-1-((S)-1-(isopropylsulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-1-(tert-butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclobutylsulfonyl)butan-2-yl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylsulfonyl)butan-2-yl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(ethylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(isopropylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-2-(*tert*-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-2-(cyclobutylsulfonyl)-1-cyclopropylethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(cyclopropylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(methylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(tert-pentylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-((2,4-difluorophenyl)sulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(ethylsulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(isopropylsulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-2-(*tert*-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(cyclopropylsulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(ethylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-3,3-dimethyl-1-(methylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(ethylsulfonyl)-3,3-dimethylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3,3-dimethylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(pentan-3-ylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-((S)-isopropylsulfinyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-((R)-isopropylsulfinyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid; more polar isomer;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((2S,3S)-2-(methylsulfonyl)pentan-3-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((2R,3S)-2-(methylsulfonyl)pentan-3-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((2S,3S)-2-(ethylsulfonyl)pentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((2R,3S)-2-(ethylsulfonyl)pentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-(oxetan-3-yl)sulfamoyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-((3-methyloxetan-3-yl)methyl)sulfamoyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-(oxetan-3-ylmethyl)sulfamoyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-2-(N-(*tert*-Butyl)sulfamoyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-methylsulfamoyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N,N-dimethylsulfamoyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-isopropylsulfamoyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(morpholinosulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(piperidin-1-ylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(pyrrolidin-1-ylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-2-(Azetidin-1-ylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-((N,N-dimethylsulfamoyl)amino)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-((N,N-dimethylsulfamoyl)(methyl)amino)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(3-methyl-2,5-dioxoimidazolidin-1-yl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(3-isopropyl-2,2-dioxido-4-oxo-3,4-dihydro-1H-benzo[c][1,2,6]thiadiazin-1-yl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chloro-4-fluorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chloro-5-fluorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-Chloro-5-fluorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chloro-5-fluorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(ethylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chloro-5-fluorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(N-methylethylsulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chloro-5-fluorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(methylsulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chloro-5-fluorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(ethylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chloro-5-fluorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-1-(*tert*-Butylsulfonyl)butan-2-yl)-5-(3-chloro-5-fluorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chloro-5-fluorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-6-(4-Chlorophenyl)-5-(5-chloropyridin-3-yl)-1-((S)-1-(cyclopropylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-1-(tert-Butylsulfonyl)butan-2-yl)-6-(4-chlorophenyl)-5-(5-chloropyridin-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-6-(4-Chlorophenyl)-5-(5-chloropyridin-3-yl)-1-((S)-1-(cyclopropanesulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-6-(4-Chlorophenyl)-5-(5-chloropyridin-3-yl)-3-methyl-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(5-chloropyridin-2-yl)-1-((S)-1-(ethylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-((S)-morpholin-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-((R)-morpholin-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((R)-1-((S)-morpholin-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((R)-1-((R)-morpholin-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((R)-1-((R)-morpholin-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;

or 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((R)-1-((S)-morpholin-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-3-(2-morpholinoethyl)-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-(2-(1,1-dioxidothiomorpholino)ethyl)-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxo-3-(2-(pyrrolidin-1-yl)ethyl)piperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-(2-(dimethylamino)ethyl)-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-((3S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-3-(2-morpholinoethyl)-2-oxopiperidin-3-yl)acetamide;

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-3-(2-morpholinoethyl)-2-oxopiperidin-3-yl)acetamide;

(1R,3S,6S,7R)-7-(3-Chlorophenyl)-6-(4-chlorophenyl)-5-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-4-oxo-5-azaspiro[2.5]octane-1-carboxylic acid;

(3S,6S,7R)-7-(3-Chlorophenyl)-6-(4-chlorophenyl)-5-((S)-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-4-oxo-5-azaspiro[2.5]octane-1-carboxylic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((2S,3S)-1,2-dihydroxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((2R,3S)-1,2-dihydroxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((2R,3S)-1,2-dihydroxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((2S,3S)-1,2-dihydroxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((1S,2S)-1-cyclopropyl-1-hydroxybutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((1R,2S)-1-cyclopropyl-1-hydroxybutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3*S*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-isopropyl-6-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-isopropyl-6-methyl-2-oxopiperidin-3-yl)acetic acid;

(3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1,1-dioxidoisothiazolidin-2-yl)butan-2-yl)-3-((6-methoxypyridin-2-yl)methyl)piperidin-2-one;

(3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1,1-dioxidoisothiazolidin-2-yl)butan-2-yl)-3-((6-methoxypyridin-2-yl)methyl)piperidin-2-one;

(3S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1,1-dioxidoisothiazolidin-2-yl)butan-2-yl)-3-((6-hydroxypyridin-2-yl)methyl)piperidin-2-one;

(3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1,1-dioxidoisothiazolidin-2-yl)butan-2-yl)-3-((6-hydroxypyridin-2-yl)methyl)piperidin-2-one;

(3S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1,1-dioxidoisothiazolidin-2-yl)butan-2-yl)-3-((6-methoxypyridin-2-yl)methyl)-3-methylpiperidin-2-one;

(3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1,1-dioxidoisothiazolidin-2-yl)butan-2-yl)-3-((6-methoxypyridin-2-yl)methyl)-3-methylpiperidin-2-one;

(3S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1,1-dioxidoisothiazolidin-2-yl)butan-2-yl)-3-((6-hydroxypyridin-2-yl)methyl)-3-methylpiperidin-2-one;

(3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1,1-dioxidoisothiazolidin-2-yl)butan-2-yl)-3-((6-hydroxypyridin-2-yl)methyl)-3-methylpiperidin-2-one;

(3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(ethylsulfonyl)ethyl)-3-(3-hydroxy-2-oxopropyl)-3-methylpiperidin-2-one;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(diethylamino)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(dimethylamino)-3-methyl-2-oxopiperidin-3-yl)acetic acid; or
(2S,3S,5S,6R,7aR,10aS)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-ethyl-2,7a-dimethylhexahydrofuro[2,3-b]oxazolo[3,2-a]pyridin-9(5H)-one.

In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, selected from:
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(thiophene-2-sulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-methylthiophene-2-sulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-(5-chlorothiophene-2-sulfonamido)-1-cyclopropylethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(1-(2-(5-Chloro-N-methylthiophene-2-sulfonamido)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-(difluoromethyl)-2-methylpropan-2-ylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-(difluoromethyl)ethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-(difluoromethyl)cyclopropanesulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
1-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-(cyclopropanesulfonamido)-1-cyclopropylethyl)-3-methyl-2-oxopiperidin-3-yl)cyclopropanecarboxylic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-(2-fluorophenyl)ethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-(2-fluorophenyl)methylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-phenylcyclopropanesulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-phenylethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(ethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-(3-fluorophenyl)ethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2-(N-(2-cyanophenyl)methylsulfonamido)-1-cyclopropylethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(propylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-phenylmethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2-(N-(3-cyanophenyl)methylsulfonamido)-1-cyclopropylethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-(pyridin-3-yl)methylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-(thiophen-2-ylmethyl)methylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-(3-methoxybenzyl)methylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(phenylmethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(pyridin-2-ylmethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(pyridin-3-ylmethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-(pyridin-2-yl)methylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(methylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-ethylmethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-isopropylmethylsulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(1-methylethylsulfonamido)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2-(cyclobutanesulfonamido)-1-cyclopropylethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2-(cyclopentanesulfonamido)-1-cyclopropylethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(3-methyl-1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(cyclopropanesulfonamido)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(ethylsulfonamido)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(cyclobutanesulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(N-ethylcyclobutanesulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(phenylsulfonyl)butan-2-yl)piperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(methylsulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-(propylsulfonyl)butan-2-yl)piperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(isobutylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-((cyclopropylmethyl)sulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-((cyclobutylmethyl)sulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(cyclopentylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(oxetan-3-ylsulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(((3-methyloxetan-3-yl)methyl)sulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(1-((tetrahydro-2H-pyran-4-yl)sulfonyl)butan-2-yl)piperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-((2-hydroxy-2-methylpropyl)sulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(1-(1-(-sec-butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-(cyclopentylsulfonyl)-1-cyclopropylethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(((3-methyloxetan-3-yl)methyl)sulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(phenylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(o-tolylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-((2-chlorophenyl)sulfonyl)-1-cyclopropylethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-((4-chlorophenyl)sulfonyl)-1-cyclopropylethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-((4-fluorophenyl)sulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(pyridin-4-ylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(1-(2-((2-Chloro-4-fluorophenyl)sulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-((cyclopropylmethyl)sulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-((2,2,2-trifluoroethyl)sulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-((trifluoromethyl)sulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(phenylsulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-((2-chlorophenyl)sulfonyl)-1-cyclopropylethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-((2-fluorophenyl)sulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-((3-fluorophenyl)sulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-((4-fluorophenyl)sulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(propylsulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;
2-(1-(2-(Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(isopentylsulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-(cyclopentylsulfonyl)-1-cyclopropylethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-(cyclohexylsulfonyl)-1-cyclopropylethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(methylsulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(3-methyl-1-((2,2,2-trifluoroethyl)sulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;
2-(1-(1-(*tert*-Butylsulfonyl)-3-methylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(3-methyl-1-(methylsulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(ethylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(cyclopropylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(isopropylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(1-(1-(tert-butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;
2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(cyclobutylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-1-(1-(ethylsulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-1-(1-(isopropylsulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(1-(1-(tert-butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(cyclobutylsulfonyl)butan-2-yl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(cyclopropylsulfonyl)butan-2-yl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(ethylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(isopropylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(1-(2-(*tert*-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-(cyclobutylsulfonyl)-1-cyclopropylethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(cyclopropylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(methylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(tert-pentylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-((2,4-difluorophenyl)sulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(ethylsulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(isopropylsulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-(1-((2-(*tert*-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(cyclopropylsulfonyl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(ethylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(3,3-dimethyl-1-(methylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(ethylsulfonyl)-3,3-dimethylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(isopropylsulfonyl)-3,3-dimethylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(pentan-3-ylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(isopropylsulfinyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(2-(methylsulfonyl)pentan-3-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(2-(ethylsulfonyl)pentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-(oxetan-3-yl)sulfamoyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-((3-methyloxetan-3-yl)methyl)sulfamoyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-(oxetan-3-ylmethyl)sulfamoyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(1-(2-(N-(*tert*-Butyl)sulfamoyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-methylsulfamoyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N,N-dimethylsulfamoyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(N-isopropylsulfamoyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(morpholinosulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(piperidin-1-ylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(pyrrolidin-1-ylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(1-(2-(Azetidin-1-ylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-((N,N-dimethylsulfamoyl)amino)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-((N,N-dimethylsulfamoyl)(methyl)amino)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(3-methyl-2,5-dioxoimidazolidin-1-yl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(3-isopropyl-2,2-dioxido-4-oxo-3,4-dihydro-1H-benzo[c][1,2,6]thiadiazin-1-yl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chloro-4-fluorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chloro-5-fluorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chloro-5-fluorophenyl)-6-(4-chlorophenyl)-1-(1-(ethylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chloro-5-fluorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(N-methylethylsulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chloro-5-fluorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(methylsulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chloro-5-fluorophenyl)-6-(4-chlorophenyl)-1-(1-(ethylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chloro-5-fluorophenyl)-6-(4-chlorophenyl)-1-(1-(cyclopropylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(1-(1-(*tert*-Butylsulfonyl)butan-2-yl)-5-(3-chloro-5-fluorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chloro-5-fluorophenyl)-6-(4-chlorophenyl)-1-(1-(isopropylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(6-(4-Chlorophenyl)-5-(5-chloropyridin-3-yl)-1-(1-(cyclopropylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(1-(1-(tert-Butylsulfonyl)butan-2-yl)-6-(4-chlorophenyl)-5-(5-chloropyridin-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(6-(4-Chlorophenyl)-5-(5-chloropyridin-3-yl)-1-(1-(cyclopropanesulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(6-(4-Chlorophenyl)-5-(5-chloropyridin-3-yl)-3-methyl-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(5-chloropyridin-2-yl)-1-(1-(ethylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(1-(morpholin-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-3-(2-morpholinoethyl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-(2-(1,1-dioxidothiomorpholino)ethyl)-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxo-3-(2-(pyrrolidin-1-yl)ethyl)piperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-(2-(dimethylamino)ethyl)-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-3-(2-morpholinoethyl)-2-oxopiperidin-3-yl)acetamide;

7-(3-Chlorophenyl)-6-(4-chlorophenyl)-5-(1-(N-methylcyclopropanesulfonamido)butan-2-yl)-4-oxo-5-azaspiro[2.5]octane-1-carboxylic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1,2-dihydroxypentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-1-hydroxybutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-isopropyl-6-methyl-2-oxopiperidin-3-yl)acetic acid;

5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-(1,1-dioxidoisothiazolidin-2-yl)butan-2-yl)-3-((6-methoxypyridin-2-yl)methyl)piperidin-2-one;

5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(1,1-dioxidoisothiazolidin-2-yl)butan-2-yl)-3-((6-hydroxypyridin-2-yl)methyl)piperidin-2-one;

5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(1,1-dioxidoisothiazolidin-2-yl)butan-2-yl)-3-((6-methoxypyridin-2-yl)methyl)-3-methylpiperidin-2-one;

5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(1-(1,1-dioxidoisothiazolidin-2-yl)butan-2-yl)-3-((6-hydroxypyridin-2-yl)methyl)-3-methylpiperidin-2-one;

(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(ethylsulfonyl)ethyl)-3-(3-hydroxy-2-oxopropyl)-3-methylpiperidin-2-one;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(diethylamino)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(dimethylamino)-3-methyl-2-oxopiperidin-3-yl)acetic acid; or

6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-ethyl-2,7a-dimethylhexahydrofuro[2,3-b]oxazolo[3,2-a]pyridin-9(5H)-one.

In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, selected from:

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(methylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-1-((S)-1-(tert-butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3,3-dimethylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(ethylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(ethylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(N-phenylcyclopropanesulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid; or

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-((cyclopropylmethyl)sulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.

In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, selected from:
2-(-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(-1-cyclopropyl-2-(methylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(-1-(-1-(tert-butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(-1-(isopropylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(-1-(isopropylsulfonyl)-3,3-dimethylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(-1-(ethylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(-1-(ethylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(-1-cyclopropyl-2-(N-phenylcyclopropanesulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(-1-((cyclopropylmethyl)sulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-l-(-l-cyclopropyl-2-(methylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

2-(-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-l-(-l-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid; or

2-(-1-(-1-(tert-butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.

The present invention provides pharmaceutical compositions comprising a compound of any one of the above aspects or embodiments, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient, diluent or carrier.

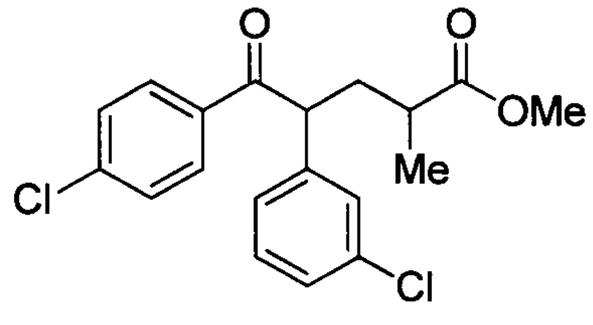
The present invention is further related to the use of a compound of the invention as an inhibitor of hMDM2-p53 interaction.

The present invention further relates to the compound 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutical acceptable salt thereof.

Use of the compound 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof, as an inhibitor of hMDM2-p53 interaction is also provided.

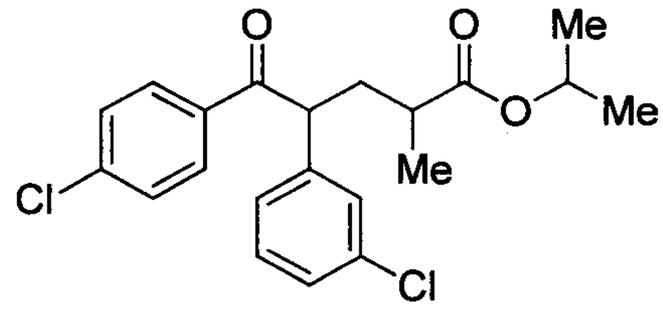
The present invention as claimed relates to:

- a compound, wherein the compound is a compound of formula



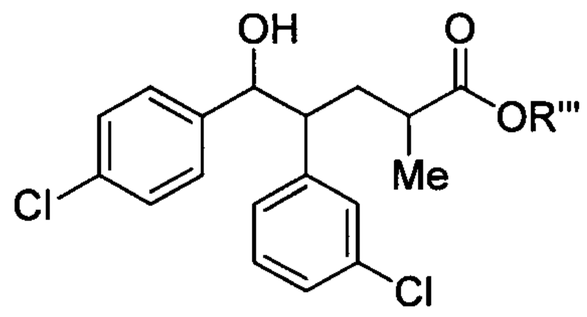
;

- a compound, wherein the compound is a compound of formula



;

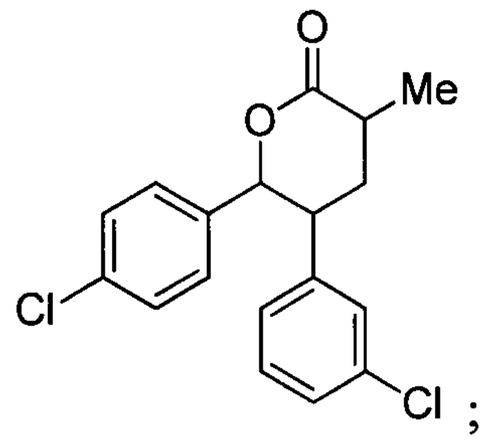
- a compound, wherein the compound is a compound of formula



, wherein

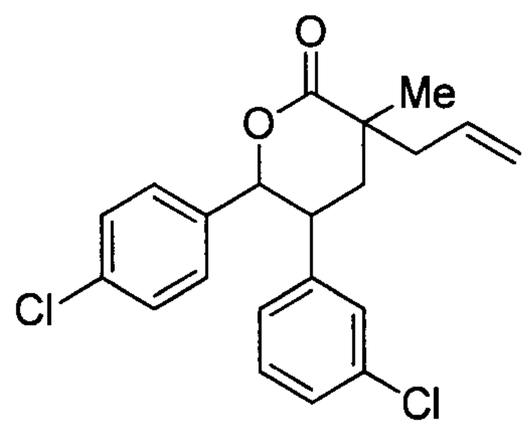
R''' is hydrogen, methyl, or isopropyl;

- a compound, wherein the compound is a compound of formula



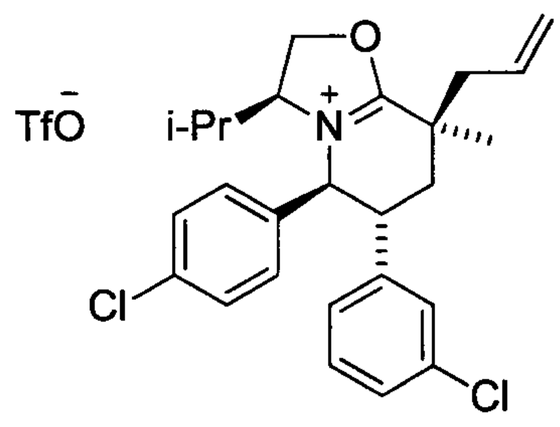
;

- a compound, wherein the compound is a compound of formula



; and

- a compound, wherein the compound is a compound of formula



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DETAILED DESCRIPTION OF THE INVENTION

The term "H" denotes a single hydrogen atom. This radical may be attached, for example, to an oxygen atom to form a hydroxyl radical.

Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" or "alkylamino", it embraces linear or branched radicals having one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isoamyl, hexyl and the like. Even more preferred are lower alkyl radicals having one or two carbon atoms. The term “alkylenyl” or “alkylene” embraces bridging divalent alkyl radicals such as methylenyl or ethylenyl. The term "lower alkyl substituted with R^2" does not include an acetal moiety. The term “alkyl” further includes alkyl radicals wherein one or more carbon atoms in the chain is substituted with a heteroatom selected from oxygen, nitrogen, or sulfur.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Most preferred lower alkenyl radicals are radicals having two to about four carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "alkynyl" denotes linear or branched radicals having at least one carbon-carbon triple bond and having two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about six carbon atoms. Most preferred are lower alkynyl radicals having two to about four carbon atoms. Examples of such radicals include propargyl, and butynyl, and the like.

Alkyl, alkylenyl, alkenyl, and alkynyl radicals may be optionally substituted with one or more functional groups such as halo, hydroxy, nitro, amino, cyano, haloalkyl, aryl, heteroaryl, and heterocyclo and the like.

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals including perhaloalkyl. A monohaloalkyl radical, for example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and

polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1 to 6 carbon atoms. Even more preferred are lower haloalkyl radicals having one to three carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

The term "perfluoroalkyl" means alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. Even more preferred are lower hydroxyalkyl radicals having one to three carbon atoms.

The term "alkoxy" embraces linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. Even more preferred are lower alkoxy radicals having one to three carbon atoms. Alkoxy radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Even more preferred are lower haloalkoxy radicals having one to three carbon atoms. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one or two rings, wherein such rings may be attached together in a fused manner. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, indenyl, tetrahydronaphthyl, and indanyl. More preferred aryl is phenyl. An "aryl" group may have 1 or more substituents such as lower alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy, and lower alkylamino, and the like. Phenyl substituted with $-O-CH_2-O-$ forms the aryl benzodioxolyl substituent.

The term "heterocyclyl" (or "heterocyclo") embraces saturated, partially saturated and unsaturated heteroatom-containing ring radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. It does not include rings containing -O-O-,-O-S- or -S-S-

portions. The "heterocyclyl" group may have 1 to 4 substituents such as hydroxyl, Boc, halo, haloalkyl, cyano, lower alkyl, lower aralkyl, oxo, lower alkoxy, amino and lower alkylamino.

Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g., pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g., morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclyl radicals include dihydrothienyl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl.

Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated 5- to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

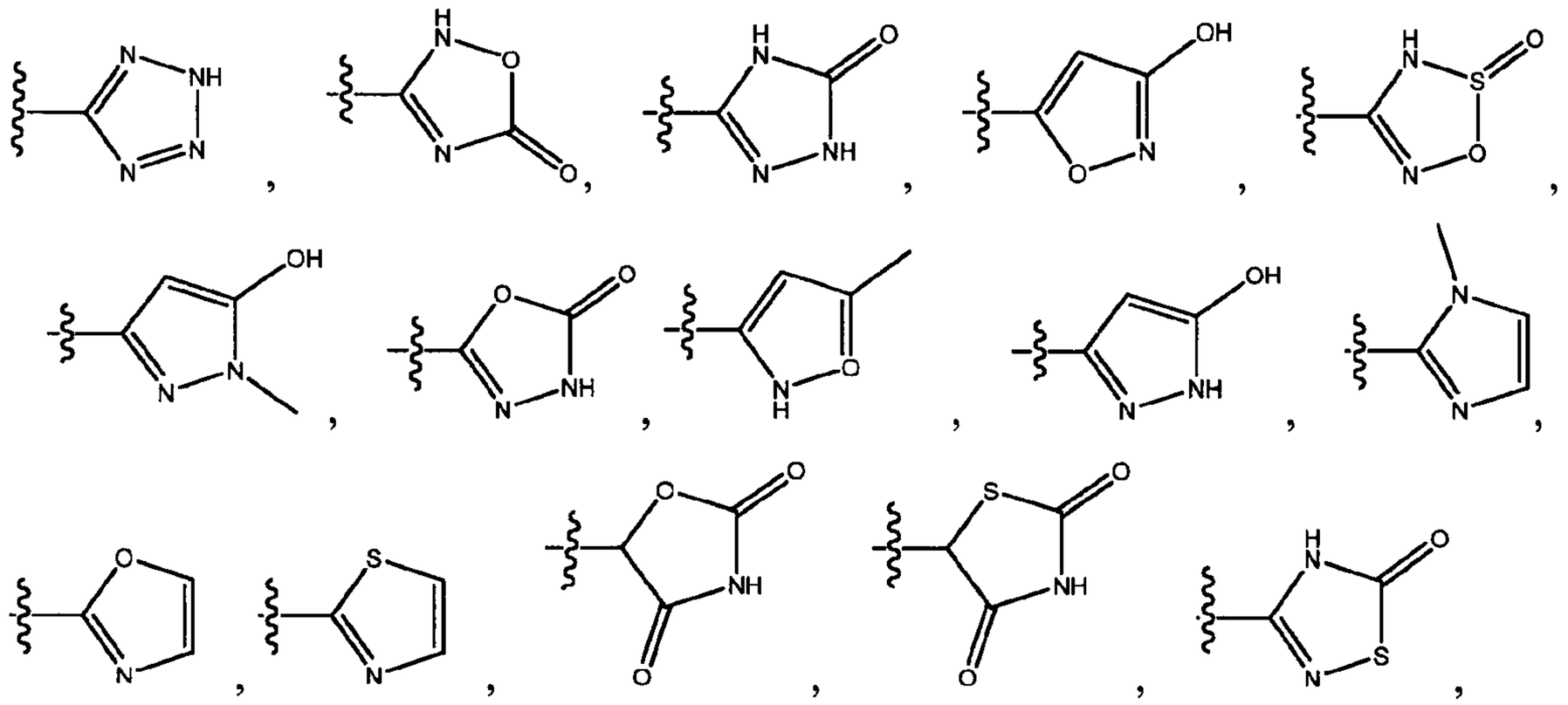
The term heterocyclyl, (or heterocyclo) also embraces radicals where heterocyclic radicals are fused/condensed with aryl radicals: unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl]; and saturated, partially unsaturated and unsaturated condensed heterocyclic group containing 1 to 2 oxygen or sulfur atoms [e.g. benzofuryl, benzothienyl, 2,3-dihydro-benzo[1,4]dioxinyl and dihydrobenzofuryl]. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. More preferred examples of heteroaryl radicals include quinolyl, isoquinolyl, imidazolyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl and pyrazinyl. Other preferred heteroaryl radicals are 5- or 6-membered

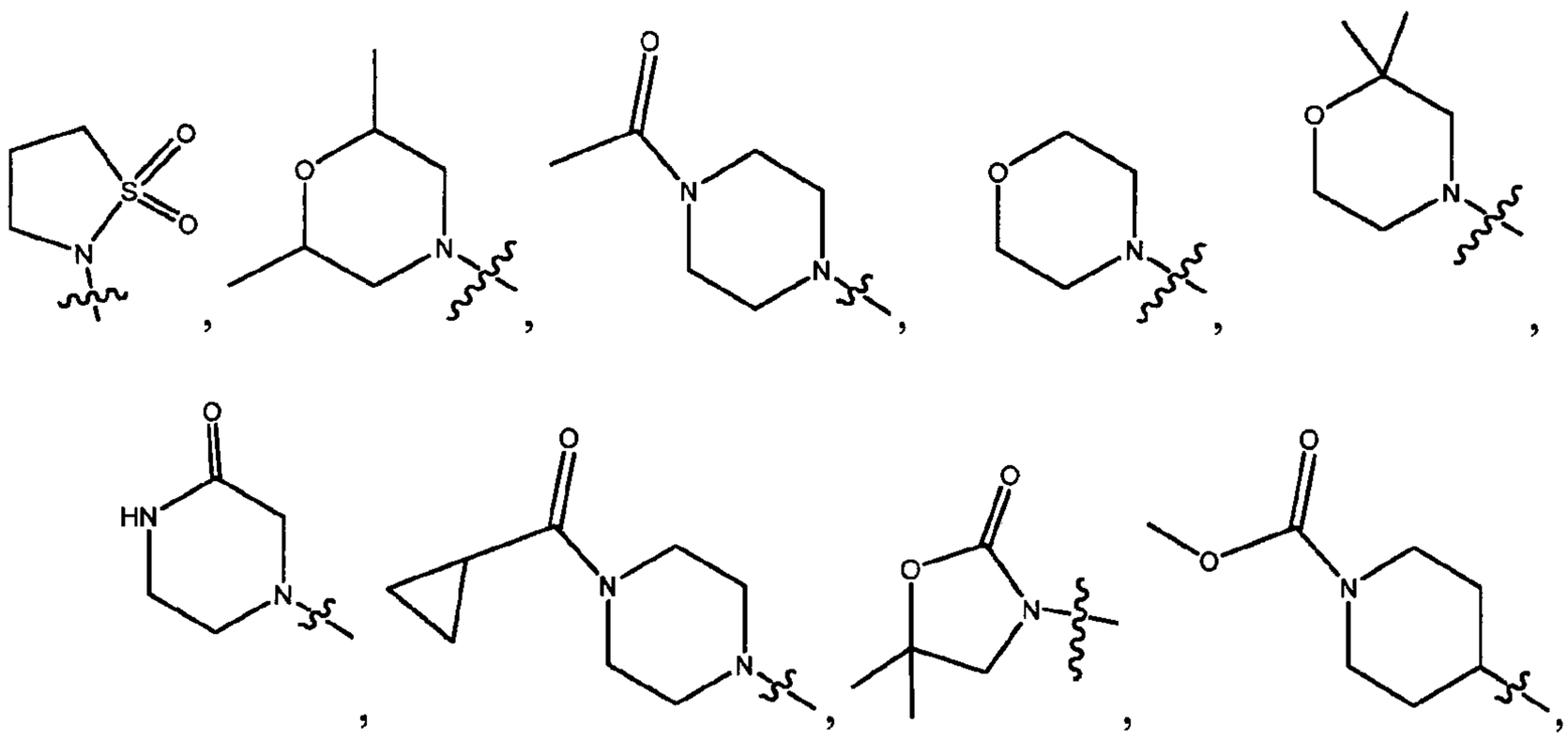
heteroaryl, containing one or two heteroatoms selected from sulfur, nitrogen and oxygen, selected from thienyl, furyl, pyrrolyl, indazolyl, pyrazolyl, oxazolyl, triazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, piperidinyl and pyrazinyl.

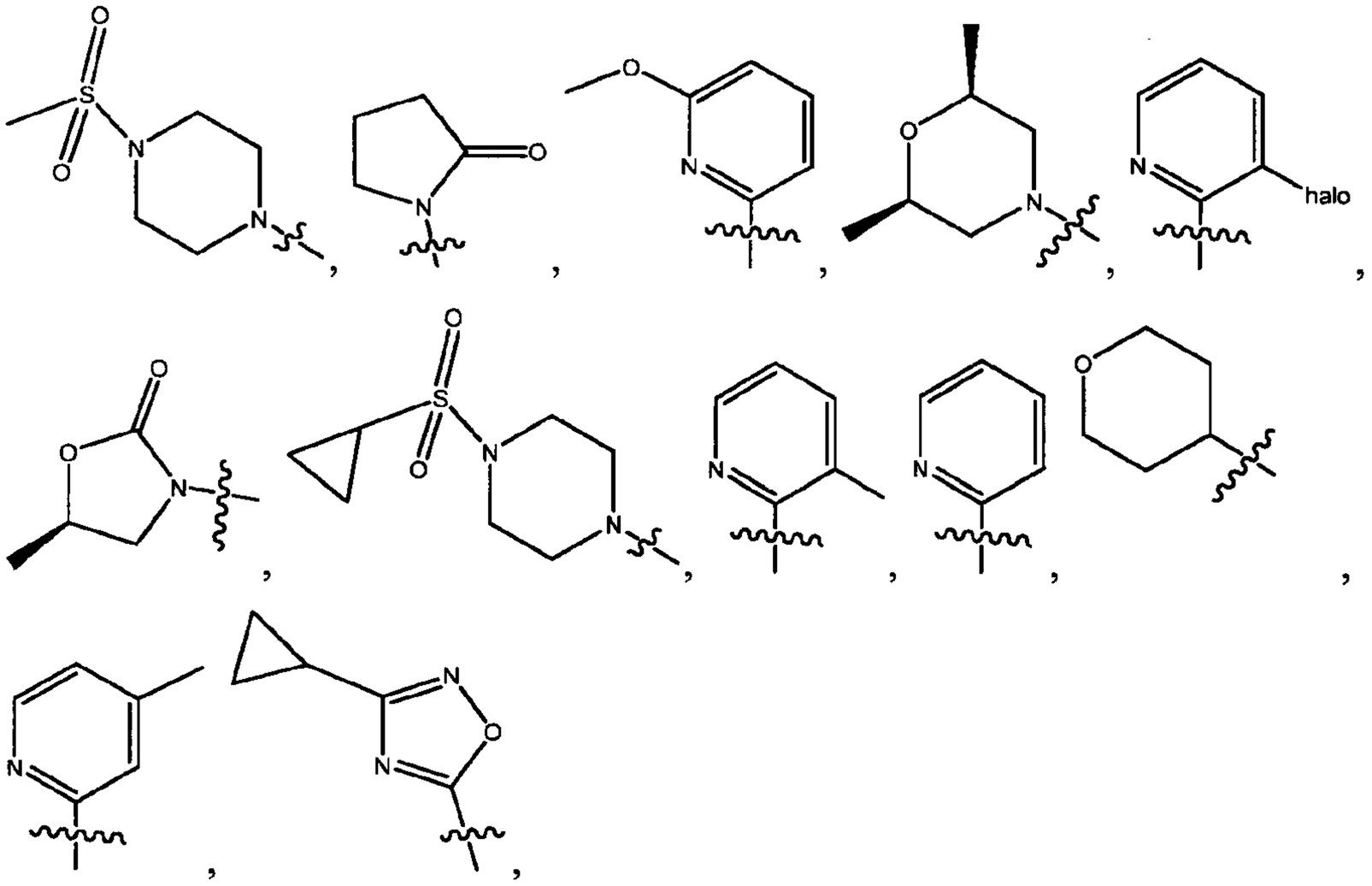
Particular examples of non-nitrogen containing heteroaryl include pyranyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, benzofuryl, and benzothienyl, and the like.

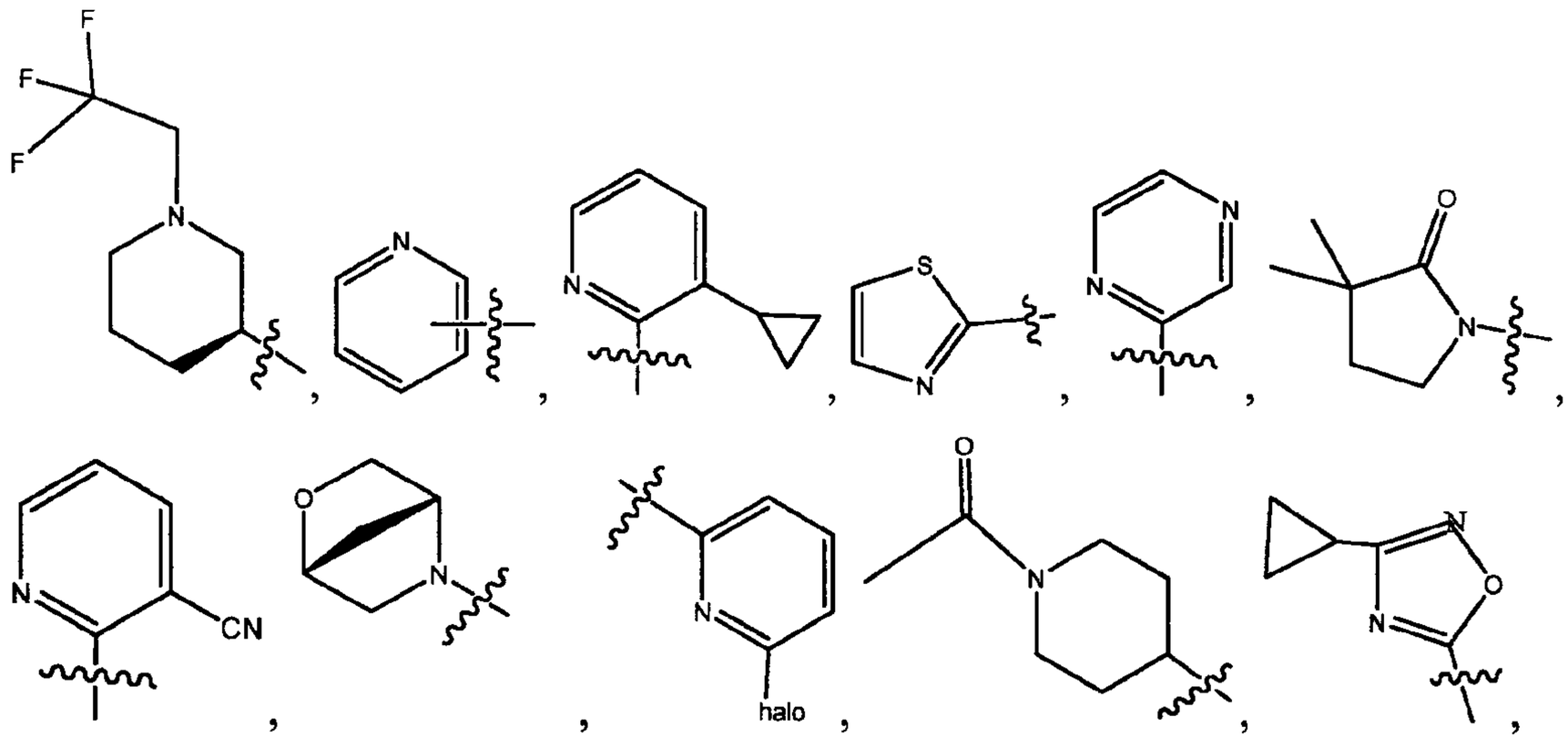
Particular examples of partially saturated and saturated heterocyclyl include pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolidinyl, dihydrothienyl, 2,3-dihydro-benzo[1,4]dioxanyl, indolinyl, isoindolinyl, dihydrobenzothienyl, dihydrobenzofuryl, isochromanyl, chromanyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxanyl, 2,3-dihydro-1H-1λ'-benzo[d]isothiazol-6-yl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl, and the like.

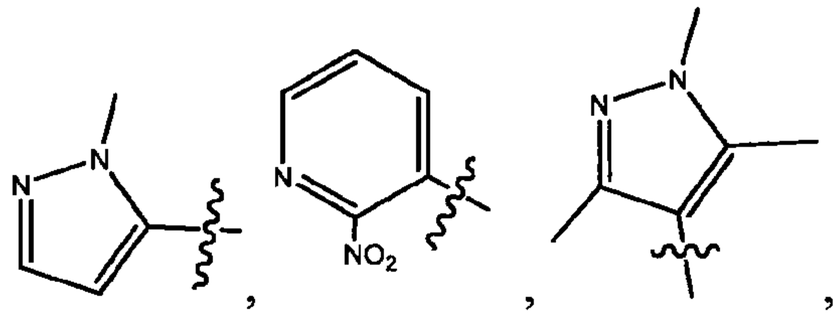
The term "heterocyclo" thus encompasses the following ring systems:











, and the like.

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$.

The terms "sulfamyl," "aminosulfonyl" and "sulfonamidyl," denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2NH_2$).

The term "alkylaminosulfonyl" includes "N-alkylaminosulfonyl" where sulfamyl radicals are independently substituted with one or two alkyl radical(s). More preferred alkylaminosulfonyl radicals are "lower alkylaminosulfonyl" radicals having one to six carbon atoms. Even more preferred are lower alkylaminosulfonyl radicals having one to three carbon atoms. Examples of such lower alkylaminosulfonyl radicals include N-methylaminosulfonyl, and N-ethylaminosulfonyl.

The terms "carboxy" or "carboxyl," whether used alone or with other terms, such as "carboxyalkyl," denotes $-CO_2H$.

The term "carbonyl," whether used alone or with other terms, such as "aminocarbonyl," denotes -(C=O)-.

The term "aminocarbonyl" denotes an amide group of the formula $C(=O)NH_2$.

The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denote aminocarbonyl radicals independently substituted with one or two alkyl radicals, respectively. More preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to an aminocarbonyl radical.

The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical.

The terms "heterocyclylalkylenyl" and "heterocyclylalkyl" embrace heterocyclic-substituted alkyl radicals. More preferred heterocyclylalkyl radicals are "5- or 6-membered heteroarylalkyl" radicals having alkyl portions of one to six carbon atoms and a 5- or 6-membered heteroaryl radical. Even more preferred are lower heteroarylalkylenyl radicals having alkyl portions of one to three carbon atoms. Examples include such radicals as pyridylmethyl and thienylmethyl.

The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are "phenylalkylenyl" attached to alkyl portions having one to three carbon atoms. Examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower alkylthio radicals having one to three carbon atoms. An example of "alkylthio" is methylthio, (CH_3S-).

The term "haloalkylthio" embraces radicals containing a haloalkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower haloalkylthio radicals having one to three carbon atoms. An example of "haloalkylthio" is trifluoromethylthio.

The term "alkylamino" embraces "N-alkylamino" and "N,N-dialkylamino" where amino groups are independently substituted with one alkyl radical and with two alkyl radicals, respectively. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Suitable alkylamino radicals may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, and N,N-diethylamino, and the like.

The term "arylamino" denotes amino groups, which have been substituted with one or two aryl radicals, such as N-phenylamino. The arylamino radicals may be further substituted on the aryl ring portion of the radical.

The term "heteroarylamino" denotes amino groups, which have been substituted with one or two heteroaryl radicals, such as N-thienylamino. The "heteroarylamino" radicals may be further substituted on the heteroaryl ring portion of the radical.

The term "aralkylamino" denotes amino groups, which have been substituted with one or two aralkyl radicals. More preferred are phenyl-C_1-C_3-alkylamino radicals, such as N-benzylamino. The aralkylamino radicals may be further substituted on the aryl ring portion.

The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups, which have been independently substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl radical, respectively, to an amino group.

The term "aminoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" radicals having one to six carbon atoms and one or more amino radicals. Examples of such radicals include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminohexyl. Even more preferred are lower aminoalkyl radicals having one to three carbon atoms.

The term "alkylaminoalkyl" embraces alkyl radicals substituted with alkylamino radicals. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" radicals having alkyl radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkyl radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkyl radicals may be mono or dialkyl substituted, such as N-methylaminomethyl, N,N-dimethyl-aminoethyl, and N,N-diethylaminomethyl, and the like.

The term "alkylaminoalkoxy" embraces alkoxy radicals substituted with alkylamino radicals. More preferred alkylaminoalkoxy radicals are "lower alkylaminoalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxy radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkoxy radicals may be mono or dialkyl substituted, such as N-methylaminoethoxy, N,N-dimethylaminoethoxy, and N,N-diethylaminoethoxy, and the like.

The term "alkylaminoalkoxyalkoxy" embraces alkoxy radicals substituted with alkylaminoalkoxy radicals. More preferred alkylaminoalkoxyalkoxy radicals are "lower alkylaminoalkoxyalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxyalkoxy radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkoxyalkoxy radicals may be mono or dialkyl substituted, such as N-methylaminomethoxyethoxy, N-methylaminoethoxyethoxy, N,N-dimethylaminoethoxyethoxy, and N,N-diethylaminomethoxymethoxy, and the like.

The term "carboxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more carboxy radicals. More preferred carboxyalkyl radicals are "lower carboxyalkyl" radicals having one to six carbon atoms and one carboxy radical. Examples of such radicals include carboxymethyl, and carboxypropyl, and the like. Even more preferred are lower carboxyalkyl radicals having one to three CH_2 groups.

The term "halosulfonyl" embraces sulfonyl radicals substituted with a halogen radical. Examples of such halosulfonyl radicals include chlorosulfonyl and fluorosulfonyl.

The term "arylthio" embraces aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. An example of "arylthio" is phenylthio.

The term "aralkylthio" embraces aralkyl radicals as described above, attached to a divalent sulfur atom. More preferred are phenyl-C_1-C_3-alkylthio radicals. An example of "aralkylthio" is benzylthio.

The term "aryloxy" embraces optionally substituted aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy.

The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having optionally substituted phenyl radicals attached to lower alkoxy radical as described above.

The term "heteroaryloxy" embraces optionally substituted heteroaryl radicals, as defined above, attached to an oxygen atom.

The term "heteroarylalkoxy" embraces oxy-containing heteroarylalkyl radicals attached through an oxygen atom to other radicals. More preferred heteroarylalkoxy radicals are "lower heteroarylalkoxy" radicals having optionally substituted heteroaryl radicals attached to lower alkoxy radical as described above.

The term "cycloalkyl" includes saturated carbocyclic groups. Preferred cycloalkyl groups include C_3-C_6 rings. More preferred compounds include, cyclopentyl, cyclopropyl, and cyclohexyl.

The term “cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals. Preferable cycloalkylalkyl radicals are "lower cycloalkylalkyl" radicals having cycloalkyl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are "5 to 6-membered cycloalkylalkyl" attached to alkyl portions having one to three carbon atoms. Examples of such radicals include cyclohexylmethyl. The cycloalkyl in said radicals may be additionally substituted with halo, alkyl, alkoxy and hydroxy.

The term "cycloalkenyl" includes carbocyclic groups having one or more carbon-carbon double bonds including "cycloalkyldienyl" compounds. Preferred cycloalkenyl groups include C_3-C_6 rings. More preferred compounds include, for example, cyclopentenyl, cyclopentadienyl, cyclohexenyl and cycloheptadienyl.

The term "comprising" is meant to be open ended, including the indicated component but not excluding other elements.

A group or atom that replaces a hydrogen atom is also called a substituent.

Any particular molecule or group can have one or more substituent depending on the number of hydrogen atoms that can be replaced.

The symbol "–" represents a covalent bond and can also be used in a radical group to indicate the point of attachment to another group. In chemical structures, the symbol is commonly used to represent a methyl group in a molecule.

The term "therapeutically effective amount" means an amount of a compound that ameliorates, attenuates or eliminates one or more symptom of a particular disease or condition, or prevents or delays the onset of one of more symptom of a particular disease or condition.

The terms "patient" and “subject”may be used interchangeably and mean animals, such as dogs, cats, cows, horses, sheep and humans. Particular patients are mammals. The term patient includes males and females.

The term "pharmaceutically acceptable" means that the referenced substance, such as a compound of Formula I, or a salt of a compound of Formula I, or a formulation containing a compound of Formula I, or a particular excipient, are suitable for administration to a patient.

The terms "treating", "treat" or "treatment" and the like include preventative (e.g., prophylactic) and palliative treatment.

The term “excipient” means any pharmaceutically acceptable additive, carrier, diluent, adjuvant, or other ingredient, other than the active pharmaceutical ingredient (API), which is typically included for formulation and/or administration to a patient.

The compounds of the present invention are administered to a patient in a therapeutically effective amount. The compounds can be administered alone or as part of a pharmaceutically acceptable composition or formulation. In addition, the compounds or compositions can be administered all at once, as for example, by a bolus injection, multiple times, such as by a series of tablets, or delivered substantially uniformly over a period of time, as for example, using transdermal delivery. It is also noted that the dose of the compound can be varied over time.

In addition, the compounds of the present invention can be administered alone, in combination with other compounds of the present invention, or with other pharmaceutically active compounds. The other pharmaceutically active compounds can be intended to treat the same disease or condition as the compounds of the present invention or a different disease or condition. If the patient is to receive or is receiving multiple pharmaceutically active compounds, the compounds can be administered simultaneously, or sequentially. For example, in the case of tablets, the active compounds may be found in one tablet or in separate tablets, which can be administered at once or sequentially in any order. In addition, it should be recognized that the compositions may be different forms. For example, one or more compound may be delivered via a tablet, while another is administered via injection or orally as a syrup. All combinations, delivery methods and administration sequences are contemplated.

The term "cancer" means a physiological condition in mammals that is characterized by unregulated cell growth. General classes of cancers include carcinomas, lymphomas, sarcomas, and blastomas.

The compounds of the present invention can be used to treat cancer. The methods of treating a cancer comprise administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I, IA, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof.

The compounds of the present invention can be used to treat tumors. The methods of treating a tumor comprise administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I, IA, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof.

The invention also concerns the use of a compound of the present invention in the manufacture of a medicament for the treatment of a condition such as a cancer.

Cancers which may be treated with compounds of the present invention include, without limitation, carcinomas such as cancer of the bladder, breast, colon, rectum, kidney, liver, lung (small cell lung cancer, and non-small-cell lung cancer), esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage (including leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma); hematopoietic tumors of myeloid lineage (including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia); tumors of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas,

e.g., soft tissue and bone); tumors of the central and peripheral nervous system (including astrocytoma, neuroblastoma, glioma and schwannomas); and other tumors (including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma). Other cancers that can be treated with a compound of the present invention include endometrial cancer, head and neck cancer, glioblastoma, malignant ascites, and hematopoietic cancers.

Particular cancers that can be treated by the compounds of the present invention include soft tissue sarcomas, bone cancers such as osteosarcoma, breast tumors, bladder cancer, Li-Fraumeni syndrome, brain tumors, rhabdomyosarcoma, adrenocortical carcinoma, colorectal cancer, non-small cell lung cancer, and acute myeleogenous leukemia (AML).

In a particular embodiment of the invention that relates to the treatment of cancers, the cancer is identified as p53wildtype ($p53^{WT}$). In another particular embodiment, the cancer is identified as $p53^{WT}$ and CDKN2A mutant. In another aspect, the present invention provides a diagnostic for determining which patients should be administered a compound of the present invention. For example, a sample of a patient's cancer cells may be taken and analyzed to determine the status of the cancer cells with respect to p53 and/or CDKN2A. In one aspect, a patient having a cancer that is $p53^{WT}$ will be selected for treatment over patients having a cancer that is mutated with respect to p53. In another aspect, a patient having a cancer that is both $p53^{WT}$ and has a mutant CDNK2A protein is selected over a patient that does not have these characteristics. The taking of a cancer cells for analyses is well known to those skilled in the art. The term "$p53^{WT}$" means a protein encoded by genomic DNA sequence no. NC_000017 version 9 (7512445..7531642)(GenBank); a protein encoded by cDNA sequence no. NM_000546 (GenBank); or a protein having the GenBank sequence no. NP_000537.3. The term "CDNK2A mutant" means a CDNK2A protein that in not wildtype. The term "CDKN2A wildtype" means a protein encoded by genomic DNA sequence no. 9:21957751-21984490 (Ensembl ID); a protein encoded by cDNA sequence no. NM_000077 (GenBank) or NM_058195 9GenBank) or; or a protein having the GenBank sequence no. NP_000068 or NP_478102.

The compounds of the present invention can also be used to treat hyperproliferative disorders such as thyroid hyperplasia (especially Grave's disease), and cysts (such as hypervascularity of ovarian stroma, characteristic of polycystic ovarian syndrome (Stein-Leventhal syndrome)).

The compounds of the present invention can also be used to treat the following diseases or conditions: asthma, chronic obstructive pulmonary disease (COPD), emphysema, psoriasis,

contact dermatitis, conjunctivitis, allergic rhinitis, systemic lupus erythematosus (SLE), ulcerative colitis, Crohn's disease, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, Alzheimer's disease, atherosclerosis and Huntington's disease.

The compounds of the present invention can also be used to treat inflammatory diseases, hypoxia, ulcers, viral infections, bacterial infections, and bacterial sepsis.

The compounds of Formula I, IA, IB, IC, ID or IE, or the pharmaceutically acceptable salts thereof, may also be administered in combination with one or more additional pharmaceutically active compounds/agents. In a particular embodiment, the additional pharmaceutically active agent is an agent that can be used to treat a cancer. For example, an additional pharmaceutically active agent can be selected from antineoplastic agents, anti-angiogenic agents, chemotherapeutic agents and peptidal cancer therapy agents. In yet another embodiment, the antineoplastic agents are selected from antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents, kinase inhibitors, miscellaneous agents and combinations thereof. It is noted that the additional pharmaceutically active compounds/agents may be a traditional small organic chemical molecules or can be macromolecules such as a proteins, antibodies, peptibodies, DNA, RNA or fragments of such macromolecules.

Examples of specific pharmaceutically active agents that can be used in the treatment of cancers and that can be used in combination with one or more compound of the present invention include: methotrexate; tamoxifen; fluorouracil; 5-fluorouracil; hydroxyurea; mercaptopurine; cisplatin; carboplatin; daunorubicin; doxorubicin; etoposide; vinblastine; vincristine; pacitaxel; thioguanine; idarubicin; dactinomycin; imatinib; gemcitabine; altretamine; asparaginase; bleomycin; capecitabine; carmustine; cladisat. aq. NaCl solution; cyclophosphamine; cytarabine; decarazine; docetaxel; idarubicin; ifosfamide; irinotecan; fludarabine; mitosmycin; mitoxane; mitoxantrone; topotecan; vinorelbine; adriamycin; mithram; imiquimod; alemtuzmab; exemestane; bevacizumab; cetuximab; azacitidine; clofarabine; decitabine; desatinib; dexrazoxane; docetaxel; epirubicin; oxaliplatin; erlotinib; raloxifene; fulvestrant; letrozole; gefitinib; gemtuzumab; trastuzumab; gefitinib; ixabepilone; lapatinib; lenalidomide; aminolevulinic acid; temozolomide; nelarabine; sorafenib; nilotinib; pegaspargase; pemetrexed; rituximab; dasatinib; thalidomide; bexarotene; temsirolimus; bortezomib; vorinostat; capecitabine; zoledronic acid; anastrozole; sunitinib; aprepitant and nelarabine, or a pharmaceutically acceptable salt thereof.

Additional pharmaceutically active agents that can be used in the treatment of cancers and that can be used in combination with one or more compound of the present invention

include: vascular endothelial growth factor (VEGF) inhibitors, hepatocyte growth factor/scatter factor (HGF/SF) inhibitors, angiopoietin 1 and/or 2 inhibitors, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) agonists, recombinant human apo2 ligand (TRAIL), insulin-like growth factor 1 receptor (IGFR-1) inhibitors, cFMS inhibitors, HER 2 inhibitors, c-met inhibitors, aurora kinase inhibitors, CDK 4 and/or 6 inhibitors, and B-raf inhibitors.

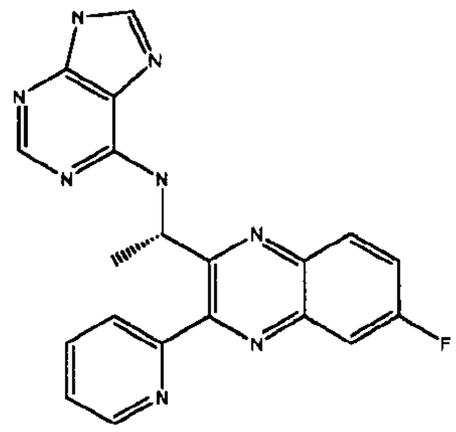
Further additional pharmaceutically active agents that can be used in the treatment of cancers and that can be used in combination with one or more compound of the present invention include antibody drug conjugates (ADCs) whereby an antibody that binds to a protein, preferably on a cancer cell, is conjugated using a linker with a chemical compound that is detrimental to the cancer cell. Examples of chemical compounds that are detrimental to a cancer cell include maytansinoids derivatives and auristatin derivatives.

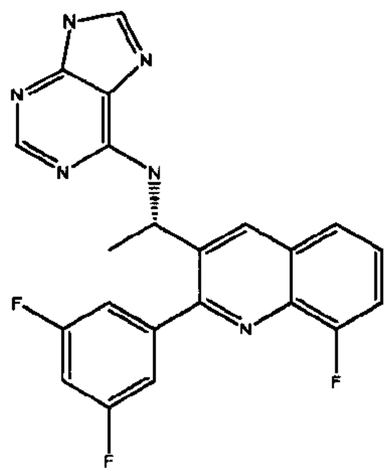
Still further additional pharmaceutically active agents that can be used in the treatment of cancers and that can be used in combination with one or more compound of the present invention include: epoetin alfa; darbepoetin alfa; panitumumab; pegfilgrastim; palifermin; filgrastim; denosumab; ancestim; AMG 102; AMG 319; AMG 386; AMG 479 (Ganitumab); AMG 511, AMG 900, AMG 655 (Conatumumab); AMG 745; AMG 951; and AMG 706 (Motesanib), or a pharmaceutically acceptable salt thereof.

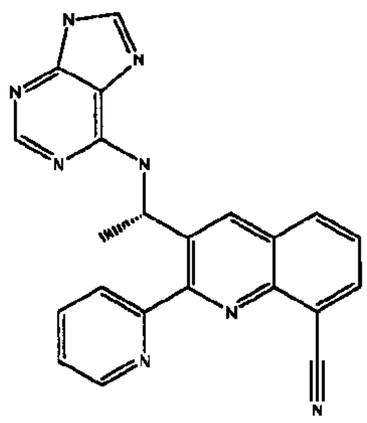
In another aspect, the present invention relates to the use of the compounds of the present invention in combination with one or more pharmaceutical agent that is an inhibitor of a protein in the phosphatidylinositol 3-kinase (PI3K) pathway. Combinations of compounds of the present invention along with inhibitors of proteins in the PI3K pathway have shown synergy in cancer cell growth assays, including enhanced apoptosis and cell killing. Examples of proteins in the PI3K pathway include PI3K, mTOR and PKB (also known as Akt). The PI3K protein exists in several isoforms including α, β, δ, or γ. It is contemplated that a PI3K inhibitor that can be used in combination with a compound of the present invention can be selective for one or more isoform. By selective it is meant that the compounds inhibit one or more isoform more that other isoforms. Selectivity is a concept well known to those is the art and can be measured with well known activity in vitro or cell-based assays. Preferred selectivity includes greater than 2 fold, preferably 10 fold, or more preferably 100 fold greater selectivity for one or more isoform over the other isoforms. In one aspect, the PI3K inhibitors that can be used in combination with compounds of the present invention is a PI3K α selective inhibitor. In another aspect the compound is a PI3K δ selective inhibitor.

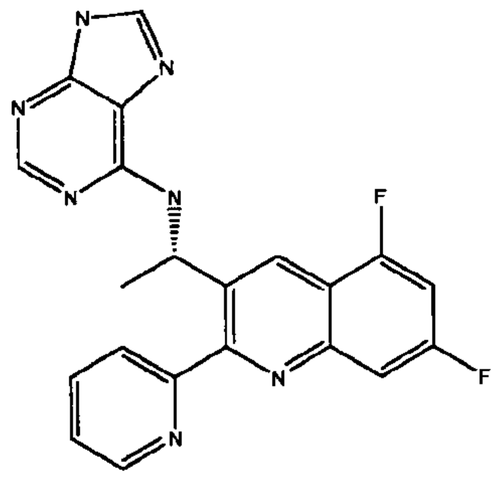
Examples of PI3K inhibitors that can be used in combination with one or more compounds of the present invention include those disclosed in the following: PCT published application no. WO2010/151791; PCT published application no. WO2010/151737; PCT published application no.WO2010/151735; PCT published application no. WO2010151740; PCT published application no. WO2008/118455; PCT published application no. WO2008/118454; PCT published application no. WO2008/118468; U.S. published application no. US20100331293; U.S. published application no. US20100331306; U.S. published application no. US20090023761; U.S. published application no. US20090030002; U.S. published application no. US20090137581; U.S. published application no. US2009/0054405; U.S. published application no. U.S. 2009/0163489; U.S. published application no. US 2010/0273764; U.S. published application no. U.S. 2011/0092504; or PCT published application no. WO2010/108074.

Preferred PI3K inhibitors for use in combination with compounds of the present invention include:


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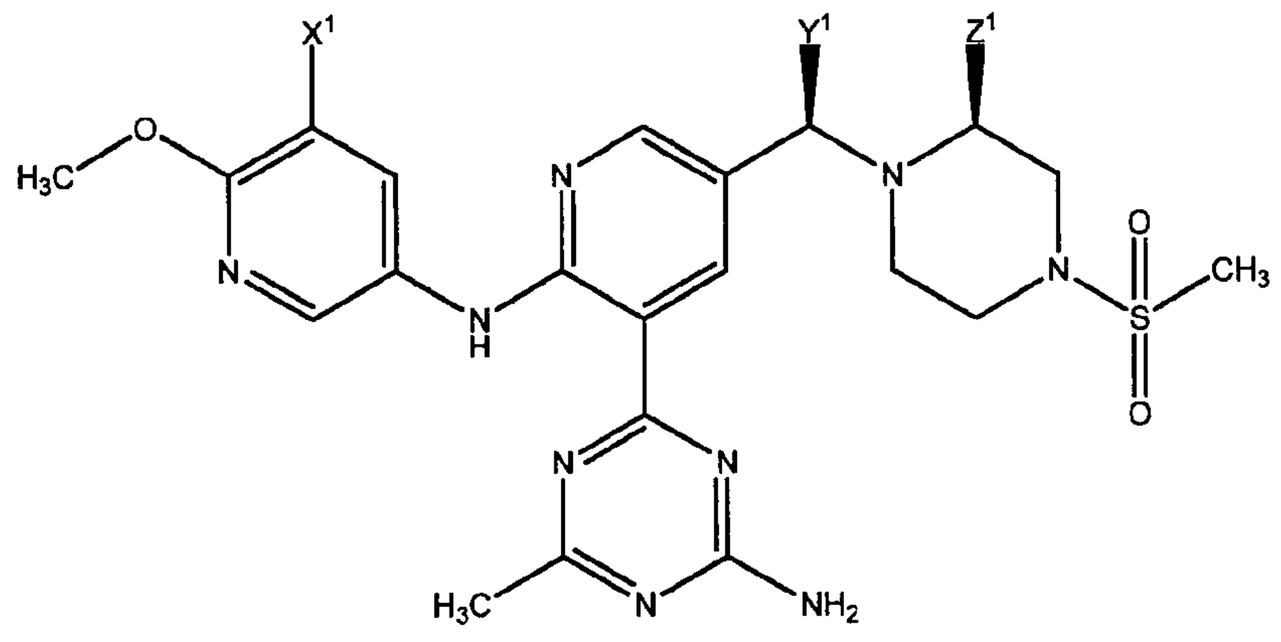

;


; or



, or a pharmaceutically acceptable salt thereof.

Also preferred is a compound of Formula IIa below, or a pharmaceutically acceptable salt thereof,



IIa

wherein X^1 is fluorine or hydrogen; Y^1 is hydrogen or methyl; and Z^1 is hydrogen or methyl.

Compounds that inhibit both PI3K and mTOR (dual inhibitors) are known. In still another aspect, the present invention provides the use of dual PI3K and mTOR inhibitors for use in combination with a compound of the present invention.

mTOR is a protein in the PI3K pathway. It is another aspect of the present invention to use an mTOR inhibitor in combination with one or more compounds of the present invention. mTOR inhibitors that can be used in combination with compounds of the present invention include those disclosed in the following documents: PCT published application no. WO2010/132598 or PCT published application no. WO2010/096314.

PKB (Akt) is also a protein in the PI3K pathway. It is another aspect of the present invention to use an mTOR inhibitor in combination with one or more compounds of the present invention. PKB inhibitors that can be used in combination with compounds of the present invention include those disclosed in the following documents: U.S. patent no. 7,354,944; U.S. patent no. 7,700,636; U.S. patent no. 7,919,514; U.S. patent no. 7,514,566;

U.S. patent application publication no. US 2009/0270445 A1; U.S. patent no. 7,919,504; U.S. patent no. 7,897,619; or PCT published application no. WO 2010/083246 A1.

The compounds of the present invention can be used in combination with CDK4 and/or 6 inhibitors. CDK 4 and/or 6 inhibitors that can be used in combination with compounds of the present invention include those disclosed in the following documents: PCT published application no. WO 2009/085185 or U.S. patent application publication no. US2011/0097305.

The compounds of the present invention can also be used in combination with pharmaceutically active agents that treat nausea. Examples of agents that can be used to treat nausea include: dronabinol; granisetron; metoclopramide; ondansetron; and prochlorperazine; or a pharmaceutically acceptable salt thereof.

In addition, the compounds of the present invention can be used in combination with other agents that can be used to treat cancer such as acemannan; aclarubicin; aldesleukin; alitretinoin; amifostine; amrubicin; amsacrine; anagrelide; arglabin; arsenic trioxide; BAM 002 (Novelos); bicalutamide; broxuridine; celmoleukin; cetrorelix; cladribine; clotrimazole; DA 3030 (Dong-A); daclizumab; denileukin diftitox; deslorelin; dilazep; docosanol; doxercalciferol; doxifluridine; bromocriptine; cytarabine; HIT diclofenac; interferon alfa; tretinoin; edelfosine; edrecolomab; eflornithine; emitefur; epirubicin; epoetin beta; etoposide phosphate; exisulind; fadrozole; finasteride; fludarabine phosphate; formestane; fotemustine; gallium nitrate; gemtuzumab zogamicin; gimeracil/oteracil/tegafur combination; glycopine; goserelin; heptaplatin; human chorionic gonadotropin; human fetal alpha fetoprotein; ibandronic acid; interferon alfa; interferon alfa natural; interferon alfa-2; interferon alfa-2a; interferon alfa-2b; interferon alfa-N1; interferon alfa-n3; interferon alfacon-1; interferon alpha natural; interferon beta; interferon beta-1a; interferon beta-1b; interferon gamma natural; interferon gamma-1a; interferon gamma-1b; interleukin-1 beta; iobenguane; irsogladine; lanreotide; LC 9018 (Yakult); leflunomide; lenograstim; lentinan sulfate; letrozole; leukocyte alpha interferon; leuprorelin; levamisole + fluorouracil; liarozole; lobaplatin; lonidamine; lovastatin; masoprocol; melarsoprol; metoclopramide; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitoxantrone; molgramostim; nafarelin; naloxone + pentazocine; nartograstim; nedaplatin; nilutamide; noscapine; novel erythropoiesis stimulating protein; NSC 631570 octreotide; oprelvekin; osaterone; paclitaxel; pamidronic acid; peginterferon alfa-2b; pentosan polysulfate sodium; pentostatin; picibanil; pirarubicin; rabbit antithymocyte polyclonal antibody; polyethylene glycol interferon alfa-2a; porfimer sodium; raltitrexed; rasburicase; rhenium Re 186 etidronate; RII retinamide; romurtide; samarium (153 Sm) lexidronam; sargramostim; sizofiran; sobuzoxane; sonermin;

strontium-89 chloride; suramin; tasonermin; tazarotene; tegafur; temoporfin; teniposide; tetrachlorodecaoxide; thymalfasin; thyrotropin alfa; toremifene; tositumomab-iodine 131; treosulfan; tretinoin; trilostane; trimetrexate; triptorelin; tumor necrosis factor alpha natural; ubenimex; bladder cancer vaccine; Maruyama vaccine; melanoma lysate vaccine; valrubicin; verteporfin; virulizin; zinostatin stimalamer; abarelix; AE 941 (Aeterna); ambamustine; antisense oligonucleotide; bcl-2 (Genta); APC 8015 (Dendreon); dexaminoglutethimide; diaziquone; EL 532 (Elan); EM 800 (Endorecherche); eniluracil; etanidazole; fenretinide; filgrastim SD01 (Amgen); galocitabine; gastrin 17 immunogen; HLA-B7 gene therapy (Vical); granulocyte macrophage colony stimulating factor; histamine dihydrochloride; ibritumomab tiuxetan; ilomastat; IM 862 (Cytran); interleukin-2; iproxifene; LDI 200 (Milkhaus); leridistim; lintuzumab; CA 125 monoclonal antibody(MAb) (Biomira); cancer MAb (Japan Pharmaceutical Development); HER-2 and Fc MAb (Medarex); idiotypic 105AD7 MAb (CRC Technology); idiotypic CEA MAb (Trilex); LYM-1-iodine 131 MAb (Techniclone); polymorphic epithelial mucin-yttrium 90 MAb (Antisoma); marimastat; menogaril; mitumomab; motexafin gadolinium; MX 6 (Galderma); nolatrexed; P 30 protein; pegvisomant; porfiromycin; prinomastat; RL 0903 (Shire); rubitecan; satraplatin; sodium phenylacetate; sparfosic acid; SRL 172 (SR Pharma); SU 5416 (Pfizer); TA 077 (Tanabe); tetrathiomolybdate; thaliblastine; thrombopoietin; tin ethyl etiopurpurin; tirapazamine; cancer vaccine (Biomira); melanoma vaccine (New York University); melanoma vaccine (Sloan Kettering Institute); melanoma oncolysate vaccine (New York Medical College); viral melanoma cell lysates vaccine (Royal Newcastle Hospital); or valspodar. It is noted that the agents recited above may also be administered as pharmaceutically acceptable salts when appropriate.

The compounds of the present invention may also be used in combination with radiation therapy, hormone therapy, surgery and immunotherapy, which therapies are well known to those skilled in the art.

Since one aspect of the present invention contemplates the treatment of the disease/conditions with a combination of pharmaceutically active compounds that may be administered separately, the invention further relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of the present invention, and a second pharmaceutical compound. The kit comprises a container for containing the separate compositions such as a divided bottle or a divided foil packet. Additional examples of containers include syringes, boxes and bags. Typically, the kit comprises directions for the use of the separate components. The kit form is particularly

advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician or veterinarian.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week, Monday, Tuesday, . . . etc . . . Second Week, Monday, Tuesday, . . . " etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of a compound of the present invention can consist of one tablet or capsule, while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this and aid in correct administration of the active agents.

