(86) Date de dépôt PCT/PCT Filing Date: 2007/01/25
(87) Date publication PCT/PCT Publication Date: 2007/08/16
(45) Date de délivrance/Issue Date: 2014/09/23
(85) Entrée phase nationale/National Entry: 2008/07/24
(86) N° demande PCT/PCT Application No.: US 2007/061012
(87) N° publication PCT/PCT Publication No.: 2007/092681
(30) Priorités/Priorities: 2006/01/27 (US60/762,801); 2007/01/23 (US11/625,874)

(51) Cl.Int./Int.Cl. C07D 211/08 (2006.01), A61K 31/445 (2006.01), C07D 401/12 (2006.01), C07D 405/12 (2006.01), C07D 417/12 (2006.01)

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(54) Titre : DERIVES DE PIPERIDINYL EN TANT QUE MODULATEURS DE L'ACTIVITE DU RECEPTEUR DE CHIMIOKINE
(54) Title: PIPERIDINYL DERIVATIVES AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

(57) Abrégé/Abstract:
The present application describes substituted piperidinyl modulators of MIP-1 or CCR-1 or stereoisomers or pharmaceutically acceptable salts thereof. In addition, methods of treating and preventing inflammatory diseases such as asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and transplant rejection using said modulators are disclosed.
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Title: PIPERIDINYL DERIVATIVES AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

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DEMANDES OU BREVETS VOLUMINEUX

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JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME _1_ OF _2_

NOTE: For additional volumes please contact the Canadian Patent Office.
PIPERIDINYL DERIVATIVES AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

FIELD OF THE INVENTION

This invention relates generally to modulators of chemokine receptor activity, pharmaceutical compositions containing the same, and methods of using the same as agents for treatment and prevention of inflammatory diseases, allergic and autoimmune diseases, and in particular, rheumatoid arthritis and transplant rejection.

BACKGROUND OF THE INVENTION

Chemokines are chemotactic cytokines, of molecular weight 6-15 kDa, that are released by a wide variety of cells to attract and activate, among other cell types, macrophages, T and B lymphocytes, eosinophils, basophils and neutrophils (reviewed in: Luster, *New Eng. J. Med.* 1998, 338, 436-445 and Rollins, *Blood* 1997, 90, 909-928). There are two major classes of chemokines, CXC and CC, depending on whether the first two cysteines in the amino acid sequence are separated by a single amino acid (CXC) or are adjacent (CC). The CXC chemokines, such as interleukin-8 (IL-8), neutrophil-activating protein-2 (NAP-2) and melanoma growth stimulatory activity protein (MGSA) are chemotactic primarily for neutrophils and T lymphocytes, whereas the CC chemokines, such as RANTES, MIP-1α, MIP-1β, the monocyte chemotactic proteins (MCP-1, MCP-2, MCP-3, MCP-4, and MCP-5) and the cotaxins (-1 and -2) are chemotactic for, among other cell types, macrophages, T lymphocytes, eosinophils, dendritic cells, and basophils. There also exist the chemokines lymphotactin-1, lymphotactin-2 (both C chemokines), and fractalkine (a CX3C chemokine) that do not fall into either of the major chemokine subfamilies.

The chemokines bind to specific cell-surface receptors belonging to the family of G-protein-coupled seven-transmembrane-domain proteins (reviewed in: Horuk, *Trends Pharm. Sci.* 1994, 15, 159-165) which are termed “chemokine receptors.” On binding their cognate ligands, chemokine receptors transduce an intracellular signal though the associated trimeric G proteins, resulting in, among other responses, a rapid increase in intracellular calcium concentration, changes in cell shape, increased expression of cellular adhesion molecules, degranulation, and

[0004] In addition to the mammalian chemokine receptors, mammalian cytomegaloviruses, herpesviruses and poxviruses have been shown to express, in infected cells, proteins with the binding properties of chemokine receptors (reviewed in: Wells and Schwartz, *Curr. Opin. Biotech.* 1997, 8, 741-748). Human CC chemokines, such as RANTES and MCP-3, can cause rapid mobilization of calcium via these virally encoded receptors. Receptor expression may be permissive for infection by allowing for the subversion of normal immune system surveillance and response to infection. Additionally, human chemokine receptors, such as CXCR4, CCR2, CCR3, CCR5 and CCR8, can act as co-receptors for the infection of mammalian cells by microbes as with, for example, the human immunodeficiency viruses (HIV).
The chemokines and their cognate receptors have been implicated as being important mediators of inflammatory, infectious, and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis (reviewed in: P. H. Carter, Current Opinion in Chemical Biology 2002, 6, 510; Trivedi, et al, Ann. Reports Med. Chem. 2000, 35, 191; Saunders and Tarby, Drug Disc. Today 1999, 4, 80; Premack and Schall, Nature Medicine 1996, 2, 1174). For example, the chemokine macrophage inflammatory protein-1 (MIP-1α) and its receptor CC Chemokine Receptor 1 (CCR-1) play a pivotal role in attracting leukocytes to sites of inflammation and in subsequently activating these cells. When the chemokine MIP-1α binds to CCR-1, it induces a rapid increase in intracellular calcium concentration, increased expression of cellular adhesion molecules, cellular degranulation, and the promotion of leukocyte migration.

In addition, demonstration of the chemotactic properties of MIP-1α in humans has been provided experimentally. Human subjects, when injected intradermally with MIP-1α, experienced a rapid and significant influx of leukocytes to the site of injection (Brummet, M. E. J. Immun. 2000, 164, 3392-3401).

Demonstration of the importance of the MIP-1α/CCR-1 interaction has been provided by experiments with genetically modified mice. MIP-1α −/− mice had normal numbers of leukocytes, but were unable to recruit monocytes into sites of viral inflammation after immune challenge (Cook, D., et al., Science. 1995, 269, 1583-1585). Recently, MIP-1α −/− mice were shown to be resistant to collagen antibody induced arthritis (Chintalacharuvu, S. R. Immun. Lett. 2005, 202-204). Likewise, CCR-1 −/− mice were unable to recruit neutrophils when challenged with MIP-1α in vivo; moreover, the peripheral blood neutrophils of CCR-1 null mice did not migrate in response to MIP-1α (Gao, B. et al. J. Exp. Med. 1997, 185, 1959-1968), thereby demonstrating the specificity of the MIP-1α/CCR-1 interaction. The viability and generally normal health of the MIP-1α −/− and CCR-1 −/− animals is noteworthy, in that disruption of the MIP-1α/CCR-1 interaction does not induce physiological crisis. Taken together, these data lead one to the conclusion that molecules that block the actions of MIP-1α would be useful in treating a number of inflammatory and
autoimmune disorders. This hypothesis has now been validated in a number of different animal disease models, as described below.

[0008] It is known that MIP-1α is elevated in the synovial fluid and blood of patients with rheumatoid arthritis (Alisa Koeh, et al., J. Clin. Invest. 1994, 93, 921–928). Moreover, several studies have demonstrated the potential therapeutic value of antagonism of the MIP-1α/CCR1 interaction in treating rheumatoid arthritis (Pease, J. E. & Horuk, R. Expert Opin. Invest. Drugs 2005, 14, 785-796).


[0010] It should also be noted that CCR-1 is also the receptor for the chemokines RANTES, MCP-3, HCC-1, Lkn-1/HCC-2, HCC-4, and MPIF-1 (Carter, P. H. Curr. Opin Chem. Bio. 2002, 6, 510-525). Since it is presumed that the new compounds of the present invention described herein antagonize MIP-1α by binding to the CCR-1 receptor, it may be that these compounds are also effective antagonists of the actions of the aforementioned ligand that are mediated by CCR-1. Accordingly, when reference is made herein to “antagonism of MIP-1α,” it is to be assumed that this is equivalent to “antagonism of chemokine stimulation of CCR-1.”


**SUMMARY OF THE INVENTION**

Accordingly, the present invention provides novel antagonists or partial agonists/antagonists of MIP-1\(\alpha\) or CCR-1 receptor activity, or pharmaceutically acceptable salts or prodrugs thereof.

The present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

The present invention provides a method for treating rheumatoid arthritis and transplant rejection, comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

The present invention provides a method for treating inflammatory diseases, comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

The present invention provides novel cyclic derivatives for use in therapy.

The present invention provides the use of novel cyclic derivatives for the manufacture of a medicament for the treatment of inflammatory diseases. These and other features of the invention, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that the substituted piperidinyl derivatives of the present invention are effective modulators of MIP-1\(\alpha\) and chemokine activity.

**DETAILED DESCRIPTION OF THE PRESENT INVENTION**

In one embodiment, the present invention provides novel compounds of formula (I):
or stereoisomers or prodrugs or pharmaceutically acceptable salt forms thereof, wherein:

5 the dashed line represents an optional double bond;

\[ T \text{ is } \begin{array}{c}
\text{C} \\
\text{O} \\
\text{N} \\
\text{O} \\
\text{S}
\end{array} \text{, or } \begin{array}{c}
\text{C} \\
\text{O} \\
\text{N} \\
\text{O} \\
\text{S}
\end{array};
\]

\( R_1 \) is alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl, all of which may be optionally substituted with 0-5 \( R_{1a} \);

\( R_{1a} \) at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, halo, \( \text{-NH}_2 \), \( \text{-CN} \), \( \text{-NO}_2 \), \( \text{-C(=O)OH} \), \( \text{-C(=O)O(CR_3R_8),R}_{10} \),

\( \text{-O(CF}_2)_n\text{CF}_3 \), \( \text{-O(CR}_8\text{R}_8)\text{R}_{10} \), \( \text{-OH} \), \( \text{-SH} \), \( \text{-S(CR}_8\text{R}_8)\text{R}_{10} \), \( \text{-S(O)H} \), \( \text{-P(O)H}_2 \),

\( \text{-C(=O)NR}_9\text{R}_{9a} \), \( \text{-NR}_9\text{R}_{9a} \), \( \text{-S(O)}_2\text{NR}_9\text{R}_{9a} \), \( \text{-NR}_9\text{S(O)}_2\text{(CF}_2)_n\text{CF}_3 \), \( \text{-C(=O)NR}_9\text{S(O)}_2\text{R}_6 \),

\( \text{-S(O)}_2\text{NR}_9\text{C(=O)OR}_6 \), \( \text{-S(O)}_2\text{NR}_9\text{C(=O)NR}_9\text{R}_{9a} \), \( \text{-C(=O)NR}_9\text{S(O)}_2\text{(CF}_2)_n\text{CF}_3 \),

\( \text{-C(=O)(CR}_8\text{R}_8)\text{R}_{10} \), \( \text{-NR}_9\text{C(=O)H} \), \( \text{-NR}_9\text{C(=O)(CR}_8\text{R}_8)\text{R}_{10} \), \( \text{-OC(=O)(CR}_8\text{R}_8)\text{R}_{10} \),

\( \text{-C(=NR}_9\text{R}_{9a})\text{NR}_9\text{R}_{9a} \), \( \text{-NHNC(=NR}_9\text{R}_{9a})\text{NR}_9\text{R}_{9a} \), \( \text{-S(O)(CR}_8\text{R}_8)\text{R}_{10} \), \( \text{-S(O)}_2\text{(CR}_8\text{R}_8)\text{R}_{10} \),

\( \text{-NR}_9\text{C(=O)OR}_6 \), \( \text{-NR}_9\text{S(O)}_2\text{R}_8 \), \( \text{-S(O)}_2\text{NR}_9\text{C(O)R}_6 \), aryloxy or arylalkyl, wherein the aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, aryloxy and arylalkyl may be optionally substituted with 0-3 \( R_{1b} \);

\( R_{1b} \) at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, halo, \( \text{-NH}_2 \), \( \text{-CN} \), \( \text{-NO}_2 \), \( \text{-C(=O)OH} \), \( \text{-C(=O)O(CR}_8\text{R}_8)\text{R}_{10} \),

\( \text{-O(CF}_2)_n\text{CF}_3 \), \( \text{-O(CR}_8\text{R}_8)\text{R}_{10} \), \( \text{-OH} \), \( \text{-SH} \), \( \text{-S(CR}_8\text{R}_8)\text{R}_{10} \), \( \text{-S(O)H} \), \( \text{-P(O)H}_2 \),

\( \text{-C(=O)NR}_9\text{R}_{9a} \), \( \text{-NR}_9\text{R}_{9a} \), \( \text{-S(O)}_2\text{NR}_9\text{R}_{9a} \), \( \text{-NR}_9\text{S(O)}_2\text{(CF}_2)_n\text{CF}_3 \), \( \text{-C(=O)NR}_9\text{S(O)}_2\text{R}_6 \),

\( \text{-S(O)}_2\text{NR}_9\text{C(=O)OR}_6 \), \( \text{-S(O)}_2\text{NR}_9\text{C(=O)NR}_9\text{R}_{9a} \), \( \text{-C(=O)NR}_9\text{S(O)}_2\text{(CF}_2)_n\text{CF}_3 \),

-
-C(=NR_{14})NR_{9}R_{9}, \ -NHC(=NR_{14})NR_{14}R_{14}, \ -S(=O)(CR_{8}R_{8})R_{10}, \ -S(O)_{2}(CR_{8}R_{8})R_{10},
-\ NR_{9}C(=O)OR_{8}, \ -NR_{9}S(O)_{2}R_{8}, \ \text{aryloxoy or arylalkyl;}

R_{2} \text{ is alkyl, cycloalkyl, cycloalkylalkyl, or alkenyl, wherein the alkyl may be}
onoptionally substituted with \text{-OH;}

R_{3}, \text{ at each occurrence, is alkyl; or any two R}_{3}^{'s} \text{ attached to the same carbon}
atom may form a 3- to 6- membered ring;  

W is hydrogen, F, -OH, -CN, -NH_{2};

R_{5} \text{ is halo, -CN or -Oalkyl; or}

W \text{ and one } R_{5} \text{ are taken together with the carbon atoms to which each is}
attached to form a 3- to 6-membered oxygen containing ring wherein said ring may
be optionally substituted with one or more R}_{3}^{'s};

R_{6}, \text{ at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl,}
aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R_{8}, \text{ at each occurrence, is independently hydrogen or alkyl;}

R_{9}, \text{ at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl,}
arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl, wherein the
aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl may be
optionally substituted with \text{0-5 } R_{9a}; \text{ and the heteroaryl, heteroarylalkyl, heterocyclyl}
or heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R_{9a}, \text{ at each occurrence, is independently selected from alkyl, haloalkyl, aryl,}
alkenyl, alkenyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl
heterocyclylalkyl, halo, -NH_{2}, -CN, -NO_{2}, -C(=O)OH, -C(=O)O(CR_{8}R_{8})R_{14},
-O(CF_{2})_{2}CF_{3}, \ -O(CR_{8}R_{8})R_{14}, \ -OH, \ -SH, \ -S(CR_{8}R_{8})R_{14}, \ -S(O)_{2}H_{2}, \ -P(O)_{3}H_{2},
-C(=O)NR_{14}R_{14}, \ -NR_{14}R_{14}, \ -S(O)_{2}NR_{14}R_{14}, \ -NR_{14}S(O)_{2}(CF_{2})_{2}CF_{3},
-C(=O)NR_{14}S(O)_{2}R_{6}, \ -S(O)_{2}NR_{14}(C(=O)NR_{14}R_{14},
-C(=O)NR_{14}S(O)_{2}(CF_{2})_{2}CF_{3}, \ -C(=O)(CR_{8}R_{8})R_{14}, \ -NR_{14}C(=O)H,
-NR_{14}C(=O)(CR_{8}R_{8})R_{14}, \ -OC(=O)(CR_{8}R_{8})R_{14}, \ -C(=NR_{14})NR_{14}R_{14},
-NHC(=NR_{14})NR_{14}R_{14}, \ -S(=O)(CR_{8}R_{8})R_{14}, \ -S(O)_{2}(CR_{8}R_{8})R_{14}, \ -NR_{14}C(=O)OR_{8},
-NR_{14}S(O)_{2}R_{8}, \ \text{aryloxoy or arylalkyl;}

R_{10}, \text{ at each occurrence, is independently selected from alkyl, aryl, arylalkyl,}
heterocyclyl or heterocyclylalkyl, wherein the alkyl, aryl, arylalkyl, heterocyclyl or
heterocyclalkyl may be optionally substituted with 0-3 $R_{10u}$, and the heterocycl and heterocyclalkyl contain 1-4 heteroatoms selected from N, O, and S;

$R_{10u}$, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocycl

heterocyclalkyl, halo, -NH$_2$, -CN, -NO$_2$, -C(=O)OH, -C(=O)O(CR$_3$R$_8$)$_m$R$_{14}$,
-$(CF_2)$CF$_3$, -O$(CR_3R_8)_m$R$_{14}$, -OH, -SH, -S$(CR_3R_8)_m$R$_{14}$, -S(O)$_2$H, -P(O)$_3$H$_2$,
-C(=O)NR$_4R_{14}$, -NR$_4R_{14}$, -S(O)$_2$NR$_4R_{14}$, -NR$_4S$(O)$_2$(CF$_2$)$_m$CF$_3$,
-C(=O)NR$_4$S(O)$_2$R$_6$, -S(O)$_2$NR$_4$C(=O)OR$_6$, -S(O)$_2$NR$_4$C(=O)NR$_4R_{14}$,
-C(=O)NR$_4$S(O)$_2$(CF$_2$)$_m$CF$_3$, -C(=O)(CR$_3$R$_8$)$_m$R$_{14}$, -NR$_4C(=O)H$,
-NR$_4C(=O)(CR_3R_8)_m$R$_{14}$, -OC(=O)(CR$_3$R$_8$)$_m$R$_{14}$, -C(=NR$_4$)NR$_4R_{14}$,
-NHC(=NR$_4$)NR$_4R_{14}$, -S(=O)(CR$_3$R$_8$)$_m$R$_{14}$, -S(O)$_2$(CR$_3$R$_8$)$_m$R$_{14}$, -NR$_4$C(=O)OR$_8$,
-NR$_4$S(O)$_2$R$_8$, aryloxy or aryalkyl;

$R_{14}$, at each occurrence, is independently selected from hydrogen, alkyl, cycloalkyl or phenyl;

m, at each occurrence, is 0-2;

n is 1-3; and

r is 0-5.

[0020] In another embodiment, compounds of Formula (I) are those compounds

having the formula (Ia):

![Diagram](image)

(Ia).

[0021] In another embodiment, compounds of the present invention are those in

which:

$T$ is $\begin{array}{c}
\text{O} \\
\text{R}_8 \\
\text{O} \\
\text{N} \\
\text{S} \\
\end{array}$,

or $\begin{array}{c}
\text{O} \\
\text{R}_8 \\
\text{O} \\
\end{array}$;
R₁ is alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl, all of which may be optionally substituted with 0-5 R₁₆;

R₁₆, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₈),R₁₀,
-O(CF₂)₃CF₃, -O(CR₃R₈),R₁₀, -OH, -SH, -S(CR₃R₈),R₁₀, -S(O)₃H, -P(O)₃H₂,
-C(=O)NR₉R₉, -NR₉R₉, -S(O)₂NR₉R₉, -NR₉S(O)(CF₂)₂CF₃, -C(=O)NR₉S(O)₂R₆,
-S(O)₂NR₉C(=O)OR₆, -S(O)₂NR₉C(=O)NR₉R₉, -C(=O)NR₉S(O)(CF₂)₂CF₃,
-C(=O)(CR₃R₈),R₁₀, -N₉R₉C(=O)H, -N₉R₉C(=O)(CR₃R₈),R₁₀, -OC(=O)(CR₃R₈),R₁₀,
-C(=N)=NR₉R₉, -NHC(=N)=NR₉R₉, -S(O)₂CR₃R₈),R₁₀, -S(O)₂CR₃R₈),R₁₀, -NR₉C(=O)OR₈, -NR₉S(O)₂R₈, -S(O)₂NR₉C(O)R₆, aryloxy or arylalkyl, wherein the aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl heterocyclylalkyl, aryloxy and arylalkyl may be optionally substituted with 0-3 R₁₆;

R₁₆, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₈),R₁₀,
-O(CF₂)₃CF₃, -O(CR₃R₈),R₁₀, -OH, -SH, -S(CR₃R₈),R₁₀, -S(O)₃H, -P(O)₃H₂,
-C(=O)NR₉R₉, -NR₉R₉, -S(O)₂NR₉R₉, -NR₉S(O)(CF₂)₂CF₃, -C(=O)NR₉S(O)₂R₆,
-S(O)₂NR₉C(=O)OR₆, -S(O)₂NR₉C(=O)NR₉R₉, -C(=O)NR₉S(O)(CF₂)₂CF₃,
-C(=O)(CR₃R₈),R₁₀, -N₉R₉C(=O)H, -N₉R₉C(=O)(CR₃R₈),R₁₀, -OC(=O)(CR₃R₈),R₁₀,
-C(=N)=NR₉R₉, -NHC(=N)=NR₉R₉, -S(O)₂CR₃R₈),R₁₀, -S(O)₂CR₃R₈),R₁₀, -NR₉C(=O)OR₈, -NR₉S(O)₂R₈, -S(O)₂NR₉C(O)R₆, aryloxy or arylalkyl;

R₂ is alkyl, cycloalkyl, cycloalkylalkyl, or alkenyl, wherein the alkyl may be optionally substituted with -OH;

R₃, at each occurrence, is alkyl; or any two R₃’s attached to the same carbon atom may form a 3- to 6- membered ring;

W is hydrogen, F, -OH, -NH₂;

R₅ is halo, -CN or -Oalkyl;

R₆, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroaryalkyl;

R₈, at each occurrence, is independently hydrogen or alkyl;
R₉, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylamyl, heterocyclyl or heterocyclalkyl, wherein the aryl, arylalkyl, heteroaryl, heteroarylamyl, heterocyclyl or heterocyclalkyl may be optionally substituted with 0-5 R₉ₙ, and the heteroaryl, heteroarylamyl, heterocyclyl or heterocyclalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₉ₙ, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylamyl, heterocyclyl or heterocyclalkyl; halogen, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₈), R₁₄, -O(CF₂)CF₃, -O(CR₃R₈), R₁₄, -OH, -SH, -S(CR₃R₈), R₁₄, -S(O)₂H, -P(O)₃H₂,

-C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)₂(CF₂)₂CF₃, -C(=O)NR₁₄S(O)₂R₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄,-C(=O)NR₁₄S(O)₂(CF₂)₂CF₃, -C(=O)(CR₃R₈), R₁₄, -NR₁₄C(=O)H, -NR₁₄C(=O)(CR₃R₈), R₁₄, -OC(=O)(CR₃R₈), R₁₄, -C(=NR₁₄)NR₁₄R₁₄, -NHC(=NR₁₄)NR₁₄R₁₄, -S(=O)(CR₃R₈), R₁₄, -S(O)₂(CR₃R₈), R₁₄, -NR₁₄C(=O)OR₆,

-NR₁₄S(O)₂R₆, aryloxy or arylalkyl;

R₁₀, at each occurrence, is independently selected from alkyl, aryl, arylalkyl, heterocyclyl or heterocyclalkyl, wherein the alkyl, aryl, arylalkyl, heterocyclyl or heterocyclalkyl may be optionally substituted with 0-3 R₁₀ₙ, and the heterocyclyl and heterocyclalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₁₀ₙ, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylamyl, heterocyclyl or heterocyclalkyl; halogen, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₈), R₁₄, -O(CF₂)CF₃, -O(CR₃R₈), R₁₄, -OH, -SH, -S(CR₃R₈), R₁₄, -S(O)₂H, -P(O)₃H₂,

-C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)₂(CF₂)₂CF₃, -C(=O)NR₁₄S(O)₂R₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄,-C(=O)NR₁₄S(O)₂(CF₂)₂CF₃, -C(=O)(CR₃R₈), R₁₄, -NR₁₄C(=O)H, -NR₁₄C(=O)(CR₃R₈), R₁₄, -OC(=O)(CR₃R₈), R₁₄, -C(=NR₁₄)NR₁₄R₁₄, -NHC(=NR₁₄)NR₁₄R₁₄, -S(=O)(CR₃R₈), R₁₄, -S(O)₂(CR₃R₈), R₁₄, -NR₁₄C(=O)OR₆,

-NR₁₄S(O)₂R₆, aryloxy or arylalkyl;

R₁₄, at each occurrence, is independently selected from hydrogen, alkyl, cycloalkyl or phenyl;

m, at each occurrence, is 0-2;
n is 1-2; and
r is 0-4.

In yet another embodiment, compounds of the present invention are those in which:

\[ \text{R}_1 \text{ is alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl, all of which may be optionally substituted with } 0-5 \text{ } \text{R}_{1a}; \]
\[ \text{R}_{1a}, \text{ at each occurrence, is independently selected from alkyl, haloalkyl, aryl, } \]
alkenyl, alkynyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CHR₈₂R₈₅)R₁₀,
-O(CF₂)₂CF₃, -O(CR₈₂R₈₅)R₁₀, -OH, -SH, -S(CR₈₂R₈₅)R₁₀, -S(O)₂H, -P(O)₂H₂,
-C(=O)NR₉₂R₉₅, -NR₉₂R₉₅, -S(O)₂R₉₂R₉₅, -NR₉₂S(O)₃R₉₅, -C(=O)NR₉₂S(O)₂R₉₅,
-S(O)₂NR₉₂C(=O)OR₆, -S(O)₂NR₉₂C(=O)NR₉₂R₉₅, -C(=O)NR₉₂S(O)₂(CF₂)₂CF₃,
-C(=NR₉₄)NR₉₂R₉₅, -NHC(=NR₉₄)NR₉₂R₉₅, -S(=O)(CR₈₂R₈₅)R₁₀, -S(O)₂(CR₈₂R₈₅)R₁₀,
-NR₉₂C(=O)OR₆, -NR₉₂S(O)₂R₉₅, -S(O)₂NR₉₂C(=O)R₆, aryloxy or arylalkyl, wherein the aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, aryloxy and arylalkyl may be optionally substituted with 0-3 \text{ } \text{R}_{1b}; \]
\[ \text{R}_{1b}, \text{ at each occurrence, is independently selected from alkyl, haloalkyl, aryl, } \]
alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CHR₈₂R₈₅)R₁₀,
-O(CF₂)₂CF₃, -O(CR₈₂R₈₅)R₁₀, -OH, -SH, -S(CR₈₂R₈₅)R₁₀, -S(O)₂H, -P(O)₂H₂,
-C(=O)NR₉₂R₉₅, -NR₉₂R₉₅, -S(O)₂R₉₂R₉₅, -NR₉₂S(O)₃(CF₂)₂CF₃, -C(=O)NR₉₂S(O)₂R₆,
-S(O)₂NR₉₂C(=O)OR₆, -S(O)₂NR₉₂C(=O)NR₉₂R₉₅, -C(=O)NR₉₂S(O)₂(CF₂)₂CF₃,
-C(=NR₉₄)NR₉₂R₉₅, -NHC(=NR₉₄)NR₉₂R₉₅, -S(=O)(CR₈₂R₈₅)R₁₀, -S(O)₂(CR₈₂R₈₅)R₁₀,
-NR₉₂C(=O)OR₆, -NR₉₂S(O)₂R₉₅, -S(O)₂NR₉₂C(=O)R₆, aryloxy or arylalkyl;
\[ \text{R}_2 \text{ is alkyl, cycloalkyl, or cycloalkylalkyl, wherein the alkyl may be optionally } \]
substituted with -OH;
R₃, at each occurrence, is alkyl; or any two R₃'s attached to the same carbon atom may form a 3- to 6- membered ring;

W is hydrogen, F, -OH, -NH₂;

R₅ is halo or -CN;

R₆, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R₈, at each occurrence, is independently hydrogen or alkyl;

R₉, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclolalkyl, wherein the aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclolalkyl may be optionally substituted with 0-5 R₉ₙ, and the heterocyclyl, heteroarylalkyl, heterocyclyl or heterocyclolalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₉ₙ, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclolalkyl, halo, -NH₂, -CN, -NO₂, -C=(=O)OH, -C(=O)O(CR₈R₉₈)R₁₄,

-O(CF₃)₂CF₃, -O(CR₈R₉₈)R₁₄, -OH, -SH, -S(CR₈R₉₈)R₁₄, -S(O)₃H, -P(O)₃H₂,

-C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)₂CF₃CF₃,

-C(=O)NR₁₄S(O)₂R₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄,

-C(=O)NR₁₄S(O)₂(CF₃)₂CF₃, -C(=O)(CR₈R₉₈)R₁₄, -NR₁₄C(=O)H,

-NR₁₄C(=O)(CR₈R₉₈)R₁₄, -OC(=O)(CR₈R₉₈)R₁₄, -C(=NR₁₄)NR₁₄R₁₄,

-NH(C(=NR₁₄)NR₁₄R₁₄, -S(=O)(CR₈R₉₈)R₁₄, -S(O)₂(CR₈R₉₈)R₁₄, -NR₁₄C(=O)OR₆,

-NR₁₄S(O)₂R₆, arylxy or arylalkyl;

R₁₀, at each occurrence, is independently selected from alkyl, aryl, arylalkyl, heterocyclyl or heterocyclolalkyl, wherein the alkyl, aryl, arylalkyl, heterocyclyl or heterocyclolalkyl may be optionally substituted with 0-3 R₁₀ₙ, and the heterocyclyl and heterocyclolalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₁₀ₙ, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclolalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₈R₉₈)R₁₄,
-C(=O)NR_{14}S(O)_{2}(CF_{2})_{n}CF_{3}, -C(=O)(CR_{8}R_{8})_{m}R_{14}, -NR_{14}C(=O)H,
-NR_{14}C(=O)(CR_{8}R_{8})_{m}R_{14}, -OC(=O)(CR_{8}R_{8})_{m}R_{14}, -C(=NR_{14})NR_{14}R_{14},
-NHC(=NR_{14})NR_{14}R_{14}, -S(=O)(CR_{8}R_{8})_{m}R_{14}, -S(O)_{2}(CR_{8}R_{8})_{m}R_{14}, -NR_{14}C(=O)OR_{8},
-NR_{14}S(O)_{2}R_{8}, aryloxy or arylalkyl;

R_{14}, at each occurrence, is independently selected from hydrogen, alkyl, cycloalkyl or phenyl;

m, at each occurrence, is 0-2;
n is 1-2; and
r is 0-3.

[0023] In still yet another embodiment, compounds of the present invention are those in which:

\[
\begin{array}{c}
\text{T is } \begin{array}{c}
\text{O} \\
\text{C} \\
\text{O} \\
\text{C} \\
\text{N} \\
\text{R}_{8}
\end{array} \quad \text{or} \quad \begin{array}{c}
\text{O} \\
\text{C} \\
\text{R}_{8}
\end{array} \\
\end{array}
\]

R_{1} is alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl, all of which may be optionally substituted with 0-5 R_{1a};

R_{1a}, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkylnyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl heterocyclylalkyl, halo, -NH_{2}, -CN, -NO_{2}, -C(=O)OH, -C(=O)O(CR_{8}R_{8})_{m}R_{10},
-O(CF_{2})_{n}CF_{3}, -O(CR_{8}R_{8})_{m}R_{10}, -OH, -SH, -S(CR_{8}R_{8})_{m}R_{10}, -S(O)_{2}H, -P(O)_{3}H_{2},
-C(=O)NR_{8}R_{9}, -NR_{8}R_{9}, -S(O)_{2}NR_{8}R_{9}, -NR_{8}S(O)_{2}(CF_{2})_{n}CF_{3}, -C(=O)NR_{8}S(O)_{2}R_{6},
-S(O)_{2}NR_{8}C(=O)OR_{6}, -S(O)_{2}NR_{8}C(=O)NR_{8}R_{9}, -C(=O)NR_{8}S(O)_{2}(CF_{2})_{n}CF_{3},
-C(=O)(CR_{8}R_{8})_{m}R_{10}, -NR_{8}C(=O)H, -NR_{8}C(=O)(CR_{8}R_{8})_{m}R_{10}, -OC(=O)(CR_{8}R_{8})_{m}R_{10},
-C(=NR_{14})NR_{8}R_{9}, -NHC(=NR_{14})NR_{14}R_{14}, -S(=O)(CR_{8}R_{8})_{m}R_{10}, -S(O)_{2}(CR_{8}R_{8})_{m}R_{10},
-NR_{8}C(=O)OR_{8}, -NR_{8}S(O)_{2}R_{8}, -S(O)_{2}NR_{8}C(O)R_{8}, aryloxy or arylalkyl, wherein the
aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl heterocyclylalkyl, aryloxy and arylalkyl may be optionally substituted with 0-3 R_{1b};

R_{1b}, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkylnyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl heterocyclylalkyl, halo, -NH_{2}, -CN, -NO_{2}, -C(=O)OH, -C(=O)O(CR_{8}R_{8})_{m}R_{10},
-O(CF_{2})_{n}CF_{3}, -O(CR_{8}R_{8})_{m}R_{10}, -OH, -SH, -S(CR_{8}R_{8})_{m}R_{10}, -S(O)_{2}H, -P(O)_{3}H_{2},

-13-
-C(=O)NR₉R₉, -NR₉R₉, -S(O)₂NR₉R₉, -NR₉S(O)₂(CF₃)₂CF₃, -C(=O)NR₉S(O)₃R₆,
-S(O)₂NR₉C(=O)OR₆, -S(O)₂NR₉C(=O)NR₉R₉, -C(=O)NR₉S(O)₃CF₃,
-C(=O)(CF₃)₃R₁₀, -NR₉C(=O)H, -NR₉C(=O)(CR₅R₆)₂R₁₀, -OC(=O)(CR₅R₆)₂R₁₀,
-C(=NR₉)NR₉R₉, -NHC(=NR₉)NR₁₄R₁₄, -S(=O)(CR₅R₆)₂R₁₀, -S(O)₂(CR₅R₆)₂R₁₀,
-NR₉C(=O)OR₈, -NR₉S(O)₂R₈, aryloxy or arylalkyl;

R₂ is alkyl or cycloalkyl, wherein the alkyl may be optionally substituted with
-OH;

R₃, at each occurrence, is alkyl; or any two R₃'s attached to the same carbon
atom may form a 3- to 6- membered ring;

W is hydrogen, F, -OH, -NH₂;

R₅ is halo;

R₆, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl,
aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R₈, at each occurrence, is independently hydrogen or alkyl;

R₉, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl,
arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl, wherein the
aryl, arylalkyl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl may be
optionally substituted with 0-5 R₉₈ and the heteroaryl, heteroarylalkyl, heterocyclyl
or heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₉₈, at each occurrence, is independently selected from alkyl, haloalkyl, aryl,
alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl
heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₅R₆)₂R₁₄,
-O(CF₃)₃CF₃, -O(CR₅R₆)₂R₁₄, -OH, -SH, -S(CR₅R₆)₂R₁₄, -S(O)₂H, -P(O)₃H₂,
-C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)₂(CF₃)₂CF₃,
-C(=O)NR₁₄S(O)₂CF₃, -C(=O)(CR₅R₆)₂R₁₄, -NR₁₄C(=O)H,
-NR₁₄C(=O)(CR₅R₆)₂R₁₄, -OC(=O)(CR₅R₆)₂R₁₄, -C(=NR₉)NR₁₄R₁₄,
-NHC(=NR₉)NR₁₄R₁₄, -S(=O)(CR₅R₆)₂R₁₄, -S(O)₂(CR₅R₆)₂R₁₄, -NR₁₄C(=O)OR₈,
-NR₁₄S(O)₂R₈, aryloxy or arylalkyl;

R₁₀, at each occurrence, is independently selected from alkyl, aryl, arylalkyl,
heterocyclyl or heterocyclylalkyl, wherein the alkyl, aryl, arylalkyl, heterocyclyl or
heterocyclylalkyl may be optionally substituted with 0-3 R$_{10a}$, and the heterocycl
and heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R$_{10a}$, at each occurrence, is independently selected from alkyl, haloalkyl, aryl,
alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycl
heterocyclylalkyl, halo, -NH$_2$, -CN, -NO$_2$, -C(=O)OH, -C(=O)O(CR$_3$R$_8$)$_2$R$_{14}$,
-O(CF$_2$)$_2$CF$_3$, -O(CR$_3$R$_8$)$_2$R$_{14}$, -OH, -SH, -S(CR$_3$R$_8$)$_2$R$_{14}$, -S(O)$_3$H, -P(O)$_3$H$_2$,
-C(=O)NR$_{14}$R$_{14}$, -NR$_{14}$R$_{14}$, -S(O)$_2$NR$_{14}$R$_{14}$, -NR$_{14}$S(O)$_2$(CF$_2$)$_2$CF$_3$,
-C(=O)NR$_{14}$S(O)$_2$R$_6$, -S(O)$_2$NR$_{14}$C(=O)OR$_6$, -S(O)$_2$NR$_{14}$C(=O)NR$_{14}$R$_{14}$,
-C(=O)NR$_{14}$S(O)$_2$(CF$_2$)$_2$CF$_3$, -C(=O)(CR$_3$R$_8$)$_3$R$_{14}$, -NR$_{14}$C(=O)H,
-NH(C=NR$_{14}$)NR$_{14}$R$_{14}$, -OC(=O)(CR$_3$R$_8$)$_3$R$_{14}$, -C(=NR$_{14}$)NR$_{14}$R$_{14}$,
-NHC(=NR$_{14}$)NR$_{14}$R$_{14}$, -S(=O)(CR$_3$R$_8$)$_3$R$_{14}$, -S(O)$_2$(CR$_3$R$_8$)$_3$R$_{14}$, -NR$_{14}$C(=O)OR$_8$,
-NR$_{14}$S(O$_2$)R$_8$, arylalkoxy or arylalkyl;

R$_{14}$, at each occurrence, is independently selected from hydrogen, alkyl,
cycloalkyl or phenyl;

m, at each occurrence, is 0-2;

n is 1-2; and

r is 0-2.

[0024] In yet another embodiment, compounds of the present invention are those
in which:

\[
\begin{align*}
T & = \text{C} \quad ; \\
R_j & \text{ is alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl, all of which may be}
\text{optionally substituted with 0-5 R$_{14}$;} \\
R_{18} & \text{ at each occurrence, is independently selected from alkyl, haloalkyl, aryl,}
\text{alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycl}
\text{heterocyclylalkyl, halo, -NH$_2$, -CN, -NO$_2$, -C(=O)OH, -C(=O)O(CR$_3$R$_8$)$_2$R$_{14}$,
-O(CF$_2$)$_2$CF$_3$, -O(CR$_3$R$_8$)$_2$R$_{14}$, -OH, -SH, -S(CR$_3$R$_8$)$_2$R$_{14}$, -S(O)$_3$H, -P(O)$_3$H$_2$,
-C(=O)NR$_{14}$R$_{14}$, -NR$_{14}$R$_{14}$, -S(O)$_2$NR$_{14}$R$_{14}$, -NR$_{14}$S(O)$_2$(CF$_2$)$_2$CF$_3$,
-C(=O)NR$_{14}$S(O)$_2$R$_6$, -S(O)$_2$NR$_{14}$C(=O)OR$_6$, -S(O)$_2$NR$_{14}$C(=O)NR$_{14}$R$_{14}$,
-C(=O)NR$_{14}$S(O)$_2$(CF$_2$)$_2$CF$_3$, -C(=O)(CR$_3$R$_8$)$_3$R$_{14}$, -NR$_{14}$C(=O)H,
-NH(C=NR$_{14}$)NR$_{14}$R$_{14}$, -OC(=O)(CR$_3$R$_8$)$_3$R$_{14}$, -C(=NR$_{14}$)NR$_{14}$R$_{14}$,
-NH(C=NR$_{14}$)NR$_{14}$R$_{14}$, -OC(=O)(CR$_3$R$_8$)$_3$R$_{14}$, -C(=NR$_{14}$)NR$_{14}$R$_{14}$,
-NHC(=NR$_{14}$)NR$_{14}$R$_{14}$, -S(=O)(CR$_3$R$_8$)$_3$R$_{14}$, -S(O)$_2$(CR$_3$R$_8$)$_3$R$_{14}$, -NR$_{14}$C(=O)OR$_8$,
-NR$_{14}$S(O$_2$)R$_8$, arylalkoxy or arylalkyl;
\end{align*}
\]
-NR₉C(=O)OR₈, -NR₉S(O)₂R₈, -S(O)₂NR₉C(O)R₆, aryloxy or arylalkyl, wherein the ary1, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl
heterocyclylalkyl, aryloxy and arylalkyl may be optionally substituted with 0-3 R₁₆;

R₁₆, at each occurrence, is independently selected from alkyl, haloalkyl, aryl,
alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl
heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅), R₁₀,
-O(CF₂)₄CF₃, -O(CR₃R₅), R₁₀, -OH, -SH, -S(CR₃R₅), R₁₀, -S(O)₂H, -P(O)₂H₂,
-C(=O)NR₉R₉, -NR₉R₈, -S(O)₂NR₉R₈, -NR₉S(O)₂(CF₂)₄CF₃, -C(=O)NR₉S(O)₂R₆,
-S(O)₂NR₉C(=O)OR₆, -S(O)₂NR₉C(=O)NR₉R₈, -C(=O)NR₉S(O)₂(CF₂)₄CF₃,

-C(=O)(CR₃R₅), R₁₀, -NR₉C(=O)H, -NR₉C(=O)(CR₃R₅), R₁₀, -OC(=O)(CR₃R₅), R₁₀,
-C(=NR₁₄)NR₉R₉, -NHC(=NR₁₄)NR₁₄R₁₄, -S(O)(CR₃R₅), R₁₄, -S(O)₂(CR₃R₅), R₁₄,
-NR₉C(=O)OR₈, -NR₉S(O)₂R₈, aryloxy or arylalkyl;

R₂ is alkyl or cycloalkyl, wherein the alkyl may be optionally substituted with
-OH;

R₃, at each occurrence, is alkyl;

W is hydrogen, -OH or -NH₂;

R₅ is halo;

R₆, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl,
aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R₈, at each occurrence, is independently hydrogen or alkyl;

R₉, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl,
arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl, wherein the
aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl may be
optionally substituted with 0-5 R₉₉, and the heteroaryl, heteroarylalkyl, heterocyclyl
or heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₉₉, at each occurrence, is independently selected from alkyl, haloalkyl, aryl,
alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl
heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅), R₁₄,
-O(CF₂)₄CF₃, -O(CR₃R₅), R₁₄, -OH, -SH, -S(CR₃R₅), R₁₄, -S(O)₂H, -P(O)₂H₂,
-C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)₂(CF₂)₄CF₃,
-C(=O)NR₁₄S(O)₂R₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄,
-C(=O)NR₁₄S(O)₂(CF₂)₄CF₃, -C(=O)(CR₃R₅), R₁₄, -NR₁₄C(=O)H,
-NR_{14}C(-O)(CR_{8}R_{8})_{2}R_{14}, -OC(-O)(CR_{8}R_{8})_{2}R_{14}, -C(-NR_{14})NR_{14}R_{14},
-NHC(-NR_{14})NR_{14}R_{14}, -S(-O)(CR_{8}R_{8})_{2}R_{14}, -S(O)_{2}(CR_{8}R_{8})_{2}R_{14}, -NR_{14}C(-O)OR_{8},
-NR_{14}S(O_{2})R_{8}, aryloxy or arylalkyl;

R_{10}, at each occurrence, is independently selected from alkyl, aryl, arylalkyl,
5 heterocyclyl or heterocyclylalkyl, wherein the alkyl, aryl, arylalkyl, heterocyclyl or
heterocyclylalkyl may be optionally substituted with 0-3 R_{10a}, and the heterocyclyl
and heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R_{10a}, at each occurrence, is independently selected from alkyl, haloalkyl, aryl,
alkenyl, alkylnyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl
10 heterocyclylalkyl, halo, -NH_{2}, -CN, -NO_{2}, -C(-O)OH, -C(-O)O(CR_{8}R_{8})_{2}R_{14},
-O(CF_{2})_{2}CF_{3}, -O(CR_{8}R_{8})_{2}R_{14}, -OH, -SH, -S(CR_{8}R_{8})_{2}R_{14}, -S(O)_{2}H, -P(O)_{2}H_{2},
-C(-O)NR_{14}R_{14}, -NR_{14}R_{14}, -S(O)_{2}NR_{14}R_{14}, -NR_{14}S(O)_{2}(CF_{2})_{2}CF_{3},
-C(-O)NR_{14}S(O)_{2}R_{8}, -S(O)_{2}NR_{14}C(-O)OR_{8}, -S(O)_{2}NR_{14}C(-O)NR_{14}R_{14},
-C(-O)NR_{14}S(O)_{2}(CF_{2})_{2}CF_{3}, -C(-O)(CR_{8}R_{8})_{2}R_{14}, -NR_{14}C(-O)H,
15 -NR_{14}C(-O)(CR_{8}R_{8})_{2}R_{14}, -OC(-O)(CR_{8}R_{8})_{2}R_{14}, -C(-NR_{14})NR_{14}R_{14},
-NHC(-NR_{14})NR_{14}R_{14}, -S(-O)(CR_{8}R_{8})_{2}R_{14}, -S(O)_{2}(CR_{8}R_{8})_{2}R_{14}, -NR_{14}C(-O)OR_{8},
-NR_{14}S(O_{2})R_{8}, aryloxy or arylalkyl;

R_{14}, at each occurrence, is independently selected from hydrogen, alkyl,
cycloalkyl or phenyl;

m, at each occurrence, is 0-2;

n is 1-2; and

r is 0-2.

[0025] In another embodiment, compounds of the present invention are those in
25 which:

T is \( \begin{array}{c}
\bigodot \\
\bigotimes \\
\bigcirc \\
\end{array} \);

R_{1} is alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl, all of which may be
optionally substituted with 0-5 R_{1a};

R_{1a}, at each occurrence, is independently selected from alkyl, haloalkyl, aryl,
alkenyl, alkylnyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl
heterocyclylalkyl, halo, -NH_{2}, -CN, -NO_{2}, -C(-O)OH, -C(-O)O(CR_{8}R_{8})_{2}R_{10},
-O(CF\textsubscript{2})\textsubscript{3}CF\textsubscript{3}, -O(CR\textsubscript{8}R\textsubscript{8})\textsubscript{3}R\textsubscript{10}, -OH, -SH, -S(CR\textsubscript{8}R\textsubscript{8})\textsubscript{3}R\textsubscript{10}, -S(O)\textsubscript{3}H, -P(O)\textsubscript{3}H\textsubscript{2},
-C(=O)NR\textsubscript{9}R\textsubscript{9}, -NR\textsubscript{8}R\textsubscript{9}, -S(O)\textsubscript{2}NR\textsubscript{9}R\textsubscript{9}, -NR\textsubscript{9}S(O)\textsubscript{2}(CF\textsubscript{2})\textsubscript{3}CF\textsubscript{3}, -C(=O)NR\textsubscript{8}S(O)\textsubscript{2}R\textsubscript{6},
-S(O)\textsubscript{2}NR\textsubscript{9}C(=O)OR\textsubscript{6}, -S(O)\textsubscript{2}NR\textsubscript{9}C(=O)NR\textsubscript{9}R\textsubscript{9}, -C(=O)NR\textsubscript{8}S(O)\textsubscript{2}(CF\textsubscript{2})\textsubscript{3}CF\textsubscript{3},
-C(=O)(CR\textsubscript{8}R\textsubscript{8})\textsubscript{3}R\textsubscript{10}, -NR\textsubscript{9}C(=O)H, -NR\textsubscript{9}C(=O)(CR\textsubscript{8}R\textsubscript{8})\textsubscript{3}R\textsubscript{10}, -OC(=O)(CR\textsubscript{8}R\textsubscript{8})\textsubscript{3}R\textsubscript{10},
-C(=NR\textsubscript{14})NR\textsubscript{9}R\textsubscript{9}, -NHC(=NR\textsubscript{14})NR\textsubscript{14}R\textsubscript{14}, -S(=O)(CR\textsubscript{8}R\textsubscript{8})\textsubscript{3}R\textsubscript{10}, -S(O)\textsubscript{2}(CR\textsubscript{8}R\textsubscript{8})\textsubscript{3}R\textsubscript{10},
-NR\textsubscript{9}C(=O)OR\textsubscript{8}, -NR\textsubscript{9}S(O)\textsubscript{2}R\textsubscript{8}, -S(O)\textsubscript{2}NR\textsubscript{9}C(O)R\textsubscript{6}, aryloxy or arylalkyl, wherein the
aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylmethyl, heterocyclcyl
heterocyclylalkyl, aryloxy and arylalkyl may be optionally substituted with 0-3 R\textsubscript{16}; 

R\textsubscript{1b}, at each occurrence, is independently selected from alkyl, haloalkyl, aryl,
alkenyl, alkylnyl, cycloalkylalkyl, cycloalkylalkylalkyl, heteroaryl, heteroarylmethyl, heterocyclcyl
heterocyclylalkyl, halo, -NH\textsubscript{2}, -CN, -NO\textsubscript{2}, -C(=O)OH, -C(=O)O(CR\textsubscript{8}R\textsubscript{8})\textsubscript{3}R\textsubscript{10},
-O(CF\textsubscript{2})\textsubscript{3}CF\textsubscript{3}, -O(CR\textsubscript{8}R\textsubscript{8})\textsubscript{3}R\textsubscript{10}, -OH, -SH, -S(CR\textsubscript{8}R\textsubscript{8})\textsubscript{3}R\textsubscript{10}, -S(O)\textsubscript{3}H, -P(O)\textsubscript{3}H\textsubscript{2},
-C(=O)NR\textsubscript{9}R\textsubscript{9}, -NR\textsubscript{8}R\textsubscript{9}, -S(O)\textsubscript{2}NR\textsubscript{9}R\textsubscript{9}, -NR\textsubscript{9}S(O)\textsubscript{2}(CF\textsubscript{2})\textsubscript{3}CF\textsubscript{3}, -C(=O)NR\textsubscript{8}S(O)\textsubscript{2}R\textsubscript{6},
-S(O)\textsubscript{2}NR\textsubscript{9}C(=O)OR\textsubscript{6}, -S(O)\textsubscript{2}NR\textsubscript{9}C(=O)NR\textsubscript{9}R\textsubscript{9}, -C(=O)NR\textsubscript{8}S(O)\textsubscript{2}(CF\textsubscript{2})\textsubscript{3}CF\textsubscript{3},
-C(=O)(CR\textsubscript{8}R\textsubscript{8})\textsubscript{3}R\textsubscript{10}, -NR\textsubscript{9}C(=O)H, -NR\textsubscript{9}C(=O)(CR\textsubscript{8}R\textsubscript{8})\textsubscript{3}R\textsubscript{10}, -OC(=O)(CR\textsubscript{8}R\textsubscript{8})\textsubscript{3}R\textsubscript{10},
-C(=NR\textsubscript{14})NR\textsubscript{9}R\textsubscript{9}, -NHC(=NR\textsubscript{14})NR\textsubscript{14}R\textsubscript{14}, -S(=O)(CR\textsubscript{8}R\textsubscript{8})\textsubscript{3}R\textsubscript{10}, -S(O)\textsubscript{2}(CR\textsubscript{8}R\textsubscript{8})\textsubscript{3}R\textsubscript{10},
-NR\textsubscript{9}C(=O)OR\textsubscript{8}, -NR\textsubscript{9}S(O)\textsubscript{2}R\textsubscript{8}, aryloxy or arylalkyl;

R\textsubscript{2} is alkyl or cycloalkyl;
R\textsubscript{3}, at each occurrence, is alkyl;

W is hydrogen or -OH;

R\textsubscript{5} is halo;
R\textsubscript{6}, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl,
arly, arylalkyl, heteroaryl or heteroarylmethyl;
R\textsubscript{6}, at each occurrence, is independently hydrogen or alkyl;

R\textsubscript{9}, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl,
arlyalkyl, heteroaryl, heteroarylmethyl, heterocyclcyl or heterocyclylalkyl, wherein the
aryl, arylalkyl, heteroaryl, heteroarylmethyl, heterocyclcyl or heterocyclylalkyl may be
optionally substituted with 0-5 R\textsubscript{9a}, and the heteroaryl, heteroarylmethyl, heterocyclcyl
or heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R\textsubscript{9a}, at each occurrence, is independently selected from alkyl, haloalkyl, aryl,
alkenyl, alkylnyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylmethyl, heterocyclcyl
heterocyclylalkyl, halo, -NH\textsubscript{2}, -CN, -NO\textsubscript{2}, -C(=O)OH, -C(=O)O(CR\textsubscript{8}R\textsubscript{8})\textsubscript{3}R\textsubscript{14},

- 18 -
-O(CF2)nCF3, -O(CR8R8)nR14, -OH, -SH, -S(CR8R8)nR14, -S(O)2H, -P(O)2H2,
-C(=O)NR14R14, -NR14R14, -S(O)2NR14R14, -NR14S(O)2(CF2)3CF3,
-C(=O)NR14S(O)2R6, -S(O)2NR14C(=O)OR6, -S(O)2NR14C(=O)NR14R14,
-C(=O)NR14S(O)2(CF2)3CF3, -C(=O)(CR8R8)nR14, -NR14C(=O)H,
5
-NR14C(=O)(CR8R8)nR14, -OC(=O)(CR8R8)nR14, -C(=NR14)NR14R14,
-NHC(=NR14)NR14R14, -S(=O)(CR8R8)nR14, -S(O)2(CR8R8)nR14, -NR14C(=O)OR8,
-NR14S(O)2R8, aryloxy or arylalkyl;

R10, at each occurrence, is independently selected from alkyl, aryl, arylalkyl,
heterocyclyl or heterocyclylalkyl, wherein the alkyl, aryl, arylalkyl, heterocyclyl or
heterocyclylalkyl may be optionally substituted with 0-3 R10a, and the heterocyclyl
and heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R10a, at each occurrence, is independently selected from alkyl, haloalkyl, aryl,
alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl
heterocyclylalkyl, halo, -NH2, -CN, -NO2, -C(=O)OH, -C(=O)(CR8R8)nR14,
15
-O(CF2)nCF3, -O(CR8R8)nR14, -OH, -SH, -S(CR8R8)nR14, -S(O)2H, -P(O)2H2,
-C(=O)NR14R14, -NR14R14, -S(O)2NR14R14, -NR14S(O)2(CF2)3CF3,
-C(=O)NR14S(O)2R6, -S(O)2NR14C(=O)OR6, -S(O)2NR14C(=O)NR14R14,
-C(=O)NR14S(O)2(CF2)3CF3, -C(=O)(CR8R8)nR14, -NR14C(=O)H,
-NR14C(=O)(CR8R8)nR14, -OC(=O)(CR8R8)nR14, -C(=NR14)NR14R14,
20
-NHC(=NR14)NR14R14, -S(=O)(CR8R8)nR14, -S(O)2(CR8R8)nR14, -NR14C(=O)OR8,
-NR14S(O)2R8, aryloxy or arylalkyl;

R14, at each occurrence, is independently selected from hydrogen, alkyl,
cycloalkyl or phenyl;

m, at each occurrence, is 0-2;

n is 1-2; and

r is 0-2.