In another specific embodiment of the invention, a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

The compounds of the present invention and other pharmaceutically active compounds, if desired, can be administered to a patient either orally, rectally, parenterally, (for example, intravenously, intramuscularly, or subcutaneously) intracisternally, intravaginally, intraperitoneally, intravesically, locally (for example, powders, ointments or drops), or as a buccal or nasal spray. All methods that are used by those skilled in the art to administer a pharmaceutically active agent are contemplated.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Microorganism contamination can be prevented by adding various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Prolonged absorption of injectable pharmaceutical compositions can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, mannitol, and silicic acid; (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (c) humectants, as for example, glycerol; (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (a) solution retarders, as for example, paraffin; (f) absorption accelerators, as for example, quatemary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid

polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, and tablets, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be used as fillers in soft and hard filled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethylene glycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may also contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage form may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame seed oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. Suspensions, in addition to the active compound, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administration are preferable suppositories, which can be prepared by mixing the compounds of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax, which are solid at ordinary room temperature, but liquid at body temperature, and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of the present invention include ointments, powders, sprays and inhalants. The active compound or fit compounds are admixed under sterile condition with a physiologically acceptable carrier, and any preservatives, buffers,

or propellants that may be required. Opthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 3,000 mg per day. For a normal adult human having a body weight of about 70 kg, a dosage in the range of about 0.01 to about 100 mg per kilogram body weight is typically sufficient. The specific dosage and dosage range that can be used depends on a number of factors, including the requirements of the patient, the severity of the condition or disease being treated, and the pharmacological activity of the compound being administered. The determination of dosage ranges and optimal dosages for a particular patient is within the ordinary skill in the art.

The compounds of the present invention can be administered as pharmaceutically acceptable salts, esters, amides or prodrugs. The term "salts" refers to inorganic and organic salts of compounds of the present invention. The salts can be prepared in situ during the final isolation and purification of a compound, or by separately reacting a purified compound in its free base or acid form with a suitable organic or inorganic base or acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, palmitiate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. The salts may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. See, for example, S. M. Berge, et al., "Pharmaceutical Salts," J Pharm Sci, 66: 1-19 (1977).

Examples of pharmaceutically acceptable esters of the compounds of the present invention include C_1-C_8 alkyl esters. Acceptable esters also include C_5-C_7 cycloalkyl esters, as well as arylalkyl esters such as benzyl. C_1-C_4 alkyl esters are commonly used. Esters of compounds of the present invention may be prepared according to methods that are well known in the art.

Examples of pharmaceutically acceptable amides of the compounds of the present invention include amides derived from ammonia, primary C_1-C_8 alkyl amines, and secondary C_1-C_8 dialkyl amines. In the case of secondary amines, the amine may also be in the form of a 5 or 6 membered heterocycloalkyl group containing at least one nitrogen atom. Amides derived from ammonia, C_1-C_3 primary alkyl amines and C_1-C_2 dialkyl secondary amines are commonly

used. Amides of the compounds of the present invention may be prepared according to methods well known to those skilled in the art.

The term "prodrug" means compounds that are transformed in vivo to yield a compound of the present invention. The transformation may occur by various mechanisms, such as through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Prodrugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

To illustrate, if the compound of the invention contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C_1-C_8 alkyl, (C_2-$C1_2$)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)aminomethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di(C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-$_3$)alkyl.

Similarly, if a compound of the present invention comprises an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, –P(O)(OH)$_2$, –P(O)(O(C_1-C_6)alkyl)$_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

The compounds of the present invention may contain asymmetric or chiral centers, and therefore, exist in different stereoisomeric forms. It is contemplated that all stereoisomeric forms of the compounds as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention contemplates all geometric and positional isomers. For example, if the compound contains a double bond, both the cis and trans forms (designated as S and E, respectively), as well as mixtures, are contemplated.

Mixture of stereoisomers, such as diastereomeric mixtures, can be separated into their individual stereochemical components on the basis of their physical chemical differences by known methods such as chromatography and/or fractional crystallization. Enantiomers can can also be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., an alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some compounds may be atropisomers (e.g., substituted biaryls).

The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water (hydrate), ethanol, and the like. The present invention contemplates and encompasses both the solvated and unsolvated forms.

It is also possible that compounds of the present invention may exist in different tautomeric forms. All tautomers of compounds of the present invention are contemplated. For example, all of the tautomeric forms of the tetrazole moiety are included in this invention. Also, for example, all keto-enol or imine-enamine forms of the compounds are included in this invention.

Those skilled in the art will recognize that the compound names and structures contained herein may be based on a particular tautomer of a compound. While the name or structure for only a particular tautomer may be used, it is intended that all tautomers are encompassed by the present invention, unless stated otherwise.

It is also intended that the present invention encompass compounds that are synthesized in vitro using laboratory techniques, such as those well known to synthetic chemists; or synthesized using in vivo techniques, such as through metabolism, fermentation, digestion, and the like. It is also contemplated that the compounds of the present invention may be synthesized using a combination of in vitro and in vivo techniques.

The present invention also includes isotopically-labelled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{16}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl. In one aspect, the present invention relates to compounds wherein one or more hydrogen atom is replaced with deuterium (^{2}H) atoms.

Compounds of the present invention that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detection. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of this invention can generally be prepared by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

The compounds of the present invention may exist in various solid states including crystalline states and as an amorphous state. The different crystalline states, also called polymorphs, and the amorphous states of the present compounds are contemplated as part of this invention.

In synthesizing compounds of the present invention, it may be desirable to use certain leaving groups. The term "leaving groups" ("LG") generally refer to groups that are displaceable by a nucleophile. Such leaving groups are known in the art. Examples of leaving groups include, but are not limited to, halides (e.g., I, Br, F, Cl), sulfonates (e.g., mesylate, tosylate), sulfides (e.g., SCH_3), N-hydroxsuccinimide, N-hydroxybenzotriazole, and the like. Examples of nucleophiles include, but are not limited to, amines, thiols, alcohols, Grignard reagents, anionic species (e.g., alkoxides, amides, carbanions) and the like.

The examples presented below illustrate specific embodiments of the present invention. These examples are meant to be representative and are not intended to limit the scope of the claims in any manner. Unless otherwise noted, when a percent is used herein with respect to a solid, the percent is by weight with respect to the referenced solid composition. When a percent is used herein with respect to a liquid, the percent is by volume with respect to the referenced solution.

^{1}H-NMR spectra were typically acquired on a Bruker Avance III 500 spectrometer system (Bruker, Bilerica, MA) operating at a ^{1}H frequency of 500.13 MHz, equipped with a Bruker 5 mm PABBI probe with a *z*-axis gradient; or on a Bruker Avance II 400 spectrometer operating at a ^{1}H frequency of 400.23 MHz, equipped with a Bruker 5 mm PABBO probe with

a *z*-axis gradient. Samples were typically dissolved in 500 μL of either DMSO-d_6 or CD_3OD for NMR analysis. ^1H chemical shifts are referenced to the residual solvent signals from DMSO-d_6 at δ 2.50 and CD_3OD at δ 3.30.

Significant peaks are tabulated and typically include: number of protons, multiplicity (s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; br s, broad singlet) and coupling constant(s) in Hertz.

Electron Ionization (EI) mass spectra were typically recorded on an Agilent Technologies 6140 Quadrupole LC/MS mass spectrometer. Mass spectrometry results are reported as the ratio of mass over charge, sometimes followed by the relative abundance of each ion (in parentheses). Starting materials in the Examples below are typically either available from commercial sources such as Sigma-Aldrich, St. Louis, MO, or via literature procedures.

The following abbreviations may be used herein:

~	about
+ve or pos. ion	positive ion
Δ	heat
Ac	acetyl
Ac_2O	acetic anhydride
aq	aqueous
AcOH	acetic acid
Bn	benzyl
Boc	tert-butyloxycarbonyl
BSA	bovine serum albumin
Bu	butyl
Bz	benzoyl
Calcd or Calc'd	calculated
Conc.	concentrated
CSA	camphor-10-sulfonic acid
d	day(s)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DEA	diethylamine

Dess-Martin periodinane; Dess-Martin reagent	1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one
DIEA or DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DTT	dithiothreitol
DVB	divinylbenzene
EDC	N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide
eq	equivalent
ESI or ES	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethyl alcohol
g	gram(s)
h	hour(s)
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HBTU	O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluorophosphate
Hex	hexanes
HMPA	hexamethylphosphoramide
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	hydroxybenzotriazole
HPLC	high pressure liquid chromatography
IPA or iPrOH	isopropyl alcohol
Jones reagent	solution of chromium(IV)oxide and sulfuric acid in water
KHMDS	potassium hexamethyldisilazide
KOAc	potassium acetate
LCMS, LC-MS or LC/MS	liquid chromatography mass spectrometry
LDA	lithium diisopropylamide

LHMDS or LiHMDS	lithium hexamethyldisilazide
L-Selectride®	lithium tri-*sec*-butylborohydride (Sigma-Aldrich, St. Louis)
M	molar (mol L^{-1})
m/z	mass divided by charge
mCPBA	m-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeI	iodomethane
MeOH	methyl alcohol
mg	milligram(s)
min	minute(s)
mL	milliliter(s)
M	mole(s)
MS	mass spectrometry
MsCl	methanesulfonyl chloride
MTBE or MtBE	methyl tert-butyl ether
m/z	mass-to-charge ratio
NaHMDS	sodium hexamethyldisilazide
NaOtBu	sodium tert-butoxide
NBS	N-bromosuccinimide
nBuLi	n-butyl lithium
NMO	N-methylmorpholine-N-oxide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
N-Selectride®	sodium tri-*sec*-butylborohydride (Sigma-Aldrich, St. Louis)
PBS	phosphate buffered saline
PMB	paramethoxybenzyl
Pr	propyl
ppm	parts per million
rac	racemic
RP-HPLC or RPHPLC	reversed phase high pressure liquid chromatography
RT or rt	room temperature
sat. or sat'd or satd	saturated
SFC	supercritical fluid chromatography

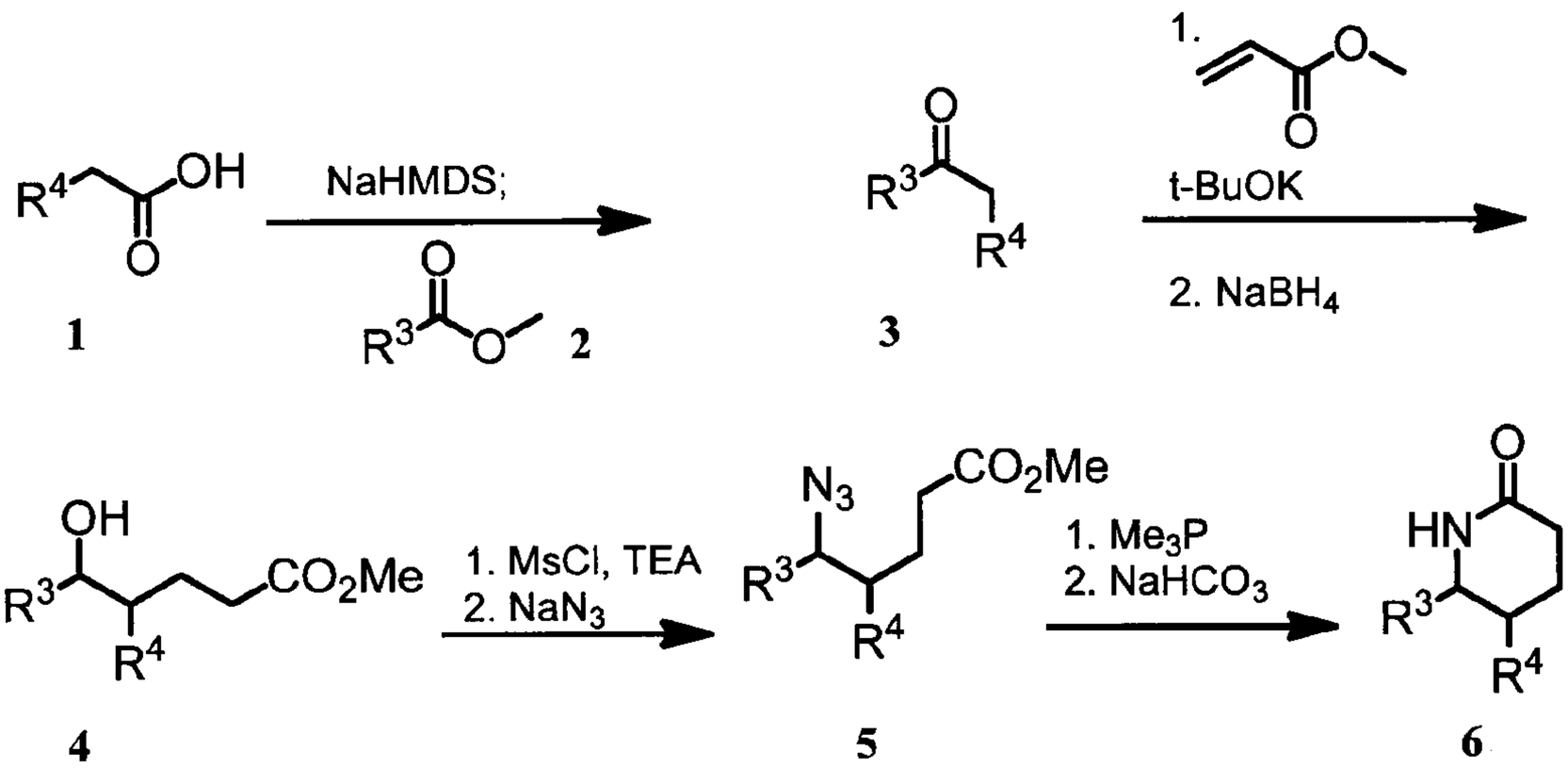
TBAF	tetrabutylammonium fluoride
TBDMS	tert-butyldimethylsilyl
TBDMS-Cl	tert-butyldimethylsilyl chloride
TBDPS	*tert*-butyldiphenylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
tert or t	tertiary
TFA	triflouroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl or trimethylsilane
TPAP	tetrapropylammonium perruthenate
t_R	retention time
tBuOH	tert-butyl alcohol
v/v	volume per volume

EXAMPLES

General Synthetic Schemes

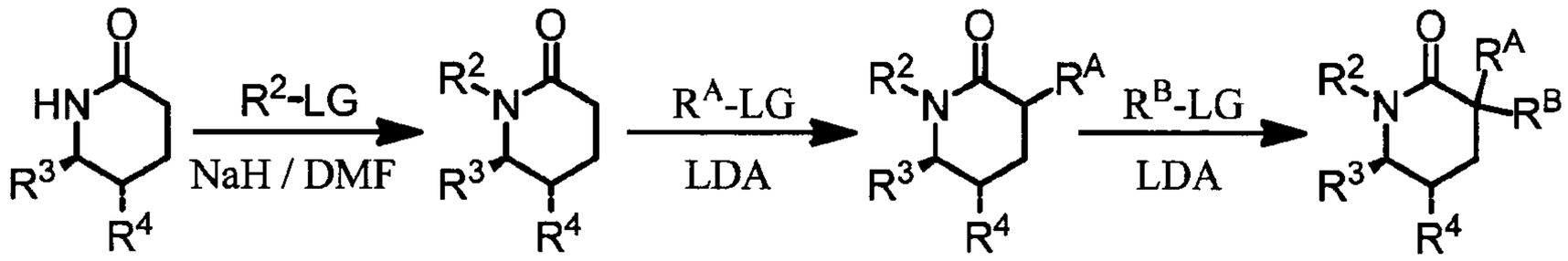
Compounds of the present invention generally can be prepared beginning with commercially available starting materials and using synthetic techniques known to those of skill in the art. Outlined below are some reaction schemes suitable for preparing compounds of the present invention. Further exemplification is found in the specific examples provided.

Scheme 1



As shown in **Scheme 1**, compounds of the present invention wherein R^a and R^b are both H, can be prepared by reacting a suitably substituted aryl acetic acid **1** and an aryl carboxylic acid **2** in an organic solvent or mixture of solvents (including aqueous mixtures) in the presence of a base, such as LHMDs or KHMDS to provide, after workup, a compound of formula **3**. Treatment of **3** with methyl acrylate in the presence of a base, such as tBuOK results in the formation of a 4,5-substituted 5-oxopentanoate, which can be reduced with a reducing reagent such as $NaBH_4$ or $LiBEt_3H$ in a suitable solvent such as THF, diethylether or dimethoxyethane to produce racemic compound **4**. **5** can in turn be obtained from **4** by converting the alcohol into a toluenesulfonate, methanesulfonate, or trifluoromethanesulfonate, followed by reaction with sodium azide in a suitable solvent such as, for example, DMF, DME or acetone. The azide can be reduced to a primary amine by a number of reducing agents including $NaBH_4$, H_2 and a catalyst, triphenylphosphine and trimethylphoshine, which in turn, upon treatment with a base, such as LiOH, K_2CO_3 or $NaHCO_3$ in an aqueous mixture with a suitable organic solvent, such as THF will cyclize to the piperidin-2-one **6**. Individual enantiomers of racemic **6** can be separated by chiral HPLC using, for example, a Chiralcel® OD-H 20 mm I.D. × 250 mm column (Daicel Chemical Industries LTD, Fort Lee, NJ) using 40% isopropyl alcohol/hexane as the eluent.

Scheme 2

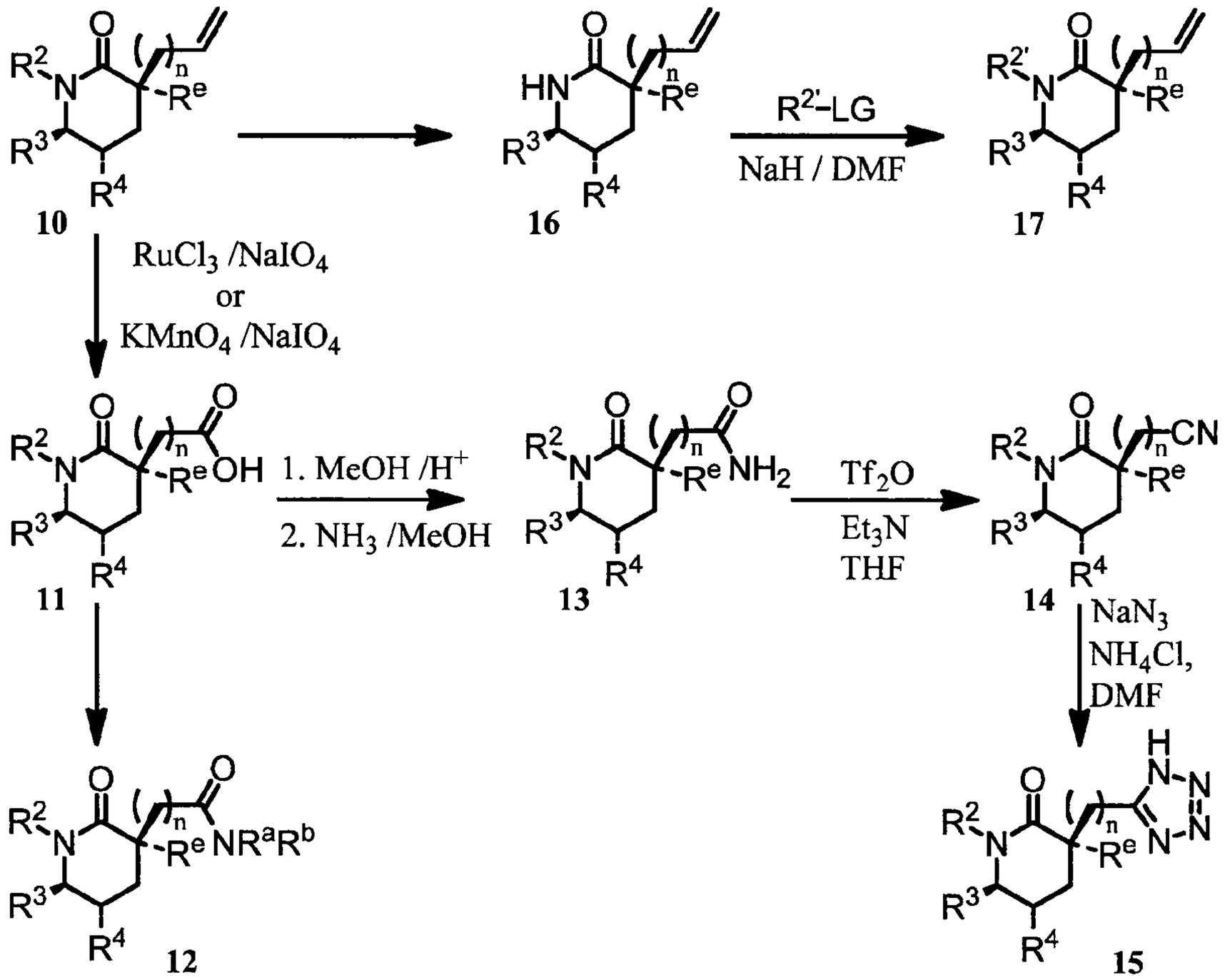


6 **7** **8** **9**

As shown in **Scheme 2**, the piperidin-2-one **6** can be further modified, for example by arylating or alkylating the nitrogen by methods well known to those of ordinary skill in the art. For example, reacting **6** with an alkyl halide in the presence of a base such as sodium hydride in a solvent such as DME, DMF or THF will accomplish this transformation. **7** may be further alkylated by treatment with a base such as lithium diisopropylamide or lithium hexamethyldisilazide in a suitable solvent such as THF, followed by reaction with an alkylating agent, such as an alkyl halide, alkyl methanesulfonate, alkyl trifluoromethanesulfonate, or alkyl toluenesulfonate to give intermediate **8**. If desired, the sequence may be repeated to give compounds of the general formula **9**. LG is a leaving group.

As shown in **Scheme 3**, the group attached to the nitrogen can potentially be removed to give intermediate **16**. For example treating a 2,4-dimethoxybenzyl derivative with TFA accomplishes such a transformation. Similar transformations are well documented (see *e.g.* P. G. M. Wuts and T. W. Greene, "Greene's protective groups in organic synthesis", 4th ed., John Wiley & Sons, New York, (2007)). Resubjecting compound **16** to alkylation conditions similar to the ones described above will give **17**.

Scheme 3

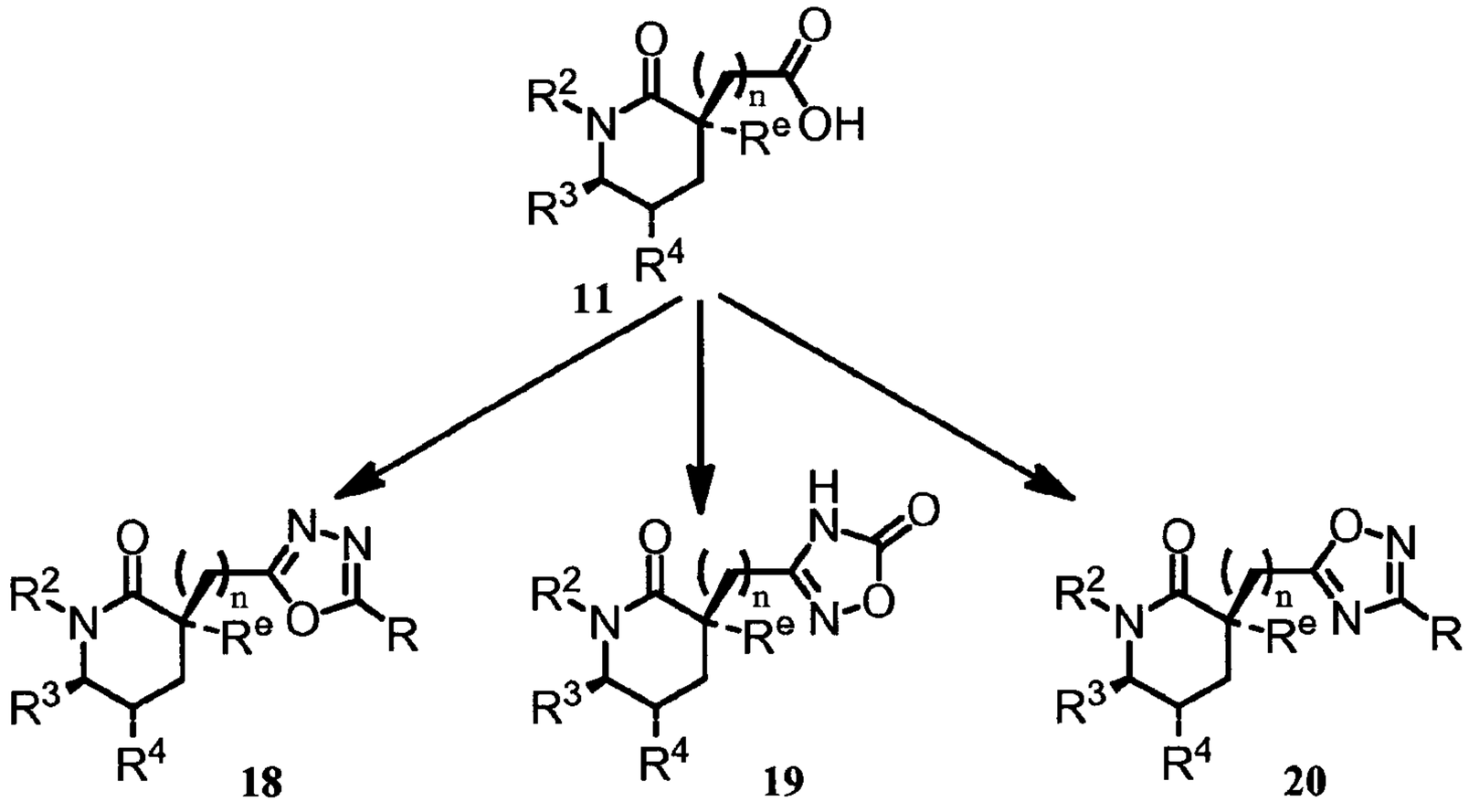


As further shown in **Scheme 3**, if one of the alkyl groups contains a double bond, this double bond can be converted into a carboxylic acid **11** by a number of methods known to those of ordinary skill in the art. For example, reacting **10** with a solution of periodate containing $KMnO_4$ or $RuCl_3$ (see *e.g.* R. U. Lemieux, E. von Rudloff, Can. J. Chem., 38, 1703, (1955)) will accomplish this transformation. The carboxylic acid **11** can, in turn, be converted into other groups such as an amide or hydrazide by methods well known to those of ordinary skill in the art. For example, the carboxylic acid **11** can be activated by condensation with a variety of coupling reagents, including hydroxybenzotriazole (HOBt) and N-hydroxysuccinimide (HOSu), for example, using dicyclohexylcarbodiimide (DCC) or a similar carbodiimide reagent or a wide variety of reagents such as those developed for formation of peptide bonds. Conditions for such reactions are well known to those of ordinary skill in the art. The activated intermediate, an ester of HOBt or HOSu, for example, can then be condensed with a wide variety of nucleophiles such as amines or alcohols.

Scheme 3 shows the conversion of a compound of formula **11** into an amide **12** by this sequence. Using ammonia as the nucleophile, compound **13** is obtained. Dehydration

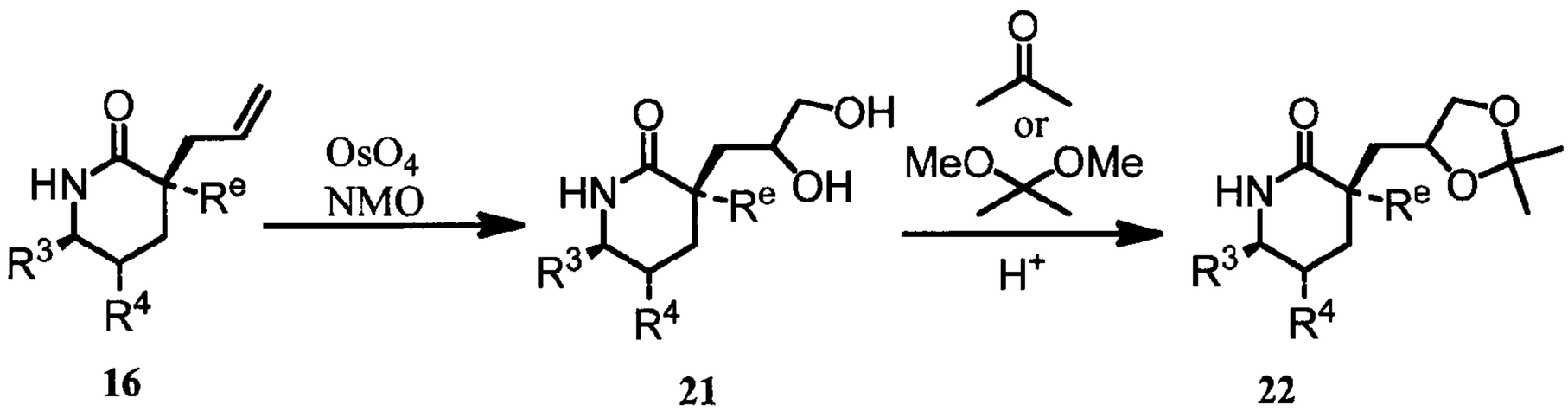
of the amide **13** to a nitrile **14** can be accomplished by a variety of methods. Phosphorous pentoxide is a common dehydrating reagent for this reaction, but many others are known to those skilled in the art (see e.g. R. C. Larock; Comprehensive Organic Transformations, 2nd ed., John Wiley & Sons, New York, pp. 1983, (1999)). The nitrile can, in turn, be converted into other groups such as a tetrazole by reacting the nitrile with an azide, such as sodium azide, lithium azide or hydrazoic acid in a solvent such as DMF or water.

Scheme 4



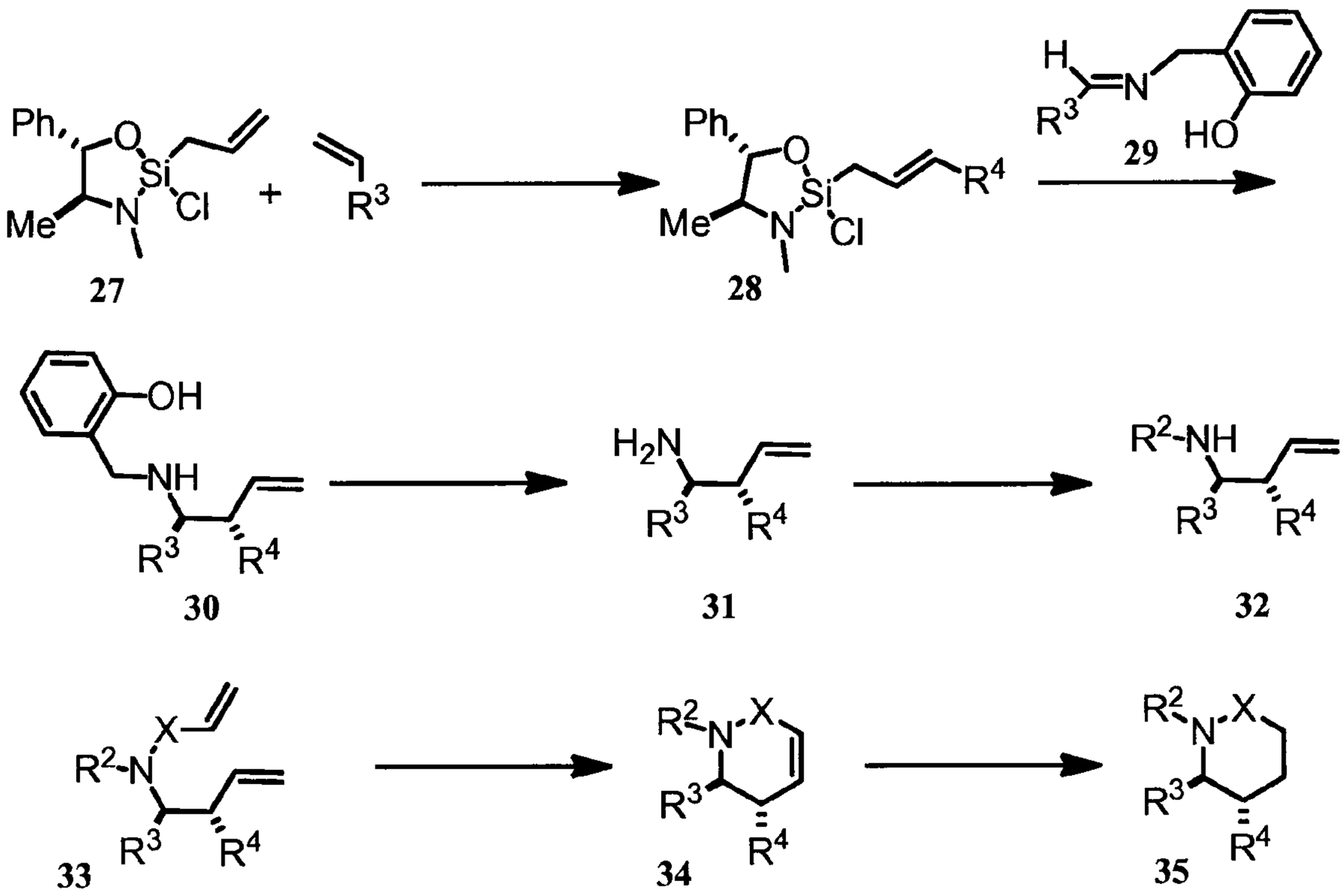
As shown in **Scheme 4,** the acid **11** can also be used to produce heterocyclic derivatives, such as, for example, [1,3,4]-oxadiazoles **18**, [1,2,4]-oxadiazol-5(4H)-ones **19**, and [1,2,4]-oxadiazoles **20** by methods well known to those of ordinary skill in the art. For example, converting the acid **11** into an diacylhydrazide, followed by treatment with a base at elevated temperature will provide **18**. In another example **11** is converted into a nitrile as described inScheme 3, which is treated with hydroxylamine. Reaction with 1,1'-carbonyldiimidazole in the presence of a base, such as DBU, generates **19** In yet another example, **11** reacts with a N-hydroxycarboxamidine derivative in the presence of 1,1'-carbonyldiimidazole, followed by treatment with tetrabutylammonium fluoride to give **20**.

Scheme 5



As shown in **Scheme 5**, a compound of formula **16** can also be dihydroxylated to give **21**. Osmiumtetroxide in the presence of a second oxidizing agent such as 4-methylmorpholine-4-oxide in a suitable solvent will accomplish such a transformation. **21** can be converted into **22** by reaction with acetone or 2,2-dimethoxypropane in the presence of an acid, such as methanesulfonic acid, p-toluenesulfonic caid or camphorsulfonic acid. Compound **22** can then be N-arylated or N-alkylated by a variety of methods well known to those of ordinary skill in the art, such as treating **22** with an alkylhalide, alkylmethanesulfonate or alkyltoluenesulfonate in the presence of a base such as butyllithium or sodium hydride in a solvent such as DME, DMF or THF. Treating **23** with an acid such as HCl or H_2SO_4 in the presence of water will give the diol **24**, which can be cleaved to the aldehyde **25** by a variety of oxidizing agents, such as periodic acid or lead tetraacetate (see e.g. Haines, A. H. *Methods for the Oxidation of Organic Compounds*, Vol 2.; p 277, Academic Press, NY, (1988)). The aldehyde **25** can be converted into the acid **26** by strong oxidizing agents including CrO_3 or a solution of periodate containing $RuCl_3$.

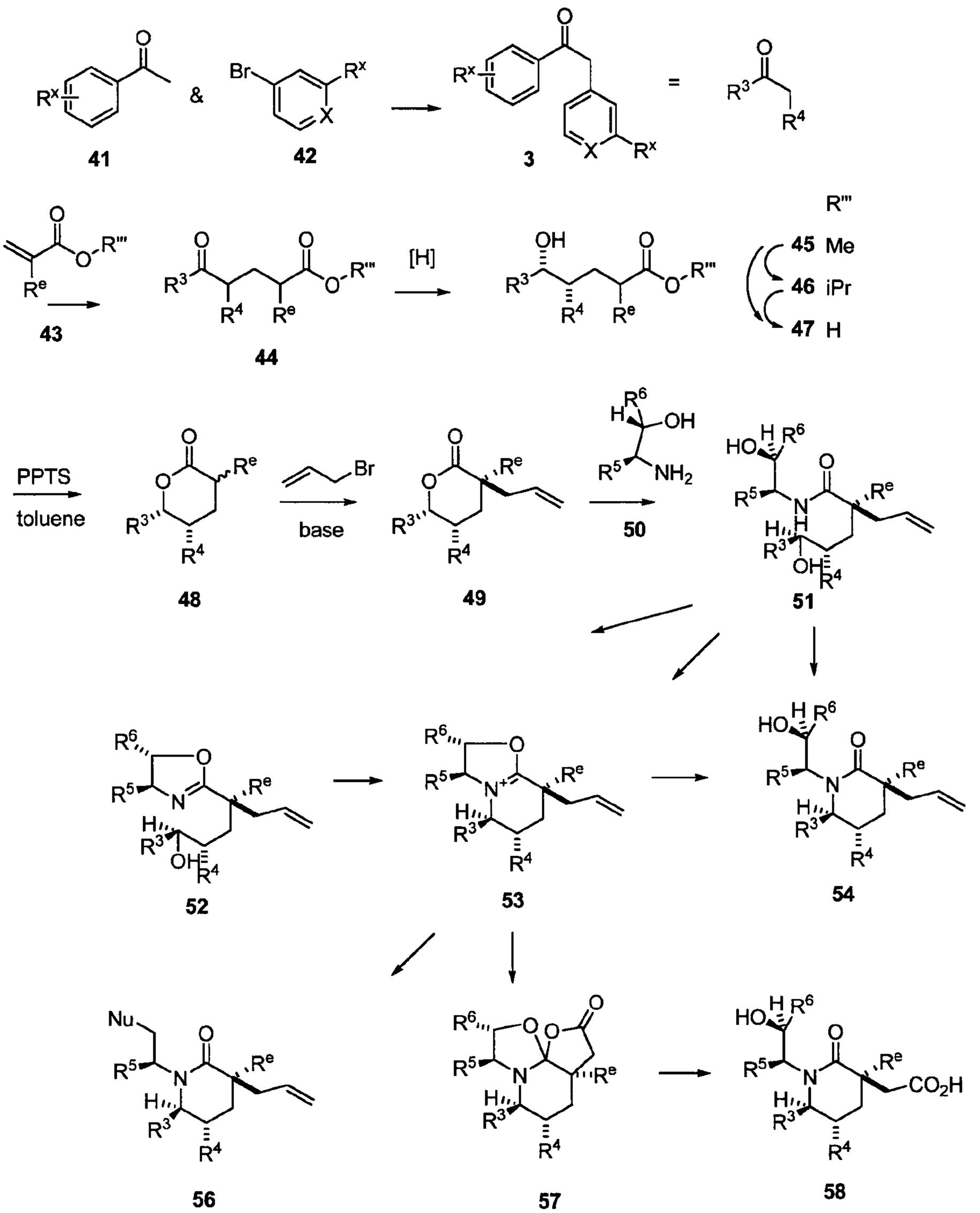
Scheme 6



Scheme 6 illustrates an alternative method for the preparation of intermediate compounds of general structure **35.** This intermiate can be used to make additional compounds in this invention. Here, a (4S,5S)-2-allyl-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazasilolidine of the general formula **28** is formed by the reaction of **27** (prepared as described in J. Am. Chem. Soc. 124, 7920, (2002) with an alkene in the presence of Grubb's catalyst. Reaction with imine **29**, which is prepared by the reaction of 2-(aminomethyl)phenol with an aldehyde using conditions well known to those skilled in the art, will yield compound **30** (See also J. Am. Chem. Soc. 129, 14552, (2007)). Intermediate **30** can in turn be converted into compound **31**, by reacting consecutively with acetic anhydride in the presence of a base such as triethylamine, toluenesulfonic acid and oxalyl chloride in the presence of propylene glycol as described in Org. Letters, 11, 433, (2009), for example. Homoallyl amine **31** can optionally be further modified, for example by arylating or alkylating the nitrogen by methods well known to those of ordinary skill in the art. For example, the reaction of **31** with a ketone or aldehyde in the presence of a reducing agent such as sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride in a solvent such as DME, DMF or THF

will accomplish this transformation. **32** can be acylated or sulfonylated by conditions well known to those of ordinary skill in the art to yield **33**. **33** can be cyclized to **34** by a Ring Closing Metathesis (RCM) reaction. Catalysts suitable for such transformations are known to those of skill in the art (see e.g. (a) Grubbs, R. H. *Handbook of* Metathesis; Wiley-VCH: Weinheim, (2003); (b) Angew. Chem., Int. Ed., 42, 1900, (2003)) and include Grubbs 1st generation and Grubbs 2nd generation catalysts. Catalytic hydrogenation of **34** using, for example, a palladium, platinum or iridium catalyst in a solvent such as DCM, THF, methanol, or an aqueous mixture containing an alcohol or THF as a co-solvent, for example, is used to reduce the double bond, producing compound **35**.

Scheme 7



Compounds of the present invention may also be prepared via the lactone route illustrated in **Scheme 7.** Aryl benzyl ketones **3**, commercially available or prepared by Dieckmann condensation or by coupling an aryl methyl ketone **41** with a bromoaryl compound **42**, can be condensed with acrylate esters **43** including methacrylate, ethacrylate, etc., to form the keto ester **44**. Stereoselective reduction occurs with sodium borohydride in methanol to

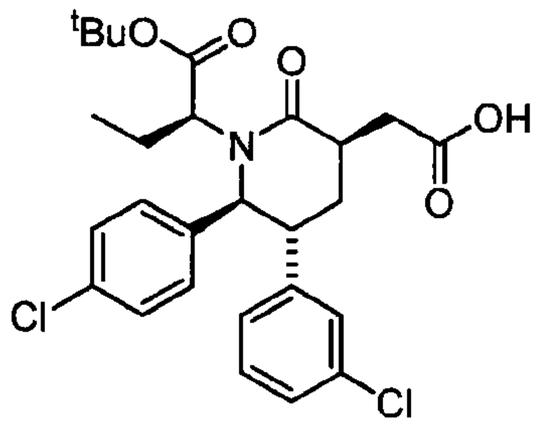
form racemic **45** as a mixture of epimers at the R^e position. Alternatively, this reduction can be carried out via dynamic kinetic resolution (see, Chen, et. al., *Organic Process Research & Development,* **2007**, *11*, 616-623 and references contained therein) to give enantioenriched **46**, also as a mixture of epimers at the R" position. In this process, isopropyl esters are produced by transesterification. . Hydrolysis to the carboxylic acid **47** followed by lactonization affords the racemic or enantioenriched lactone **48** as a mixture of diastereomers at the R^e position. The diastereomers as a mixture can be enolized with strong base such as LiHMDS or LDA to give a common enolate which is alkylated with allyl bromide to afford lactone **49** as a single diastereomer. (see Example 261 Step E). Condensation of racemic lactone **49** with enantiopure aminoalcohols **50** results in diastereomeric hydroxylamides **51** which can be converted into oxazolines **52**, oxazolinium salts **53** or hydroxylactams **54**. Separation of the diastereomers can generally be done on any of these intermediates by normal phase silica chromatography. Alternatively, condensation of enantioenriched lactone **49** with enantioenriched amino alcohols **50** leads to enhanced enantiopurity of the resulting **51,52,53** or **54**. For example 94%ee lactone combined with 98%ee amino alcohol results in the major diastereomer of 99.94% ee.

Hydroxylactam **54** (R^5=Et, cPr) has been prepared by alternate procedures (see Example 91 Step B; and Example 252 Step A) and used as an intermediate for many of the compounds of the present invention (equivalent to lactam **10** of **Scheme 3**). Using the lactone procedure, additional examples (R^5= iPr [Example 261, Step H], tBu, etc.) can be prepared. Additionally, aminoalcohols containing two adjacent stereocenters (i.e., R^6 not H) can be incorporated into this route. The oxazolinium salt **53** is also a versatile intermediate. It can be intercepted with various nucleophiles such as azide, thiols or sulfinate salts to form lactams **56**, leading to amines, amides, sulfonamides and sulfones. The allyl group of oxazolinium salt **53** can be oxidized to the carboxylic acid oxidation state with minimal complication from the primary or secondary alcohol center which is tied up in the oxazoline ring. The resulting orthoamide **57** releases the lactam carboxylate **58** under mild hydrolysis conditions.

Thus lactone **49** [R^3=pClPh, R^4=mClPh, R^e=Me] and (2S,3S)-3-aminopentan-2-ol [WO2007/110649A2] were combined. The corresponding oxazoline **52** [R^3=pClPh, R^4=mClPh, R^e=Me R^5=Et, R^6=Me] was formed by dehydration under Dean-Stark conditions in toluene with ammonium molybdate as a catalyst. Treatment with triflic anhydride in dichloromethane with lutidine at -50°C gave oxazolinium salt **53** [R^3=pClPh, R^4=mClPh, R^e=Me R^5=Et, R^6=Me]. Oxidation with $KMnO_4$ in dichloromethane/water facilitated by tetrabutylammonium chloride gave after workup and hydrolysis with sodium bicarbonate

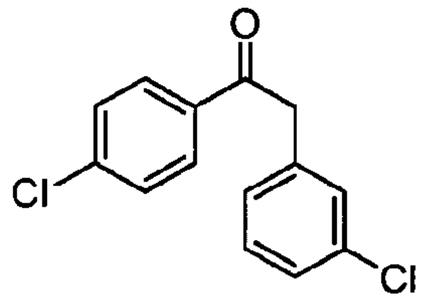
solution in isopropyl acetate at 70 °C, compound **58** [R^3=pClPh, R^4=mClPh, R^e=Me R^5=Et, R^6=Me] identical to material prepared in Example 152.

EXAMPLE 1



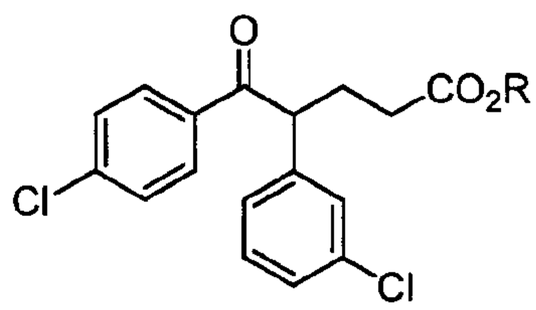
2-((3R,5R,6S)-1-((S)-1-tert-butoxy-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid

Step A. 2-(3-Chlorophenyl)-1-(4-chlorophenyl)ethanone



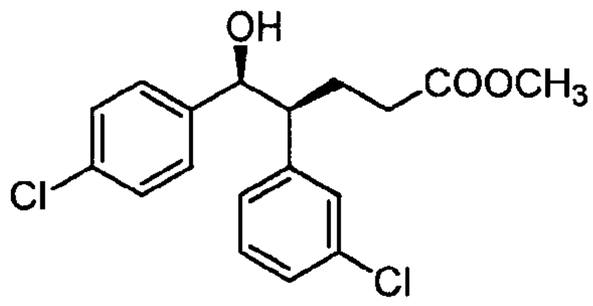
To a solution of 2-(3-chlorophenyl) acetic acid (10g, 58.6 mmol) in THF (58ml) was added 117 mL of a 1M solution of sodium bis-(trimethylsilyl) amide in THF slowly over 1 h at -78 °C. After being stirred at -78 °C for 40 min, a solution of methyl 4-chlorobenzoate (10g, 58.6mmol) in THF (35ml) was added over a period of 10 min. The reaction was stirred at -78 °C for 3 h, then allowed to warm to 25 °C, and stirred an additional 2 h until completion. The reaction was quenched with saturated aqueous NH_4Cl solution and most of the THF was removed under reduced pressure. The residue was extracted with ethyl acetate (2 × 100ml). The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated. The product was recrystallized from ether/pentane to provide the title compound as a white solid.

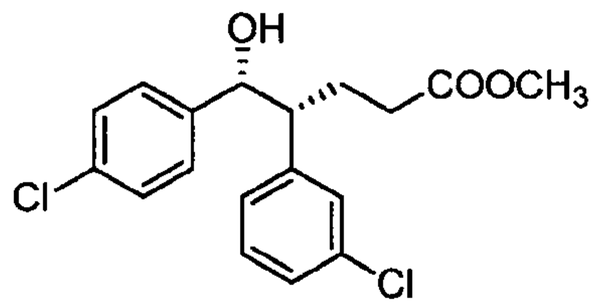
Step B. Methyl 4-(3-chlorophenyl)-5-(4-chlorophenyl)-5-oxopentanoate



To a solution of 52.1g (197 mmol) of 2-(3-chlorophenyl)-1-(4-chlorophenyl)ethanone (Example 1, Step A) and methyl acrylate (19.5 ml, 216 mmol) in 360 mL of THF was added 20mL of a 1M solution of potassium tert-butoxide in THF slowly at 0 °C over a period of 20 min (reaction solution temp kept < 10 °C). The reaction was allowed to warm to ambient temperature. After being stirred at rt for 1h, the reaction was concentrated under reduced pressure, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by flash chromatography on silica gel (eluent: 15% EtOAc/hexanes) provided the title compound as a colorless liquid. R is CH_3.

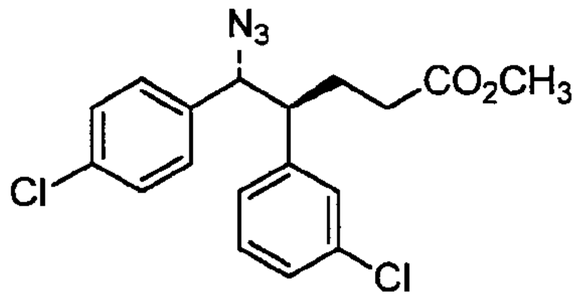
Step C. (4S,5S)-Methyl 4-(3-chlorophenyl)-5-(4-chlorophenyl)-5-hydroxy pentanoate and (4R,5R)-Methyl 4-(3-chlorophenyl)-5-(4-chlorophenyl)-5-hydroxy pentanoate

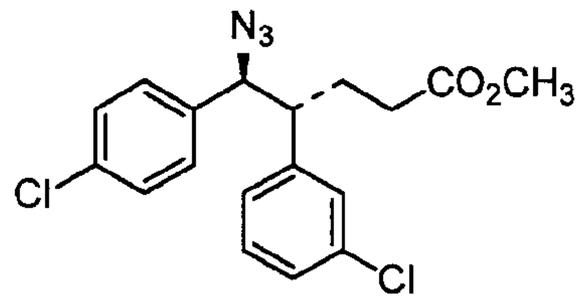




To a solution of 75.1 g (213 mmol) of methyl 4-(3-chlorophenyl)-5-(4-chlorophenyl)-5-oxopentanoate (Example 1, Step B) in MeOH (0.71 L, c = 0.3 M) at 0 °C was added sodium borohydride (8058 mg, 213 mmol) in several small portions. After being stirred at 0 °C for 30 min, the reaction mixture was quenched with ice-cold H_2O, concentrated under reduced pressure, and extracted with EtOAc. The combined organic layers were washed (sat. aq. NaCl solution), dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by flash chromatography on silica gel (eluent: 20 to 30% EtOAc/hexanes, gradient elution) provided a racemic mixture of the title compounds as a colorless liquid.

Step D. (4S,5R)-Methyl 5-azido-4-(3-chlorophenyl)-5-(4-chlorophenyl) pentanoate and (4R,5S)-Methyl 5-azido-4-(3-chlorophenyl)-5-(4-chlorophenyl)pentanoate



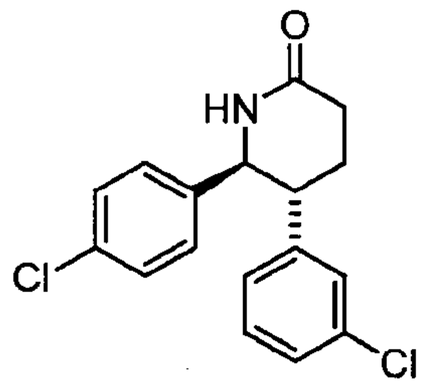


To a solution of 63.1g (179 mmol) of (4S,5S)-methyl 4-(3-chlorophenyl)-5-(4-chlorophenyl)-5-hydroxy pentanoate and (4R,5R)-methyl 4-(3-chlorophenyl)-5-(4-chlorophenyl)-5-hydroxy pentanoate (Example 1, Step C) and triethylamine (49.8 ml, 357 mmol) in DCM (600 mL, 0.3

M) was added methanesulfonyl chloride (18 ml, 232 mmol) at 0 °C dropwise over a period of 10 min. The reaction was stirred at 0 °C for 40 min and monitored by TLC for completion. Then the reaction was quenched with ice-cold water, extracted (3 × DCM), and washed with sat aq. NaCl solution. The combined organic layers were dried (Na_2SO_4), and concentrated under the reduced pressure.

The crude mesylate synthesized above was dissolved in DMF (350 mL, 0.5 M) and sodium azide (58 g, 893 mmol) was added in several portions. The mixture was heated to 100 °C and after being stirred at 100 °C for 30 min, the reaction mixturewas cooled to room temperature, diluted with water and extracted with EtOAc. The combined organic layers were washed (sat. aq. NaCl solution), dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by flash chromatography on silica gel (eluent: 5 to 20% EtOAc/hexanes, gradient elution) provided the title compound as a colorless liquid.

Step E. (5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one



To a solution of 45.9 g (121 mmol) of methyl 5-azido-4-(3-chlorophenyl)-5-(4-chlorophenyl) pentanoate (Example 1, Step D) in THF/H_2O (4:1, 375 mL) was added 152 mL of a 1M solution of trimethylphosphine in THF (152 mmol). After being stirred for 1 h at 25 °C, most of the THF was removed under reduced pressure. The residue was basified (ice-cold 2 M LiOH) and the product was extracted with methylene chloride. The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to provide a white solid.

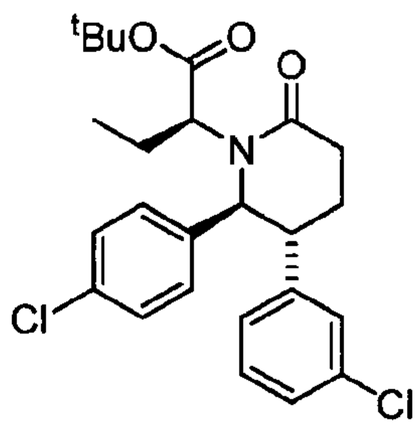
This solid was dissolved in MeOH/saturated aq. $NaHCO_3$ (4:1, 2.4 L, c = 0.05 M) and the reaction was heated to reflux for 3 h. Excess organic solvent was removed under reduced pressure, the residue was diluted with water and extracted (2 × 10% MeOH/DCM). The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to provide trans - 5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one as a mixture of stereoisomers. Individual stereoisomers were separated by chiral HPLC (flowrate: 18 ml/min on a Chiralcel® OD-H 20 mm I.D. × 250 mm,

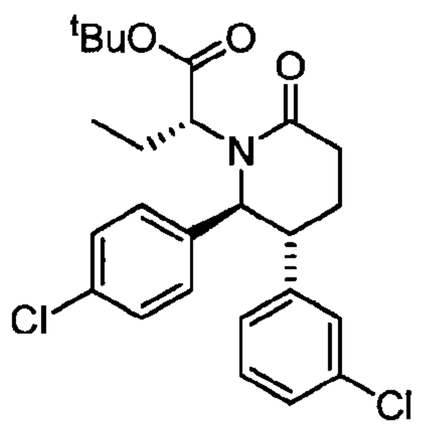
5 mic column (Daicel Inc., Fort Lee, NJ), using 40% isopropyl alcohol/hexane as the eluent) to to give the title compound (t_R = 8.2 min) as a white solid.

$[\alpha]_D$ = + 158 (T = 23.4 °C, c = 1.12, MeOH); ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.21 (2 H, d, *J* = 8.2 Hz), 7.09–7.19 (3 H, m), 7.04–7.01 (1 H, m), 6.97 (2 H, d, *J* = 8.2 Hz), 6.80–6.77 (1 H, m), 5.83 (1 H, s, br), 4.51 (1 H, d, *J* = 9.8 Hz), 2.94–2.77 (1 H, m), 2.74–2.60 (2 H, m), 2.34–2.20 (1 H, m), 2.17–2.08 (1 H, m); MS (ESI) 320.0 $[M + H]^+$.

Also obtained by the above method was the enantiomer of the title compound, (5S,6R)-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one: t_R = 12.4 min; $[\alpha]_D$ = –156 (T = 23.4 °C, c = 1.13, MeOH).

Step F. tert-butyl (2S)-2-((2S,3R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-6-oxo-1-piperidinyl)butanoate and tert-butyl (2R)-2-((2S,3R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-6-oxo-1-piperidinyl)butanoate





To a solution of 13.5 g (42.2 mmol) of (5*R*,6*S*)-5,6-bis(4-chlorophenyl)piperidin-2-one (Exampe 1, Step E) in 140 mL of DMF was added 4.22 g (105 mmol) of a dispersion of 60% sodium hydride in mineral oil at 0 °C. After being stirred for 20 min, *tert*-butyl 2-bromobutanoate (28.2 g, 126 mmol) was added at 0 °C and the resulting solution was stirred at 25 °C for 1.5 h until completion of the reaction. Then sat. aq. NH_4Cl solution was added and the mixture was extracted with ethylacetate. The combined organic layers were washed with water and sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (eluent: 20 to 50% EtOAc/hexanes, gradient elution) provided tert-butyl (2S)-2-((2S,3R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-6-oxo-1-piperidinyl)butanoate as the faster eluting minor isomer:

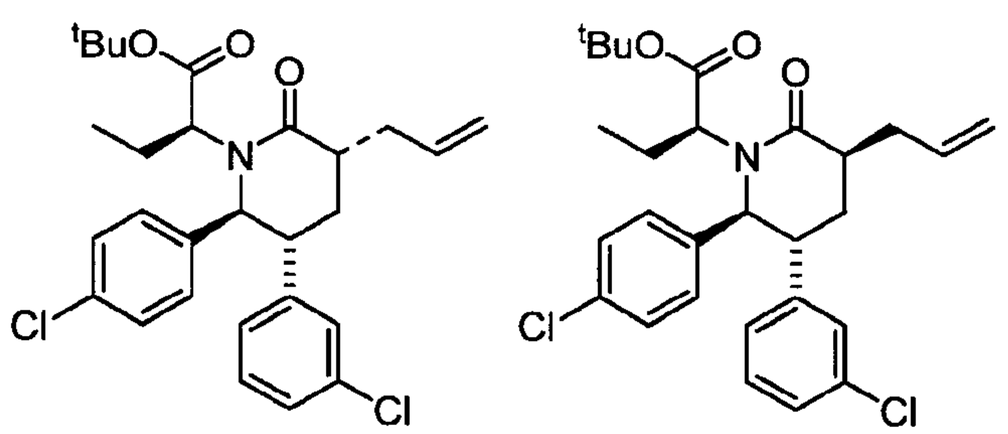
^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.22 (2 H, d, *J* = 8.2 Hz), 7.20–7.10 (2 H, m), 7.08 (2 H, t, *J* = 8.2 Hz) 6.99–6.96 (1 H, m), 6.77–6.73 (1 H, m), 4.48 (1 H, d, *J* = 9.4 Hz), 3.24 (1 H, t, *J* = 7.0 Hz), 3.04–2.94 (1 H, m), 2.72–2.58 (2 H, m), 2.25–2.00 (3 H, m), 1.93–1.82 (1 H, m), 1.45 (9 H, s), 0.98 (3 H, t, *J* = 7.4 Hz); MS (ESI) 462.1 $[M + H]^+$.

Further elution provided

tert-butyl (2R)-2-((2S,3R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-6-oxo-1-piperidinyl)butanoate as the slower eluting major isomer.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.24 (2 H, d, *J* = 8.2 Hz), 7.18–7.10 (2 H, m), 7.01 (2 H , d, *J* = 8,2 Hz), 7.02–6.98 (1 H, m), 6.82–6.78 (1 H, m), 5.83 (1 H, s), 4.54 (1 H, d, *J* = 9.8 Hz), 3.09 (1 H, dd, *J* = 8.2, 4.3 Hz), 3.05–2.99 (1 H, m), 2.70–2.64 (2 H, m), 2.28–2.18 (2 H, m), 2.08–2.02 (1 H, m), 1.48 (9 H, s), 0.57 (3 H, t, *J* = 7.4 Hz); MS (ESI) 462.1 $[M + H]^+$.

Step G. tert-Butyl (2S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanoate and . tert-Butyl (2S)-2-((3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanoate



To a solution of 1.45 g (3.14 mmol) of tert-butyl (2S)-2-((2S,3R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-6-oxo-1-piperidinyl)butanoate (Example 1, Step F) and allyl bromide (0.326 mL, 3.76 mmol) in 12.5 mL of THF was added dropwise at -78 °C 3.3 mL of a 1 M solution of lithium bis(trimethylsilyl)-amide in THF (3.3 mmol). After being stirred at -78 °C for 3 h, the reaction was quenched with sat. aqueous NH_4Cl solution, extracted with ethyl acetate. The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (50g SiO_2, eluent: 5 to 20% EtOAc/hexanes, gradient elution)

provided tert-butyl (2S)-2-((3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanoate as the faster eluting major isomer.

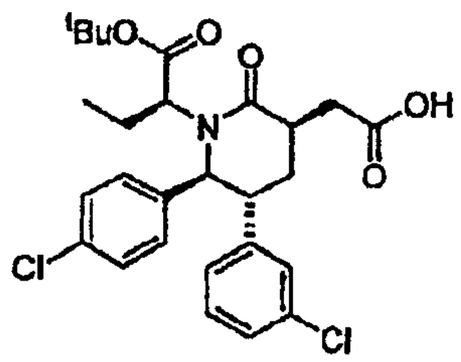
^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.27–7.24 (2 H, m), 7.21–7.12 (2 H, m), 7.11–7.00 (3 H, m), 6.93–6.87 (1 H, m), 5.90–5.77 (1 H, m), 5.19–5.09 (2 H, m), 4.64 (1 H, d, *J*= 8.6 Hz), 3.21–3.10 (2 H, m), 2.80–2.71 (1 H, m), 2.70–2.63 (1 H, m), 2.56–2.48 (1 H, m), 2.30–2.15 (2 H, m), 2.07–1.99 (1 H, m), 1.60–1.48 (1 H, m), 1.47 (9 H, s), 0.61 (3 H, t, *J*= 7.6 Hz); MS (ESI) 446.0 $[M+H]^+$.

Further elution provided

tert-butyl (2S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanoate as the slower eluting, minor isomer.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.23 (2 H, d, *J*= 8.2 Hz), 7.19–7.07 (2 H, m), 7.01–6.95 (3 H, m), 6.77–6.72 (1 H, m), 5.95–5.77 (1 H, m), 5.16–4.99 (2 H, m), 4.51 (1 H, d, *J*= 10.6 Hz), 3.13–3.04 (1 H, m), 2.94 (1 H, dd, *J*=7.8, 4.3 Hz), 2.87–2.77 (1 H, m), 2.68–2.58 (1 H, m), 2.39–2.27 (2 H, m), 2.16–1.95 (2 H, m), 1.54–1.50 (1 H, m), 1.51 (9 H, s), 0.55 (3 H, t, *J*= 7.4 Hz); MS (ESI) 446.0 $[M+H]^+$.

Step H. 2-((3R,5R,6S)-1-((S)-1-tert-Butoxy-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid

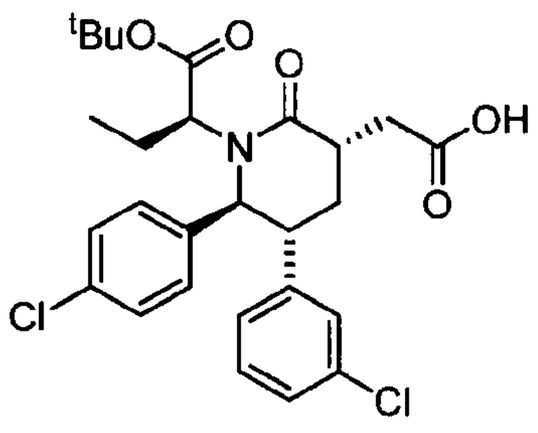


To a rapidly stirring solution of 842 mg (1.67 mmol) of *tert*-butyl (2S)-2-((3*S*, 5*R*, 6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl) butanoate (Example 1, Step G) in a mixture of 7 mL of water, 5 mL of acetonitrile and 5mL of CCl_4 was added sodium periodate (1.43 g, 6.70 mmol), followed by ruthenium(III) chloride hydrate (37.8 mg, 0.168 mmol). After being stirred vigorously for 18 h, the reaction was acidified (10% citric acid) and diluted with EtOAc. The reaction mixture was filtered through celite™ and the filtrate

was extracted with EtOAc. The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reversed phase preparatory HPLC (GeminiTM Prep C18 5μm column, Phenomenex, Torrance, CA; eluent: 60 to 80% acetonitrile +0.1% TFA in water + 0.1% TFA, gradient elution) to give the title compound as a white solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.35 (2 H, d, *J* = 8.6 Hz), 7.27–7.24 (3 H, m), 7.22–7.16 (1 H, m), 7.18 (2 H, d, *J* = 8.6 Hz), 4.85 (1 H, d, *J* = 5.1 Hz), 3.36 (1 H, dd, *J* = 8.6, 3.5 Hz), 3.18–3.14 (1 H, m), 2.92–2.80 (2 H, m), 2.79–2.72 (1 H, m), 2.32–2.18 (2 H, m), 2.15–2.06 (1 H, m), 1.63–1.50 (1 H, m), 1.44 (9 H, s), 0.67 (3 H, t, *J* = 7.4 Hz); MS (ESI) 520.2 $[M + H]^+$, 518.0 $[M - H]^-$.

EXAMPLE 2



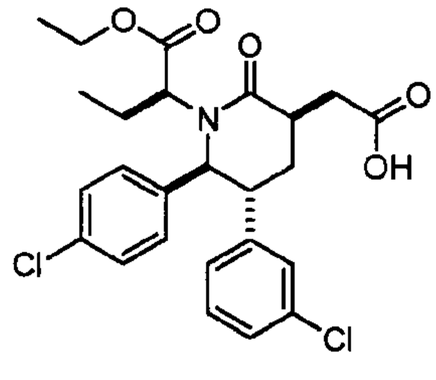
2-((3S,5R,6S)-1-((S)-1-tert-Butoxy-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acidThe title compound was prepared from (S)-tert-butyl 2-((3R, 5R, 6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl) butanoate (Example 1, Step G) by the procedure described in Example 1, Step H.

^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.27–7.26 (2 H, m), 7.12–7.16 (1 H, m), 7.13–7.10 (1 H, m), 7.02–6.94 (3 H, m), 6.74–6.71 (1 H, m), 4.51 (1 H, d, *J* = 10.8 Hz), 3.18–3.08 (2 H, m), 3.06–2.96 (2 H, m), 2.47 (1 H, dd, *J* = 15.4, 3.2 Hz), 2.35–2.25 (1 H, m), 2.24–2.12 (2 H, m), 1.52–1.57 (1 H, m), 1.51 (9 H, s), 0.56 (3 H, t, *J*=7.5 Hz); MS (ESI) 520.2 $[M + H]^+$, 518.0 $[M - H]^-$.

The following examples 3 to 6 were prepared as described in Example 1, substituting tert-butyl 2-bromobutanoate in step F, with the appropriate amount of ethyl 2-bromobutanoate,

ethyl 2-bromo-3-methylpentanoate, ethyl 2-bromopentanoate, and ethyl 2-bromo-2-cyclopropylacetate, respectively.

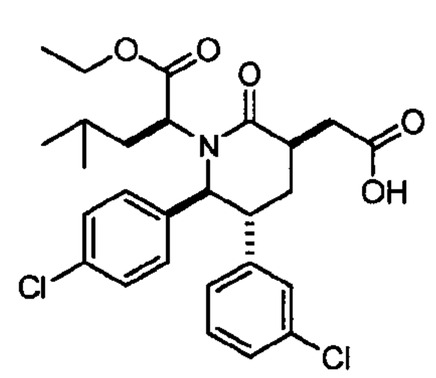
EXAMPLE 3



2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-ethoxy-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.42–7.33 (3 H, m), 7.32–7.28 (3 H, m), 7.27–7.24 (2 H, m), 4.91 (1 H, d, *J* = 3.5 Hz), 4.23–4.10 (2 H, m), 3.54 (1 H, dd, *J* = 8.6, 3.5 Hz), 3.22–3.16 (1 H, m), 2.84–2.73 (3 H, m), 2.38–2.30 (2 H, m), 2.05–1.97 (1 H, m), 1.60–1.50 (1 H, m), 1.27 (3 H, t, *J* = 7.4 Hz), 0.70 (3 H, t, *J* = 7.4 Hz); MS (ESI) 491.8 $[M + H]^+$, 489.9 $[M - H]^-$.