[0026] In one embodiment, the present invention provides novel compounds of
formula (Ib):
or stereoisomers or prodrugs or pharmaceutically acceptable salt forms thereof,
wherein:

\[
T = \begin{array}{c}
\text{O} & \text{N} & \text{O} \\
\text{O} & \text{O} & \text{O} \\
\end{array}
\]

\( R_1 \) is alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl, all of which may be optionally substituted with 0-5 \( R_{1a} \);

\( R_{1b} \), at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl

\[
\text{heterocyclylalkyl, halo, } -\text{NH}_2, -\text{CN}, -\text{NO}_2, -\text{C}(=\text{O})\text{OH}, -\text{C}(=\text{O})\text{O(CR}_3\text{R}_8)\text{R}_{10}, -\text{O(CF}_2\text{CF}_3}, -\text{O(CR}_3\text{R}_8)\text{R}_{10}, -\text{OH}, -\text{SH}, -\text{S(CR}_3\text{R}_8)\text{R}_{10}, -\text{S(O)}_2\text{H}, -\text{P(O)}_3\text{H}_2,
\]

\[
-\text{C}(=\text{O})\text{NR}_9\text{R}_9, -\text{NR}_9\text{R}_9, -\text{S(O)}_2\text{NR}_9\text{R}_9, -\text{NR}_9\text{S(O)}_2\text{CF}_2\text{CF}_3, -\text{C}(=\text{O})\text{NR}_9\text{S(O)}_2\text{R}_6,
\]

\[
-\text{S(O)}_2\text{NR}_9\text{C}(=\text{O})\text{OR}_6, -\text{S(O)}_2\text{NR}_9\text{C}(=\text{O})\text{NR}_9\text{R}_9, -\text{C}(=\text{O})\text{NR}_9\text{S(O)}_2\text{CF}_2\text{CF}_3,
\]

\[
-\text{C}(=\text{O})(\text{CR}_3\text{R}_8)\text{R}_{10}, -\text{NR}_9\text{C}(=\text{O})\text{H}, -\text{NR}_9\text{C}(=\text{O})(\text{CR}_3\text{R}_8)\text{R}_{10}, -\text{OC}(=\text{O})(\text{CR}_3\text{R}_8)\text{R}_{10},
\]

\[
-\text{NR}_9\text{C}(=\text{O})\text{OR}_8, -\text{NR}_9\text{S(O)}_2\text{R}_8, -\text{S(O)}_2\text{NR}_9\text{C}(=\text{O})\text{R}_6, \text{aryloxy or arylalkyl, wherein the aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl}
\]

\[
\text{heterocyclylalkyl, arylloxy and arylalkyl may be optionally substituted with 0-3 } R_{1b};
\]

\( R_{1b} \), at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl

\[
\text{heterocyclylalkyl, halo, } -\text{NH}_2, -\text{CN}, -\text{NO}_2, -\text{C}(=\text{O})\text{OH}, -\text{C}(=\text{O})\text{O(CR}_3\text{R}_8)\text{R}_{10}, -\text{O(CF}_2\text{CF}_3}, -\text{O(CR}_3\text{R}_8)\text{R}_{10}, -\text{OH}, -\text{SH}, -\text{S(CR}_3\text{R}_8)\text{R}_{10}, -\text{S(O)}_2\text{H}, -\text{P(O)}_3\text{H}_2,
\]

\[
-\text{C}(=\text{O})\text{NR}_9\text{R}_9, -\text{NR}_9\text{R}_9, -\text{S(O)}_2\text{NR}_9\text{R}_9, -\text{NR}_9\text{S(O)}_2\text{CF}_2\text{CF}_3, -\text{C}(=\text{O})\text{NR}_9\text{S(O)}_2\text{R}_6,
\]

\[
-\text{S(O)}_2\text{NR}_9\text{C}(=\text{O})\text{OR}_6, -\text{S(O)}_2\text{NR}_9\text{C}(=\text{O})\text{NR}_9\text{R}_9, -\text{C}(=\text{O})\text{NR}_9\text{S(O)}_2\text{CF}_2\text{CF}_3,
\]

\[
-\text{C}(=\text{O})(\text{CR}_3\text{R}_8)\text{R}_{10}, -\text{NR}_9\text{C}(=\text{O})\text{H}, -\text{NR}_9\text{C}(=\text{O})(\text{CR}_3\text{R}_8)\text{R}_{10}, -\text{OC}(=\text{O})(\text{CR}_3\text{R}_8)\text{R}_{10},
\]

\[
-\text{NR}_9\text{C}(=\text{O})\text{OR}_8, -\text{NR}_9\text{S(O)}_2\text{R}_8, -\text{S(O)}_2\text{NR}_9\text{C}(=\text{O})\text{R}_6, \text{aryloxy or arylalkyl}.
\]

- 20 -
R₂ is alkyl, cycloalkyl, cycloalkylalkyl, arylalkyl, -CH₂CH₂CH₂NH(C=NR₁₄)NR₁₄R₁₄, -CH₂CH₂S(CR₈R₈)₂R₁₀ or -CH₂CH₂CN, wherein the alkyl and arylalkyl may be optionally substituted with -OH;

R₄, at each occurrence, is F, -OH or alkyl; or any two alkyl R₄’s attached to the same carbon atom may form a 3- to 6-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S;

W is hydrogen, F, -OH, -CN, -NH₂;

R₅ is halo, -CN or -Oalkyl;

R₆, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroaryalkyl;

R₈, at each occurrence, is independently hydrogen or alkyl;

R₉, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl, heterocyclylalkyl, wherein the aryalkyl, heteroaryl, heterocyclyl, heterocyclylalkyl may be optionally substituted with 0-5 R₉₈, and the heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₉₈, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl, heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₈R₈)₂R₁₄, -O(CF₂)₂CF₃, -O(CR₈R₈)₂R₁₄, -OH, -SH, -S(CR₈R₈)₂R₁₄, -S(O)₂H, -P(O)₃H₂, -C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)₂(CF₂)₂CF₃, -C(=O)NR₁₄S(O)₂R₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄, -C(=O)NR₁₄S(O)₂(CF₂)₂CF₃, -C(=O)(CR₈R₈)₂R₁₄, -NR₁₄C(=O)H, -NR₁₄C(=O)(CR₈R₈)₂R₁₄, -OC(=O)(CR₈R₈)₂R₁₄, -C(=NR₁₄)NR₁₄R₁₄, -NHC(=NR₁₄)NR₁₄R₁₄, -S(=O)(CR₈R₈)₂R₁₄, -S(O)₂(CR₈R₈)₂R₁₄, -NR₁₄C(=O)OR₆, -NR₁₄S(O)₂R₆, aryloxy or arylalkyl;

R₁₀, at each occurrence, is independently selected from alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, wherein the alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl may be optionally substituted with 0-3 Rₐ₀, and the heterocyclyl and heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₁₀₈, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl
heterocyclalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅)₉R₁₄,
-O(CF₂)₃CF₃, -O(CR₃R₅)₉R₁₄, -OH, -SH, -S(CR₃R₅)₉R₁₄, -SO(=O)₃H, -P(=O)H₂,
-C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)₂(CF₂)₃CF₃,
-C(=O)NR₁₄S(O)₂R₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄,
-C(=O)NR₁₄S(O)₂(CF₂)₃CF₃, -C(=O)(CR₃R₅)₉R₁₄, -NR₁₄C(=O)H,
-NR₁₄C(=O)(CR₃R₅)₉R₁₄, -OC(=O)(CR₃R₅)₉R₁₄, -C(=NR₁₄)NR₁₄R₁₄,
-NHC(=NR₁₄)NR₁₄R₁₄, -S(=O)(CR₃R₅)₉R₁₄, -S(O)₂(CR₃R₅)₉R₁₄, -NR₁₄C(=O)OR₆,
-NR₁₄S(O)₂R₆, aryloxy or arylalkyl;

R₁₄, at each occurrence, is independently selected from hydrogen, alkyl,
cycloalkyl or phenyl;
m, at each occurrence, is 0-2; and
r is 0-5.

[0027] In another embodiment, compounds of Formula (Ib) are those compounds
having the formula (Ib'):

\[
\text{(Ib')} \]

in which W is hydrogen or OH and m is 1 or 2.

[0028] In another embodiment, compounds of the present invention are those in
which:

T is \(-\text{C} = \) , \(-\text{C} = \text{O} \), \(-\text{C} = \text{N} \), or \(-\text{S} = \) ;

R₁ is alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl, all of which may be
optionally substituted with 0-5 R₁₄;

R₁₄, at each occurrence, is independently selected from alkyl, haloalkyl, aryl,
alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl
heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅)₉R₁₆,
-O(CF<sub>2</sub>)<sub>3</sub>CF<sub>3</sub>, -O(CR<sub>8</sub>R<sub>8</sub>)<sub>3</sub>R<sub>10</sub>, -OH, -SH, -S(CR<sub>8</sub>R<sub>8</sub>)<sub>3</sub>R<sub>10</sub>, -S(O)<sub>2</sub>H, -P(O)<sub>2</sub>H<sub>2</sub>, -C(=O)NR<sub>6</sub>R<sub>9</sub>, -NR<sub>9</sub>R<sub>9</sub>, -S(O)<sub>2</sub>NR<sub>6</sub>R<sub>9</sub>, -NR<sub>8</sub>S(O)<sub>2</sub>(CF<sub>2</sub>)CF<sub>3</sub>, -C(=O)NR<sub>6</sub>S(O)<sub>2</sub>R<sub>6</sub>, -S(O)<sub>2</sub>NR<sub>6</sub>C(=O)OR<sub>9</sub>, -S(O)<sub>2</sub>NR<sub>6</sub>C(=O)R<sub>6</sub>, -C(=O)NR<sub>6</sub>S(O)<sub>2</sub>(CF<sub>2</sub>)CF<sub>3</sub>, -C(=O)(CR<sub>8</sub>R<sub>8</sub>)<sub>3</sub>R<sub>10</sub>, -NR<sub>9</sub>C(=O)H, -NR<sub>9</sub>C(=O)(CR<sub>8</sub>R<sub>8</sub>)<sub>3</sub>R<sub>10</sub>, -OC(=O)(CR<sub>8</sub>R<sub>8</sub>)<sub>3</sub>R<sub>10</sub>, -NR<sub>9</sub>C(=O)OR<sub>8</sub>, -NR<sub>9</sub>S(O)<sub>2</sub>R<sub>8</sub>, -S(O)<sub>2</sub>NR<sub>9</sub>C(O)R<sub>6</sub>, aryloxy or arylalkyl, wherein the aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, aryloxy and arylalkyl may be optionally substituted with 0-3 R<sub>16</sub>:

R<sub>1b</sub>, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, halo, -NH<sub>2</sub>, -CN, -NO<sub>2</sub>, -C(=O)OH, -C(=O)O(CR<sub>8</sub>R<sub>8</sub>)<sub>3</sub>R<sub>10</sub>, -O(CF<sub>2</sub>)CF<sub>3</sub>, -O(CR<sub>8</sub>R<sub>8</sub>)<sub>3</sub>R<sub>10</sub>, -OH, -SH, -S(CR<sub>8</sub>R<sub>8</sub>)<sub>3</sub>R<sub>10</sub>, -S(O)<sub>2</sub>H, -P(O)<sub>2</sub>H<sub>2</sub>, -C(=O)NR<sub>9</sub>R<sub>9</sub>, -NR<sub>9</sub>R<sub>9</sub>, -S(O)<sub>2</sub>NR<sub>9</sub>R<sub>9</sub>, -NR<sub>8</sub>S(O)<sub>2</sub>(CF<sub>2</sub>)CF<sub>3</sub>, -C(=O)NR<sub>9</sub>S(O)<sub>2</sub>R<sub>6</sub>, -S(O)<sub>2</sub>NR<sub>9</sub>C(=O)OR<sub>9</sub>, -S(O)<sub>2</sub>NR<sub>9</sub>C(=O)R<sub>6</sub>, -C(=O)NR<sub>9</sub>S(O)<sub>2</sub>(CF<sub>2</sub>)CF<sub>3</sub>, -C(=O)(CR<sub>8</sub>R<sub>8</sub>)<sub>3</sub>R<sub>10</sub>, -NR<sub>9</sub>C(=O)H, -NR<sub>9</sub>C(=O)(CR<sub>8</sub>R<sub>8</sub>)<sub>3</sub>R<sub>10</sub>, -OC(=O)(CR<sub>8</sub>R<sub>8</sub>)<sub>3</sub>R<sub>10</sub>, -NR<sub>9</sub>C(=O)OR<sub>8</sub>, -NR<sub>9</sub>S(O)<sub>2</sub>R<sub>8</sub>, aryloxy or arylalkyl:

R<sub>2</sub> is alkyl, cycloalkyl, cycloalkylalkyl, -CH<sub>2</sub>CH<sub>2</sub>CH=CH(NH)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C=NH, -CH<sub>2</sub>CH=CH,C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>CH<sub>2</sub>CN, or CH<sub>2</sub>CH=CH(C<sub>2</sub>H<sub>5</sub>). Wherein the alkyl may be optionally substituted with -OH;

R<sub>4</sub>, at each occurrence, is -OH or alkyl; or any two alkyl R<sub>4</sub>’s attached to the same carbon atom may form a 3- to 6-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S;

R<sub>5</sub> is halo, -CN or -Oalkyl;

R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R<sub>8</sub>, at each occurrence, is independently hydrogen or alkyl;

R<sub>9</sub>, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl, wherein the aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl may be
optionally substituted with 0-5 R₉a, and the heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₉a, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl

heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₈)R₁₄,
-OC(F₂)₂CF₃, -O(CR₃R₈)R₁₄, -OH, -SH, -S(CR₃R₈)R₁₄, -S(O)₃H, -P(O)₃H₂,
-C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)(CF₂)₂CF₃,
-C(=O)NR₁₄S(O)₂R₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄,
-C(=O)NR₁₄S(O)₂(CF₂)₂CF₃, -C(=O)(CR₃R₈)R₁₄, -NR₁₄C(=O)H,
-NRC(=NR₁₄)NR₁₄R₁₄, -OC(=O)(CR₃R₈)R₁₄, -C(=NR₁₄)NR₁₄R₁₄,
-NH₂C(=NR₁₄)NR₁₄R₁₄, -S(=O)(CR₃R₈)R₁₄, -S(O)₂(CR₃R₈)R₁₄, -NR₁₄C(=O)OR₆,
-NR₁₄S(O)₂R₆, arylxoy or arylalkyl;

R₁₀a, at each occurrence, is independently selected from alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, wherein the alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl may be optionally substituted with 0-3 R₁₀a, and the heterocyclyl and heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₁₀a, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl

heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₈)R₁₄,
-OC(F₂)₂CF₃, -O(CR₃R₈)R₁₄, -OH, -SH, -S(CR₃R₈)R₁₄, -S(O)₃H, -P(O)₃H₂,
-C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)(CF₂)₂CF₃,
-C(=O)NR₁₄S(O)₂R₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄,
-C(=O)NR₁₄S(O)₂(CF₂)₂CF₃, -C(=O)(CR₃R₈)R₁₄, -NR₁₄C(=O)H,
-NRC(=NR₁₄)NR₁₄R₁₄, -OC(=O)(CR₃R₈)R₁₄, -C(=NR₁₄)NR₁₄R₁₄,
-NH₂C(=NR₁₄)NR₁₄R₁₄, -S(=O)(CR₃R₈)R₁₄, -S(O)₂(CR₃R₈)R₁₄, -NR₁₄C(=O)OR₆,
-NR₁₄S(O)₂R₆, arylxoy or arylalkyl;

R₁₄, at each occurrence, is independently selected from hydrogen, alkyl, cycloalkyl or phenyl; and

r is 0-4.

[0029] In yet another embodiment, compounds of the present invention are those in which:
R₁ is alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl, all of which may be optionally substituted with 0-5 R₁ₕ;

R₁ₕ, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅)R₁₀,
-O(CF₂)₂CF₃, -O(CR₃R₅)R₁₀, -OH, -SH, -S(CR₃R₅)R₁₀, -S(O)₂H, -P(O)₂H₂,
-C(=O)NR₃R₉, -NR₃R₉, -S(O)₂NR₃R₉, -NR₃S(O)₂(CF₂)CF₃, -C(=O)NR₃S(O)₂R₆,
-S(O)₂NR₃C(=O)OR₆, -S(O)₂NR₃C(=O)NR₃R₆, -C(=O)NR₃S(O)₂(CF₂)CF₃,
-C(=O)(CR₃R₅)R₁₀, -NR₃C(=O)H, -NR₃C(=O)(CR₃R₅)R₁₀, -OC(=O)(CR₃R₅)R₁₀,
-C(=NR₄)NR₃R₉, -NHC(=NR₄)NR₄R₄, -S(=O)(CR₃R₅)R₁₀, -S(O)₂(CR₃R₅)R₁₀,
-NR₃C(=O)OR₆, -NR₃S(O)₂R₆, -S(O)₂NR₃C(O)R₆, aryloxy or arylalkyl, wherein the aryloxy and arylalkyl may be optionally substituted with 0-3 R₆;

R₁₆, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅)R₁₀,
-O(CF₂)₂CF₃, -O(CR₃R₅)R₁₀, -OH, -SH, -S(CR₃R₅)R₁₀, -S(O)₂H, -P(O)₂H₂,
-C(=O)NR₃R₉, -NR₃R₉, -S(O)₂NR₃R₉, -NR₃S(O)₂(CF₂)CF₃, -C(=O)NR₃S(O)₂R₆,
-S(O)₂NR₃C(=O)OR₆, -S(O)₂NR₃C(=O)NR₃R₆, -C(=O)NR₃S(O)₂(CF₂)CF₃,
-C(=O)(CR₃R₅)R₁₀, -NR₃C(=O)H, -NR₃C(=O)(CR₃R₅)R₁₀, -OC(=O)(CR₃R₅)R₁₀,
-C(=NR₄)NR₃R₉, -NHC(=NR₄)NR₄R₄, -S(=O)(CR₃R₅)R₁₀, -S(O)₂(CR₃R₅)R₁₀,
-NR₃C(=O)OR₆, -NR₃S(O)₂R₆, aryloxy or arylalkyl;

R₂ is alkyl, cycloalkyl, cycloalkylalkyl, -CH₂CH₂SCH₃, -CH₂CH₂CN,

; wherein the alkyl may be optionally substituted with -OH;

R₄, at each occurrence, is -OH or alkyl; or any two alkyl R₄'s attached to the same carbon atom may form a 3- to 6-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S;

R₅ is halo or -CN;
R₆, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroaryalkyl;

R₈, at each occurrence, is independently hydrogen or alkyl;

R₉, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, heterocyclylalkyl, wherein the aryl, arylalkyl, heteroaryl, heteroaryalkyl, heterocyclylalkyl or heterocyclylalkyl may be optionally substituted with 0-5 R₉₈, and the heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₉₈, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclylalkyl, heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅)R₁₄, -O(CF₂)₂CF₃, -O(CR₃R₅)R₁₄, -OH, -SH, -S(CR₃R₅)R₁₄, -S(O)₂H, -P(O)₃H₂, -C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)₂(CF₂)₂CF₃, -C(=O)NR₁₄S(O)₂R₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄, -C(=O)NR₁₄S(O)₂(CF₂)₂CF₃, -C(=O)(CR₃R₅)R₁₄, -NR₁₄C(=O)O(CR₃R₅)R₁₄, -OC(=O)(CR₃R₅)R₁₄, -C(=NR₁₄)NR₁₄R₁₄, -NH(C(=NR₁₄)NR₁₄R₁₄, -S(O)₂(CR₃R₅)R₁₄, -S(O)₂(CR₃R₅)R₁₄, -S(O)₂(CR₃R₅)R₁₄, -NR₁₄C(=O)OR₆, -NR₁₄S(O)₂R₆, aryloxy or arylalkyl;

R₁₀, at each occurrence, is independently selected from alkyl, aryl, aryloxy and arylalkyl, heterocyclylalkyl, wherein the alkyl, aryl, aryloxy or heterocyclylalkyl may be optionally substituted with 0-3 R₁₀₈, and the heterocyclyl and heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₁₀₈, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclylalkyl, heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅)R₁₄, -O(CF₂)₂CF₃, -O(CR₃R₅)R₁₄, -OH, -SH, -S(CR₃R₅)R₁₄, -S(O)₂H, -P(O)₃H₂, -C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)₂(CF₂)₂CF₃, -C(=O)NR₁₄S(O)₂R₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄, -C(=O)NR₁₄S(O)₂(CF₂)₂CF₃, -C(=O)(CR₃R₅)R₁₄, -NR₁₄C(=O)O(CR₃R₅)R₁₄, -OC(=O)(CR₃R₅)R₁₄, -C(=NR₁₄)NR₁₄R₁₄, -NH(C(=NR₁₄)NR₁₄R₁₄, -S(O)₂(CR₃R₅)R₁₄, -S(O)₂(CR₃R₅)R₁₄, -S(O)₂(CR₃R₅)R₁₄, -NR₁₄C(=O)OR₆, -NR₁₄S(O)₂R₆, aryloxy or arylalkyl;

- 26 -
R₁₄, at each occurrence, is independently selected from hydrogen, alkyl, cycloalkyl or phenyl; and
r is 0-3.

5  [0030] In still yet another embodiment, compounds of the present invention are those in which:

T is \( \begin{array}{c} O \\ \text{R₈} \end{array} \) or \( \begin{array}{c} O \\ \text{N} \end{array} \);

R₁ is alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl, all of which may be optionally substituted with 0-5 R₁₄;

10  R₁₄, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CH₃)₃, -O(CF₃)CF₃, -O(CR₃R₅)R₁₀, -OH, -SH, -S(CR₃R₅)R₁₀, -S(O)H, -P(O)H₂, -C(=O)NR₉R₉, -NR₉R₉, -S(O)₂NR₉R₉, -NR₉S(O)₂(CF₂)CF₃, -C(=O)NR₉S(O)₂R₆,

15  -S(O)₂NR₉C(=O)OR₆, -S(O)₂NR₉C(=O)NR₉R₉, -C(=O)NR₉S(O)₂(CF₂)CF₃, -C(=O)(CR₃R₅)R₁₀, -NR₉C(=O)H, -NR₉C(=O)(CR₃R₅)R₁₀, -OC(=O)(CR₃R₅)R₁₀, -C(=O)(CR₃R₅)R₁₀, -NR₉C(=O)NR₉R₉, -NH(C=NR₉)NR₉R₉, -S(O)(CR₃R₅)R₁₀, -S(O)(CR₃R₅)R₁₀, -NR₉C(=O)OR₆, -NR₉S(O)₂R₆, -S(O)₂NR₉C(=O)R₆, aryloxy or arylalkyl, wherein the aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl

20  heterocyclylalkyl, aryloxy and arylalkyl may be optionally substituted with 0-3 R₁₆;

R₁₆, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl

25  heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CH₃)₃, -O(CF₃)CF₃, -O(CR₃R₅)R₁₀, -OH, -SH, -S(CR₃R₅)R₁₀, -S(O)H, -P(O)H₂, -C(=O)NR₉R₉, -NR₉R₉, -S(O)₂NR₉R₉, -NR₉S(O)₂(CF₂)CF₃, -C(=O)NR₉S(O)₂R₆, -S(O)₂NR₉C(=O)OR₆, -S(O)₂NR₉C(=O)NR₉R₉, -C(=O)NR₉S(O)₂(CF₂)CF₃, -C(=O)(CR₃R₅)R₁₀, -NR₉C(=O)H, -NR₉C(=O)(CR₃R₅)R₁₀, -OC(=O)(CR₃R₅)R₁₀, -C(=O)(CR₃R₅)R₁₀, -NR₉C(=O)NR₉R₉, -NH(C=NR₉)NR₉R₉, -S(O)(CR₃R₅)R₁₀, -S(O)(CR₃R₅)R₁₀, -NR₉C(=O)OR₆, -NR₉S(O)₂R₆, aryloxy or arylalkyl;
R₂ is alkyl, cycloalkyl, cycloalkylalkyl, 

wherein the alkyl may be optionally substituted with -OH;

R₄, at each occurrence, is alkyl; or any two alkyl R₄’s attached to the same 
carbon atom may form a 3- to 6-membered ring, which optionally may contain 1-4 
heteroatoms selected from N, O, and S;

R₅ is halo;

R₆, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl, 
aryl, aryalkyl, heteroaryl or heteroaryalkyl;

R₈, at each occurrence, is independently hydrogen or alkyl;

R₉, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, 
arylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclylalkyl, wherein the 
aryl, arylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclylalkyl may be 
optionally substituted with 0-5 R₉ₙ, and the heteroaryl, heteroaryalkyl, heterocyclyl 
or heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₉ₙ, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, 
alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl 
heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₈), R₁₄, 
-O(CF₂)CF₃, -O(CR₃R₈), R₁₄, -OH, -SH, -S(CR₃R₈), R₁₄, -S(O)₃H, -P(O)₃H₂, 
-C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)₂(CF₂)CF₃, 

-C(=O)NR₁₄S(O)₂R₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄, 
-C(=O)NR₁₄S(O)₂(CF₂)CF₃, -C(=O)(CR₃R₈), R₁₄, -NR₁₄C(=O)H, 
-NR₁₄C(=O)(CR₃R₈), R₁₄, -OC(=O)(CR₃R₈), R₁₄, -C(=NR₁₄)NR₁₄R₁₄, 
-NHC(=NR₁₄)NR₁₄R₁₄, -S(O)(CR₃R₈), R₁₄, -S(O)₂(CR₃R₈), R₁₄, -NR₁₄C(=O)OR₆, 
-NR₁₄S(O)₂R₆, aryloxy or arylalkyl;

R₁₀, at each occurrence, is independently selected from alkyl, aryl, aryalkyl, 
heterocyclyl or heterocyclylalkyl, wherein the alkyl, aryl, aryalkyl, heterocyclyl or 
heterocyclylalkyl may be optionally substituted with 0-3 R₁₀ₙ, and the heterocyclyl 
and heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₁₀ₙ, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, 
alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl 
heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₈), R₁₄.
[0031] In still yet another embodiment, compounds of the present invention are those in which:

\[
\begin{align*}
&\text{T is } \\
&\text{R}_1 \text{ is alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl, all of which may be optionally substituted with 0-5 } \text{R}_{1a};
\end{align*}
\]

\[
\begin{align*}
&R_{1a}, \text{ at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl heterocyclylalkyl, halo, } \text{-NH}_2, \text{-CN, } \text{-NO}_2, \text{-C(=O)OH, } \text{-C(=O)(CR}_3\text{R}_5)_3\text{R}_{10}, \\
&\text{-O(CF}_2\text{)}_2\text{CF}_3, \text{-O(CR}_3\text{R}_5)_3\text{R}_{10}, \text{-OH, } \text{-SH, } \text{-S(CR}_3\text{R}_5)_3\text{R}_{10}, \text{-S(O)}_2\text{H, } \text{-P(O)}_3\text{H}_2,
\end{align*}
\]

-\text{C(=O)NR}_3\text{R}_9, \text{-NR}_3\text{R}_9, \text{-S(O)}_2\text{NR}_3\text{R}_9, \text{-NR}_3\text{S(O)}_2\text{CF}_2\text{CF}_3, \text{-C(=O)NR}_3\text{S(O)}_2\text{R}_6,

-\text{S(O)}_2\text{NR}_3\text{C(=O)OR}_6, \text{-S(O)}_2\text{NR}_3\text{C(=O)NR}_3\text{R}_9, \text{-C(=O)NR}_3\text{S(O)}_2\text{CF}_2\text{CF}_3,

-\text{C(=O)(CR}_3\text{R}_5)_3\text{R}_{10}, \text{-NR}_3\text{C(=O)OH, } \text{-NR}_3\text{C(=O)(CR}_3\text{R}_5)_3\text{R}_{10}, \text{-OC(=O)(CR}_3\text{R}_5)_3\text{R}_{10},

-\text{C(=NR}_3\text{NR}_3\text{R}_9, \text{-NHC(=NR}_3\text{NR}_3\text{R}_9, \text{-S(O)}_2\text{NR}_3\text{C(O)R}_6, \text{aryl oxy or arylalkyl, wherein the aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl heterocyclylalkyl, aryl oxy and arylalkyl may be optionally substituted with 0-3 } \text{R}_{1b};
\end{align*}
\]

\[
\begin{align*}
&R_{1b}, \text{ at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl heterocyclylalkyl, halo, } \text{-NH}_2, \text{-CN, } \text{-NO}_2, \text{-C(=O)OH, } \text{-C(=O)(CR}_3\text{R}_5)_3\text{R}_{10}, \\
&\text{-O(CF}_2\text{)}_2\text{CF}_3, \text{-O(CR}_3\text{R}_5)_3\text{R}_{10}, \text{-OH, } \text{-SH, } \text{-S(CR}_3\text{R}_5)_3\text{R}_{10}, \text{-S(O)}_2\text{H, } \text{-P(O)}_3\text{H}_2,
\end{align*}
\]

- 29 -
-C(=O)NR₉R₉, -NR₉R₉, -S(O)₂NR₉R₉, -NR₉S(O)₂(CF₂)CF₃, -C(=O)NR₉S(O)₂R₆,
-S(O)₂NR₉C(=O)OR₆, -S(O)₂NR₉C(=O)NR₉R₉, -C(=O)NR₉S(O)₂(CF₂)CF₃,
-C(=O)(CR₉R₉)₂R₁₀, -NR₉C(=O)H, -NR₉C(=O)(CR₉R₉)₂R₁₀, -OC(=O)(CR₉R₉)₂R₁₀,
-C(=O)(NR₉)₂NR₉, -NHC(=NR₁₄)NR₁₄R₁₄, -S(=O)(CR₉R₉)₂R₁₀, -S(O)₂(CR₉R₉)₂R₁₀,
-NR₉C(=O)OR₈, -NR₉S(O)₂R₈, arylxoy or arylalkyl;

R₂ is alkyl, cycloalkyl, or cycloalkylalkyl, wherein the alkyl may be optionally substituted with -OH;

R₄, at each occurrence, is alkyl;

R₅ is halo;

R₆, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroaryalkyl;

R₈, at each occurrence, is independently hydrogen or alkyl;

R₉, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclyalkyl, wherein the aryl, arylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclyalkyl may be optionally substituted with 0-5 R₉a, and the heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclyalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₉a, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₉R₉)₂R₁₄,
-O(CF₂)₂CF₃, -O(CR₉R₉)₂R₁₄, -OH, -SH, -S(CR₉R₉)₂R₁₄, -S(O)₂H, -P(O)₃H₂,
-C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)₂(CF₂)CF₃,
-C(=O)NR₁₄S(O)₂R₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄,
-C(=O)NR₁₄S(O)₂(CF₂)CF₃, -C(=O)(CR₉R₉)₂R₁₄, -NR₁₄C(=O)H,
-NR₁₄C(=O)(CR₉R₉)₂R₁₄, -OC(=O)(CR₉R₉)₂R₁₄, -C(=NR₁₄)NR₁₄R₁₄,
-NHC(=NR₁₄)NR₁₄R₁₄, -S(=O)(CR₉R₉)₂R₁₄, -S(O)₂(CR₉R₉)₂R₁₄, -NR₁₄C(=O)OR₈,
-NR₁₄S(O)₂R₈, arylxoy or arylalkyl;

R₁₀, at each occurrence, is independently selected from alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, wherein the alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl may be optionally substituted with 0-3 R₁₀a, and the heterocyclyl and heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;
R$_{10u}$, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclic
heterocyclicalkyl, halo, -NH$_2$, -CN, -NO$_2$, -C(=O)OH, -C(=O)O(CR$_3$R$_3$)$_3$R$_{14}$,
-O(CF$_2$)$_2$CF$_3$, -O(CR$_8$R$_8$)$_3$R$_{14}$, -OH, -SH, -S(CR$_8$R$_8$)$_3$R$_{14}$, -S(O)$_3$H, -P(O)$_3$H$_2$,
5
-C(=O)NR$_{14}$R$_{14}$, -NR$_{14}$R$_{14}$, -S(O)$_2$NR$_{14}$R$_{14}$, -NR$_{14}$S(O)$_2$(CF$_2$)$_2$CF$_3$,
-C(=O)NR$_{14}$S(O)$_2$R$_{6}$, -S(O)$_2$NR$_{14}$C(=O)OR$_{6}$, -S(O)$_2$NR$_{14}$C(=O)NR$_{14}$R$_{14}$,
-C(=O)NR$_{14}$S(O)$_2$(CF$_2$)$_2$CF$_3$, -C(=O)(CR$_8$R$_8$)$_3$R$_{14}$, -NR$_{14}$C(=O)H,
-NR$_{14}$C(=O)(CR$_8$R$_8$)$_3$R$_{14}$, -OC(=O)(CR$_8$R$_8$)$_3$R$_{14}$, -C(=NR$_{14}$)NR$_{14}$R$_{14}$,
-NHC(=NR$_{14}$)NR$_{14}$R$_{14}$, -S(=O)(CR$_8$R$_8$)$_3$R$_{14}$, -S(O)$_2$(CR$_8$R$_8$)$_3$R$_{14}$, -NR$_{14}$C(=O)OR$_{8}$,
10
-NR$_{14}$S(O)$_2$R$_{8}$, aryloxy or arylalkyl;
R$_{14}$, at each occurrence, is independently selected from hydrogen, alkyl,
cycloalkyl or phenyl; and
r is 0-2.

15 [0032] In another embodiment, compounds of the present invention are those in which:

\[
T = \begin{pmatrix} 0 \\ 1 \end{pmatrix};
\]

R$_1$ is alkyl, cycloalkyl, aryl, heterocyclic or heteroaryl, all of which may be
optionally substituted with 0-5 R$_{1u}$;

20
R$_{1u}$, at each occurrence, is independently selected from alkyl, haloalkyl, aryl,
alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclic
heterocyclicalkyl, halo, -NH$_2$, -CN, -NO$_2$, -C(=O)OH, -C(=O)O(CR$_3$R$_3$)$_3$R$_{10}$,
-O(CF$_2$)$_2$CF$_3$, -O(CR$_8$R$_8$)$_3$R$_{10}$, -OH, -SH, -S(CR$_8$R$_8$)$_3$R$_{10}$, -S(O)$_3$H, -P(O)$_3$H$_2$,
-C(=O)NR$_9$R$_9$, -NR$_9$R$_9$, -S(O)$_2$NR$_9$R$_9$, -NR$_9$S(O)$_2$(CF$_2$)$_2$CF$_3$, -C(=O)NR$_9$S(O)$_2$R$_6$,
25
-S(O)$_2$NR$_9$C(=O)OR$_6$, -S(O)$_2$NR$_9$C(=O)NR$_9$R$_9$, -C(=O)NR$_9$S(O)$_2$(CF$_2$)$_2$CF$_3$,
-C(=O)(CR$_8$R$_8$)$_3$R$_{10}$, -NR$_9$C(=O)(CR$_8$R$_8$)$_3$R$_{10}$, -OC(=O)(CR$_8$R$_8$)$_3$R$_{10}$,
-C(=NR$_{14}$)NR$_9$R$_9$, -NHC(=NR$_{14}$)NR$_14$R$_{14}$, -S(=O)(CR$_8$R$_8$)$_3$R$_{10}$, -S(O)$_2$(CR$_8$R$_8$)$_3$R$_{10}$,
-NR$_9$C(=O)OR$_8$, -NR$_9$S(O)$_2$R$_8$, -S(O)$_2$NR$_9$C(O)R$_6$, aryloxy or arylalkyl, wherein the
aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclic
heterocyclicalkyl, aryloxy and arylalkyl may be optionally substituted with 0-3 R$_{16}$;
R₁₁b, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkylnyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, halo, -NH₃, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅)R₆, -O(CF₂)CF₃, -O(CR₃R₅)R₁₀, -OH, -SH, -S(CR₃R₅)R₁₀, -S(O)₃H, -P(O)₃H₂, -C(=O)NR₃R₆, -NR₃R₆, -O(O)₃S(O)₂(CF₂)CF₃, -C(=O)NR₃S(O)₂R₆, -S(O)₂NR₃C(=O)OR₆, -S(O)₂NR₃C(=O)NR₃R₆, -C(=O)NR₃S(O)₂(CF₂)CF₃, -C(=O)(CR₃R₅)R₁₀, -NR₃C(=O)H, -NR₃C(=O)(CR₃R₅)R₁₀, -OC(=O)(CR₃R₅)R₁₀, -NHC(=NR₃)NR₃R₆, -NR₃C(=O)OR₆, -NR₃S(O)₂R₆, arlyloxy or aryalkyl;

R₂ is alkyl or cycloalkyl;
R₄, at each occurrence, is alkyl;
R₅ is halo;
R₆, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R₈, at each occurrence, is independently hydrogen or alkyl;
R₉, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl, wherein the aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl may be optionally substituted with 0-5 R₉ₙ, and the heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;
R₉ₙ, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkylnyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, halo, -NH₃, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅)R₁₄, -O(CF₂)CF₃, -O(CR₃R₅)R₁₄, -OH, -SH, -S(CR₃R₅)R₁₄, -S(O)₃H, -P(O)₃H₂, -C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)₂(CF₂)CF₃, -C(=O)NR₁₄R₁₄, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄, -C(=O)NR₁₄S(O)₂(CF₂)CF₃, -C(=O)(CR₃R₅)R₁₄, -O(C=O)(CR₃R₅)R₁₄, -NR₁₄C(=O)H, -NR₁₄C(=O)(CR₃R₅)R₁₄, -O(C=O)(CR₃R₅)R₁₄, -C(=NR₁₄)NR₁₄R₁₄, -NHC(=NR₁₄)NR₁₄R₁₄, -S(O)(CR₃R₅)R₁₄, -S(O)₂(CR₃R₅)R₁₄, -NR₁₄C(=O)OR₈, -NR₁₄S(O)₂R₈, arlyloxy or aryalkyl;

R₁₀, at each occurrence, is independently selected from alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, wherein the alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, halo, -NH₃, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅)R₁₄, -O(CF₂)CF₃, -O(CR₃R₅)R₁₀, -OH, -SH, -S(CR₃R₅)R₁₀, -S(O)₃H, -P(O)₃H₂, -C(=O)NR₃R₆, -NR₃R₆, -O(O)₃S(O)₂(CF₂)CF₃, -C(=O)(CR₃R₅)R₁₀, -NR₃C(=O)H, -NR₃C(=O)(CR₃R₅)R₁₀, -OC(=O)(CR₃R₅)R₁₀, -NHC(=NR₃)NR₃R₆, -NR₃C(=O)OR₆, -NR₃S(O)₂R₆, arlyloxy or aryalkyl;

R₂ is alkyl or cycloalkyl;
R₄, at each occurrence, is alkyl;
R₅ is halo;
R₆, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R₈, at each occurrence, is independently hydrogen or alkyl;
R₉, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl, wherein the aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl may be optionally substituted with 0-5 R₉ₙ, and the heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;
R₉ₙ, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkylnyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, halo, -NH₃, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅)R₁₄, -O(CF₂)CF₃, -O(CR₃R₅)R₁₄, -OH, -SH, -S(CR₃R₅)R₁₄, -S(O)₃H, -P(O)₃H₂, -C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)₂(CF₂)CF₃, -C(=O)NR₁₄R₁₄, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄, -C(=O)NR₁₄S(O)₂(CF₂)CF₃, -C(=O)(CR₃R₅)R₁₄, -O(C=O)(CR₃R₅)R₁₄, -NR₁₄C(=O)H, -NR₁₄C(=O)(CR₃R₅)R₁₄, -O(C=O)(CR₃R₅)R₁₄, -C(=NR₁₄)NR₁₄R₁₄, -NHC(=NR₁₄)NR₁₄R₁₄, -S(O)(CR₃R₅)R₁₄, -S(O)₂(CR₃R₅)R₁₄, -NR₁₄C(=O)OR₈, -NR₁₄S(O)₂R₈, arlyloxy or aryalkyl;

R₁₀, at each occurrence, is independently selected from alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, wherein the alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, halo, -NH₃, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅)R₁₄, -O(CF₂)CF₃, -O(CR₃R₅)R₁₀, -OH, -SH, -S(CR₃R₅)R₁₀, -S(O)₃H, -P(O)₃H₂, -C(=O)NR₃R₆, -NR₃R₆, -O(O)₃S(O)₂(CF₂)CF₃, -C(=O)(CR₃R₅)R₁₀, -NR₃C(=O)H, -NR₃C(=O)(CR₃R₅)R₁₀, -OC(=O)(CR₃R₅)R₁₀, -NHC(=NR₃)NR₃R₆, -NR₃C(=O)OR₆, -NR₃S(O)₂R₆, arlyloxy or aryalkyl;
heterocyclylalkyl may be optionally substituted with 0-3 R_{10a}, and the heterocyclylalkyl and heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R_{10a}, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₈R₉)₂R₁₈, -O(CF₂)₂CF₃, -O(CR₈R₉)₂R₁₄, -OH, -SH, -S(CR₈R₉)₂R₁₄, -S(O)₂H, -P(O)₃H₂, -C(=O)NR₁₄R₁₈, -NR₁₄R₁₈, -S(O)₂NR₁₄R₁₈, -NR₁₄S(O)₂(CF₂)₂CF₃, -C(=O)NR₁₄S(O)₂R₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₈, -C(=O)NR₁₄S(O)₂(CF₂)₂CF₃, -C(=O)(CR₈R₉)₂R₁₄, -NR₁₄C(=O)H, -NR₁₄C(=O)(CR₈R₉)₂R₁₄, -OC(=O)(CR₈R₉)₂R₁₄, -C(=NR₁₄)NR₁₄R₁₈, -NHC(=NR₁₄)NR₁₄R₁₈, -S(=O)(CR₈R₉)₂R₁₄, -S(O)₂(CR₈R₉)₂R₁₄, -NR₁₄C(=O)OR₆, -NR₁₄S(O)₂R₆, aryloxy or arylalkyl;

R_{1₄}, at each occurrence, is independently selected from hydrogen, alkyl, cycloalkyl or phenyl; and

r is 0-2.

[0033] In another embodiment, compounds of the present invention are those in which R₂ is isopropyl, sec-butyl or cyclopropyl; R₄ is methyl; R₅ is Cl, F or Br; and R₁ is alkyl, cycloalkyl, aryl or heteroaryl, all of which may be optionally substituted with 0-5 R_{1₄a}.

[0034] In still another embodiment, compounds of the present invention are those in which:

\[ \text{T is } \begin{array}{c} \text{O} \\ \text{C} \end{array}, \begin{array}{c} \text{O} \\ \text{C} \end{array} - \begin{array}{c} \text{O} \\ \text{C} \end{array}, \begin{array}{c} \text{C} \\ \text{N} \end{array} \text{ or } \begin{array}{c} \text{O} \\ \text{O} \end{array}. \]

[0035] In one embodiment, the present invention provides novel compounds of formula (Ic):

- 33 -
or stereoisomers or prodrugs or pharmaceutically acceptable salt forms thereof, wherein:

R$_{15}$ is –NHR$_1$, heteroaryl or aryl, wherein the heteroaryl and aryl may be optionally substituted with 0-3 R$_{1a}$;

R$_1$ is aryl or heteroaryl, both of which may be optionally substituted with 0-3 R$_{1a}$, provided that when R$_1$ is phenyl, R$_{1a}$ cannot be ortho-methoxy;

R$_{1a}$, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkylnyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, halo, -NH$_2$, -CN, -NO$_2$, -C(=O)OH, -C(=O)O(CR$_5$R$_8$)$_3$R$_{10}$, -O(CF$_2$)$_2$CF$_3$, -O(CR$_5$R$_8$)$_3$R$_{10}$, -OH, -SH, -S(CR$_5$R$_8$)$_3$R$_{10}$, -S(O)$_2$H, -P(O)$_3$H$_2$, -C(=O)NR$_9$R$_9$, -NR$_9$R$_9$, -S(O)$_2$NR$_9$R$_9$, -NR$_9$S(O)$_2$(CF$_2$)$_2$CF$_3$, -C(=O)NR$_9$S(O)$_2$R$_6$, -S(O)$_2$NR$_9$C(=O)OR$_6$, -S(O)$_2$NR$_9$C(=O)NR$_9$R$_9$, -C(=O)NR$_9$S(O)$_2$(CF$_2$)$_2$CF$_3$,

R$_{1b}$, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkylnyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, halo, -NH$_2$, -CN, -NO$_2$, -C(=O)OH, -C(=O)O(CR$_5$R$_8$)$_3$R$_{10}$, -O(CF$_2$)$_2$CF$_3$, -O(CR$_5$R$_8$)$_3$R$_{10}$, -OH, -SH, -S(CR$_5$R$_8$)$_3$R$_{10}$, -S(O)$_2$H, -P(O)$_3$H$_2$, -C(=O)NR$_9$R$_9$, -NR$_9$R$_9$, -S(O)$_2$NR$_9$R$_9$, -NR$_9$S(O)$_2$(CF$_2$)$_2$CF$_3$, -C(=O)NR$_9$S(O)$_2$R$_6$, -S(O)$_2$NR$_9$C(=O)OR$_6$, -S(O)$_2$NR$_9$C(=O)NR$_9$R$_9$, -C(=O)NR$_9$S(O)$_2$(CF$_2$)$_2$CF$_3$,
R₂ is alkyl, cycloalkyl or cycloalkylalkyl, wherein the alkyl may be optionally substituted with -OH;

R₄, at each occurrence, is F, -OH or alkyl; or any two alkyl R₄’s attached to the same carbon atom may form a 3- to 6-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S;

W is hydrogen, F, -OH or -NH₂;

R₅ is halo, -CN or -Oalkyl;

R₆, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl, aryl, aryalkyl, heteroaryl or heteroaryalkyl;

R₈, at each occurrence, is independently hydrogen or alkyl;

R₉, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, aryalkyl, heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclylalkyl, wherein the aryl, aryalkyl, heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclylalkyl may be optionally substituted with 0-5 R₉₈ and the heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₉₈, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl, heteroaryalkyl, heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -(O=O)OR, -(O=O)O(CR₃R₅)R₁₄, -O(CF₂)CF₃, -O(CR₃R₅)R₁₄, -OH, -SH, -S(CR₃R₅)R₁₄, -S(O)₃H, -P(O)₃H₂,

-C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)₂(CF₂)CF₃,

-C(=O)NR₁₄S(O)₂R₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄,

-C(=O)NR₁₄S(O)₂(CF₂)CF₃, -C(=O)(CR₃R₅)R₁₄, -NR₁₄C(=O)OR₁₄,

-NR₁₄C(=O)(CR₃R₅)R₁₄, -OC(=O)(CR₃R₅)R₁₄, -C(=N)NR₁₄NR₁₄R₁₄,

-NHC(=NR₁₄)NR₁₄R₁₄, -S(=O)(CR₃R₅)R₁₄, -S(O)₂(CR₃R₅)R₁₄, -NR₁₄C(=O)OR₁₄,

-NR₁₄S(O)₂R₆, aryloxy or aryalkyl;

R₁₀, at each occurrence, is independently selected from alkyl, aryl, aryalkyl, heterocyclyl or heterocyclylalkyl, wherein the alkyl, aryl, aryalkyl, heterocyclyl or heterocyclylalkyl may be optionally substituted with 0-3 R₁₀₈ and the heterocyclyl and heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₁₀₈, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -(O=O)OH, -(O=O)O(CR₃R₅)R₁₄,
-O(CF₂)₂CF₃, -O(CR₈R₉), R₁₄, -OH, -SH, -S(CR₈R₉)R₁₄, -S(O)₂H, -P(O)₂H₂,
-C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)₂(CF₂)₂CF₃,
-C(=O)NR₁₄S(O)₂R₁₆, -S(O)₂NR₁₄C(=O)OR₁₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄,
-C(=O)NR₁₄S(O)₂(CF₂)₂CF₃, -C(=O)(CR₈R₉)R₁₄, -NR₁₄C(=O)H,
5 -NR₁₄C(=O)(CR₈R₉)R₁₄, -OC(=O)(CR₈R₉)R₁₄, -C(=NR₁₄)NR₁₄R₁₄,
-NHC(=NR₁₄)NR₁₄R₁₄, -S(=O)(CR₈R₉)R₁₄, -S(O)₂(CR₈R₉)R₁₄, -NR₁₄C(=O)OR₈,
-NR₁₄S(O)₂R₈, aryloxy or arylalkyl;
R₁₄, at each occurrence, is independently selected from hydrogen, alkyl, cycloalkyl or phenyl;
m, at each occurrence, is 0-2;
n is 1-3; and
r is 0-5.

[0036] In another embodiment, compounds of Formula (Ic) are those compounds
having the formula (Id):

[0037] In yet another embodiment, compounds of the present invention are those
in which:
R₁₅ is –NHR₁, heteroaryl or aryl, wherein the heteroaryl and aryl may be
optionally substituted with 0-3 R₁₆;
R₁ is aryl or heteroaryl, both of which may be optionally substituted with 0-3
R₁₆;
R₁₈, at each occurrence, is independently selected from alkyl, haloalkyl, aryl,
alkenyl, alkylnyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl
heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₈R₉)R₁₀,
-O(CF₂)₂CF₃, -O(CR₈R₉)R₁₀, -OH, -SH, -S(CR₈R₉)R₁₀, -S(O)₂H, -P(O)₂H₂,
-C(=O)NR₈R₉, -NR₈R₉, -S(O)₂NR₈R₉, -NR₈S(O)₂(CF₂)₂CF₃, -C(=O)NR₈S(O)₂R₆,
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-S(O)2NR9C(=O)OR10, -S(O)2NR9C(=O)NR9R9, -C(=O)NR9S(O)2(CF3)2CF3,
-C(=O)(CR8R8),R10, -NR9C(=O)H, -NR9C(=O)(CR8R8),R10, -OC(=O)(CR8R8),R10,
-C(=NR14)NR9R9, -NHC(=NR14)NR14R14, -S(=O)(CR8R8),R10, -S(O)2(CR8R8),R10,
-NR9S(=O)OR10, -NR9S(O2)R8, -S(O)2NR9C(O)R6, aryloxy or arylalkyl, wherein the
aryl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycl
heterocyclylalkyl, aryloxy and arylalkyl may be optionally substituted with 0-3 R16;
R16, at each occurrence, is independently selected from alkyl, haloalkyl, aryl,
alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycl
heterocyclylalkyl, halo, -NH2, -CN, -NO2, -C(=O)OH, -C(=O)O(CR8R8),R10,
-O(CF3)2CF3, -O(CR8R8),R10, -OH, -SH, -S(CR8R8),R10, -O(OH), -P(O)H2,
-C(=O)NR9R9, -NR9R9, -S(O)2NR9R9, -NR9S(O2)2(CF3)2CF3, -C(=O)NR9S(O)2R6,
-S(O)2NR9C(=O)OR6, -S(O)2NR9C(=O)NR9R9, -C(=O)NR9S(O)2(CF3)2CF3,
-C(=O)(CR8R8),R10, -NR9C(=O)H, -NR9C(=O)(CR8R8),R10, -OC(=O)(CR8R8),R10,
-C(=NR14)NR9R9, -NHC(=NR14)NR14R14, -S(=O)(CR8R8),R10, -S(O)2(CR8R8),R10,
-NR9S(=O)OR10, -NR9S(O2)R8, aryloxy or arylalkyl;
R2 is alkyl or cycloalkyl, wherein the alkyl may be optionally substituted with
-OH;
R4, at each occurrence, is F, -OH or alkyl; or any two alkyl R4’s attached to
the same carbon atom may form a 3- to 6-membered ring, which optionally may
contain 1-4 heteroatoms selected from N, O, and S;
W is hydrogen, F, or -OH;
R5 is halo, -CN or -Oalkyl;
R6, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl,
aryl, arylalkyl, heteroaryl or heteroarylalkyl;
R8, at each occurrence, is independently hydrogen or alkyl;
R9, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl,
cycloalkyl, heteroaryl, heteroarylalkyl, heterocyclic or heterocyclylalkyl, wherein the
aryl, cycloalkyl, heteroaryl, heteroarylalkyl, heterocyclic or heterocyclylalkyl may be
optionally substituted with 0-5 R9a, and the heteroaryl, heteroarylalkyl, heterocycl
or heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;
R9a, at each occurrence, is independently selected from alkyl, haloalkyl, aryl,
alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclic
heterocyclalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₅R₆)R₄, -O(CF₂)CF₃, -O(CR₅R₆)R₄, -OH, -SH, -S(CR₅R₆)R₄, -S(O)₂H, -P(O)₃H₂, 
-C(=O)NR₄R₅, -NR₄NR₅, -S(O)₂NR₄R₅, -NR₄S(O)₃CF₃, -C(=O)NR₄S(O)₃R₆, -S(O)₂NR₄C(=O)OR₆, -S(O)₂NR₄C(=O)NR₄R₅, 
-C(=O)NR₄S(O)₂CF₃, -C(=O)(CR₅R₆)R₄, -OC(=O)(CR₅R₆)R₄, -C(=NR₄)NR₄R₅, 
-NHC(=NR₄)NR₄R₅, -S(=O)(CR₅R₆)R₄, -S(O)₂(CR₅R₆)R₄, -NR₄C(=O)OR₆, 
-NR₄S(O)₂R₆, -aryl or arylalkyl; 

R₁₀, at each occurrence, is independently selected from alkyl, aryl, arylalkyl, heterocycl or heterocyclalkyl, wherein the alkyl, aryl, arylalkyl, heterocycl or heterocyclalkyl may be optionally substituted with 0-3 R₁₀a, and the heterocycl and heterocyclalkyl contain 1-4 heteroatoms selected from N, O, and S; 

R₁₀a, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkylnyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocycl or heterocyclalkyl, heterocycl or heterocyclalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₅R₆)R₄, 
-O(CF₂)CF₃, -O(CR₅R₆)R₄, -OH, -SH, -S(CR₅R₆)R₄, -S(O)₂H, -P(O)₃H₂, 
-C(=O)NR₄R₅, -NR₄NR₅, -S(O)₂NR₄R₅, -NR₄S(O)₃CF₃, -C(=O)NR₄S(O)₃R₆, -S(O)₂NR₄C(=O)OR₆, -S(O)₂NR₄C(=O)NR₄R₅, 
-C(=O)NR₄S(O)₂CF₃, -C(=O)(CR₅R₆)R₄, -OC(=O)(CR₅R₆)R₄, -C(=NR₄)NR₄R₅, 
-NHC(=NR₄)NR₄R₅, -S(=O)(CR₅R₆)R₄, -S(O)₂(CR₅R₆)R₄, -NR₄C(=O)OR₆, 
-NR₄S(O)₂R₆, -aryl or arylalkyl; 

R₁₄, at each occurrence, is independently selected from hydrogen, alkyl, cycloalkyl or phenyl; 
m, at each occurrence, is 0-2; 
n is 1-2; and 
r is 0-4.

[0038] In still yet another embodiment, compounds of the present invention are those in which:

R₁₅ is -NHR₁, heteroaryl or aryl, wherein the heteroaryl and aryl may be optionally substituted with 0-3 R₁₅a;
R_1 is aryl or heteroaryl, which may be optionally substituted with 0-3 R_{1a},

R_{1a}, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkylnyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, halo, -NH_2, -CN, -NO_2, -(==O)OH, -(==O)(CR_3R_8),R_{10},

5 -O(CF_2)_nCF_3, -O(CR_3R_8),R_{10}, -OH, -SH, -(==S)(CR_3R_8),R_{10}, -(==S)(O_2),H, -(==P)(O)_3H_2,
-C(==O)NR_9R_9, -NR_9R_9, -(==S)(O_2)NR_9R_9, -(==NR_9S(O)_2)(CF_2)_nCF_3, -(==C)(==O)NR_9S(O)_2R_6,
-S(O)_2NR_9C(==O)OR_9, -(==S)(O)_2NR_9C(==O)NR_9R_9, -(==C)(==O)NR_9S(O)_2R_6,
-C(==O)(CR_3R_8),R_{10}, -NR_9C(==O)H, -NR_9C(==O)(CR_3R_8),R_{10}, -(==O)(CR_3R_8),R_{10},
-C(==NR_9)NR_9R_9, -(==S)(O_2)NR_9R_9, -(==O)(CR_3R_8),R_{10}, -(==S)(O_2)(CR_3R_8),R_{10},
-10 NR_9C(==O)OR_8, -NR_9S(O_2)R_8, -(==S)(O_2)NR_9C(==O)R_6, aryloxy or arylalkyl, wherein the aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, aryloxy and arylalkyl may be optionally substituted with 0-3 R_{1b};

R_{1b}, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkylnyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, aryloxy and arylalkyl may be optionally substituted with 0-3 R_{1b};

heterocyclylalkyl, halo, -NH_2, -CN, -NO_2, -(==O)OH, -(==O)(CR_3R_8),R_{10},
-15 O(CF_2)_nCF_3, -O(CR_3R_8),R_{10}, -OH, -SH, -(==S)(CR_3R_8),R_{10}, -(==S)(O_2),H, -(==P)(O)_3H_2,
-C(==O)NR_9R_9, -NR_9R_9, -(==S)(O_2)NR_9R_9, -(==NR_9S(O)_2)(CF_2)_nCF_3, -(==C)(==O)NR_9S(O)_2R_6,
-S(O)_2NR_9C(==O)OR_9, -(==S)(O)_2NR_9C(==O)NR_9R_9, -(==C)(==O)NR_9S(O)_2R_6,
-C(==O)(CR_3R_8),R_{10}, -NR_9C(==O)H, -NR_9C(==O)(CR_3R_8),R_{10}, -(==O)(CR_3R_8),R_{10},
-C(==NR_9)NR_9R_9, -(==S)(O_2)NR_9R_9, -(==O)(CR_3R_8),R_{10}, -(==S)(O_2)(CR_3R_8),R_{10},
-20 NR_9C(==O)OR_8, -NR_9S(O_2)R_8, aryloxy or arylalkyl;

R_2 is alkyl or cycloalkyl, wherein the alkyl may be optionally substituted with
-OH;

R_4, at each occurrence, is OH or alkyl; or any two alkyl R_4's attached to the same carbon atom may form a 3- to 6-membered ring, which optionally may contain

1-4 heteroatoms selected from N, O, and S;

W is hydrogen or -OH;

R_5 is halo or -CN;

R_6, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R_8, at each occurrence, is independently hydrogen or alkyl;
R₉, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclylalkyl, wherein the aryl, arylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclylalkyl may be optionally substituted with 0-5 R₉ₐ and the heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₉ₐ, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkylnyl, cycloalkyl, heterocyclylalkyl, heteroaryalkyl, heterocyclylalkyl, heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅), R₁₄, -O(CF₃)CF₃, -O(CR₃R₅)R₁₄, -OH, -SH, -S(CR₃R₅)R₁₄, -S(O)₂H, -P(O)₃H₂, -C(=O)NR₁₄R₉, -NR₁₄R₉, -S(O)₂NR₁₄R₉, -NR₁₄SO₂CF₂CF₃, -C(=O)NR₁₄S(O)₂R₉₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄, -C(=O)NR₁₄S(O)₂CF₂CF₃, -C(=O)CR₃R₅R₁₄, -OC(=O)(CR₃R₅)R₁₄, C(=O)NR₁₄R₁₄, -NH(=NR₁₄)NR₁₄R₁₄, -S(O)₂(CR₃R₅)R₁₄, -S(O)₂(CR₃R₅)S(O)₂R₁₄, -NR₁₄C(=O)OR₆,

R₁₀, at each occurrence, is independently selected from alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, wherein the alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl may be optionally substituted with 0-3 R₁₀ₐ, and the heterocyclyl and heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₁₀ₐ, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkylnyl, cycloalkyl, heterocyclylalkyl, heteroaryalkyl, heterocyclylalkyl, heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅), R₁₄, -O(CF₂)CF₃, -O(CR₃R₅)R₁₄, -OH, -SH, -S(CR₃R₅)R₁₄, -S(O)₂H, -P(O)₃H₂, -C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄SO₂CF₂CF₃, -C(=O)NR₁₄S(O)₂R₉₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄, -C(=O)NR₁₄S(O)₂CF₂CF₃, -C(=O)CR₃R₅R₁₄, -OC(=O)(CR₃R₅)R₁₄, -C(=O)NR₁₄R₁₄, -NH(=NR₁₄)NR₁₄R₁₄, -S(O)₂(CR₃R₅)R₁₄, -S(O)₂(CR₃R₅)S(O)₂R₁₄, -NR₁₄C(=O)OR₆,

R₁₄, at each occurrence, is independently selected from hydrogen, alkyl, cycloalkyl or phenyl;

m, at each occurrence, is 0-2;

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n is 1-2; and
r is 0-3.