EXAMPLE 4

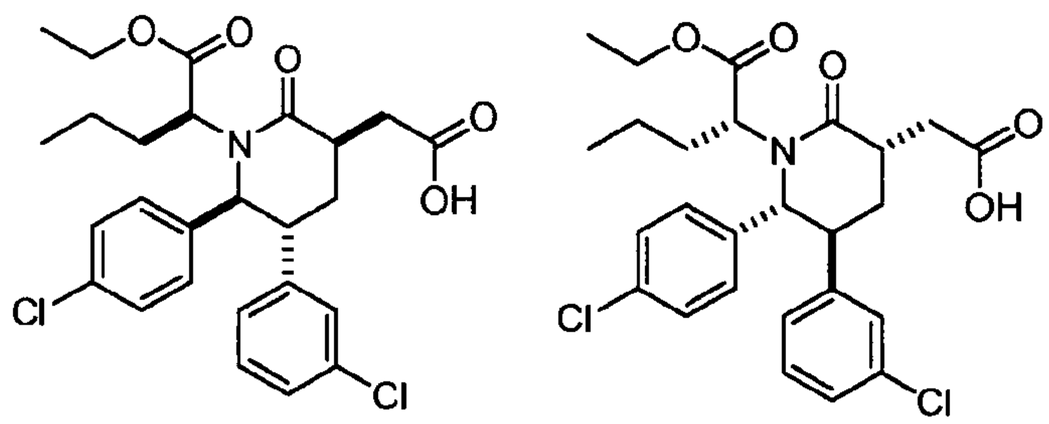


2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-ethoxy-4-methyl-1-oxopentan-2-yl)-2-oxopiperidin-3-yl)acetic acid

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δppm 0.34 (d, *J*=6.7 Hz, 3 H), 0.77 (d, *J*=6.7 Hz, 3 H), 1.13 (m, 1 H), 1.28 (t, *J*=7.1 Hz, 3 H), 1.30 - 1.44 (m, 1 H), 1.98 (m,1 H), 2.32 - 2.47 (m, 2 H), 2.75 (m, 1 H), 2.79 - 2.86 (m, 2 H), 3.14 - 3.19 (m, 1 H), 3.66 (dd, *J*=9.2, 2.4 Hz, 1 H),

4.11 - 4.24 (m, 2 H), 4.95 (m, 1 H), 7.23 - 7.34 (m,5 H), 7.36 - 7.41 (m, 3 H), MS (ESI) 520.2 $[M+H]^+$. 518.0 $[M-H]^-$.

EXAMPLE 5

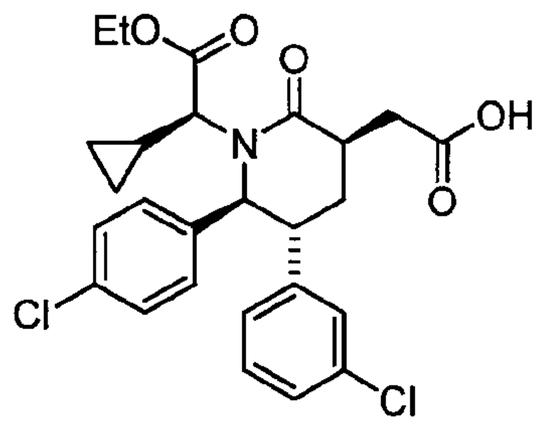


2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-ethoxy-1-oxopentan-2-yl)-2-oxopiperidin-3-yl)acetic acid and 2-((3S,5S,6R)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-ethoxy-1-oxopentan-2-yl)-2-oxopiperidin-3-yl)acetic acid

The compounds described in Example 5 were derived from racemic piperidinone which was prepared in Example 1, Step E.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.40–7.37 (3 H, m), 7.31–7.27 (3 H, m), 7.27–7.24 (2 H, m), 4.92 (1 H, d, *J* = 3.5 Hz), 4.20–4.10 (2 H, m), 3.60 (1 H, dd, *J* = 8.6, 3.5 Hz), 3.20–3.15 (1 H, m), 2.83–2.72 (3 H, m), 2.40–2.30 (2 H, m), 2.03–1.97 (1 H, m), 1.44–1.37 (1 H, m), 1.27 (3 H, t, *J* = 7.2 Hz), 1.26–1.17 (1 H, m), 0.92–0.80 (1 H, m), 0.54–0.78 (3 H, t, *J* = 7.4 Hz); MS (ESI) 506.0 $[M + H]^+$, 504.0 $[M - H]^-$.

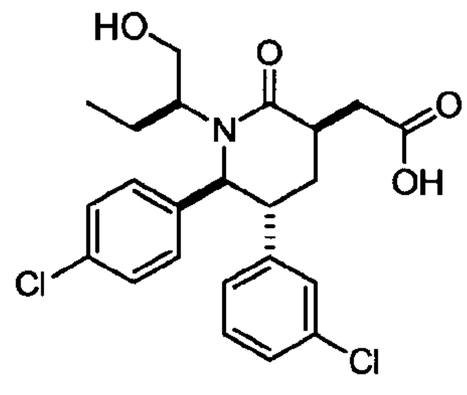
EXAMPLE 6



2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-ethoxy-2-oxoethyl)-2-oxopiperidin-3-yl)acetic acid

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 0.08 (1 H, m), 0.34 (1 H, m), 0.47 (1 H, m), 0.58 (1 H, m), 1.06 (1 H, m), 1.13 (3 H, t, *J* = 7.1 Hz), 1.83 (1 H, m), 2.19 (1 H, m), 2.50–2.63 (2 H, m), 2.74 (1 H, dd, *J* = 16, 6.8 Hz), 3.08 (1 H, m), 3.42 (1 H, d, *J* = 10.8 Hz), 3.97 (2 H, m), 5.20 (1 H, s), 7.08 (1 H, m), 7.15–7.25 (7 H, m); MS (ESI) 504.1 $[M + H]^+$.

EXAMPLE 7



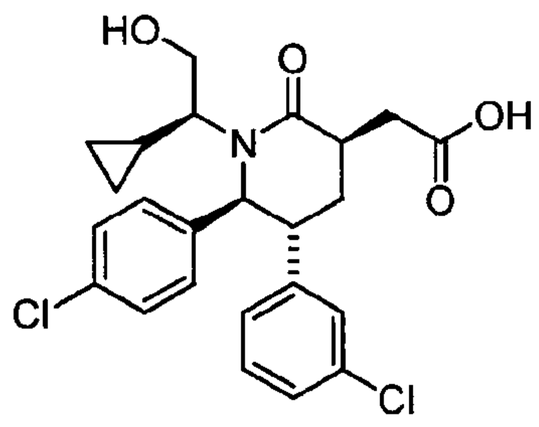
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-hydroxybutan-2-yl)-2-oxopiperidin-3-yl)acetic acid

To a solution of 300mg (0.61 mmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-ethoxy-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid (Example 3) in 12 mL of Et_2O was added lithium tetrahydroborate (39.8 mg, 1.83 mmol) at 0 °C. After being stirred for 20 min, methanol (37.0 µl, 914 µmol) was added at 0 °C and the resulting solution was stirred at 25 °C for 2 h. The reaction was quenched (10% citric acid), extracted (2 × EtOAc) and washed (1 × sat. aq. NaCl solution). The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under

reduced pressure. Purification by reversed phase preparatory HPLC (GeminiTM Prep C18 5μm column, Phenomenex, Torrance, CA; eluent: 35 to 75% acetonitrile +0.1% TFA in water + 0.1% TFA, gradient elution) provided the title compound as a white foam.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δppm 7.42–7.37 (3 H, m), 7.34–7.27 (4 H, m), 7.18–7.13 (1 H, m), 4.89 (1 H, d, *J* = 2.7 Hz), 3.99–3.90 (1 H, m), 3.78 (1 H, dd, *J* = 11.5, 3.3 Hz), 3.32–3.23 (1 H, m), 3.13–3.07 (1 H, m), 2.88–2.65 (3 H, m), 2.35–2.25 (1 H, m), 2.12–2.03 (1 H, m), 1.95–1.84 (1 H, m), 1.58–1.46 (1 H, m), 0.71 (3 H, t, *J* = 7.4 Hz); MS (ESI) 450.1 $[M + H]^+$, 448.0 $[M - H]^-$.

EXAMPLE 8

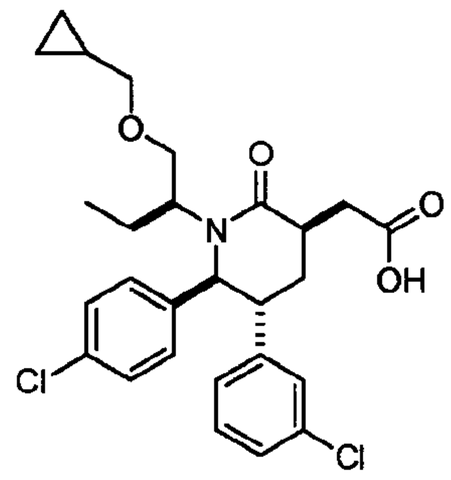


2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-hydroxyethyl)-2-oxopiperidin-3-yl)acetic acid

The title compound was prepared from 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-ethoxy-2-oxoethyl)-2-oxopiperidin-3-yl)acetic acid (Example 6) as described in Example 7.

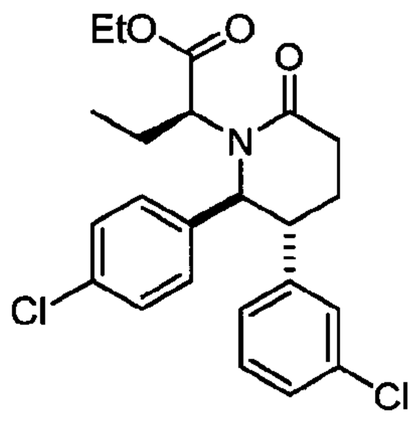
^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 0.23 (m, 1 H), 0.36 (m, 1 H), 0.65–0.69 (m, 2 H), 0.95 (m, 1 H), 1.90 (m, 1 H), 2.40 (m, 1 H), 2.68 (m, 1 H), 2.80 (2 H, d, *J* = 5.3 Hz), 3.13 (1 H, m), 3.48 (m, 1 H), 3.60–3.85 (m, 2 H), 5.32 (s, 1 H), 7.20 (m, 1 H), 7.27–7.40 (m, 3 H), 7.40–7.43 (m, 4 H); MS (ESI) 462.1 $[M + H]^+$.

EXAMPLE 9



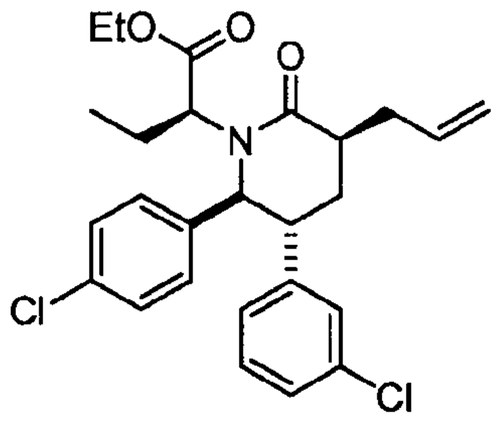
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid

Step A. (S)-Ethyl 2-((2S,3R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-6-oxopiperidin-1-yl)butanoate



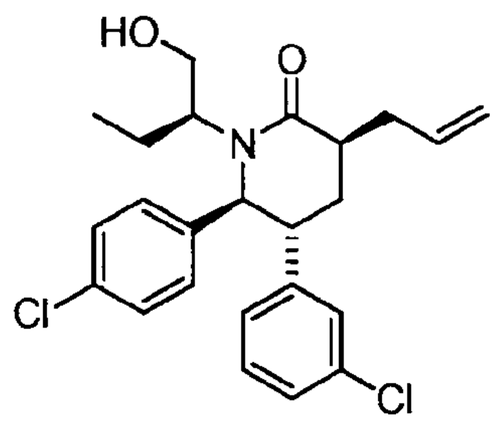
To a solution of 15 g (46.8 mmol) of ((5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one (Exampe 1, Step E) in 140 mL of DMF was added 3.75 g (94 mmol) of a dispersion of 60% sodium hydride in mineral oil at 0 °C. After being stirred for 20 min, ethyl 2-bromobutanoate (17.2 mL, 117 mmol) was added at 0 °C and the resulting solution was stirred at 25 °C for 12 h until completion of the reaction. Then sat. aq. NH_4Cl solution was added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with water and sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (eluent: 30% EtOAc/hexanes, gradient elution) provided the title compound as the faster eluting isomer.

Step B. (S)-Ethyl 2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanoate



To a solution of 0.62g (1.4 mmol) of (S)-ethyl 2-((2S,3R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-6-oxopiperidin-1-yl)butanoate (Example 9, Step A) and allyl bromide (0.14 ml, 1.7 mmol) in THF (6.0 mL, 0.25 M) was added lithium bis(trimethylsilyl)- amide (1M solution in THF, 1.5 ml, 1.5 mmol) at -78 °C. The reaction was allowed to warm to R.T., then was quenched (sat. aqueous NH_4Cl) and extracted with EtOAc. The combined organic layers were washed with water and sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (15 to 20% EtOAc/Hex, gradient elution) provided the title compound as the slower eluting isomer as a colorless oil.

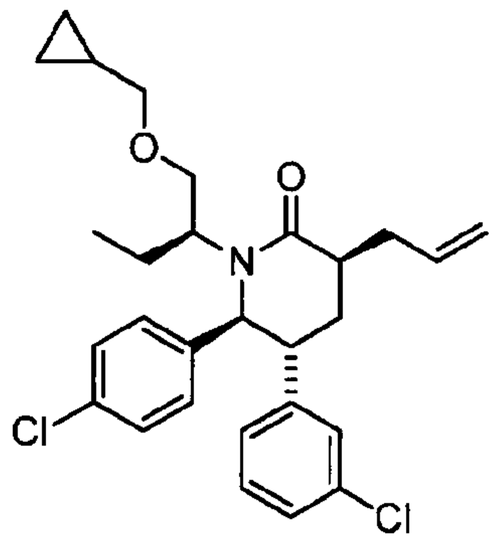
Step C. (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-hydroxybutan-2-yl)piperidin-2-one



To a solution of 256 mg (0.54 mmol) of (S)-ethyl 2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanoate (Example 9, Step B) in Et_2O(5.5 mL) was added lithium borohydride of 90% purity (17.6 mg, 0.809 mmol) at 0 °C. After being stirred at 0 °C for 10 min, the reaction was quenched (ice cold 10% citric acid), extracted (2 × EtOAc) and washed (sat. aq. NaCl solution). The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated

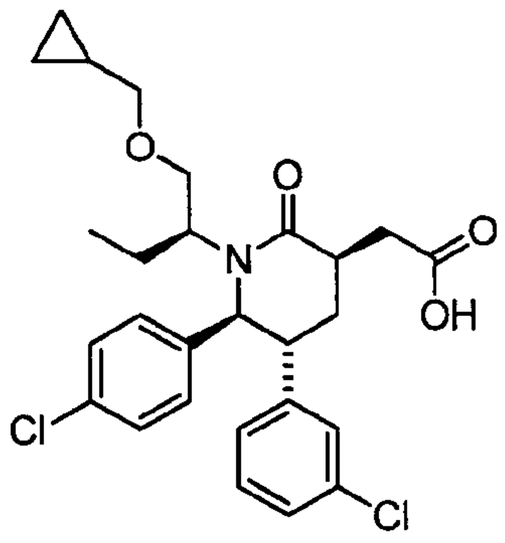
under reduced pressure. Purification by chromatography on silica gel (eluent 30% to 50% EtOAc/Hexanes, a gradient elution) provided the title compound.

Step D. (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethoxy) butan-2-yl)piperidin-2-one



To a solution of (3S,5R,6S)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-hydroxybutan-2-yl)piperidin-2-one (98 mg, 0.227 mmol) in DMF (1.10 mL) was added 60% sodium hydride in mineral oil (27.2 mg, 0.680 mmol) at 0 °C. After being stirred at 0 °C for 2 min, (bromomethyl)cyclopropane (47.3 μL, 0.680 mmol) was added. The mixture was stirred at 0 °C for 2 h and then warmed to rt. Then the reaction was stirred at rt overnight. The reaction was quenched (sat aq. NH_4Cl), extracted (2 × EtOAc) and washed (sat. aq. NaCl solution). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography on silica gel (10% to 20% EtOAc/Hexanes gradient) provided (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-(cyclopropylmethoxy)butan-2-yl)piperidin-2-one as the less polar isomer and the title compound as the more polar stereoisomer.

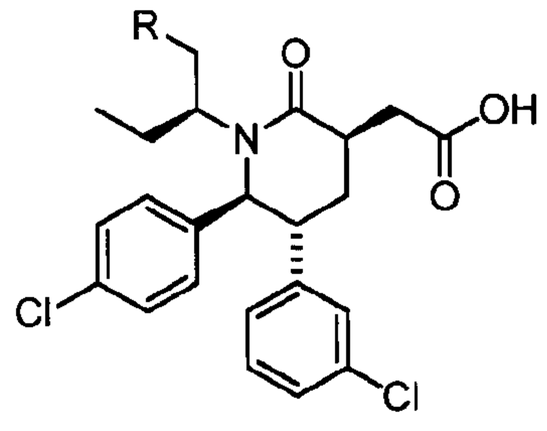
Step E. 2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid

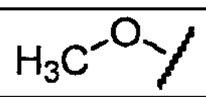
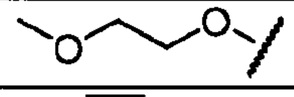
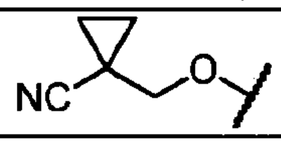


(3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethoxy) butan-2-yl)piperidin-2-one was converted into the carboxylic acid by a procedure similar to the one described in Example 1, Step H. Purification by reversed phase preparatory HPLC (GeminiTM Prep C18 5μm column, Phenomenex, Torrance, CA; eluent: 50 to 80% acetonitrile +0.1% TFA in water + 0.1% TFA, gradient elution) provided the title compound as a white solid.

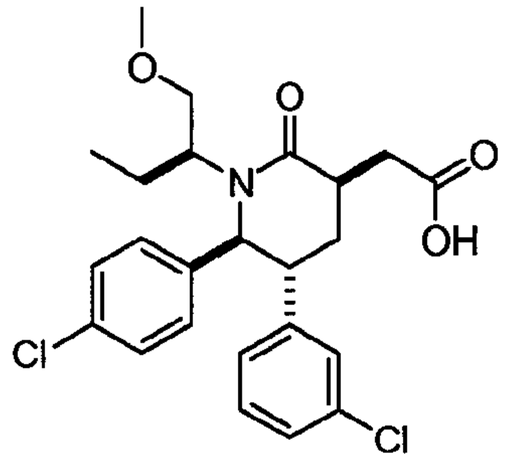
^{1}H NMR (400 MHz, *CHLOROFORM-d*) δppm 7.39 (2 H, d, *J* = 8.2 Hz), 7.38–7.36 (1 H, m), 7.33–7.28 (3 H, m), 7.23 (2 H, d, *J* = 8.2 Hz), 5.09 (1 H, d, *J* = 2.0 Hz), 4.17–4.07 (1 H, m), 3.47–3.40 (2 H, m), 3.23–3.15 (m, 2 H), 3.12–3.08 (1 H, m), 2.85 (1 H, dd, *J* = 15.8, 8.8 Hz), 2.66–2.55 (2 H, m), 2.22–2.12 (1 H, m), 2.07–1.99 (1 H, m), 1.95–1.85 (1 H, m), 1.62–1.54 (1 H, m), 1.07–1.00 (1 H, m), 0.65 (3 H, t, *J* = 7.4 Hz), 0.60– 0.52 (2 H, m), 0.24– 0.18 (2 H, m); MS (ESI) 504.1 $[M + H]^+$, 502.1 $[M - H]^-$.

The following Examples 10 to 12 were prepared from (3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-hydroxybutan-2-yl)piperidin-2-one (Example 9, Step C) by procedures similar to those described in Example 9, Steps D and E, substituting (bromomethyl)cyclopropane in step D for the appropriate amount of methyliodide, 2-methoxyethylbromide, and 1-(bromomethyl)cyclopropanecarbonitrile, respectively.



Example	R
10	
11	
12	

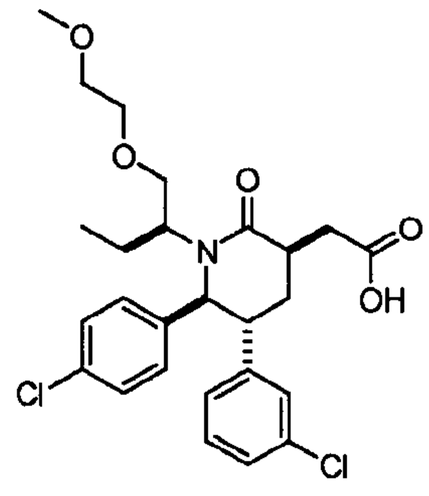
EXAMPLE 10



2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-methoxybutan-2-yl)-2-oxopiperidin-3-yl)acetic acid

1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.52–7.48 (1 H, m), 7.40 (2 H, d, *J* = 8.2 Hz), 7.31–7.28 (2 H, m), 7.27–7.24 (1 H, m), 7.24–7.27 (2 H, m), 5.05 (1 H, s), 4.08 (1 H, t, *J* = 9.6 Hz), 3.39 (3 H, s), 3.34 (1 H, dd, *J* = 9.8, 3.1 Hz), 3.20–3.10 (2 H, m), 2.88–2.78 (1 H, m), 2.64–2.55 (2 H, m), 2.25–2.16 (1 H, m), 2.10–2.00 (1 H, m), 1.90– 1.81 (1 H, m), 1.56–1.50 (1 H, m), 0.65 (3 H, t, *J* = 7.4 Hz); MS (ESI) 464.0 $[M + H]^+$, 462.1 $[M - H]^-$.

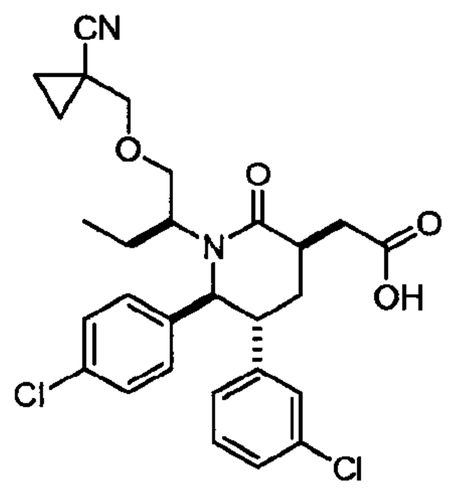
EXAMPLE 11



2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(2-methoxyethoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.41–7.35 (3 H, m), 7.28–7.26 (2 H, m), 7.25–7.21 (3 H, m), 5.09 (1 H, d, *J* = 2.7 Hz), 4.17–4.10 (1 H, m), 3.74–3.65 (1 H, m), 3.60–3.52 (3 H, m), 3.44 (1 H, dd, *J* = 10.4, 3.3 Hz), 3.35 (3 H, s), 3.25–3.15 (1 H, m), 3.12–3.07 (1 H, m), 2.91–2.80 (1 H, m), 2.71–2.58 (2 H, m), 2.21–2.12 (1 H, m), 2.05–1.89 (2 H, m), 1.61–1.52 (1 H, m), 0.64 (3 H, t, *J* = 7.6 Hz); MS (ESI) 508.1 $[M + H]^+$, 506.0 $[M - H]^-$.

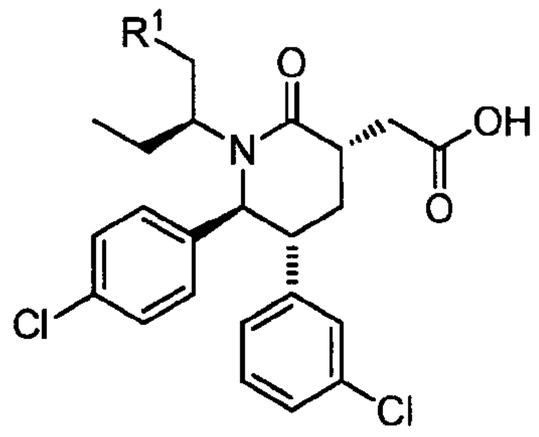
EXAMPLE 12

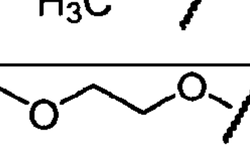
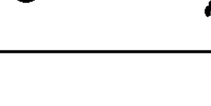
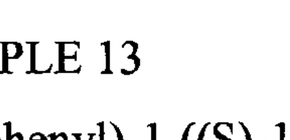


2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-((1-cyanocyclopropyl)methoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.43–7.30 (3 H, m), 7.28–7.20 (4 H, m), 7.18–7.10 (1 H, m), 5.04 (1 H, d, *J* = 3.9 Hz), 4.13 (1 H, t, *J* = 9.4 Hz), 3.52–3.43 (2 H, m), 3.42–3.33 (1 H, m), 3.32–3.24 (1 H, m), 3.13–3.05 (1 H, m), 2.92–2.75 (2 H, m), 2.72–2.60 (1 H, m), 2.20–2.10 (1 H, m), 2.10–1.90 (1 H, m), 1.64–1.49 (1 H, m), 1.35–1.25 (2 H, m), 1.00–0.90 (2 H, m), 0.71–0.57 (3 H, m); MS (ESI) 529.2 $[M + H]^+$, 527.0 $[M - H]^-$.

Examples 13–15 were prepared from (3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-hydroxyethyl)piperidin-2-one in a process similar to that described for Example 9, Step D and E.



Example	R^1
13	
14	
15	

EXAMPLE 13

2-((3S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid

1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.25 (2 H, d, *J* = 8.6 Hz), 7.22–7.18 (1 H, m), 7.15–7.11 (1 H, m), 7.08–7.04 (1 H, m), 6.96 (2 H, d, *J* = 8.6 Hz), 6.77–6.73 (1 H, m), 4.69 (1 H, d, *J* = 10.2 Hz), 4.03 (1 H, t, *J* = 9.8 Hz), 3.42–3.33 (2 H, m), 3.28–3.22 (1 H, m), 3.10–2.90 (4 H, m), 2.50 (1 H, dd, *J* = 15.3, 3.1 Hz), 2.20–2.10 (1 H, m), 2.01–2.01 (1 H, m), 1.92–1.80 (1 H, m), 1.65–1.53 (1 H, m), 1.16–1.08 (1 H, m), 0.66–0.60 (2 H, m), 0.53 (3 H, t, *J* = 7.6 Hz), 0.28–0.24 (2 H, m); MS (ESI) 504.1 $[M + H]^+$, 502.1 $[M - H]^-$.

EXAMPLE 14

2-((3S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-methoxybutan-2-yl)-2-oxopiperidin-3-yl)acetic acid

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.55 (t, *J*=7.53 Hz, 3 H), 1.49 - 1.60 (m, 1 H), 1.77 - 1.91 (m, 1 H), 2.02 - 2.15 (m, 2 H), 2.51 (dd, *J*=15.26, 3.33 Hz, 1 H), 2.89 - 2.99 (m, 1 H), 2.99 - 3.09 (m, 2 H), 3.09 - 3.17 (m, 1 H), 3.29 (dd, *J*=9.68, 4.21 Hz, 1 H), 3.34 (s, 3 H), 3.90 (t, *J*=9.49 Hz, 1 H), 4.57 (d, *J*=9.98 Hz, 1 H), 6.75 (d, *J*=7.43 Hz, 1 H), 6.97 (d, *J*=8.41

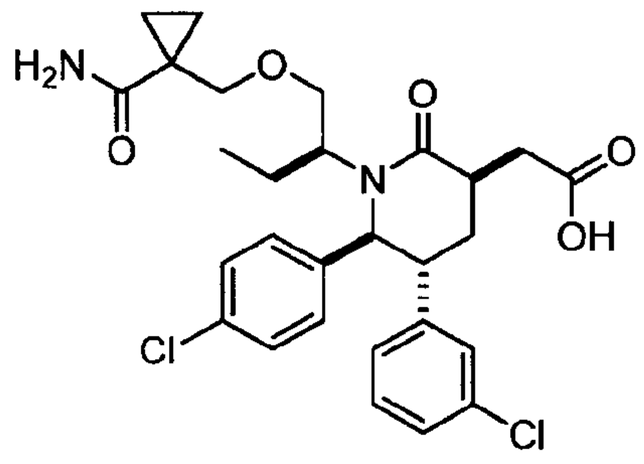
Hz, 2 H), 7.00 (t, *J*=1.76 Hz, 1 H), 7.14 (t, *J*=7.73 Hz, 1 H), 7.17 - 7.22 (m, 1 H), 7.25 (d, *J*=8.41 Hz, 2 H).

EXAMPLE 15

2-((3S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(2-methoxyethoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.24 (2 H, d, *J* = 8.2 Hz), 7.21–7.16 (1 H, m), 7.14–7.09 (1 H, m), 7.05–7.03 (1 H, m), 6.97 (2 H, d, *J* = 8.2 Hz), 6.75–6.71 (1 H, m), 4.66 (1 H, d, *J* = 10.6 Hz), 4.09 (1 H, t, *J* = 9.8 Hz), 3.70–3.55 (4 H, m), 3.47 (3 H, s), 3.44 (1 H, dd, *J* = 9.8, 4.3 Hz), 3.05–2.90 (4 H, m), 2.53 (1 H, dd, *J* = 15.1, 2.5 Hz), 2.28–2.15 (1 H, m), 2.05–1.97 (1 H, m), 1.92–1.82 (1 H, m), 1.65–1.55 (1 H, m), 0.50 (3 H, t, *J* = 7.6 Hz); MS (ESI) 508.1 $[M + H]^+$, 506.0 $[M - H]^-$.

EXAMPLE 16



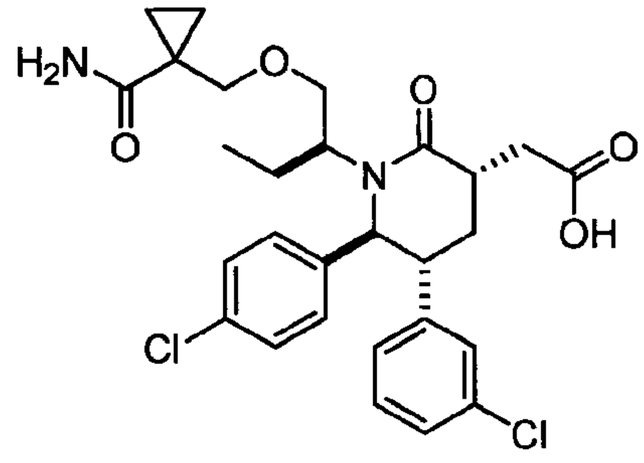
2-((3R,5R,6S)-1-((S)-1-((1-carbamoylcyclopropyl)methoxy)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid

A solution of 10mg (0.02 mmol) 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-((1-cyanocyclopropyl)methoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid (Example 11) and potassium hydroxide (3.2 mg, 0.06 mmol) in *t*-BuOH (189 μL) was stirred at 85 ^{o}C for 24 h. The reaction was acidified (10% citric acid) and extracted (2 x EtOAc). The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification by reversed phase preparatory HPLC (GeminiTM Prep C18 5μm column, Phenomenex, Torrance, CA; eluent: 35 to 75% acetonitrile +0.1% TFA in water + 0.1% TFA, gradient elution) provided the title compound.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δppm 0.67 (m, 5 H), 1.34 (m., 2 H), 1.54 (m., 1 H), 1.87 - 2.18 (m, 4 H), 2.65 (m, 1 H), 2.71 - 2.90 (m, 2 H), 3.08 (m, 1 H), 3.38-3.64 (m, 4 H), 3.94 (m, 1 H), 4.84 (m, 1 H),6.35 (br.s., 1 H), 6.91 (br. s., 1 H) 7.13 (m, 1 H) 7.21-7.38 (m, 7 H). MS (ESI) 547.2 $[M+H]^+$, 545.0 $[M-H]^-$.

Further elution provided Example 17.

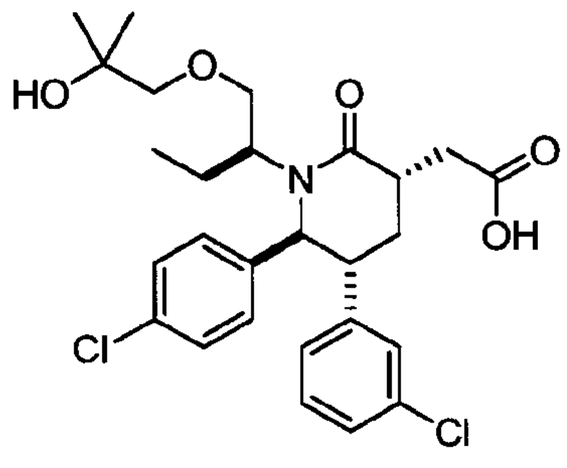
EXAMPLE 17



2-((3S,5R,6S)-1-((S)-1-((1-carbamoylcyclopropyl)methoxy)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid

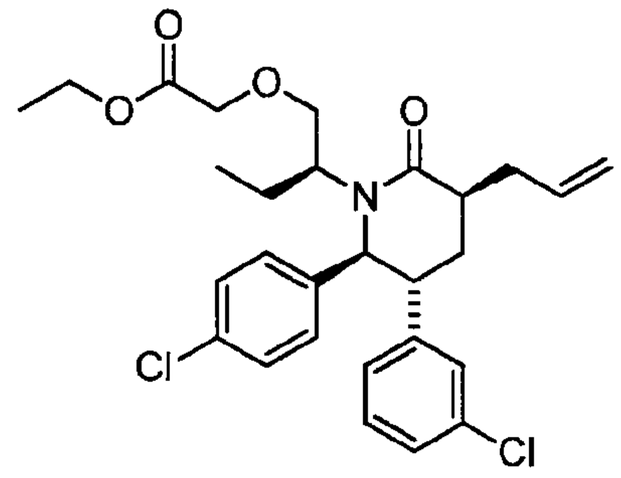
^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.26–7.21 (2 H, m), 7.17–7.12 (2 H, m), 7.06 (1 H, br, s), 6.95–6.90 (2 H, m), 6.88–6.80 (1 H, s), 6.79–6.76 (1 H, m), 6.74 (1 H, br, s), 4.63 (1 H, d, J = 10.2 Hz), 4.10–4.00 (1 H, m), 3.33–3.10 (3 H, m), 3.02–2.92 (2 H, m), 2.90–2.78 (1 H, m), 2.70–2.60 (1 H, m), 2.44–2.34 (1 H, m), 2.00–1.90 (1 H, m), 1.85–1.75 (1 H, m), 1.65–1.55 (1 H, m), 1.43–1.35 (2 H, m), 0.85–0.73 (2 H, m), 0.63–0.52 (3 H, m); MS (ESI) 547.2 $[M + H]^+$, 545.0 $[M - H]^-$.

EXAMPLE 18



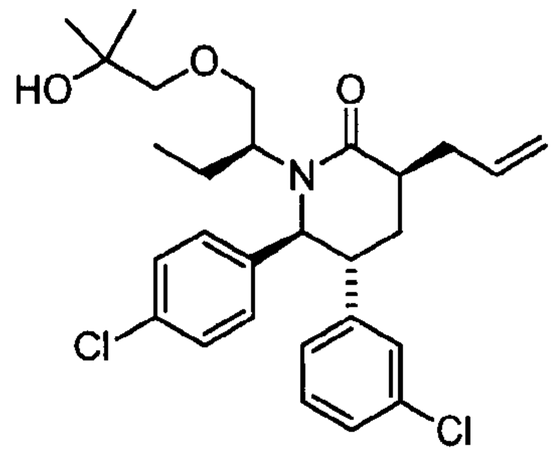
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(2-hydroxy-2-methylpropoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid

Step A. Ethyl 2-((S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butoxy)acetate



To a solution of 203mg (0.47mmol) of (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-hydroxybutan-2-yl)piperidin-2-one (Example 9, Step B) and rhodium(II)acetate dimmer (10.4 mg, 0.047 mmol) in CH_2Cl_2 (1.90 mL) was added dropwise ethyl diazoacetate (286 μL, 2.35 mmol) at 25 °C. After being stirred at 25 °C for 14h, the reaction was concentrated under reduced pressure and purified by chromatography on silica gel (20% to 30% EtOAc/Hexanes, gradient elution) to provide the title compound as a colorless liquid:

Step B. (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(2-hydroxy-2-methylpropoxy)butan-2-yl)piperidin-2-one



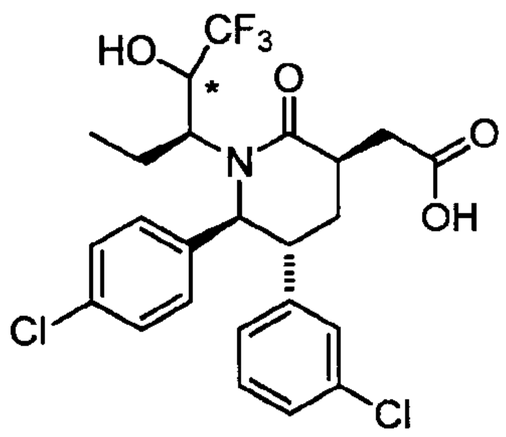
To a solution of ethyl 2-((S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butoxy)acetate (69.0 mg, 0.133 mmol) in THF (2.22 mL) was added methylmagnesium bromide, 1.4M in Toluene/THF, (0.38 mL, 0.532 mmol) at 0 °C. After being stirred at 25 °C for 3 h, the reaction was quenched (sat. aq. NH_4Cl), and extracted with EtOAc. The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification by chromatography on silica gel (20% to 50% EtOAc/Hexanes, gradient elution) provided the title compound as a colorless liquid.

Step C. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(2-hydroxy-2-methylpropoxy)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid

To a rapidly stirring solution of (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(2-hydroxy-2-methylpropoxy)butan-2-yl)piperidin-2-one (51.0 mg, 0.101 mmol) in a mixture of water (361 μL), acetonitrile (241 μL), and CCl_4 (241 μL) was added sodium periodate (86 mg, 0.404 mmol), followed by ruthenium(III) chloride hydrate (2.28 mg, 10.1 μmol). After being stirred vigorously for 18 h, the reaction was acidified (10% citric acid) and diluted (EtOAc). The mixture was filtered through Celite® (J.T. Baker, Phillipsberg, NJ, J.T. Baker, Phillipsberg, NJ, diatomaceous earth) and the filtrate was extracted with EtOAc. The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification by reversed phase preparatory HPLC (GeminiTM Prep C18 5μm column, Phenomenex, Torrance, CA; eluent: 50 to 76% acetonitrile +0.1% TFA in water + 0.1% TFA, gradient elution) provided the title compound as a white solid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.64 - 0.74 (t, J=7.6Hz, 3 H), 1.21 (d, *J*=3.7 Hz, 6 H), 1.58 (ddd, *J*=14.0, 7.6, 4.4 Hz, 1 H), 1.84 - 1.99 (m, 2 H), 2.21 (m, 1 H), 2.64 - 2.83 (m, 3 H), 3.04 - 3.15 (m, 1 H), 3.19 (d, *J*=9.2 Hz, 1 H), 3.29 (d, *J*=9.2 Hz, 1 H), 3.38 (m, 1 H), 3.41 - 3.55 (m, 1 H), 3.98 (t, *J*=8.6 Hz, 1 H), 4.98 (d, *J*=2.9 Hz, 1 H) 7.12 - 7.20 (m, 1 H), 7.21 - 7.34 (m, 5 H), 7.34 - 7.41 (m, 2 H); MS (ESI) 522.1 $[M+H]^+$. 520.2 $[M-H]^-$.

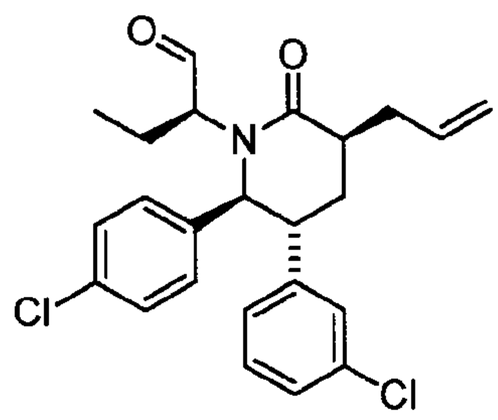
EXAMPLE 19



** absolute stereochemistry unknown*

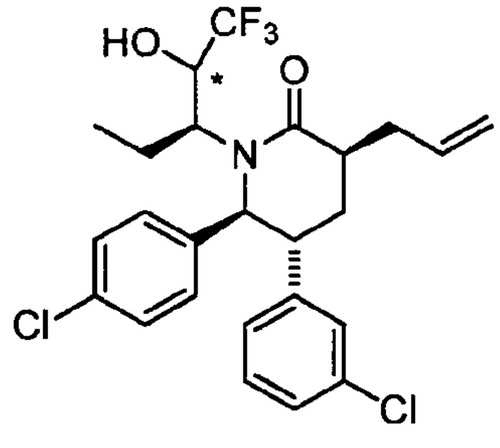
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((3S)-1,1,1-trifluoro-2-hydroxypentan-3-yl)piperidin-3-yl)acetic acid (Isomer 1)

Step A. (S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl) butanal



To a solution of oxalyl dichloride (166 μL, 1.87 mmol) in DCM (4.16 mL) at -60 °C was added a solution of DMSO (222 μL, 3.12 mmol) in DCM (4.16 mL) under N_2. After about 20 min, a solution of 540mg (1.25 mmol) of (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-hydroxybutan-2-yl)piperidin-2-one (Example 9, Step B) in 4.2mL of DCM was added, and the resulting solution was stirred for 15 min. Triethylamine (872 μL, 6.24 mmol) was then added. After being stirred at -60 °C for 5 min, the reaction was allowed to warm to rt, and 5 mL of water was added. The solution was extracted (2 × DCM), washed (sat. aq. NaCl solution), dried ($MgSO_4$) and concentrated under the reduced pressure to give the crude title compound containing 20% starting material (SM).

Step B. (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((3S)-1,1,1-trifluoro-2-hydroxypentan-3-yl)piperidin-2-one



*absolute stereochemistry unknown

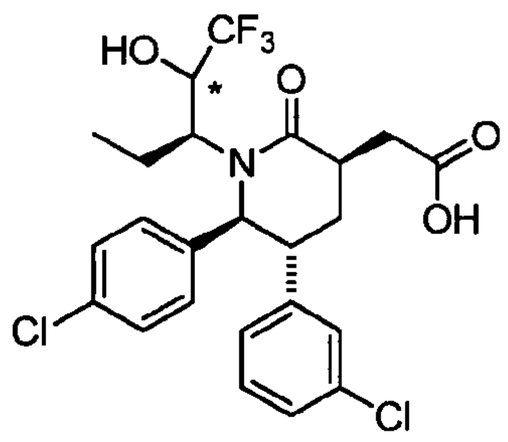
A solution of (S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanal (80 mg, 0.186 mmol) and trimethyl(trifluoromethyl)silane (82 μL, 0.558 mmol) in THF (929 μL) was treated at 0 °C with 1 M tetrabutylammonium fluoride in THF (93 μL, 0.093 mmol). After being stirred for 1 h, three additional equivalents of trimethyl(trifluoromethyl)silane (82 μL, 0.558 mmol) and 1 M tetrabutylammonium fluoride in THF (93 μL, 0.093 mmol) were added to the reaction at 0 °C and the reaction was stirred for 14h . The reaction mixture was diluted (EtOAc), washed (1 × H_2O and 1 × sat. aq. NaCl solution), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by reverse phase preparatory HPLC (GeminiTM Prep C18 5μm column, Phenomenex, Torrance, CA; eluent: 60 to 90% acetonitrile +0.1% TFA in water + 0.1% TFA, gradient elution) provided two compounds which are diastereomers at the secondary alcohol.

Step C. 2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((3S)-1,1,1-trifluoro-2-hydroxypentan-3-yl)piperidin-3-yl)acetic acid

The title compound was prepared from a single diastereomer of (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((3S)-1,1,1-trifluoro-2-hydroxypentan-3-yl)piperidin-2-one by a procedure similar to the one described in Example 18, Step C.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.53 (t, *J*=7.5 Hz, 3 H), 1.66 (m, 1 H), 1.97 - 2.05 (m, 1 H), 2.18 (m, 1 H), 2.32 - 2.45 (m, 1 H), 2.68 - 2.83 (m, 2 H), 2.94 - 3.05 (m, 1 H), 3.15 - 3.25 (m, 1 H), 4.42 (m, 1 H), 4.69 (d, *J*=3.9 Hz, 1 H), 6.95 - 7.02 (m, 1 H), 7.12 (m, 1 H), 7.22 - 7.37 (m, 5 H), 7.37 - 7.46 (m, 2 H); MS (ESI) 518.0 $[M+H]^+$. 516.0 $[M-H]^-$.

EXAMPLE 20



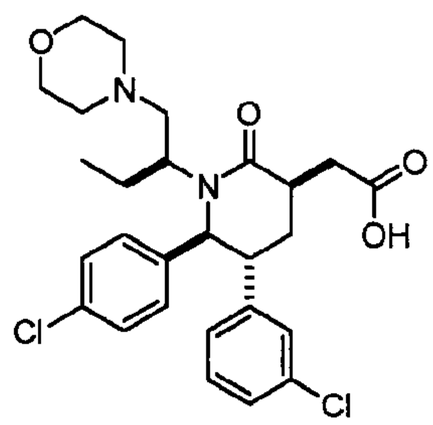
*absolute stereochemistry unkonwn

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((3S)-1,1,1-trifluoro-2-hydroxypentan-3-yl)piperidin-3-yl)acetic acid (Isomer 2)

To a rapidly stirring solution of 6.3 mg (0.013 mmol) of (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((3S)-1,1,1-trifluoro-2-hydroxypentan-3-yl)piperidin-2-one (Example 19, Step B, the diastereomer not used for Example 19 Step B)) (6.30 mg, 0.013 mmol) in a mixture of water (108 µL), acetonitrile (71.9 µL), and CCl_4 (71.9 µL) was added sodium periodate (10.7 mg, 0.050 mmol), followed by ruthenium(III) chloride hydrate (0.284 mg, 1.26 µmol). After being stirred vigorously for 18 h, the reaction was acidified (10% citric acid) and diluted (EtOAc). The reaction mixture was filtered through Celite® (J.T. Baker, Phillipsberg, NJ, J.T. Baker, Phillipsberg, NJ, diatomaceous earth). The filtrate was extracted (2 × EtOAc). The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification by reversed phase preparatory HPLC (GeminiTM Prep C18 5µm column, Phenomenex, Torrance, CA; eluent: 45 to 70% acetonitrile +0.1% TFA in water + 0.1% TFA, gradient elution) provided the title compound as a white solid.

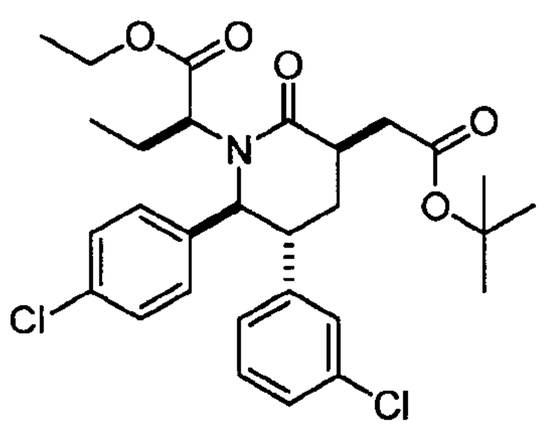
^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 0.44–0.72 (m, 3H); 1.28–1.46 (m, 1 H), 2.15–2.28 (m, 2 H), 2.45–2.55 (m, 1 H), 2.89–3.05 (m, 3 H), 3.10–3.18 (m, 2 H), 4.02–4.16 (m, 1 H), 4.56 (d, J = 7.8 Hz, 1 H), 6.84–6.93 (m, 1 H), 7.01–7.04 (m, 1 H), 7.08–7.14 (m, 2 H), 7.17–7.20 (m, 2 H), 7.32–7.38 (m, 2 H); MS (ESI) 518.0 $[M + H]^+$. 516.0 $[M - H]^-$.

EXAMPLE 21



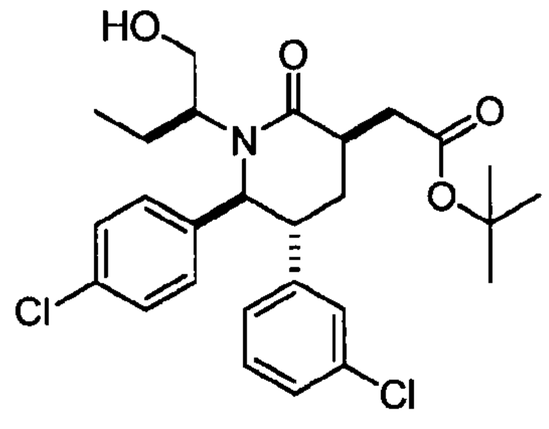
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid

Step A. (S)-ethyl 2-((3R,5R,6S)-3-(2-tert-butoxy-2-oxoethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanoate



To a stirred solution of 1.14g (2.3 mmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-ethoxy-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid (Example 3) in DCM (21.0 mL) was added sulfuric acid (0.247 mL, 4.63 mmol) followed by isobutylene (4.42 mL, 46.3 mmol) at -78 °C. The reaction vessel was sealed and the mixture was slowly warmed to rt and vigorously stirred for 3 days. After cooling to -78 °C, the tube was opened and the reaction was quenched with aqueous saturated $NaHCO_3$ to pH 8. The organic solvent was removed under reduced pressure, and the remaining mixture was extracted (2 x EtOAc). The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (eluent: 20 to 35% EtOAc/hexanes) to provide the title compound as a foam.

Step B. *tert*-butyl 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-hydroxybutan-2-yl)-2-oxopiperidin-3-yl)acetate

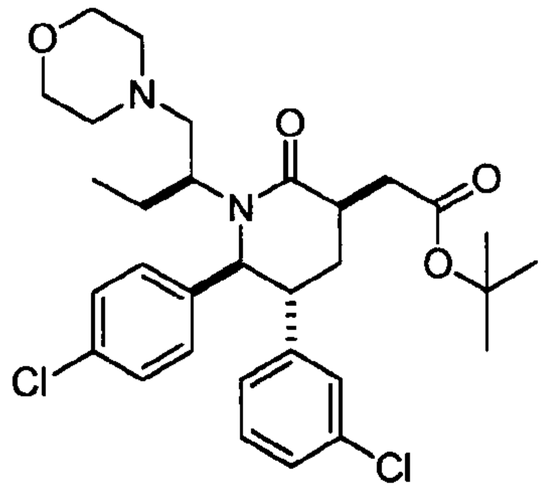


To a solution of (S)-ethyl 2-((3R,5R,6S)-3-(2-tert-butoxy-2-oxoethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanoate (1.94 g, 3.54 mmol, Example 21, Step A) in Et_2O (35.4 mL) was added 90% lithium borohydride (0.154 g, 7.07 mmol) at 0 °C. After being stirred at 0 °C for 30 min, the reaction was quenched (ice cold 10% citric acid), extracted (2 × EtOAc) and washed (sat. aq. NaCl solution). The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification by chromatography on silica gel (50% to 100% EtOAc/Hexanes, gradient elution) provided the title compound.

Step C. tert-butyl 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((S)-1-oxobutan-2-yl)piperidin-3-yl)acetate

To a solution of oxalyl chloride (0.261 mL, 2.99 mmol) in DCM (5.87 mL) at -60°C was added a solution of DMSO (0.512 mL, 5.98 mmol) in DCM (5.87 mL) under N_2. After being stirred for 20 min, a solution of *tert*-butyl 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-hydroxybutan-2-yl)-2-oxopiperidin-3-yl)acetate (1.01 g, 1.99 mmol, Example 21, Step B) in DCM (5.87 mL) was added, and the resulting solution was stirred for 15 min. To this solution was added triethylamine (1.39 mL, 9.97 mmol). After being stirred at -60 °C for 5 min, the reaction was allowed to warm to rt, and quenched (H_2O). The solution was extracted (3 × DCM) and washed (H_2O and sat. aq. NaCl solution). The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give the title compound.

Step D. tert-butyl 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)acetate



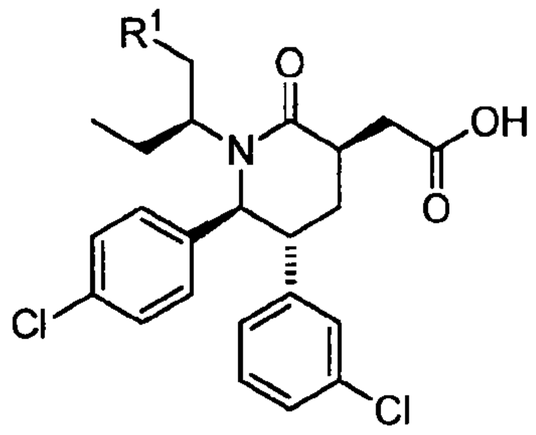
To a solution of tert-butyl 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((S)-1-oxobutan-2-yl)piperidin-3-yl)acetate (0.050 g, 0.099 mmol, Example 21, Step C) and morpholine (0.013 mL, 0.149 mmol) in DCE (1.0 mL) was added sodium triacetoxyhydroborate (0.063 g, 0.297 mmol) at 0 °C . After being stirred at 25 °C for 18 h, the reaction was quenched by adding ice-cold saturated aqueous $NaHCO_3$ and extracted (2 × DCM) and the combined organic layers were washed (1 × sat. aq. NaCl solution) and concentrated under the reduced pressure. This was used in next step without further purification.

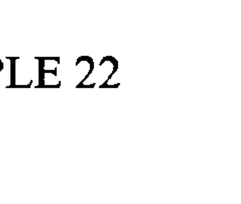
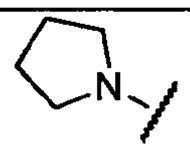
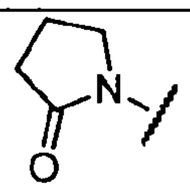
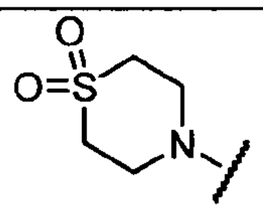
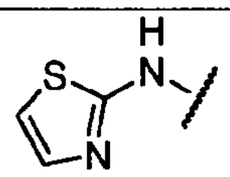
Step E. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid

To a round-bottomed flask with tert-butyl 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)acetate (0.057 g, 0.099 mmol; Example 21, Step D) in DCM (1mL) was added TFA (1.129 g, 9.90 mmol) at 0 °C. The ice-bath was removed and the mixture was stirred at rt for 3h. The solvent was removed. Purification by reversed phase preparatory HPLC (GeminiTM Prep C18 5µm column, Phenomenex, Torrance, CA; eluent: 10 to 90% acetonitrile +0.1% TFA in water + 0.1% TFA, gradient elution) provided the title compound as a white powder.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.99 (m, 3 H), 1.60 - 2.43 (m., 4 H), 2.60 - 2.86 (m, 5 H), 3.11 - 3.40 (m, 2 H), 3.83 - 4.04 (m, 5 H), 4.43 (m, 2 H), 4.90 (m, 1 H), 7.01 (m, 1 H) 7.12 (m, 1 H) 7.20 - 7.36 (m, 2 H) 7.46 (m., 4 H) ; MS (ESI) 519.1 $[M+H]^+$. 517.2 $[M-H]^-$

Examples 22 to 27 were prepared in a process similar to that described for Example 21, substituting morpholine in step D for the appropriate amine.



Example	R^1
22	
23	
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EXAMPLE 22

2-((3RS,5RS,6SR)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((SR)-1-(ethylamino)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid (prepared from racemic intermediate)

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 0.91–1.13 (t, *J* = 7.8 Hz, 3 H), 1.28 (t, *J* = 7.14 Hz, 3 H), 1.55–1.65 (m, 1 H), 1.76–1.86 (m, 1 H), 1.95–2.05 (m, 1 H), 2.31–2.59 (m, 2 H), 2.73–2.85 (m, 2 H), 2.90–3.09 (m, 5 H), 4.78–4.82 (m, 1 H), 4.88–5.02 (m, 1 H), 6.90–6.98 (m, 1 H), 7.04–7.12 (m, 1 H), 7.20–7.30 (m, 3 H), 7.36–7.42 (m, 2 H), 7.45–7.56 (m, 1H); MS (ESI) 477.1 $[M + H]^+$, 475.1 $[M - H]^-$.

EXAMPLE 23

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((S)-1-(2,2,2-trifluoroethylamino)butan-2-yl)piperidin-3-yl)acetic acid

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 0.96 (t, *J* = 7.3 Hz, 3 H), 1.62–1.74 (m, 1 H), 1.79–1.98 (m, 2 H), 2.41–2.51 (m, 1 H), 2.61–2.75 (m, 2 H), 3.01–3.21 (m, 4 H), 3.74–3.91 (m, 2 H), 4.57 (m, 1 H), 4.89 (d, *J* = 2.9 Hz, 1 H), 6.96–7.02 (m, 1 H), 7.12 (m, 1 H), 7.24–7.31 (m, 2 H), 7.36–7.49 (m, 4 H); MS (ESI) 531.1 $[M + H]^+$, 529.0 $[M - H]^-$.

EXAMPLE 24

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((S)-1-(pyrrolidin-1-yl)butan-2-yl)piperidin-3-yl)acetic acid

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 0.93 (m., 3 H), 1.67–1.75 (m, 2 H), 2.03–2.39 (m., 7 H), 2.74–2.91 (m, 6 H), 3.09–3.17 (m, 2 H), 3.86 (m, 1 H), 4.05 (m, 1 H), 4.86 (m, 1 H), 6.82–7.04 (m, 1 H) 7.09 (m, 1 H) 7.25 (m, 2 H) 7.44 (m, 4 H); MS (ESI) 503.2 $[M + H]^+$, 501.1 $[M - H]^-$.

EXAMPLE 25

2-((3RS,5RS,6SR)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((SR)-1-(2-oxopyrrolidin-1-yl)butan-2-yl)piperidin-3-yl)acetic acid (prepared from racemic intermediate.)

Ethyl 4-aminobutanoate hydrochloride was used at the amine. After reductive amination the intermediate was cyclized by heating to 120 °C in acetic acid and toluent to provide the title compound.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 0.93 (m., 3 H), 1.67 (m, 1 H), 1.82 (m, 1 H), 2.07–2.20 (m., 5 H), 2.44–2.46 (m, 3 H), 2.71–3.06 (m, 3 H), 3.20–3.30 (m, 2 H), 3.40–3.55 (m, 3 H), 3.69 (m, 1 H), 4.70 (m, 1 H), 6.99–7.04 (m, 1 H) 7.12–7.16 (m, 3 H) 7.24–7.27 (m, 2 H) 7.35 (m, 2 H); MS (ESI) 517.2 $[M + H]^+$.

EXAMPLE 26

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(1,1-dioxidothiomorpholino)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid

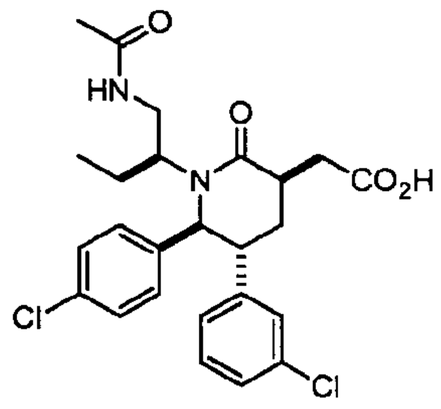
^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 0.85 (m., 3 H) 1.71 (m, 2 H) 1.83–1.98 (m, 1 H) 2.37 (m, 1 H) 2.58 (m, 1 H) 2.63–2.83 (m, 2 H) 3.04–3.15 (m, 3 H), 3.25–3.35 (m., 6 H) 3.43–3.64 (m, 2 H) 4.88 (m, 1 H) 7.09 (m., 1 H) 7.19 (m, 1 H) 7.29 (m, 2 H) 7.34–7.50 (m, 4 H); MS (ESI) 567.1 $[M + H]^+$, 565.2 $[M - H]^-$.

EXAMPLE 27

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((S)-1-(thiazol-2-ylamino)butan-2-yl)piperidin-3-yl)acetic acid

^{1}H NMR (500 MHz, *ACETONITRILE-d_3*) δ ppm 0.58 (t, J = 7.2 Hz, 3 H), 1.52–1.64 (m, 1 H), 1.73–1.89 (m, 1 H), 1.98–2.05 (m, 1 H), 2.05–2.16 (m, 1 H), 2.67–2.81 (m, 1 H), 2.81–2.92 (m, 2 H), 3.11–3.32 (m, 2 H), 3.50 (m, 1 H), 3.68 (m, 1 H), 4.81 (d, J = 6.8 Hz, 1 H), 6.72–6.79 (m, 1 H), 7.04–7.12 (m, 1 H), 7.14 (s, 1 H), 7.17–7.23 (m, 2 H), 7.25 (d, J = 4.4 Hz, 1 H), 7.29–7.41 (m, 4 H); MS (ESI) 530.0 $[M - H]^-$.

EXAMPLE 28



2-((3RS,5RS,6SR)-1-((SR)-1-acetamidobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl)acetic acid (racemic)

Step A. (3SR,5RS,6SR)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((SR)-1-(4-methoxybenzylamino)butan-2-yl) piperidin-2-one

To a solution of 79mg (0.184 mmol) of (SR)-2-((3SR,5RS,6SR)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanal (racemate of Example 19, Step A) and 4-methoxybenzylamine (35.7 µL, 0.275 mmol) in 1.8 mL of dichloroethane was added sodium triacetoxyborohydrate (117 mg, 0.551 mmol)at 0 °C in several portions. After being stirred at 25 °C for 18 h, the reaction was quenched by adding ice-cold saturated aqueous $NaHCO_3$ and extracted (2 × DCM) and the combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification by flash chromatography on silica (0% to 3% MeOH/DCM with 1% aq. NH_4OH) provided the title compound as a yellow film.

Step B. (3SR,5RS,6SR)-3-allyl-1-((SR)-1-aminobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl) piperidin-2-one

To a solution of (3SR,5RS,6SR)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((SR)-1-(4-methoxybenzylamino)butan-2-yl)piperidin-2-one (88 mg, 0.160 mmol) in acetonitrile (1899 µL) and water (380 µL) was added ceric ammonium nitrate (350 mg, 0.638 mmol) at 25 oC. The reaction was moniterd by LCMS and HPLC and on completion was diluted with 0.5 M aq. NaOH and EtOAc and the resulting emulsion was filtered through a pad of Celite® (J.T. Baker, Phillipsberg, NJ, J.T. Baker, Phillipsberg, NJ, diatomaceous earth). The fitrate was extracted with ethyl acetate and the combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to provide the crude product which was used n subsequent steps without further purification.

Step C. N-((SR)-2-((3SR,5RS,6SR)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butyl) acetamide

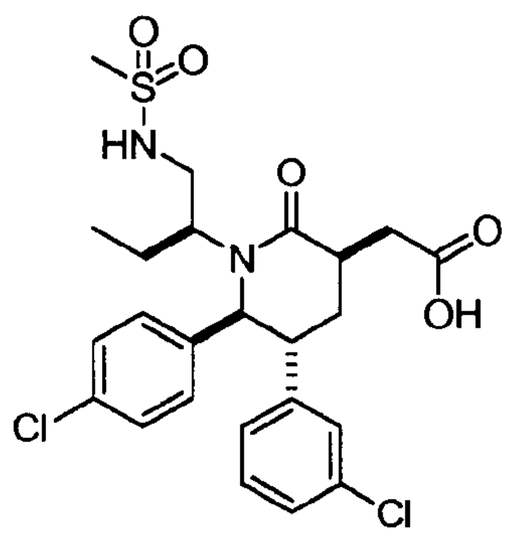
To a solution of 53 mg (0.123 mmol) of (3SR,5RS,6SR)-3-allyl-1-((RS)-1-aminobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one (Step B) in DMF (307 µL) was added acetic anhydride (116 µL, 1.229 mmol) at 25 °C. After being stirred at 25 °C for 14h the reaction was quenched (H_2O) and extracted (2 x EtOAc). The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Separation by reversed phase HPLC (50 to 80% AcCN/H_2O in 25 min, 2 injections, t_R =15.683 min) provided the title compound as a yellow solid.

Step D. 2-((3RS,5RS,6SR)-1-((SR)-1-acetamidobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-3-yl) acetic acid

The oxidation of N-((SR)-2-((3SR,5RS,6SR)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butyl) acetamide to the title compound was carried out as described in Example 1, Step H to give the title compound as white solid.

^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 0.80 (t, *J* = 7.4 Hz, 3 H,) 1.62–1.75 (m, 1 H), 1.84–1.97 (m, 2 H), 2.07 (s, 3 H), 2.36–2.49 (m, 1 H), 2.64–2.80 (m, 2 H), 3.02–3.16 (m, 2 H), 3.16–3.31 (m, 1 H), 3.32–3.40 (m, 1 H), 3.74–3.90 (m, 1H), 4.76–4.82 (m, 1 H), 7.04–7.08 (m, 1 H), 7.16–7.19 (m, 1 H), 7.22–7.30 (m, 2 H), 7.32–7.38 (m, 4 H); MS (ESI) 491.0 $[M + H]^+$, 489.1 $[M - H]^-$.

EXAMPLE 29



2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(methylsulfonamido) butan-2-yl)-2-oxopiperidin-3-yl)acetic acid

Step A. N-((S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butyl)methanesulfonamide

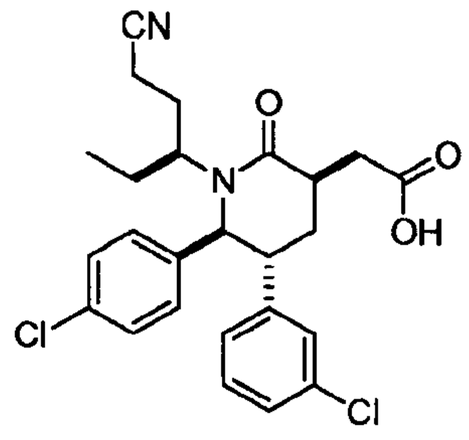
To a solution of 69 mg (0.16 mmol) of (3S,5R,6S)-3-allyl-1-((S)-1-aminobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one (Example 28, Step B from the non-racemic precursor described in Example 19, Step A) in 1.6 mL of DCM was added methanesulfonyl chloride (13.7 μL, 0.175 mmol) and pyridine (38.7 μL, 0.478 mmol) successively at 0 °C. After being stirred at rt for 14h the reaction mixture was acidified with 10% aq. citric acid and extracted (2 x DCM). The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification by reversed phase HPLC (40 to 90% MeCN/H_2O in 45 min, 2 injections, t_R =25.94 min) provided the title compound as a yellow solid.

Step B. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(methylsulfonamido) butan-2-yl)-2-oxopiperidin-3-yl)acetic acid

The title compound was prepared as described in Example 28, Step D, using N-((S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butyl)methanesulfonamide (Step A).

^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 0.67 (t, *J* = 7.6 Hz, 3 H), 1.51–1.61 (m, 1 H), 1.88–1.92 (m, 1 H), 2.13–2.26 (m, 2 H), 2.79–2.89 (m, 2 H), 2.89–2.95 (m, 1 H), 2.98 (s, 3 H), 3.02–3.10 (m, 1 H), 3.17–3.21(m, 1 H), 3.42–3.52 (m, 1 H), 4.85 (d, *J* = 5.4 Hz, 1 H), 5.27 (br. s., 1 H), 7.02–7.10 (m, 1 H), 7.10–7.15 (m, 1 H), 7.18–7.30 (m, 4 H), 7.34 (d, *J* = 8.6 Hz, 2 H); MS (ESI) 527.0 $[M + H]^+$, 525.1 $[M - H]^-$.

EXAMPLE 30



2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyanopentan-3-yl)-2-oxopiperidin-3-yl)acetic acid

Step A. tert-butyl 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyanopent-1-en-3-yl)-2-oxopiperidin-3-yl)acetate

To a solution of diethyl cyanomethylphosphonate (62.4 µL, 0.396 mmol) and DMPU (239 µL, 1.98 mmol) in THF (661 µL) was added 60% sodium hydride a s asuspension in mineral oil (11.89 mg, 0.297 mmol) at 0 °C. The mixture was stirred for 30 min, and then treated with a solution of 100mg (0.2 mmol) of tert-butyl 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((R)-1-oxobutan-2-yl)piperidin-3-yl)acetate (Example 21, Step C) in THF (661 µL). After being stirred for 12 h, the reaction was quenched with water, extracted (2 x EtOAc) and the combined organic layers were washed with sat. NaCl solution, dried over

Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10 to 20% EtOAc/Hex, a gradient elution) provided the of the title compound as a mixture of E- and Z-isomers.
MS (ESI) 527.2 $[M + H]^+$.

Step B. tert-butyl 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyanopentan-3-yl)-2-oxopiperidin-3-yl)acetate

To a solution of 56 mg (0.106 mmol) of tert-butyl 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyanopent-1-en-3-yl)-2-oxopiperidin-3-yl)acetate (Example 30, Step A) in 3.5 mL of EtOH) was added 10% palladium on activated carbon (11.30 mg, 10.62 μmol). Then the reaction mixture was subjected to regular hydrogenation with hydrogen. After being stirred under a hydrogen atmosphere at rt for 2 h, the catalyst was filtered using a short plug of silica gel. The plug was washed several times with EtOAc. The combined filtrates were concentrated under reduced pressure to provide the crude title compound as a colorless film which was used in the subsequent reaction without further purification. MS (ESI) 529.2 [M+H]+.

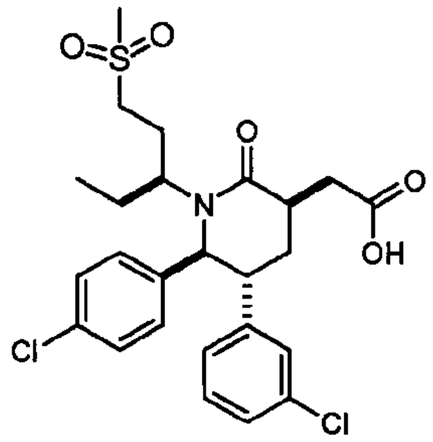
Step C. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyanopentan-3-yl)-2-oxopiperidin-3-yl)acetic acid

To a solution of 57 mg (0.11 mmol) of tert-butyl 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyanopentan-3-yl)-2-oxopiperidin-3-yl)acetate (Example 30, Step B) in DCM (359 μL) was added trifluoroacetic acid (415 μL, 5.38 mmol) at 0 °C. After being stirred at 25 C for 2 h, solvents were removed under reduced pressure and the residual TFA was removed by azeotroping with toluene under reduced pressure three times. Separation of the crude product by reversed phase HPLC (45 to 70% AcCN/H_2O in 30 min, 3 time runs, t_R = 18.52 min) provided the title compound as a white solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.37 (2 H, d, *J* = 8.6 Hz), 7.27–7.25 (2 H, m), 7.21 (2 H, d, *J* = 8.6 Hz), 7.15–7.12 (1 H, m), 7.04–6.98 (1 H, m), 4.74 (1 H, d, *J* = 5.3 Hz), 3.42–3.32 (1 H, m), 3.13–3.08 (1 H, m), 3.08–3.00 (1 H, m), 2.99–2.92 (1 H, m), 2.85–2.77 (1 H, m), 2.43–2.33 (2 H, m), 2.23–2.15 (2 H, m), 2.13–2.03 (1 H, m), 1.94–1.77 (2 H, m), 1.64–1.54 (1 H, m), 0.64 (3 H, t, *J*=7.4 Hz); MS (ESI) 473.0 $[M + H]^+$, 471.1 $[M - H]^-$.

Examples 31 and 32 were prepared in a process similar to that described for Example 30, using the appropriately substituted phosphonates in Step A:

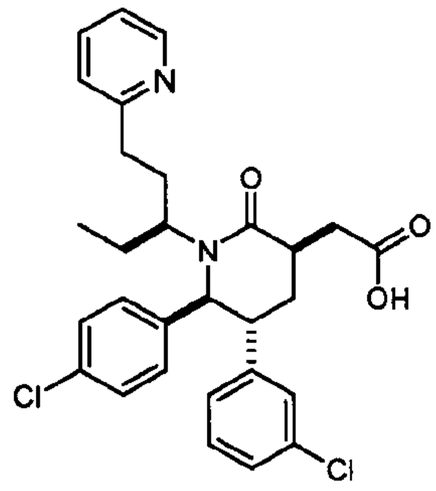
EXAMPLE 31



2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(methylsulfonyl)pentan-3-yl)-2-oxopiperidin-3-yl)acetic acid

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.71 (t, *J*=8.0 Hz, 3 H), 1.58 - 1.69 (m, 1 H), 1.82 (m, 1 H), 1.98 - 2.17 (m, 3 H), 2.20 - 2.34 (m, 1 H), 2.83 - 3.13 (m, 10 H), 4.80 - 4.84 (m, 1 H), 7.00 - 7.07 (m, 1 H), 7.13 - 7.18 (m, 1 H), 7.23 - 7.32 (m, 4 H), 7.34 - 7.41 (m, 2 H); MS (ESI) 526.2 $[M+H]^+$.

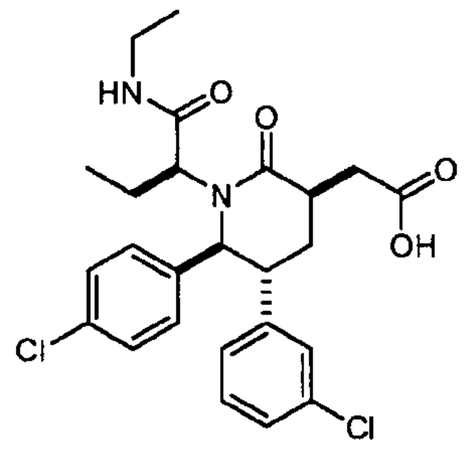
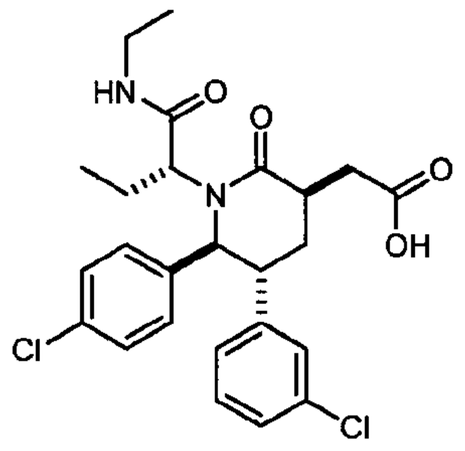
EXAMPLE 32



2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-((S)-1-(pyridin-2-yl)pentan-3-yl)piperidin-3-yl)acetic acid

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.89 (t, *J*=7.5 Hz, 3 H), 1.60 - 1.79 (m, 4 H), 1.90 - 1.98 (m, 1 H), 2.53 (m, 1 H), 2.61 - 2.69 (m, 1 H), 2.72 - 2.79 (m, 1 H), 2.90 - 3.03 (m, 2 H), 3.07 - 3.12 (m, 1 H), 3.19 - 3.28 (m, 1 H), 4.15 (m, 1 H), 4.80 - 4.81 (m, 1 H), 7.01 - 7.07 (m, 1 H), 7.15 (s, 1 H), 7.22 - 7.35 (m, 4 H), 7.40 - 7.47 (m, 1 H), 7.59 (d, *J*=7.82 Hz, 1 H), 7.75 (t, *J*=6.75 Hz, 1 H), 8.28 (t, *J*=7.92 Hz, 1 H), 8.85 - 8.89 (m, 1 H); MS (ESI) 525.1 $[M+H]^+$

EXAMPLE 33

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(ethylamino)-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid and 2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-(ethylamino)-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid

Step A. (R)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanoic acid

To a solution of 320 mg (0.64 mmol) of tert-butyl (2S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanoate (Example 1, Step G) in DCM (3184 μL) was added trifluoroacetic acid (2453 μL, 31.8 mmol) at 0 °C. After being stirred at 25 C for 3 h, solvents were removed under reduced pressure and the residual TFA was removed by azeotroping with toluene under reduced pressure 3-times to provide the title compound as a pale yellow foam which was used in the subsequent reaction without further purification.

Step B. (S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)-N-ethylbutanamide

A solution of 107mg (0.24 mmol) of (S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanoic acid (Example 33, Step A) and ethylamine (31.4 μL, 0.479 mmol) in DCM (539 μL) and DMF (59.9 μL) was treated at 0 °C with N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (138 mg, 0.719

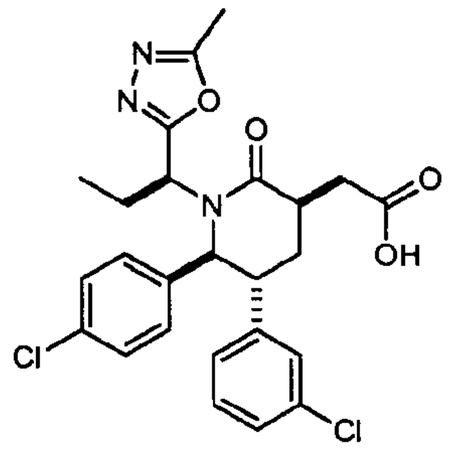
mmol), 3H-[1,2,3]triazolo[4,5-b]pyridin-3-ol (98 mg, 0.719 mmol), and sodium bicarbonate (60.4 mg, 0.719 mmol), successively. Then the reaction was stirred at 25 °C for 12 h. The reaction was diluted (1 N aq. HCl), extracted (2 × EtOAc), the combined organic layers were washed with sat. aq. NaCl and $NaHCO_3$-solutions, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification by chromatography on silica gel (30% to 40% EtOAc/Hexanes, a gradient elution) provided the title compound as a mixture of diastereomers (dr = 5:1) as a white solid: MS (ESI) 473.2 $[M+H]^+$.

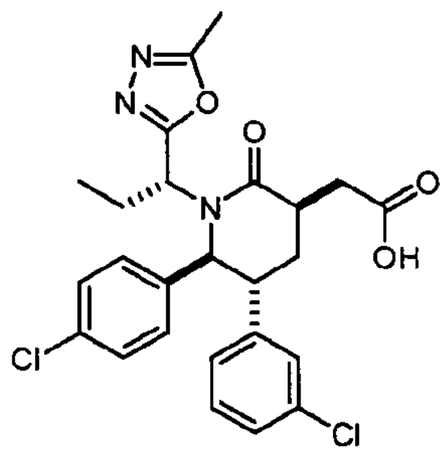
Step C. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(ethylamino)-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid and 2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-(ethylamino)-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid

2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)-N-ethylbutanamide (Example 33, Step B) was converted to the acid as described in Example 1, Step H to give the title compounds as a mixture of diastereomers (dr = 5:1).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 0.81 (t, *J* = 7.8 Hz, 3 H), 1.10 (t, *J*=7.2 Hz, 3 H), 1.65–1.75 (m, 1 H), 1.87 (m, 1 H), 2.24–2.41 (m, 2 H), 2.57–2.66 (m, 1 H), 2.70 (dd, *J*=16.8, 5.09 Hz, 1 H), 2.98 (dd, *J* = 16.9, 5.58 Hz, 1 H), 3.04–3.26 (m, 3 H), 3.97 (dd, *J*=10.37, 4.89 Hz, 1 H), 5.05–5.10 (m, 1 H), 7.06–7.19 (m, 2 H), 7.19–7.24 (m, 1 H) 7.24–7.38 (m, 5 H); MS (ESI) 491.0 $[M + H]^+$. 489.1 $[M - H]^-$.

EXAMPLE 34





2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(5-methyl-1,3,4-oxadiazol-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid and 2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid

Step A. (S)-N'-acetyl-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanehydrazide

A solution of 95 mg (0.213 mmol) of (S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanoic acid (Example 33, Step A) and acetic hydrazide (23.65 mg, 0.319 mmol) in DCM (479 μL) and DMF (53.2 μL) was treated at 0°C with N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (122 mg, 0.638 mmol), 3H-[1,2,3]triazolo[4,5-b]pyridin-3-ol (87 mg, 0.638 mmol), and sodium bicarbonate (53.6 mg, 0.638 mmol) at 0 °C, successively. Then the reaction was stirred at 25 °C for 12 h. The reaction was diluted with 1 N aq. HCl and extracted (2 × EtOAc). The combined organic layers were washed with sat. aq. NaCl and $NaHCO_3$-solutions, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification by chromatography on silica gel (60% to 80% EtOAc/Hexanes, gradient elution) provided the title compound as a colorless film. MS (ESI) 502.1 $[M+H]^+$.

Step B. (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(5-methyl-1,3,4-oxadiazol-2-yl)propyl)piperidin-2-one

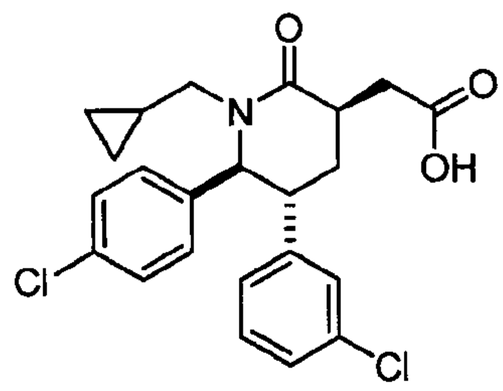
A solution of 58 mg (0.115 mmol) of (S)-N'-acetyl-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanehydrazide (Example 34, Step A) and Burgess' reagent (110 mg, 0.462 mmol) in dichloroethane (1154 μL) was heated in the microwave at 120 °C for 30 min. Then the reaction mixture was diluted with water and extracted with DCM. The combined organic layers were washed with sat. aq. NaCl and $NaHCO_3$-solutions, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Separation by reversed phase HPLC (55 to 90% $MeCN/H_2O$ in 35 min, 29 mg injection each time) provided the title compound as a colorless film. MS (ESI) 484.1 $[M + H]^+$.

Step C. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(5-methyl-1,3,4-oxadiazol-2-yl)propyl)-2-oxopiperidin-3-yl)acetic acid

(3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(5-methyl-1,3,4-oxadiazol-2-yl)propyl)piperidin-2-one (Example 34, Step B) was converted to the acid as described in Example 1, Step H to give the title compound as a mixture of diastereomers (dr = 10:1).

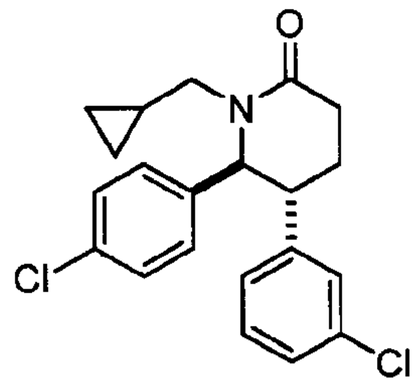
^{1}H NMR (400 MHz, *CHLOROFORM-d*) δppm 0.81 (t, *J* = 7.8 Hz, 3 H), 1.93–2.04 (m, 2 H), 2.25 (m, 1 H), 2.26 (s, 3 H), 2.33–2.44 (m, 1 H), 2.83–2.94 (m, 3 H), 3.12 (d, *J* = 2.3 Hz, 1 H), 5.08–5.18 (m, 1 H), 5.60 (br. s., 1 H), 7.07 (d, *J* = 8.2 Hz, 2 H), 7.18–7.23 (m, 1 H), 7.26 (m, 1 H), 7.28 (m, 1 H), 7.30–7.35 (m, 3 H); MS (ESI) 502.1 $[M + H]^+$, 500.0 $[M - H]^-$.

EXAMPLE 35



2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid

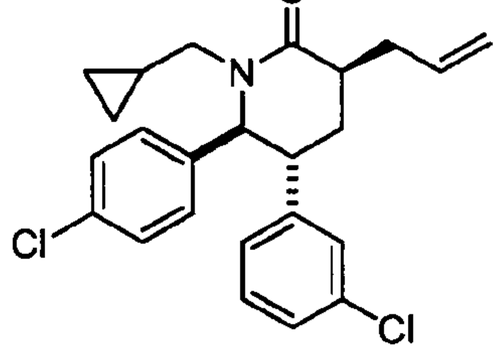
Step A. (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one



To a solution of 1.5 g (4.7 mmol) of (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one (Example 1, Step E) in 9.4 mL of DMF was added sodium hydride (60% suspension in mineral oil, 244 mg, 6.1 mmol) at 0 °C. The reaction was stirred at 0 °C for 20 min and then treated with cyclopropylmethyl bromide (759 µl, 5621 µmol).

After being stirred at 25 °C for 5 h, the reaction was quenched (sat. aqueous NH_4Cl), extracted (2 x EtOAc). The combined organic layers were washed with sat. aq. NaCl and $NaHCO_3$-solutions, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (30 to 50% EtOAc/hexanes, gradient elution) provided the title compound as a colorless foam.

Step B. (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one



To a solution of (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one (1481 mg, 3957 μmol; Example 35, Step A) and allyl bromide (360 μl, 4155 μmol) in THF (16 mL, 0.25 M) was added dropwise lithium bis(trimethylsilyl) amide (1M solution in THF, 4352 μl, 4352 μmol) at -78 °C. After being stirred at -78 °C for 3 h, the reaction was quenched (sat. aqueous NH_4Cl), extracted (2 x EtOAc). The combined organic layers were washed with sat. aq. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO_2, 20 to 30% EtOAc/Hex, gradient elution) provided the title compound as a mixture of stereoisomers.

Individual stereoisomers were separated by HPLC on a Chiralcel OD column (eluent: 25% iPA/ hexanes).

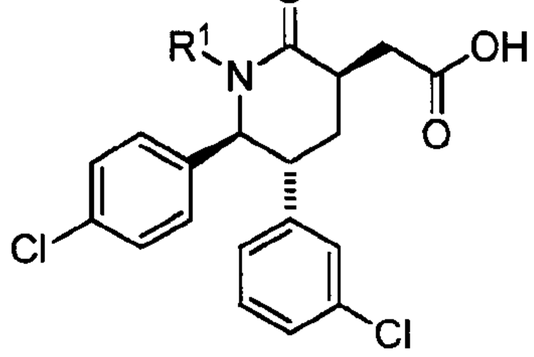
Step C. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid

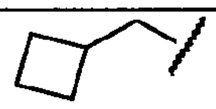
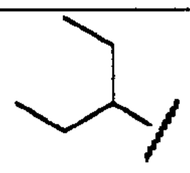
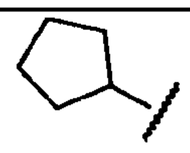
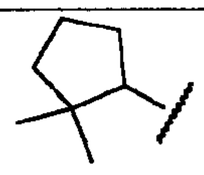
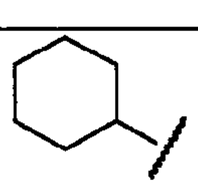
(3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one (Example 35, Step B) was converted to the acid as described in Example 1, Step H to give the title compound as a white solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.48–7.46 (1 H, m), 7.40 (2 H, d, *J* = 8.6 Hz), 7.31–7.35 (2 H, m), 7.22–7.26 (1 H, m), 7.13 (2 H, d, *J* = 8.6 Hz), 5.17 (1 H, s), 4.24 (1 H, dd,

J = 14.1, 6.7 Hz), 3.23–3.19 (1 H, m), 2.96–2.78 (1 H, m), 2.64–2.50 (2 H, m), 2.36 (1 H, dd, J = 14.1, 7.8 Hz), 2.17–2.08 (1 H, m), 1.93–1.83 (1 H, m), 1.29–1.17 (1 H, m), 0.77–0.69 (1 H, m), 0.67–0.58 (1 H, m), 0.37–0.25 (2 H, m); MS (ESI) 432.1 $[M + H]^+$, 429.9 $[M - H]^-$.

Examples 36 to 40 were prepared in a process similar to that described for Example 35, substituting (bromomethyl)cyclopropane in Step A for the appropriate amount of alkylbromide or alkyliodide.



Example	R^1
36	
37	
38	
39	
40	

EXAMPLE 36

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclobutylmethyl)-2-oxopiperidin-3-yl)acetic acid

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.62 - 1.74 (m, 1 H), 1.75 - 1.84 (m, 2 H), 1.84 - 2.01 (m, 2 H), 2.03 - 2.17 (m, 2 H), 2.18 - 2.29 (m, 1 H), 2.53 (dd, J = 13.69 and 7.24 Hz, 1 H), 2.57 -

2.63 (m, 1 H), 2.63 - 2.70 (m, 1 H), 2.69 - 2.76 (m, 1 H), 2.76 - 2.85 (m, 1 H), 3.04 - 3.17 (m, 1 H), 4.25 (dd, *J* = 13.69 and 7.63 Hz, 1 H), 4.76 - 4.89 (m, 1 H), 7.07 - 7.17 (m, 1 H), 7.22 (d, *J* = 8.61 Hz, 2 H), 7.27 - 7.31 (m, 3 H), 7.39 (d, *J* = 8.61 Hz, 2 H). MS (ESI) 446.2 $[M + H]^+$.

EXAMPLE 37

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2-ethylbutyl)-2-oxopiperidin-3-yl)acetic acid

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.37 (2 H, d, *J* = 8.4 Hz), 7.27 (2 H, m), 7.18 (1 H, s), 7.15 (2 H, d, *J* = 8.4 Hz), 7.03 (1 H, m), 4.67 (1 H, d, *J* = 7.5 Hz), 3.29 (1 H, m), 3.09–2.97 (3 H, m), 2.72 (1 H, dd, *J* = 15.4, 3.7 Hz), 2.20–2.00 (2 H, m), 1.83 (1 H, m), 1.68 (1 H, m), 1.55–1.40 (2 H, m), 0.89 (3 H, t, *J*= 8.0 Hz), 0.55 (3 H, t, *J*= 8 Hz); MS (ESI) 448.1 $[M - H]^-$.

EXAMPLE 38

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopentylmethyl)-2-oxopiperidin-3-yl)acetic acid

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.42 (2 H, d, *J* = 8.4 Hz), 7.31 (2 H, m), 7.24 (1 H, s), 7.20 (2 H, d, *J* = 8.4 Hz), 7.11 (1 H, m), 4.93 (1 H, s), 3.87 (1 H, m), 3.16 (1 H, m), 2.81 (1 H, dd, *J* =16.4, 7.8 Hz), 2.68 (1 H, dd, *J* =16.4, 3.9 Hz), 2.57 (1 H, m), 2.12 (1 H, m), 2.00 (1 H, m), 1.90–1.65 (6 H, m), 1.55–1.40 (2 H, m); MS (ESI) 446.0 $[M - H]^-$.

EXAMPLE 39

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((2,2-dimethylcyclopentyl)methyl)-2-oxopiperidin-3-yl)acetic acid

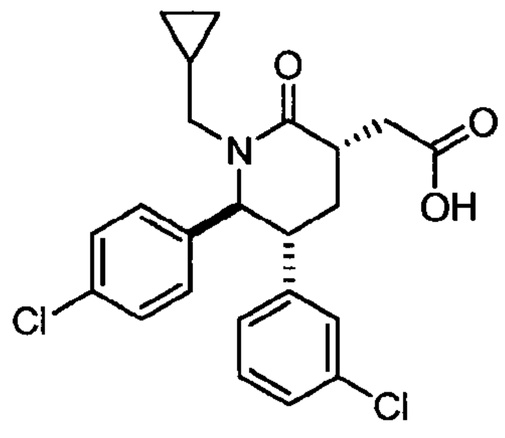
^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.41 (2 H, d, *J* = 8.2 Hz), 7.39 (1 H, m), 7.35–7.27 (3 H, m), 7.13 (2 H, d, *J* = 8.2 Hz), 4.93 (1 H, s), 4.45 (1 H, m), 3.20 (2 H, m), 3.00 (1 H, dd, *J* = 16.8, 8.0 Hz), 2.51 (1 H, dd, *J* = 16.8, 3.3 Hz), 2.10 (1H, m), 1.90 (1 H, m), 1.65–1.35 (5 H, m), 0.88 (3 H, s), 0.53 (3 H, s); MS (ESI) 474.1 $[M - H]^-$.

EXAMPLE 40

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclohexylmethyl)-2-oxopiperidin-3-yl)acetic acid

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.41 (2 H, d, *J* = 8.6 Hz), 7.35–7.27 (3 H, m), 7.18 (2 H, d, *J* = 8.6 Hz), 7.14 (1 H, m), 4.95 (1 H, s), 3.08 (1 H, m), 2.90 (1 H, dd, *J* = 15.8, 9.2 Hz), 2.65 (1 H, m), 2.51 (1 H, dd, *J* = 15.8, 2.7 Hz), 2.10 (1 H, m), 1.90–1.55 (4 H, m), 1.35–1.20 (8 H, m); MS (ESI) 460.4 $[M - H]^-$.

EXAMPLE 41



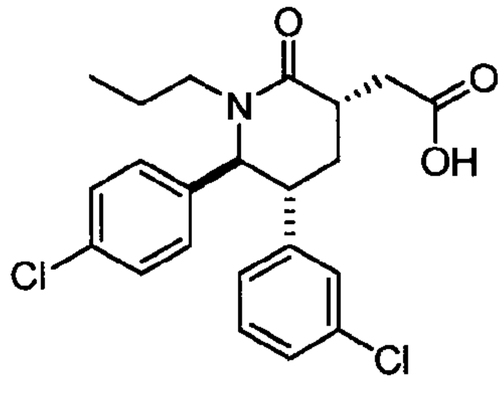
2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid

(3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one (Example 35, Step B) was converted to the acid as described in Example 1, Step H to give the title compound as a white solid.

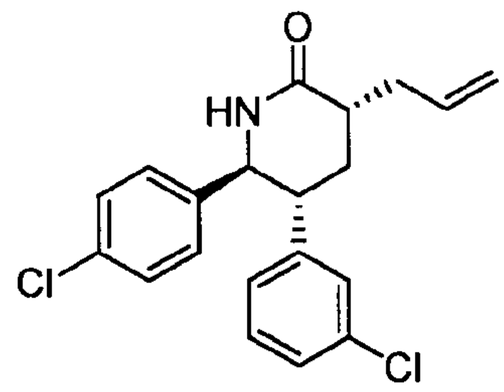
^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.24 (2 H, d, *J* = 8.2 Hz), 7.23–7.19 (1 H, m), 7.17–7.12 (1 H, t, *J* = 7.4 Hz), 7.01 (1 H, s), 6.86 (2 H, d, *J*=8.2 Hz), 6.74 (1 H, d, *J* = 7.4 Hz), 4.63 (1 H, d, *J* = 10.2 Hz), 3.92 (1 H, dd, *J*=14.1, 6.3 Hz), 3.12–2.92 (3 H, m), 2.60 (1 H, dd, *J*=15.5, 3.3 Hz), 2.34 (1 H, dd, *J* = 14.1, 7.4 Hz), 2.29–2.08 (2 H, m), 0.95–0.85 (1 H, m), 0.55 – 0.47 (1 H, m), 0.46 – 0.39 (1 H, m), 0.15–(–)0.02 (2 H, m); MS (ESI) 432.0 $[M + H]^+$, 429.9 $[M - H]^-$.

EXAMPLE 42

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-propylpiperidin-3-yl)acetic acid

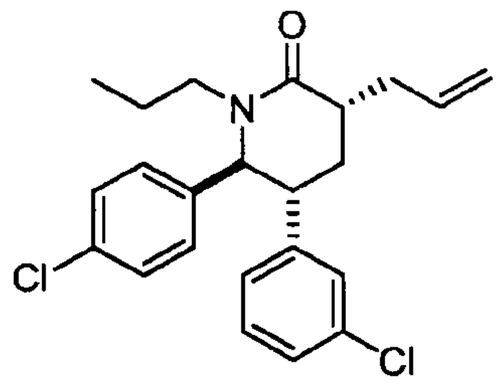


Step A. (3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one.



A 100 mL flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one (1.32 g, 4.12 mmol) (Example 1, Step E) and anhydrous THF (41.2 mL). This solution was cooled to 0 °C under argon and BuLi (3.30 mL, 8.24 mmol) was added. After 10 minutes allyl bromide (0.357 mL, 4.12 mmol) was added. After an additional 45 minutes the reaction was quenched by the addition of sat. aq. NH_4Cl and the layers were separated. The aqueous layer was extracted with EtOAc twice and the organics were pooled, washed with sat. aq. NaCl solution, dried ($MgSO_4$), filtered and concentrated in vacuo to provide a colorless oil. Purification using a Combiflash Companion (flash column chromatography, Teledyne Isco, Lincoln, NE) with a 120 g SiO_2 column and eluting with 10 to 100% EtOAc/hexanes provided the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.07 (m, 1H), 2.15 (m, 1H), 2.45 (m, 1H), 2.69 (m, 1H), 2.80 (m, 1H), 2.88 (m, 1H), 4.49 (d, J = 10.3 Hz, 1H), 5.13 (m, 2H), 5.82 (br s, 1H), 5.84 (m, 1H), 6.77 (m, 1H), 6.95 (d, J = 8.4 Hz, 2H), 7.01 (m, 1H), 7.12 (t, J = 7.7 Hz, 1H), 7.18 (m, 1H), 7.21 (d, J = 8.6 Hz, 2H).



Step B. (3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-propylpiperidin-2-one.

To a solution of (3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one (Example 42, Step A) (70 mg, 0.19 mmol) in 430 μL of DMF was added sodium hydride (60% suspension in mineral oil, 20 mg, 0.51 mmol) at 0 °C. The reaction was stirred at 0 °C for 15 min and then treated with 1-bromopropane (53 μL, 0.58 mmol). After being stirred at 25 °C for 4 h, the reaction was quenched with sat. aqueous $NaHCO_3$ and extracted (2 x EtOAc). The combined organic layers were washed with sat. aq. NaCl and $NaHCO_3$-solutions, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by silica gel prep plate (25% EtOAc/hexanes) provided the title compound as a colorless solid.

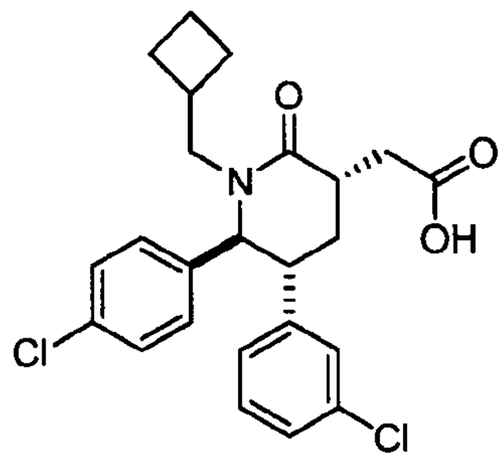
Step C. 2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-propylpiperidin-3-yl)acetic acid

The title compound was obtained from (3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-propylpiperidin-2-one (Example 42, Step B) by a procedure similar to the one described in Example 1, Step H. Purification by silica gel prep plate (5% MeOH/DCM) provided the title compound as a white solid.

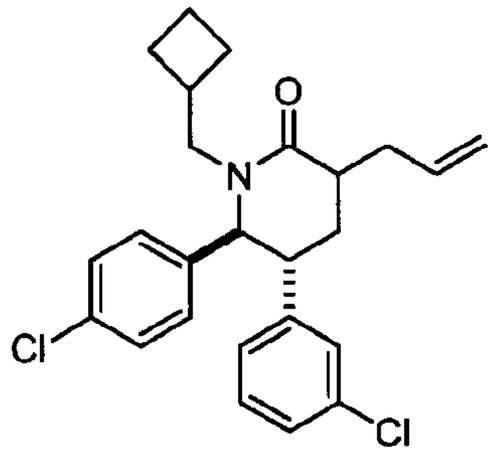
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.78 (t, J = 7.34 Hz, 3 H) 1.33 - 1.45 (m, 1 H) 1.45 - 1.57 (m, 1 H) 2.05 - 2.21 (m, 2 H) 2.48 (ddd, J = 13.89, 9.39 and 5.09 Hz, 1 H) 2.60 (dd, J = 15.94 and 4.79 Hz, 1 H) 2.96 (dd, J = 16.04 and 7.43 Hz, 1 H) 2.97 - 3.02 (m, 1 H) 3.02 - 3.12 (m, 1 H) 3.75 (ddd, J = 13.69, 9.68 and 6.36 Hz, 1 H) 4.41 (d, J = 10.17 Hz, 1 H) 6.66 - 6.76 (m, 1 H) 6.87 (d, J = 8.41 Hz, 2 H) 6.97 (t, J = 1.66 Hz, 1 H) 7.12 (t, J = 7.83 Hz, 1 H) 7.16 - 7.20 (m, 1 H) 7.23 (d, J = 8.41 Hz, 2 H). MS (ESI) 420.2 $[M + H]^+$.

EXAMPLE 43

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclobutylmethyl)-2-oxopiperidin-3-yl)acetic acid



Step A. (5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclobutylmethyl)piperidin-2-one.



To a solution of (3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl) piperidin-2-one (Example 42, Step A) (70 mg, 0.19 mmol) in 430 μL of DMF was added sodium hydride (60% suspension in mineral oil, 20 mg, 0.51 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and after treatment with (bromomethyl)cyclobutane (66 μL, 0.58 mmol) the reaction mixture was heated to 70 °C for 15 h. The reaction mixture was cooled to room temperature, quenched with sat. aqueous $NaHCO_3$ and extracted (2 x EtOAc). The combined organic layers were washed with sat. aq. NaCl and $NaHCO_3$-solutions, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by silica gel prep plate (25% EtOAc/hexanes) provided the title compound as a colorless solid.

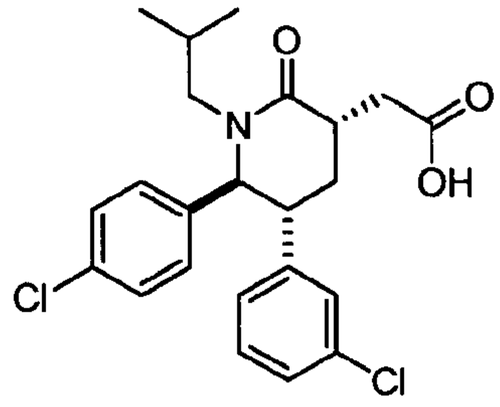
Step B. 2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclobutylmethyl)-2-oxopiperidin-3-yl)acetic acid

The title compounds were prepared from (5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclobutylmethyl)piperidin-2-one (Example 43, Step A) as described in Example 1 Step H and purified by reversed phase HPLC on an Eclipse column (45-60% acetonitrile/water, gradient elution) to provide the title compound as a white solid.

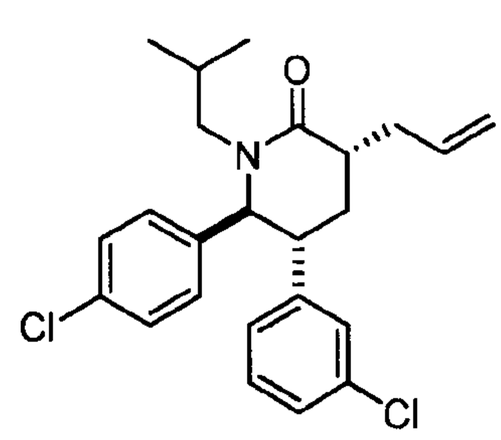
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.52 - 1.69 (m, 2 H), 1.72 - 1.90 (m, 2 H), 1.91 - 2.09 (m, 3 H), 2.14 (t, *J* = 12.52 Hz, 1 H), 2.42 (dd, *J* = 13.50 and 7.43 Hz, 1 H), 2.46 - 2.57 (m, 1 H), 2.62 (dd, *J* = 16.43 and 6.85 Hz, 1 H), 2.86 - 3.01 (m, 2 H), 3.01 - 3.12 (m, 1 H), 4.05 (dd, *J* = 13.50 and 7.24 Hz, 1 H), 4.38 (d, *J* = 9.98 Hz, 1 H), 6.70 (d, *J* = 7.43 Hz, 1 H), 6.84 (d, *J* = 8.22 Hz, 2 H), 6.97 (s, 1 H), 7.12 (t, *J* = 7.83 Hz, 1 H), 7.16 - 7.20 (m, 1 H), 7.22 (d, *J* = 8.22 Hz, 2 H). MS (ESI) 446.2 $[M + H]^+$.

EXAMPLE 44

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isobutyl-2-oxopiperidin-3-yl)acetic acid.



Step A. (3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isobutylpiperidin-2-one



To a solution of (3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one (Example 42, Step A) (78 mg, 0.22 mmol) in 480 μL of DMF was added potassium tert-butoxide (40 mg, 0.54 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and

then treated with 1-bromo-2-methylpropane (82 μL, 0.76 mmol). After being stirred at 25 °C for 4 h, the reaction was quenched with sat. aqueous $NaHCO_3$ and extracted (2 x EtOAc). The combined organic layers were washed with sat. aq. NaCl and $NaHCO_3$-solutions, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by silica gel prep plate (25% EtOAc/hexanes) provided the title compound as a colorless solid.

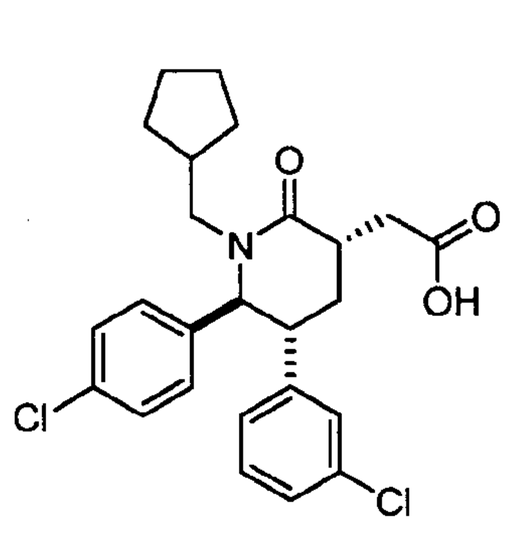
Step B. 2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isobutyl-2-oxopiperidin-3-yl)acetic acid.

The title compound was prepared from (3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isobutylpiperidin-2-one (Example 44, Step A) as described in Example 1, Step H to provide a white solid.

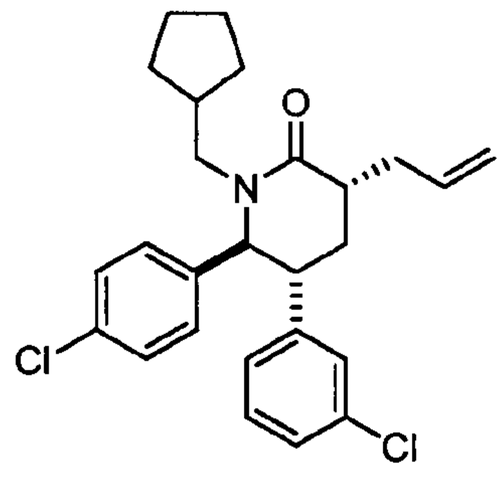
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.83 (d, J = 6.65 Hz, 3 H), 0.85 (d, J = 6.85 Hz, 3 H), 1.93 (dq, J = 8.39 and 6.66 Hz, 1 H), 2.06 - 2.16 (m, 2 H), 2.17 - 2.24 (m, 1 H), 2.60 (dd, J = 15.85 and 4.30 Hz, 1 H), 2.90 - 2.97 (m, 1 H), 2.97 - 3.03 (m, 1 H), 3.04 - 3.13 (m, 1 H), 3.86 (dd, J = 13.69 and 8.80 Hz, 1 H), 4.41 (d, J = 10.17 Hz, 1 H), 6.68 - 6.76 (m, 1 H), 6.84 (d, J = 8.41 Hz, 2 H), 6.96 (t, J = 1.76 Hz, 1 H), 7.14 (t, J = 7.82 Hz, 1 H), 7.18 - 7.22 (m, 1 H), 7.24 (m, 2 H). MS (ESI) 434.2 $[M + H]^+$.

EXAMPLE 45

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopentylmethyl)-2-oxopiperidin-3-yl)acetic acid



Step A. (3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopentylmethyl)piperidin-2-one



The title compound was prepared from (3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one (Example 42, Step A) and (bromomethyl)cyclopentane as described in Example 44, Step A. Purification of the residue by silica gel prep plate (25% EtOAc/hexanes) provided the title compound as a colorless solid.

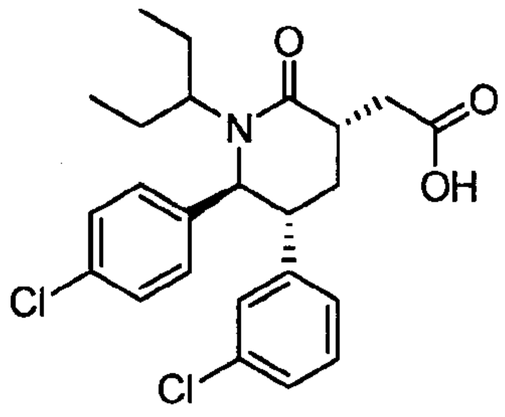
Step B. 2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopentylmethyl)-2-oxopiperidin-3-yl)acetic acid.

The title compound was prepared from (3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopentylmethyl)piperidin-2-one (Example 45, Step A) as described in Example 1, Step H to provide a white solid.

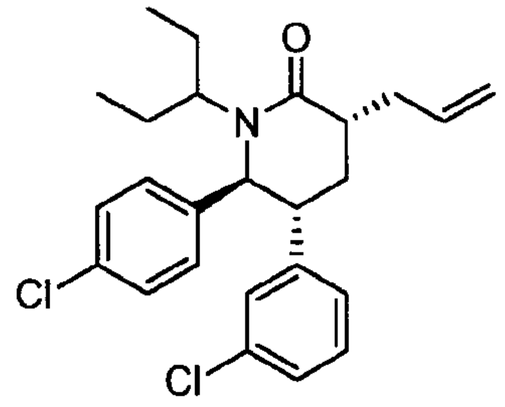
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.02 - 1.10 (m, 1 H), 1.12 - 1.19 (m, 1 H), 1.46 - 1.57 (m, 2 H), 1.59 - 1.71 (m, 4 H), 2.04 - 2.21 (m, 3 H), 2.32 (dd, *J* = 13.69 and 6.85 Hz, 1 H), 2.60 (dd, *J* = 15.77 and 4.03 Hz, 1 H), 2.92 - 3.01 (m, 2 H), 3.06 (dd, *J* = 11.98 and 7.09 Hz, 1 H), 4.02 (dd, *J* = 13.69 and 8.56 Hz, 1 H), 4.48 (d, *J* = 10.03 Hz, 1 H), 6.72 (d, *J* = 7.82 Hz, 1 H), 6.84 (d, *J* = 8.31 Hz, 2 H), 6.93 - 7.00 (m, 1 H), 7.14 (t, *J* = 7.70 Hz, 1 H), 7.18 - 7.22 (m, 1 H), 7.24 (m, 2 H). MS (ESI) 460.2 $[M + H]^+$.

EXAMPLE 46

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid



Step A. (3R, 5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(pentan-3-yl)piperidin-2-one



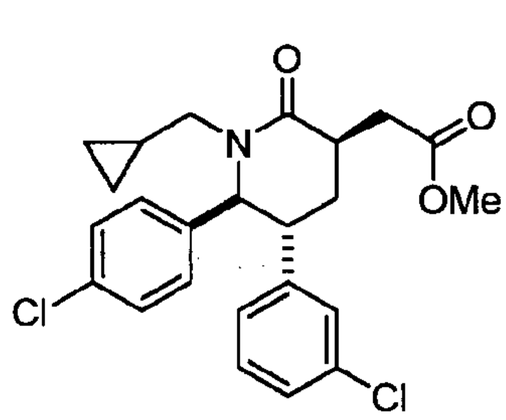
To a solution of (3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one (Example 42, Step A) (440 mg, 1.221 mmol) in 3-bromopentane (3196 μL, 25.6 mmol) under nitrogen at rt was added a dispersion of 60% sodium hydride in mineral oil (244 mg, 6.11 mmol). Evolution of gas was observed. The reaction was stirred at room temperature for 10 min and then heated to 120 °C under N_2 for 19 h. The reaction mixture was cooled to room temperature and quenched with sat. NH_4Cl. The layers were separated and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 0 to 25% EtOAc in hexanes) to give the title compound (375 mg, 71% yield) as a mixture of diastereomers.

Step B. 2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid

The title compound was prepared from (5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-1-(pentan-3-yl)piperidin-2-one (Example 46, Step A) as described in Example 1 Step H. Purification by reversed phase preparatory HPLC (eluent: 0 to 100% MeCN +0.1% TFA in water + 0.1% TFA, over 20 minutes) provided the title compound.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.55 (t, *J* = 7.53 Hz, 3 H) 0.94 (t, *J* = 7.34 Hz, 3 H) 1.32 - 1.54 (m, 2 H) 1.85 (tt, *J* = 14.38 and 7.24 Hz, 2 H) 2.04 - 2.12 (m, 1 H) 2.18 (q, *J* = 12.72 Hz, 1 H) 2.66 (dd, *J* = 16.14 and 4.40 Hz, 1 H) 2.85 - 3.01 (m, 2 H) 3.01 - 3.17 (m, 2 H) 4.33 (d, *J* = 9.98 Hz, 1 H) 6.71 (d, *J* = 7.63 Hz, 1 H) 6.90 - 7.01 (m, 3 H) 7.09 - 7.22 (m, 2 H) 7.23 - 7.26 (m, 1 H) 10.11 (br. s., 1 H). Mass spectrum (ESI) m/z = 448 $[M + H]^+$.

EXAMPLE 47

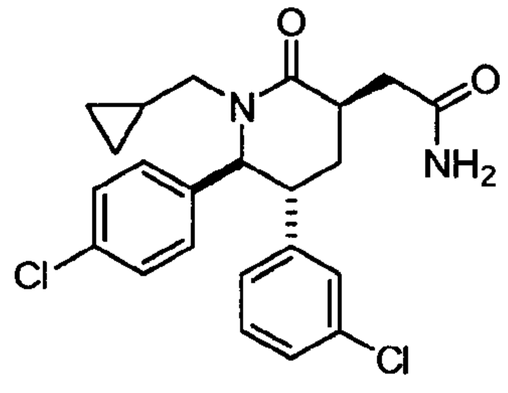


Methyl 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetate

To a suspension of 250mg (0.578 mmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid (Example 35) in MeOH (3 mL) was added thionyl chloride (78.0 µl, 1070 µmol) dropwise at 0 °C. After being stirred at 25 °C for 14h, the reaction was diluted (EtOAc), basified (sat $NaHCO_3$), extracted (2 x EtOAc). The combined organic layers were washed with sat. aq. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to provide the title compound as a colorless liquid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.53–7.49 (1 H, m), 7.39 (2 H, d, *J* = 8.6 Hz), 7.31–7.28 (2 H, m), 7.27–7.22 (3 H, m), 5.12 (1 H, s), 4.25–4.18 (1 H, m), 3.69 (3 H, s), 3.20–3.14 (1 H, m), 2.85–2.82 (1 H, m), 2.69–2.63 (1 H, m), 2.60–2.53 (1 H, m), 2.33–2.20 (2 H, m), 1.85–1.77 (1 H, m), 1.20–1.15 (1 H, m), 0.70–0.63 (1 H, m), 0.61–0.53 (1 H, m), 0.30–0.20 (2 H, m); MS (ESI) 445.9 $[M + H]^+$.

EXAMPLE 48

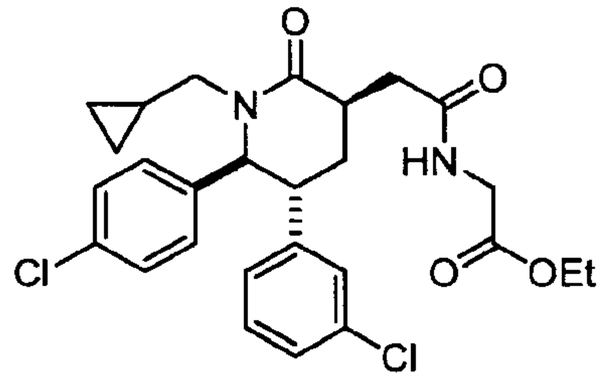


2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetamide

In a sealed tube, 60mg (134 μmol) of methyl 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetate (Example 47) and 4.8 mL of a solution of ammonia in methanol (7N, 3.4mmol) were stirred at 25 °C for 5 days. Then NaCN (3 mg) was added and the resulting solution was stirred at 50 °C for 3 days. Excess NH_3 and MeOH were removed under reduced pressure. Separation by reversed phase HPLC (10 to 90% AcCN/H_2O in 45 min) provided the title compound as a a white solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.52–7.45 (1 H, m), 7.37 (2 H, d, *J* = 8.2 Hz), 7.33–7.29 (2 H, m), 7.26–7.22 (1 H, m), 7.17 (2 H, d, *J* = 8.6 Hz), 6.40 (1 H, br. s.), 5.42 (1 H, br. s.), 5.11 (1 H, br. s.), 4.21 (1 H, dd, *J* = 14.1, 6.3 Hz), 3.20–3.16 (1 H, m), 2.77–2.70 (1 H, m), 2.60–2.48 (2 H, m), 2.33–2.25 (2 H, m), 1.92–1.85 (1 H, m), 1.22–1.15 (1 H, m), 0.72–0.64 (1 H, m), 0.62–0.54 (1 H, m), 0.32–0.20 (2 H, m); MS (ESI) 430.9 [M + H]$^+$.

EXAMPLE 49



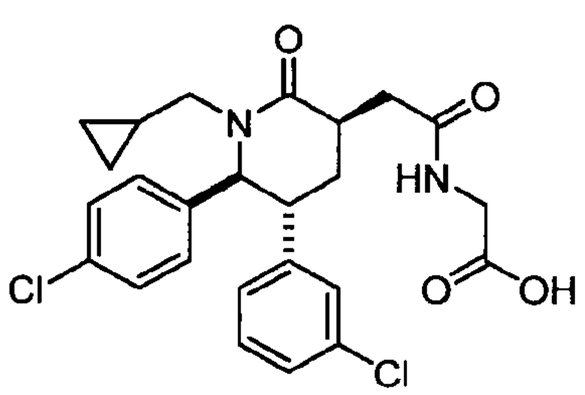
Ethyl 2-(2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetamido)acetate

A solution of 40mg (93 μmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid (Example 35) and ethyl

2-aminoacetate hydrochloride (14 mg, 102 μmol) in DMF (0.31 mL) was treated at 0°C with N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (27 mg, 139 μmol), 3H-[1,2,3]triazolo[4,5-b]pyridin-3-ol (19 mg, 139 μmol), and sodium hydrogencarbonate (23 mg, 278 μmol), successively. After being stirred at 25 °C for 12 h, the reaction was diluted with water and extracted with EtOAc. The combined organic layers were successively washed with 10% aq. citric acid solution, sat. aq. $NaHCO_3$ solution and sat. aq. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO_2, 40% to 60% EtOAc/Hexanes, gradient elution) provided the title compound as a colorless film.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.51–7.47 (1 H, m), 7.35 (2 H, d, *J* = 8.6 Hz), 7.32–7.28 (2 H, m), 7.26–7.24 (1 H, m), 7.16 (2 H, d, *J* = 8.2 Hz), 6.89 (1 H, br, s), 5.11 (1 H, s), 4.27–4.18 (3 H, m), 4.11–3.98 (2 H, m), 3.20–3.15 (1 H, d, J=1.6 Hz), 2.83–2.72 (1 H, m), 2.63–2.55 (2 H, m), 2.32–2.16 (2 H, m), 1.95–1.87 (1 H, m), 1.29 (3 H, t, J=7.0 Hz), 1.22–1.12 (1 H, m), 0.72–0.62 (1 H, m), 0.60–0.52 (1 H, m), 0.30–0.18 (2 H, m); MS (ESI) 516.8 [M + H]$^+$.

EXAMPLE 50



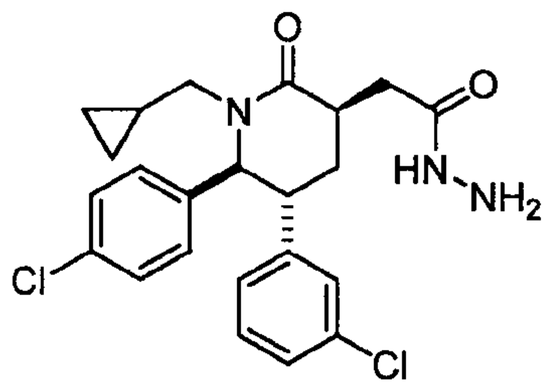
2-(2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetamido)acetic acid

To a solution of 38mg (73 μmol) of ethyl 2-(2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetamido)acetate (Example 49) in 0.75mL of MeOH/THF/H_2O (2/2/1) was added a 2M solution of lithium hydroxide in water (70 μl, 141 μmol) at 25 °C and the mixture was stirred for 10 h. The reaction was acidified (1N aq. HCl) and extracted with DCM (2X). The combined organic layers were successively washed with 10% aq. citric acid solution and sat. aq. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by

reversed phase HPLC (10 to 90% AcCN/H_2O with 0.1% TFA in 45 min) provided the title compound as a white solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.37–7.34 (1 H, m), 7.35 (2 H, d, *J* = 8.2 Hz), 7.27–7.25 (1 H, m), 7.23–7.19 (1 H, m), 7.17–7.14 (1 H, m), 7.08 (2 H, d, *J* = 8.2 Hz), 5.00 (1 H, d, *J* = 3.9 Hz), 4.18–4.08 (2 H, m), 4.07–3.99 (1 H, m), 3.23–3.18 (1 H, m), 2.83–2.75 (2 H, m), 2.72–2.64 (1 H, m), 2.35–2.23 (2 H, m), 2.05–1.95 (1 H, m), 1.16–1.05 (1 H, d, *J* = 1.2 Hz), 0.68–0.60 (1 H, m), 0.58–0.50 (1 H, m), 0.27–0.13 (2 H, m); MS (ESI) 488.8 $[M + H]^+$, 486.9 $[M - H]^-$.

EXAMPLE 51

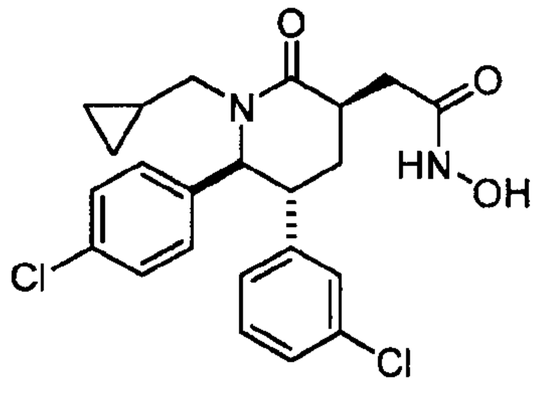


2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetohydrazide

To a solution of 120mg (0.27 mmol) of methyl 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetate (Example 47) in EtOH was added hydrazine, monohydrate (135 µl, 2688 µmol). After being refluxed for 14h, the reaction was concentrated, diluted (H_2O) and extracted (2 x EtOAc). The combined organic layers were washed with sat. aq. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5% MeOH/CH_2Cl_2, gradient elution) provided the title compound as a white solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.52–7.46 (1 H, m), 7.37 (2 H, d, *J* = 8.6 Hz), 7.33–7.28 (2 H, m), 7.26–7.22 (1 H, m), 7.15 (2 H, d, *J* = 8.6 Hz), 5.10 (1 H, s), 4.20 (1 H, dd, *J* = 14.1, 6.7 Hz), 3.20–3.15 (1 H, m), 2.71–2.63 (1 H, m), 2.60–2.48 (2 H, m), 2.31–2.18 (1 H, m), 1.92–1.82 (1 H, m), 1.20–1.10 (1 H, dt, *J* = 7.9, 3.3 Hz), 0.70–0.63 (1 H, m), 0.59–0.52 (1 H, m), 0.30–0.18 (2 H, m); MS (ESI) 445.9 $[M + H]^+$.

EXAMPLE 52

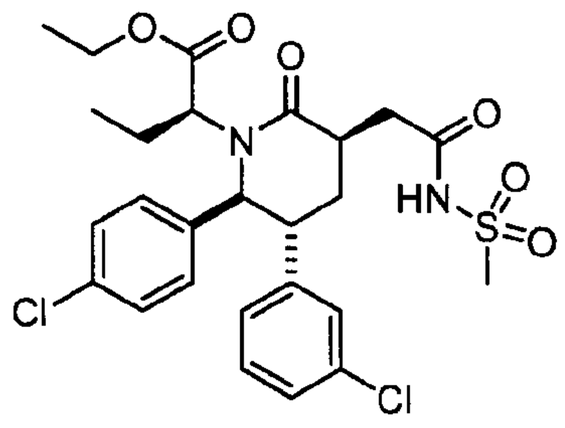


2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)-N-hydroxyacetamide

A solution of 30mg (0.07 mmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid (Example 35) in DMF (0.5 mL, c = 0.14 M) was treated with N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (0.03 g, 0.1 mmol), 3H-[1,2,3]triazolo[4,5-b]pyridin-3-ol (0.02 g, 0.1 mmol), hydroxylamine hydrochloride (0.006 ml, 0.1 mmol) and sodium hydrogencarbonate (0.02 g, 0.2 mmol) successively. After being stirred at 25 °C for 12 h, the reaction was diluted with water and extracted with EtOAc. The combined organic layers were successively washed with sat. aq. $NaHCO_3$ solution and sat. aq. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reversed phase HPLC (10 to 90% AcCN/H2O with 0.1% TFA in 45 min) to give the title compound as a white solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.45 (1 H, s), 7.41–7.16 (5 H, m), 7.16–6.98 (2 H, m), 5.10 (1 H, br. s.), 4.26–4.13 (1 H, m), 3.25–3.17 (1 H, m), 2.65 (3 H, br. s.), 2.30 (2 H, dd, *J* = 14.1, 7.8 Hz), 1.91 (1 H, br. s.), 1.15 (1 H, d, *J* = 2.0 Hz), 0.77–0.65 (1 H, m), 0.65–0.51 (1 H, m), 0.37–0.14 (2 H, m).

EXAMPLE 53

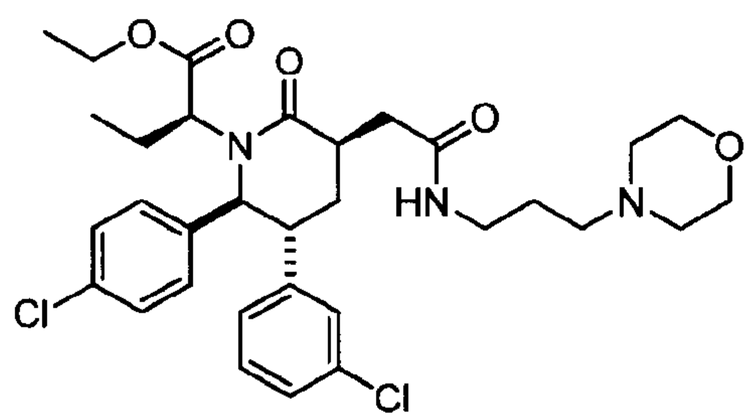


(S)-Ethyl 2-((2S,3R,5R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-5-(2-(methylsulfonamido)-2-oxoethyl)-6-oxopiperidin-1-yl)butanoate

Methanesulfonamide (0.02 g, 0.2 mmol), N-ethyl-N-isopropylpropan-2-amine (0.05 ml, 0.3 mmol), di(1H-imidazol-1-yl)methanone (0.04 g, 0.2 mmol) and 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-ethoxy-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid (Example 3, 0.030 g, 0.06 mmol) were combined in 2mL of THF. After being stirred at 25 °C for 12 h, sat. NH_4Cl solution was added and the reaction mixture was extracted with EtOAc. The combined organic layers were successively washed with sat. aq. $NaHCO_3$ solution and sat. aq. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reversed phase HPLC (10 to 90% AcCN/H_2O with 0.1% TFA in 45 min) to give the title compound as a white solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.45–7.33 (3 H, m), 7.33–7.21(5 H, m), 4.88 (1 H, d, *J* = 3.9 Hz), 4.27–4.10 (2 H, m), 3.48 (1 H, dd, *J* = 8.8, 3.3 Hz), 3.30 (3 H, s), 3.20 (1 H, dd, *J* = 4.7, 0.8 Hz), 3.04–2.74 (2 H, m), 2.72–2.59 (1 H, m), 2.48–2.28 (2 H, m), 2.03 (1 H, s), 1.63–1.46 (1 H, m), 1.28 (3 H, t, *J* = 7.2 Hz), 0.69 (3 H, t, *J* = 7.4 Hz).

EXAMPLE 54

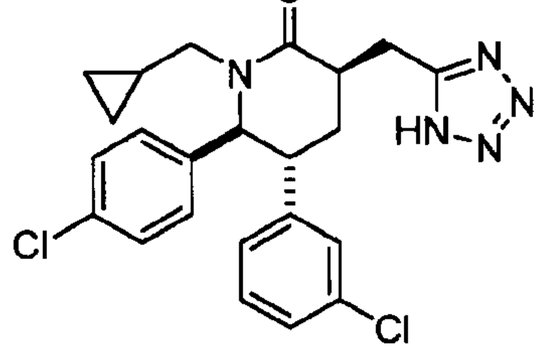


(S)-Ethyl 2-((2S,3R,5R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-5-(2-((3-morpholinopropyl)amino)-2-oxoethyl)-6-oxopiperidin-1-yl)butanoate

The title compound was prepared as described in Example 49, using 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-ethoxy-1-oxobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid (Example 3) as starting material.

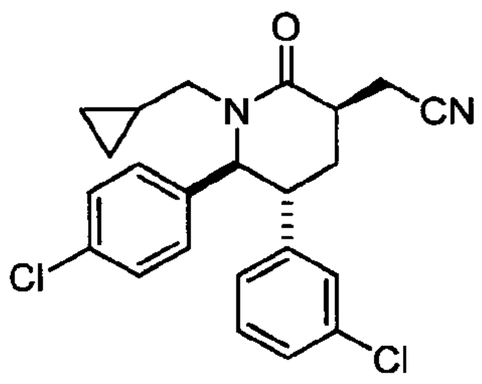
^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.34 (2 H, d, *J* = 8.6 Hz), 7.30–7.16 (5 H, m), 7.11–7.03 (1 H, m), 4.73 (1 H, d, *J* = 5.5 Hz), 4.14 (2 H, q, *J* = 7.3 Hz), 4.09–3.92 (4 H, m), 3.67–3.51 (2 H, m), 3.50–3.40 (1 H, m), 3.39–3.30 (2 H, m), 3.25 (1 H, dd, *J*=8.8, 3.3 Hz), 3.22–3.12 (2 H, m), 2.98–2.50 (5 H, m), 2.33–2.03 (5 H, m), 1.52–1.37 (0 H, m), 1.26 (3 H, t, *J* = 7.2 Hz), 0.60 (3 H, t, *J* = 7.4 Hz).

EXAMPLE 55



(3R,5R,6S)-3-((1H-Tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one

Step A. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetonitrile



A solution of 136mg (0.315mmmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetamide (Example 48) and triethylamine (220 µl, 1576 µmol) in 5mL of THF was treated with trifluoroacetic anhydride (111 µl, 788 µmol) at 0 °C. After being stirred at 0 °C for 2 h, the reaction was quenched (sat. NH_4Cl), extracted (2 × EtOAc) and washed (sat. aq. NaCl solution). The combined organic layer were dried (Na_2SO_4) and concentrated under the reduced pressure.

After being stirred at 0 °C for 2 h, sat. NH_4Cl solution was added and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with sat. aq. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure.

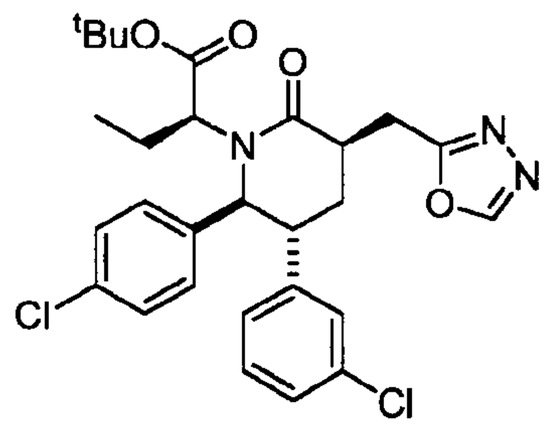
Purification of the residue by flash chromatography (SiO_2, 20-25% EtOAc/Hexanes) provided the title compound which was used without further purification.

Step B. (3R,5R,6S)-3-((1H-Tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one

To a solution of 136mg (0.33 mmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetonitrile (Example 55, Step A) in 1.8 mL of DMF was added ammonium chloride (176 mg, 3290 μmol) and sodium azide (214 mg, 3290 μmol). The resulting mixture was stirred at 90 °C for 4 days. Then, the reaction was acidified (aq. 10% citric acid) and extracted (2 x EtOAc). The combined organic layers were washed with sat. aq. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Separation by reversed phase HPLC (60-90% AcCN/H_2O in 30 min) provided the title compound as a white solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.51–7.48 (1 H, s), 7.35 (2 H, d, *J* = 8.2 Hz), 7.32–7.28 (2 H, m), 7.25–7.21 (1 H, m), 6.86 (2 H, d, *J* = 8.2 Hz), 5.14 (1 H, s), 4.23 (1 H, dd, *J* = 14.1, 6.7 Hz), 3.40 (1 H, dd, *J* = 15.3, 3.1 Hz), 3.28–3.20 (1 H, m), 3.15 (1 H, dd, *J* = 15.1, 8.0 Hz), 2.60 – 2.52 (1 H, m), 2.33 (1 H, dd, *J* = 14.1, 8.2 Hz), 2.26–2.18 (2 H, br. s.), 2.04–1.93 (1 H, m), 1.25–1.15 (1 H, m), 0.77–0.70 (1 H, m), 0.68–0.59 (1 H, m), 0.36–0.24 (2 H, m); MS (ESI) 456.0$[M + H]^+$, 453.9$[M - H]^-$.

EXAMPLE 56



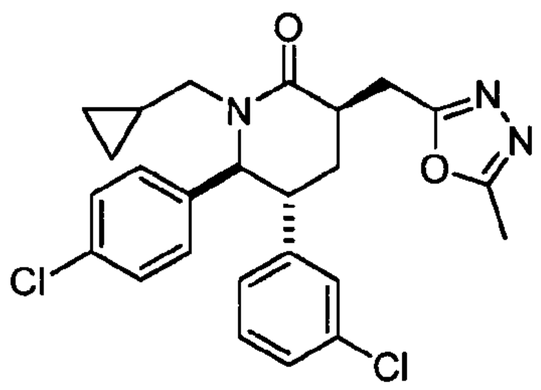
(3R,5R,6S)-3-((1,3,4-oxadiazol-2-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one

To a solution of 20mg (45 μmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetohydrazide (Example 51) in 0.2

mL of toluene was added ethyl formimidate hydrochloride (6.4 mg, 58 μmol). The reaction mixture was heated to reflux for 14h and then the reaction was concentrated under reduced pressure. Separation by reversed phase HPLC (10 to 90% AcCN/H_2O in 40 min) provided the title compound as a colorless film.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.35 (1 H, s), 7.50–7.45 (1 H, m), 7.37 (2 H, d, *J* = 8.6 Hz), 7.34–7.28 (2 H, m), 7.26–7.22 (1 H, m), 7.13 (2 H, d, *J* = 8.6 Hz), 5.13 (1 H, s), 4.22–4.17 (1 H, m), 3.38–3.35 (2 H, m), 3.24–3.18 (1 H, m), 2.80–2.72 (1 H, m), 2.35–2.28 (1 H, m), 2.25–2.18 (1 H, m), 1.96–1.86 (1 H, m), 1.21–1.12 (1 H, m), 0.70–0.62 (1 H, m), 0.61–0.54 (1 H, m), 0.30–0.20 (2 H, m); MS (ESI) 456.0$[M + H]^+$.

EXAMPLE 57

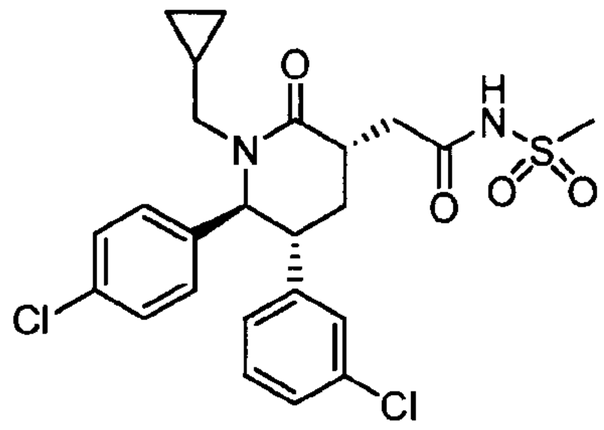


(3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)piperidin-2-one

To a solution of 40mg (90 μmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetohydrazide (Example 51) in 0.2 mL of toluene was added methyl acetimidate hydrochloride (13 mg, 116 μmol). The reaction mixture was heated to reflux for 14h and then the reaction was concentrated under reduced pressure. Separation by reversed phase HPLC (10 to 90% AcCN/H_2O in 45 min) provided the title compound as a colorless film.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.47–7.45 (1 H, s), 7.38 (2 H, d, *J* = 8.6 Hz), 7.33–7.29 (2 H, m), 7.24–7.19 (1 H, m), 7.15 (2 H, d, *J* = 8.6 Hz), 5.12–5.10 (1 H, m), 4.18 (1 H, dd, *J* = 14.1, 6.7 Hz), 3.38–3.23 (2 H, m), 3.22–3.18 (1 H, m), 2.80–2.72 (1 H, m), 2.54 (3 H, s), 2.36–2.22 (2 H, m), 1.94–1.88 (1 H, m), 1.20–1.10 (1 H, m), 0.70–0.63 (1 H, m), 0.60–0.52 (1 H, m), 0.30–0.20 (2 H, m); MS (ESI) 469.9 $[M + H]^+$.

EXAMPLE 58



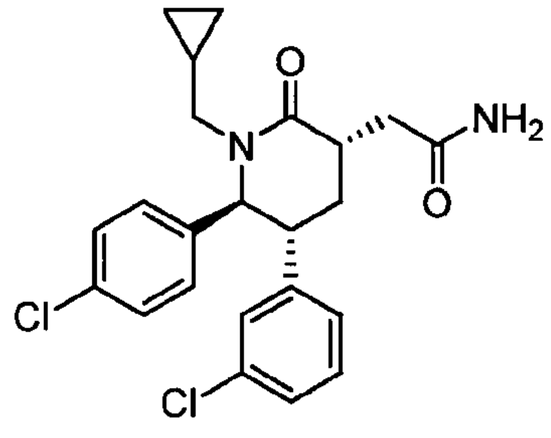
2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)-N-(methylsulfonyl)acetamide.

To a solution of 2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid (Example 41) (83 mg, 0.192 mmol), methanesulfonamide (22.59 mg, 0.230 mmol) and 4-dimethylaminopyridine (1.057 mg, .00865 mmol) in DCM (2 mL) was added diisopropylethylamine (80 μL, 0.461 mmol). The reaction mixture was stirred at room temperature for one minute before adding bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (125 mg, 0.269 mmol). The reaction mixture was stirred at room temperature for 3 hours. The reaction was quenched with 1N HCl and the aqueuos layer was extracted with DCM (10 mL). The combined organic layers were washed with 1N HCl, 1N NaOH, sat. aq. NaCl solution and concentrated under reduced pressure. The residue was purified by reversed phase preparatory HPLC (column: Gemini-NX C_{18} 5um column; Phenomonex, Torrance, CA; eluent: 0 to 100% MeCN +0.1% TFA in water + 0.1% TFA, over 20 minutes) to afford the title compound.