[0039] In yet another embodiment, compounds of the present invention are those in which:

R₁₅ is –NHR₁, heteroaryl or aryl, wherein the heteroaryl and aryl may be optionally substituted with 0-3 R₁₆;

R₁ is aryl or heteroaryl, which may be optionally substituted with 0-3 R₁₆;

R₁₆, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₈),R₁₆;
-O(CF₂)₂CF₃, -O(CR₃R₈),R₁₆; -OH, -SH, -S(CR₃R₈),R₁₆; -S(O)₂H, -P(O)₃H₂;
-C(=O)NR₉R₉, -NR₉R₉; -S(O)₂NR₉R₉, -NR₉S(O)₂(CF₂)CF₃, -C(=O)NR₉S(O)₂R₆,
-S(O)₂NR₉C(=O)OR₆, -S(O)₂NR₉C(=O)NR₉R₉; -C(=O)NR₉S(O)₂(CF₂)CF₃,
-C(=O)(CR₃R₈),R₁₆; -NR₉C(=O)H, -NR₉C(=O)(CR₃R₈),R₁₆; -OC(=O)(CR₃R₈),R₁₆;
-C(=O)NR₉R₉, -NH(C=NR₉)NR₉R₉; -S(O)₂(CR₃R₈),R₁₆; -S(O)₂(CR₃R₈),R₁₆;
-NR₉S(O)₂(CR₃R₈),R₁₆; -S(O)₂NR₉C(O)R₆, aryloxy or arylalkyl, wherein the aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, aryloxy and arylalkyl may be optionally substituted with 0-3 R₁₆;

R₁₆, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₈),R₁₆;
-O(CF₂)₂CF₃, -O(CR₃R₈),R₁₆; -OH, -SH, -S(CR₃R₈),R₁₆; -S(O)₂H, -P(O)₃H₂;
-C(=O)NR₉R₉, -NR₉R₉; -S(O)₂NR₉R₉, -NR₉S(O)₂(CF₂)CF₃, -C(=O)NR₉S(O)₂R₆,
-S(O)₂NR₉C(=O)OR₆, -S(O)₂NR₉C(=O)NR₉R₉; -C(=O)NR₉S(O)₂(CF₂)CF₃,
-C(=O)(CR₃R₈),R₁₆; -NR₉C(=O)H, -NR₉C(=O)(CR₃R₈),R₁₆; -OC(=O)(CR₃R₈),R₁₆;
-C(=O)NR₉R₉, -NH(C=NR₉)NR₉R₉; -S(O)₂(CR₃R₈),R₁₆; -S(O)₂(CR₃R₈),R₁₆;
-NR₉S(O)₂(CR₃R₈),R₁₆; -S(O)₂NR₉C(O)R₆, aryloxy or arylalkyl;

R₂ is alkyl or cycloalkyl, wherein the alkyl may be optionally substituted with

-OH;
R₄, at each occurrence, is alkyl; or any two R₄’s attached to the same carbon atom may form a 3- to 6-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S;

W is hydrogen or -OH;

R₅ is halo;

R₆, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R₇, at each occurrence, is independently hydrogen or alkyl;

R₈, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclalkyl, wherein the aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclalkyl may be optionally substituted with 0-5 R₉a, and the heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₉a, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkylnyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅)R₁₄, -O(CF₃)₂CF₃, -O(CR₃R₅)R₁₄, -OH, -SH, -S(CR₃R₅)R₁₄, -S(O)₂H, -P(O)₂H₂, -C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)(CF₂)₂CF₃, -C(=O)NR₁₄S(O)₂R₆, -S(O)₂NR₁₄C(=O)OR₆, -S(O)₂NR₁₄C(=O)NR₁₄R₁₄, -C(=O)NR₁₄S(O)₂(CF₂)₂CF₃, -C(=O)(CR₃R₅)R₁₄, -CR₃R₅R₁₄, -OC(=O)(CR₃R₅)R₁₄, -C(=O)NR₁₄NR₁₄R₁₄, -NHC(=NR₁₄)NR₁₄R₁₄, -S(O)(CR₃R₅)R₁₄, -S(O)₂(CR₃R₅)R₁₄, -NR₁₄C(=O)OR₆, -NR₁₄S(O)₂R₆, aryloxy or arylalkyl;

R₁₀, at each occurrence, is independently selected from alkyl, aryl, arylalkyl, heterocyclyl or heterocyclalkyl, wherein the alkyl, aryl, arylalkyl, heterocyclyl or heterocyclalkyl may be optionally substituted with 0-3 R₁₀a, and the heterocyclyl and heterocyclalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₁₀a, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkylnyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅)R₁₄, -O(CF₃)₂CF₃, -O(CR₃R₅)R₁₄, -OH, -SH, -S(CR₃R₅)R₁₄, -S(O)₂H, -P(O)₂H₂, -C(=O)NR₁₄R₁₄, -NR₁₄R₁₄, -S(O)₂NR₁₄R₁₄, -NR₁₄S(O)(CF₂)₂CF₃,
-C(=O)NR_{14}S(O)_{2}R_{6}, -S(O)_{2}NR_{14}C(=O)OR_{6}, -S(O)_{2}NR_{14}C(=O)NR_{14}R_{14},
-C(=O)NR_{14}S(O)_{2}(CF_{2}) CF_{3}, -C(=O)(CR_{8}R_{8})R_{14}, -NR_{14}C(=O)H,
-NR_{14}C(=O)(CR_{8}R_{8})R_{14}, -OC(=O)(CR_{8}R_{8})R_{14}, -C(=O)NR_{14}NR_{14}R_{14},
-NHC(=NR_{14})NR_{14}R_{14}, -S(=O)(CR_{8}R_{8})R_{14}, -S(O)_{2}(CR_{8}R_{8})R_{14}, -NR_{14}C(=O)OR_{8},
-NR_{14}S(O)_{2}R_{8}, aryloxy or arylalkyl;

R_{14}, at each occurrence, is independently selected from hydrogen, alkyl, cycloalkyl or phenyl;

m, at each occurrence, is 0-2;
n is 1-2; and

r is 0-2.

[0040] In one embodiment, compounds of the present invention are those in which:

R_{15} is -NHR_{1} or heteroaryl, wherein the heteroaryl may be optionally substituted with 0-3 R_{1a}:

R_{1} is aryl or heteroaryl, which may be optionally substituted with 0-3 R_{1a};

R_{1a}, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heteroarylsyl, heterocyclicalkyl, halo, -NH_{2}, -CN, -NO_{2}, -C(=O)OH, -C(=O)O(CR_{8}R_{8})R_{10},

-O(CF_{2}) CF_{3}, -O(CR_{8}R_{8})R_{10}, -OH, -SH, -S(CR_{8}R_{8})R_{10}, -S(O)_{2}H, -P(O)_{3}H_{2},

-C(=O)NR_{8}R_{8}, -NR_{8}R_{8}, -S(O)_{2}NR_{8}R_{8}, -NR_{8}S(O)_{2}(CF_{2}) CF_{3}, -C(=O)NR_{8}S(O)_{2}R_{6},

-S(O)_{2}NR_{8}C(=O)OR_{8}, -S(O)_{2}NR_{8}C(=O)NR_{8}R_{8}, -C(=O)NR_{8}S(O)_{2}(CF_{2}) CF_{3},

-C(=O)(CR_{8}R_{8})R_{10}, -NR_{8}C(=O)H, -NR_{8}C(=O)(CR_{8}R_{8})R_{10}, -OC(=O)(CR_{8}R_{8})R_{10},

-C(=NR_{14})NR_{9}R_{9}, -NHC(=NR_{14})NR_{14}R_{14}, -S(=O)(CR_{8}R_{8})R_{10}, -S(O)_{2}(CR_{8}R_{8})R_{10},

-NR_{8}C(=O)OR_{8}, -NR_{8}S(O)_{2}R_{8}, -S(O)_{2}NR_{8}C(O)R_{6}, aryloxy or arylalkyl, wherein the aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclicalkyl, heterocyclicalkylalkyl, aryloxy and arylalkyl may be optionally substituted with 0-3 R_{1b}:

R_{1b}, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclicalkyl, halo, -NH_{2}, -CN, -NO_{2}, -C(=O)OH, -C(=O)O(CR_{8}R_{8})R_{10},

-O(CF_{2}) CF_{3}, -O(CR_{8}R_{8})R_{10}, -OH, -SH, -S(CR_{8}R_{8})R_{10}, -S(O)_{2}H, -P(O)_{3}H_{2},

-C(=O)NR_{9}R_{9}, -NR_{9}R_{9}, -S(O)_{2}NR_{9}R_{9}, -NR_{9}S(O)_{2}(CF_{2}) CF_{3}, -C(=O)NR_{9}S(O)_{2}R_{6},

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-S(O)\textsubscript{2}NR\textsubscript{9}C(=O)OR\textsubscript{6}, -S(O)\textsubscript{2}NR\textsubscript{9}C(=O)NR\textsubscript{9}R\textsubscript{9}, -C(=O)NR\textsubscript{9}S(O)\textsubscript{2}(CF\textsubscript{3})\textsubscript{2},CF\textsubscript{3},
-C(=O)(CR\textsubscript{3}R\textsubscript{9})\textsubscript{2},R\textsubscript{10}, -NR\textsubscript{9}C(=O)H, -NR\textsubscript{9}C(=O)(CR\textsubscript{3}R\textsubscript{9})\textsubscript{2},R\textsubscript{10}, -OC(=O)(CR\textsubscript{3}R\textsubscript{9})\textsubscript{2},R\textsubscript{10},
-C(=NR\textsubscript{14})NR\textsubscript{9}R\textsubscript{9}, -NHC(=NR\textsubscript{14})NR\textsubscript{14}R\textsubscript{14}, -S(=O)(CR\textsubscript{3}R\textsubscript{9})\textsubscript{2},R\textsubscript{10}, -S(O)\textsubscript{2}(CR\textsubscript{3}R\textsubscript{9})\textsubscript{2},R\textsubscript{10},
-NR\textsubscript{9}C(=O)OR\textsubscript{8}, -NR\textsubscript{9}S(O)\textsubscript{2}R\textsubscript{8}, aryloxy or arylalkyl;

R\textsubscript{2} is alkyl or cycloalkyl, wherein the alkyl may be optionally substituted with -OH;

R\textsubscript{4}, at each occurrence, is alkyl;

W is hydrogen or -OH;

R\textsubscript{5} is halo;

R\textsubscript{6}, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R\textsubscript{8}, at each occurrence, is independently hydrogen or alkyl;

R\textsubscript{9}, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl, wherein the aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl may be optionally substituted with 0-5 R\textsubscript{9a}, and the heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R\textsubscript{9a}, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl heterocyclylalkyl, halo, -NH\textsubscript{2}, -CN, -NO\textsubscript{2}, -C(=O)OH, -C(=O)O(CR\textsubscript{3}R\textsubscript{9})\textsubscript{2},R\textsubscript{14},
-O(CF\textsubscript{2})\textsubscript{2},CF\textsubscript{3}, -O(CR\textsubscript{3}R\textsubscript{9})\textsubscript{2},R\textsubscript{14}, -OH, -SH, -S(CR\textsubscript{3}R\textsubscript{9})\textsubscript{2},R\textsubscript{14}, -S(O)\textsubscript{2}H, -P(O)\textsubscript{2}H\textsubscript{2},
-C(=O)NR\textsubscript{14}R\textsubscript{14}, -NR\textsubscript{14}R\textsubscript{14}, -S(O)\textsubscript{2}NR\textsubscript{14}R\textsubscript{14}, -NR\textsubscript{14}S(O)\textsubscript{2}(CF\textsubscript{3})\textsubscript{2},CF\textsubscript{3},
-C(=O)NR\textsubscript{14}S(O)\textsubscript{2}R\textsubscript{6}, -S(O)\textsubscript{2}NR\textsubscript{14}C(=O)OR\textsubscript{6}, -S(O)\textsubscript{2}NR\textsubscript{14}C(=O)NR\textsubscript{14}R\textsubscript{14},
-C(=O)NR\textsubscript{14}S(O)\textsubscript{2}(CF\textsubscript{3})\textsubscript{2},CF\textsubscript{3}, -C(=O)(CR\textsubscript{3}R\textsubscript{9})\textsubscript{2},R\textsubscript{14}, -NR\textsubscript{14}C(=O)H,
-NR\textsubscript{14}C(=O)(CR\textsubscript{3}R\textsubscript{9})\textsubscript{2},R\textsubscript{14}, -OC(=O)(CR\textsubscript{3}R\textsubscript{9})\textsubscript{2},R\textsubscript{14}, -C(=NR\textsubscript{14})NR\textsubscript{14}R\textsubscript{14},
-NHC(=NR\textsubscript{14})NR\textsubscript{14}R\textsubscript{14}, -S(=O)(CR\textsubscript{3}R\textsubscript{9})\textsubscript{2},R\textsubscript{14}, -S(O)\textsubscript{2}(CR\textsubscript{3}R\textsubscript{9})\textsubscript{2},R\textsubscript{14}, -NR\textsubscript{14}C(=O)OR\textsubscript{8},
-NR\textsubscript{14}S(O)\textsubscript{2}R\textsubscript{8}, aryloxy or arylalkyl;

R\textsubscript{10}, at each occurrence, is independently selected from alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, wherein the alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl may be optionally substituted with 0-3 R\textsubscript{10a}, and the heterocyclyl and heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;
R_{10a}, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl
heterocyclylalkyl, halo, -NH_{2}, -CN, -NO_{2}, -C(=O)OH, -C(=O)O(\text{CR}_{3}\text{R}_{8})_{R_{14}},
-O(\text{CF}_{2})_{CF}_{3}, -O(\text{CR}_{8}\text{R}_{8})_{R_{14}}, -OH, -SH, -S(\text{CR}_{8}\text{R}_{8})_{R_{14}}, -S(\text{O})_{3}\text{H}, -P(\text{O})_{3}\text{H}_{2},
-C(=O)\text{NR}_{14}\text{R}_{14}, -\text{NR}_{14}\text{R}_{14}, -\text{S}(\text{O})_{2}\text{NR}_{14}\text{R}_{14}, -\text{NR}_{14}\text{S}(\text{O})(\text{CF}_{2})_{CF}_{3},
-C(=O)\text{NR}_{14}\text{S}(\text{O})_{2}\text{R}_{6}, -\text{S}(\text{O})_{2}\text{NR}_{14}\text{C}(=O)\text{OR}_{6}, -\text{S}(\text{O})_{2}\text{NR}_{14}\text{C}(=O)\text{OR}_{6},
-C(=O)\text{NR}_{14}\text{S}(\text{O})(\text{CF}_{2})_{CF}_{3}, -C(=O)(\text{CR}_{8}\text{R}_{8})_{R_{14}}, -\text{NR}_{14}\text{C}(=O)\text{H},
-\text{NR}_{14}\text{C}(=O)(\text{CR}_{8}\text{R}_{8})_{R_{14}}, -\text{OC}(=O)(\text{CR}_{8}\text{R}_{8})_{R_{14}}, -\text{C}(=\text{NR}_{14})\text{NR}_{14}\text{R}_{14},
-\text{NHC}(=\text{NR}_{14})\text{NR}_{14}\text{R}_{14}, -\text{S}(\text{O})(\text{CR}_{8}\text{R}_{8})_{R_{14}}, -\text{S}(\text{O})_{2}(\text{CR}_{3}\text{R}_{8})_{R_{14}}, -\text{NR}_{14}\text{C}(=O)\text{OR}_{8},
\text{NR}_{14}\text{S}(\text{O})(\text{OR})_{8}, \text{aryloxy or arylalkyl};
R_{14}, at each occurrence, is independently selected from hydrogen, alkyl,
cycloalkyl or phenyl;
m, at each occurrence, is 0-2;
n is 1-2; and
r is 0-2.

[0041] In another embodiment, compounds of the present invention are those in
which:
R_{15} is -\text{NHR}_{1};

R_{1} is aryl or heteroaryl, which may be optionally substituted with 0-3 R_{16};
R_{1n}, at each occurrence, is independently selected from alkyl, haloalkyl, aryl,
alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyl
heterocyclylalkyl, halo, -NH_{2}, -CN, -NO_{2}, -C(=O)OH, -C(=O)O(\text{CR}_{3}\text{R}_{8})_{R_{10}},
-O(\text{CF}_{2})_{CF}_{3}, -O(\text{CR}_{8}\text{R}_{8})_{R_{10}}, -OH, -SH, -S(\text{CR}_{8}\text{R}_{8})_{R_{10}}, -S(\text{O})_{3}\text{H}, -P(\text{O})_{3}\text{H}_{2},
-C(=O)\text{NR}_{9}\text{R}_{9}, -\text{NR}_{9}\text{R}_{9}, -\text{S}(\text{O})_{2}\text{NR}_{9}\text{R}_{9}, -\text{NR}_{9}\text{S}(\text{O})(\text{CF}_{2})_{CF}_{3}, -C(=O)\text{NR}_{9}\text{S}(\text{O})_{2}\text{R}_{6},
-S(\text{O})_{2}\text{NR}_{9}\text{C}(=O)\text{OR}_{6}, -\text{S}(\text{O})_{2}\text{NR}_{9}\text{C}(=O)\text{OR}_{6}, -\text{C}(=O)\text{NR}_{9}\text{S}(\text{O})(\text{CF}_{2})_{CF}_{3},
-C(=O)(\text{CR}_{8}\text{R}_{8})_{R_{10}}, -\text{NR}_{9}\text{C}(=O)\text{H}, -\text{NR}_{9}\text{C}(=O)(\text{CR}_{8}\text{R}_{8})_{R_{10}}, -\text{OC}(=O)(\text{CR}_{8}\text{R}_{8})_{R_{10}},
-C(=\text{NR}_{14})\text{NR}_{9}\text{R}_{9}, -\text{NHC}(=\text{NR}_{14})\text{NR}_{14}\text{R}_{14}, -\text{S}(\text{O})(\text{CR}_{8}\text{R}_{8})_{R_{10}}, -\text{S}(\text{O})_{2}(\text{CR}_{3}\text{R}_{8})_{R_{10}},
-\text{NR}_{9}\text{C}(=O)\text{OR}_{8}, -\text{NR}_{9}\text{S}(\text{O})(\text{OR})_{8}, -\text{S}(\text{O})_{2}\text{NR}_{9}\text{C}(=O)\text{OR}_{6}, \text{aryloxy or arylalkyl}, wherein the
aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl
heterocyclylalkyl, aryloxy and arylalkyl may be optionally substituted with 0-3 R_{16};
R_{1b}, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclylalkyl, halo, -NH_{2}, -CN, -NO_{2}, -C(=O)OH, -C(=O)O(CR_{3}R_{8})\text{R}_{10}, -O(CF_{2})_{2}CF_{3}, -O(CR_{3}R_{8})\text{R}_{10}, -OH, -SH, -S(CR_{3}R_{8})\text{R}_{10}, -S(O)\text{H}_{3}, -P(O)\text{H}_{2},
\begin{align*}
-C(=O)NR_{3}R_{8}, -NR_{3}R_{9}, -S(O)_{2}NR_{3}R_{9}, -NR_{8}S(O)_{2}(CF_{2})\text{CF}_{3}, -C(=O)NR_{3}S(O)_{2}R_{6}, \\
-S(O)_{2}NR_{3}C(=O)OR_{6}, -S(O)_{2}NR_{3}C(=O)NR_{3}R_{9}, -C(=O)NR_{8}S(O)_{2}(CF_{2})\text{CF}_{3}, \\
-C(=O)(CR_{3}R_{8})\text{R}_{10}, -NR_{8}C(=O)H, -NR_{8}C(=O)(CR_{3}R_{8})\text{R}_{10}, -OC(=O)(CR_{3}R_{8})\text{R}_{10}, \\
-C(=NR_{14})NR_{8}R_{9}, -NHC(=NR_{14})NR_{14}R_{14}, -S(=O)(CR_{3}R_{8})\text{R}_{10}, -S(O)_{2}(CR_{3}R_{8})\text{R}_{10}, \\
-NR_{8}C(=O)OR_{8}, -NR_{8}S(O)_{2}R_{8}, aryloxy or arylalkyl;
\end{align*}

R_{2} is alkyl or cycloalkyl;
R_{4}, at each occurrence, is alkyl;
W is hydrogen or -OH;
R_{5} is halo;
R_{6}, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl,
aryl, arylalkyl, heteroaryl or heteroaryalkyl;
R_{8}, at each occurrence, is independently hydrogen or alkyl;
R_{9}, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclylalkyl, wherein the aryl, arylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclylalkyl may be optionally substituted with 0-5 R_{9a}, and the heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;
R_{9a}, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclylalkyl, halo, -NH_{2}, -CN, -NO_{2}, -C(=O)OH, -C(=O)O(CR_{3}R_{8})\text{R}_{14}, -O(CF_{2})_{2}CF_{3}, -O(CR_{3}R_{8})\text{R}_{14}, -OH, -SH, -S(CR_{3}R_{8})\text{R}_{14}, -S(O)\text{H}_{3}, -P(O)\text{H}_{2},
\begin{align*}
-C(=O)NR_{14}R_{14}, -NR_{14}R_{14}, -S(O)_{2}NR_{14}R_{14}, -NR_{14}S(O)_{2}(CF_{2})\text{CF}_{3}, \\
-C(=O)NR_{14}S(O)_{2}R_{6}, -S(O)_{2}NR_{14}C(=O)OR_{6}, -S(O)_{2}NR_{14}C(=O)NR_{14}R_{14}, \\
-C(=O)NR_{14}S(O)_{2}(CF_{2})\text{CF}_{3}, -C(=O)(CR_{3}R_{8})\text{R}_{14}, -NR_{14}C(=O)H, \\
-NR_{14}C(=O)(CR_{3}R_{8})\text{R}_{14}, -OC(=O)(CR_{3}R_{8})\text{R}_{14}, -C(=NR_{14})NR_{14}R_{14}, \\
-NH(=NR_{14})NR_{14}R_{14}, -S(=O)(CR_{3}R_{8})\text{R}_{14}, -S(O)_{2}(CR_{3}R_{8})\text{R}_{14}, -NR_{14}C(=O)OR_{8}, \\
-NR_{14}S(O)_{2}R_{8}, aryloxy or arylalkyl;
\end{align*}
R₁₀, at each occurrence, is independently selected from alkyl, aryl, aroyl, heterocyclyl or heterocyclylalkyl, wherein the alkyl, aryl, aroyl, heterocyclyl or heterocyclylalkyl may be optionally substituted with 0-3 R₁₀ₐ, and the heterocyclyl and heterocyclylalkyl contain 1-4 heteroatoms selected from N, O, and S;

R₁₀ₐ, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryalkyl, heterocyclyl heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₃R₅),R₁₄, -O(CF₂)CF₃, -O(CR₃R₅),R₁₄, -OH, -SH, -S(CR₃R₅),R₁₄, -S(O)₂H, -P(O)₃H₂, -C(=O)NR₄R₁₄, -NR₄R₁₄, -S(O)₂NR₄R₁₄, -NR₄S(O)₂(CF₂)CF₃, -C(=O)NR₄S(Ο)₂R₆, -S(O)₂NR₄C(=O)OR₆, -S(O)₂NR₄C(=O)NR₄R₁₄, -C(=O)NR₄S(O)₂(CF₂)CF₃, -C(=O)(CR₃R₅),R₁₄, -NR₄C(=O)H, -NR₄C(=O)(CR₃R₅),R₁₄, -OC(=O)(CR₃R₅),R₁₄, -C(=NR₄)NR₄R₁₄, -NH(C(=NR₄))NR₄R₁₄, -S(=O)(CR₃R₅),R₁₄, -S(O)₂(CR₃R₅),R₁₄, -NR₄C(=O)OR₆, -NR₄S(O)₂R₆, aryls or aroylalkyl;

R₁₄, at each occurrence, is independently selected from hydrogen, alkyl, cycloalkyl or phenyl;

m, at each occurrence, is 0-2;

n is 1-2; and

r is 0-2.

[0042] In one embodiment, the present invention provides novel compounds of formula (Ic):

![Image of formula (Ic)]

or stereoisomers or prodrugs or pharmaceutically acceptable salt forms thereof, wherein:

the dashed line represents an optional double bond;

T is "C" or "O" or "N" or "S";

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R₁ is alkyl, cycloalkyl, aryl, heterocyclic or heteroaryl, all of which may be optionally substituted with 0-5 R₁₅; 

R₁₅, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylmethyl, heterocyclyl heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₅R₈)R₁₀, -O(CF₂)₃CF₃, -O(CR₅R₈)R₁₀, -OH, -SH, -S(CR₅R₈)R₁₀, -S(O)₂H, -P(O)₃H₂, 
-C(=O)NR₅R₉, -NR₅R₉, -S(O)₂NR₅R₉, -NR₅O(S(O)₂)(CF₂)₃CF₃, -C(=O)NR₅O(S(O)₂)R₆, -S(O)₂NR₅C(=O)OR₆, -S(O)₂NR₅C(=O)NR₅R₉, -C(=O)NR₅O(S(O)₂)(CF₂)₃CF₃, -C(=O)(CR₅R₈)R₁₀, -NR₅C(=O)H, -NR₅C(=O)(CR₅R₈)R₁₀, -OC(=O)(CR₅R₈)R₁₀, -C(=O)NR₅R₉, -NH(=NR₅)NR₅R₁₄, -S(O)(CR₅R₈)R₁₀, -S(O)₂(CR₅R₈)R₁₀, -NR₅C(=O)OR₈, -NR₅O(S(O)₂)R₈, -S(O)₂NR₅C(=O)R₆, aryloxy or arylalkyl, wherein the aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylmethyl, heterocyclyl heterocyclylalkyl, aryloxy and arylalkyl may be optionally substituted with 0-3 R₁₅; 

R₁₅, at each occurrence, is independently selected from alkyl, haloalkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylmethyl, heterocyclyl heterocyclylalkyl, halo, -NH₂, -CN, -NO₂, -C(=O)OH, -C(=O)O(CR₅R₈)R₁₀, -O(CF₂)₃CF₃, -O(CR₅R₈)R₁₀, -OH, -SH, -S(CR₅R₈)R₁₀, -S(O)₂H, -P(O)₃H₂, 
-C(=O)NR₅R₉, -NR₅R₉, -S(O)₂NR₅R₉, -NR₅O(S(O)₂)(CF₂)₃CF₃, -C(=O)NR₅O(S(O)₂)R₆, -S(O)₂NR₅C(=O)OR₆, -S(O)₂NR₅C(=O)NR₅R₉, -C(=O)NR₅O(S(O)₂)(CF₂)₃CF₃, -C(=O)(CR₅R₈)R₁₀, -NR₅C(=O)H, -NR₅C(=O)(CR₅R₈)R₁₀, -OC(=O)(CR₅R₈)R₁₀, -C(=O)NR₅R₉, -NH(=NR₅)NR₅R₁₄, -S(O)(CR₅R₈)R₁₀, -S(O)₂(CR₅R₈)R₁₀, -NR₅C(=O)OR₈, -NR₅O(S(O)₂)R₈, -S(O)₂NR₅C(=O)R₆, aryloxy or arylalkyl; 

R₂ is alkyl, cycloalkyl, cycloalkylalkyl, or alkenyl, wherein the alkyl may be optionally substituted with -OH; 

R₅ is halo, -CN or -Oalkyl; 

R₆, at each occurrence, is independently alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylmethyl; 

R₈, at each occurrence, is independently hydrogen or alkyl; 

R₉, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylmethyl, heterocyclyl or heterocyclylalkyl, wherein the aryl, arylalkyl, heteroaryl, heteroarylmethyl, heterocyclyl or heterocyclylalkyl may be
optionally substituted with 0-5 $R_{9a}$, and the heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclalkyl contain 1-4 heteroatoms selected from N, O, and S;

$R_{9a}$, at each occurrence, is independently selected from alkyl, haloalkyl, aroyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl halogenoalkylalkyl, halo, -NH$_2$, -CN, -NO$_2$, -C(=O)OH, -C(=O)O(CR$_3$R$_8$)$_3$R$_{14}$, -O(CF$_2$)$_2$CF$_3$, -O(CR$_3$R$_8$)$_3$R$_{14}$, -OH, -SH, -S(CR$_3$R$_8$)$_3$R$_{14}$, -S(O)$_2$H, -P(O)$_3$H$_2$,

-C(=O)NR$_{14}$R$_{14}$, -NR$_{14}$R$_{14}$, -S(O)$_2$NR$_{14}$R$_{14}$, -NR$_{14}$S(O)$_2$(CF$_2$)$_2$CF$_3$,

-C(=O)NR$_{14}$S(O)$_2$R$_6$, -S(O)$_2$NR$_{14}$C(=O)OR$_6$, -S(O)$_2$NR$_{14}$C(=O)NR$_{14}$R$_{14}$,

-C(=O)NR$_{14}$S(O)$_2$(CF$_2$)$_2$CF$_3$, -C(=O)(CR$_3$R$_8$)$_3$R$_{14}$, -NR$_{14}$C(=O)H,

-OC(=O)(CR$_3$R$_8$)$_3$R$_{14}$, -C(=NR$_{14}$)NR$_{14}$R$_{14}$, -NHC(=NR$_{14}$)NR$_{14}$R$_{14}$, -S(=O)(CR$_3$R$_8$)$_3$R$_{14}$, -S(O)$_2$(CR$_3$R$_8$)$_3$R$_{14}$, -NR$_{14}$C(=O)OR$_8$,

-NR$_{14}$S(O)$_2$R$_8$, arylxloxy or aryalkyl;

$R_{10}$, at each occurrence, is independently selected from alkyl, aroyl, arylalkyl, heterocyclyl or heterocyclalkyl, wherein the alkyl, aroyl, arylalkyl, heterocyclyl or heterocyclalkyl may be optionally substituted with 0-3 $R_{10a}$, and the heterocyclyl and heterocyclalkyl contain 1-4 heteroatoms selected from N, O, and S;

$R_{10a}$, at each occurrence, is independently selected from alkyl, haloalkyl, aroyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl halogenoalkylalkyl, halo, -NH$_2$, -CN, -NO$_2$, -C(=O)OH, -C(=O)O(CR$_3$R$_8$)$_3$R$_{14}$, -O(CF$_2$)$_2$CF$_3$, -O(CR$_3$R$_8$)$_3$R$_{14}$, -OH, -SH, -S(CR$_3$R$_8$)$_3$R$_{14}$, -S(O)$_2$H, -P(O)$_3$H$_2$,

-C(=O)NR$_{14}$R$_{14}$, -NR$_{14}$R$_{14}$, -S(O)$_2$NR$_{14}$R$_{14}$, -NR$_{14}$S(O)$_2$(CF$_2$)$_2$CF$_3$,

-C(=O)NR$_{14}$S(O)$_2$R$_6$, -S(O)$_2$NR$_{14}$C(=O)OR$_6$, -S(O)$_2$NR$_{14}$C(=O)NR$_{14}$R$_{14}$,

-C(=O)NR$_{14}$S(O)$_2$(CF$_2$)$_2$CF$_3$, -C(=O)(CR$_3$R$_8$)$_3$R$_{14}$, -NR$_{14}$C(=O)H,

-OC(=O)(CR$_3$R$_8$)$_3$R$_{14}$, -C(=NR$_{14}$)NR$_{14}$R$_{14}$, -NHC(=NR$_{14}$)NR$_{14}$R$_{14}$, -S(=O)(CR$_3$R$_8$)$_3$R$_{14}$, -S(O)$_2$(CR$_3$R$_8$)$_3$R$_{14}$, -NR$_{14}$C(=O)OR$_8$,

-NR$_{14}$S(O)$_2$R$_8$, arylxloxy or aryalkyl;

$R_{14}$, at each occurrence, is independently selected from hydrogen, alkyl, cycloalkyl or phenyl;

$m$, at each occurrence, is 0-2;

$n$ is 1-3; and

$r$ is 0-5.
[0043] In one embodiment, compounds of the present invention are selected from the compounds exemplified in the examples.

In one embodiment, compounds of the present invention are selected from the group consisting of:

![Chemical structures](image)

[0044] In another embodiment, the present invention is directed to a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the present invention.

[0045] In another embodiment, the present invention is directed to a method for modulation of chemokine or chemokine receptor activity comprising administering to
a patient in need thereof a therapeutically effective amount of a compound of the present invention.

[0046] In another embodiment, the present invention is directed to a method for modulation of CCR-1 receptor activity comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.

[0047] In another embodiment, the present invention is directed to a method for modulation of MIP-1α, MCP-3, MCP-4, RANTES activity, preferably modulation of MIP-1α activity, that is mediated by the CCR-1 receptor comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.

[0048] In another embodiment, the present invention is directed to a method for treating disorders, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention, said wherein said disorder is selected from osteoarthritis, aneurysm, fever, cardiovascular effects, Crohn’s disease, congestive heart failure, autoimmune diseases, HIV-infection, HIV-associated dementia, psoriasis, idiopathic pulmonary fibrosis, transplant arteriosclerosis, physically- or chemically-induced brain trauma, inflammatory bowel disease, alveolitis, colitis, systemic lupus erythematosus, nephrotoxic serum nephritis, glomerulonephritis, asthma, multiple sclerosis, artherosclerosis, rheumatoid arthritis, restinosis, organ transplantation, psoriatic arthritis, multiple myeloma, allergies, for example, skin and mast cell degranulation in eye conjunctiva, hepatocellular carcinoma, osteoporosis, renal fibrosis and cancer, preferably, Crohn’s disease, psoriasis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, multiple myeloma, allergies, for example, skin and mast cell degranulation in eye conjunctiva, hepatocellular carcinoma, osteoporosis and renal fibrosis.

[0049] In another embodiment, the present invention is directed to a method for treating inflammatory diseases, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.

[0050] In another embodiment, the present invention is directed to a method for treating inflammatory bowel disease, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.
[0051] In another embodiment, the present invention is directed to a method for treating Crohn’s disease, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.

[0052] In another embodiment, the present invention is directed to a method for treating psoriasis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.

[0053] In another embodiment, the present invention is directed to a method for treating systemic lupus erythematosus, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.

[0054] In another embodiment, the present invention is directed to a method for treating multiple sclerosis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.

[0055] In another embodiment, the present invention is directed to a method for treating rheumatoid arthritis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.

[0056] In another embodiment, the present invention is directed to a method for treating psoriatic arthritis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.

[0057] In another embodiment, the present invention is directed to a method for treating multiple myeloma, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.

[0058] In another embodiment, the present invention is directed to a method for treating allergies, for example, skin and mast cell degranulation in eye conjunctiva, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.

[0059] In another embodiment, the present invention is directed to a method for treating hepatocellular carcinoma, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.

[0060] In another embodiment, the present invention is directed to a method for treating osteoporosis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.
[0061] In another embodiment, the present invention is directed to a method for treating renal fibrosis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.

[0062] In another embodiment, the present invention is directed to a method for treating inflammatory diseases, for example, inflammatory diseases which are at least partially mediated by CCR-1, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.

[0063] In another embodiment, the present invention is directed to a method for modulation of CCR1 activity comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention.

[0064] In another embodiment, the present invention is directed the use of a compound of the present invention in the preparation of a medicament for the treatment of a disorder, said disorder is selected from osteoarthritis, aneurysm, fever, cardiovascular effects, Crohn's disease, congestive heart failure, autoimmune diseases, HIV-infection, HIV-associated dementia, psoriasis, idiopathic pulmonary fibrosis, transplant arteriosclerosis, physically- or chemically-induced brain trauma, inflammatory bowel disease, alveolitis, colitis, systemic lupus erythematosus, nephrotoxic serum nephritis, glomerulonephritis, asthma, multiple sclerosis, artherosclerosis, rheumatoid arthritis, restinosis, organ transplantation, psoriatic arthritis, multiple myeloma, allergies, for example, skin and mast cell degranulation in eye conjunctiva, hepatocellular carcinoma, osteoporosis, renal fibrosis and cancer, preferably, Crohn's disease, psoriasis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, multiple myeloma, allergies, for example, skin and mast cell degranulation in eye conjunctiva, hepatocellular carcinoma, osteoporosis and renal fibrosis.

[0065] In another embodiment, the present invention is directed to a compound of the present invention for use in therapy.

[0066] In another embodiment, the present invention is directed to a pharmaceutical composition comprising a compound of the present invention and one or more active ingredients.

[0067] In another embodiment, the present invention is directed to a method for modulation of chemokine or chemokine receptor activity comprising administering to
a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprised of a compound of the present invention and one or more active ingredients.

[0068] In another embodiment, the present invention is directed to a method for modulation of CCR-1 receptor activity comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprised of a compound of the present invention and one or more active ingredients.

[0069] In yet another embodiment, the present invention is directed to a method for modulation of MIP-1α, MCP-3, MCP-4, RANTES activity, preferably modulation of MIP-1α activity, that is mediated by the CCR-1 receptor comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprised of a compound of the present invention and one or more active ingredients.

[0070] In another embodiment, the present invention is directed to a method for treating a disorder, comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprised of a compound of the present invention and one or more active ingredients, wherein said disorder is selected from osteoarthritis, aneurysm, fever, cardiovascular effects, Crohn’s disease, congestive heart failure, autoimmune diseases, HIV-infection, HIV-associated dementia, psoriasis, idiopathic pulmonary fibrosis, transplant arteriosclerosis, physically- or chemically-induced brain trauma, inflammatory bowel disease, alveolitis, colitis, systemic lupus erythematosus, nephrotic serum nephritis, glomerulonephritis, asthma, multiple sclerosis, artherosclerosis, rheumatoid arthritis, restinosis, organ transplantation, psoriatic arthritis, multiple myeloma, allergies, for example, skin and mast cell degranulation in eye conjunctiva, hepatocellular carcinoma, osteoporosis, renal fibrosis and cancer, preferably, Crohn’s disease, psoriasis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, multiple myeloma, allergies, for example, skin and mast cell degranulation in eye conjunctiva, hepatocellular carcinoma, osteoporosis and renal fibrosis.

[0071] In yet another embodiment, the present invention, is directed to a method for treating inflammatory diseases, preferably, inflammatory diseases which are at
least partially mediated by CCR-1, comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprised of a compound of present invention and one or more active ingredients.

[0072] In another embodiment, the present invention is directed to a method for modulation of CCR-1 activity comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprised of a compound of the present invention and one or more active ingredients.

[0073] In another embodiment, the present invention is directed to the use of a pharmaceutical composition comprised of a compound of the present invention and one or more active ingredients in the preparation of a medicament for the treatment of a disorder, said disorder is selected from osteoarthritis, aneurysm, fever, cardiovascular effects, Crohn's disease, congestive heart failure, autoimmune diseases, HIV-infection, HIV-associated dementia, psoriasis, idiopathic pulmonary fibrosis, transplant arteriosclerosis, physically- or chemically-induced brain trauma, inflammatory bowel disease, alveolitis, colitis, systemic lupus erythematosus, nephrotic serum nephritis, glomerulonephritis, asthma, multiple sclerosis, atherosclerosis, rheumatoid arthritis, restinosis, organ transplantation, psoriatic arthritis, multiple myeloma, allergies, for example, skin and mast cell degranulation in eye conjunctiva, hepatocellular carcinoma, osteoporosis, renal fibrosis and cancer, preferably, Crohn's disease, psoriasis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, multiple myeloma, allergies, for example, skin and mast cell degranulation in eye conjunctiva, hepatocellular carcinoma, osteoporosis and renal fibrosis.

[0074] In still yet another embodiment, the present invention is directed to the use of a pharmaceutical composition comprised of a compound of the present invention and one or more active ingredients in therapy.

[0075] The invention may be embodied in other specific forms. This invention also encompasses all combinations of alternative aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment to describe additional embodiments of the present invention. Furthermore, any elements of an embodiment may be combined with any...
and all other elements from any of the embodiments to describe additional embodiments.

**DEFINITIONS**

5 [0076] The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

[0077] One enantiomer of a compound of The present invention may display superior activity compared with the other. Thus, all of the stereochemistries are considered to be a part of the present invention. When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Steven D. Young, et al, *Antimicrobial Agents and Chemotherapy*, 1995, 2602-2605.

[0078] The term “substituted,” as used herein, means that any one or more hydrogens on the designated atom or ring is replaced with a selection from the indicated group, provided that the designated atom’s or ring atom’s normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., –O), then 2 hydrogens on the atom are replaced.

[0079] When any variable (e.g., R₄) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with (R₄)ₘ and m is 0-3, then said group may optionally be substituted with up to three R₄ groups and R₄ at each occurrence is selected independently from
the definition of $R_4$. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. 

[0080] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0081] As used herein, “alkyl” is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups containing 1 to 20 carbons, preferably 1 to 10 carbons, more preferably 1 to 8 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups may optionally include 1 to 4 substituents such as halo, for example F, Br, Cl, or I, or CF3, alkyl, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, hydroxy, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkyloxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl, and/or alkylthio.

[0082] Unless otherwise indicated, the term “alkenyl” as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 1 to 8 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, alkylthio, and/or any of the alkyl substituents set out herein.
Unless otherwise indicated, the term “alkynyl” as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonylnyl, 4-decynyl, 3 undecynyl, 4-dodecynyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, and/or any of the alkyl substituents set out herein.

Unless otherwise indicated, the term “cycloalkyl” as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclic alkyl, bicyclic alkyl (or bicycloalkyl) and tricyclic alkyl, containing a total of 3 to 20 carbons forming the ring, preferably 3 to 10 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl, any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol, and/or alkylthio, and/or any of the substituents for alkyl.

Where alkyl groups as defined above have single bonds for attachment to other groups at two different carbon atoms, they are termed “alkylene” groups and may optionally be substituted as defined above for “alkyl.”
[0086] Where alkenyl groups as defined above and alkynyl groups as defined above, respectively, have single bonds for attachment at two different carbon atoms, they are termed “alkenylene groups” and “alkynylene groups”, respectively, and may optionally be substituted as defined above for “alkenyl” and “alkynyl”.

[0087] “Halo” or “halogen” as used herein refers to fluoro, chloro, bromo, and iodo; and “haloalkyl” is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups, for example CF₃, having the specified number of carbon atoms, substituted with 1 or more halogen (for example -CᵥFₜ where v = 1 to 3 and w = 1 to (2v+1)).

[0088] Unless otherwise indicated, the term “aryl” as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl, including 1-naphthyl and 2-naphthyl) and may optionally include 1 to 3 additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl, or cycloheteroalkyl rings for example

![Chemical Structures]

and may be optionally substituted through available carbon atoms with 1, 2, or 3 substituents, for example, hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy,
aryloxyalkyl, arylalkoxy, arylthio, arylazo, heteroarylalkyl, heteroarylationkyl, heteroarylhydroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl, or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio,

heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, aminocarbonyl, alkoxyalkyl, alkylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfanyl, arylsulfinyllalkyl, arylsulfonlamino, or arylsulfonylaminocarbonyl, and/or any of the alkyl substituents set out herein.

Unless otherwise indicated, the term “lower alkoxy”, “alkoxy”, “aryloxy” or “aralkoxy” as employed herein alone or as part of another group includes any of the above alkyl, aralkyl, or aryl groups linked to an oxygen atom.

Unless otherwise indicated, the term “amino” as employed herein alone or as part of another group refers to amino that may be substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cyclohetoroealkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, or thioalkyl. These substituents may be further substituted with a carboxylic acid and/or any of the R^1 groups or substituents for R^1 as set out above. In addition, the amino substituents may be taken together with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholino, 4-thiomorpholino, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-aryalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl, or hydroxy.

Unless otherwise indicated, the term “lower alkylthio,” “alkylthio,” “arylthio,” or “aralkylthio” as employed herein alone or as part of another group includes any of the above alkyl, aralkyl, or aryl groups linked to a sulfur atom.

Unless otherwise indicated, the term “lower alkylamino,” “alkylamino,” “arylamino,” or “aralkylamino” as employed herein alone or as part of another group includes any of the above alkyl, aryl, or arylalkyl groups linked to a nitrogen atom.
As used herein, the term “heterocyclyl” or “heterocyclic system” is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic ring which is saturated, partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, NH, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom, which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another.

As used herein, the term “aromatic heterocyclic system” or “heteroaryl” is intended to mean a stable 5- to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heterotams independently selected from the group consisting of N, O and S and is aromatic in nature.

Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 1H-indolyl, 4-piperidonyl, 4H-carbazole, 4H-quinolinizyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benz tetrazolyl, benzoisoxazolyl, benzoisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazoyl, β-carbolinyl, chromanyl, chromenyl, cinnoliny, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazoliny1, imidazolonyl, indazolyl, indolenyl, indolinyl, indoliziny1, indoly1, isobenzofuranyl, isochromany1, isoindolazolyl, isoindolly1, isoindoliny1, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadia zolyl, 1,2,5-oxadia zolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenaziny1, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalaziny1, piperazinyl,
piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyln, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, tetrazolyl, and xanthenyl. In another aspect of the invention, the heterocycles include, but are not limited to, pyridinyl, thiophenyl, furanyl, indazolyl, benzothiazolyl, benzimidazolyl, benzothiophenyl, benzofuranyl, benzoazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, imidazolyl, indolyl, isoidolyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pyrazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, thiazolyl, oxazolyl, pyrazinyl, and pyrimidinyl.

Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

[0095] Examples of heteroaryls are 1H-indazole, 2H,6H-1,5,2-dithiazinyl, indolyl, 4aH-carbazolyl, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyln, benzothiofuranyln, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benzetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyn, carbazolyl, 4aH-carbazolyl, β-carbolinyl, chromanyln, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofururo[2,3-b]tetrahydrofuranyln, furanyl, furazanlyln, imidazolidinyl, imidazolinyl, imidazolyl, indazolyl, indolenyl, indolinyln, indolizinyl, indolyl, isobenzofuralnyln, isochromanyln, isoindazolyl, isoindolinyln, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthrydinyln, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolindinyl, oxazolyl, oxazolidinylperimidinyl, phenanthridinyl, phenanthroinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxythiinyl, phenoxyazinyl, phthalazinyl, piperezinyl, piperidinyl, piperidonyln, 4-piperidonyln, piperonyln, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyln, pyrazolyl, pyrazotriaizinyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl,
pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl,
quinoxaliny, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl,
tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl,
1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thieryl, thienothiazolyl,
thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl,
1,2,5-triazolyl, 1,3,4-triazolyl, tetrazolyl, and xanthenyl. In another aspect of the
invention, examples of heteroaryl are indolyl, benzimidazolyl, benzofuranyl,
benzothiofuranyl, benzoazolyl, benzthiazolyl, benztriazolyl, benzotetrazolyl,
benzisoxazolyl, benzisothiazolyl, benzimidazolonyl, cinnolinyl, furanyl, imidazolyl,
indazolyl, indolyl, isoquinolinyl isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl,
pyrazolyl, pyrazolotriazinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolyl,
quinolinyl, thiazolyl, thieryl, and tetrazolyl.

[0096] The term “heterocyclylalkyl” or “heterocycl” as used herein alone or as
part of another group refers to heterocyclyl groups as defined above linked through a
C atom or heteroatom to an alkyl chain.

[0097] The term “heteroaryllalkyl” or “heteroarylalkenyl” as used herein alone or as
part of another group refers to a heteroaryl group as defined above linked through a
C atom or heteroatom to an alkyl chain, alkylene, or alkenylene as defined above.

[0098] The term “cyano” as used herein, refers to a -CN group.

[0099] The term “nitro” as used herein, refers to an –NO₂ group.

[0100] The term “hydroxy” as used herein, refers to an OH group.

[0101] The phrase “pharmacologically acceptable” is employed herein to refer to
those compounds, materials, compositions, and/or dosage forms which are, within the
scope of sound medical judgment, suitable for use in contact with the tissues of
human beings and animals without excessive toxicity, irritation, allergic response, or
other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0102] As used herein, “pharmacologically acceptable salts” refer to derivatives of
the disclosed compounds wherein the parent compound is modified by making acid or
base salts thereof. Examples of pharmacically acceptable salts include, but are not
limited to, mineral or organic acid salts of basic residues such as amines; alkali or
organic salts of acidic residues such as carboxylic acids; and the like. The
pharmacologically acceptable salts include the conventional non-toxic salts or the
quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfuric, 2-acetoxybenzoic, fumaric, tolunesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

[00103] The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418.

[00104] Any compound that can be converted in vivo to provide the bioactive agent (i.e., the compound of formula I, Ia, Ib, Ib', Ic, Id or Ie) is a prodrug.

[00105] The term "prodrugs" as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of the present invention with alkyl, alkoxyl, or aryl substituted acylating agents employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates, and the like.

[00106] Various forms of prodrugs are well known in the art and are described in:

a) The Practice of Medicinal Chemistry, Camille G. Wermuth et al., (Academic Press, 1996);

b) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985);


In addition, compounds of the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 99% of the compound ("substantially pure" compound), which is then used or formulated as described herein. Such "substantially pure" compounds of the present invention are also contemplated herein as part of the present invention.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one of the R substituents and/or exhibit polymorphism.

Consequently, compounds of the present invention can exist in enantiomeric, or diastereomeric forms, or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers, or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. The present invention is intended to embody stable compounds.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention alone or an amount of the combination of compounds claimed or an amount of a compound of the present invention in combination with other active ingredients effective to inhibit MIP-1α or effective to treat or prevent inflammatory disorders.

As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the
disease-state, i.e., arresting its development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

SYNTHESIS

[00112] The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below.

[00113] The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and work up procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (Protective Groups In Organic Synthesis, Third Edition, Wiley and Sons, 1999).

[00114] Chemokine receptor antagonists of the present invention can be prepared from the protected amino acid derivative 1.1 by coupling with a piperidine 1.2 under
standard amide bond forming conditions to yield 1.3 as shown in Scheme 1. Deprotection of the nitrogen can provide an amine 1.4 which can be reacted further with derivatizing reagents to provide (I & 1a). Additionally, protected amino acid derivatives, such as 1.5, can be reacted with a substituted piperidine 1.6, and further transformed to compounds of the invention 1b and 1b' using a similar sequence as in the preparation of I.

**SCHEME 1**

1.1 \[O = N \quad R_2 \] \[N = P \]

1.2 EDC, HOBT, \(i\)-Pr₂NEt

1.3 \[O = N \quad R_2 \]

1.4 various

1.5 \[O = N \quad R_2 \]

1.6 \[O = N \quad R_2 \]

1. deprotection
2. amine functionalization
3. amine functionalization

**[00115]** Alternatively, compounds of the present invention can be synthesized as shown in Scheme 2. Coupling of the functionalized amino acid derivative 2.1 with piperidine 1.2 or 1.6 under standard amide bond forming conditions can provide compound 1 and 1a, (A) or 1b and 1b' (B).
[00116] Hydroxypiperidine and dihydropiperidine analogs can be prepared according to the methods outlined in Scheme 3. The functionalized acid 2.1 can be coupled to the hydroxy piperidine 3.1 to furnish 3.2, which in itself can be used as a chemokine inhibitor. Elimination of the hydroxyl group under acidic conditions can yield dihydropiperidines of the present invention.
A resin supported synthesis can also be employed using the reactions outlined in Scheme 4. Coupling of an amine ester to a properly functionalized resin can give 4.1 which upon amine functionalization can form 4.2. Standard saponification can yield the pendant acid derivatized resin 4.3. Amide bond formation with amine 1.2 or 3.1 can furnish analogs 4.4 and 4.5, respectively. Removal from the resin using acid can furnish the dihydropiperidine (1e) from hydroxypiperidine 4.5 and the piperidine (1 & 1a) from 4.4.
Compounds of the invention can also be prepared according to the methods outlined in Scheme 5. An appropriately functionalized amine 1.4 can be reacted with an isothiocyanate followed by alkylation in the presence of a base with iodomethane to furnish 5.1. Compound 5.1 can be further reacted with, for example a hydrazine or a hydroxylamine derivative, to furnish the substituted triazole or the oxadiazole of the present invention.

Furthermore, compounds of the present invention can be prepared by reaction compound 6.1 with an appropriate acid containing a displaceable leaving group, such as bromine to give compound 6.2. Compound 6.2 can be reacted with an amine in an appropriate solvent to furnish compounds of the present invention.
[00120] Alternatively, compounds of the present invention can be synthesized as shown in Schemes 7a and 7b. Reacting a properly functionalized analog of compounds of the present invention under a variety of conditions known to those skilled in the art can provide additional compounds of the present invention. It is to be assumed that the examples shown in Schemes 7a and 7b are merely representative of a variety of transformations and interconversions of functionality that are possible with the knowledge of one skilled in the art of organic synthesis.

SCHEME 7a
Additional compounds of the present invention can be prepared according to the methods in Scheme 8. Compound 8.1 can be reacted with an aryl halide or
hereroaryl halide to give the appropriately substituted amine. Furthermore, compound 8.1 could be reacted with an anhydride to provide the amide or reacted with a haloacetyl halide, such as chloroacetyl chloride, followed by a nucleophile, such as pyrazole to give the substituted amide.

**SCHEME 8**

![Chemical structure](image)

Additional compounds of the present invention can also be prepared according to the methods outlined in Scheme 9. An amino acid, such as D-valine (9.1), can be reacted with an aryl halide, such as -iodobenzene to give the N-aryl amino acid 9.2. This amino acid can then be reacted with an appropriately substituted piperidine, such as 9.3 to provide compounds of the invention of the general formula (Id).
Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

Abbreviations used in the Examples are defined as follows: “1 x” for once, “2 x” for twice, “3 x” for thrice, “Boe” for tert-butyloxy carbonyl, “°C” for degrees Celsius, “Cbz” for benzyl oxy carbonyl, “DCM” for dichloromethane, “DMF” for N,N-dimethylformamide, “DIEA” for N,N-diisopropylethylamine, “EDC” for N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride, “eq” for equivalent or equivalents, “g” for gram or grams, “HOBt” for 1-hydroxybenzotriazole, “LC” for liquid chromatography, “mg” for milligram or milligrams, “mL” for milliliter or milliliters, “µL” for microliter or microliters, “h” for hour or hours, “M” for molar, “MeOH” for methanol, “min” for minute or minutes, “MS” for mass spectroscopy, “rt.” for room temperature, “TFA” for trifluoroacetic acid, “THF” for tetrahydrofuran, and “v/v” for volume to volume ratio. “D”, “L”, “R” and “S” are stereochemical designations familiar to those skilled in the art. Chemical names were derived using ChemDraw Ultra, version 8.0.8. When this program failed to provide a name for the exact structure in question, an appropriate name was assigned using the same methodology utilized by the program.

INTERMEDIATES

Preparation A: (R)-2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)butan-1-one hydrochloride
Step 1: (R)-Tert-butyl 1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxobutan-2-ylcarbamate

5

[00125] N-Boc-D-2-aminobutanoic acid was dissolved in 2 mL of chloroform. DIEA (0.65 mL), HOBt (0.19 g) and 4-(4-chlorophenyl)piperidine hydrochloride (0.32 g) were added and the solution was stirred at rt for 15 minutes. After this time, EDC (0.26 g) was added and the resulting solution was allowed to stir overnight. At the conclusion of this period, the resulting solution was diluted with chloroform and washed with 5% v/v HCl/water. The organic fraction was extracted with a saturated aqueous solution of sodium bicarbonate. The combined organic fractions were dried over solid magnesium sulfate, filtered, and concentrated by rotary evaporation to give (R)-tert-butyl 1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxobutan-2-ylcarbamate. MS found: (M + Na)^+ = 403.

Step 2: (R)-2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)butan-1-one hydrochloride

[00126] A 4M solution of HCl in dioxane (8 mL) was added to (R)-tert-butyl 1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxobutan-2-ylcarbamate (0.46 g) and the resulting solution was allowed to stir at rt. for 1.5 h. After this time, the solvent was removed by rotary evaporation to provide an oil. The oil was dried overnight in vacuo to provide (R)-2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)butan-1-one hydrochloride. MS found: (M + H)^+ = 281.
Preparation B: 2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride

[00127] 2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride was prepared in a similar manner as described in Preparation A with the exception that N-Boc-DL-valine was substituted for N-Boc-D-2-aminobutanoic acid in Step 1. MS found: (M + H)^+ = 295.

Preparation C: (R)-2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride

[00128] (R)-2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride was prepared in a similar manner as described in Preparation A with the exception that N-Boc-D-valine was substituted for N-Boc-D-2-aminobutanoic acid in Step 1. MS found: (M + H)^+ = 295.

Preparation D: (2R,3R)-2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylpentan-1-one hydrochloride

[00129] (2R,3R)-2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylpentan-1-one hydrochloride was prepared in a similar manner as described in Preparation A with the exception that N-Boc-D-isoleucine was substituted for N-Boc-D-2-aminobutanoic acid in Step 1. MS found: (M + H)^+ = 309.
Preparation E: (R)-2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-2-cyclohexylmethanone hydrochloride

5 (R)-2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-2-cyclohexylmethanone hydrochloride was prepared in a similar manner as described in Preparation A with the exception that N-Boc-D-cyclohexylglycine was substituted for N-Boc-D-2-aminobutanoic acid in Step 1. MS found: (M + H)$^+$ = 335.

Preparation F: 2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)pentan-1-one hydrochloride

10 2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)pentan-1-one hydrochloride was prepared in a similar manner as described in Preparation A with the exception that N-Boc-DL-norvaline was substituted for N-Boc-D-2-aminobutanoic acid in Step 1. MS found: (M + H)$^+$ = 295.

Preparation G: 2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-4-methylpentan-1-one hydrochloride

20 2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-4-methylpentan-1-one hydrochloride was prepared in a similar manner as described in Preparation A with
the exception that N-Boc-DL-leucine was substituted for N-Boc-D-2-aminobutanoic acid in Step 1. MS found: (M + H)^+ = 309.

**Preparation H:** 2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3,3-dimethylbutan-1-one hydrochloride

![Chemical Structure]

[00133] 2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3,3-dimethylbutan-1-one hydrochloride was prepared in a similar manner as described in Preparation A with the exception that N-Boc-DL-α-tert-butylglycine was substituted for N-Boc-D-2-aminobutanoic acid in Step 1. MS found: (M + H)^+ = 309.