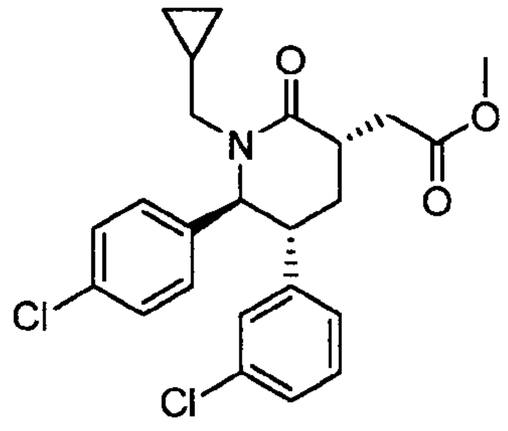
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm -0.06 - 0.04 (m, 1 H) 0.06 - 0.16 (m, 1 H) 0.43 (dd, *J* = 8.51 and 4.60 Hz, 1 H) 0.47 - 0.60 (m, 1 H) 0.88 (d, *J* = 6.26 Hz, 1 H) 2.09 - 2.18 (m, 1 H) 2.29 (dt, *J* = 14.04 and 6.77 Hz, 2 H) 2.62 (dd, *J* = 15.26 and 3.52 Hz, 1 H) 2.90 (dd, *J* = 15.26 and 7.63 Hz, 1 H) 3.02 (t, *J* = 2.64 Hz, 1 H) 3.14 (d, *J* = 3.72 Hz, 1 H) 3.32 (s, 3 H) 3.93 (dd, *J* = 14.28 and 6.26 Hz, 2 H) 4.64 (d, *J* = 10.17 Hz, 1 H) 6.74 (d, *J* = 7.63 Hz, 1 H) 6.85 - 6.91 (m, 2 H) 7.00 (d, *J* = 1.76 Hz, 1 H) 7.10 - 7.26 (m, 4 H). Mass Spectrum (ESI) m/z = 509 $[M + H]^+$.

EXAMPLE 59

2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetamide.

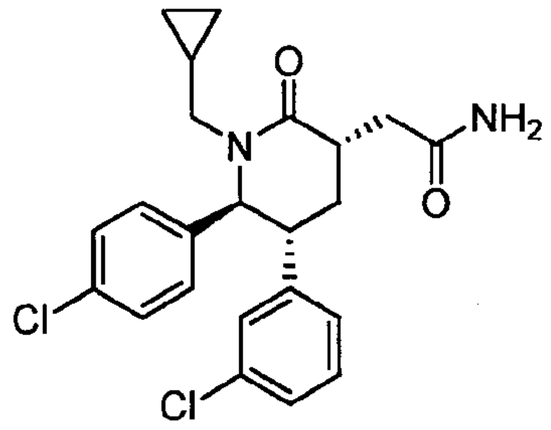


Step A. Methyl 2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetate



To a solution of 2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid (Example 41) (500 mg, 1.156 mmol) in 10% MeOH in DCM (10 mL) was added (trimethylsilyl)diazomethane (2.0 M in diethyl ether) (1 mL). The yellow colored reaction mixture was stirred at room temperature for 30 min. The reaction was concentrated under reduced pressure and was purified by flash chromatography on silica gel (eluent : 0 to 50% EtOAc in hexanes) to give the title compound as a clear oil.

Step B. 2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetamide.

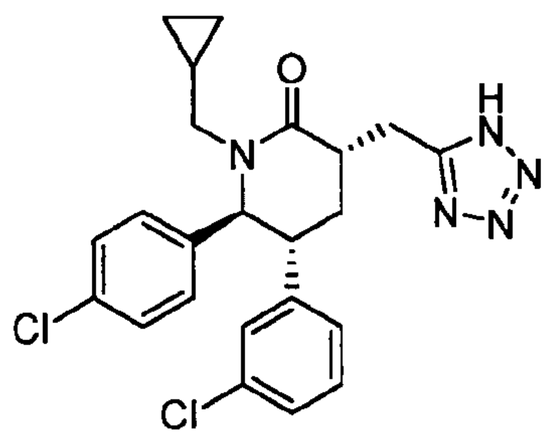


A sealed tube was charged with methyl 2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetate (Example 59, Step A) (109 mg, 0.244 mmol), ammonia, 7N solution in methanol (2 ml, 14.00 mmol) and sodium cyanide (1.197 mg, 0.024 mmol). The tube was sealed and heated to 50° C. The pressure reached 35 kilopascals after 1 hour. The reaction was stirred at 50 °C for 18 h. The reaction was cooled to rt and anhydrous ammonia (gas) was bubbled through the solution for ten minutes at room temperature. The reaction mixture was capped and heated to 50° C for 18 h. The reaction was cooled to rt and anhydrous ammonia (gas) was bubbled through the solution for twenty minutes at room temperature. The reaction mixture was capped and heated to 50 °C for 2 days. The crude reaction was concentrated under reduced pressure and purified by reversed phase preparatory HPLC (column: Gemini-NX C_{18} 5um column; Phenomonex, Torrance, CA; eluent: 0 to 100% MeCN +0.1% TFA in water + 0.1% TFA, over 20 minutes) to afford the title compound.

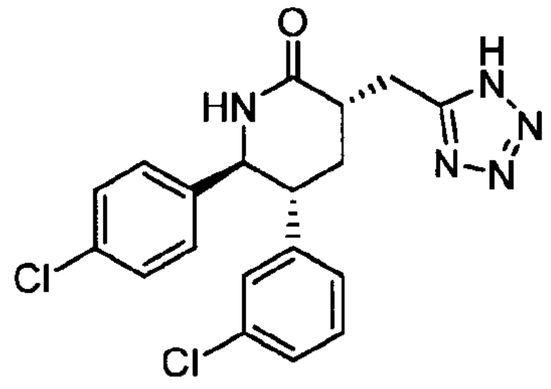
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm -0.05 - 0.04 (m, 1 H) 0.06 - 0.15 (m, 1 H) 0.36 - 0.45 (m, 1 H) 0.46 - 0.56 (m, 1 H) 0.79 - 0.93 (m, 1 H) 2.11 - 2.20 (m, 1 H) 2.29 (dt, *J*=13.99, 6.90 Hz, 1 H) 2.64 - 2.73 (m, 1 H) 2.75 - 2.83 (m, 1 H) 2.96 - 3.13 (m, 2 H) 3.91 (dd, *J*=14.09, 6.46 Hz, 1 H) 4.63 (d, *J*=9.98 Hz, 1 H) 6.41 (br. s., 1 H) 6.75 (dt, *J*=7.58, 1.59 Hz, 2 H) 6.83 - 6.90 (m, 2 H) 7.01 (t, *J*=1.96 Hz, 1 H) 7.10 - 7.26 (m, 4 H) . Mass Spectrum (ESI) m/z = 431 $[M + H]^+$.

EXAMPLE 60

(3S,5R,6S)-3-((1H-tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one



Step A. (3S,5R,6S)-3-((1H-tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one



A 100 mL round-bottomed flask was placed under vacuum and heated with a heat gun to ensure dryness. The flask was allowed to cool to room temperature and a solution of 500 mg (1.56 mmol) of (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one (Example 1, Step E) in THF (12 mL) under argon was added and cooled to 0 °C. Butyllithium (1.6M in hexanes, 2440 µL, 3.90 mmol) was added followed by 5-chloromethyl-1H-tetrazole (185 mg, 1.561 mmol) and the reaction mixture was stirred for 15 minutes at 0 °C. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The aqueous layer was acidified with 1M HCl. The aqueous layer was extracted with ethyl acetate (2 x 30 mL) and the combined organic layers were washed with sat. aq. NaCl solution, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by reversed phase preparatory HPLC (column: Gemini-NX C_{18} 5um column; Phenomonex, Torrance, CA; eluent: 0 to100% MeCN +0.1% TFA in water + 0.1% TFA, over 25 minutes) to afford the title compound.

Step B. (3S,5R,6S)-3-((1H-tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one

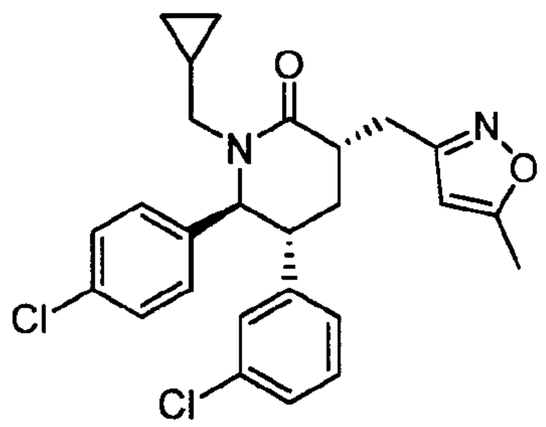
A solution of (3S,5R,6S)-3-((1H-tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one (Example 60, Step A) (65 mg, 0.162 mmol) in DMF (1.6 mL) was cooled to 0 °C and sodium tert-butoxide (31.1 mg, 0.323 mmol) was added. The reaction mixture was stirred at 0 °C for ten minutes before adding (bromomethyl)cyclopropane (78 µL,

0.808 mmol). The reaction mixture was warmed to room temperature and stirred for 16 hours, quenched with saturated ammonium chloride and diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate and the organic layers were combined, washed with 1M LiCl, sat. aq. NaCl solution, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by reversed phase preparatory HPLC (column: Gemini-NX C_{18} 5um column; Phenomonex, Torrance, CA; eluent: 0 to 100% MeCN +0.1% TFA in water + 0.1% TFA, over 20 minutes) to afford the title compound.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm -0.08 - 0.02 (m, 1 H) 0.11 (dt, *J* = 9.44 and 4.77 Hz, 1 H) 0.38 - 0.46 (m, 1 H) 0.50 (td, *J* = 8.31 and 4.50 Hz, 1 H) 0.78 - 0.89 (m, 1 H) 2.18 - 2.28 (m, 2 H) 2.31 - 2.41 (m, 1 H) 2.96 - 3.07 (m, 2 H) 3.29 (dd, *J* = 14.87 and 7.82 Hz, 1 H) 3.47 - 3.56 (m, 1 H) 3.89 (dd, *J* = 14.09 and 6.46 Hz, 1 H) 4.58 (d, *J* = 9.98 Hz, 1 H) 6.71 - 6.76 (m, 1 H) 6.80 - 6.87 (m, 2 H) 6.98 (d, *J* = 1.76 Hz, 1 H) 7.12 - 7.18 (m, 1 H) 7.19 - 7.25 (m, 3 H). Mass Spectrum (ESI) m/z = 456 $[M + H]^+$.

EXAMPLE 61

(3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-((5-methylisoxazol-3-yl)methyl)piperidin-2-one



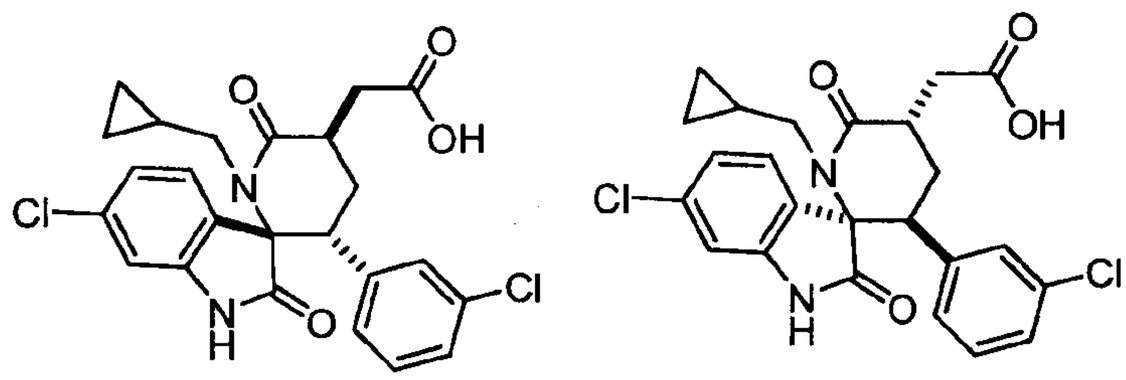
The title compound was prepared from (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one (Example 1, Step E), 3-(bromomethyl)-5-methylisoxazole, and (bromomethyl)cylopropane as described in Example 60.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm -0.05 - 0.04 (m, 1 H) 0.05 - 0.14 (m, 1 H) 0.32 - 0.41 (m, 1 H) 0.42 - 0.51 (m, 1 H) 0.79 - 0.94 (m, 1 H) 2.04 - 2.09 (m, 2 H) 2.28 (dd, *J* = 14.28 and 7.24 Hz, 1 H) 2.37 (d, *J* = 0.59 Hz, 3 H) 2.86 - 3.04 (m, 3 H) 3.33 - 3.41 (m, 1 H)

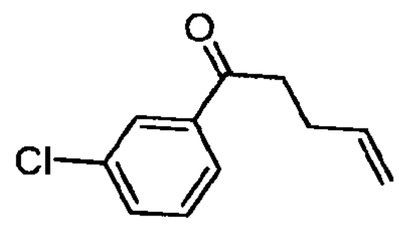
3.93 (dd, J = 14.18 and 6.55 Hz, 1 H) 4.56 (d, J = 9.98 Hz, 1 H) 5.92 (d, J = 0.78 Hz, 1 H) 6.70 (dt, J = 7.58 and 1.30 Hz, 1 H) 6.80 - 6.86 (m, 2 H) 6.95 (t, J = 1.76 Hz, 1 H) 7.06 - 7.11 (m, 1 H) 7.13 - 7.17 (m, 1 H) 7.17 - 7.23 (m, 2 H). Mass Spectrum (ESI) m/z = 469 $[M + H]^+$.

EXAMPLE 62

(*rac*) 2-((2'S,3'R,5'R)-6-chloro-3'-(3-chlorophenyl)-1'-(cyclopropylmethyl)-2,6'-dioxospiro[indoline-3,2'-piperidine]-5'-yl)acetic acid.

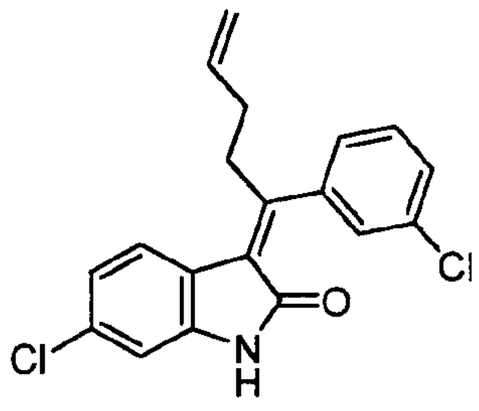


Step A. 1-(3-chlorophenyl)pent-4-en-1-one



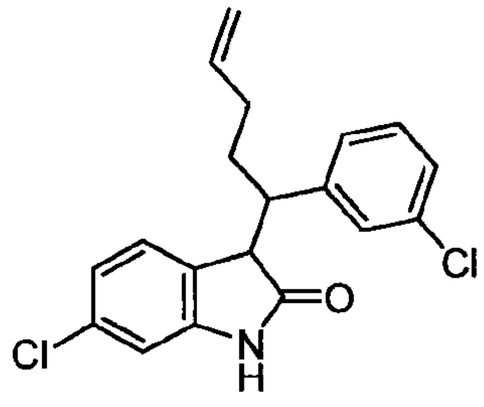
To a solution of 3-chlorobenzoyl chloride (7 ml, 54.7 mmol) in THF (60 mL) was added copper (I) iodide (0.521 g, 2.73 mmol). The slurry was cooled to -10 °C and 3-butenylmagnesium bromide (0.5M in THF) (112 ml, 55.8 mmol) was added dropwise via cannula over 30 min. The reaction mixture was stirred at -10 °C for 1 h and then warmed to room temperature. The reaction mixture was concentrated to 25 mL and diluted with 100 mL DCM and 100 mL 1M HCl. The layers were separated and the organic layer was filtered. The filtrate was washed with sat. $NaHCO_3$, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 0 to 50% DCM in hexanes) to give the title compound.

Step B. 6-chloro-3-(1-(3-chlorophenyl)pent-4-enylidene)indolin-2-one



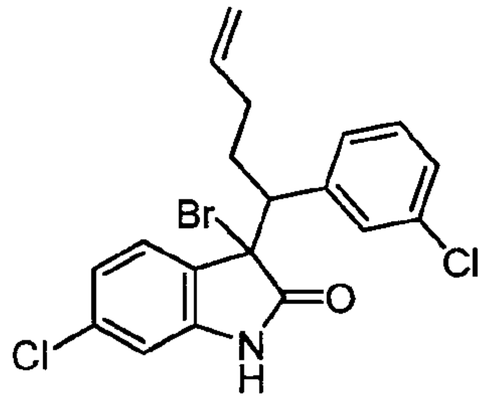
To a mixture of 1-(3-chlorophenyl)pent-4-en-1-one (Example 62, Step A) (14.86 g, 76 mmol) and 6-chloroindolin-2-one (12.79 g, 76 mmol) in toluene (50 mL) at room temperature was added pyrrolidine (6.31 mL, 76 mmol). The slurry was heated at reflux with a Dean Stark trap for 6 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 10 to 20% EtOAc in hexanes) to give the title compound.

Step C. 6-chloro-3-(1-(3-chlorophenyl)pent-4-enyl)indolin-2-one



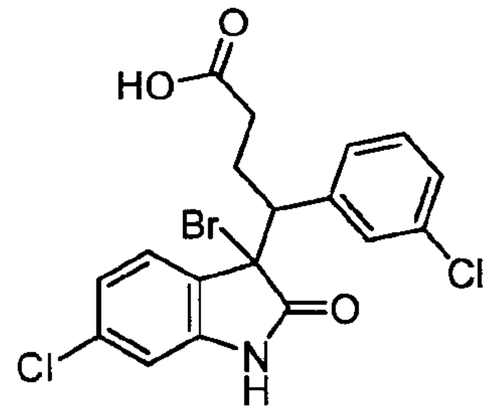
To a yellow slurry of 6-chloro-3-(1-(3-chlorophenyl)pent-4-enylidene)indolin-2-one (Example 62, Step B) (12.81 g, 37.2 mmol) in MeOH (200 mL) at room temperature was slowly added sodium borohydride (1.689 g, 44.7 mmol). Evolution of gas was observed. The yellow reaction mixture was stirred at room temperature for 30 min. Additional sodium borohydride (1.689 g, 44.7 mmol) was slowly added and the reaction mixture was stirred at room temperature for 1h. The reaction mixture was poured into water (200 mL). A precipitate formed and the mixture was sonicated for 15 min then filtered. The filtrate was concentrated under reduced pressure to 36 mL and then extracted with EtOAc twice. The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure to provide the title compound.

Step D. 3-bromo-6-chloro-3-(1-(3-chlorophenyl)pent-4-enyl)indolin-2-one



To a solution of 6-chloro-3-(1-(3-chlorophenyl)pent-4-enyl)indolin-2-one (Example 62, Step C (13.0 g, 37.5 mmol) in THF (200 mL) (previously degassed with Ar) at -78 °C under Ar was added N1,N1,N2,N2-tetramethylethane-1,2-diamine (11.79 mL, 79 mmol) (previously degassed with Ar) and butyllithium (1.6 M in hexanes) (49.3 mL, 79 mmol) (previously degassed with Ar) via addition funnel. The light brown reaction mixture was stirred at -78 °C for 30 min., wrapped in foil and recrystallized 1-bromopyrrolidine-2,5-dione (6.68 g, 37.5 mmol) in THF (50 mL) (previously degassed with Ar) was added via cannula. After the addition the reaction was quenched immediately with sat. potassium phosphate mono basic and warmed to room temperature. The mixture was extracted with EtOAc twice. The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 0 to 10% EtOAc in hexanes) to give the title compound as a 1:1.7 ratio of diastereomers.

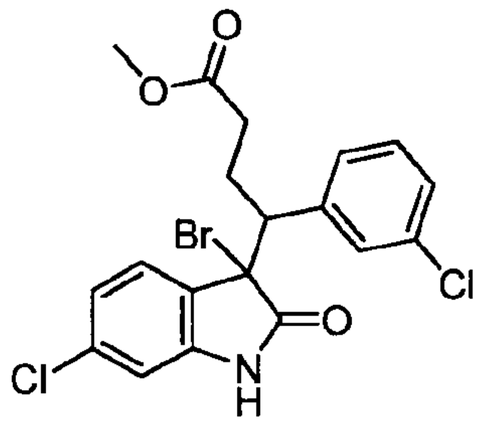
Step E. 4-(3-bromo-6-chloro-2-oxoindolin-3-yl)-4-(3-chlorophenyl)butanoic acid



To a rapidly stirred solution of 3-bromo-6-chloro-3-(1-(3-chlorophenyl)pent-4-enyl)indolin-2-one (Example 62, Step D) (7.74 g, 18.21 mmol) in $H_2O/CCl_4/MeCN$ (1.5/1/1) (80mL/50mL/50 mL) was added sodium periodate (15.58 g, 72.8 mmol) and ruthenium(III) chloride hydrate (0.205 g, 0.910 mmol). The reaction mixture was stirred vigorously for 30 min and the reaction monitored by TLC. The reaction mixture was acidified (10% citric acid)

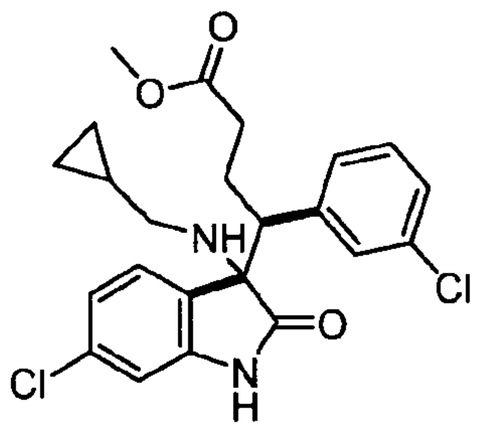
and extracted with EtOAc. The organic layer was washed with sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 30 to 70% EtOAc in hexanes) to give the title compound.

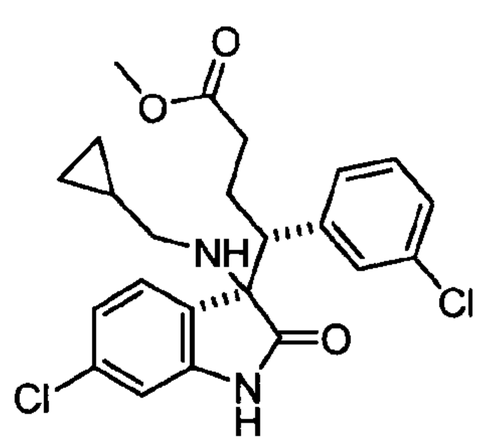
Step F. methyl 4-(3-bromo-6-chloro-2-oxoindolin-3-yl)-4-(3-chlorophenyl)butanoate

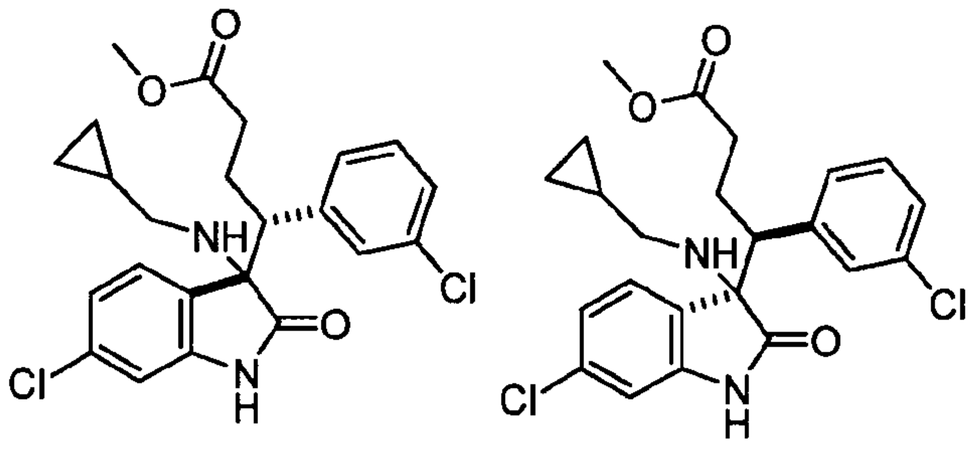


To a solution of 4-(3-bromo-6-chloro-2-oxoindolin-3-yl)-4-(3-chlorophenyl)butanoic acid (Example 62, Step E) (5.38 g, 12.14 mmol) in MeOH (120 mL) at room temperature was added one drop of concentrated sulfuric acid. The reaction mixture was stirred at room temperature for 18 h and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 0 to 50% EtOAc in hexanes) to give the title compound.

Step G. (*rac*) (S)-methyl 4-((S)-6-chloro-3-(cyclopropylmethylamino)-2-oxoindolin-3-yl)-4-(3-chlorophenyl)butanoate and (*rac*) (R)-methyl 4-((S)-6-chloro-3-(cyclopropylmethylamino)-2-oxoindolin-3-yl)-4-(3-chlorophenyl)butanoate

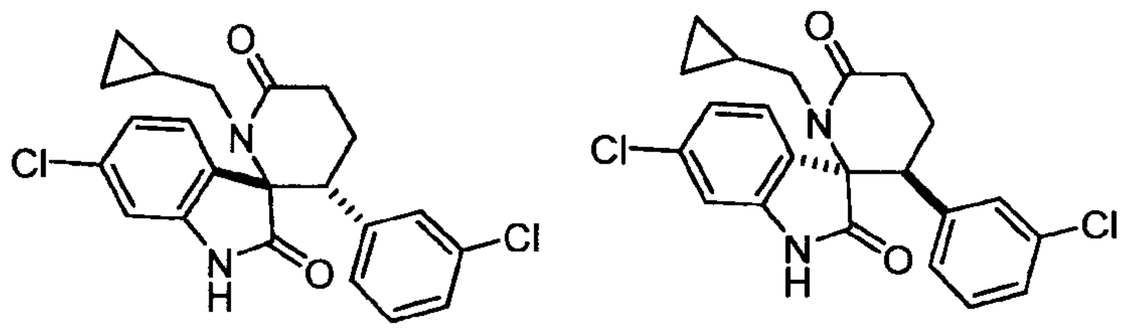






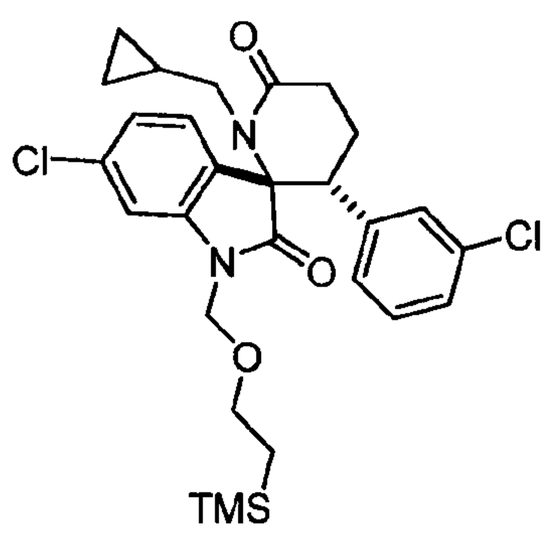
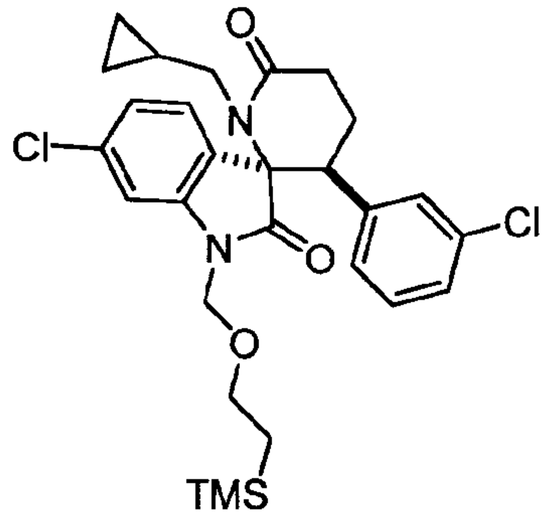
A solution of methyl 4-(3-bromo-6-chloro-2-oxoindolin-3-yl)-4-(3-chlorophenyl) butanoate (Example 62, Step F) (110 mg, 0.241 mmol) in DCE (4 mL) was heated at reflux. Cesium carbonate (157 mg, 0.481 mmol) and cyclopropylmethylamine hydrochloride (25.9 mg, 0.241 mmol) in DCE (1 mL) were added in one portion. The reaction mixture was heated at reflux for 5 h and then cooled to room temperature. The reaction mixture was filtered through celite and washed with DCM. The filtrate was concentrated and the the diastereomeric pairs were separated by flash chromatography on silica gel (eluent: 20 to 60% EtOAc in hexanes) to give the title compounds. The more polar isomer is used in Example 62, Step H.

Step H. (rac) (2'S,3'R)-6-chloro-3'-(3-chlorophenyl)-1'-(cyclopropylmethyl)spiro [indoline-3,2'-piperidine]-2,6'-dione



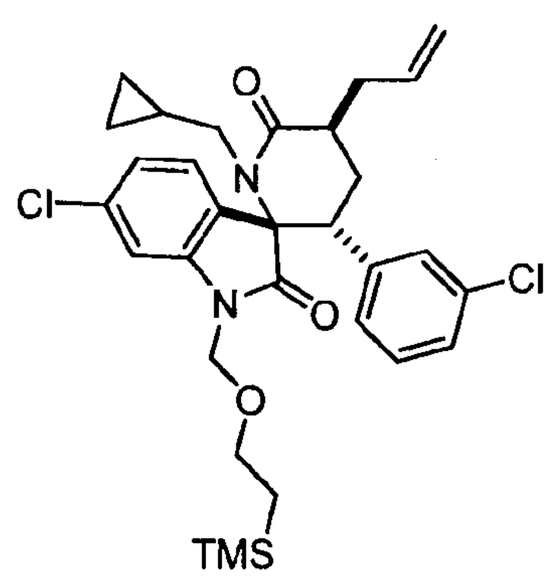
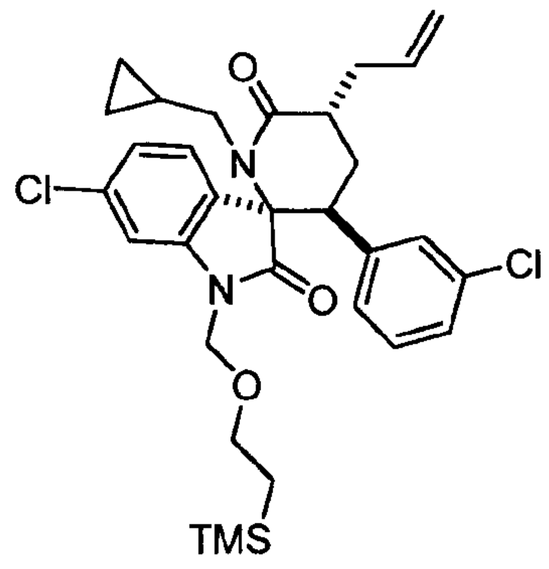
A solution of (*rac*) (R)-methyl 4-((S)-6-chloro-3-(cyclopropylmethylamino)-2-oxoindolin-3-yl)-4-(3-chlorophenyl)butanoate (Example 62, Step G, more polar isomer) in DCM was washed with sat $NaHCO_3$, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in distilled xylene (5 mL) and the reaction mixture was heated to 135 °C for 24 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 20 to 60% EtOAc in hexanes) to give the title compound.

Step I. (*rac*) (2'S,3'R)-6-chloro-3'-(3-chlorophenyl)-1'-(cyclopropylmethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)spiro[indoline-3,2'-piperidine]-2,6'-dione

To a solution of (*rac*) (2'S,3'R)-6-chloro-3'-(3-chlorophenyl)-1'-(cyclopropylmethyl)spiro [indoline-3,2'-piperidine]-2,6'-dione (Example 62, Step H) (114 mg, 0.274 mmol) in DMF (2 mL) at 0 °C was added a dispersion of 60% sodium hydride in mineral oil (10.98 mg, 0.274 mmol) followed by (2-(chloromethoxy)ethyl)trimethylsilane (48.4 μL, 0.274 mmol). The reaction mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred at room temperature for 24 h. The reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with 1M LiCl, sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 0 to 50% EtOAc in hexanes) to give the title compound.

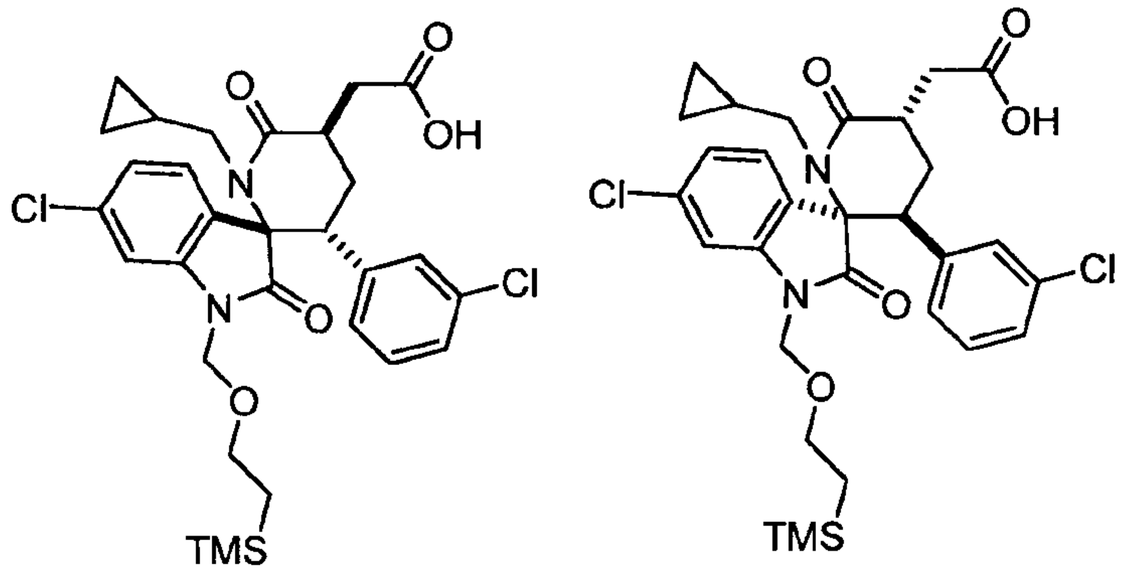
Step J. (*rac*) (2'S,3'R,5'S)-5'-allyl-6-chloro-3'-(3-chlorophenyl)-1'-(cyclopropylmethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)spiro[indoline-3,2'-piperidine]-2,6'-dione

To a solution of (*rac*) (2'S,3'R)-6-chloro-3'-(3-chlorophenyl)-1'-(cyclopropylmethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)spiro[indoline-3,2'-piperidine]-2,6'-dione (Example 62, Step I) (97mg, 0.178 mmol) in THF (1 mL) at -78°C under Ar was added fresly prepared LDA (1.0 M in THF) (178 μL, 0.178 mmol). The reaction color turned yellowish orange. The reaction

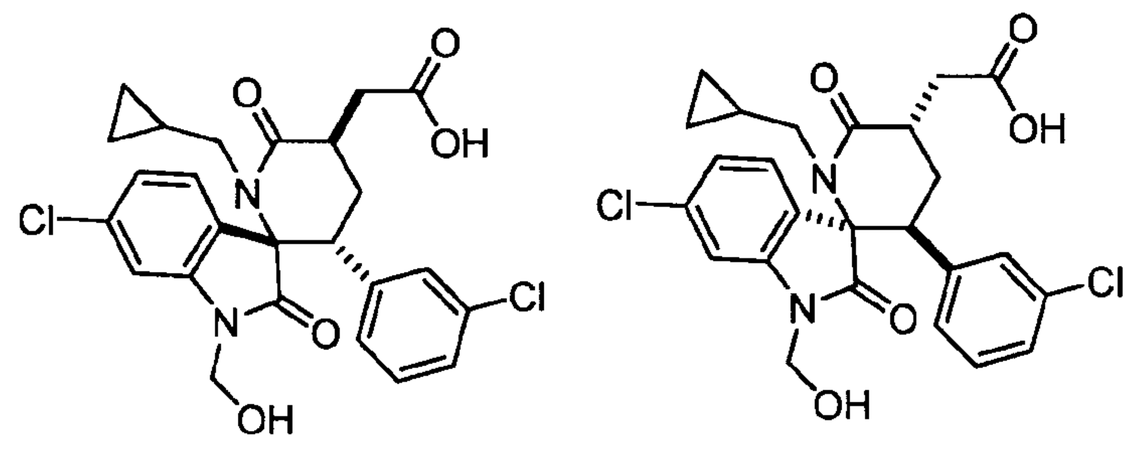
was stirred at -78 °C for 30 min then distilled allyl bromide (15.39 μL, 0.178 mmol) was added. The reaction was stirred at -78 °C for 10 min then warmed to 0 °C. The reaction was quenched with sat. NH_4Cl and warmed to room temperature. The mixture was diluted with EtOAc and the layers were separated. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 0 to 25% EtOAc in hexanes) to give the title compound.

Step K. (*rac*) 2-((2'S,3'R,5'R)-6-chloro-3'-(3-chlorophenyl)-1'-(cyclopropylmethyl)-2,6'-dioxo-1-((2-(trimethylsilyl)ethoxy)methyl)spiro[indoline-3,2'-piperidine]-5'-yl)acetic acid



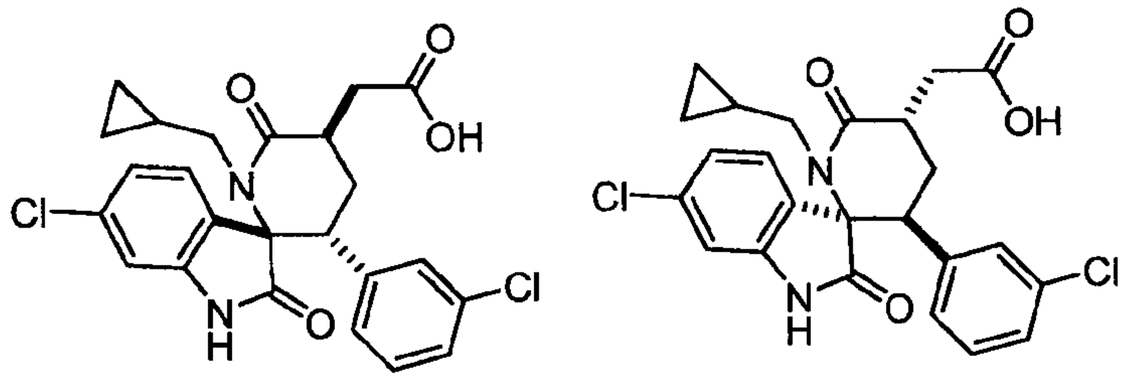
To a rapidly stirred solution of (*rac*) (2'S,3'R,5'S)-5'-allyl-6-chloro-3'-(3-chlorophenyl)-1'-(cyclopropylmethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)spiro[indoline-3,2'-piperidine]-2,6'-dione (Example 62, Step J) (46 mg, 0.079 mmol) in $H_2O/CCl_4/MeCN$ (0.75ml/.5 mL/.5 mL) was added sodium periodate (67.2 mg, 0.314 mmol) and ruthenium(III) chloride hydrate (1.771 mg, 7.85 μmol). The reaction mixture was stirred vigorously for 19 h and then acidified (10% citric acid) and filtered through a plug of celite and washed with EtOAc. The filtrate was transferred to a separatory funnel and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide the title compound.

Step L. (*rac*) 2-((2'S,3'R,5'R)-6-chloro-3'-(3-chlorophenyl)-1'-(cyclopropylmethyl)-1-(hydroxymethyl)-2,6'-dioxospiro[indoline-3,2'-piperidine]-5'-yl)acetic acid



To a solution of (*rac*) 2-((2'S,3'R,5'R)-6-chloro-3'-(3-chlorophenyl)-1'-(cyclopropylmethyl)-2,6'-dioxo-1-((2-(trimethylsilyl)ethoxy)methyl)spiro[indoline-3,2'-piperidine]-5'-yl)acetic acid (Example 62, Step K) (47 mg, 0.078 mmol) in DCM (0.8 mL) at room temperature was added 0.2 mL TFA. The reaction mixture was stirred at room temperature for 19 h before concentrating under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 50 to 100% EtOAc in hexanes) to give the title compound.

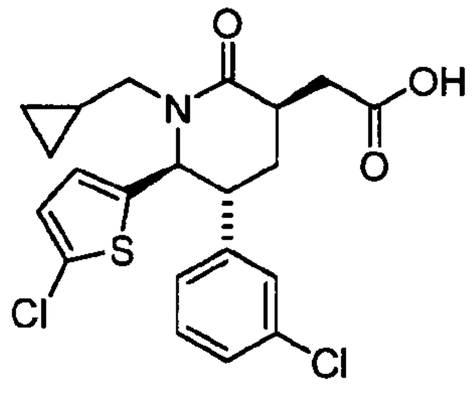
Step M. (*rac*) 2-((2'S,3'R,5'R)-6-chloro-3'-(3-chlorophenyl)-1'-(cyclopropylmethyl)-2,6'-dioxospiro[indoline-3,2'-piperidine]-5'-yl)acetic acid



To a solution of (*rac*) 2-((2'S,3'R,5'R)-6-chloro-3'-(3-chlorophenyl)-1'-(cyclopropylmethyl)-1-(hydroxymethyl)-2,6'-dioxospiro[indoline-3,2'-piperidine]-5'-yl)acetic acid (Example 62, Step L) (12.6 mg, 0.025 mmol) in MeOH (1 mL) at room temperature was added DIEA (8.74 μL, 0.050 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with 10% citric acid and concentrated under reduced pressure. The residue was purified by reversed phase preparatory HPLC (column: Gemini-NX C_{18} 5um column; Phenomonex, Torrance, CA; eluent: 0 to 100% MeCN +0.1% TFA in water + 0.1% TFA) to give the title compound.

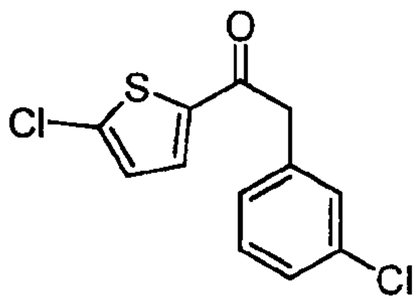
^{1}H NMR (400 MHz, *ACETONITRILE-d_3*) δ ppm -0.25 - -0.18 (1 H, m) -0.12 - -0.04 (1 H, m) 0.20 - 0.34 (2 H, m) 0.66 - 0.77 (1 H, m) 1.64 - 1.73 (1 H, m) 2.68 (1 H, dd, *J* = 14.3 and 7.0 Hz) 2.73 - 2.81 (1 H, m) 2.86 - 3.02 (1 H, m) 3.12 - 3.33 (3 H, m) 3.53 - 3.65 (1 H, m) 6.61 (1 H, d, *J* = 1.8 Hz) 6.79 - 6.91 (2 H, m) 7.08 (1 H, t, *J* = 7.8 Hz) 7.11 - 7.20 (2 H, m) 7.49 (1 H, d, *J* = 8.2 Hz) 8.29 (1 H, br s). Mass Spectrum (ESI) m/z = 473 $[M + H]^+$.

EXAMPLE 63



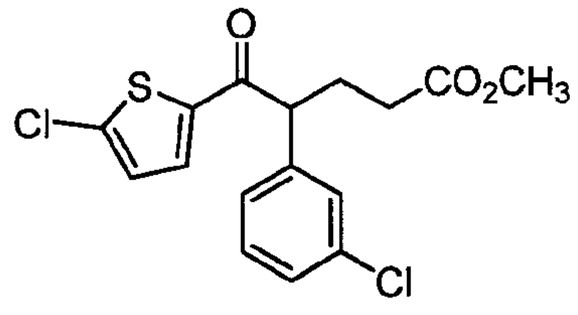
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(5-chlorothiophen-2-yl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid

Step A. 2-(3-Chlorophenyl)-1-(5-chlorothiophen-2-yl)ethanone



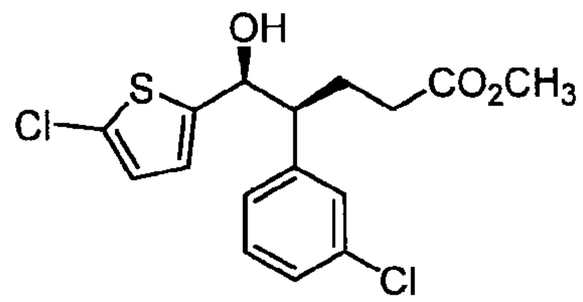
To a 500-mL round-bottomed flask was added silica gel 60 (21 g, 350 mmol) and the flask was heated with a heat gun under high vaccum for 30 min. The system was cooled to room temperature and phosphorus pentoxide (8.75 mL, 148 mmol) was added. The mixture was stirred at 110 °C (oil bath) under high vaccum for 120 min. The mixture was allowed to cool to room temperature. 3-chlorophenylacetic acid (15.6 g, 91 mmol), 2-chlorothiophene (33.8 mL, 366 mmol) and DCE (50 mL) were added. The reaction mixture was stirred at reflux for 4 hours. LCMS analysis showed the reaction was complete. The reaction mixture was allowed to cool to room temperature. The reaction mixture was diluted with ether (300 mL) and filtered. The organic solution was concentrated under reduced pressure. The residue was triturated with hexane to afford the title compound as an off-white solid. The hexane mother liquid was concentrated and purified by flash chromatography (SiO_2, 0 to 30% EtOAc/Hex, a gradient elution) provided another batch of the title compounde as a light yellow solid. Mass Spectrum (ESI) m/z = 271 (M+1).

Step B. *rac*. Methyl 4-(3-chlorophenyl)-5-(5-chlorothiophen-2-yl)-5-oxopentanoate



To a solution of 7.35g (27.1 mmol) of 2-(3-chlorophenyl)-1-(5-chlorothiophen-2-yl)ethanone (Example 63, Step A) and acrylic acid methyl ester (2.81 mL, 31.2 mmol) in DCM (60 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (4.05 mL, 27.1 mmol) in DCM (10 mL) slowly at 0 °C over 20 min. Then the reaction was allowed to warm to ambient temperature. After being stirred at 25°C for two days, the reaction mixture was diluted with DCM and washed with 2N HCl, water and sat. aq. NaCl solution. The organic extract was dried over Na_2SO_4. The solution was filtered and concentrated in vacuo to give the crude material as light yellow oil. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a pre-packed silica gel column (220 g), eluting with a gradient of 0 % to 30% EtOAc in hexane, to provided the title compound as a light-yellow oil. Mass Spectrum (ESI) m/z = 357 (M+1).

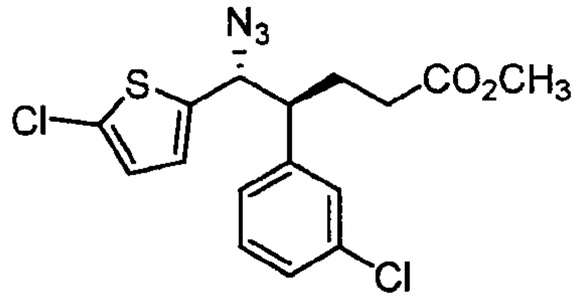
Step C. *rac* (4S, 5S)(4R, 5R) methyl 4-(3-chlorophenyl)-5-(5-chlorothiophen-2-yl)-5-hydroxypentanoate



To a solution of 8.20g (22.95 mmol) of methyl 4-(3-chlorophenyl)-5-(5-chlorothiophen-2-yl)-5-oxopentanoate (Example 63, Step B) in MeOH (100 mL) was added sodium borohydrate (0.809 mL, 22.95 mmol) portion-wise at 0 °C. Then the reaction was stirred at 0 °C for 30min. LCMS analysis showed the reaction went to completion. Ice-water was added to quench the reaction. The reaction mixture was concentrated under reduced pressure to remove most of MeOH. The residue was extracted with DCM (3 X 100 mL). The combined organic layers were washed with sat. aq. NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash chromatography

(TLC, SiO_2, 20 to 30% EtOAc/hexanes, gradient elution) provided the title compound as a colorless oil.

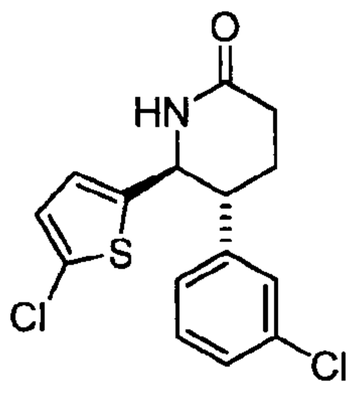
Step D. *rac*. (4S,5R)(4R, 5S)-methyl-5-azido-4-(3-chlorophenyl)-5-(5-chlorothiophen-2-yl) pentanoate



To a solution of 1.18 g (3.28 mmol) of racemic (4S, 5S)(4R, 5R)-methyl 4-(3-chlorophenyl)-5-(5-chlorothiophen-2-yl)-5-hydroxypentanoate (Example 63, Step C) in toluene (10 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.639 mL, 4.27 mmol) over 5 min at 0 °C with stirring. To the above solution, diphenylphosphoryl azide (0.852 mL, 3.94 mmol) was added dropwise over a period of 8 min. The reaction mixture was stirred at 0 °C to rt for 14 hours and monitored by LCMS analysis. The reaction mixture was diluted (sat. aq. NH_4Cl), extracted (3 x EtOAc), and washed (2 x sat. aq. NaCl solution). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was dissolved in small amount of DCM for chromatography. The insoluble material was removed by filtration and the solution was absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep pre-packed silica gel column (40 g), eluting with a gradient of 0% to 60% EtOAc in hexane, to provide the racemic title compound as a colorless oil.

Mass Spectrum (ESI) m/z = 406 (M+23).

Step E. (5R,6S)-5-(3-chlorophenyl)-6-(5-chlorothiophen-2-yl)piperidin-2-one



To a solution of 7.8 g (20.3 mmol) of racemic (4S,5R)(4R, 5S)-methyl 5-azido-4-(3-chlorophenyl)-5-(5-chlorothiophen-2-yl)pentanoate (Example 63, Step D) in THF/H_2O (4/1, 75 mL) was added trimethylphosphine, 1.0M solution in tetrahydrofuran (24.36 mL, 24.36 mmol). After being stirred for 1 h at 23 °C, LCMS analysis showed reaction was complete. Most of THF was removed under reduced pressure and the residue was basified (ice-cold 2 M LiOH) and the product was extracted (3 × DCM) and washed (2 × sat. aq. NaCl solution). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide a crude mixture of amines as a yellow solid.

The crude amine from above was dissolved in MeOH/saturated aq. $NaHCO_3$(4/1, 60 mL, c = 0.04 M) and the reaction was refluxed for 3 h. After LCMS analysis showed the reaction to be complete, excess solvent was removed under reduced pressure, the residue was diluted (water), extracted (2 × 10% MeOH/DCM), and washed (1 × sat. aq. NaCl solution). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide the crude title compound.

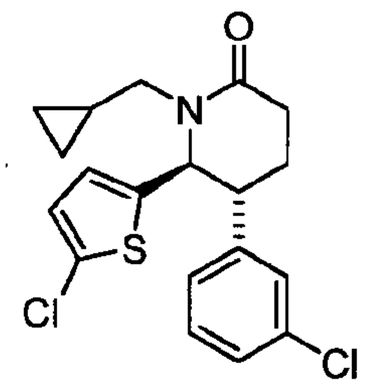
The crude material was absorbed onto a plug of silica gel and purified by chromatography through a pre-packed silica gel column (220 g), eluting with a gradient of 20 % to 100% EtOAc in CH_2Cl_2, to provide the racemic title compound as a white solid.

Individual enantiomers of the racemic (5R,6S)(5S, 6R)-5-(3-chlorophenyl)-6-(5-chlorothiophen-2-yl)piperidin-2-one were separated by chiral SFC on a 250 x 30 mm Chiralcel AS-H column with 50 g/min MeOH(+ 20 mM NH_3) + 50 g/min CO_2 on Thar 350 SFC (Thar Technologies, Inc., Pittsburg, PA). Outlet pressure = 100 bar; Temp. = 46 °C; Wavelength = 245 nm. Run time = 20 min.; cycle time = 17 min. The title compound (5R,6S)-5-(3-chlorophenyl)-6-(5-chlorothiophen-2-yl)piperidin-2-one was obtained as the faster eluting isomer.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.18 - 7.24 (2 H, m), 7.10 (1 H, m), 6.93 - 6.95 (1 H, m) 6.23 (1 H, d, *J* = 4 Hz), 6.42 (1 H, d, *J* = 4 Hz), 6.09 (1 H, s), 4.73 (1 H, d, *J* = 8 Hz), 2.87 - 2.94 (1 H, m), 2.60 - 2.65 (2 H, m), 2.05 - 2.25 (2 H, m); Mass Spectrum (ESI) m/z = 326 (M+1); $[\alpha]_D$ = + 165.8 (T = 24.7 °C, c = 0.104, $CHCl_3$)

Also obtained by the above method was the enantiomer of the title compound, (5S,6R)-5-(3-chlorophenyl)-6-(5-chlorothiophen-2-yl)piperidin-2-one as the slower eluting isomer. $[\alpha]_D$ = - 158 (T = 24.8 °C, c = 0.104, $CHCl_3$)

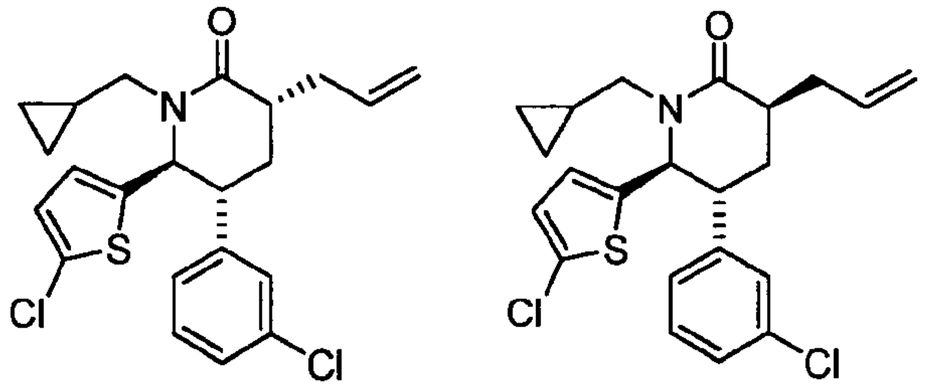
Step F. *rac*. (5R,6S)(5S,6R)-5-(3-chlorophenyl)-6-(5-chlorothiophen-2-yl)-1-(cyclopropylmethyl)piperidin-2-one



The title compound was prepared from racemic (5R,6S), (5S,6R)-5-(3-chlorophenyl)-6-(5-chlorothiophen-2-yl)piperidin-2-one (Example 63, Step E) as described in Example 35, Step A.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) α ppm 7.34 (1H, br s), 7.25 - 7.30 (2 H, m), 7.13 – 7.17 (1 H, m), 6.74 (1 H, d, *J* = 4 Hz), 6.56 (1 H, d, *J* = 4 Hz), 5.06 (1 H, d, *J* = 4 Hz), 4.13 – 4.19 (1H, m), 3.19 – 3.23 (1 H, m), 2.46 – 2.60 (3H, m), 2.23 - 2.29 (1 H, m), 2.01 - 2.10 (1 H, m), 1.05 – 1.13 (1 H, m), 0.59 – 0.66 (1 H, m), 0.49 – 0.56 (1 H, m), 0.27 – 0.33 (1 H, m), 0.18 – 0.24 (1 H, m). Mass Spectrum (ESI) m/z = 380 (M+1).

Step G. (3R,5R,6S) (3S,5S,6R)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one and (3S,5R,6S) (3R,5S,6R)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one



The title compounds were prepared from racemic ((5R, 6S)(5S, 6R)-5-(3-chlorophenyl)-6-(5-chlorothiophen-2-yl)-1-(cyclopropylmethyl)piperidin-2-one (Example 63, Step F) as described in Example 1, Step G and were obtained as a mixture of stereoisomers. The individual racemic stereoisomers were separated by silica gel chromatography.

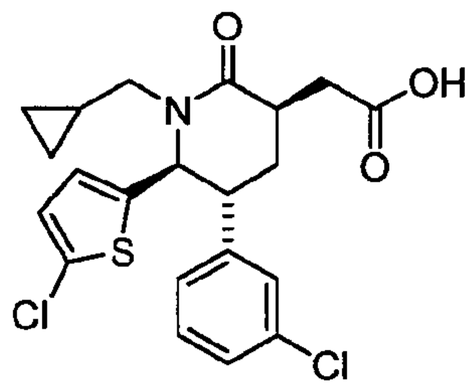
The title compound (3R,5R,6S) (3S,5S,6R)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one was obtained as the faster eluting isomer (less polar isomer) by silica gel chromatography.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.16 - 7.23 (2 H, m), 7.10 – 7.12 (1 H, m), 6.60 (1 H, d, *J* = 4 Hz), 6.32 (1 H, d, *J* = 4 Hz), 5.75 – 5.84 (1H, m), 5.05 – 5.12 (2 H, m), 4.76 (1 h, d, *J* = 8 Hz), 3.98 – 4.03 (1 H, m), 3.04 – 3.10 (1 H, m), 2.75 – 2.81 (1 H, m), 2.51 – 2.63 (2H, m), 2.35 - 2.42 (1 H, m), 2.05 - 2.11 (1 H, m), 1.89 – 1.99 (1 H, m), 0.88 – 0.98 (1 H, m), 0.49 – 0.56 (1 H, m), 0.39 – 0.46 (1 H, m), 0.19 – 0.25 (1 H, m), 0.07 -0.13 (1 H, m). Mass Spectrum (ESI) m/z = 420 (M+1).

The title compound (3S,5R,6S) (3R,5S,6R)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one was obtained as the slower eluting isomer on silica gel chromatography.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.42 (1 H, br s) 726 - 7.31 (1 H, m), 7.19 - 7.23 (1 H, m),6.79 (1 H, d, *J* = 4 Hz), 6.60 (1 H, d, *J* = 4 Hz), 5.70 – 5.80 (1H, m), 5.06 – 5.15 (3 H, m), 4.18 – 4.23 (1 H, m), 3.26 – 3.29 (1 H, m), 2.62 – 2.68 (1 H, m), 2.41 – 2.51 (2H, m), 2.31 - 2.38 (1 H, m), 2.15 - 2.22 (1 H, m), 1.92 – 1.98 (1 H, m), 1.11 – 1.21 (1 H, m), 0.63 – 0.69 (1 H, m), 0.54 – 0.60 (1 H, m), 0.24 – 0.34 (2 H, m). Mass Spectrum (ESI) m/z = 420 (M+1).

Step H. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(5-chlorothiophen-2-yl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid



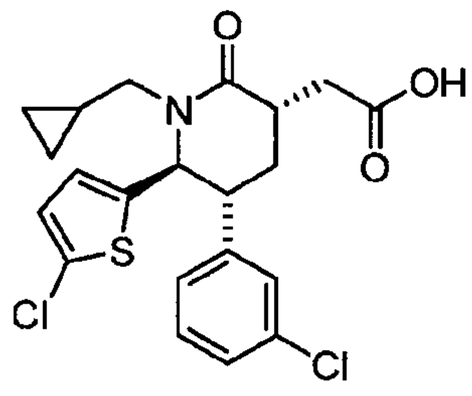
The title compound was prepared from racemic (3R,5R,6S)(3S,5S,6R)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one (Example 63, Step G)

as described in Example 1, Step H and resolved by chiral SFC on a CHRALCEL® OJ column (Daicel, Fort Lee, NJ). It was obtained as the slower eluting isomer.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.45 (1 H, br s) 7.31 - 7.34 (2 H, m), 7.23 - 7.35 (1 H, m),6.84 (1 H, d, *J* = 4 Hz), 6.74 (1 H, d, *J* = 4 Hz), 5.27 (1 H, br s), 4.22 – 4.27 (1 H, m), 3.33 (1 H, br s), 2.76 – 2.84 (1 H, m), 2.52 – 2.63 (3H, m), 2.31 - 2.36 (1 H, m), 1.96 – 2.02 (1 H, m), 1.15 – 1.24 (1 H, m), 0.71 – 0.77 (1 H, m), 0.60 – 0.67 (1 H, m), 0.34 – 0.40 (1 H, m), 0.27 -0.33 (1 H, m). Mass Spectrum (ESI) m/z = 438 (M+1).

EXAMPLE 64

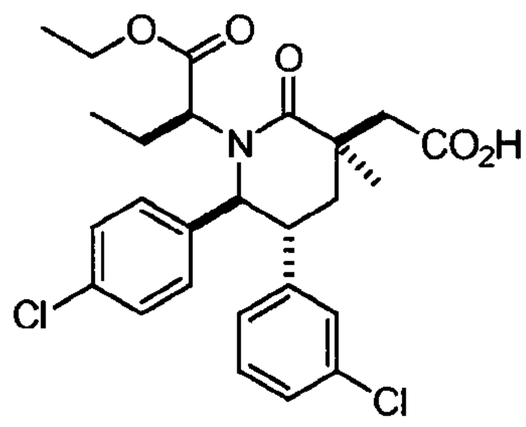
2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(5-chlorothiophen-2-yl)-1-(cyclopropylmethyl)-2-oxopiperidin-3-yl)acetic acid



The title compound was prepared from racemic (3R,5R,6S)(3S,5S,6R)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-one (Example 63, Step G) as described in Example 1, Step H and resolved by chiral SFC on an AD column. It was obtained as the slower eluting isomer on a CHIRALCEL® (Daicel, Fort Lee, NJ) AD column.

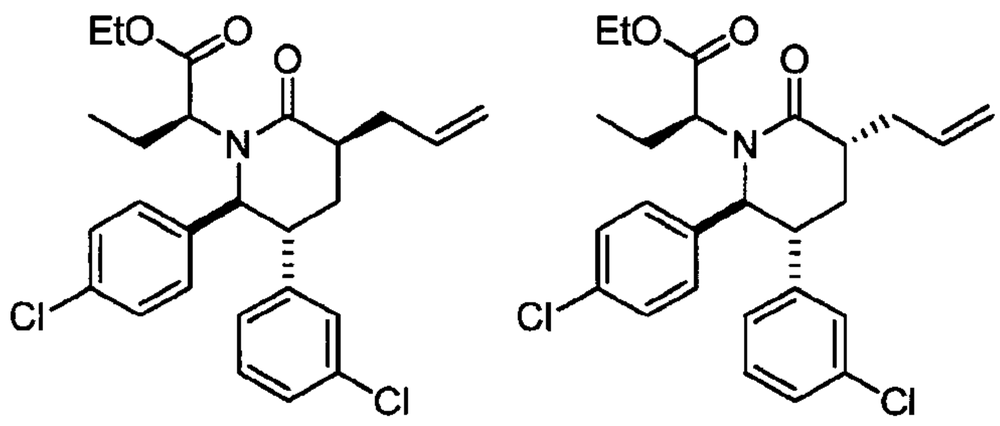
^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.17 - 7.24 (2 H, m), 7.09 – 7.10 (1 H, m), 6.90 – 6.92 (1H, m), 6.62 (1 H, d, *J* = 4 Hz), 6.35 (1 H, d, *J* = 4 Hz), 4.80 (1 H, d, *J* = 12 Hz), 3.94 – 3.99 (1 H, m), 3.11 – 3.18 (1 H, m), 2.99 – 3.16 (1 H, m), 2.54 – 2.66 (2H, m), 2.09 - 2.22 (2 H, m), 0.87 – 0.98 (1 H, m), 0.50 – 0.57 (1 H, m), 0.40 – 0.47 (1 H, m), 0.18 – 0.24 (1 H, m), 0.07 -0.13 (1 H, m). Mass Spectrum (ESI) m/z = 438 (M+1).

EXAMPLE 65



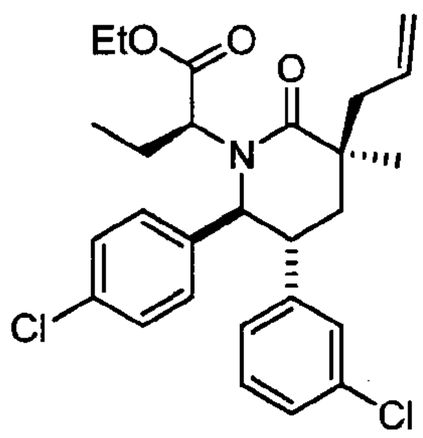
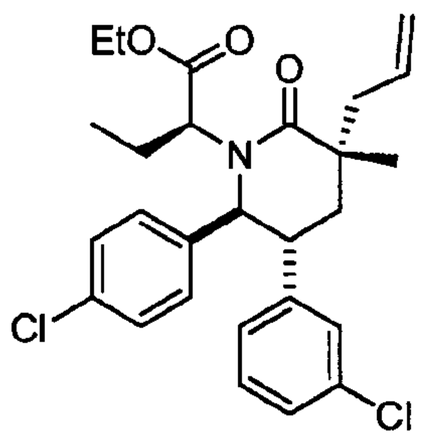
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-ethoxy-1-oxobutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

Step A. (S)-Ethyl 2-((3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanoate and (S)-Ethyl 2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanoate



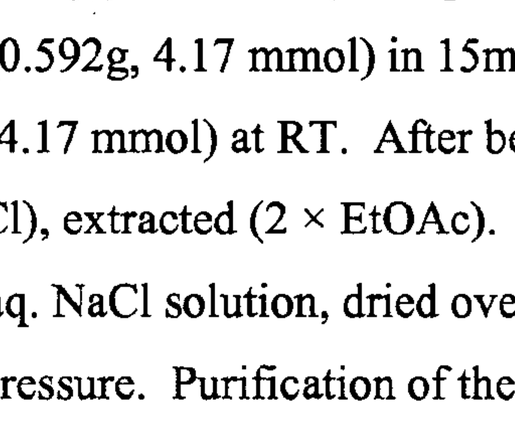
To a solution of 362 mg (833 μmol) of (S)-Ethyl 2-((2S,3R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-6-oxopiperidin-1-yl)butanoate (Example 9, Step A) and allyl bromide (87 μl, 1000 μmol) in THF (3.30 mL, 0.25 M) was added dropwise lithium bis(trimethylsilyl) amide (1M solution in THF; 875 μl, 875 μmol) at -78 °C. After being stirred at -78 °C for 3 h, the reaction was quenched (sat. aqueous NH_4Cl), extracted (2 × EtOAc). The combined organic layers were washed with water and sat. aq. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by chromatography (12 g SiO_2, 15 to 20% EtOAc/Hex, a gradient elution) provided the title compounds as a mixture of stereoisomers.

Step B. (2S)-Ethyl 2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoate and (2S)-Ethyl 2-((3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoate

To a solution of 0.66 g (1.39 mmol) of (S)-ethyl 2-((5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-2-oxopiperidin-1-yl)butanoate (Example 65, Step A; mixture of diastereomers) and iodomethane (0.592g, 4.17 mmol) in 15mL of THF was added LHMDS (1.0M solution in THF; 4.17 mL, 4.17 mmol) at RT. After being stirred for 12h, the reaction was quenched (sat. aqueous NH_4Cl), extracted (2 × EtOAc). The combined organic layers were washed with water and sat. aq. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by reversed phase preparatory HPLC (GeminiTM Prep C18 5μm column, Phenomenex, Torrance, CA; eluent: 10 to 90% acetonitrile +0.1% TFA in water + 0.1% TFA, gradient elution) gave the title compound as a mixture of stereoisomers.

Step D. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-ethoxy-1-oxobutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

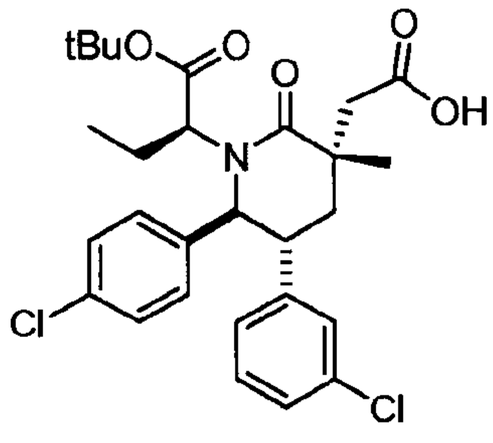


To a rapidly stirring solution of 0.28g (0.573 mmol) of (2S)-ethyl 2-((5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl) butanoate (Example 65, Step B; mixt. of diastereomers) in $H_2O/CCl_4/MeCN$ (4.0/2.0/2.0, 8.0mL) was added sodium periodate (0.490 g, 2.29 mmol), followed by ruthenium(III) chloride hydrate (0.013 g, 0.057

mmol). After being stirred vigorously for 12 h, the reaction was acidified (10% citric acid) and diluted with EtOAc. The insoluble material was removed by filtration through a pad of Celite® (J.T. Baker, Phillipsberg, NJ, diatomaceous earth). The filtrate was extracted (2 × EtOAc). The combined organic layers were washed with water and sat. aq. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reversed phase preparatory HPLC (GeminiTM Prep C18 5μm column, Phenomenex, Torrance, CA; eluent: 10 to 90% acetonitrile +0.1% TFA in water + 0.1% TFA, gradient elution) to give the title compound as the first eluting isomer as a white powder.

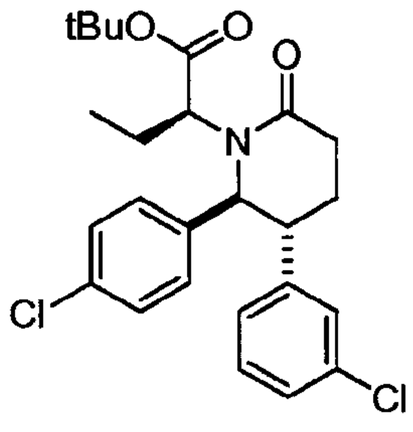
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.59 (t, *J*=7.6 Hz, 3 H), 1.28 (t, *J*=7.2 Hz, 3 H), 1.44 (s, 3 H), 1.50 - 1.64 (m, 1 H), 2.10 - 2.19 (m, 1 H), 2.19 - 2.37 (m, 2 H), 2.86 (q, *J*=14.5 Hz, 2 H), 3.19 - 3.35 (m, 2 H), 4.11 - 4.27 (m, 2 H), 4.58 (d, *J*=10.5 Hz, 1 H), 6.77 (m, 1 H) 6.93 - 7.05 (m, 3 H) 7.05 - 7.17 (m, 2 H) 7.20 - 7.33 (m, 2 H); MS (ESI) 506.2 $[M+H]^+$. 504.1 $[M-H]^-$.

EXAMPLE 66



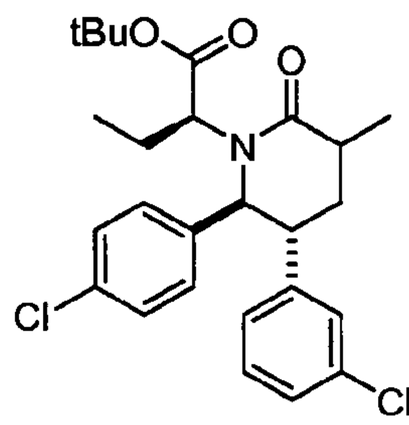
2-((3S,5R,6S)-1-((S)-1-tert-butoxy-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid:

Step A. (S)-tert-butyl 2-((2S,3R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-6-oxopiperidin-1-yl)butanoate



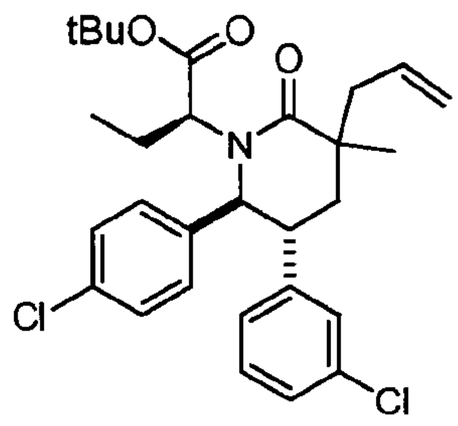
The title compound was synthesized as described in Example 9, Step A, substituting ethyl 2-bromobutanoate for *t*-butyl 2-bromobutanoate. Purification by flash chromatography on silica gel (30% EtOAc/Hexanes) provided the title compound as the faster eluting component as a white foam.

Step B. (2S)-tert-butyl 2-((2S,3R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-5-methyl-6-oxopiperidin-1-yl)butanoate



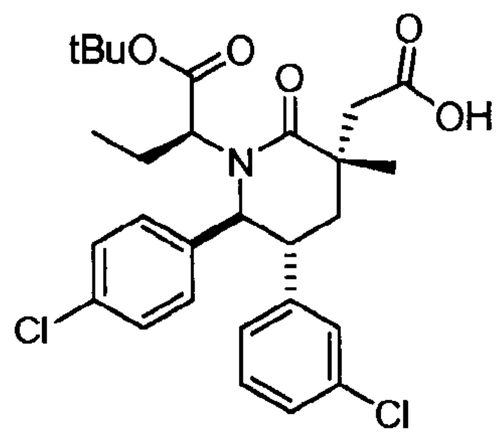
To a solution of 11.2 g (24.2 mmol) of (*S*)-*tert*-butyl 2-((2S,3R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-6-oxopiperidin-1-yl)butanoate (Example 66, Step A) and iodomethane (1.813 mL, 29.1 mmol) in THF (120.0 mL) was added a lithium bis(trimethylsilyl)amide, (1M solution in THF; 26.6 mL, 26.6 mmol) at -78 °C. The reaction was allowed to warm to R.T., then was quenched (sat. aqueous NH_4Cl) and extracted (2 × EtOAc). The combined organic layers were washed with water and sat. aq. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was absorbed onto a plug of silica gel and purified by chromatography on silica gel, eluting with a gradient of 10 % to 30 % EtOAc in hexane, to provide the title compound as a mixture of stereoisomers.

Step C. (2S)-tert-butyl 2-((5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoate



To a solution of 10.2 g(21.4 mmol) of (2S)-*tert*-butyl 2-((2S,3R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-5-methyl-6-oxopiperidin-1-yl)butanoate (Example 66, Step B, mixture of diastereomers) and allyl bromide (7.24 mL, 86 mmol) in THF (210 mL) was added LHMDS, (1.0M solution in THF; 64.2 mL, 64.2 mmol) at R.T. Let it stir at R.T. for 5min. Then the reaction mixture was heated at 50 °C for 3h. Sat. aq. NH_4Cl solution was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with water and sat. aq. NaCl solution, dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography, eluting with a gradient of 0 % to 20% EtOAc in hexane, to provide the title compound as a mixture of stereoisomers at C-3.

Step D. 2-((3S,5R,6S)-1-((S)-1-tert-butoxy-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

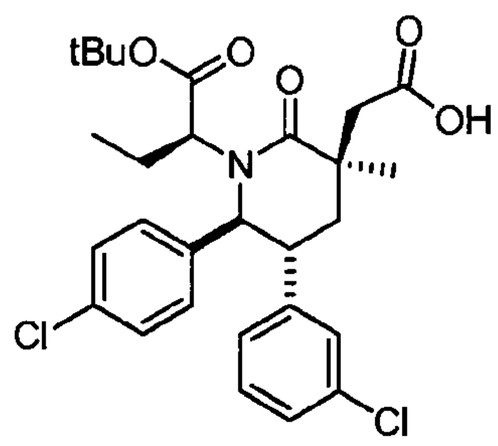


(2S)-*tert*-butyl 2-((5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoate (Example 66, Step C, mixture of diastereomers) was converted to the acid by a procedure similar to the one described in Example 65, Step D. The crude product was purified by reversed phase preparatory HPLC (GeminiTM Prep C18 5μm column, Phenomenex, Torrance, CA; eluent: 10 to 90% acetonitrile +0.1% TFA in water + 0.1% TFA, gradient elution) to give, the title compound as the first eluting isomer.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.54 (t, *J*=7.5 Hz, 3 H), 1.41 - 1.55 (m, 14 H), 2.07 - 2.17 (m, 1 H), 2.25 (d, *J*=13.5 Hz, 1 H), 2.28 - 2.42 (m, 1 H), 2.81 (d, *J*=15.4 Hz, 1 H), 2.93 - 3.03 (m, 2 H), 3.24 (ddd, *J*=13.3, 10.5, 3.1 Hz, 1 H), 4.58 (d, *J*=10.5 Hz, 1 H), 6.76 (m, 1 H) 6.97 - 7.06 (m, 3 H) 7.08 - 7.20 (m, 2 H) 7.25 (s, 2 H); MS (ESI) 534.1 $[M+H]^+$. 532.0 $[M-H]^-$.

Further elution provided Example 67.

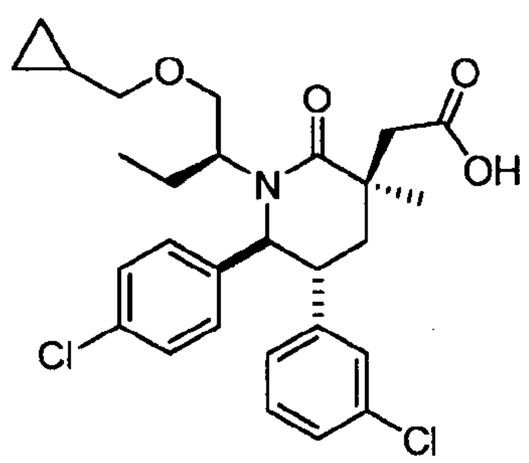
EXAMPLE 67



2-((3R,5R,6S)-1-((S)-1-tert-butoxy-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

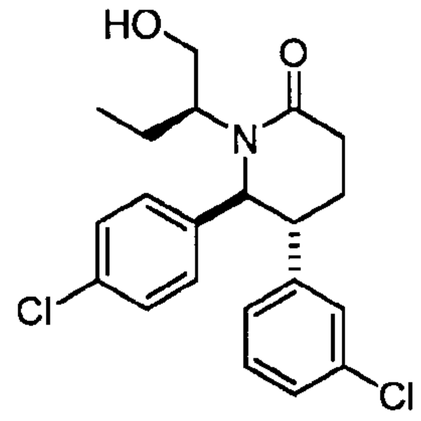
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.00 (t, *J*=7.5 Hz, 3 H), 1.43 (s, 9 H), 1.50 (s, 3 H), 1.93 - 2.27 (m, 4 H), 2.79 (d, *J*=15.3 Hz, 1 H), 3.04 (d, *J*=15.5 Hz, 1 H), 3.15 - 3.29 (m, 2 H), 4.52 (d, *J*=10.4 Hz, 1 H), 6.68 - 6.78 (m, 1 H), 6.90 - 6.98 (m, 1 H), 7.05 - 7.29 (m, 6 H); MS (ESI) 534.1 $[M+H]^+$. 532.0 $[M-H]^-$.

EXAMPLE 68



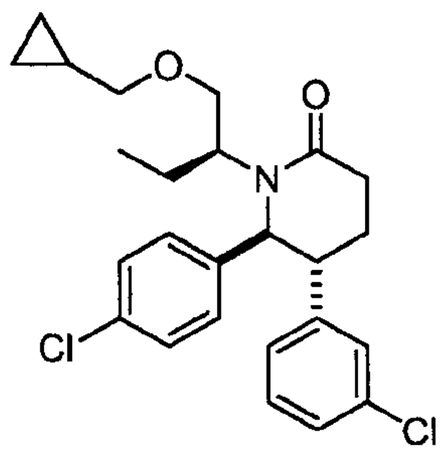
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethoxy)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

Step A. (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-hydroxybutan-2-yl)piperidin-2-one



To a solution of 3g (6.9 mmol) of (S)-ethyl 2-((2S,3R)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-6-oxopiperidin-1-yl)butanoate (Example 9, Step A) in 45 mL of Et_2O was added lithium tetrahydroborate (0.334 g, 13.81 mmol) at 0 °C. After being stirred at 0 °C for 50 min, the reaction was quenched (ice cold 10% citric acid) and extracted (2 × EtOAc). The combined organic layers were washed with water and sat. aq. NaCl solution, dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. Purification by flash chromatography on silica gel (eluent: 30% to 60% EtOAc/Hexanes, gradient elution) provided the title compound.

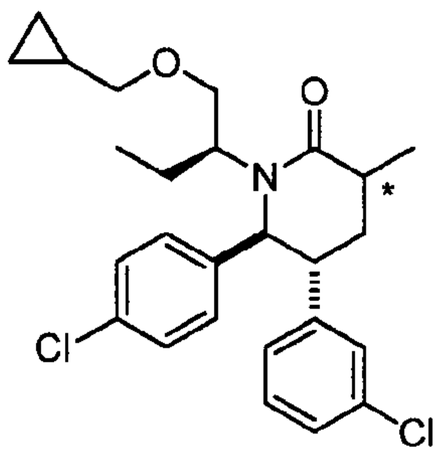
Step B. (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethoxy)butan-2-yl)piperidin-2-one



To a solution of 1.48g (3.77 mmol) of (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-hydroxybutan-2-yl)piperidin-2-one (Example 68, Step A) and bromomethylcyclopropane (0.828 mL, 7.54 mmol) in DMF (20mL) was added sodium t-butoxide (0.544 g, 5.66 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h and then warmed to rt. Then the reaction was stirred at rt for 14h. The reaction was quenched with sat. aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with water and sat. aq. NaCl solution, dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. Purification by flash chromatography on silica gel

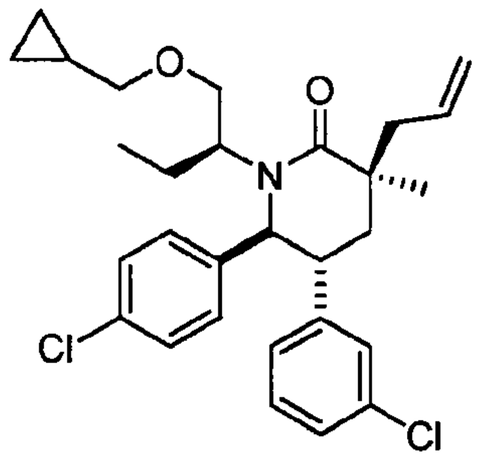
(eluent: 20%-40% EtOAc/Hexanes, gradient elution) provided the title compound as a colorless oil.

Step C. (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethoxy)butan-2-yl)-3-methylpiperidin-2-one



To a solution of 0.325g (0.73 mmol) of (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethoxy)butan-2-yl)piperidin-2-one (Example 68, Step B) and iodomethane (0.055 mL, 0.874 mmol) in THF (7.0 mL) was added lithium bis(trimethylsilyl) amide (1M solution in THF, 0.8 mL, 0.8 mmol) at -78 °C. The reaction was allowed to warm to R.T., then was quenched with sat. aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with water and sat. aq. NaCl solution, dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The crude material was absorbed onto a plug of silica gel and purified by chromatography on silica gel, eluting with a gradient of 10 % to 30 % EtOAc in hexane, to provide the title compound as a mixture of C-3 stereoisomers, as indicated by *.

Step D. (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethoxy)butan-2-yl)-3-methylpiperidin-2-one



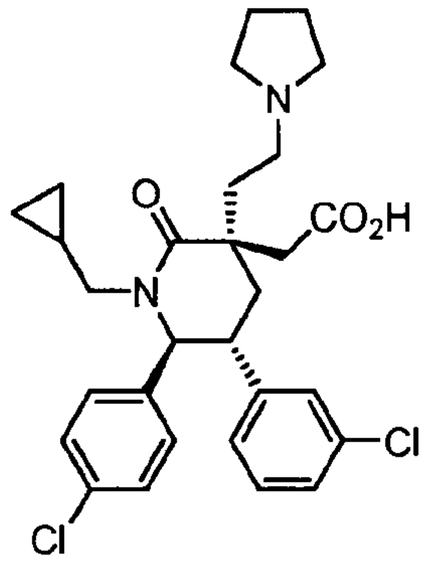
To a solution of 0.2 g (0.434 mmol) of (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethoxy)butan-2-yl)-3-methylpiperidin-2-one (Example 68, Step C, mixture of diastereomers) and allyl bromide (0.147 mL, 1.737 mmol) in THF (5 mL) was added LHMDS, (1.0M solution in THF, 1.3 mL, 1.3 mmol) at RT. Let it stir at RT for 5min. Then the raction mixture was heated at 50 °C for 3h. The reaction mixture was diluted with satd. NH_4Cl. and extracted with CH_2Cl_2. The combined organic layers were washed with water and sat. aq. NaCl solution, dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The crude material was purified by chromatography, eluting with a gradient of 0 % to 20% EtOAc in hexane, to provide the title compound as a colorless oil.

Step E. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethoxy)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

(3S,5R,6S)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(cyclopropylmethoxy)butan-2-yl)-3-methylpiperidin-2-one (Example 68, Step E) was converted to the acid by a procedure similar to the one described in Example 1, Step H, to provide the title compound.

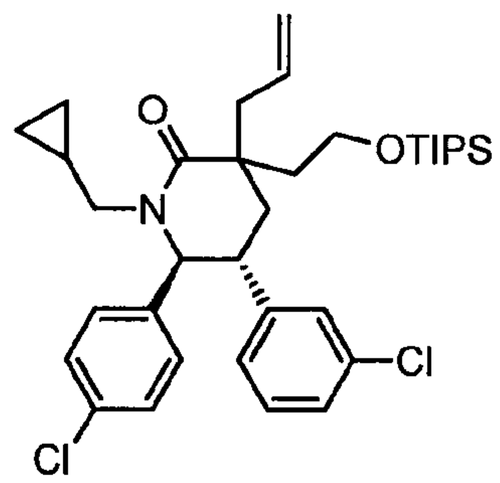
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.20 - 0.33 (m, 2 H), 0.51 (t, *J*=7.5 Hz, 3 H), 0.57 - 0.70 (m, 2 H), 1.05 - 1.17 (m, 1 H), 1.44 (s, 3 H), 1.48 - 1.62 (m, 1 H), 1.82 - 1.95 (m, 1 H), 2.01 (dd, *J*=13.9, 3.3 Hz, 1 H), 2.20 (t, *J*=13.5 Hz, 1 H), 2.72 (d, *J*=15.1 Hz, 1 H), 2.95 - 3.12 (m, 3 H), 3.24 - 3.40 (m, 3 H), 3.95 (t, *J*=9.8 Hz, 1 H), 4.69 (d, *J*=10.0 Hz, 1 H), 6.72 - 6.80 (m, 1 H), 6.94 - 7.07 (m, 3 H), 7.07 - 7.21 (m, 2 H), 7.25 (d, *J*=8.61 Hz, 2 H);

EXAMPLE 69



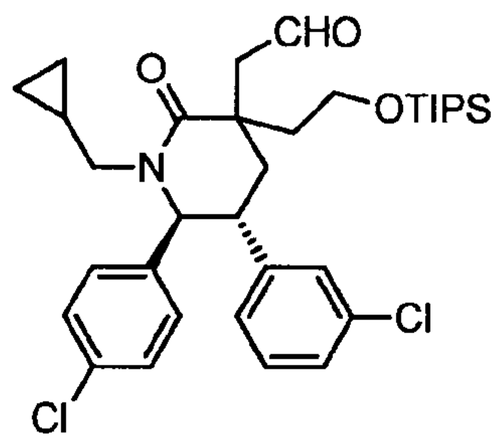
2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3-(2-(pyrrolidin-1-yl)ethyl)piperidin-3-yl)acetic acid

Step A. (5R,6S)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-(2-(triisopropylsilyloxy)ethyl)piperidin-2-one



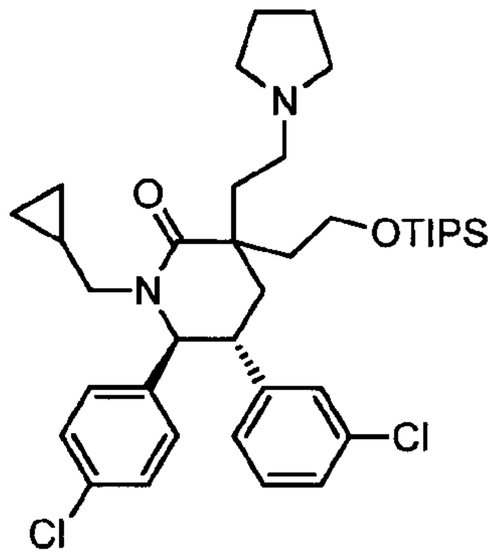
To a solution of 3.70 g (8.9 mmol) of a mixture of C-3 diastereomers of (5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)piperidin-2-oneoxopentanoate (Example 35, Step B) and 20.7 g (63 mmol) of (2-iodoethoxy)triisopropylsilane in dry, degassed THF (60 mL) was added 54.5 mL (54.5 mmol) of a 1 M solution of lithium bis(trimethylsilyl)amide in THF slowly via syringe over 6 min. After 10 min, the orange solution was warmed to 40 °C and stirred for an additional 2.25 h. The reaction was cooled to room temperature, quenched with saturated aqueous ammonium chloride, and extracted with EtOAc (3X). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by flash chromatography on silica gel (2-25% EtOAc/hexanes, gradient elution) provided the title compound (mixture of C-3 epimers) as a light yellow oil.

Step B. 2-((5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3-(2-(triisopropylsilyloxy)ethyl)piperidin-3-yl)acetaldehyde



To a solution of 1.28 g (2.08 mmol) of (5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-(2-(triisopropylsilyloxy)ethyl)piperidin-2-one (Example 69, Step A, mixture of diastereomers) in THF (50 mL) and water (17.5 mL) was added a catalytic amount of osmium tetroxide. After 25 min, 1.34 g (6.25 mmol) of sodium periodate was added. The resulting light brown slurry was stirred for 19 h and then was filtered through a fritted funnel. The filtrate was partially concentrated under reduced pressure, then was diluted with water and extracted with ethyl acetate (2X). The combined organic layers were washed with saturated aqueous sodium thiosulfate and then saturated aqueous sodium chloride. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated. The crude title compound (mixture of C-3 epimers) was used directly in the next step.

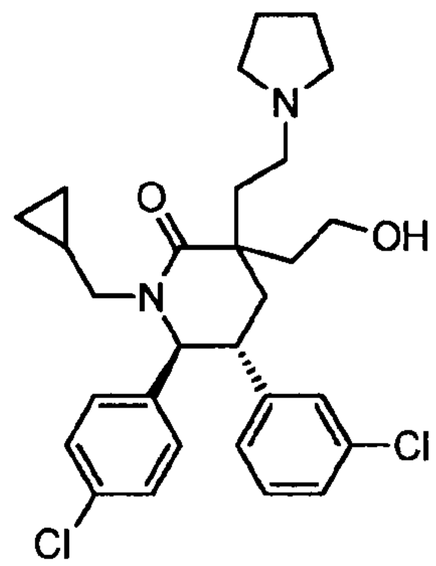
Step C. Synthesis of (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-(2-(pyrrolidin-1-yl)ethyl)-3-(2-(triisopropylsilyloxy)ethyl)piperidin-2-one



A mixture of 1.02 g (1.66 mmol) of crude 2-((5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3-(2-(triisopropylsilyloxy)ethyl)piperidin-3-yl)acetaldehyde (Example 69, Step B, mixture of diastereomers), 0.55 mL (6.6 mmol) of pyrrolidine, 880 mg (4.15 mmol) of sodium triacetoxyborohydride and 285 μL (4.98 mmol) of acetic acid was suspended in a mixture of 1,2-dichloroethane (36 mL) and DMF (12 mL).

After being stirred at room temperature for 20 h, the reaction mixture was quenched with saturated aqueous sodium bicarbonate and extracted with DCM (3X). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated. The crude title compound (mixture of C-3 epimers) was used directly in the next step.

Step D. (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-(2-hydroxyethyl)-3-(2-(pyrrolidin-1-yl)ethyl)piperidin-2-one



To an ice-cooled solution of 1.12 g (1.66 mmol) of crude (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-(2-(pyrrolidin-1-yl)ethyl)-3-(2-(triisopropylsilyloxy)ethyl)piperidin-2-one (Example 69, Step C, mixture of diastereomers) in THF (55 mL) added 8.3 mL (8.3 mmol) of a 1M solution of TBAF in THF. After being stirred at room temperature for 1.5 h, the reaction mixture was quenched with water and extracted with EtOAc (3X). The combined organic layers were dried (Na_2SO_4), and concentrated under the reduced pressure. Purification of the residue by flash chromatography on silica gel (3-30% MeOH/DCM, gradient elution) provided the title compound (mixture of C-3 epimers) as a light yellow oil.

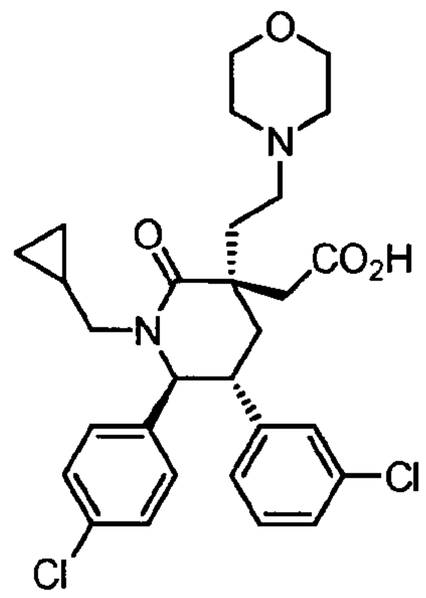
Step E. 2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3-(2-(pyrrolidin-1-yl)ethyl)piperidin-3-yl)acetic acid

An ice-cooled solution of 2.05 g (20.5 mmol) of chromium(VI) oxide in water (4 mL) was treated with 1.75 mL (32.7 mmol) of sulfuric acid via syringe. The mixture was diluted with additional water (4 mL) and stored at 0 °C at prior to use. In a separate flask, 105 mg (0.21 mmol) of (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-(2-hydroxyethyl)-3-(2-(pyrrolidin-1-yl)ethyl)piperidin-2-one (Example 69, Step D, mixture of diastereomers) was dissolved in acetone (20 mL) and then treated with Jones reagent (see

above) slowly via pipette at room temperature. After 30 min, the resulting dark red solution was heated at 55 °C for an additional 17.5 h. The reaction was concentrated under reduced pressure, then was diluted with water and extracted with ethyl acetate (4X). The organic layers were over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by reversed phase prep. HPLC (Sunfire Prep C_{18} OBD 10 μm column (Waters, Milford, MA), gradient elution of 40% MeCN in water to 55% MeCN in water over a 35 min period, where both solvents contain 0.1% TFA) provided the title compound (single enantiomer) as a white solid. [Note that the desired C-3 (3S) epimer is the less polar epimer and elutes off second].

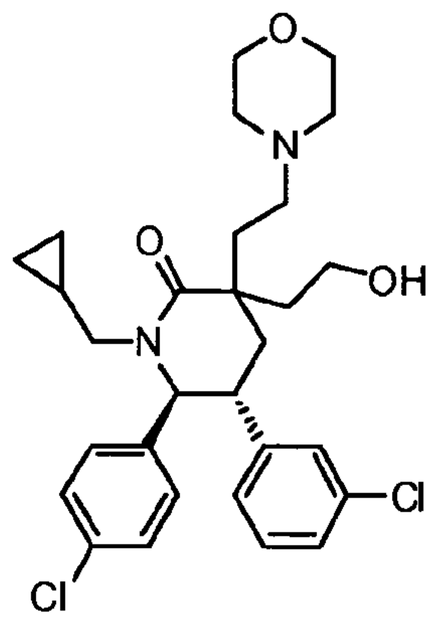
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 11.11 (1 H, br s), 7.18-7.24 (2 H, m), 7.08-7.18 (2 H, m), 6.99 (1 H, br s), 6.77-6.87 (3 H, m), 4.61 (1 H, dd, *J* = 10.1 Hz, 4.7 Hz), 3.72-3.86 (3 H, m), 3.61 (1 H, br s), 3.36 (1 H, br s), 3.13 (1 H, br s), 2.75-2.97 (4 H, m), 2.20-2.35 (2 H, m), 1.99-2.22 (7 H, m), 0.84 (1 H, br s), 0.36-0.54 (2 H, m), -0.05-0.13 (2 H, m). Mass Spectrum (ESI) m/z = 529 (M+1).

EXAMPLE 70



2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-(2-morpholinoethyl)-2-oxopiperidin-3-yl)acetic acid

Step A. (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-(2-hydroxyethyl)-3-(2-morpholinoethyl)piperidin-2-one



A mixture of 94 mg (0.15 mmol) of crude 2-((5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3-(2-(triisopropylsilyloxy)ethyl)piperidin-3-yl)acetaldehyde (Example 69, Step B, mixture of diastereomers), 66 μL (0.76 mmol) of morpholine, 97 mg (0.46 mmol) of sodium triacetoxyborohydride and 30 μL (0.53 mmol) of acetic acid was suspended in a mixture of 1,2-dichloroethane (6 mL) and DMF (2 mL). After being stirred at room temperature for 20 h, the reaction mixture was quenched with saturated aqueous sodium bicarbonate and extracted with DCM (3X). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by reversed phase preparatory HPLC (SunFire™ Prep C_{18} OBD 10 μm column (Waters, Milford, MA), gradient elution of 50% MeCN in water to 90% MeCN in water over a 30 min period, where both solvents contain 0.1% TFA) provided the title compound (mixture of C-3 epimers) along with the corresponding TIPS ether (mixture of C-3 epimers) and the corresponding trifluoroacetate (mixture of C-3 epimers) as a colorless oil.

This mixture was dissolved in THF (5 mL) and treated with 0.76 mL (0.76 mmol) of a 1M solution of TBAF in THF. After being stirred at room temperature for 3.5 h, the reaction mixture was quenched with water and extracted with EtOAc (3X). The combined organic layers were dried (Na_2SO_4), and concentrated under the reduced pressure. Purification of the residue by flash chromatography on silica gel (8-35% MeOH/DCM, gradient elution) provided the title compound (mixture of C-3 epimers) as a white solid.

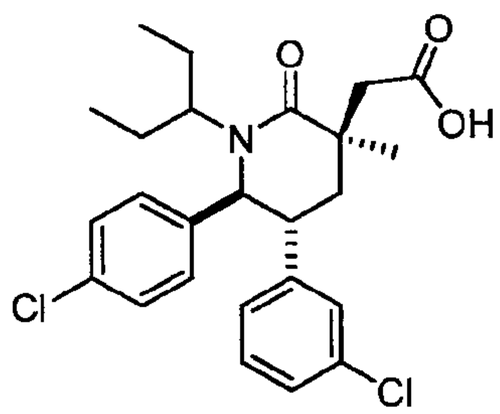
Step B. 2-((3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-(2-morpholinoethyl)-2-oxopiperidin-3-yl)acetic acid

An ice-cooled solution of 403 mg (4.03 mmol) of chromium(VI) oxide in water (1 mL) was treated with 343 μL (6.44 mmol) of sulfuric acid via syringe. The solution was diluted

with additional water (1 mL) and stored at 0 °C at prior to use. In a separate flask, (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-(2-hydroxyethyl)-3-(2-morpholinoethyl)piperidin-2-one (Example 70, Step A, mixture of diastereomers) was dissolved in acetone (5 mL) and then treated with Jones reagent (see above) slowly via pipette at room temperature. After 30 min, the resulting dark red solution was heated at 55 °C for an additional 17 h. The reaction was concentrated under reduced pressure, then was diluted with water and extracted with ethyl acetate (3X). The organic layers were over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by reversed phase prep. HPLC (SunFire™ Prep C_{18} OBD 10 μm column (Waters, Milford, MA), gradient elution of 40% MeCN in water to 60% MeCN in water over a 35 min period, where both solvents contain 0.1% TFA) provided the title compound (single enantiomer) as a white solid. [Note that the desired (3S) C-3 epimer is the less polar epimer and elutes off second].

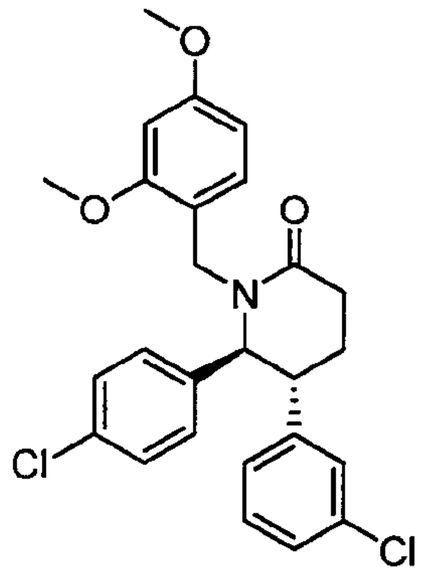
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 12.05 (1 H, br s), 6.95-7.26 (5 H, m), 6.76-6.88 (3 H, m), 4.64 (1 H, d, J = 10.0 Hz), 4.23 (1 H, br s), 3.76-4.10 (5 H, m), 3.43-3.65 (2 H, m), 3.08-3.34 (2 H, m), 2.78-3.01 (3 H, m), 2.41-2.76 (2 H, m), 2.26-2.39 (2 H, m), 2.08-2.24 (2 H, m), 0.85 (1 H, br s), 0.33-0.55 (2 H, m), -0.10-0.15 (2 H, m). Mass Spectrum (ESI) m/z = 545 (M+1).

EXAMPLE 71



2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid

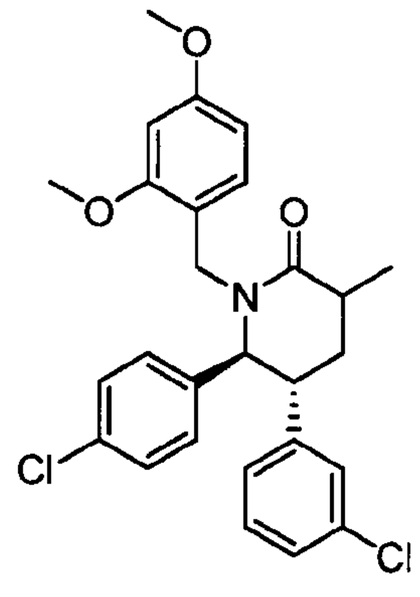
Step A. (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,4-dimethoxybenzyl)piperidin-2-one.



Thionyl chloride (116 mL, 1586 mmol) was added dropwise over 1 hour to a turbid solution of (2,4-dimethoxyphenyl)methanol (97.00 g, 577 mmol) and pyridine (93 mL, 1153 mmol) in anhydrous Et_2O (1153 mL) at 0 °C under nitrogen with mechanical stirring. After 1 hour the reaction mixture was poured into 2 L of ice water and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 1 L) and the organics were pooled, washed with ice water (1.2 L), cold 5:1 sat. aq. NaCl solution/sat. aq. $NaHCO_3$ (1.2 L), dried ($MgSO_4$), filtered and most of the ether was removed in vacuo at 12 °C. Benzene (300 mL) was added and the mixture was concentrated at 12 °C until 100 mL of benzene remained to provide a solution of 1-(chloromethyl)-2,4-dimethoxybenzene.

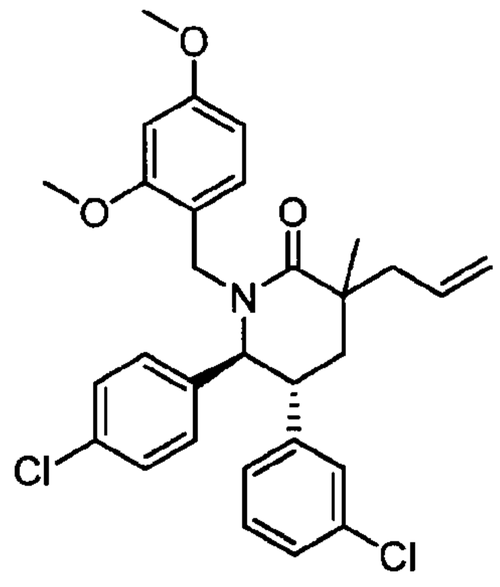
80g (250 mmol) of (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one (Example 1, Step E) was added in portions over 20 minutes to a mixture of NaH (19.98 g, 500 mmol) in anhydrous DMF (400 mL) at 0 °C under nitrogen. After the addition was complete the ice bath was removed and the mixture was stirred at rt for 1 hour before cooling the solution to 0 °C. To the cooled solution was added a solution of 1-(chloromethyl)-2,4-dimethoxybenzene (107 g, 575 mmol) in benzene and the reaction mixture was allowed to warm to rt. After 16 hours the reaction mixture was poured into ice water (2 L) and extracted with EtOAc (3 x 1 L). The organics were pooled, washed with water (3 x 1 L), sat. aq. NaCl solution (1 L), dried ($MgSO_4$), filtered and concentrated in vacuo to provide a thick yellow oil. Purification on the Combiflash XL (flash column chromatography, Teledyne Isco, Lincoln, NE) using four stacked 330 g columns and one 1.5 kg column and eluting with 35-40-45-50-55% EtOAc/hexanes provided a very pale yellow oil. This was dissolved in benzene and the solvent removed in vacuo and dried under vacuum for 2 days to provide the title compound as a white foam (105.8 g, 90%).

Step B. (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,4-dimethoxybenzyl)-3-methylpiperidin-2-one.



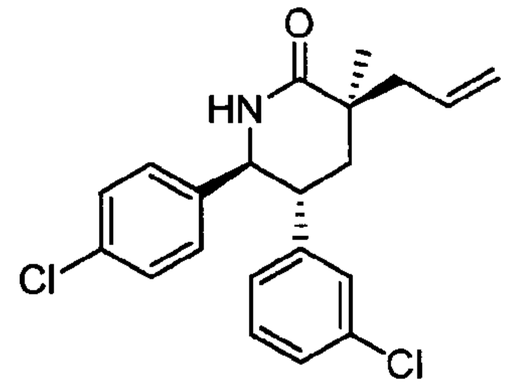
A solution of (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,4-dimethoxybenzyl) piperidin-2-one (Example 71, Step A) (140.34 g, 298 mmol) in anhydrous THF (994 mL) was degassed by bubbling argon through the solution for 20 minutes while it cooled to -78 °C. Iodomethane (23.32 mL, 373 mmol) was added followed by the addition of LHMDS (328 mL, 328 mmol) over 15 minutes. The reaction mixture was stirred for 15 minutes at -78 °C and then the reaction was removed from the cold bath and stirred at rt for 12 hours. The reaction was quenched by the addition of sat. aq. NH_4Cl and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 500 mL) and the organics were pooled, washed with sat. aq. NaCl solution, dried ($MgSO_4$), filtered and concentrated in vacuo to provide an orange oil. Purification (wet loaded with small amount of DCM) using the Combiflash Companion XL (flash column chromatography, Teledyne Isco, Lincoln, NE) with a 1.5 kg SiO_2 column and eluting with 4 L each of 15-20-25-30-35% EtOAc/hexanes provided the title compound as a thick very pale yellow oil and a 3.7:1 mixture of C-3 diastereomers.

Step C. (5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,4-dimethoxybenzyl)-3-methylpiperidin-2-one.



A solution of (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,4-dimethoxybenzyl)-3-methylpiperidin-2-one (Example 71, Step B, mixture of C-3 diastereomers) (117.0 g, 242 mmol) in anhydrous THF (966 mL) was degassed by bubbling argon through the solution for 20 minutes. Allyl bromide (105 mL, 1208 mmol) was added followed by the addition of LHMDS (725 mL, 725 mmol) over 20 minutes. The reaction mixture was heated at 40 °C under argon for 5 hours. The reaction mixture was cooled to rt. and the reaction was quenched by the addition of sat. aqueous NH_4Cl (500 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 1 L) and the organics were pooled, washed with sat. aq. NaCl solution (1 L), dried ($MgSO_4$), filtered and concentrated in vacuo to provide a red oil (180 g). Purification using the Biotage system (Charlotte, NC) with a 1.5 kg SiO_2 column and eluting with 10-30% EtOAc/hexanes provided the title compound as a very pale yellow oil as a 3.7:1 mixture of (3S):(3R) diastereomers. .

Step D. (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one.

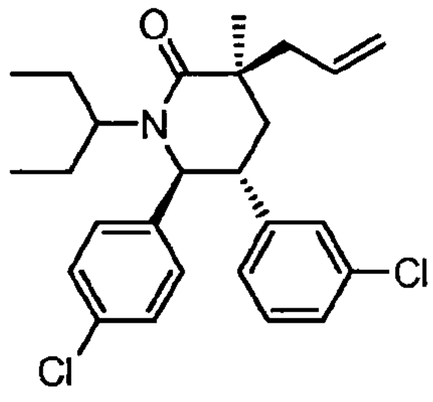


A solution of (5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,4-dimethoxybenzyl)-3-methylpiperidin-2-one (Example 71, Step C, mixture of diastereomers) (105.87 g, 202 mmol) in TFA (778 mL, 1.01E+04 mmol) was heated at 50 °C for 2 hours before concentrating the reaction mixture in vacuo. The residue was azeotroped with hexanes to remove all of the TFA. The deep purple oil containing some residue was taken up in a minimum amount of DCM, filtered and washed liberally with DCM. The filtrate was

concentrated in vacuo to provide a dark purple oil. Purification (wet packed with a minimum amount of DCM) using the Biotage Isolera (Biotage, Charlotte, NC) with a 1.5 kg column and eluting with 25-40% EtOAc/hexanes provided the title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.30 (s, 3H), 2.06 (m, 2H), 2.52 (dd, J = 13.7 and 7.1 Hz, 1H), 2.60 (dd, J = 13.7 and 7.8 Hz, 1H), 3.06 (m, 1H), 4.50 (d, J = 10.7 Hz, 1H), 5.17 (m, 2H), 5.81 (br s, 1H), 5.86 (m, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 8.3 Hz, 2H), 7.00 (s, 1H), 7.12 (t, J = 7.7 Hz, 1H), 7.17 (m, 1H), 7.20 (d, J = 8.3 Hz, 2H). [ ]$^{22}_D$ +182.2° (*c* 1.55, $CHCl_3$).

Step E. (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(pentan-3-yl)piperidin-2-one



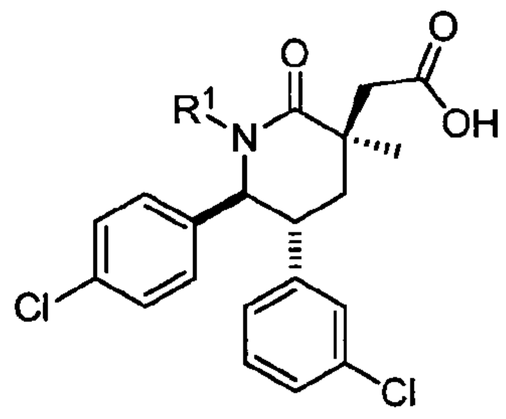
To a suspension of 1.81 g (4.8 mmol) of (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one (Example 71, Step D) in 3-bromopentane (17.6 mL) added 967 mg (60 wt. % in mineral oil, 24.2 mmol) of sodium hydride. The resulting milky white slurry was heated at 120 °C for 20 h, and then more 3-bromopentane (5.1 mL) was added. After an additional 24 h at 120 °C, the reaction was cooled to room temperature and quenched with saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by flash chromatography on silica gel (2 to 26% EtOAc/hexanes, gradient elution) provided the title compound as a white solid.

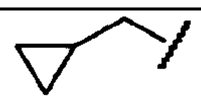
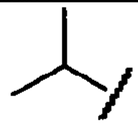
Step F. Synthesis of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid

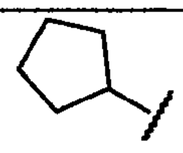
To a solution of 725 mg (1.63 mmol) of (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(pentan-3-yl)piperidin-2-one (Example 3, Step A) in a mixture of acetonitrile (4 mL), carbon tetrachloride (4 mL) and water (5.9 mL) added 1.40 g (6.53 mmol) of sodium periodate followed by 44 mg (0.20 mmol) of ruthenium(III) chloride hydrate. The dark brown biphasic mixture was stirred vigorously at room temperature for 21 h, and then was acidified with 1 N HCl. The mixture was diluted with EtOAc and filtered through a pad of Celite® (J.T. Baker, Phillipsberg, NJ, diatomaceous earth). After filtration, the layers were separated and the aqueous layer was extracted with EtOAc (1X). The combined organic layers were washed with saturated aqueous sodium chloride (1X), then were dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by flash chromatography on silica gel (0 to 25% MeOH/DCM, gradient elution) provided the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.06-7.27 (5 H, m), 6.90-7.01 (2 H, m), 6.68 (d, 1 H, J = 7.8 Hz), 4.34 (1 H, d, J = 10.4 Hz), 3.00-3.15 (2 H, m), 2.63-2.79 (2 H, m), 2.15-2.27 (1 H, m), 1.85-2.03 (3 H, m), 1.51 (s, 3 H), 1.38-1.51 (2 H, m), 0.95 (3 H, t, J = 7.4 Hz), 0.50 (3 H, t, J = 7.4 Hz). Mass Spectrum (ESI) m/z = 462 (M+1).

Examples 72 – 75 were prepared in a process similar to that described for Example 71, substituting 3-bromopentane in Step E for the appropriate amount of alkylhalide.



Example	R^1
72	
73	
74	

75	

EXAMPLE 72

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopropylmethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.29 (2 H, d, *J* = 8.6 Hz), 7.12 – 7.24 (3 H, m), 6.90 (2 H, d, J = 8.6 Hz), 6.88 – 6.82 (1 H, m), 4.80 (1 H, d, *J* = 8.4 Hz), 4.02 (1 H, dd, *J* = 14.1, 6.8 Hz), 3.11 – 3.03 (1 H, m), 2.98 (1 H, d, *J* = 15.5 Hz), 2.68 (1 H, d, *J* = 15.5 Hz), 2.37 (1 H, dd, *J* = 14.1, 7.4 Hz), 2.23 – 2.14 (1 H, m), 2.13 – 2.05 (1 H, m), 1.39 (3 H, s), 1.03 – 0.94 (1 H, m), 0.62 – 0. 46 (2 H, m), 0.23 – 0.08 (1 H, m); MS (ESI) 446.0 $[M + H]^+$, 444.1 $[M - H]^-$.

EXAMPLE 73

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methyl-2-oxopiperidin-3-yl)acetic acid

1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.27 (2 H, d, *J* = 7.8 Hz), 7.14 – 7.20 (2 H, m), 7.02 (1 H, s), 6.97 (2 H, d, *J* = 7.8 Hz), 6.75 (1 H, d, *J* = 7.6 Hz), 4.49 (1 H, d, *J* = 9.0 Hz), 3.45 (1 H, m), 3.08 (1 H, m), 2.98 (1 H, d, *J* = 15.2 Hz), 2.77 (1 H, d, *J* = 15.2 Hz), 2.08 (2 H, m), 1.38 (3 H, s), 1.24 (6 H, t, *J* = 6.7 Hz); MS (ESI) 434.0 $[M + H]^+$.

EXAMPLE 74

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-cyclobutyl-3-methyl-2-oxopiperidin-3-yl)acetic acid

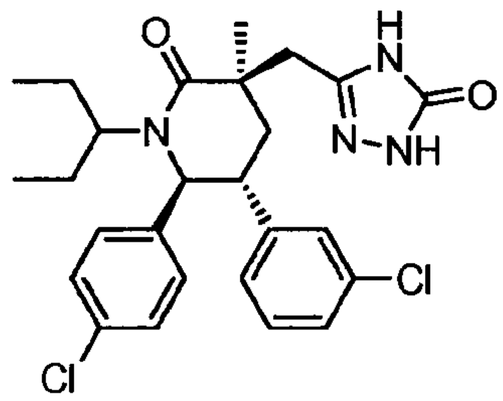
1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.15-7.26 (3 H, m), 7.17 (1 H, m), 7.04 (1 H, s), 6.65-6.79 (3 H, m), 4.65 (1 H, d, *J* = 8.8 Hz), 3.85 (1 H, m), 3.05 (1 H, d, *J* = 15.8 Hz), 2.85 (1 H, m), 2.60 (1 H, d, *J* = 15.8 Hz), 2.45 (1 H, m), 2.20 (1 H, m), 1.90-2.2.20 (2 H, m), 1.65 (1 H, m), 1.42-1.55 (3 H, m), 1.42 (3 H, s); MS (ESI) 446.0 $[M + H]^+$.

EXAMPLE 75

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-cyclopentyl-3-methyl-2-oxopiperidin-3-yl)acetic acid

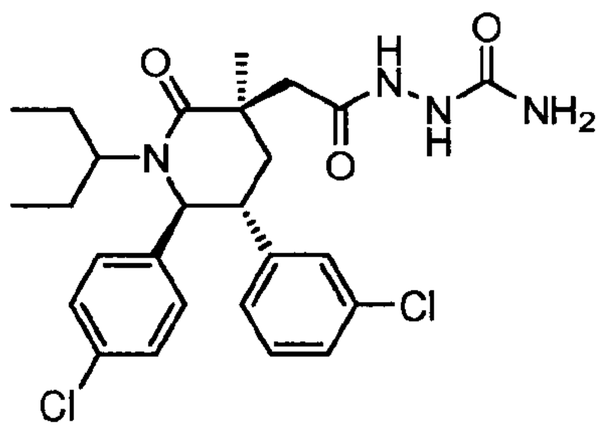
1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.28 (2 H, d, *J* = 8.3 Hz), 7.14 – 7.25 (2 H, m), 7.06 (1 H, s), 6.93 (2 H, d, *J* = 8.3 Hz), 6.80 (1 H, d, *J* = 7.6 Hz), 4.63 (1 H, d, *J* = 8.1 Hz), 3.40 (1 H, m), 3.03 (1 H, d, *J* = 15.7 Hz), 3.02 (1 H, m), 2.62 (1 H, d, *J* = 15.7 Hz), 1.75-2.13 (7 H, m), 1.26-1.45 (3 H, m), 1.33 (3 H, s); MS (ESI) 460.1 $[M + H]^+$.

EXAMPLE 76



(3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-((5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)-1-(pentan-3-yl)piperidin-2-one

Step A. 2-(2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetyl)hydrazinecarboxamide



To a solution of 320 mg (0.69 mmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid (Example 71, Step F) and 921 mg (2.42 mmol) of HOBt in DMF (13 mL) was added 0.58 mL (4.15 mmol) of

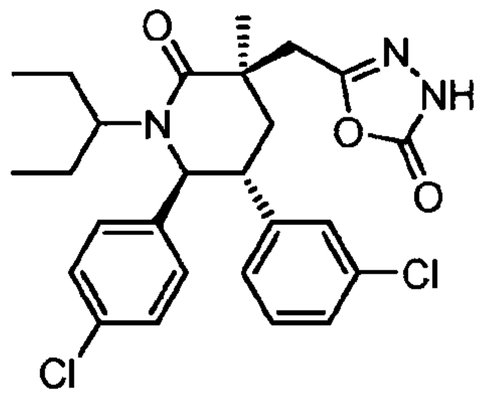
triethylamine. After stirring at room temperature for 40 min, added 270 mg (2.42 mmol) of semicarbazide hydrochloride. The resulting dark red solution was stirred at room temperature for 2.5 h, and then was concentrated under reduced pressure. Purification of the residue by reversed phase prep. HPLC (Sunfire™ Prep C_{18} OBD 10 μm column (Waters, Milford, MA), gradient elution of 40% MeCN in water to 90% MeCN in water over a 30 min period, where both solvents contain 0.1% TFA) provided the title compound as a light yellow solid.

Step B. (3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-((5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)-1-(pentan-3-yl)piperidin-2-one

259 mg (0.50 mmol) of 2-(2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetyl)hydrazinecarboxamide (Example 76, Step A) was suspended in 2 N aqueous sodium hydroxide (16 mL) and heated at reflux for 3.25 h. Upon cooling to room temperature, the mixture was acidified with conc. HCl until strongly acidic and then extracted with EtOAc (3X). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by reversed phase prep. HPLC (Sunfire™ Prep C_{18} OBD 10 μm column (Waters, Milford, MA), gradient elution of 40% MeCN in water to 75% MeCN in water over a 30 min period, where both solvents contain 0.1% TFA) provided the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.36 (1 H, br s), 9.35 (1 H, br s), 7.20-7.27 (3 H, m), 7.05-7.17 (2 H, m), 6.86-6.95 (2 H, m), 6.68 (1 H, d, *J* = 7.8 Hz), 4.34 (1 H, d, *J* = 10.5 Hz), 2.90-3.09 (3 H, m), 2.68-2.76 (1 H, m), 2.21 (1 H, t, *J* = 13.8 Hz), 2.05 (1 H, dd, *J* = 13.9 Hz, 2.9 Hz) 1.85-1.99 (2 H, m), 1.37-1.52 (2 H, m), 1.36 (3 H, s), 0.94 (3 H, t, *J* = 7.4 Hz), 0.50 (3 H, t, *J* = 7.5 Hz). Mass Spectrum (ESI) m/z = 501 (M+1), 523 (M+23).

EXAMPLE 77

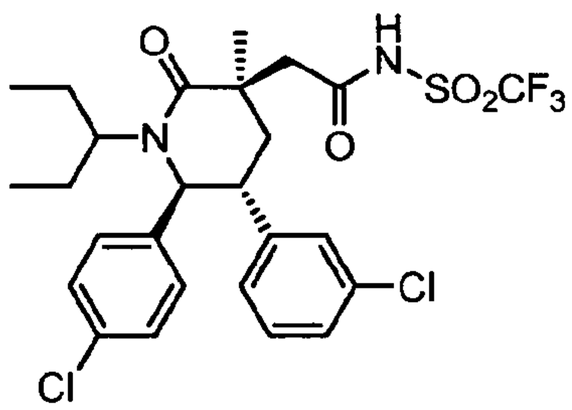


5-(((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)methyl)-1,3,4-oxadiazol-2(3H)-one

A solution of 56 mg (0.19 mmol) of triphosgene in DCM (1 mL) was added dropwise to a solution of 62 mg (0.13 mmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetohydrazide (obtained as a byproduct in Example 76, Step B) and 170 μL (0.98 mmol) of diisopropylethylamine in DCM (4 mL). The resulting light yellow solution was stirred at room temperature for 18 h, then was quenched with saturated aqueous sodium bicarbonate and extracted with EtOAc (3X). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by reversed phase preparative HPLC (Sunfire™ Prep C_{18} OBD 10 μm column, (Waters, Milford, MA) gradient elution of 40% MeCN in water to 75% MeCN in water over a 30 min period, where both solvents contain 0.1% TFA) provided the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.68 (1 H, br s), 7.08-7.27 (4 H, m), 6.90-7.01 (3 H, m), 6.70 (1 H, d, J = 7.4 Hz), 4.35 (1 H, d, J = 10.4 Hz), 3.01-3.15 (3 H, m), 2.70-2.79 (1 H, m), 2.15 (1 H, t, J = 13.8 Hz), 2.01 (1 H, dd, J = 13.8 Hz, 3.1 Hz) 1.82-1.95 (2 H, m), 1.35-1.57 (2 H, m), 1.43 (3 H, s), 0.93 (3 H, t, J = 7.4 Hz), 0.51 (3 H, t, J = 7.4 Hz). Mass Spectrum (ESI) m/z = 502 (M+1).

EXAMPLE 78

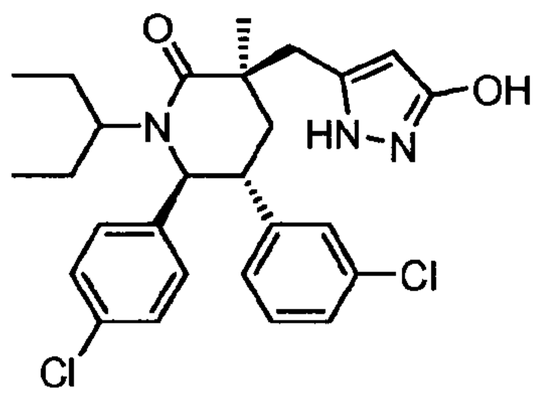


2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)-N-(trifluoromethylsulfonyl)acetamide

To a solution of 47 mg (0.10 mmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid (Example 71, Step F) in DMF (4 mL) was added 64 mg (0.34 mmol) of EDC, 48 mg (0.36 mmol) of HOBt, and a catalytic amount of DMAP. After 30 min, 45.5 mg (0.30 mmol) of trifluoromethanesulfonamide was added. The resulting light yellow solution was stirred at room temperature for 3 h, and then was concentrated under reduced pressure. Purification of the residue by reversed phase prep. HPLC (Sunfire™ Prep C_{18} OBD 10 μm column (Waters, Milford, MA), gradient elution of 50% MeCN in water to 90% MeCN in water over a 30 min period, where both solvents contain 0.1% TFA) provided the title compound as a white solid.

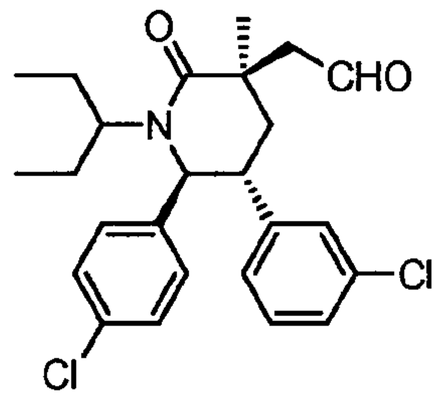
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.25-7.32 (3 H, m), 7.16-7.20 (1 H, m), 7.11 (t, 1 H, J = 7.8 Hz), 6.92-7.00 (2 H, m), 6.67 (d, 1 H, J = 7.6 Hz), 4.35 (1 H, d, J = 10.4 Hz), 3.19 (d, 1 H, J = 15.7 Hz), 2.97-3.06 (1 H, m), 2.73-2.83 (1 H, m), 2.68 (1 H, d, J = 15.7 Hz), 2.26 (1 H, t, J = 13.8 Hz), 1.86-2.08 (3 H, m), 1.52 (3 H, s), 1.39-1.52 (2 H, m), 0.95 (3 H, t, J = 7.4 Hz), 0.50 (3 H, t, J = 7.4 Hz). Mass Spectrum (ESI) m/z = 593 (M+1), 615 (M+23).

EXAMPLE 79



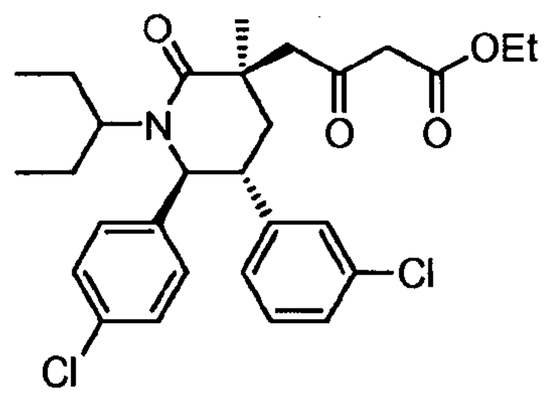
(3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-((3-hydroxy-1H-pyrazol-5-yl)methyl)-3-methyl-1-(pentan-3-yl)piperidin-2-one

Step A. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetaldehyde



To a solution of 240 mg (0.54 mmol) of (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(pentan-3-yl)piperidin-2-one (Example 71, Step E) in THF (8 mL) and water (2.8 mL) added a catalytic amount of osmium tetroxide. After 1.25 h, 323 mg (1.51 mmol) of sodium periodate were added. The resulting light brown slurry was stirred at room temperature for 18.5 h, and then filtered through a fritted funnel. The filtrate was partially concentrated under reduced pressure, then was diluted with water and extracted with ethyl acetate (2X). The combined organic layers were washed with saturated aqueous sodium thiosulfate and then saturated aqueous sodium chloride. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated. The crude title compound was used directly in the next step.

Step B. Ethyl 4-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)-3-oxobutanoate



To a suspension of 160 mg (0.36 mmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetaldehyde (Example 79, Step A) and 20.4 mg (0.11 mmol) of tin(II) chloride in DCM (6 mL) was added 104 μL (1.00 mmol) of ethyl diazoacetate via syringe over 3 min. The resulting yellow slurry was stirred at room temperature for 14.25 h, then was quenched with 1 N HCl and extracted with EtOAc (2X). The combined organic layers were washed with 1 N HCl (1X), then were dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by reversed phase prep. HPLC (Sunfire™ Prep C_{18} OBD 10 μm column (Waters, Milford, MA), gradient elution

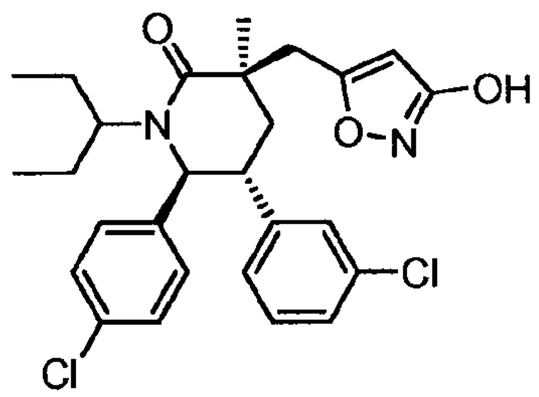
of 55% MeCN in water to 85% MeCN in water over a 30 min period, where both solvents contain 0.1% TFA) provided the title compound as a light yellow oil.

Step C. (3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-((3-hydroxy-1H-pyrazol-5-yl)methyl)-3-methyl-1-(pentan-3-yl)piperidin-2-one

To a solution of 42 mg (0.08 mmol) of ethyl 4-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)-3-oxobutanoate (Example 79, Step B) in ethanol (4 mL) was added 36 μL (0.48 mmol) hydrazine monohydrate (64-65% weight percent hydrazine). The resulting colorless solution was heated at 65 °C for 3.5 h, and then was concentrated under reduced pressure. Purification of the residue by reversed phase prep. HPLC (Sunfire Prep C_{18} OBD 10 μm column, gradient elution of 45% MeCN in water to 80% MeCN in water over a 30 min period, where both solvents contain 0.1% TFA) provided the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.23-7.30 (3 H, m), 7.18-7.22 (1 H, m), 7.12 (1 H, t, *J* = 7.7 Hz), 6.90-6.96 (2 H, m), 6.67 (1 H, d, *J* = 7.8 Hz), 5.66 (1 H, s), 4.34 (1 H, d, *J* = 10.6 Hz), 3.42 (1 H, d, *J* = 15.9 Hz), 3.02-3.11 (1 H, m), 2.82 (1 H, d, *J* = 15.9 Hz), 2.68-2.77 (1 H, m), 2.36 (1 H, t, *J* = 13.9 Hz), 1.87-2.03 (3 H, m), 1.40-1.51 (2 H, m), 1.36 (3 H, s), 0.96 (3 H, t, *J* = 7.4 Hz), 0.50 (3 H, t, *J* = 7.5 Hz). Mass Spectrum (ESI) m/z = 500 (M+1), 522 (M+23).

EXAMPLE 80



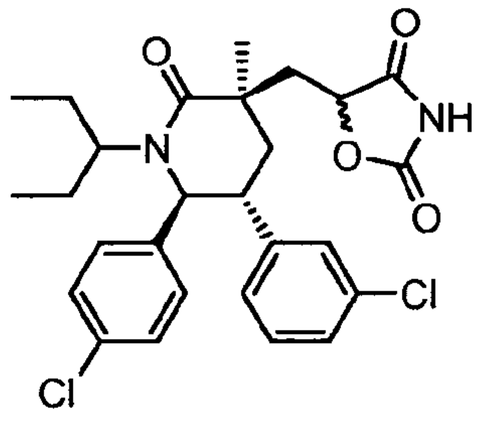
(3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-((3-hydroxyisoxazol-5-yl)methyl)-3-methyl-1-(pentan-3-yl)piperidin-2-one

To an ice-cooled slurry of 65 mg (0.12 mmol) of ethyl 4-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)-3-oxobutanoate (Example 79, Step B) in water (2 mL) was added 53.5 mg (0.77 mmol) of

hydroxylamine hydrochloride and 62 mg (1.55 mmol) of sodium hydroxide. After 5 min, THF (1 mL) and MeOH (1 mL) were added. The resulting cloudy light yellow solution was stirred at 0 °C for 20 min, then was warmed to room temperature and stirred for an additional 6 h. The reaction was acidified by dropwise addition of conc. HCl until strongly acidic, then was diluted with water and extracted with EtOAc (4X). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by reversed phase prep. HPLC (Sunfire™ Prep C_{18} OBD 10 μm column (Waters, Milford, MA), gradient elution of 55% MeCN in water to 85% MeCN in water over a 30 min period, where both solvents contain 0.1% TFA) provided the title compound as a white solid.

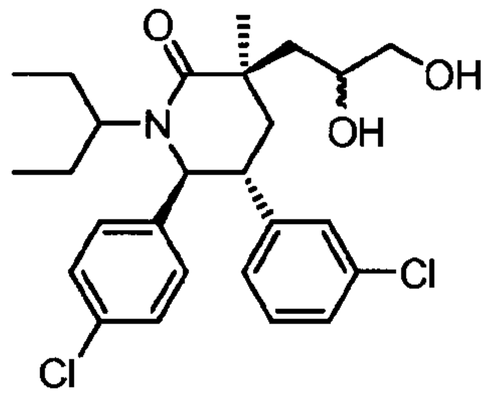
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.20-7.27 (3 H, m), 7.14-7.20 (1 H, m), 7.11 (1 H, dt, *J* = 7.8 Hz, 3.8 Hz), 6.89-7.01 (3 H, m), 6.70 (1 H, d, *J* = 7.4 Hz), 4.33 (1 H, dd, *J* = 10.5 Hz, 3.4 Hz), 3.59-3.78 (2 H, m), 3.13-3.23 (1 H, m), 3.07 (1 H, dd, *J* = 14.1 Hz, 3.1 Hz), 2.66-2.77 (2 H, m), 2.15-2.26 (1 H, m), 1.96-2.04 (1 H, m), 1.78-1.94 (2 H, m), 1.40-1.51 (1 H, m), 1.41 (3 H, s), 0.93 (3 H, dt, *J* = 7.4 Hz, 3.5 Hz), 0.51 (3 H, dt, *J* = 7.5 Hz, 3.6 Hz). Mass Spectrum (ESI) m/z = 501 (M+1).

EXAMPLE 81



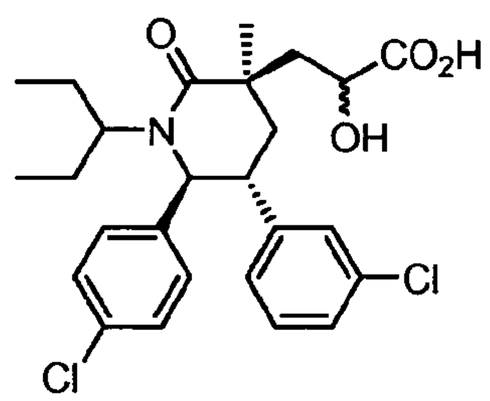
5-(((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)methyl)oxazolidine-2,4-dione

Step A. (3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-(2,3-dihydroxypropyl)-3-methyl-1-(pentan-3-yl)piperidin-2-one



To a solution of 298 mg (0.67 mmol) of (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-(pentan-3-yl)piperidin-2-one (Example 71, Step E) in a mixture of acetone (11.5 mL) and water (4 mL) added a catalytic amount of osmium tetroxide. After 4 min, 275 mg (2.35 mmol) of N-methylmorpholine-N-oxide was added. The resulting brown solution was stirred at room temperature for 3.5 h, and then was partitioned between water and DCM (3X). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by flash chromatography on silica gel (1 to 20% MeOH/DCM, gradient elution) provided the title compound (mixture of alcohol epimers) as a yellow oil.

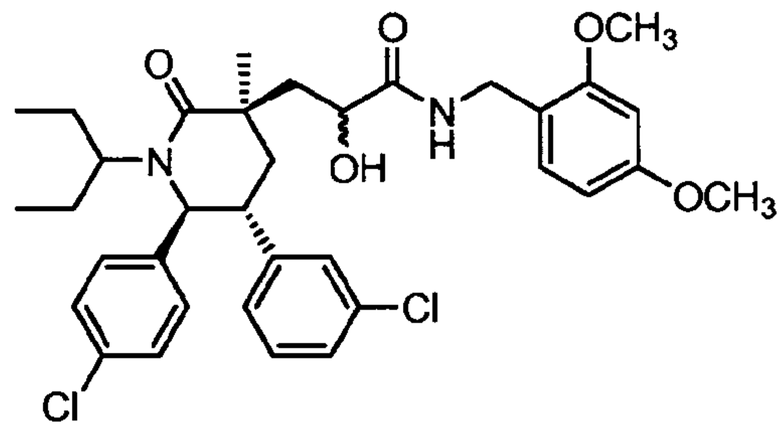
Step B. 3-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)-2-hydroxypropanoic acid



A mixture of 142 mg (0.30 mmol) of (3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-(2,3-dihydroxypropyl)-3-methyl-1-(pentan-3-yl)piperidin-2-one (Example 81, Step A) and 28 mg (0.18 mmol) of TEMPO in a mixture of acetonitrile (6 mL) and sodium phosphate-sodium hydroxide buffer (pH 6.7, 4.5 mL) at 35 °C was treated simultaneously with a solution of 105 mg (1.16 mmol) of sodium chlorite in water (1.2 mL) and a solution of 106 µL (0.07 mmol) of bleach solution (ca. 0.7 N) in water (0.6 mL) over 10 min. The resulting dark orange solution was stirred at 35 °C for 1.75 h, and then was partitioned between 1 N HCl and EtOAc (3X). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by reversed phase prep. HPLC (Sunfire™ Prep

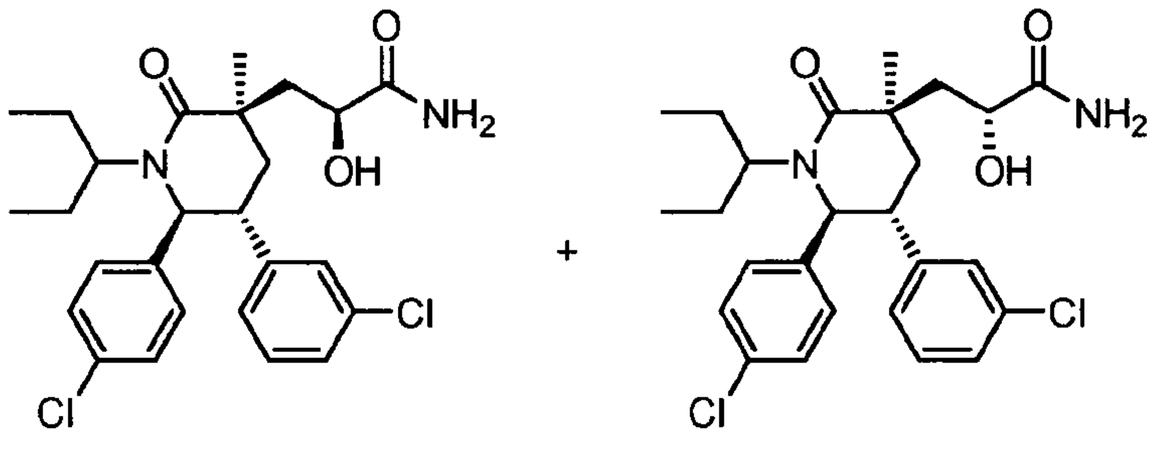
C_{18} OBD 10 μm column (Waters, Milford, MA), gradient elution of 60% MeCN in water to 80% MeCN in water over a 30 min period, where both solvents contain 0.1% TFA) provided the title compound (mixture of alcohol epimers) as a white solid.