**Preparation I:** (2R, 3S)-2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylpentan-1-one hydrochloride

![Chemical Structure]

[00134] (2R,3S)-2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylpentan-1-one hydrochloride was prepared in a similar manner as described in Preparation A with the exception that N-Boc-D-allo-isoleucine was substituted for N-Boc-D-2-aminobutanoic acid in Step 1. MS found: (M + H) = 309.3.

**Preparation J:** (R)-2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-2-cyclopropylethaone hydrochloride

![Chemical Structure]

[00135] (R)-2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-2-cyclopropylethaone hydrochloride was prepared in a similar manner as described in Preparation A with
the exception that N-Boc-D-cyclopropyl glycine was substituted for N-Boc-D-2-
aminobutanoic acid in Step 1. MS found: (M + H)^+ = 293.2.

Preparation K: (R)-2-Amino-1-(4-(4-fluorophenyl)piperidin-1-yl)-3-
methylbutan-1-one hydrochloride

![Chemical Structure]

[00136] (R)-2-Amino-1-(4-(4-fluorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride was prepared in a similar manner as described in Preparation C starting from 4-fluorophenyl piperidine hydrochloride. MS found: (M + H)^+ = 279.3.

EXAMPLE 1

(R)-N-(1-(4-(4-Chlorophenyl)piperidin-1-yl)-1-oxobutan-2-yl)benzamide

![Chemical Structure]

[00137] A reaction vessel was charged with HOBr (8 mg), benzoic acid (7 mg) and EDC (11 mg) in DMF (0.6 mL), and the resulting solution was allowed to agitate at rt. for 15 min. After this time, a solution of (R)-2-amino-1-(4-(4-
chlorophenyl)piperidin-1-yl)butan-1-one hydrochloride (14 mg) in DIEA (38 µL) and DMF (187 µL) was added. Upon completion of addition, the reaction mixture was shaken overnight at rt. At the conclusion of this period, the resulting solution was diluted with MeOH and purified by preparative LC-MS to provide Example 1. MS found: (M + H)^+ = 386.
Examples 2 to 8, as described in Table 1, were prepared in a similar manner as described for the preparation of Example 1. In the synthesis of Examples 2 to 8, the appropriate acid needed to produce the product listed was used in place of the benzoic acid used in Example 1. The data in the “MS” column represents the values observed for the \((M + H)^+\) ions in MS experiments.

### Table 1

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
<th>MS</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td><img src="image" alt="Structure 2" /></td>
<td>380</td>
<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxobutan-2-yl)-4-methylpentanamide</td>
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<td>3</td>
<td><img src="image" alt="Structure 3" /></td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxobutan-2-yl)-3-methylbutanamide</td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxobutan-2-yl)-2-phenylacetamide</td>
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<td><img src="image" alt="Structure 5" /></td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxobutan-2-yl)-3-phenylpropanamide</td>
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<td><img src="image" alt="Structure 6" /></td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxobutan-2-yl)-3-phenylbenzamide</td>
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<td>7</td>
<td><img src="image" alt="Structure 7" /></td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxobutan-2-yl)-2-phenylbenzamide</td>
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<tr>
<td>8</td>
<td><img src="image" alt="Structure 8" /></td>
<td>443</td>
<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxobutan-2-yl)benzo[d]thiazole-2-carboxamide</td>
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</tbody>
</table>
EXAMPLE 9

N-(1-(4-(4-chlorophenyl)piperdin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-phenylacetamide

5

[00139] A reaction tube was charged with HOBT (10 mg), phenylacetic acid (12 mg) and EDC (14 mg) in DMF (0.7 mL). The resulting mixture was agitated at rt. for 15 min, and then a solution of 2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride (20 mg) in DIEA (50 µL) and DMF (250 µL) was added and the resulting mixture was shaken overnight at rt. At the conclusion of this period, the resulting solution was diluted with MeOH and purified by preparative LC-MS to provide Example 9. MS found: (M + H)^+ = 414.

EXAMPLES 10 TO 74

15 [00140] Examples 10 to 74, as described in Table 2, were prepared in a similar manner as described for the preparation of Example 9. In the synthesis of the Examples 10 to 74, the appropriate acid needed to produce the product listed was used in place of the phenylacetic acid used in Example 9. The data in the “MS” column represents the values observed for the (M + H)^+ ions in MS experiments.

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<tr>
<th>Example</th>
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<th>MS</th>
<th>Chemical Name</th>
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</thead>
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<td><img src="attachment" alt="Structure" /></td>
<td>432</td>
<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-(4-fluorophenyl)acetamide</td>
</tr>
<tr>
<td>Example</td>
<td>Structure</td>
<td>MS</td>
<td>Chemical Name</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-cyclopentylacetamide</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-phenylbutanamide</td>
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<td><img src="image3" alt="Structure" /></td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-o-tolylpropanamide</td>
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<td><img src="image4" alt="Structure" /></td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3,4-difluorobenzamide</td>
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<td><img src="image5" alt="Structure" /></td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2,5-dimethylbenzamide</td>
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<td><img src="image7" alt="Structure" /></td>
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<tr>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-(4-fluorophenyl)propanamide</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-(2-fluorophenyl)acetamide</td>
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<tr>
<td>Example</td>
<td>Structure</td>
<td>MS</td>
<td>Chemical Name</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2,3-dimethylbenzamide</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-p-tolylpropanamide</td>
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<tr>
<td>25</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzo[d]thiazole-2-carboxamide</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-phenylpropanamide</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-(3-fluorophenyl)propanamide</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-methylbenzamide</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-p-tolylacetamide</td>
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<td>34</td>
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<td>432</td>
<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-(3-fluorophenyl)acetamide</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-methoxybenzamide</td>
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<td><img src="image2.png" alt="Structure" /></td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)quinoline-4-carboxamide</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3,3-dimethylbutanamide</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-phenylpropanamide</td>
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<td>43</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-ethylbenzamide</td>
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<td>Example</td>
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<td>48</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3,4-dimethylbenzamide</td>
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<td>49</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-m-tolylacetamide</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-phenoxybenzamide</td>
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<td>53</td>
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<td>3,5-dichloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide</td>
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<td>2-(benzo[b]thiophen-3-yl)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)acetamide</td>
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<td>55</td>
<td><img src="image9.png" alt="Structure" /></td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-4-methoxybenzamide</td>
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<td>Example</td>
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<tr>
<td>56</td>
<td><img src="image" alt="Structure 56" /></td>
<td>468</td>
<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-(trifluoromethyl)benzamide</td>
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<td>57</td>
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<td>401</td>
<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)nicotinamide</td>
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<td>58</td>
<td><img src="image" alt="Structure 58" /></td>
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<td>2-(benzyloxy)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)acetamide</td>
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<tr>
<td>59</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-4-(trifluoromethyl)benzamide</td>
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<tr>
<td>60</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-(phenylsulfonyl)propanamide</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3,5-dimethylbenzamide</td>
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<tr>
<td>62</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3,3-diphenylpropanamide</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-1-methyl-1H-pyrrole-2-carboxamide</td>
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<td>64</td>
<td><img src="image" alt="Structure 64" /></td>
<td>483</td>
<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-phenylthiazole-4-carboxamide</td>
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<tr>
<td>Example</td>
<td>Structure</td>
<td>MS</td>
<td>Chemical Name</td>
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<td>65</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-4-isopropylbenzamide</td>
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<td><img src="image2.png" alt="Structure" /></td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-4-(trifluoromethoxy)benzamide</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)picolinamide</td>
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<td>68</td>
<td><img src="image4.png" alt="Structure" /></td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)isobutyramide</td>
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<td>69</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)isonicotinamide</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-methoxypropanamide</td>
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<td>71</td>
<td><img src="image7.png" alt="Structure" /></td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2,2-diphenylacetamide</td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)furan-2-carboxamide</td>
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<td>73</td>
<td><img src="image9.png" alt="Structure" /></td>
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<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)tetrahydrofuran-2-carboxamide</td>
</tr>
</tbody>
</table>
EXAMPLE 75

(R)-N-[(1-(4-(4-Chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide

[00141] (R)-2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride (41 mg) was added to DMF (1 mL). The resulting mixture was stirred until homogeneous and then HOBt (19 mg), DIEA (65 μL), benzoic acid (17 mg) and EDC (26 mg) were added. The resulting solution was allowed to stir overnight at rt. After this time, the solution was diluted with MeOH and purified by preparative LC-MS to provide Example 75. MS found: (M + Na)$^+$ = 421.

EXAMPLES 76 TO 148

[00142] Examples 76 to 148, as described in Table 3, were prepared in a similar manner as described for the preparation of Example 75. In the synthesis of Examples 76 to 148, the appropriate acid needed to produce the product listed was used in place of the benzoic acid used in Example 75. In Examples # 139, 140, 143, 144 and 149, the acids were obtained from their corresponding commercially available esters after standard saponification (NaOH, THF). The data in the “MS” column represents the values observed for the (M + H)$^+$ ions in MS experiments.

TABLE 3

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
<th>MS</th>
<th>Chemical Name</th>
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<tr>
<td>74</td>
<td><img src="image" alt="Structure" /></td>
<td>402</td>
<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)pyrazine-2-carboxamide</td>
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<td>Example</td>
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<td>76</td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-4-methylpentanamide</td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-4-fluorobenzamide</td>
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<tr>
<td>78</td>
<td><img src="image3" alt="Structure" /></td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)cyclopentanecarboxamide</td>
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<td>79</td>
<td><img src="image4" alt="Structure" /></td>
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<td>81</td>
<td><img src="image6" alt="Structure" /></td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-methylbutanamide</td>
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<td>82</td>
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<td>83</td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-4-methylbenzamide</td>
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<td>88</td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3,4-difluorobenzamide</td>
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<td>N-((R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-4,4,4-trifluoro-3-methylbutanamide</td>
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<td><img src="image" alt="Structure 96" /></td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-5-fluoro-2-methylbenzamide</td>
</tr>
<tr>
<td>97</td>
<td><img src="image" alt="Structure 97" /></td>
<td>442</td>
<td>(R)-N-((R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-phenylbutanamide</td>
</tr>
<tr>
<td>98</td>
<td><img src="image" alt="Structure 98" /></td>
<td>432</td>
<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-(3-fluorophenyl)acetamide</td>
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<tr>
<td>99</td>
<td><img src="image" alt="Structure 99" /></td>
<td>448</td>
<td>(R)-2-(3-chlorophenyl)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)acetamide</td>
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<td>378</td>
<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-cyclopropylacetamide</td>
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<td>N-((R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-phenylbutanamide</td>
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<td>102</td>
<td><img src="image" alt="Structure 102" /></td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzofuran-2-carboxamide</td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)cinnamamide</td>
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<td><img src="image1" alt="Structure" /></td>
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<td>105</td>
<td><img src="image2" alt="Structure" /></td>
<td>456</td>
<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzo[b]thiophene-3-carboxamide</td>
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<td>106</td>
<td><img src="image3" alt="Structure" /></td>
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<td>(R)-N-[1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl]-2-(2-(trifluoromethyl)phenyl)acetamide</td>
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<td>107</td>
<td><img src="image4" alt="Structure" /></td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-(octyl)oxaacetamide</td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2,4,6-trimethylbenzamide</td>
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<td>111</td>
<td><img src="image8" alt="Structure" /></td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-(4-(phenyl)phenyl)acetamide</td>
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<tr>
<td>112</td>
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<td>115</td>
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</tr>
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<td>117</td>
<td><img src="image5.png" alt="Structure 117" /></td>
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<td>MS</td>
<td>Chemical Name</td>
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<td>128</td>
<td><img src="image6" alt="Structure 128" /></td>
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<td>(R)-N-(1-(4-(4-chlorophenyl)piperdin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-nitrobenzamide</td>
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<tr>
<td>129</td>
<td><img src="image7" alt="Structure 129" /></td>
<td>444.3</td>
<td>(R)-N-(1-(4-(4-chlorophenyl)piperdin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-nitrobenzamide</td>
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<tr>
<td>130</td>
<td><img src="image8" alt="Structure 130" /></td>
<td>479.25 (M+H)</td>
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<td>131</td>
<td><img src="image9" alt="Structure 131" /></td>
<td>457.4</td>
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<td>MS</td>
<td>Chemical Name</td>
</tr>
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<td>136</td>
<td><img src="image2" alt="Structure Image" /></td>
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</tr>
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<td>137</td>
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<td>(M+Na)</td>
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<td>145</td>
<td><img src="image11" alt="Structure Image" /></td>
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<td>146</td>
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<td>Example</td>
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</tr>
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<td>147</td>
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<td>420.4 (M-boc)</td>
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<tr>
<td>148</td>
<td><img src="image" alt="Structure Image" /></td>
<td>438.3</td>
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</tbody>
</table>

**EXAMPLE 149**

(R)-N-(1-(4-(4-Bromophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide

![Structure Image](image)

5

Step 1: (R)-2-Amino-1-(4-(4-bromophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride

(R)-2-Amino-1-(4-(4-bromophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride was prepared in a similar manner as described in Preparation A with the exception that 4-bromophenyl piperidine was substituted for 4-chlorophenyl piperidine hydrochloride in Step 1.

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**Step 2: Example 149**

Example 149 was prepared in a similar manner as described for the preparation of Example 75. MS found: (M + Na)⁺ = 443.2.

**EXAMPLE 150**

N-((2R,3R)-1-(4-(4-Chlorophenyl)piperidin-1-yl)-3-methyl-1-oxopentan-2-
A reaction tube was charged with HOBt (8 mg), benzoic acid (7 mg) and EDC (11 mg) in DMF (0.6 mL) and then agitated at rt. for 15 min. After this time, a solution of (2R)-2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylpentan-1-one hydrochloride (16 mg) in DIEA (38 μL) and DMF (187 μL) was added. Upon completion of addition, the reaction mixture was shaken overnight at rt. At the conclusion of this period, the resulting solution was diluted with MeOH and purified by preparative LC-MS to provide Example 150. MS found: (M + H)$^+$ = 414.

**EXAMPLES 151 TO 177**

Examples 151 to 177, as described in Table 4, were prepared in a similar manner as described for the preparation of Example 150. In the synthesis of Examples 151 to 177, the appropriate acid needed to produce the product listed was used in place of the benzoic acid used in Example 150. The data in the “MS” column represents the values observed for the (M + H)$^+$ ions in MS experiments.

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
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</tr>
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<tbody>
<tr>
<td>151</td>
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<td>380</td>
<td>N-((2R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxopentan-2-yl)isobutyramide</td>
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<td>-------------------------------------------------------------------------------</td>
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<tr>
<td>152</td>
<td><img src="image1" alt="Structure" /></td>
<td>394</td>
<td>N-((2R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxopentan-2-yl)-3-methylbutanamide</td>
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<tr>
<td>153</td>
<td><img src="image2" alt="Structure" /></td>
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<td>N-((2R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxopentan-2-yl)-4-methylpentanamide</td>
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<td>154</td>
<td><img src="image3" alt="Structure" /></td>
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<td>N-((2R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxopentan-2-yl)-2-phenylacetamide</td>
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<td>155</td>
<td><img src="image4" alt="Structure" /></td>
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<td>N-((2R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxopentan-2-yl)-3-phenylpropanamide</td>
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<tr>
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<td><img src="image5" alt="Structure" /></td>
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<td>N-((2R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxopentan-2-yl)-2-phenylbenzamide</td>
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<tr>
<td>157</td>
<td><img src="image6" alt="Structure" /></td>
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<td>N-((2R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxopentan-2-yl)-3-phenylbenzamide</td>
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<td>158</td>
<td><img src="image7" alt="Structure" /></td>
<td>471</td>
<td>N-((2R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxopentan-2-yl)benzo[d]thiazole-2-carboxamide</td>
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<td>177</td>
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<td>465.5</td>
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</tbody>
</table>

**EXAMPLE 178**

(R)-N-(2-(4-(4-Chlorophenyl)piperidin-1-yl)-1-cyclohexyl-2-oxoethyl)benzamide

![Chemical Structure](image)

5. **[00147]** A reaction tube was charged with HOBr (8 mg), benzoic acid (7 mg) and EDC (11 mg) in DMF (0.6 mL) and then allowed to agitate at rt. for 15 min. After this time, a solution of (R)-2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-2-cyclohexylethane hydrochloride (16 mg) in DIEA (38 µL) and DMF (187 µL) was
added. Upon completion of addition, the reaction mixture and was shaken overnight at rt. At the conclusion of this period, the resulting solution was diluted with MeOH and purified by preparative LC-MS to provide Example 178. MS found: (M + H)$^+$ = 440.

**EXAMPLE 179**

(R)-N-(2-(4-(4-Chlorophenyl)piperidin-1-yl)-1-cyclohexyl-2-oxoethyl)-4-methylpentanamide

![Chemical Structure](image)

[00148] Example 179 was prepared, substituting 4-methylpentanoic acid for benzoic acid, in a similar manner as described for the preparation of Example 178. MS found: (M + H)$^+$ = 434.

**EXAMPLE 180**

N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxopentan-2-yl)benzamide

![Chemical Structure](image)

[00149] A reaction tube was charged with HOBT (13 mg), benzoic acid (9 mg) and EDC (18 mg) in DMF (0.75 mL) and then agitated at rt. for 15 min. A solution of 2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)pentan-1-one hydrochloride (20 mg) in DIEA (65 μL) and DMF (185 μL) was added to the reaction tube, and the resulting mixture was shaken overnight at rt. After this time, the resulting solution was diluted with MeOH and purified by preparative LC-MS to provide Example 180. MS found: (M + H)$^+$ = 400.

**EXAMPLES 181 TO 186**

- 102 -
Examples 181 to 186, as described in Table 5, were prepared in a similar manner as described for the preparation of Example 180. In the synthesis of Examples 181 to 186, the appropriate acid needed to produce the product listed was used in place of the benzoic acid used in Example 180. The data in the “MS” column represents the values observed for the (M + H)$^+$ ions in MS experiments.

**TABLE 5**

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
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<tbody>
<tr>
<td>181</td>
<td><img src="image1.png" alt="Structure 181" /></td>
<td>414</td>
<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxopentan-2-yl)-2-methylbenzamide</td>
</tr>
<tr>
<td>182</td>
<td><img src="image2.png" alt="Structure 182" /></td>
<td>434</td>
<td>2-chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxopentan-2-yl)benzamide</td>
</tr>
<tr>
<td>183</td>
<td><img src="image3.png" alt="Structure 183" /></td>
<td>434</td>
<td>3-chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxopentan-2-yl)benzamide</td>
</tr>
<tr>
<td>184</td>
<td><img src="image4.png" alt="Structure 184" /></td>
<td>434</td>
<td>4-chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxopentan-2-yl)benzamide</td>
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<tr>
<td>185</td>
<td><img src="image5.png" alt="Structure 185" /></td>
<td>450</td>
<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxopentan-2-yl)-1-naphthamide</td>
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<tr>
<td>186</td>
<td><img src="image6.png" alt="Structure 186" /></td>
<td>450</td>
<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxopentan-2-yl)-2-naphthamide</td>
</tr>
</tbody>
</table>
EXAMPLE 187
N-(1-(4-(4-Chlorophenyl)piperidin-1-yl)-4-methyl-1-oxopentan-2-yl)benzamide

[00151] A reaction tube was charged with HOBT (13 mg), benzoic acid (9 mg) and EDC (18 mg) in DMF (0.75 mL) and then agitated for 15 min. After this time, a solution of 2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-4-methylpentan-1-one hydrochloride (21 mg) in DIEA (65 μL) and DMF (185 μL) was added to the reaction tube. After the reaction mixture was shaken overnight at rt., the resulting solution was diluted with MeOH and purified by preparative LC-MS to provide Example 187.

MS found: (M + H)^+ = 414.

EXAMPLES 188 TO 192

[00152] Examples 188 to 192, as described in Table 6, were prepared in a similar manner as described for the preparation of Example 187. In the synthesis of Examples 188 to 192, the appropriate acid needed to produce the product listed was used in place of the benzoic acid used in Example 187. The data in the “MS” column represents the values observed for the (M + H)^+ ions in MS experiments.

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
<th>MS</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>188</td>
<td><img src="image1" alt="Structure" /></td>
<td>448</td>
<td>2-chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-4-methyl-1-oxopentan-2-yl)benzamide</td>
</tr>
<tr>
<td>189</td>
<td><img src="image2" alt="Structure" /></td>
<td>448</td>
<td>3-chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-4-methyl-1-oxopentan-2-yl)benzamide</td>
</tr>
<tr>
<td>190</td>
<td><img src="image3" alt="Structure" /></td>
<td>448</td>
<td>4-chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-4-methyl-1-oxopentan-2-yl)benzamide</td>
</tr>
</tbody>
</table>
EXAMPLE 193

\[ \text{Cl} \quad \text{N} \quad \text{NH} \quad \text{O} \quad \text{O} \quad \text{N} \quad \text{C} \quad \text{C} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{Cl} \]

[00153] Example 193 was prepared in a similar manner as described for the
preparation of Example 187. In the synthesis of Example 193, the appropriate acid
needed to produce the product was used in place of the benzoic acid used in Example
187. MS found: (M + H)\(^+\) = 428.

EXAMPLE 194

\[ \text{N-} (1-(4-(4-chlorophenyl)piperidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)benzamide \]

[00154] A reaction tube was charged with HOBT (13 mg), benzoic acid (9 mg) and
EDC (18 mg) in DMF (0.75 mL) and then agitated for 15 min. After this time, a
solution of 2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3,3-dimethylbutan-1-one
hydrochloride (21 mg) in DIEA (65 \(\mu\)L) and DMF (185 \(\mu\)L) was added to the tube
and the reaction mixture was shaken overnight at \(\text{rt}\). At the conclusion of this period,
the resulting solution was diluted with MeOH and purified by preparative LC-MS to
provide Example 194. MS found: (M + H)\(^+\) = 414.

EXAMPLES 195 TO 199
Examples 195 to 199, as described in Table 7, were prepared in a similar manner as described for the preparation of Example 194. In the synthesis of Examples 195 to 199, the appropriate acid needed to produce the product listed was used in place of the benzoic acid used in Example 194. The data in the “MS” column represents the values observed for the (M + H)^+ ions in MS experiments.

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
<th>MS</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>195</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>428</td>
<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-2-methylbenzamide</td>
</tr>
<tr>
<td>196</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>448</td>
<td>2-chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)benzamide</td>
</tr>
<tr>
<td>197</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>448</td>
<td>3-chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)benzamide</td>
</tr>
<tr>
<td>198</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>448</td>
<td>4-chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)benzamide</td>
</tr>
<tr>
<td>199</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>464</td>
<td>N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1-naphthamide</td>
</tr>
</tbody>
</table>

**EXAMPLE 200**

N-(1-(4-(4-Chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-
yl)(phenyl)methanesulfonamide

[00156] A reaction tube was charged with benzylsulfonyl chloride (14 mg), DIEA (50 μL) and 2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride (20 mg) in DCM (0.3 mL). The reaction mixture was shaken overnight at rt. At the conclusion of this period, the resulting solution was diluted with MeOH and purified by preparative LC-MS to provide Example 200. MS found: (M + H)^+ = 450.

EXAMPLE 201
(R)-1-(1-(4-(4-Chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-phenylurea

[00157] A reaction tube was charged with phenyl isocyanate (12 mg), (R)-2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride (17 mg) and 1,4-dioxane (0.75 mL). The reaction mixture was shaken overnight at rt. After this time, the resulting solution was diluted with MeOH and purified by preparative LC-MS to provide Example 201. MS found: (M + H)^+ = 429.
Examples 202 to 206, as described in Table 8, were prepared in a similar manner as described for the preparation of Example 201. In the synthesis of Examples 202 to 206, the appropriate isocyanate needed to produce the product listed was used in place of the isocyanate used in Example 201. The data in the “MS” column represents the values observed for the (M + H)^+ ions in MS experiments.

### TABLE 8

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
<th>MS</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>202</td>
<td><img src="image" alt="Structure 202" /></td>
<td>407</td>
<td>(R)-1-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-cyclopentylurea</td>
</tr>
<tr>
<td>203</td>
<td><img src="image" alt="Structure 203" /></td>
<td>433</td>
<td>(R)-1-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-(2-fluorophenyl)urea</td>
</tr>
<tr>
<td>204</td>
<td><img src="image" alt="Structure 204" /></td>
<td>433</td>
<td>(R)-1-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-(3-fluorophenyl)urea</td>
</tr>
<tr>
<td>205</td>
<td><img src="image" alt="Structure 205" /></td>
<td>415</td>
<td>(R)-1-benzyl-3-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)urea</td>
</tr>
<tr>
<td>206</td>
<td><img src="image" alt="Structure 206" /></td>
<td>443</td>
<td>(R)-1-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-phenethylurea</td>
</tr>
</tbody>
</table>

### EXAMPLE 207

![Example 207](image)
Example 207 was prepared in a similar manner as described for the preparation of Example 201. In the synthesis of Examples 207, the appropriate isocyanate needed to produce the product was used in place of the isocyanate used in Example 201. MS found: \((M + H)^+ = 380.6\).

**EXAMPLE 208**

N-(1-(4-(4-Chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide

A reaction vessel was charged with benzoyl-DL-valine (24 mg), HOBt (16 mg), DIEA (57 \(\mu\)L), 4-(4-chlorophenyl)piperidine hydrochloride (28 mg) and EDC (23 mg) in DMF (1.5 mL) and then agitated at rt. for 16 h. At the conclusion of this period, the resulting solution was diluted with MeOH and purified by preparative LC-MS to provide Example 208. MS found: \((M + H)^+ = 399\).

**EXAMPLE 209**

N-(1-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide

Example 209 was prepared in a similar manner as described for the preparation of Example 208 with the exception that 4-(4-chlorophenyl)-4-hydroxypiperidine was substituted for 4-(4-chlorophenyl)piperidine hydrochloride. MS found: \((M + H)^+ = 415\).
EXAMPLE 210

N-(1-(4-(4-Bromophenyl)-4-hydroxypiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide

5 [00162] Example 210 was prepared in a similar manner as described for the preparation of Example 208 with exception that 4-(4-bromophenyl)-4-hydroxypiperidine was substituted for 4-(4-chlorophenyl)piperidine hydrochloride. MS found: (M + H)$^+$ = 460.

EXAMPLE 211

N-(1-(4-(4-Chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)-3-methyl-1-oxobutan-2-yl)benzamide

[00163] Example 211 was prepared in a similar manner as described for the preparation of Example 208 with the exception that 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride was substituted for 4-(4-chlorophenyl)piperidine hydrochloride. MS found: (M + H)$^+$ = 398.

EXAMPLE 212

N-(1-(4-(4-Fluorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide
[00164] Example 212 was prepared in a similar manner as described for the preparation of Example 208 with the exception that 4-(4-fluorophenyl)piperidine hydrochloride was substituted for 4-(4-chlorophenyl)piperidine hydrochloride, to provide the title compound. MS found: (M + H)$^+$ = 383.

EXAMPLE 213

Benzyl 1-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

[00165] Example 213 was prepared in a similar manner as described for the preparation of Example 208 with the exceptions that Cbz-DL-valine and 4-(4-chlorophenyl)-4-hydroxypiperidine were substituted for benzoyl-DL-valine and 4-(4-chlorophenyl)piperidine hydrochloride, respectively. MS found: (M + H)$^+$ = 446.

EXAMPLE 214

(R)-Benzyl 1-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-1-oxobutan-2-ylcarbamate
Example 214 was prepared in a similar manner as described for the preparation of Example 208 with the exceptions that Cbz-D-2-aminobutyric acid and 4-(4-chlorophenyl)-4-hydroxypiperidine were substituted for benzoyl-DL-valine and 4-(4-chlorophenyl)piperidine hydrochloride, respectively. MS found: (M + H)$^+$ = 431.

**EXAMPLE 215**

N-(1-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-4-methyl-1-oxopentan-2-yl)benzamide

Example 215 was prepared in a similar manner as described for the preparation of Example 208 with the exceptions that benzoyl-DL-leucine and 4-(4-chlorophenyl)-4-hydroxypiperidine were substituted for benzoyl-DL-valine and 4-(4-chlorophenyl)piperidine hydrochloride, respectively. MS found: (M + H)$^+$ = 430.

**EXAMPLE 216**

N-(1-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-1-oxopentan-2-yl)benzamide

Example 216 was prepared in a similar manner as described for the preparation of Example 208 with the exceptions that benzoyl-2-aminopentanoic acid and 4-(4-chlorophenyl)-4-hydroxypiperidine were substituted for benzoyl-DL-valine and 4-(4-chlorophenyl)piperidine hydrochloride, respectively. MS found: (M + H)$^+$ = 415.
EXAMPLE 217

N-(1-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-4-(methylthio)-1-oxobutan-2-yl)benzamide

[00169] Example 217 was prepared in a similar manner as described for the preparation of Example 208 with the exceptions that benzoyl-DL-methionine and 4-(4-chlorophenyl)-4-hydroxypiperidine were substituted for benzoyl-DL-valine and 4-(4-chlorophenyl)piperidine hydrochloride, respectively. MS found: (M + H)$^+$ = 448.