Step C. 3-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)-N-(2,4-dimethoxybenzyl)-2-hydroxypropanamide



To a solution of 43 mg (0.09 mmol) of 3-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)-2-hydroxypropanoic acid (Example 81, Step B) in DMF (5 mL) was added 67 mg (0.18 mmol) of HATU, 58.5 mg (0.35 mmol) of 2,4-dimethoxybenzylamine and 36 μL (0.26 mmol) of triethylamine. The resulting yellow solution was stirred at room temperature for 1.1 h, and then was partitioned between saturated aqueous sodium bicarbonate and EtOAc (2X). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated. The crude title compound (mixture of alcohol epimers) was used directly in the next step.

Step D. (S)-3-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)-2-hydroxypropanamide and (R)-3-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)-2-hydroxypropanamide



A solution of 56 mg (0.09 mmol) of 3-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)-N-(2,4-dimethoxybenzyl)-2-hydroxypropanamide (Example 81, Step C) in trifluoroacetic acid (2.3 mL) was heated at 50 °C for 2.5 h, and then was concentrated under reduced pressure. Purification of the residue by reversed phase prep. HPLC (Sunfire™ Prep C_{18} OBD 10 μm column (Waters, Milford, MA), gradient elution of 50% MeCN in water to 75% MeCN in water over a 30 min period, where both solvents contain 0.1% TFA) provided the two title compounds (in each case the stereochemistry at alcohol stereocenter is arbitrarily assigned) each as a light green solid.

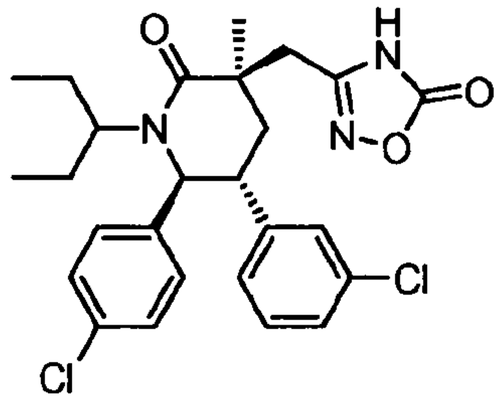
Step E. 5-(((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)methyl)oxazolidine-2,4-dione

To a solution of 10.3 mg (0.02 mmol) of (S)-3-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)-2-hydroxypropanamide (Example 81, Step D) in MeOH (2.5 mL) was added 0.50 mL (1.22 mmol) of sodium ethoxide (21 wt.% solution in ethanol) and 1.20 mL (9.90 mmol) of diethyl carbonate. The resulting mixture was heated at reflux for 15 min, and then was concentrated under reduced pressure. The residue was partitioned between 0.5 M HCl and EtOAc (3X). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by reversed phase prep. HPLC (Sunfire™ Prep C_{18} OBD 10 μm column (Waters, Milford, MA), gradient elution of 60 MeCN in water to 80 MeCN in water over a 30 min period, where both solvents contain 0.1% TFA) provided the title compound (mixture of ether epimers) as a white solid.

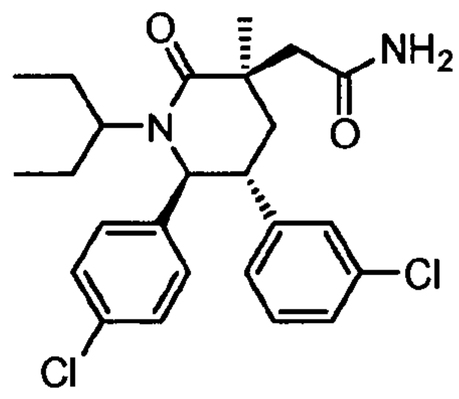
^{1}H NMR (400 MHz, $CDCl_3$, mixture of epimers) δ ppm 8.90 (1 H, br s, major epimer), 8.83 (1 H, br s, minor epimer), 7.20-7.27 (3 H, m), 7.15-7.20 (1 H, m), 7.11 (1 H, dt, *J* = 7.7 Hz, 1.9 Hz), 6.94-7.02 (2 H, m), 6.71 (1 H, d, *J* = 7.6 Hz), 5.37 (1 H, t, *J* = 10.0 Hz), 4.33 (1 H, d, *J* = 10.4 Hz), 2.67-2.79 (1 H, m), 2.67-2.79 (1 H, m, major epimer) 2.41 (1 H, dd, *J* = 15.2 Hz, 8.6 Hz, minor epimer), 1.82-2.31 (6 H, m), 1.48-1.61 (1 H, m), 1.35-1.45 (1 H, m), 1.45 (3 H, s, minor epimer), 1.44 (s, 3 H, major epimer), 0.94 (3 H, t, *J* = 7.4 Hz), 0.52 (3 H, t, *J* = 7.5 Hz). Mass Spectrum (ESI) m/z = 517 (M+1), 539 (M+23).

EXAMPLE 82

3-(((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)methyl)-1,2,4-oxadiazol-5(4H)-one

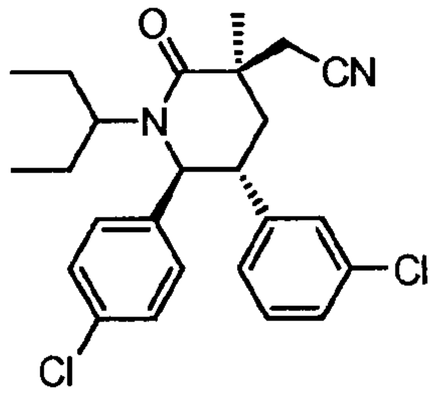


Step A. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3 yl)piperidin-3-yl)acetamide



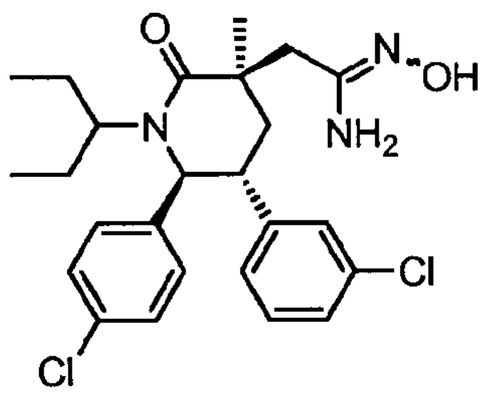
To an ice-cooled solution of 1.15 g (2.49 mmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid (Example 71, Step F) in THF (12.5 mL) was added 383 μL (3.48 mmol) of N-methylmorpholine and 392 μL (2.98 mmol) of isobutyl chloroformate. The resulting off-white slurry was stirred at 0 °C for 2 h, and then 336 μL (28% ammonia in water, 4.97 mmol) of ammonium hydroxide was added. After an additional 3 h at 0 °C, the reaction was quenched with saturated aqueous ammonium chloride and extracted with EtOAc (3X). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated. The crude title compound was used directly in the next step.

Step B. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetonitrile



To an ice-cooled solution of 1.15 g (2.49 mmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetamide (Example 82, Step A) in THF (21 mL) was added 1.73 mL (12.4 mmol) of triethylamine and 865 µL (6.22 mmol) of TFA. The resulting tan solution was stirred at 0 °C for 2.75 h, then was warmed to room temperature and stirred for an additional 2 h. The reaction was recooled to 0 °C, quenched with 1 N citric acid, and then extracted with EtOAc (3X). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated. The combined organic layers were washed with saturated aqueous sodium chloride (1X), then were dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by flash chromatography on silica gel (5 to 35% EtOAc/hexanes, gradient elution) provided the title compound as a white solid.

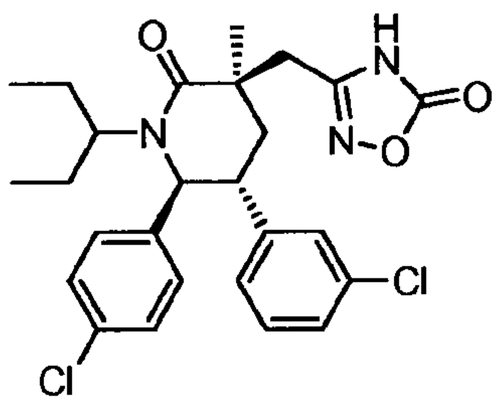
Step C. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)-N'-hydroxyacetimidamide



To a suspension of 1.49 g (20.6 mmol) of hydroxylamine hydrochloride in DMSO (10 mL) was added 2.88 mL (20.6 mmol) of triethylamine. The slurry was stirred for 5 min and then filtered twice through cotton, rinsing with THF, to remove the solids. The filtrate was partially concentrated under reduced pressure to remove THF, and then was added to a flask containing 915 mg (2.06 mmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetonitrile (Example 82, Step B). The resulting yellow solution was heated at 75 °C for 22 h, and then was partitioned between water and

EtOAc. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by flash chromatography on silica gel (1 to 7% MeOH/DCM, gradient elution) provided the title compound as a white solid.

Step D. 3-(((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)methyl)-1,2,4-oxadiazol-5(4H)-one

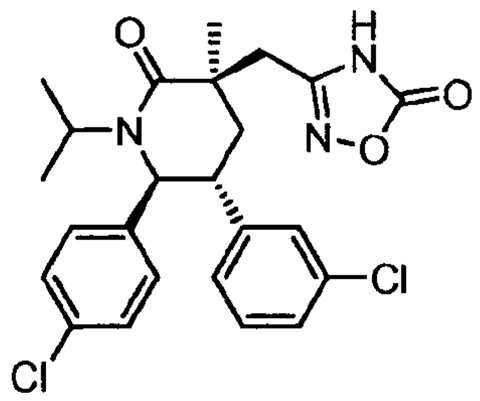


To a solution of 385 mg (0.81 mmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)-N'-hydroxyacetimidamide (Example 82, Step C) in dioxane (12.5 mL) was added 211 μL (1.41 mmol) of DBU and 262 mg (1.62 mmol) of 1,1'-carbonyldiimidazole. The resulting colorless solution was heated at 100 °C for 25 min, and then was quenched with water and extracted with EtOAc. The organic layer was washed with saturated aqueous sodium chloride, and then was dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by reversed phase prep. HPLC (Sunfire™ Prep C_{18} OBD 10 μm column (Waters, Mlford, MA), gradient elution of 55% MeCN in water to 80% MeCN in water over a 35 min period, where both solvents contain 0.1% TFA) provided the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.39 (1 H, br s), 7.22-7.27 (3 H, m), 7.18 (1 H, d, J = 8.1 Hz), 7.12 (1 H, t, *J* = 7.8 Hz), 6.87-6.98 (2 H, m), 6.68 (1 H, d, *J* = 7.6 Hz), 4.35 (1 H, d, *J* = 10.3 Hz), 3.19 (1 H, d, *J* = 15.4 Hz), 3.05 (1 H, ddd, *J* = 13.3 Hz, 10.5 Hz, 2.6 Hz), 2.82 (1 H, d, *J* = 15.4 Hz), 2.69-2.78 (1 H, m), 2.31 (1 H, t, *J* = 13.8 Hz), 2.06 (1 H, dd, *J* = 13.9 Hz, 2.7 Hz), 1.84-2.00 (2 H, m), 1.39-1.51 (2 H, m), 1.38 (3 H, s), 0.95 (3 H, t, *J* = 7.5 Hz), 0.50 (3 H, t, *J* = 7.5 Hz). Mass Spectrum (ESI) m/z = 502 (M+1), 524 (M+23).

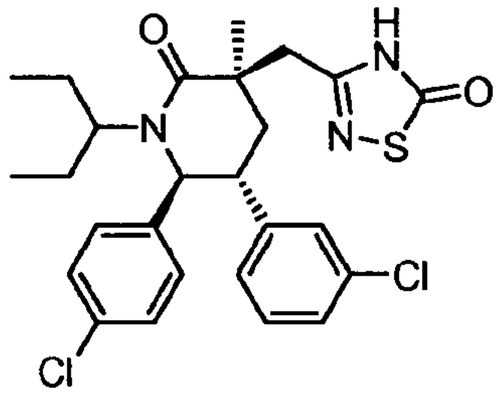
EXAMPLE 83

3-(((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methyl-2-oxopiperidin-3-yl)methyl)-1,2,4-oxadiazol-5(4H)-one



The title compound was prepared by methods similar to those described in Example 82. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.38 (1 H, br s), 7.24-7.32 (2 H, m), 7.18-7.23 (m, 1 H), 7.15 (1 H, dt, *J* = 7.8 Hz, 3.6 Hz), 7.04 (1 H, br s), 6.90 (2 H, d, *J* = 5.4 Hz), 6.76 (1 H, d, *J* = 7.1 Hz), 4.52 (1 H, dd, *J* = 8.6 Hz, 3.2 Hz), 3.40-3.50 (1 H, m), 3.09 (1 H, dd, *J* = 15.3 Hz, 2.8 Hz), 2.99-3.06 (1 H, m), 2.78 (1 H, dd, *J* = 15.3 Hz, 3.1 Hz), 2.18 (1 H, dt, *J* = 11.9 Hz, 3.2 Hz), 2.05-2.13 (1 H, m), 1.22-1.27 (m, 9 H). Mass Spectrum (ESI) m/z = 474 (M+1).

EXAMPLE 84



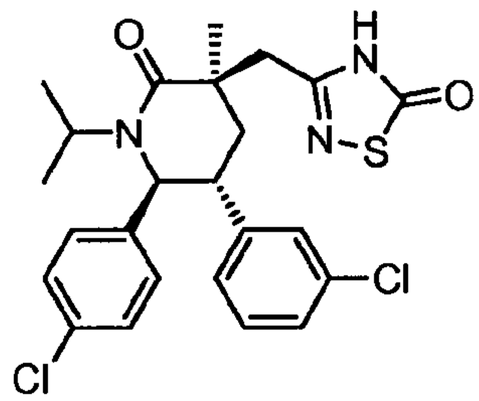
3-(((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)methyl)-1,2,4-thiadiazol-5(4H)-one

To a solution of 83 mg (0.17 mmol) of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)-N'-hydroxyacetimidamide (Example 82, Step C) in THF (4 mL) was added 50 mg (0.28 mmol) of 1,1'-thiocarbonyldiimidazole. The resulting yellow solution was stirred at room temperature for 1 h, and then was quenched with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated. The residue was dissolved in THF (4.5 mL), and 69 μL (0.56 mmol) of boron trifluoride etherate was added via syringe. The resulting light yellow solution was stirred at room temperature for 2.5 h, and then was quenched with

water and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by reversed phase prep. HPLC (Sunfire Prep C_{18} OBD 10 μm column, gradient elution of 55% MeCN in water to 85% MeCN in water over a 35 min period, where both solvents contain 0.1% TFA) provided the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.94 (1 H, br s), 7.20-7.27 (3 H, m), 7.13-7.18 (1 H, m), 7.09 (1 H, t, *J* = 7.7 Hz), 6.85-6.95 (2 H, m), 6.66 (1 H, d, *J* = 7.6 Hz), 4.34 (1 H, d, *J* = 10.2 Hz), 3.09 (1 H, d, *J* = 14.8 Hz), 2.87-3.01 (2 H, m), 2.68-2.77 (1 H, m), 2.25 (1 H, t, *J* = 13.5 Hz), 2.04-2.13 (1 H, m), 1.87-2.04 (2 H, m), 1.39-1.51 (2 H, m), 1.38 (3 H, s), 0.95 (3 H, t, *J* = 7.4 Hz), 0.50 (3 H, t, *J* = 7.4 Hz). Mass Spectrum (ESI) m/z = 518 (M+1), 540 (M+23).

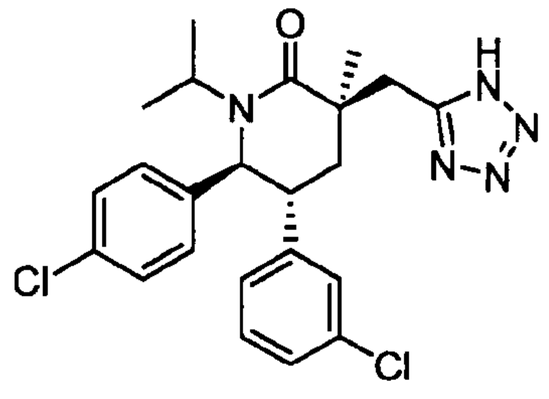
EXAMPLE 85



3-(((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methyl-2-oxopiperidin-3-yl)methyl)-1,2,4-thiadiazol-5(4H)-one

The title compound was prepared by methods similar to those described in Example 84. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.89 (1 H, br s), 7.24-7.30 (2 H, m), 7.18-7.22 (m, 1 H), 7.15 (1 H, t, *J* = 7.8 Hz), 7.04 (1 H, br s), 6.86 (2 H, d, *J* = 8.3 Hz), 6.77 (1 H, d, *J* = 7.8 Hz), 4.53 (1 H, d, *J* = 8.3 Hz), 3.41-3.50 (1 H, m), 2.90-3.04 (3 H, m), 2.05-2.19 (2 H, m), 1.27 (6 H, dd, J = 6.6 Hz, 6.6 Hz), 1.23 (s, 3 H). Mass Spectrum (ESI) m/z = 490 (M+1), 512 (M+23).

EXAMPLE 86



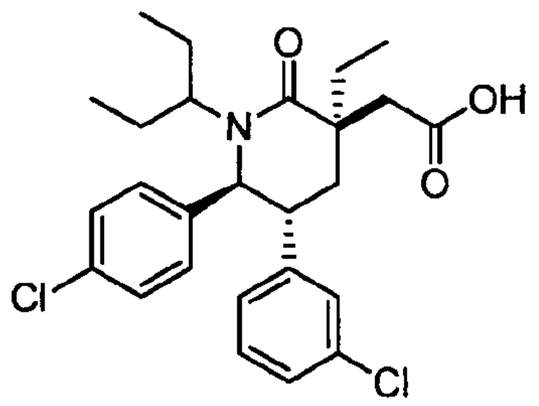
(3R,5R,6S)-3-((1H-Tetrazol-5-yl)methyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methylpiperidin-2-one

The title compound was prepared from 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-isopropyl-3-methyl-2-oxopiperidin-3-yl)acetic acid (Example 73) as described in Example 51.

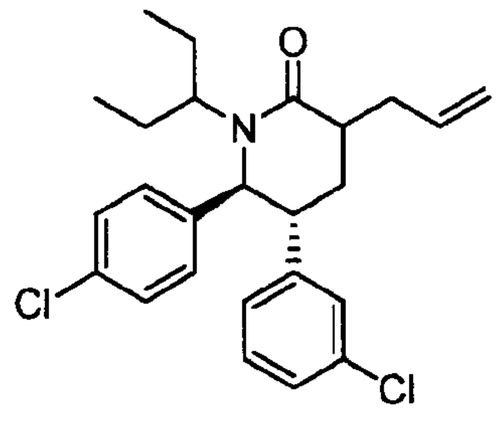
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.20 (s, 3H), 1.27 (d, J = 6.9 Hz, 3H), 1.29 (d, J = 6.8 Hz, 3H), 2.20 (m, 2H), 3.08 (m, 1H), 3.41 (d, J = 15.7 Hz, 1H), 3.47 (m, 1H), 3.50 (d, J = 15.6 Hz, 1H), 4.52 (d, J = 8.8 Hz, 1H), 6.78 (m, 3H), 7.06 (m, 1H), 7.16 (m, 1H), 7.23 (m, 3H). Mass spectrum (ESI) *m/z* 458.0 $[M + H]^+$.

EXAMPLE 87

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid

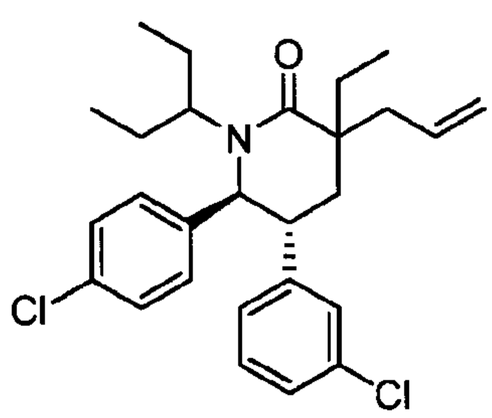


Step A. (5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-1-(pentan-3-yl)piperidin-2-one.



To a solution of (3R,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one (Example 42, Step A) (440 mg, 1.221 mmol) in 3-bromopentane (3196 μL, 25.6 mmol) under nitrogen at rt was added a dispersion of 60% sodium hydride in mineral oil (244 mg, 6.11 mmol). Evolution of gas was observed. The reaction was stirred at room temperature for 10 min and then heated to 120 °C under N_2 for 19 h. The reaction mixture was cooled to room temperature and quenched with sat. NH_4Cl. The layers were separated and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 0 to 25% EtOAc in hexanes) to give the title compound as a mixture of diastereomers.

Step B. (5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-1-(pentan-3-yl)piperidin-2-one.



To (5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(pentan-3-yl)piperidin-2-one (Example 87, Step A) (125 mg, 0.290 mmol) was added toluene (15 mL) and the mixture was concentrated under reduced pressure. This step was repeated three times. Inhibitor free THF (1 mL) was added and the mixture was cooled to -78 °C. Freshly prepared LDA (1.0M in THF) (290 μL, 0.290 mmol) was added and the reaction turned a golden-yellow color. The reaction was warmed to 0 °C for 30 min and the reaction color turned orange. The reaction was cooled to -78 °C and ethyl iodide (281 μL, 3.49 mmol) was added. The reaction mixture was warmed to 0 °C and stirred for 30 min. The reaction was quenched with sat. NH_4Cl,

warmed to room temperature, diluted with EtOAc and the layers were separated. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 0 to 10% EtOAc in hexanes) to give the title compound as a 1:1 mixture of diastereomers.

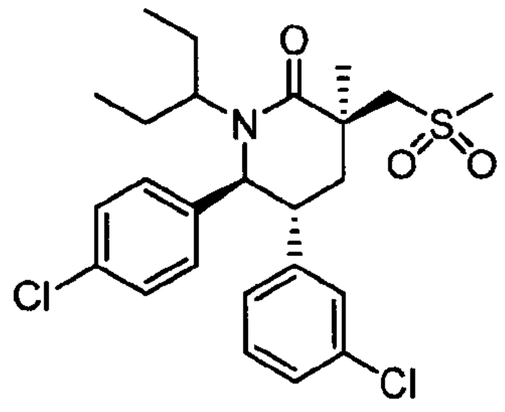
Step C. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-2-oxo-1-(pentan-3-yl)piperidin-3-yl)acetic acid

The title compound was prepared from (5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-ethyl-1-(pentan-3-yl)piperidin-2-one (Example 87, Step B) as described in Example 42, Step C. Purification by reversed phase preparatory HPLC (eluent: 0 to 100% MeCN +0.1% TFA in water + 0.1% TFA) provided the title compound as the first eluting diastereomer.

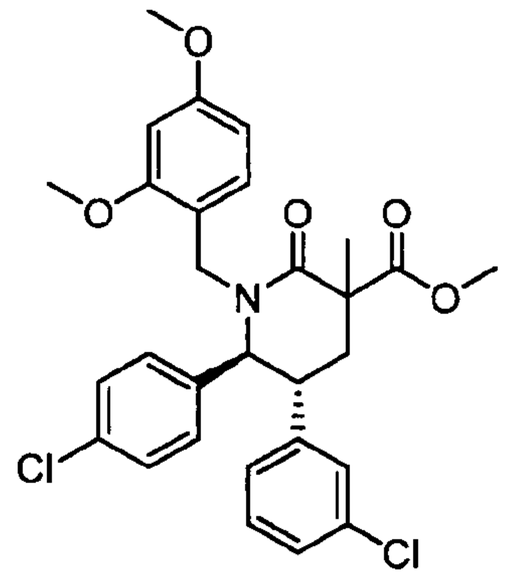
^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 0.50 (3 H, t, *J* = 7.5 Hz) 0.95 (3 H, t, *J* = 7.5 Hz) 1.00 (3 H, t, *J* = 7.5 Hz) 1.29 - 1.45 (2 H, m) 1.45 - 1.53 (1 H, m) 1.84- 2.01 (4 H, m) 2.30 (1 H, t, *J* = 13.8 Hz) 2.72 - 2.80 (2 H, m) 3.03 - 3.11 (2 H, m) 4.34 (1 H, d, *J* = 10.3 Hz) 6.69 (1 H, d, *J* = 7.6 Hz) 6.95 (2 H, br s) 7.05 - 7.20 (2 H, m) 7.08 - 7.17 (2 H, m) 7.22-7.25 (1 H, m). Mass Spectrum (ESI) m/z = 476 $[M + H]^+$.

EXAMPLE 88

(3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-(methylsulfonylmethyl)-1-(pentan-3-yl)piperidin-2-one

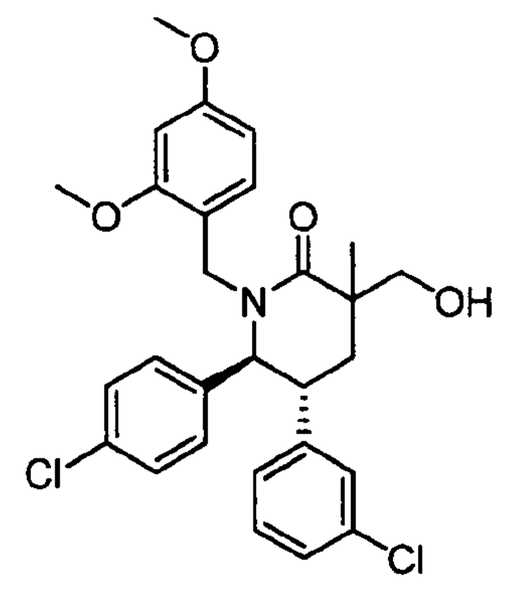


Step A. (5R,6S)-methyl 5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,4-dimethoxybenzyl)-3-methyl-2-oxopiperidine-3-carboxylate.



LHMDS (5.42 mL, 5.42 mmol) was added to a solution of (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,4-dimethoxybenzyl)-3-methylpiperidin-2-one (Example 71, Step B) (1.75 g, 3.61 mmol) in anhydrous THF (14.45 mL) at rt under argon. After 5 minutes dimethyl dicarbonate (1.159 mL, 10.84 mmol) was added. After 4 hours TLC indicated that a significant amount of product had formed but some starting material remained. Additional LHMDS (5.42 mL, 5.42 mmol) was added followed by dimethyl dicarbonate (1.159 mL, 10.84 mmol). After 2.5 hours the reaction was quenched by the addition of sat. aq. NH_4Cl and the layers were separated. The aqueous layer was extracted with EtOAc twice and the organics were pooled, washed with sat. aq. NaCl solution, dried ($MgSO_4$), filtered and concentrated in vacuo to provide a yellow oil. Purification using a 120 g SiO_2 column and eluting with 25 to 40% EtOAc/hexanes provided the title compound as a colorless oil as a mixture of isomers.

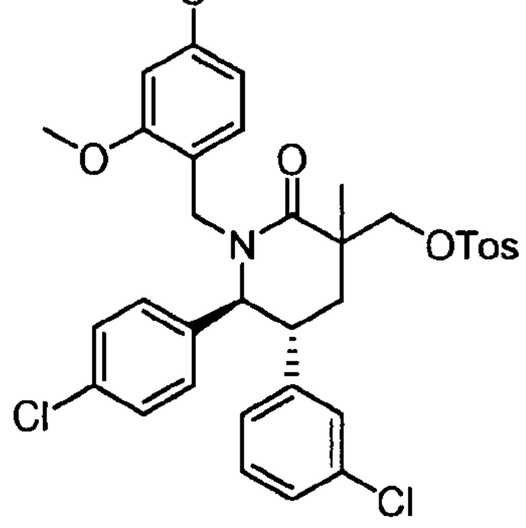
Step B. (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,4-dimethoxybenzyl)-3-(hydroxymethyl)-3-methylpiperidin-2-one



2M lithium borohydride (1.078 mL, 2.157 mmol) was added to a solution of (5R,6S)-methyl 5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,4-dimethoxybenzyl)-3-methyl-2-oxopiperidine-3-carboxylate (Example 88, Step A) (1.17 g, 2.157 mmol) in anhydrous THF

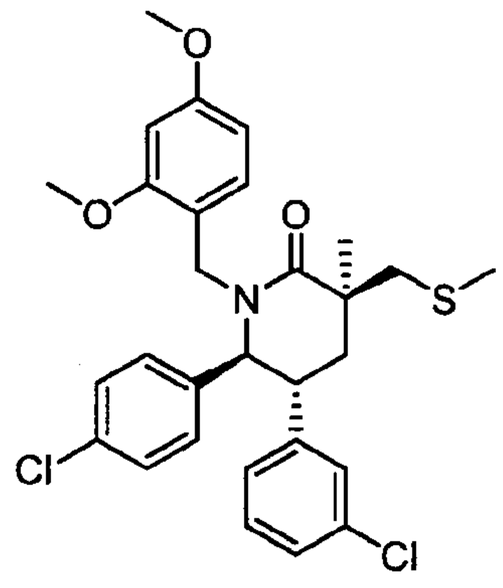
(21.57 mL) and anhydrous ether (20 mL) at 0 °C under nitrogen. The reaction was quenched after 58 hours with the addition of sat. aq. NH_4Cl and the layers were separated. The aqueous layer was extracted with EtOAc twice and the organics were pooled, washed with sat. aq. NaCl solution, dried ($MgSO_4$), filtered and concentrated in vacuo to provide a colorless oil. Purification using a 80 g SiO_2 column and eluting with 35 to 65% EtOAc/hexanes provided the title compound as a ~30:1 mixture of isomers.

Step C. ((5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,4-dimethoxybenzyl)-3-methyl-2-oxopiperidin-3-yl)methyl 4-methylbenzenesulfonate



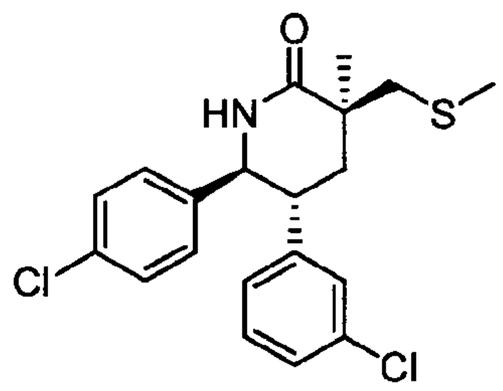
DMAP (0.015 g, 0.120 mmol) was added to a solution of (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,4-dimethoxybenzyl)-3-(hydroxymethyl)-3-methylpiperidin-2-one (Example 88, Step B) (0.616 g, 1.197 mmol) and tosyl-Cl (0.457 g, 2.395 mmol) in pyridine (5.99 mL) at rt. The reaction mixture was heated at 100 °C for 5 hours before removing the solvent in vacuo to provide a beige oil. Purification using a 80 g SiO_2 column and eluting with 25 to 55% EtOAc/hexanes provided the title compound as a colorless oil as a 33:1 mixture of isomers.

Step D. (3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,4-dimethoxybenzyl)-3-methyl-3-(methylthiomethyl)piperidin-2-one



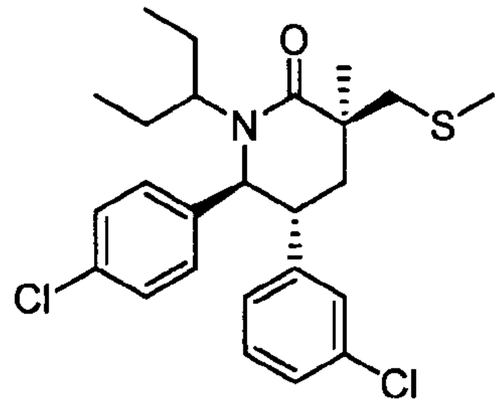
Sodium thiomethoxide (0.193 g, 2.76 mmol) was added to a solution of ((5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,4-dimethoxybenzyl)-3-methyl-2-oxopiperidin-3-yl)methyl 4-methylbenzenesulfonate (Example 88, Step C) (0.738 g, 1.104 mmol) in anhydrous DMF (5.52 mL) at rt under nitrogen. The reaction mixture was heated at 50 °C for 8 hours before being cooled to rt, diluted with water and extracted with ether three times. The organics were pooled, washed with water three times, sat. aq. NaCl solution, dried ($MgSO_4$), filtered and concentrated in vacuo to provide a colorless oil. Purification using a 40 g SiO_2 column and eluting with 15 to 40% EtOAc/hexanes provided the title compound as a colorless foam.

Step E. (3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-(methylthiomethyl)piperidin-2-one



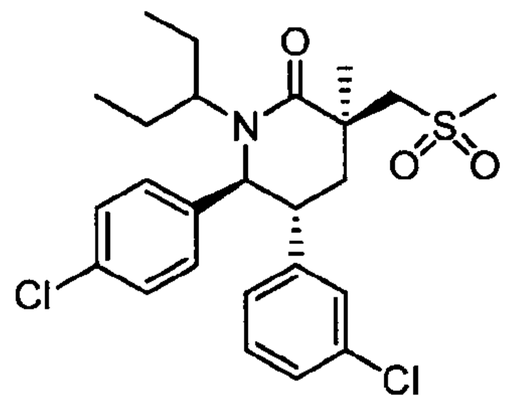
A solution of (3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,4-dimethoxybenzyl)-3-methyl-3-(methylthiomethyl)piperidin-2-one (Example 88, Step D) (0.406 g, 0.746 mmol) in TFA (6.00 mL) was heated at 50 °C under nitrogen for 2 hours. The reaction mixture was concentrated in vacuo to provide a purple oil. Purification using a 40 g SiO_2 column and eluting with 35 to 60% EtOAc/hexanes provided the title compound as a white solid.

Step F. (3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-(methylthiomethyl)-1-(pentan-3-yl)piperidin-2-one



NaH (0.076 g, 1.900 mmol) was added to a solution of (3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-(methylthiomethyl)piperidin-2-one (Example 88, step E) (0.150 g, 0.380 mmol) in 3-bromopentane (1.42 mL, 11.41 mmol) at rt under nitrogen. The reaction mixture was heated at 120 °C for 24 hours, cooled to rt, diluted with water and extracted with DCM three times. The organics were pooled, washed with sat. aq. NaCl solution, dried ($MgSO_4$), filtered and concentrated in vacuo to provide a yellow oil. Purification using a 24 g SiO_2 column and eluting with 15% EtOAc/hexanes provided the title compound as a colorless syrup.

Step G. (3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-(methylsulfonylmethyl)-1-(pentan-3-yl)piperidin-2-one

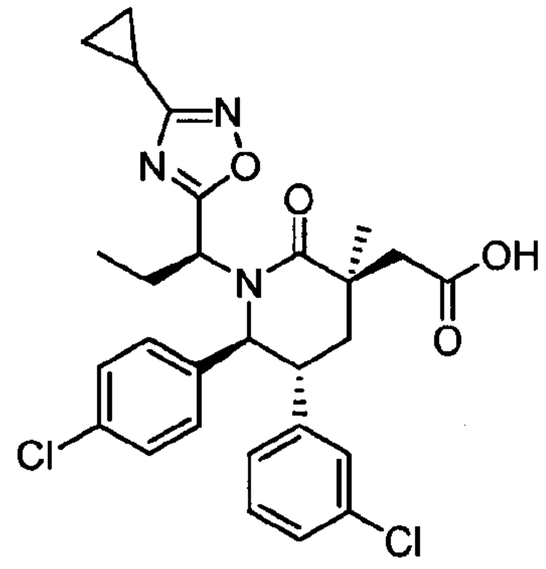


3-Chloroperbenzoic acid (0.054 g, 0.242 mmol) was added to a solution of (3S,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-(methylthiomethyl)-1-(pentan-3-yl)piperidin-2-one (Example 88, Step F) (0.045 g, 0.097 mmol) in DCM (0.969 mL) at 0 °C. The reaction mixture was stirred at rt for 1 hour, washed with sat. $NaHCO_3$, sat. aq. NaCl solution, dried ($MgSO_4$), filtered and concentrated in vacuo to provide a colorless oil. Purification using a 4 g SiO_2 ISCO column and eluting with 25 to 75% EtOAc/hexanes provided the title compound as a colorless glass.

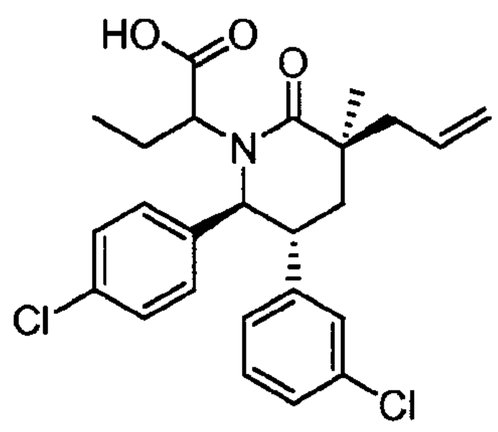
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.49 (t, *J* = 7.6 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H), 1.39 (m, 1H), 1.54 (s, 3H), 1.56 (m, 1H), 1.89 (m, 2H), 2.10 (m, 1H), 2.57 (dd, *J* = 14.4 and 3.1 Hz, 1H), 2.72 (m, 1H), 3.05 (s, 3H), 3.24 (d, *J* = 13.9 Hz, 1H), 3.63 (m, 1H), 3.82 (d, *J* = 13.9 Hz, 1H), 4.40 (d, *J* = 10.7 Hz, 1H), 6.78 (m, 1H), 7.02 (br s, 1H), 7.06 (m, 2H), 7.10 (m, 2H), 7.20 (m, 2H). Mass spectrum (ESI) *m/z* 496.2 $[M + H]^+$.

EXAMPLE 89

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.



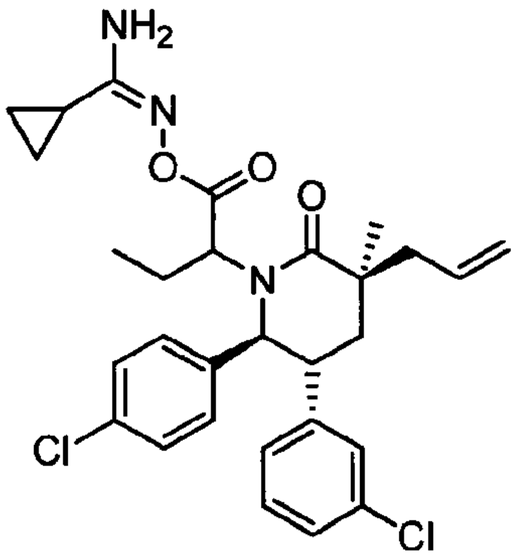
Step A. 2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoic acid.



LiOH (0.267 g, 11.13 mmol) in water (2.6 mL) was added to a solution of methyl 2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoate (Example 65, Step B) (0.528 g, 1.113 mmol) in MeOH (7.5 mL) at rt. The reaction mixture was heated at 80 °C for 14 hours, cooled to rt and acidified to pH = 1 with 3M HCl. The mixture was extracted with EtOAc three times and the organics were pooled, washed with sat. aq. NaCl solution, dried ($MgSO_4$), filtered and concentrated in vacuo to

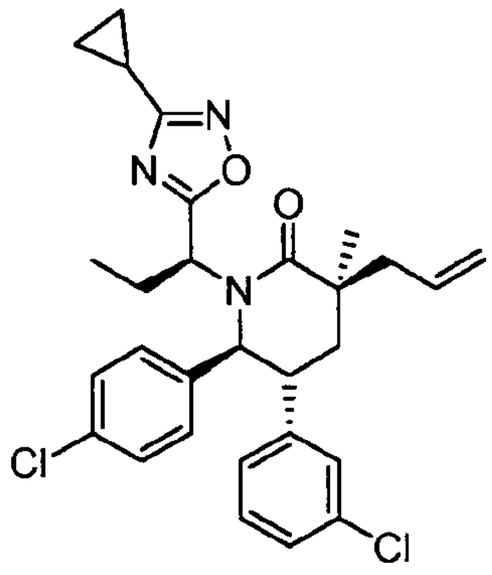
provide a white solid. Purification using a 40 g SiO_2 column and eluting with 35-60% EtOAc/hexanes provided the title compound as a mixture of isomers.

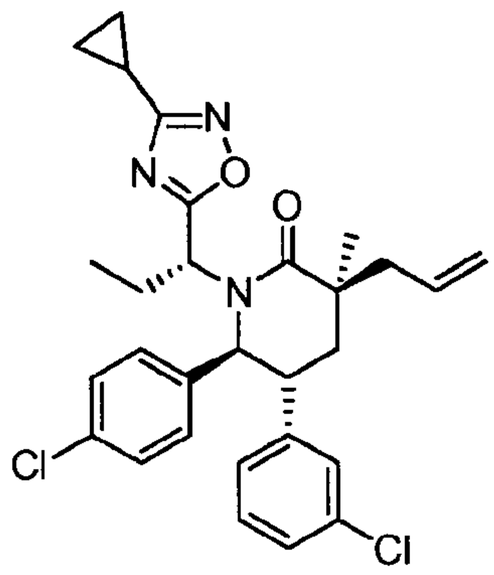
Step B. N'-(2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoyloxy)cyclopropanecarboximidamide



1,1'-Carbonyldiimidazole (0.104 g, 0.639 mmol) was added to a solution of 2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoic acid (Example 89, Step A) (0.196 g, 0.426 mmol) in dichloromethane (1.703 mL) at rt and stirred for 22 hours before adding n-hydroxycyclopropanecarboxamidine (0.064 g, 0.639 mmol). After 6 hours the reaction mixture was adsorbed onto silica and purified using a 12 g SiO_2 ISCO column and eluting with 35 to 60% EtOAc/hexanes to provide a 2:1 mixture of isomers.

Step C. (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)propyl)-3-methylpiperidin-2-one and (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)propyl)-3-methylpiperidin-2-one

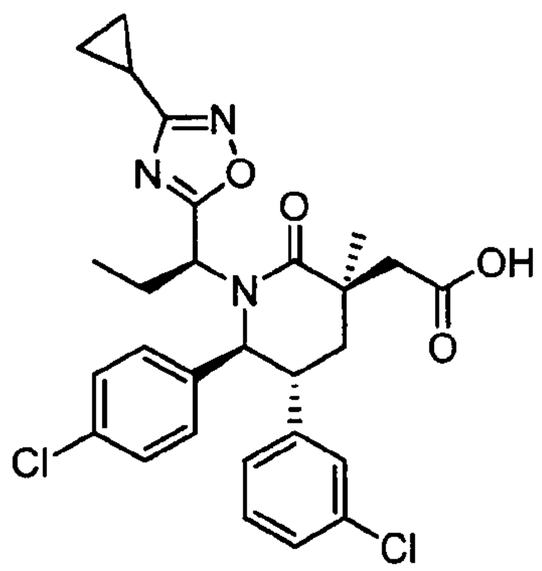




A solution of tetrabutylammonium fluoride (1.0M in THF, 1.880 mL, 1.880 mmol) was added to a solution of N'-(2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoyloxy)cyclopropanecarboximidamide (Example 89, Step B) (0.204 g, 0.376 mmol) in THF (3.76 mL) at rt. After 2 hours the reaction mixture was concentrated in vacuo and purified using a 24 g SiO_2 column eluting with 25% Et_2O/hexames to provide (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)propyl)-3-methylpiperidin-2-one.

Further elution provided (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)propyl)-3-methylpiperidin-2-one.

Step D. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

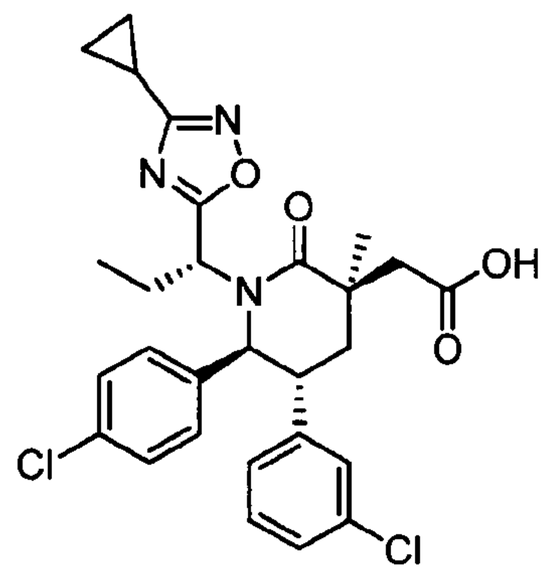


The title compound was prepared from (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)propyl)-3-methylpiperidin-2-one (Example 89, Step C), as described in Example 42 Step C. Purification using a 4 g SiO_2 column and eluting with 35 to 100% EtOAc/hexanes provided the title compound as a colorless film.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.84 (t, J = 7.5 Hz, 3H), 0.89 (m, 2 H), 1.01 (m, 2H), 1.25 (m, 1H), 1.43 (s, 3H), 1.95 (m, 1H), 1.98 (m, 1H), 2.20 (m, 2H), 2.37 (m, 1H), 2.90 (m, 2H), 3.26 (m, 1H), 4.60 (t, J = 6.9 Hz, 1H), 4.63 (d, J = 10.3 Hz, 1H), 6.76 (m, 1H), 6.90 (m, 2H), 7.00 (br s, 1H), 7.10 (t, J = 7.9 Hz, 1H), 7.16 (m, 3H). Mass spectrum (ESI) *m/z* 542.2 $[M + H]^+$.

EXAMPLE 90

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)propyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.

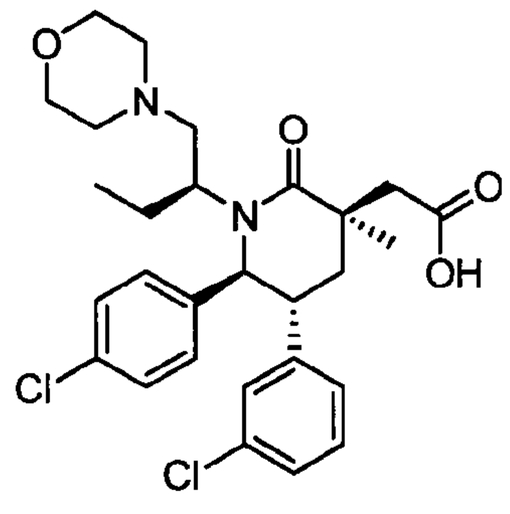


The title compound was prepared from (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)propyl)-3-methylpiperidin-2-one (Example 89, Step C) as described in Example 42, Step C.

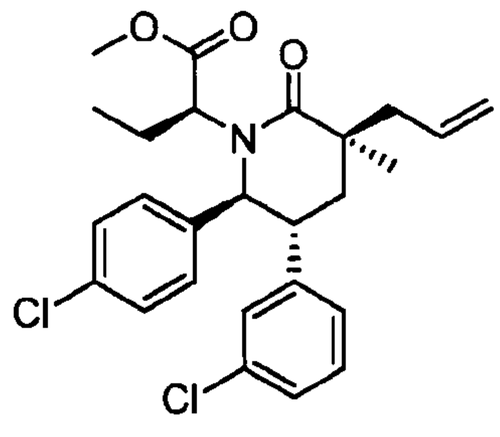
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.85-1.05 (m, 3H) 1.09 (t, *J* = 7.6 Hz, 3H), 1.44 (s, 3H), 2.01 (m, 1H), 2.19 (m, 1H), 2.26 (m, 3H), 2.83 (d, *J* = 14.7 Hz, 1H), 2.91 (d, *J* = 14.7 Hz, 2H), 3.32 (m, 1H), 3.95 (t, *J* = 7.2 Hz, 1H), 4.57 (d, *J* = 10.4 Hz, 1H), 6.73 (m, 1H), 6.98 (m, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 7.16 (m, 2H), 7.20 (m, 3H). Mass spectrum (ESI) *m/z* 542.2 [M + H]$^+$.

EXAMPLE 91

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid



Step A. (S)-Methyl 2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoate

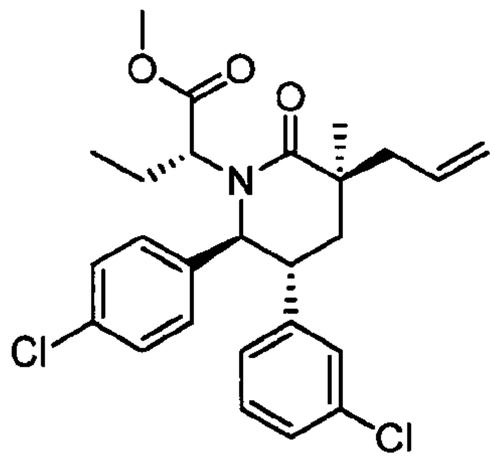


To a solution of (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one (Exampe 71, Step D) (4.00 g, 10.7 mmol) in 45 mL of DMF was added a dispersion of 60% sodium hydride in mineral oil (1.71 g, 42.7 mmol) at 0 °C. After being stirred for 20 min, methyl 2-bromobutanoate (6.15 mL, 53.4 mmol) was added at 0 °C and the resulting solution was stirred at 25 °C for 12 h until completion of the reaction. Then sat. aq. NH_4Cl solution was added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with water and sat. aq. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (eluent: 0 to 100% MTBE/hexanes, gradient elution), followed by separation of individual stereoisomers by chiral SFC (flowrate: 65 mL/min on a ChiralPak ®AD-H column (Diacel Inc., Fort Lee, NJ) using 3:1 heptanes / IPA (0.1% DEA) / CO_2 as the eluent) provided the title compound as the faster eluting isomer.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.23 (2 H, d, *J* = 8.4 Hz), 7.06 - 7.17 (2 H, m), 7.00 (3 H, t, *J* = 1.8 Hz), 6.77 (1 H, d, *J* = 7.6 Hz), 5.79 - 5.94 (1 H, m), 5.20 (1 H, d, *J* = 4.7 Hz), 5.17 (1 H, s), 4.56 (1 H, d, *J* = 10.8 Hz), 3.73 (3 H, s), 3.25 - 3.37 (1 H, m), 3.18 (1 H, dd, *J* = 7.6 Hz, 4.9 Hz), 2.61 (2 H, d, *J* = 7.4 Hz), 2.20 - 2.34 (1 H, m), 2.09 - 2.19 (1 H, m), 1.99 (1 H, d, *J* = 3.1 Hz), 1.57 - 1.72 (1 H, m), 1.24 (3 H, s), 0.61 (3 H, t, *J* = 7.5 Hz); Mass Spectrum (ESI) m/z = 474.1 $[M+H]^+$.

Further elution provided:

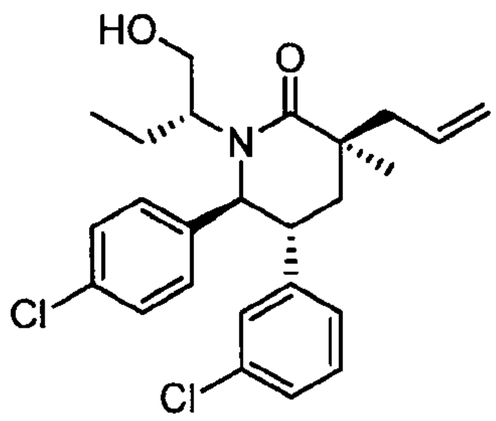
(R)-Methyl 2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoate



as the slower eluting isomer.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.22 (2 H, d, *J* = 8.0 Hz), 6.99 - 7.19 (4 H, m), 6.95 (1 H, t, *J* = 1.8 Hz), 6.71 (1 H, d, *J* = 7.6 Hz), 5.81 - 5.95 (1 H, m), 5.19 (1 H, d, *J* = 2.7 Hz), 5.16 (1 H, d, *J* = 1.0 Hz), 4.48 (1 H, d, *J* = 10.6 Hz), 3.67 (3 H, s), 3.24 - 3.32 (1 H, m), 3.20 (1 H, dd, *J* = 7.8 Hz, 6.1 Hz), 2.61 - 2.72 (1 H, m), 2.49 - 2.60 (1 H, m), 1.91 - 2.21 (4 H, m), 1.27 (3 H, s), 1.00 (3 H, t, *J* = 7.5 Hz); MS (ESI) m/z = 474.1 $[M+H]^+$.

Step B. (3S,5R,6S)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((R)-1-hydroxybutan-2-yl)-3-methylpiperidin-2-one

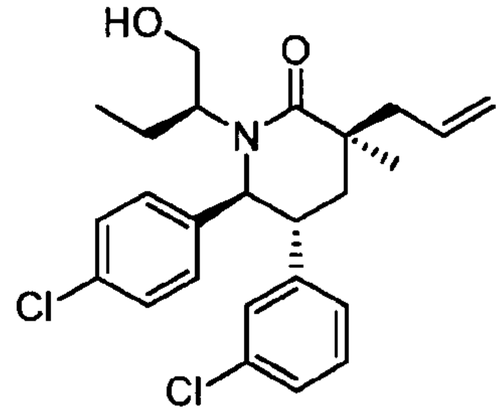


To a solution of (S)-methyl 2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoate and (R)-methyl 2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoate (1.73 g, 3.64 mmol) (mixture of stereoisomers from Example 91, Step A) in 27 mL of Et_2O and 9 mL of THF was added a solution of lithium tetrahydroborate in THF (0.238 mL, 7.28 mmol) at 0 °C. The resulting solution was stirred at 25 °C for 2 h. The reaction was quenched (10% citric acid), extracted (2 × EtOAc) and washed (1 × Sat. aq. NaCl solution). The combined organic layers were washed with sat. aq. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 0-60% EtOAc in hexanes) to give the title compound as the faster eluting isomer.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.99 (t, *J* = 7.4 Hz, 3 H), 1.29 (s, 3 H), 1.79 - 2.03 (m, 4 H), 2.62 (d, *J* = 7.4 Hz, 2 H), 2.80 – 2.85 (m, 1 H), 3.05 - 3.16 (m, 1 H), 3.40 – 3.49 (m, 2 H), 4.33 (d, *J* = 10.4 Hz, 1 H), 5.13 - 5.22 (m, 2 H), 5.79 - 5.95 (m, 1 H), 6.7 (d, *J* = 7.6 Hz, 1 H), 6.85 - 6.97 (m, 3 H), 7.08 - 7.15 (m, 1 H), 7.17 – 7.19 (m, 1 H), 7.23 (d, *J* = 8.6 Hz, 2 H); Mass Spectrum (ESI) m/z = 446 (M+1).

Further elution provided:

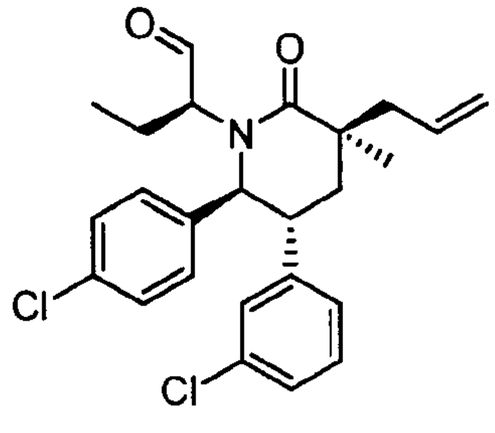
(3S,5R,6S)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-hydroxybutan-2-yl)-3-methylpiperidin-2-one



as the slower eluting isomer.

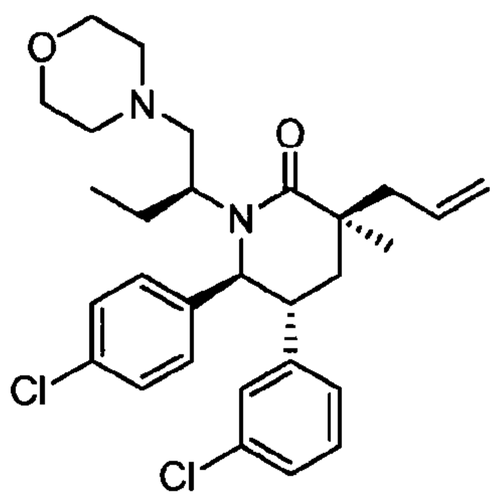
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.68 (t, *J* = 7.5 Hz, 3 H), 1.27 (s, 3 H), 1.38 - 1.52 (m, 1 H), 1.90 - 2.08 (m, 4 H), 2.61 (d, *J* = 7.4 Hz, 2 H), 3.10 - 3.25 (m, 2 H), 3.59 – 3.68 (m, 2 H), 4.46 (d, *J* = 10.2 Hz, 1 H), 5.18 (dd, *J* = 13.7, 1.8 Hz, 2 H), 5.79 - 5.93 (m, 1 H), 6.72 (d, *J* = 7.6 Hz, 1 H), 6.93 - 7.04 (m, 2 H), 7.09 – 7.13 (m, 1 H), 7.15 - 7.20 (m, 1 H), 7.24 (d, *J* = 8.6 Hz, 2 H); Mass Spectrum (ESI) m/z = 446 (M+1).

Step C. (S)-2-((3S,5R,6S)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanal



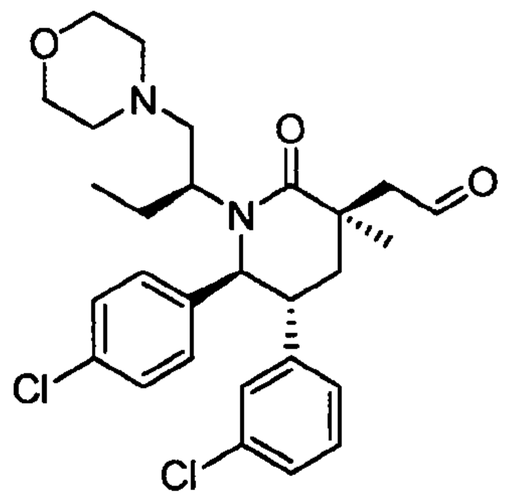
To a solution of 218 mg (0.49 mmol) of (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-hydroxybutan-2-yl)-3-methylpiperidin-2-one (Example 91, Step B) in a micture of water (13.20 μL, 0.733 mmol) and DCM (4883 μL) was added 1,1,1,-tris(acetoxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)one ("Dess Martin periodinane") (311 mg, 0.733 mmol) at ambient temperature. The reaction was monitored by LCMS, and several small portions of additional periodinane were added until the reaction was complete. The reaction was quenched (2 mL, 1 M $Na_2S_2O_3$), extracted (2 x DCM), and the combined organic layers were washed with sat. $NaHCO_3$ solution (2X), sat NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Purication of the residue by flash chromatography on silica gel (eluent: 20 to 35% EtOAc/hexanes, gradient elution) provided the title compound.

Step D. (3S,5R,6S)-3Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-morpholinobutan-2-yl)piperidin-2-one.



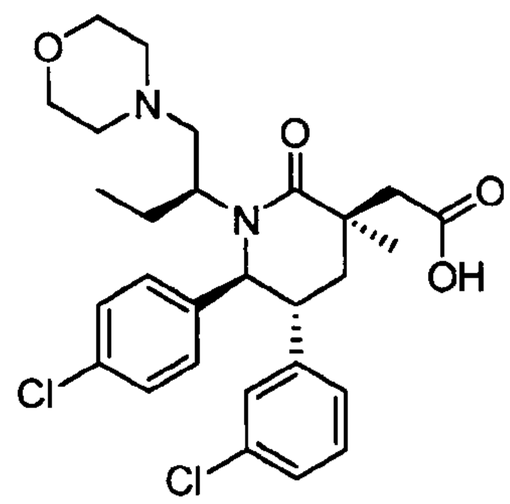
To a solution of 100 mg (0.225 mmol) of (S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanal (Example 91, Step C) in DCE (2420 μL) was addded morpholine (200 μL, 2.297 mmol), acetic acid (1.288 μL, 0.023 mmol) and sodium triacetoxyborohydride (95 mg, 0.450 mmol). The reaction mixture was stirred at room temperature for 18 hours. The reaction was quenched with sat. sodium bicarbonate solution and extracted with DCM (2x10 mL). The combined organic layers were washed with sat NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to afford the crude title compound as an oil.

Step E. 2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)acetaldehyde.



To a round-bottomed flask charged with (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-morpholinobutan-2-yl)piperidin-2-one (Example 91, Step D) (125 mg, 0.242 mmol) was added THF (2 mL). Approximately 1 mL water was added dropwise until the solution became and remained cloudy with gentle stirring. t-BuOH (0.350 mL) was added dropwise until the solution became homogeneous. NMO (42.6 mg, 0.364 mmol) was added followed by osmium tetroxide, 4 wt. %, in water (1 drop from glass Pasteur pipette). The reaction mixture was stirred at room temperature for 16 hours. An additional drop of osmium tetroxide, 4 wt. %, in water was added. After 5 hours, two additional drops of osmium tetroxide, 4 wt. %, in water were added and the reaction mixture was stirred at room temperature for an additional 16 hours. Sodium periodate (145 mg, 0.679 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate (10 mL) and water (10 mL) and filtered. The aqueous layer of the filtrate was extracted with additional ethyl acetate (10 mL) and the combined organic layers were washed with sat. aq. NaCl solution, dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to provide the title compound.

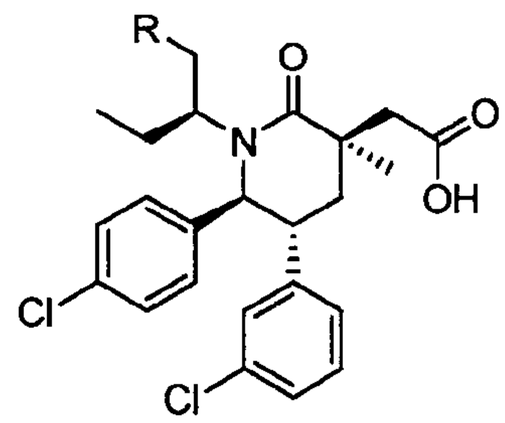
Step F. 2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid

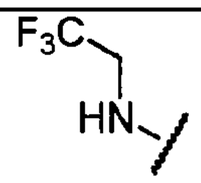


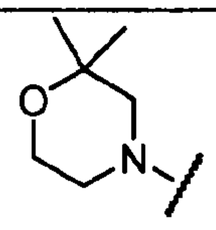
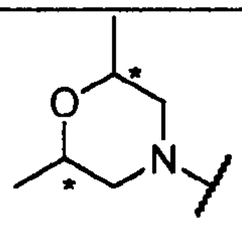
To a solution of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)acetaldehyde (Example 91, Step E) (125 mg, 0.242 mmol) in acetone (2 mL) was added 3 mL of a mixture of CrO_3 in water (2 mL) and concentrated H_2SO_4 (1 ml). The reaction mixture was stirred at room temperature for 2 hours and then diluted with water (10 mL) and ethyl acetate (10 mL) and the layers were separated. The aqueous layer was extracted with additional ethyl acetate (10 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reversed phase preparatory HPLC (column: Gemini-NX C_{18} 5um column; Phenomonex, Torrance, CA; eluent: 0 to 100% MeCN +0.1% TFA in water + 0.1% TFA) to provide the title compound.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.57 (t, *J* = 7.53 Hz, 1 H) 1.26 (s, 1 H) 1.39 (s, 3 H) 1.54 - 1.70 (m, 1 H) 1.72 - 1.89 (m, 1 H) 2.02 - 2.27 (m, 3 H) 2.49 (br. s., 2 H) 2.69 (br. s., 2 H) 2.82 (m, 2 H) 3.02 (br. s., 2 H) 3.13 - 3.30 (m, 2 H) 3.74 - 3.93 (m, 4 H) 4.47 - 4.72 (m, 1 H) 6.75 (d, *J* = 7.82 Hz, 1 H) 6.96 (t, *J* = 1.86 Hz, 1 H) 7.01 (br. s., 1 H) 7.04 - 7.17 (m, 3 H) 7.22 (d, *J* = 8.41 Hz, 2 H). Mass Spectrum (ESI) m/z = 533 $[M + H]^+$.

Examples 92 - 94 were prepared from (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-hydroxyethyl)piperidin-2-one by procedures similar to those described in Example 91, substituting morpholine in step D for the appropriate amount of amine



Example	R=
92	

93	
94	

EXAMPLE 92

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((S)-1-(2,2,2-trifluoroethylamino)butan-2-yl)piperidin-3-yl)acetic acid

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.56 (t, *J*=7.43 Hz, 3 H) 1.23 - 1.35 (m, 1 H) 1.44 (s, 3 H) 1.48 - 1.65 (m, 2 H) 1.77 - 1.91 (m, 1 H) 2.02 - 2.11 (m, 1 H) 2.13 - 2.25 (m, 1 H) 2.59 - 2.71 (m, 1 H) 2.73 - 2.84 (m, 1 H) 2.90 - 3.24 (m, 5 H) 4.60 (d, *J*=10.17 Hz, 1 H) 6.69 - 6.77 (m, 1 H) 6.91 - 7.05 (m, 3 H) 7.06 - 7.13 (m, 1 H) 7.13 - 7.18 (m, 1 H) 7.23 (d, *J*=8.22 Hz, 2 H). Mass Spectrum (ESI) m/z = 545 $[M + H]^+$.

EXAMPLE 93

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(2,2-dimethylmorpholino)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.49 (t, *J* = 7.34 Hz, 3 H) 1.21 - 1.30 (m, 4 H) 1.34 (s, 3 H) 1.37 (s, 3 H) 1.42 (s, 3 H) 1.51 - 1.68 (m, 1 H) 1.86 (dd, *J* = 14.48 and 7.24 Hz, 1 H) 2.08 - 2.22 (m, 2 H) 2.30 (br. s., 1 H) 2.35 - 2.48 (m, 2 H) 2.74 - 2.84 (m, 1 H) 2.86 - 2.94 (m, 1 H) 3.00 - 3.22 (m, 2 H) 3.68 - 3.91 (m, 2 H) 4.57 (d, *J* = 10.37 Hz, 1 H) 6.68 (d, *J* = 7.63 Hz, 1 H) 6.91 - 7.00 (m, 2 H) 7.03 - 7.11 (m, 1 H) 7.14 (d, *J* = 7.24 Hz, 2 H) 7.23 (d, *J* = 7.43 Hz, 2 H). Mass Spectrum (ESI) m/z = 561 $[M + H]^+$.

EXAMPLE 94

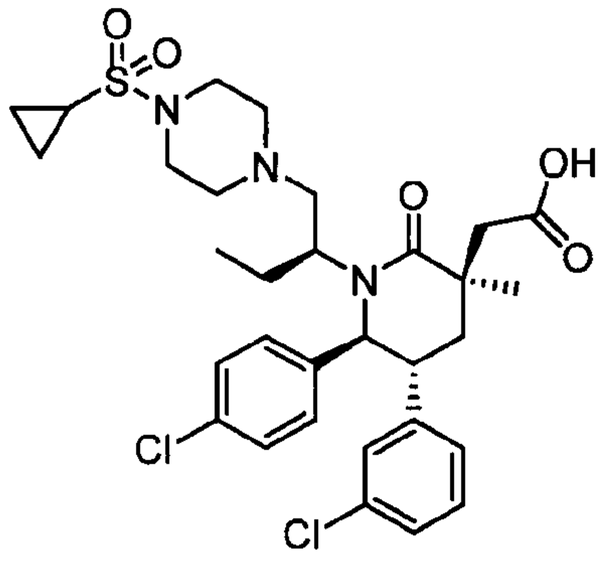
2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((2S)-1-(2,6-dimethylmorpholino)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

The crude product was purified by reversed phase preparatory HPLC (column: Gemini-NX C_{18} 5um column; Phenomonex, Torrance, CA; eluent: 0 to 100% MeCN +0.1% TFA in water + 0.1% TFA) to provide a 4:1 ratio of diastereomers of undetermined configuration at the positions indicated by *.

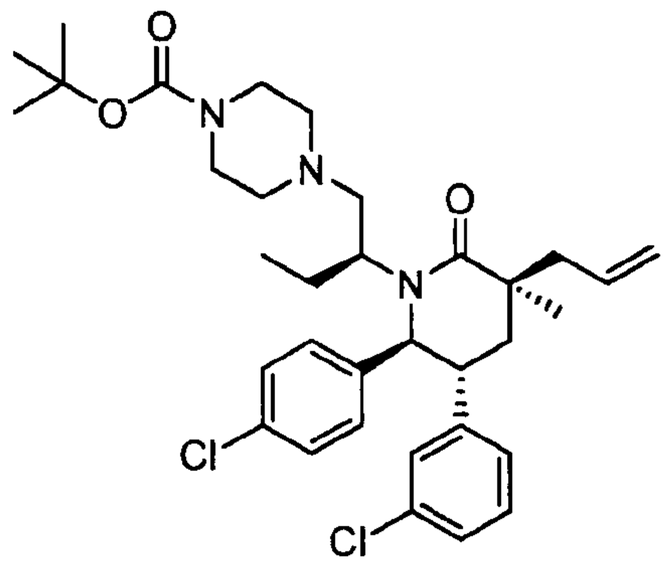
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.02 (br. s., 1 H) 1.24 (d, *J* = 6.06 Hz, 6 H) 1.35 - 1.49 (m, 4 H) 2.02 - 2.44 (m, 4 H) 2.68 (s, 1 H) 2.79 - 2.89 (m, 2 H) 3.20 - 3.32 (m, 2 H) 3.37 - 3.49 (m, 1 H) 3.80 - 4.00 (m, 2 H) 4.10 (br. s., 3 H) 4.23 - 4.34 (m, 1 H) 4.41 - 4.58 (m, 1 H) 4.91 - 5.10 (m, 1 H) 6.89 - 6.98 (m, 2 H) 6.99 - 7.15 (m, 4 H) 7.20 – 7.30 (m, 2 H). Mass Spectrum (ESI) m/z = 561 $[M + H]^+$.

EXAMPLE 95

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(4-(cyclopropylsulfonyl)piperazin-1-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

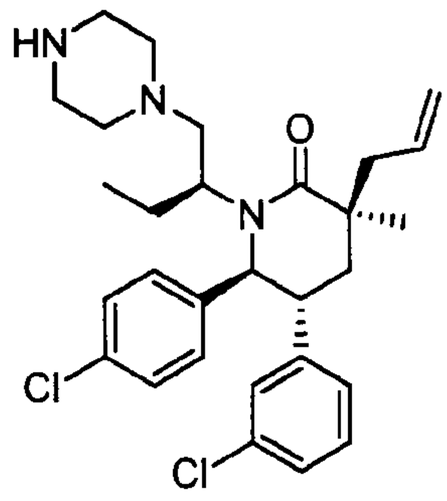


Step A. tert-butyl 4-((S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butyl)piperazine-1-carboxylate.



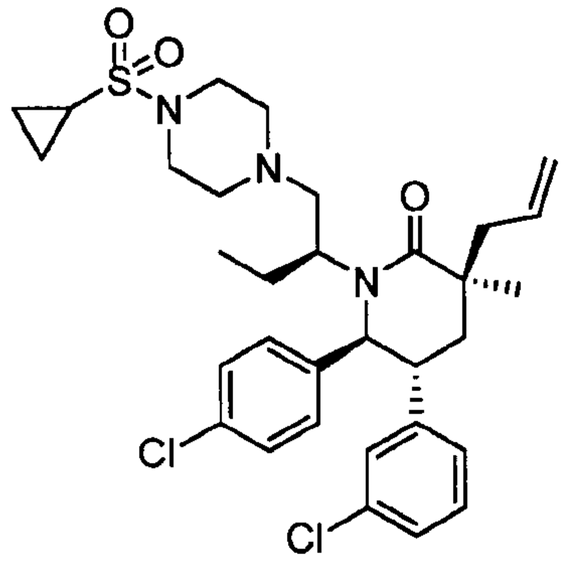
The title compound was prepared from (S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanal (Example 91, Step C) and tert-butyl piperazine-1-carboxylate according to the procedure described in Example 91 Step D.

Step B. (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(piperazin-1-yl)butan-2-yl)piperidin-2-one



To a solution of tert-butyl 4-((S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butyl)piperazine-1-carboxylate (Example 95, Step A) (187 mg, 0.304 mmol in DCM (2.4 mL) was added TFA (600 μL, 7.79 mmol). The reaction mixture was stirred at room temperature for 16 hours before concentrating under reduced pressure. The residue was taken up in DCM (15 mL) and washed with sat. sodium bicarbonate solution (10 mL) and saturated sodium chloride solution (10 mL). The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under reduced pressure to afford the title compound as a white foam.

Step C. (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(4-(cyclopropylsulfonyl)piperazin-1-yl)butan-2-yl)-3-methylpiperidin-2-one



To a solution of (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(piperazin-1-yl)butan-2-yl)piperidin-2-one (Example 95, Step B) (60 mg, 0.117 mmol) in DCE (1.2 mL) was added cyclopropanesulfonyl chloride (23.76 μL, 0.233 mmol) followed by diisopropylethylamine (40.6 μL, 0.233 mmol). The reaction mixture was stirred at room temperature for 16 hours, diluted with water (10 mL) and the layers were separated. The aqueous layer was extracted with DCM (2 x 10 mL). The combined organc layers were washed with saturated NaCl solution (10 mL), dried over sodium sulfate, filtered, and the filtrate concentrated under reduced pressure to afford the title compound as a solid.

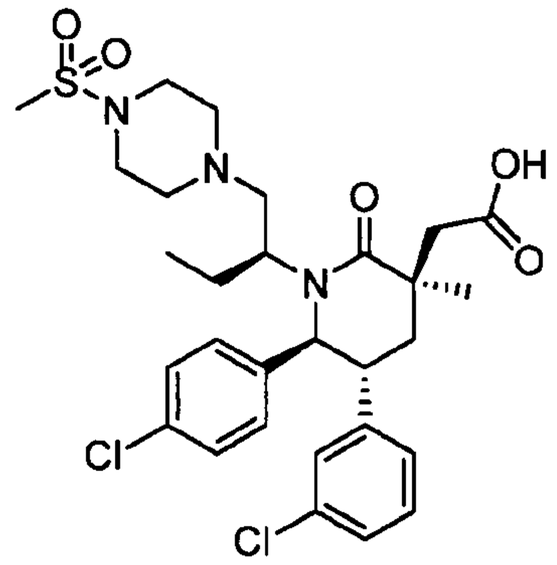
Step D. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(4-(cyclopropylsulfonyl)piperazin-1-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

To a 10 mL round-bottomed flask charged with (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(4-(cyclopropylsulfonyl)piperazin-1-yl)butan-2-yl)-3-methylpiperidin-2-one (Example 23, Step C) (85.1 mg, 0.138 mmol) was added THF (~800 uL) followed by water (~600 uL, until the reaction remains cloudy with gentle stirring) followed by tBuOH (~200 uL, untril the reaction becomes translucent). NMO (24.17 mg, 0.206 mmol) was added followed by 5 drops of osmium tetroxide, 4 wt. %, in water (33.6 μL, 0.138 mmol) via pasteur pipette. The reaction was stirred at rt over night before adding Jones reagent (0.154 mL). The reaction was stirred at room temperature for 2 hours, diluted with water (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers are washed with water (3 x 20 mL), saturated sodium chloride solution (20 mL), dried over sodium sulfate, filtered and the filtrate concentrated under reduced pressure. The residue was purified by reversed phase preparatory HPLC (column: Gemini-NX C_{18} 5um column; Phenomonex, Torrance, CA; eluent: 0 to 100% MeCN +0.1% TFA in water + 0.1% TFA, over 20 minutes) to give the title compound.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.92 - 1.25 (m, 10 H) 1.43 (s, 3 H) 1.85 (br. s., 1 H) 2.08 (d, *J* = 13.50 Hz, 1 H) 2.16 - 2.30 (m, 1 H) 2.40 (d, *J* = 5.87 Hz, 2 H) 2.52 (br. s., 2 H) 2.69 - 2.79 (m, 2 H) 2.79 - 2.92 (m, 2 H) 3.21 - 3.34 (m, 2 H) 3.83 (br. s., 3 H) 4.51 (br. s., 1 H) 6.67 (br. s., 1 H) 6.91 - 7.01 (m, 2 H) 7.03 - 7.09 (m, 2 H) 7.11 - 7.18 (m, 3 H). Mass Spectrum (ESI) m/z = 636 $[M + H]^+$.

EXAMPLE 96

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(4-(methylsulfonyl)piperazin-1-yl)butan-2-yl)-2-oxopiperidin-3-yl)acetic acid

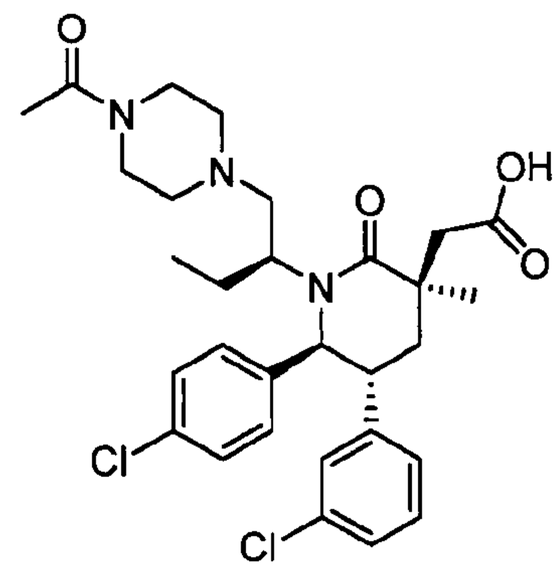


The title compound was prepared from (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(piperazin-1-yl)butan-2-yl)piperidin-2-one (Example 95, Step B) and methanesulfonyl chloride as described in Example 95, Steps C and D.

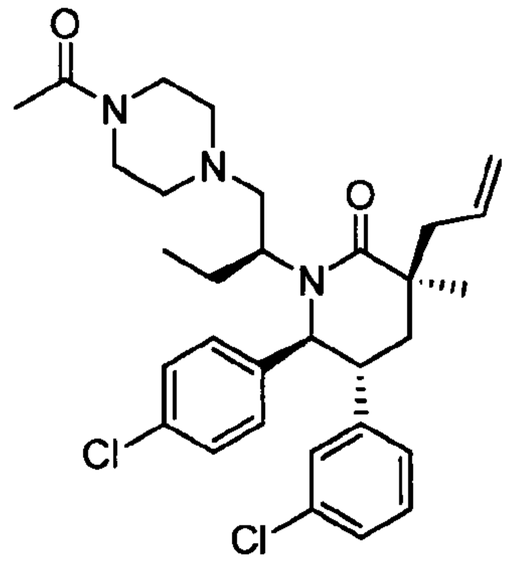
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.04 (br. s., 3 H) 1.42 (s, 3 H) 1.85 (br. s., 2 H) 2.00 - 2.13 (m, 1 H) 2.14 - 2.28 (m, 1 H) 2.56 (br. s., 3 H) 2.66 - 2.77 (m, 3 H) 2.85 (d, *J* = 14.48 Hz, 2 H) 2.90 - 2.99 (m, 3 H) 3.27 (t, *J* = 10.27 Hz, 3 H) 3.80 (br. s., 3 H) 4.51 (br. s., 1 H) 6.63 - 6.71 (m, 1 H) 6.97 (s, 2 H) 7.03 - 7.10 (m, 2 H) 7.11 - 7.17 (m, 3 H). Mass Spectrum (ESI) m/z = 610 $[M + H]^+$.

EXAMPLE 97

2-((3R,5R,6S)-1-((S)-1-(4-acetylpiperazin-1-yl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid



Step A. (3S,5R,6S)-1-((S)-1-(4-acetylpiperazin-1-yl)butan-2-yl)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one.



To a solution of (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(piperazin-1-yl)butan-2-yl)piperidin-2-one (Example 95, Step B) (80 mg, 0.155 mmol) in DCE (1.5 mL) was added acetyl chloride (22.1 μL, 0.31 mmol) followed by diisopropylethylamine (54.1 μL, 0.311 mmol). The reaction mixture was stirred at room temperature for 16 hours and then concentrated under reduced pressure to provide the title compound.

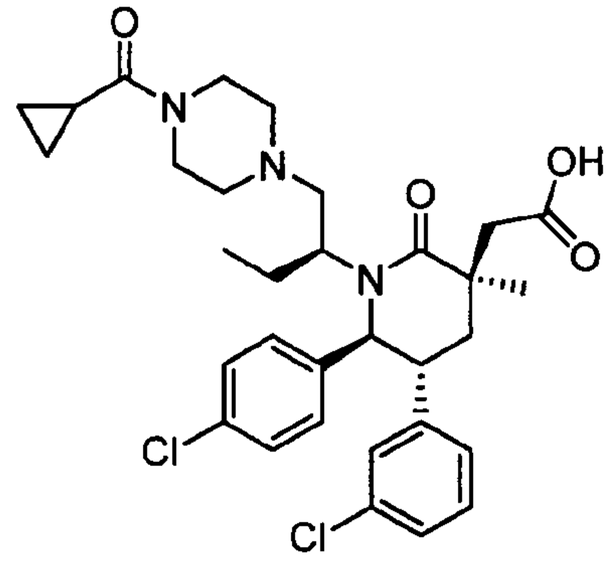
Step B. 2-((3R,5R,6S)-1-((S)-1-(4-acetylpiperazin-1-yl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

The title compound was prepared from (3S,5R,6S)-1-((S)-1-(4-acetylpiperazin-1-yl)butan-2-yl)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one (Example 97, Step A) as described in Example 95, Step D. The residue was purified by reversed phase preparatory HPLC (column: Gemini-NX C_{18} 5um column; Phenomonex, Torrance, CA; eluent: 0 to 100% MeCN +0.1% TFA in water + 0.1% TFA, over 20 minutes) to give the title compound.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.94 - 1.18 (m, 3 H) 1.42 (s, 3 H) 1.77 - 1.98 (m, 1 H) 2.12 (s, 4 H) 2.23 (s, 2 H) 2.48 - 2.63 (m, 3 H) 2.67 (s, 3 H) 2.84 (br. s., 3 H) 3.16 - 3.35 (m, 2 H) 3.83 - 4.05 (m, 3 H) 4.43 - 4.61 (m, 1 H) 6.62 - 6.75 (m, 1 H) 6.97 (s, 2 H) 7.07 (d, *J* = 7.83 Hz, 2 H) 7.10 - 7.17 (m, 3 H). Mass Spectrum (ESI) m/z = 574 $[M + H]^+$.

EXAMPLE 98

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(4-(cyclopropanecarbonyl)piperazin-1-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

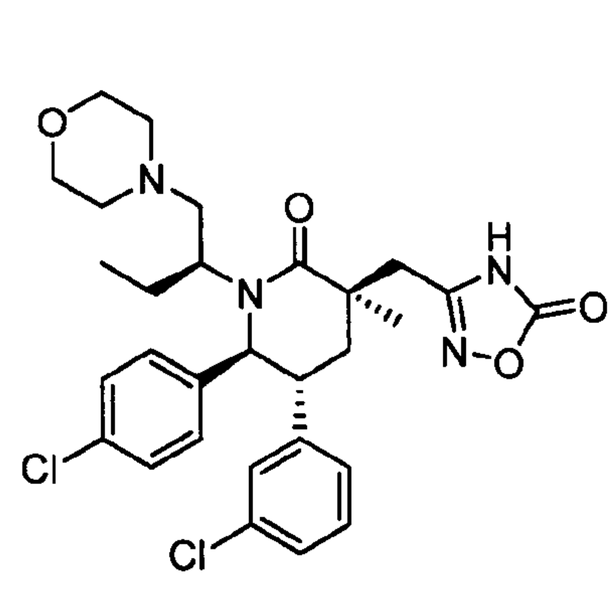


The title compound was prepared from (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-(piperazin-1-yl)butan-2-yl)piperidin-2-one (Example 95, Step B) and cyclopropanecarbonyl chloride as described in Example 97.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.79 - 0.91 (m, 6 H) 1.02 (br. s., 6 H) 1.43 (s, 3 H) 1.65 - 1.75 (m, 2 H) 2.11 (br. s., 2 H) 2.17 - 2.30 (m, 2 H) 2.51 (br. s., 3 H) 2.65 (s, 2 H) 2.80 - 2.88 (m, 2 H) 3.29 (t, *J* = 11.44 Hz, 2 H) 6.98 (s, 2 H) 7.06 (t, *J* = 7.83 Hz, 2 H) 7.10 - 7.16 (m, 2 H) 7.19 - 7.26 (m, 2 H). Mass Spectrum (ESI) m/z = 600 $[M + H]^+$.

EXAMPLE 99

3-(((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)methyl)-1,2,4-oxadiazol-5(4H)-one.



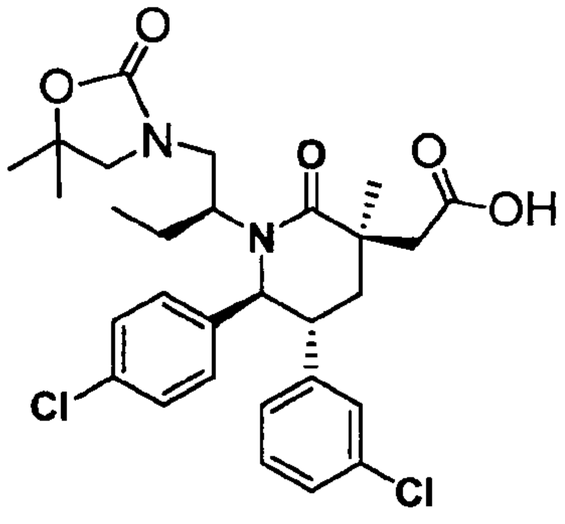
The title compound was prepared from 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((S)-1-morpholinobutan-2-yl)-2-oxopiperidin-3-yl)acetic acid

(Example 91) using a similar procedure as the one described for Example 82. The crude prduct was purified by flash chromatography on silica gel (eluent: 0 to 10% MeOH in DCM) to give the title compound.

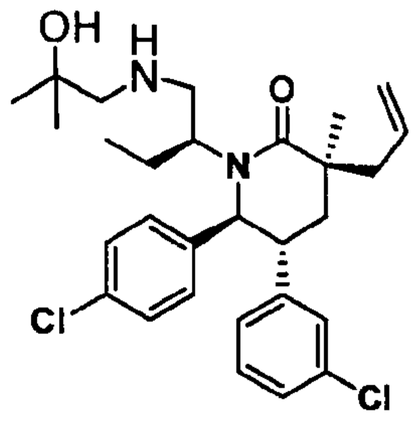
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.56 (t, *J* = 7.34 Hz, 3 H) 1.29 (br. s., 1 H) 1.30 - 1.38 (m, 3 H) 1.57 (ddd, *J* = 13.99, 7.53 and 3.91 Hz, 1 H) 1.81 (dt, *J* = 14.48 and 7.43 Hz, 1 H) 2.09 (dd, *J* = 13.99 and 3.03 Hz, 1 H) 2.18 (d, *J* = 9.98 Hz, 1 H) 2.22 - 2.32 (m, 1 H) 2.46 (d, *J* = 3.72 Hz, 2 H) 2.66 (br. s., 2 H) 2.90 (d, *J* = 15.06 Hz, 1 H) 2.95 - 3.21 (m, 4 H) 3.74 - 3.89 (m, 4 H) 4.59 (d, *J* = 10.17 Hz, 1 H) 6.72 (d, *J* = 7.63 Hz, 1 H) 6.84 - 6.99 (m, 3 H) 7.08 - 7.13 (m, 1 H) 7.14 - 7.18 (m, 1 H) 7.23 (d, *J* = 8.22 Hz, 2 H). Mass Spectrum (ESI) m/z = 573 $[M + H]^+$.

EXAMPLE 100

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(5,5-dimethyl-2-oxooxazolidin-3-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.

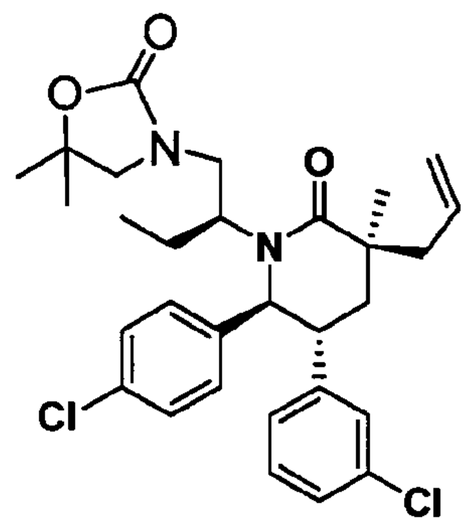


Step A. (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(2-hydroxy-2-methylpropylamino)butan-2-yl)-3-methylpiperidin-2-one.



The title compound was prepared as described in Example 91, Step D and using and using 1-amino-2-methylpropan-2-ol (Tyger Scientific, Inc., Ewing, NJ).

Step B. 3-((S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butyl)-5,5-dimethyloxazolidin-2-one.



To a solution of 42 mg (0.081 mmol) of (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(2-hydroxy-2-methylpropylamino)butan-2-yl)-3-methylpiperidin-2-one (Example 100, Step A) in dioxane (2705 μL) was added carbonyldiimidazole (132 mg, 0.812 mmol). The reaction was heated to 100° for 6h. Purification of the residue by reversed phase HPLC (Sunfire™ Prep C_{18} OBD 10 μm column (Waters, Milford, MA) (eluent: 60 to 85% MeCN/water (0.1% TFA), gradient elution) provided the title compound.

Step C. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(5,5-dimethyl-2-oxooxazolidin-3-yl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.

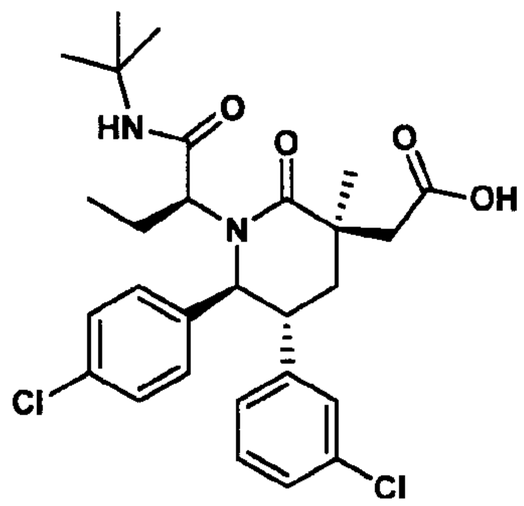
To a rapidly stirring solution of 20 mg (0.037 mmol) of 3-((S)-2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butyl)-5,5-dimethyloxazolidin-2-one (Example 100, Step B) in a mixture of CCl4 (210 μL), MeCN (210 μL), and water (315 μL) was added sodium periodate (31.5 mg, 0.147 mmol), followed by catalytic ruthenium(III) chloride hydrate (4.15 mg, 0.018 mmol). When complete by LCMS monitoring, acidified the reaction with citric acid and diluted with chloroform. Insoluble material was removed by filtration through celite. Extracted to ethyl acetate and the combined organic layer was washed with sat. NaCl, dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuo. Purification of the residue by reversed phase HPLC (Sunfire™ Prep C_{18} OBD 10 μm column (Waters, Milford, MA) (eluent: 60 to 80% MeCN/water (0.1% TFA), gradient elution) provided the title compound as a white powder.

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 0.55 (t, *J*=7.21 Hz, 2 H) 0.94 (br. s., 2 H) 1.27 (d, *J*=2.93 Hz, 1 H) 1.33 (d, *J*=2.69 Hz, 1 H) 1.52 (t, 7 H) 1.88 - 1.99 (m, 2 H) 2.34 (t, *J*=13.82

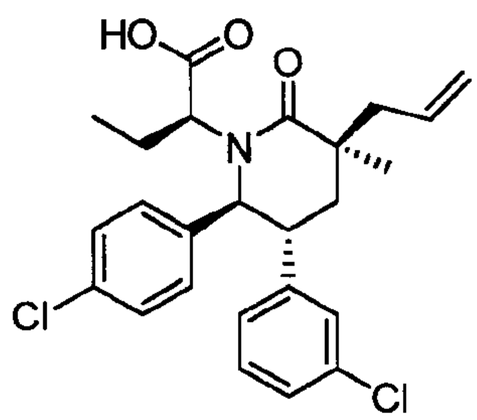
Hz, 1 H) 2.71 (d, *J*=14.92 Hz, 2 H) 2.95 - 3.12 (m, 4 H) 3.29 - 3.39 (m, 2 H) 4.44 (d, *J*=10.27 Hz, 1 H) 6.73 (d, *J*=7.58 Hz, 1 H) 6.95 (s, 2 H) 7.11 (t, *J*=7.70 Hz, 1 H) 7.13 - 7.20 (m, 1 H). Mass Spectrum (ESI) m/z = 561 (M+1).

EXAMPLE 101

2-((3R,5R,6S)-1-((S)-1-(tert-butylamino)-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.



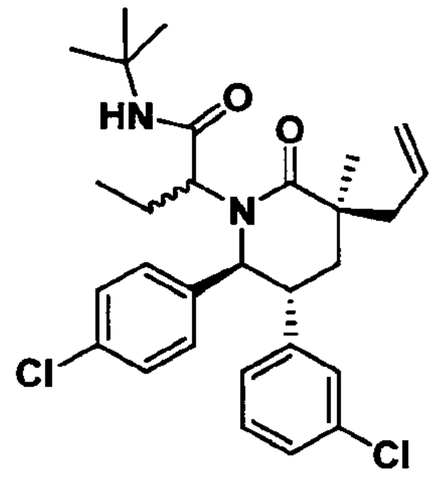
Step A. 2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoic acid



To a 15-mL round-bottomed flask was added (S)-tert-butyl 2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoate (420 mg, 0.813 mmol) (Example 1, Step F) and anisole (444 μL, 4.07 mmol), followed by TFA (4066 μL) which had been pre-cooled to 0°C. The reaction mixture was stirred at 0°C for 1h, diluted with 50ml of ether, and the combined organics were washed with 20 ml water, $NaHCO_3$ / sat NaCl solution until neutral, then dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by flash chromatography on silica gel (eluent: 0 to 20% EtOAc/hexanes, gradient elution) provided the title compound.

1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.25 (1 H, s), 7.07 - 7.19 (2 H, m), 7.00 (3 H, br. s.), 6.76 (1 H, d, J=7.4 Hz), 5.77 - 5.93 (1 H, m), 5.15 - 5.25 (2 H, m), 4.58 (1 H, d, J=10.8 Hz), 3.35 (1 H, br. s.), 3.23 - 3.33 (1 H, m), 2.62 (2 H, d, J=7.2 Hz), 2.27 (1 H, dquin, J=14.6, 7.5, 7.5, 7.5, 7.5 Hz), 2.14 (1 H, t, J=13.5 Hz), 1.99 (1 H, dd, J=13.7, 2.9 Hz), 1.50 - 1.64 (1 H, m), 1.29 (3 H, s), 0.66 (3 H, t, J=7.4 Hz).

Step B. 2-((5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)-N-tert-butylbutanamide



To a solution of 2-((3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butanoic acid (81 mg, 0.176 mmol) (Example 101, Step A) in dry DMF (880 μL) with 3eq TEA (73.6 μL, 0.528 mmol) at 0° was added 2 eq HATU (134 mg, 0.352 mmol). The reaction was stirred at 0° for 5 min, followed by addition of t-butyl amine (25.7 mg, 0.352 mmol). It was stirred for 30 min at 0°, quenched with sat. $NaHCO_3$ and extracted to EtOAc. The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4, filtered and the filtrate was concentrated. Purification of the residue by flash chromatography on silica gel (eluent: 0-30% EtOAc/hexanes, gradient elution) provided the title compound as a mixture of stereoisomers.

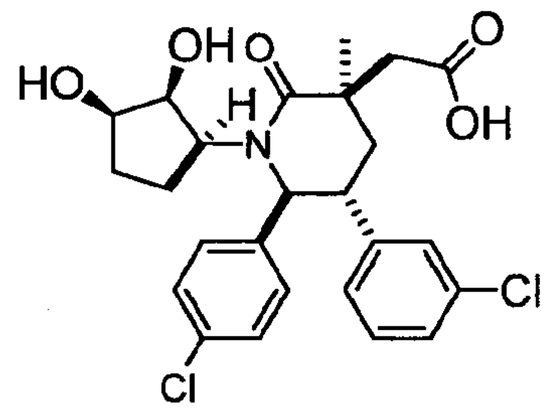
Step C. 2-((3R,5R,6S)-1-((S)-1-(tert-butylamino)-1-oxobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.

The title compound was prepared from (5R,6S)-5-(3-chlorophenyl)-6-(5-chloropyridin-2-yl)piperidin-2-one (Example 101, Step B) as described in Example 1, Step H. The crude product was purified by reversed phase preparatory HPLC (Sunfire™ Prep C_{18} OBD 10 μm column (Waters, Milford, MA) (eluent: 55% acetonitrile, water, 0.1%TFA, gradient elution).

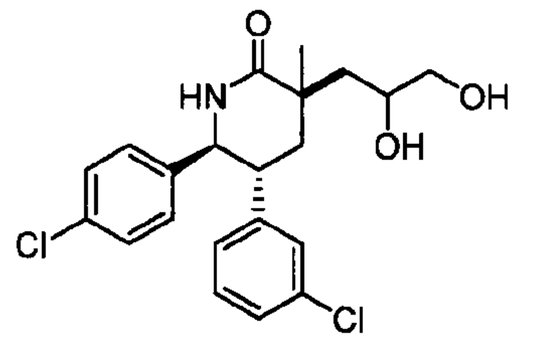
^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 0.71 (t, *J*=7.46 Hz, 3 H), 1.32 (s, 9 H), 1.40 (s, 3 H), 1.60 - 1.71 (m, 1 H), 2.07 - 2.25 (m, 3 H), 2.86 (d, *J*=2.20 Hz, 2 H), 3.16 (ddd, *J*=12.65, 9.60, 3.42 Hz, 1 H), 3.67 (dd, *J*=8.80, 5.62 Hz, 1 H), 4.70 (d, *J*=9.78 Hz, 1 H), 6.78 (d, *J*=7.58 Hz, 1 H), 6.97 (s, 1 H), 6.98 - 7.05 (m, 3 H), 7.11 (t, *J*=7.83 Hz, 1 H), 7.14 - 7.19 (m, 1 H), 7.21 (d, *J*=8.56 Hz, 2 H). Mass Spectrum (ESI) m/z = 533 (M+1).

EXAMPLE 102

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((1S,2S,3R)-2,3-dihydroxycyclopentyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid



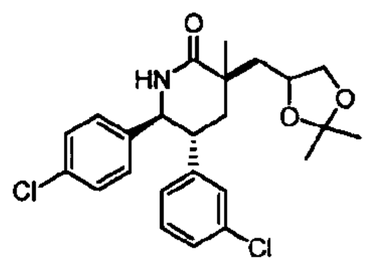
Step A. (3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-(2,3-dihydroxypropyl)-3-methylpiperidin-2-one.



To a solution of 4g (10.69 mmol) of (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one (Example 71, Step D) in 100 mL of THF was added water (60mL) followed by 4-methylmorpholine 4-oxide (1.878 g, 16.03 mmol). The cloudy reaction mixture became clear within 5 min and osmium(VIII) oxide (4% aq) (0.340 mL, 0.053 mmol) was added and the reaction mixture remained clear. The reaction mixture was stirred at room temperature for 18 h. Osmium(VIII) oxide (4% aq) (0.1 mL) was added and the reaction

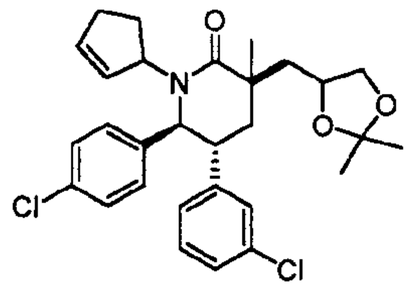
mixture was stirred at room temperature for 24 h. Sat NaCl solution was added and the mixture was extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered and the filtrate was concentrated to give the title compound as a 1:1 ratio of diastereomers.

Step B. (3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3-methylpiperidin-2-one



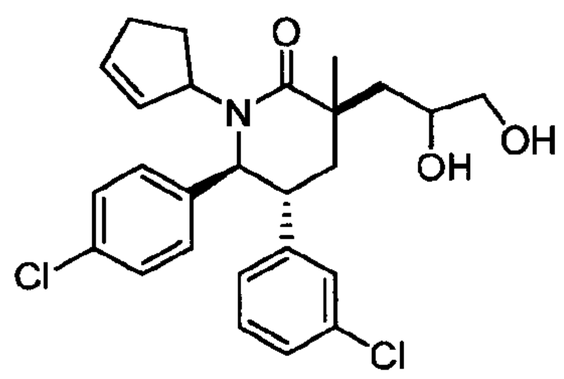
To a solution of (3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-(2,3-dihydroxypropyl)-3-methylpiperidin-2-one (Example 102, Step A) (4.900 g, 12.00 mmol) and 2,2-dimethoxypropane (14.76 mL, 120 mmol) in N,N-dimethylformamide (34 mL) at room temperature was added CSA (0.279 g, 1.200 mmol) and the reaction mixture was allowed to stir for 1 hr at room temperature. The reaction was quenched with sodium bicarbonate (100 mL) and EtOAc (100 mL). The layers were separated and the organic layer was washed three times with sat. sodium carbonate (100 mL). The aqueous layers were combined and were extracted with EtOAc (200 mL). The organic layers were combined, washed with sat. aq. NaCl solution, dried with sodium sulfate, filtered, and concentrated under reduced pressure to provide the title compound.

Step C. (3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopent-2-enyl)-3-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3-methylpiperidin-2-one



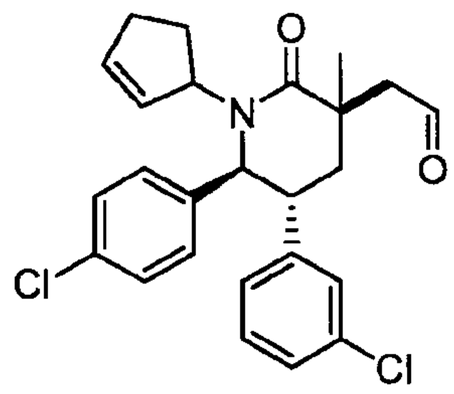
To (3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3-methylpiperidin-2-one (Example 102, Step B) (0.909 g, 2.027 mmol) was added toluene (15 mL) and the mixture was concentrated under reduced pressure. This step was repeated three times. Inhibitor free THF (20 mL) was added and the solution was cooled to -78 °C. Butyllithium in pentane (2.0M) (1.014 mL, 2.027 mmol) was added dropwise and the reaction mixture remained colorless. The reaction mixture warmed to 0 °C and the reaction color turned very light yellow. nBuLi in pentane (2.0M) was added dropwise until the reaction mixture remained bright yellow. The reaction mixture was cooled to -78 °C and freshly prepared 3-bromocyclopent-1-ene (0.4 g, 2.72 mmol) in THF (2 mL) was added dropwise. The reaction mixture was wrapped in foil and warmed to 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then at rt for 2 days. The reaction was quenched with sat. NH_4Cl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 0 to 100% EtOAc in hexanes) to give the title compound as a colorless film.

Step D. (3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopent-2-enyl)-3-(2,3-dihydroxypropyl)-3-methylpiperidin-2-one



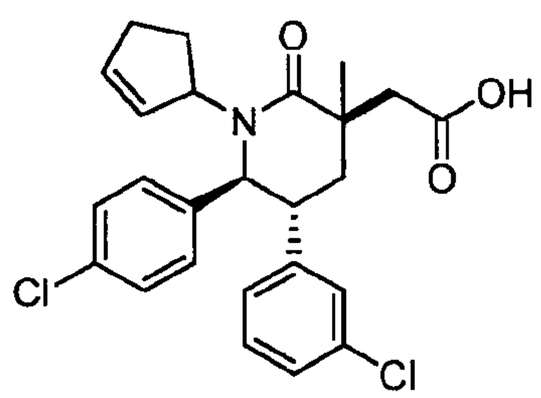
To a solution of (3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopent-2-enyl)-3-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3-methylpiperidin-2-one (Example 28, Step C) (310 mg, 0.603 mmol) in THF (3 mL) at room temperature was added aq. HCl (1 M) (3013 µL, 3.01 mmol). The reaction mixture was stirred at room temperature for 19 h. The reaction mixture was diluted with EtOAc and the layers were separated. The organic layer was washed with sat. $NaHCO_3$, sat. aq. NaCl solution and dried over Na_2SO_4 and concentrated under reduced pressure to provide the title compound.

Step E. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopent-2-enyl)-3-methyl-2-oxopiperidin-3-yl)acetaldehyde



To a solution of (3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopent-2-enyl)-3-(2,3-dihydroxypropyl)-3-methylpiperidin-2-one (Example 102, Step D) (286 mg, 0.603 mmol) in THF (3 mL) and water (3 mL) was added sodium periodate (258 mg, 1.206 mmol) at room temperature. The slurry was stirred at room temperature for 1 h and then diluted with EtOAc and the layers were separated. The organic layer was washed with sat. $Na_2S_2O_3$ and sat. aq. NaCl solution and dried over Na_2SO_4 and concentrated under reduced pressure to provide the title compound.

Step F. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopent-2-enyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid



To 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopent-2-enyl)-3-methyl-2-oxopiperidin-3-yl)acetaldehyde (Example 102, Step E) (267 mg, 0.604 mmol) in acetone (4 mL) was added freshly prepared Jones reagent (0.5 mL) at rt. The reaction mixture was stirred at room temperature for 15 min. before it was diluted with EtOAc and washed with water and sat. aq. NaCl solution. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 50 to 100% EtOAc in hexanes) to give the title compound as a colorless film as a 3.6:1 mixture of diastereomers.

Step G. 2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((1S,2S,3R)-2,3-dihydroxycyclopentyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

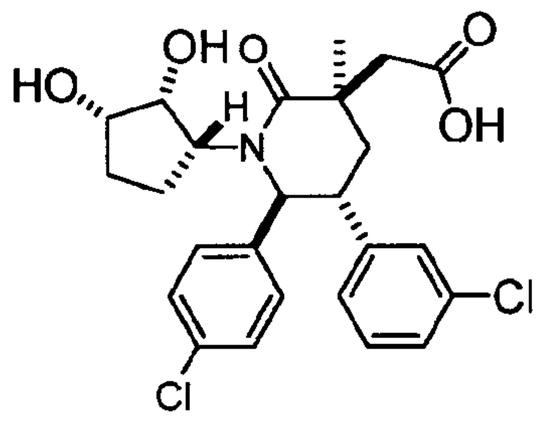
To a solution of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopent-2-enyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid (Example 102, Step F) (94 mg, 0.205 mmol) in THF (1.0 mL) was added water (0.25 mL) and tBuOH (0.2 mL) at room temperature. NMO (36.0 mg, 0.308 mmol) was added followed by osmium tetroxide (4% aq) (1.303 µL, 0.205 µmol). The reaction mixture was stirred at room temperature for 24 h. Water (10 mL) was added and the mixture was extracted with DCM twice. The organic layers were combined and dried over Na_2SO_4 and concentrated under reduced pressure. The residue, containing a mixture of three stereoisomers, was purified by reversed phase preparatory HPLC (column: Gemini-NX C_{18} 5um column; Phenomonex, Torrance, CA; eluent: 30 to 50% MeCN +0.1% TFA in water + 0.1% TFA, over 20 minutes) to provide the title compound as the first eluting isomer.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 1.21 - 1.36 (3 H, m), 1.38 (3 H, s), 1.53 - 1.56 (2 H, m), 2.20 - 2.02 (3 H, m), 2.22 (1 H, t, *J* = 13.2 Hz), 2.62 - 2.78 (1 H, m), 2.85 - 3.00 (1 H, m), 3.00 - 3.13 (1 H, m), 4.06 - 4.17 (1 H, m), 4.35 (1 H, br s), 4.70 (1 H, d, *J* = 8.8 Hz), 6.76 - 6.88 (1 H, m), 6.93 - 7.12 (4 H, m), 7.12 - 7.25 (3 H, m). Mass Spectrum (ESI) m/z = 492 $[M + H]^+$.

Further elution provided as the last eluting isomer Example 103.

EXAMPLE 103

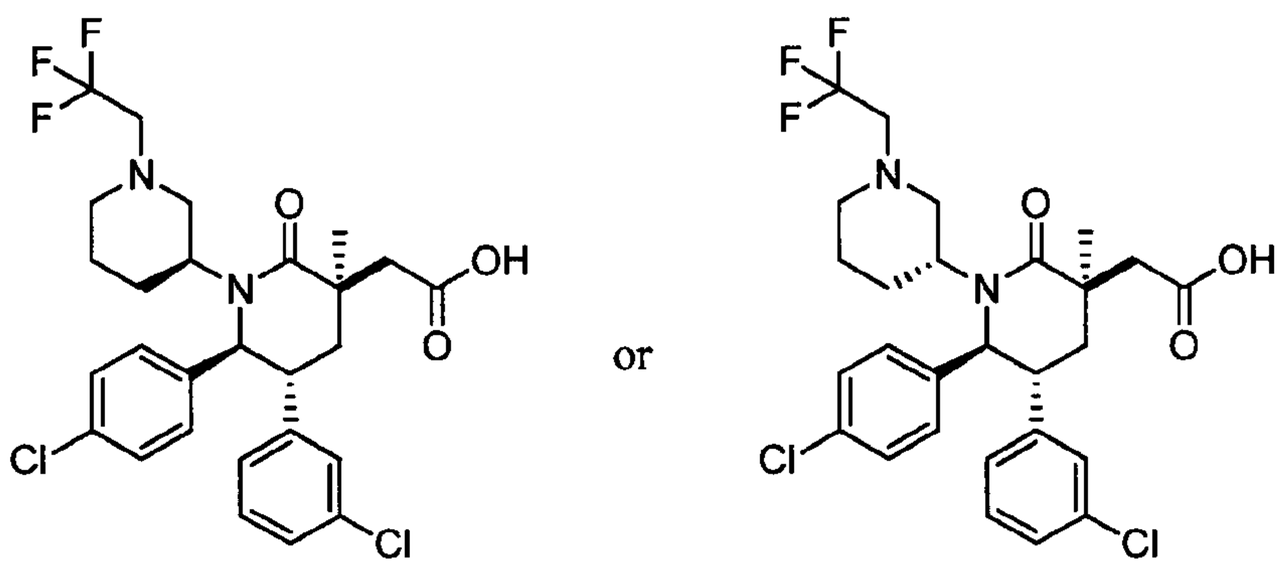
2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((1R,2R,3S)-2,3-dihydroxycyclopentyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid



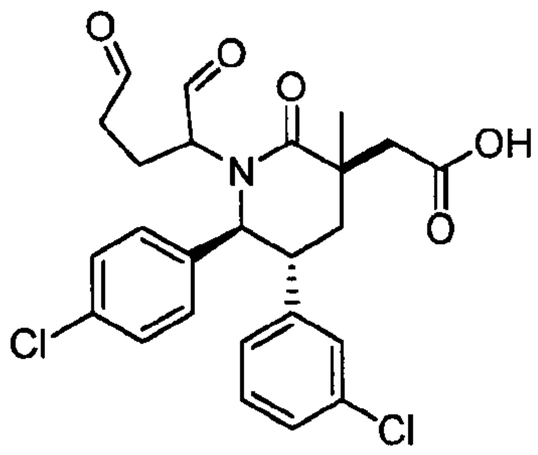
^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 1.19 - 1.38 (1 H, m) 1.38 - 1.50 (3 H, m) 1.38 - 1.50 (1 H, m) 1.71 - 1.98 (2 H, m) 2.06 - 2.27 (3 H, m) 2.33 (1 H, d, *J* = 8.2 Hz) 2.70 - 2.79 (1 H, m) 2.79 - 2.90 (1 H, m) 3.20 - 3.37 (2 H, m) 3.40 (1 H, d, *J* = 5.1 Hz) 3.86 (1 H, br. s.) 4.50 (1 H, d, *J* = 10.2 Hz) 6.67 - 6.77 (1 H, m) 6.93 - 7.07 (1 H, m) 7.06 - 7.19 (3 H, m) 7.23 (3 H, d, *J* = 8.6 Hz). Mass Spectrum (ESI) m/z = 492 $[M + H]^+$.

EXAMPLE 104

2-((3R,3'S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1'-(2,2,2-trifluoroethyl)-1,3'-bipiperidin-3-yl)acetic acid or 2-((3R,3'R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1'-(2,2,2-trifluoroethyl)-1,3'-bipiperidin-3-yl)acetic acid



Step A. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1,5-dioxopentan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.



To a solution of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(2,3-dihydroxycyclopentyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid (Example 102, Step F) (110 mg, 0.223 mmol) in THF (3 mL) and water (3 mL) was added sodium periodate (134 mg, 0.626 mmol) at room temperature. The reaction mixture was stirred at room temperature for 45 min and was diluted with EtOAc and the layers were separated. The organic layer was washed with sat. aq. $Na_2S_2O_3$ solution, sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated under reduced pressure to provide the title compound.

Step B.

2-((3R,3'S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1'-(2,2,2-trifluoroethyl)-1,3'-bipiperidin-3-yl)acetic acid or 2-((3R,3'R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1'-(2,2,2-trifluoroethyl)-1,3'-bipiperidin-3-yl)acetic acid (Isomer 1)

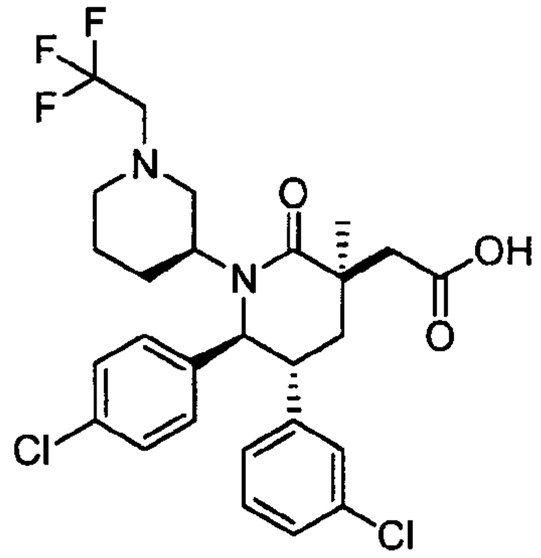
To a solution of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1,5-dioxopentan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid (Example 104, Step A) (55 mg, 0.112 mmol) in DCE (1 mL) was added 2,2,2-trifluoroethanamine (9.24 μL, 0.118 mmol) and sodium triacetoxyborohydride (76 mg, 0.359 mmol) at room temperature. The cloudy reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, diluted with DCM and washed with sat. aq. $NaHCO_3$ solution and sat. aq. NaCl solution. The layers were separated and the aqueous layer was extracted three times with DCM. The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by reversed phase preparatory HPLC (column: Gemini-NX C_{18} 5um column; Phenomonex, Torrance, CA; eluent: 40% MeCN +0.1% TFA in water + 0.1% TFA, over 20 minutes) and concentrated in vacuo to provide the first eluting diastereomer. The residue was dissolved in DCM (1 mL) and HCl in ether (1M) (1 mL) was added and the solvent was removed under reduced pressure to provide the hydrochloride salt of one of the title compounds as the first eluting isomer.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 0.73 - 1.00 (4 H, m), 1.13 - 1.53 (6 H, m), 1.58 - 1.84 (2 H, m), 1.98 - 2.13 (1 H, m), 2.24 - 2.44 (1 H, m), 2.67 - 2.99 (3 H, m), 3.17 - 3.32 (1 H, m), 4.22 (2 H, t, J = 6.0 Hz), 6.65 - 6.91 (1 H, m), 7.00 (1 H, d, J = 0.6 Hz), 7.05 - 7.24 (4 H, m), 7.48 - 7.59 (1 H, m), 7.63 - 7.79 (1 H, m). Mass Spectrum (ESI) m/z = 557 [M + H]$^+$.

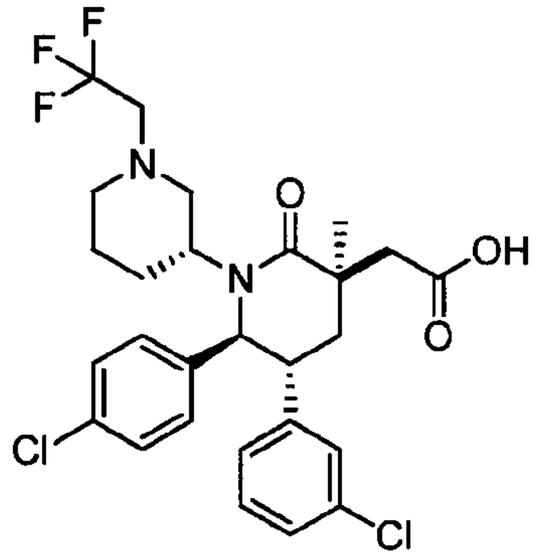
Further elution and concentration in vacuo provided example 105.

EXAMPLE 105

2-((3R,3'S,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1'-(2,2,2-trifluoroethyl)-1,3'-bipiperidin-3-yl)acetic acid or 2-((3R,3'R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1'-(2,2,2-trifluoroethyl)-1,3'-bipiperidin-3-yl)acetic acid (Isomer 2)



or

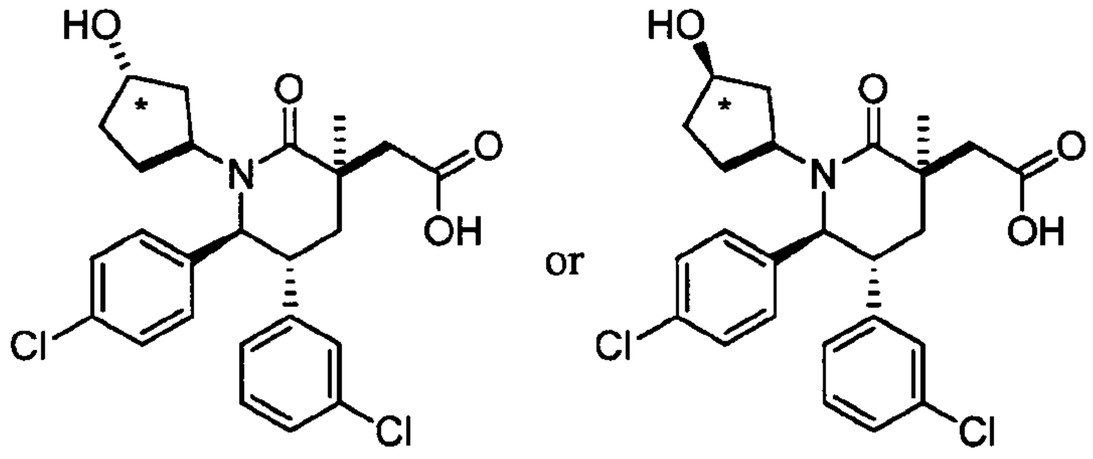


The residue was dissolved in DCM (1 mL) and HCl in ether (1M) (1 mL) was added and the solvent was removed under reduced pressure to provide the hydrochloride salt of one of the title compounds as the second eluting isomer.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 0.73 - 1.08 (7 H, m), 1.13 - 1.50 (7 H, m), 1.69 (6 H, d, *J* = 6.1 Hz), 7.54 (4 H, dd, *J* = 5.7 and 3.3 Hz), 7.72 (4 H, dd, *J* = 5.7 and 3.3 Hz). Mass Spectrum (ESI) m/z = 557 $[M + H]^+$.

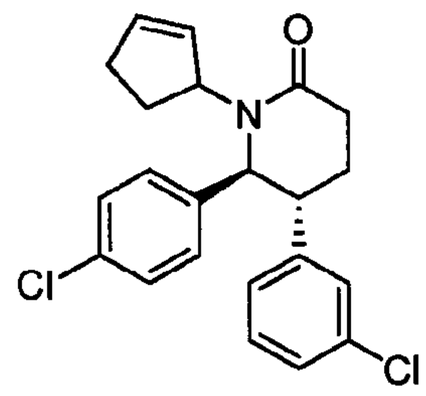
EXAMPLE 106

2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((1S,3S)-3-hydroxycyclopentyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid or 2-((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((1S,3R)-3-hydroxycyclopentyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid



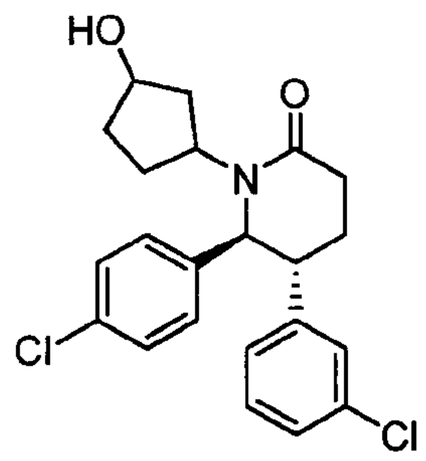
** stereochemistry unknown*

Step A. (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopent-2-enyl)piperidin-2-one.



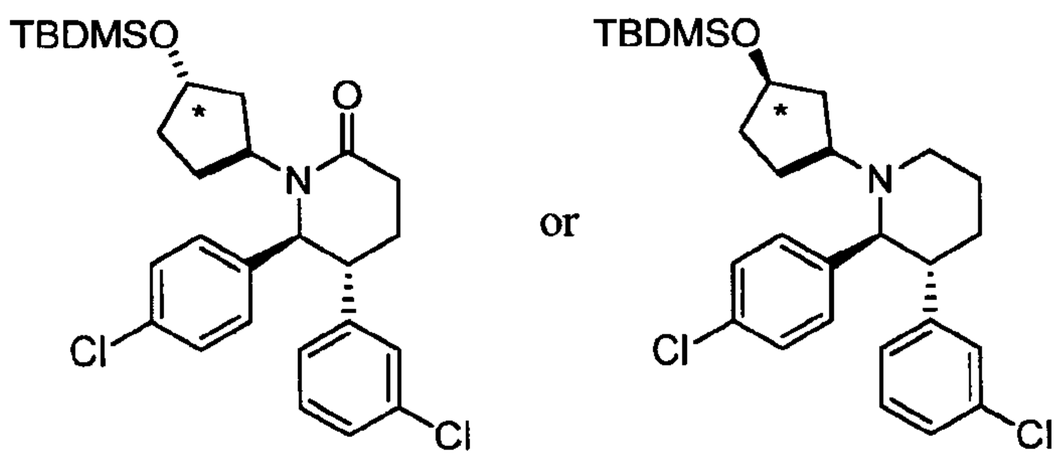
To a solution of 3.25 g (10.16 mmol) of (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one (Example 1, Step E) in DMF (150 mL) at 0 °C was added a dispersion of 60% sodium hydride in mineral oil (1.016 g, 25.4 mmol). Evolution of gas was observed. The cloudy reaction mixture was stirred at 0 °C for 20 min before adding 3-bromocyclopent-1-ene (4.48 g, 30.5 mmol). The cloudy reaction mixture warmed to room temperature and stirred at room temperature for 18 h. The reaction was quenched with sat. aq. NH_4Cl solution, diluted with EtOAc and the layers were separated. The organic layer was washed with 1M LiCl, sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 25 to 100% EtOAc in hexanes) to give the title compound as a 5:2 mixture of diastereomers.

Step B. (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(3-hydroxycyclopentyl)piperidin-2-one



To a solution of (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(cyclopent-2-enyl)piperidin-2-one (Example 106, Step A) (394 mg, 1.020 mmol) in THF (10 mL) was added borane tetrahydrofuran complex (1.0m in THF) (1020 μL, 1.020 mmol). Evolution of gas was observed. The reaction was stirred at room temperature for 30 min. before adding aq. NaOH (6 M) (1.25 mL) and 30% H_2O_2 (1.25 mL). The reaction mixture became cloudy and was stirred at room temperature for 1 h. The reaction mixture was extracted with EtOAc. The organic layers were washed with sat. aq. NaCl solution and dried over Na_2SO_4. The residue was purified by flash chromatography on silica gel (eluent: 40 to 100% EtOAc in hexanes) to give the title compound as a mixture of diastereomers.

Step C. (5R,6S)-1-((1S,3S)-3-((*tert*-Butyldimethylsilyl)oxy)cyclopentyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one or (2S,3R)-1-((1S,3R)-3-((*tert*-Butyldimethylsilyl)oxy)cyclopentyl)-3-(3-chlorophenyl)-2-(4-chlorophenyl)piperidine

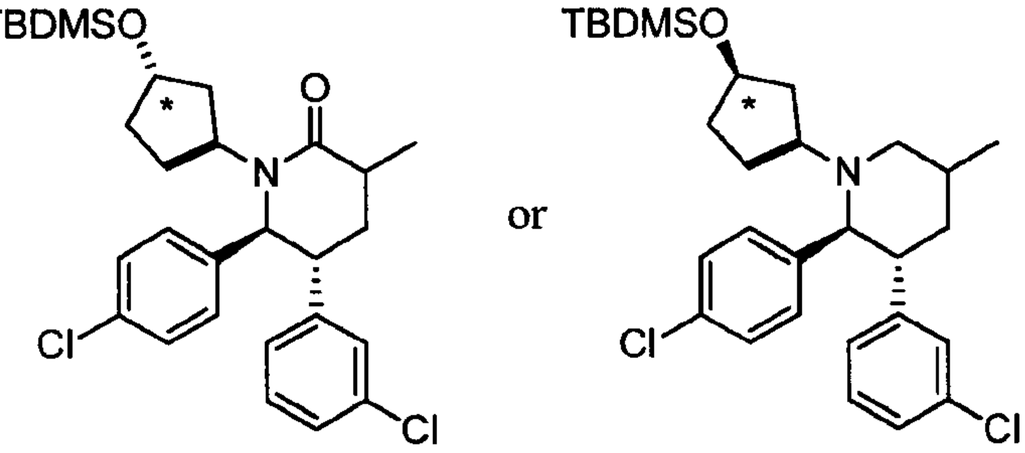


* *stereochemistry unknown*

To a solution of (5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(3-hydroxycyclopentyl)piperidin-2-one (Example 106, Step B) (175 mg, 0.433 mmol) in DMF (4 mL) at room temperature was added TBDMS-Cl (71.8 mg, 0.476 mmol) and imidazole (29.5 mg, 0.433 mmol). The reaction mixture was stirred at room temperature for 18 h. Additional imidazole (29.5 mg, 0.433 mmol) and TBDMS-Cl (71.8 mg, 0.476 mmol) were added. The reaction mixture was stirred at room temperature for 18 h and was then diluted with EtOAc,

washed with aq. 1M LiCl solution, 1M HCl and sat. aq. Na_2CO.solution. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 0 to 100% EtOAc in hexanes) to give the title compound as the major single isomer.

Step D. (5R,6S)-1-((1S,3S)-3-(*tert*-Butyldimethylsilyloxy)cyclopentyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one or (2S,3R)-1-((1S,3R)-3-((*tert*-Butyldimethylsilyl)oxy)cyclopentyl)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-5-methylpiperidine

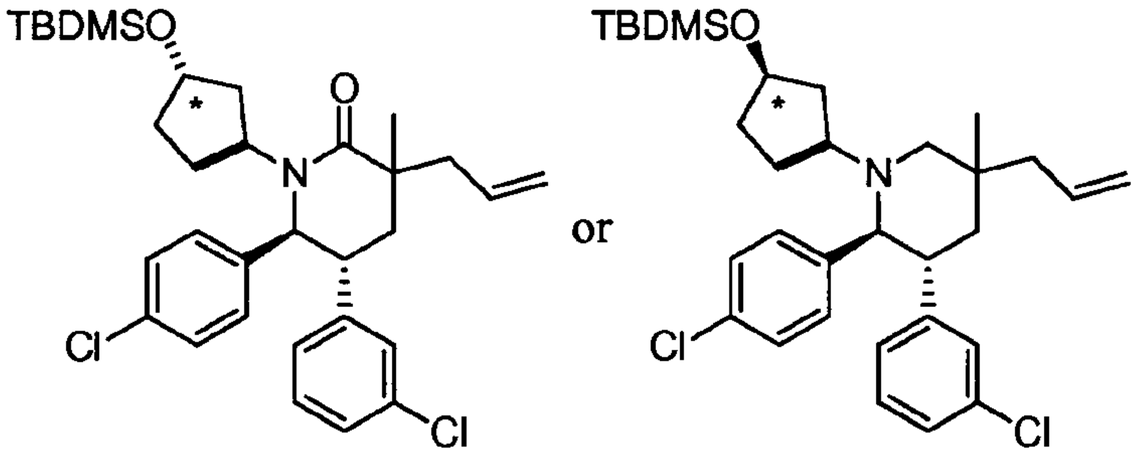


* *stereochemistry unknown*

To (5R,6S)-1-((1S,3S)-3-((*tert*-Butyldimethylsilyl)oxy)cyclopentyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)piperidin-2-one or (2S,3R)-1-((1S,3R)-3-((*tert*-Butyldimethylsilyl)oxy)cyclopentyl)-3-(3-chlorophenyl)-2-(4-chlorophenyl)piperidine from above (Example 106, Step C) (104 mg, 0.201 mmol) was added toluene (15 mL) and the mixture was concentrated under reduced pressure. This step was repeated three times. The residue was dissolved in inhibitor free THF (2 mL) that was previously degassed with Ar and the mixture was cooled to 0 °C under Ar. Methyliodide (13.79 μL, 0.221 mmol) was added followed by LHMDS (previously degassed with Ar) (1.0M in THF) (221 μL, 0.221 mmol). The reaction mixture was warmed to room temperature and stirred under Ar for 24 h. Additional LHMDS (1.0 M in THF) (221 μL, 0.221 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with sat. aq. NH_4Cl solution and extracted with EtOAc. The organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuo to provide the title compound.

Step E. (5R,6S)-3-Allyl-1-((1S,3S)-3-((tert-butyldimethylsilyl)oxy)cyclopentyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one or (2S,3R)-5-Allyl-1-((1S,3R)-3-

((tert-butyldimethylsilyl)oxy)cyclopentyl)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-5-methylpiperidine



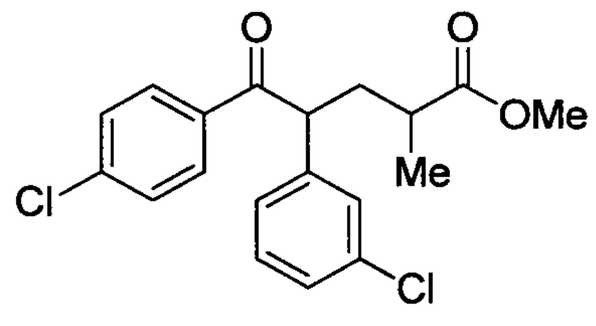
** stereochemistry unknown*

To (5R,6S)-1-((1S,3S)-3-(*tert*-Butyldimethylsilyloxy)cyclopentyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one or (2S,3R)-1-((1S,3R)-3-((*tert*-Butyldimethylsilyl)oxy)cyclopentyl)-3-(3-chlorophenyl)-2-(4-chlorophenyl)-5-methylpiperidine from above (Example 106, Step D) (107 mg, 0.201 mmol) was added toluene (15 mL) and the mixture was concentrated under reduced pressure. This step was repeated three times. The residue was dissolved in inhibitor free THF (2 mL) that was previously degassed with Ar and the mixture was cooled to 0 °C under Ar. Distilled allyl bromide (87 μL, 1.004 mmol) and LHMDS (1M in THF) (502 μL, 0.502 mmol) were added and the reaction mixture was warmed to room temperature and stirred at room temperature for 1 h before heating the reaction mixture at 50 °C under Ar overnight. The reaction mixture was cooled to room temperature and additional allyl bromide (87 μL, 1.004 mmol) and LHMDS (1.0 M in THF) (502 μL, 0.502 mmol) were added and the reaction mixture was heated to 60 °C for 6 h under Ar. The reaction mixture was cooled to room temperature and the reaction was quenched with sat. NH_4Cl solution and extracted with EtOAc. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 0 to 20% MTBE in hexanes) to give the title compound as a mixture of diastereomers.

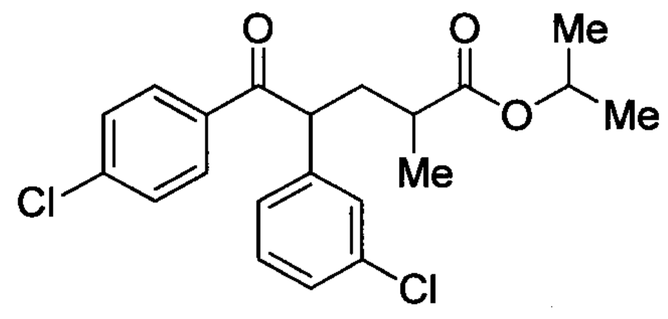
Step F. 2-((5R,6S)-1-((1S,3S)-3-(*tert*-Butyldimethylsilyloxy)cyclopentyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid or 2-((5R,6S)-1-((1S,3R)-3-((*tert*-Butyldimethylsilyl)oxy)cyclopentyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-3-yl)acetic acid

CLAIMS:

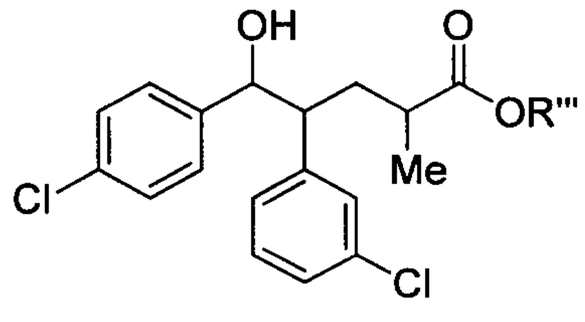
1. A compound, wherein the compound is a compound of formula



2. A compound, wherein the compound is a compound of formula



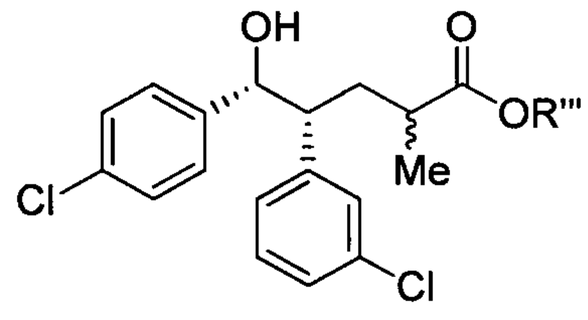
3. A compound, wherein the compound is a compound of formula



, wherein

R''' is hydrogen, methyl, or isopropyl.

4. The compound of claim 3, wherein the compound is a compound of formula

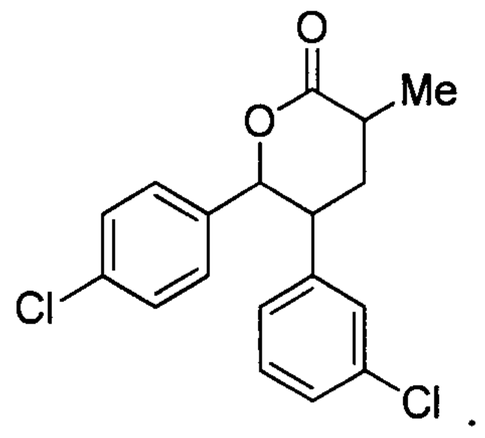


5. The compound of claim 3 or claim 4, wherein R''' is hydrogen.

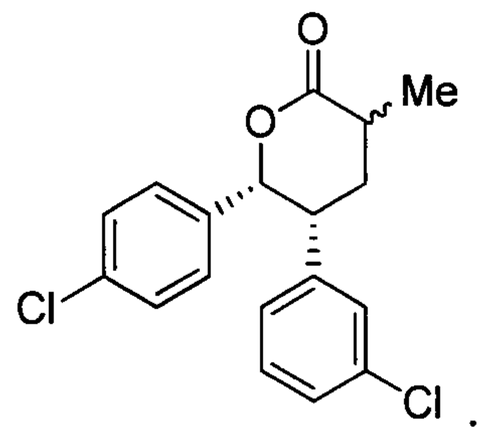
6. The compound of claim 3 or claim 4, wherein R''' is methyl.

7. The compound of claim 3 or claim 4, wherein R''' is isopropyl.

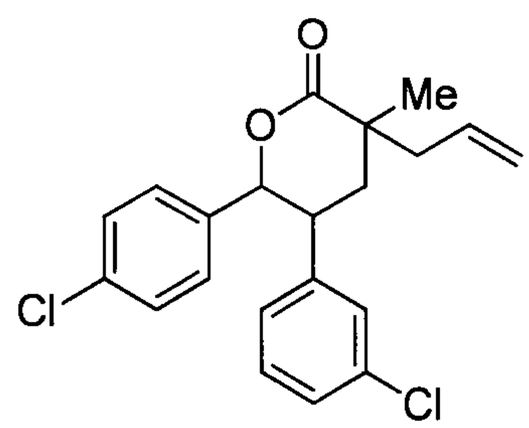
8. A compound, wherein the compound is a compound of formula



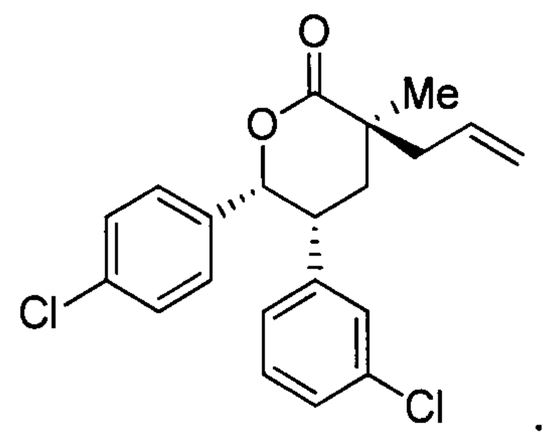
9. The compound of claim 8, wherein the compound is a compound of formula



10. A compound, wherein the compound is a compound of formula

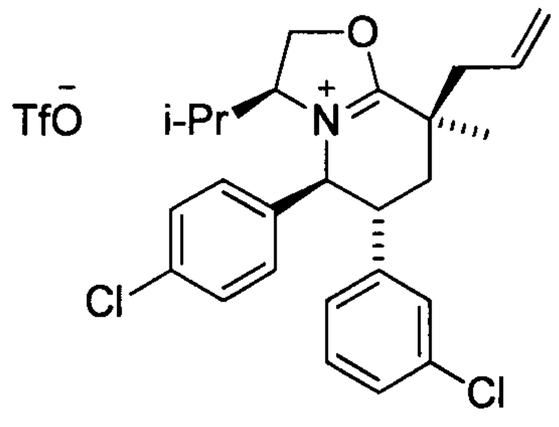


11. The compound of claim 10, wherein the compound is a compound of formula



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12. A compound, wherein the compound is a compound of formula



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