EXAMPLE 218

Benzyl 1-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-1-oxohexan-2-ylcarbamate

[00170] Example 218 was prepared in a similar manner as described for the preparation of Example 208 with the exceptions that Cbz-2-aminohexanoic acid and 4-(4-chlorophenyl)-4-hydroxypiperidine were substituted for benzoyl-DL-valine and 4-(4-chlorophenyl)piperidine hydrochloride, respectively. MS found: (M + H)$^+$ = 460.
EXAMPLE 219

(R)-Benzyl 2-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-1-cyclohexyl-2-oxoethylcarbamate

Example 219 was prepared in a similar manner as described for the preparation of Example 208 with the exceptions that Cbz-D-cyclohexylglycine and 4-(4-chlorophenyl)-4-hydroxypiperidine were substituted for benzoyl-DL-valine and 4-(4-chlorophenyl)piperidine hydrochloride, respectively. MS found: (M + H)$^+$ = 486.

EXAMPLE 220

N-(1-(4-(4-Fluorophenyl)-4-hydroxypiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide

Example 220 was prepared in a similar manner as described for the preparation of Example 208 with the exception that 4-(4-fluorophenyl)-4-hydroxypiperidine was substituted for 4-(4-chlorophenyl)piperidine hydrochloride, to provide the title compound. MS found: (M + H)$^+$ = 399.
EXAMPLE 221
3-Chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxopropan-2-yl)benzamide

5 Step 1: Alanine ester derivatized resin

[00173] A 250 mL peptide vessel was charged with polystyrene resin functionalized with a 4-formyl-3-methoxyphenyl linker (1.1 mmol/g, 4.7 g) and DMF (50 mL). To this suspension was added DIEA (4.5 mL), DL-alanine ethyl ester hydrochloride (2.0 g), acetic acid (4.3 mL) and sodium triacetoxyborohydride (2.2 g).

10 Following 16 h of shaking at rt. the resin was filtered and washed with solvents as follows: DMF (1 x 50 mL); 6:3:1 THF/water/acetic acid (2 x 50 mL); DMF (2 x 50 mL); THF (2 x 50 mL); and DCM (2 x 50 mL) to provide an alanine ester derivatized resin.

15 Step 2: A set of microkans

[00174] The alanine ester derivatized resin of Step 1 was loaded into an Irori microkans (20 mg per microkan). A set of 60 microkans were suspended in DMF (200 mL) and then charged with 3-chlorobenzoic acid (3.95 g), HOBT (3.41 g), DIEA (8.8 mL), and N,N′-disopropylcarbodiimide (3.95 mL). The resulting mixture was shaken at rt for 16 h. After this time, the solvents were removed by filtration and the microkans were washed with DMF (4 x 200 mL), THF (4 x 200 mL), and DCM (4 x 200 mL) to provide a set of microkans.

Step 3: 2-(3-Chlorobenzamido)propanoic acid resin

[00175] A set of 180 microkans of Step 2 were added to a mixture of THF (150 mL), 40% tetra-N-butylammonium hydroxide/water (50 mL), and methanol (30 mL). The resulting mixture was shaken at 40° C for 40 h and then allowed to cool to rt. Once at the prescribed temperature, the solvents were removed by filtration, and the
microkans were washed with 8:1:1 THF/water/acetic acid (2 x 200 mL), THF (3 x 200 mL), and DCM (3 x 200 mL). The reaction mixture was checked for completion by treating a small sample of the ethyl 2-(3-chlorobenzamido)propanoate resin with 40% v/v TFA/DCM. Said treatment indicated that the reaction was completed and that the desired product, namely, 2-(3-chlorobenzamido)propanoic acid resin, had been provided. MS found: (M + Na)$^+$ = 250.

**Step 4: Microkans containing resin-bound 3-chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxopropan-2-yl)benzamide**

A set of 30 microkans of Step 3 was suspended in DMF (80 mL) and treated with HOBT (0.57 g), DIEA (1.57 mL), N,N’-diisopropylcarbodiimide (0.66 mL) and 4-(4-chlorophenyl)piperidine hydrochloride (1.39 g). The resulting microkans were shaken at rt. For 16 h, After this time, the microkans were isolated by filtration and washed with DMF (4 x 100 mL), THF (3 x 100 mL), and DCM (3 x 100 mL) to provide microkans containing resin-bound 3-chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxopropan-2-yl)benzamide.

**Step 5: Example 221**

The microkans containing resin-bound 3-chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxopropan-2-yl)benzamide produce in Step 4 were opened and the loose resin was suspended in 30% v/v TFA/DCM. The resulting suspension was stirred at rt. For 1 h. Upon completion of this period, the resin was removed by filtration and the filtrate was concentrated in vacuo to provide an oil. The oil was dissolved in methanol (2 mL) and purified by preparative LC-MS to provide Example 221. MS found: (M + Na)$^+$ = 427.

**EXAMPLE 222**

3-Chloro-N-(1-(4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)-1-oxopropan-2-
Example 222 was prepared in a similar manner as described for the preparation of Example 221 with the exception that 4-(4-chlorophenyl)-4-hydroxypiperidine was substitute for 4-(4-chlorophenyl)piperidine hydrochloride in Step 4. Example 222 was provided via elimination during Step 5. MS found: \((M + H)^+ = 405\).

**EXAMPLE 223**

4-Chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxobutan-2-yl)benzamide

Example 223 was prepared in a similar manner as described for the preparation of Example 221 with the exceptions that 2-aminobutyric acid methyl ester hydrochloride was substituted for DL-alanine ethyl ester hydrochloride in Step 1 and 4-chlorobenzoic acid was substituted for 3-chlorobenzoic acid in Step 2. MS found: \((M + H)^+ = 419\).

**EXAMPLE 224**

4-Chloro-N-(1-(4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)-1-oxobutan-2-
Example 224 was prepared in a similar manner as described for the preparation of Example 221 with the exceptions that 2-aminobutyric acid methyl ester hydrochloride was substituted for DL-alanine ethyl ester hydrochloride in Step 1, 4-chlorobenzoic acid was substituted for 3-chlorobenzoic acid in Step 2, and 4-(4-chlorophenyl)-4-hydroxypiperidine was substituted for 4-(4-chlorophenyl)piperidine hydrochloride in Step 4. Example 224 was provided by elimination during Step 5. MS found: \((M + H)^+ = 417\).

**EXAMPLE 225**

3-Chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-1-oxobutan-2-yl)benzamide

Example 225 was prepared in a similar manner as described for the preparation of Example 221 with the exception that 2-aminobutyric acid methyl ester hydrochloride was substituted for DL-alanine ethyl ester hydrochloride in Step 1. MS found: \((M + H)^+ = 419\).

**EXAMPLE 226**

N-(1-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-1-oxobut-2-en-2-
A reaction vessel was charged with N-benzoyl-L-threonine (56 mg), HOBt (42 mg), DIEA (130 μL), 4-(4-chlorophenyl)-4-hydroxypiperidine (66 mg), EDC (60 mg), DMF (1 mL) and 1,2-dichloroethane (1 mL). The reaction mixture was stirred for 16 h at rt and then diluted with methanol (0.5 mL). Upon completion of dilution, the reaction mixture was purified by preparative LC-MS to provide Example 226. MS found: (M + H)^+ = 399.

EXAMPLES 227 TO 252

Examples 227 to 252, as described in Table 9, were prepared in a similar manner as described for the preparation of Example 150 substituting (2R,3S)-2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylpentan-1-one hydrochloride for (2R)-2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylpentan-1-one hydrochloride. In the synthesis of Examples 227 to 252, the appropriate acid needed to produce the product listed was used in place of the benzoic acid used in Example 150.

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>227</td>
<td><img src="image1.png" alt="Structure" /></td>
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<tr>
<td>228</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>393.6</td>
</tr>
<tr>
<td>229</td>
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<td>-----------</td>
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</table>
EXAMPLES 253 TO 271

[00184] Examples 253 to 271, as described in Table 10, were prepared in a similar manner as described for the preparation of Example 75 using (R)-2-amino-1-(4-(4-fluorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride instead of (R)-2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride. In the synthesis of Examples 253 to 271, the appropriate acid needed to produce the product listed was used in place of the benzoic acid used in Example 75.

TABLE 10

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
<th>MS (M+H)</th>
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<tr>
<td>254</td>
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EXEMPLARY STRUCTURES

TABLE 11

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EXAMINES 272 TO 275

Examples 272 to 275, as described in Table 11, were prepared in a similar manner as described for the preparation of Example 201. In the synthesis of Examples 272 to 275, the appropriate chloroformate needed to produce the product listed was used in place of the isocyanate used in Example 201. The data in the “MS” column represents the values observed for the (M + H)^+ ions in MS experiments.
EXAMPLE 276

(R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-2-(1-methyl-3-phenyl-1H-1,2,4-triazol-5-ylamino)butan-1-one

5

Step 1: (R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-ylicarbamothioyl)benzamide

[00186] To a solution of (R)-2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride (250 mg, 0.75 mmol) in DCM (2 mL) was added DIEA (175 µL, 1 mmol) followed by the dropwise addition of benzyloisothiocyanate (106 µL, 0.78 mmol). The reaction was stirred for 2 h at rt., acidified with 1 N aqueous HCl solution to pH 3 and then extracted with Et₂O (3X10 mL). The extracts were combined, washed sequentially with sat. aqueous NaHCO₃ solution (1X10 mL) and sat. aqueous NaCl solution (1X10 mL), dried (MgSO₄), and the solvent removed to give (R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-ylicarbamothioyl)benzamide (m/z, 458, M+1) as an oil (300 mg) in greater than 90% HPLC purity.

Step 2: (R,Z)-methyl N’-benzoyl-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamimidothioate
To a solution of (R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamothioyl)benzamide (300 mg, crude) in CH$_3$CN (2 mL) was added K$_2$CO$_3$ (275 mg, 2 mmol) followed by MeI (75 µL, 2 mmol). The reaction was stirred for 4 h at rt., diluted with Et$_2$O (10 mL) and the solids were filtered through a plug of celite. The filtrate was condensed in vacuo to give (R,Z)-methyl N'-benzoyl-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamimidothioate (300 mg, m/z 473, M+1) as a foam, which was used in subsequent steps without purification.

Step 3: (R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-2-(3-phenyl-1H-1,2,4-triazol-5-ylamino)butan-1-one

(R,Z)-Methyl N'-benzoyl-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamimidothioate (47 mg, 0.1 mmol) was dissolved in THF (0.5 mL) and treated with anhydrous hydrazine (10 µL, 0.3 mmol). The reaction was stirred at rt. overnight. After this time, the THF was removed in vacuo and the resulting residue was dissolved in methanol and then purified by preparative HPLC to give (R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-2-(3-phenyl-1H-1,2,4-triazol-5-ylamino)butan-1-one (20 mg, 45%). MS found: 438 (M+H).

Step 4: (R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-2-(1-methyl-3-phenyl-1H-1,2,4-triazol-5-ylamino)butan-1-one
[00189] (R)-1-(4-(4-Chlorophenyl)piperidin-1-yl)-3-methyl-2-(3-phenyl-1H-1,2,4-triazol-5-ylamino)butan-1-one (40 mg, 0.09 mmol) was dissolved in THF (0.5 mL) and then treated with MeNHNNH₂ (10 μL, excess). The reaction was stirred at rt. overnight. After this time, the THF was removed in vacuo and the remains were taken up in MeOH and then purified by preparative HPLC to give (R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-2-(1-methyl-3-phenyl-1H-1,2,4-triazol-5-ylamino)butan-1-one (18 mg, 47%) as a 90/10 mixture of N₁-CH₃/N₂-CH₃ isomers. MS found: 452 (M+H).

EXAMPLE 277

[00190] To a solution of 2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride in ethanol was added TEA (4 eq) and 4-chloro-6-(trifluoromethyl)quinazoline (1.1 eq, see WO 05/021500). Upon completion of addition, the reaction mixture was heated at 100 °C for 30 min. After this time, the reaction mixture was concentrated and purified directly on silica gel (25% EtOAc/hexane to 50% EtOAc/hexane) to give Example 280 in 50% yield. MS found: 491.4, (M+H).

EXAMPLE 278
1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-2-(5-phenyl-2H-tetrazol-2-yl)butan-1-one
Step 1: 2-bromo-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one

[00191] A mixture of 2-bromo-3-methylbutanoic acid (14) (400mg, 2.2 mmol), 4-(4-chlorophenyl)piperidine hydrochloride (500mg, 2.2 mmol), HOBr (300mg, 2.2 mmol) and EDCI (425 mg, 2.2 mmol) was suspended in DMF (10 mL). DIEA (1.4 mL, 8 mmol) was added and the reaction was stirred overnight. After this time, the reaction was diluted with Et₂O (100 mL) and washed sequentially with H₂O (2X40 mL); aqueous 1N HCl (2X20 mL); aqueous sat. NaHCO₃ (1X20 mL) solution and aqueous sat. NaCl (1X20 mL) solution. The Et₂O layer was dried (MgSO₄), and the solvents were removed to give 2-bromo-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one (600 mg, 85%) as an impure oil, which was used without purification. MS found: 360 (M+H).

Step 2: 1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-2-(5-phenyl-2H-tetrazol-2-yl)butan-1-one

[00192] A mixture of 2-bromo-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one (40 mg, 0.11 mmol), K₂CO₃ (50 mg, 0.36 mmol) and 5-phenyl-2H-tetrazole (15 mg, 0.1 mmol) in CH₃CN (1 mL) was heated at 170 °C for 30 min in a microwave reactor. After this time, the reaction was filtered through a plug of celite™ diluted with MeOH and purified directly by preparative HPLC to give 1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-2-(5-phenyl-2H-tetrazol-2-yl)butan-1-one (9 mg, 21%) as a solid. MS found: 424 (M+H).

EXAMPLE 279
1-(4-(4-Chlorophenyl)piperidin-1-yl)-3-methyl-2-(5-phenyl-1,3,4-oxadiazol-2-ylamino)butan-1-one

Step 1: Ethyl 2-(2-benzoylhydrazinecarboxamido)-3-methylbutanoate

[00193] To a solution of benzoylhydrazide (489 mg, 5.0 mmol) in DCM (10 ml) was added dropwise a solution of ethyl-2-cyanato-3-methyl butyrate (0.856 g, 5.0 mmol) in DCM (5 mL). The reaction was stirred at rt for 3h and the solvent was removed in vacuo to give ethyl 2-(2-benzoylhydrazinecarboxamido)-3-methylbutanoate in greater than >90% purity as judged by LCMS. MS found: 308 (M+H).

Step 2: ethyl 3-methyl-2-(5-phenyl-1,3,4-oxadiazol-2-ylamino)butanoate

[00194] To a solution of crude ethyl 2-(2-benzoylhydrazinecarboxamido)-3-methylbutanoate (assumed 5 mmol) in DCE (10 ml) was added POCl₃ (1.5 g, 10 mmol). Upon completion of addition, the reaction was heated at 75-80 °C overnight. After this time, the excess solvent and POCl₃ were removed in vacuo. The resulting remains were dissolved in EtOAc (75 ml) and washed sequentially with sat. aqueous NaHCO₃ (2X25 mL) solution and sat. aqueous NaCl (25 mL) solution and dried over MgSO₄. The solvent was removed in vacuo to give ethyl 3-methyl-2-(5-phenyl-1,3,4-oxadiazol-2-ylamino)butanoate in greater than 90% purity by LCMS; m/z (290, M+1).
Step 3: 3-methyl-2-(5-phenyl-1,3,4-oxadiazol-2-ylamino)butanoic acid

![Structure of 3-methyl-2-(5-phenyl-1,3,4-oxadiazol-2-ylamino)butanoic acid]

[00195] Crude ethyl 3-methyl-2-(5-phenyl-1,3,4-oxadiazol-2-ylamino)butanoate (assumed 5 mmol) was dissolved in a mixture of THF (10 ml) and MeOH (2ml) and then treated dropwise (exothermic) with aqueous 1 N NaOH (6 ml) solution. The reaction was stirred for 1h, diluted with H₂O (50 ml) and then extracted with Et₂O (1X50 ml). The aqueous layer was acidified to pH 3 with aqueous 1N HCl solution and then extracted with EtOAc (3 X 35 ml). The EtOAc extracts were combined, washed with sat. aqueous NaCl solution, dried (MgSO₄) and the solvent was removed in vacuo to give 3-methyl-2-(5-phenyl-1,3,4-oxadiazol-2-ylamino)butanoic acid in 50-75% yield over 3 steps in purity >90% as judged by LCMS. MS found: 262 (M+H).

Step 4: 1-(4-(4-Chlorophenyl)piperidin-1-yl)-3-methyl-2-(5-phenyl-1,3,4-oxadiazol-2-ylamino)butan-1-one

[00196] 3-Methyl-2-(5-phenyl-1,3,4-oxadiazol-2-ylamino)butanoic acid (80 mg, 0.3 mmol), EDCI (65 mg, 0.33 mmol), 4-(4-chlorophenyl)-piperidine hydrochloride (78 mg, 0.33 mmol) and HOBt (40 mg, 0.3 mmol) were combined and suspended in DMF (2 mL). Diisopropylethylamine (210 μL, 1.2 mmol) was added and the reaction was stirred at rt. overnight. After this time, methanol (2mL) was added to the reaction and the mixture was purified directly by preparative HPLC to give 1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-2-(5-phenyl-1,3,4-oxadiazol-2-ylamino)butan-1-one (60mg, 30%). MS found: 439 (M+H).

EXAMPLES 280 TO 287
Examples 280 to 287, as described in Table 12, were prepared in a similar manner as described for the preparation of Example 279. Typical yields ranged from 20-55%.

**TABLE 12**

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N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobut-2-en-2-yl)benzamide

Step 1: 2-benzamido-3-methylbut-2-enoic acid

To a suspension of 3-fluoro-DL-valine (165 mg, 1 mmol) in ethyl acetate (10 mL) was added NaHCO₃ (sat. aq., 5 mL) followed by benzoyl chloride (1 mmol). The solution was stirred for 4h, acidified with 1N HCl, and then extracted into ethyl acetate. The organic extracts were dried over MgSO₄, filtered and concentrated to provide the crude 2-benzamido-3-methylbut-2-enoic acid.

Step 2: N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobut-2-en-2-yl)benzamide

The crude 2-benzamido-3-methylbut-2-enoic acid from Step 1 was coupled with 4-(4-chlorophenyl)piperidine hydrochloride in a similar manner as described for the preparation of Example 75 to provide Example 288, N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobut-2-en-2-yl)benzamide. MS found: 397 (M + H).

EXAMPLE 289

Sodium (R)-(3-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-ylicarbamoyl)phenyl)methanesulfonate
Step 1: (R)-3-(chloromethyl)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide

To a solution of (R)-2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride (30.5 mg, 0.092 mmol) in DCM (1 mL) cooled to 0°C was added DIEA (17.4 µL, 0.1 mmol) followed by 3-chloromethyl benzoyl chloride (14.2 µL, 0.1 mmol). Upon completion of addition, the reaction mixture was allowed to warm slowly to rt. where it stirred overnight. After this time, the solution was diluted with dichloromethane and quenched by the addition of aqueous NaHCO₃. The layers were separated and the organic layer was dried over Na₂SO₄, filtered, and concentrated to yield a residue. The residue was purified via SiO₂ chromatography to give the (R)-3-(chloromethyl)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide as a clear glassy solid (23.7 mg, 58% yield). MS found: 447.3 (M+), 449.3 (M+2).

Step 2: (R)-3-(chloromethyl)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide

To (R)-3-(chloromethyl)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide (23.7 mg, 0.053 mmol) was added Na₂SO₃ (34 mg, 0.27 mmol), water (0.25 mL), and ethanol (0.25 mL). The resulting solution was heated at 100 °C for 3 h. After this time, the solution was cooled to rt. and then concentrated to a residue. The residue was loaded onto a pre-washed C18 cartridge in water (1-2 mL) and the column was then eluted with water followed by 20% acetonitrile/water to provide Example 289, (R)-3-(chloromethyl)-N-(1-(4-(4-
chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide (19.2 mg, 70% yield), as a white solid. MS found: 493.3 (M+), 495.3 (M+2).

EXEMPLARY 290

(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-(1H-pyrazol-1-yl)acetamide

Step 1: (R)-2-chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)acetamide

To a solution of (R)-2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride (340 mg, 1.03 mmol) in DCM (10 mL) cooled to 0°C was added TEA (144 µL, 1.03 mmol) followed by chloroacetylchloride (82 µL, 1.03 mmol). Upon completion of addition, the reaction mixture was held at 0 °C for 4 h. After this time, an additional aliquot of chloroacetyl chloride (60 µL) was added followed by additional TEA (150 µL). The resulting solution was diluted with dichloromethane (40 mL) and quenched by the addition of aqueous NaHCO₃ (25 mL). The layers were separated. The organic layer was dried over Na₂SO₄, filtered, and concentrated to yield a residue. The residue was purified via SiO₂ chromatography (20% to 50% EtOac/heptane) to give (R)-2-chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)acetamide as a clear glassy solid (349 mg, 92% yield). MS found: 371.3 (M+), 373.3 (M+2).

Step 2: (R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-(1H-pyrazol-1-yl)acetamide
[00203] In a sealed vial were added consecutively (R)-2-chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)acetamide (31.4 mg, 0.085 mmol), pyrazole (11.5 mg, 0.17 mmol), K₂CO₃ (35.2 mg, 0.26 mmol) and acetonitrile (0.4 mL). The reaction mixture was then heated at 75 °C for 36 h, cooled to rt., and the solids were filtered. The filtrate was concentrated and purified by preparative HPLC to provide Example 290, (R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-(1H-pyrazol-1-yl)acetamide (32 mg, 94% yield) as a white solid. MS found: 403.3 (M+H).

EXAMPLE 291

![Chemical Structure](image)

[00204] Example 291 was prepared from Example 122 in a similar manner as described by Sharpless and Demko (J. Org. Chem. 2001, 66, 7945-7950). A 5 mL microwave reaction tube was charged with Example 122 (115 mg, 0.27 mmol, 1.0 eq.), zinc bromide (92 mg, 0.41 mmol, 1.5 eq.), sodium azide (53 mg, 0.81 mmol, 3.0 eq.), water (2 mL) and isopropanol (1 mL). The tube was sealed and then heated via microwave at 175 °C for 5 h. After this time, the reaction mixture was partitioned between methylene chloride (5 mL) and 1 N aqueous HCl (5 mL), the layers were separated, and the organic layer was washed with 1 N HCl (2 times), water, and then brine. The combined aqueous phases were extracted with methylene chloride. The combined organic phases were dried over sodium sulfate and then concentrated in-vacuo to yield a residue. The residue was purified over silica gel, eluting with 5% - 10% - 15% - 20% methanol/methylene chloride, to provide Example 291 (33 mg) as a colorless glass. MS (APCI) found: 467.2 (M + H)⁺.
EXAMPLE 292

[00205] Example 292 was prepared in a similar manner as described for the preparation of Example 291 starting from Example 123. MS found: 467.3 (M + H)^+.

EXAMPLE 293

[00206] A 20 ml scintillation vial was charged with Example 291 (47 mg, 0.10 mmol, 1.0 eq.), trimethylsloxonium fluoroborate (20 mg, 0.13 mmol, 1.3 eq.), proton sponge (60 mg, 0.25 mmol, 2.5 eq.), 4 A molecular sieves (200 mg), and DCM (2 mL). The vial was filled with argon gas and sealed. The mixture was allowed to stir overnight at room temperature. After this time, the reaction mixture was diluted with ethyl acetate (50 mL), washed 3 X with water (20 mL) followed by brine. The organic phase was dried over sodium sulfate and concentrated in-vacuo to yield a residue. The residue was purified over silica gel, eluting with 30% - 50% ethyl acetate/hexanes – 100% ethyl acetate, to yield crude product (38 mg) as a colorless glass contaminated with proton sponge. The crude product was purified by prep HPLC, using a Phenomenex Luna 5 μ, C18 (2), 250 x 21.2 mm column, under the following conditions: 100% water (5 min) then 0% to 90% acetonitrile in water (0.05% TFA in each solvent) over 15 minutes. Lyophilization of the fractions containing the major peak yielded Example 293 (11 mg) as a colorless powder. MS (ESI) found: 481.3 (M+H)^+.
EXAMPLE 294

[00207] A 5 mL microwave reaction tube was charged with Example 130 (298 mg, 0.62 mmol, 1.0 eq.), 3-cyanophenylboronic acid (101 mg, 0.69 mmol, 1.1 eq.), 2 M aqueous potassium phosphate solution (0.93 mL, 1.86 mmol, 3.0 eq.), and DMF (3 mL). The resulting solution was degassed under vacuum and then backfilled with argon. Tetrakis(triphenylphosphine)palladium(0) (50 mg) was added and the resulting mixture was again degassed as described above. The tube was sealed, and the reaction mixture was heated via microwave at 150 °C for 30 minutes. After this time, the reaction mixture was cooled to rt. The reaction mixture was filtered to remove some solids, and the filter cake was rinsed with ethyl acetate. The combined filtrates were concentrated in-vacuo to yield a residue. The residue was purified over silica gel, eluting with 25% - 50% ethyl acetate/hexanes, to yield Example 294 (202 mg) as a colorless foam. MS (ESI) found: 500.3 (M+H)⁺.

EXAMPLE 295

[00208] Example 295 was prepared in a similar manner as described for the preparation of Example 294 using 4-cyanophenylboronic acid. MS found: 500.3 (M + H)⁺.
EXAMPLE 296

Example 296 was prepared in a similar manner as described for the preparation of Example 294 using 2-cyanophenylboronic acid. MS found: 500.3 (M + H)^+.

EXAMPLE 297

Example 297 was prepared in a similar manner as described for the preparation of Example 294 using 3-cyanophenylboronic acid and (R)-2-bromo-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide. MS found: 500.4 (M + H)^+.

EXAMPLE 298

Example 298 was prepared in a similar manner as described for the preparation of Example 291 using Example 296. MS found: 543 (M + H).
EXAMPLE 299

[00212] Example 299 was isolated as a by-product of the conversion of Example 296 to Example 298. MS found: 518 (M + H).

EXAMPLE 300

[00213] Example 300 was prepared in a similar manner as described for the preparation of Example 291 using Example 295. MS found: 543.4 (M + H).

EXAMPLE 301

[00214] Example 301 was prepared in a similar manner as described for the preparation of Example 291 using Example 294. MS found: 543.5 (M + H).

EXAMPLE 302
Example 302 was prepared in a similar manner as described for the preparation of Example 291 using Example 297. MS found: 543.5 (M + H).

**EXAMPLE 303**

![Chemical Structure]

**Step 1:** (R)-3-((1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamoyl)phenyl acetate

(R)-2-Amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride was coupled with 3-acetoxy benzoic acid in a similar manner as described for the preparation of Example 75 to give (R)-3-((1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamoyl)phenyl acetate (115 mg, 50% yield). MS found: 457.3 (M+).

**Step 2: Example 303**

To a solution of (R)-3-((1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamoyl)phenyl acetate (115 mg, 0.25 mmol) in methanol (2 mL) was added a solution of sodium methoxide (0.5 M, 0.5 mL) in methanol. The mixture was stirred at room temperature for one hour. After this time, the mixture was concentrated and then neutralized to pH = 5 with 1 N HCl. The resulting precipitated solid was collected by filtration, rinsed with water, and dried under vacuum to give Example 303 (90 mg, 86.7% yield) as an off-white solid. MS found: 415.2 (M + H).
Example 304 was prepared in a similar manner as described for the preparation of Example 303 using 2-acetoxy benzoic acid. MS found 415.2 (M + H).

**EXAMPLE 305**

TFA Salt of (R)-3-amino-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide

Example 128 (120 mg, 0.27 mmol) was dissolved in a mixture of methanol (5 mL) and ethyl acetate (5 mL). 5% Pd on carbon (8 mg) was added. The reaction system was degassed and charged with hydrogen three times and then allowed to stir at rt for one hour with a hydrogen balloon. The mixture was filtered and washed with ethyl acetate. The combined filtration was concentrated and purified by prep-HPLC. The product containing fraction was concentrated and lyophilized to give Example 305 (89 mg, 62%). MS found: 414.2 (M + H).

**EXAMPLE 306**

Example 306 was prepared in a similar manner as described for the preparation of Example 305 using Example 129. MS found: 414.2 (M + H).

**EXAMPLE 307**
Sodium cyanate (2 mg, 0.031 mmol) was added into a solution of Example 305 (10 mg, 0.024 mmol) in acetic acid (1 mL). The mixture was stirred at rt for two hours and then concentrated to yield a residue. The residue was purified by prep-HPLC. The product containing fraction was concentrated and lyophilized to give Example 307 as a yellow solid (10 mg, 91.2% yield). MS found: 457.3 (M + H).

Example 308 was prepared in a similar manner as described for the preparation of Example 307 using Example 306. MS found: 457.3 (M + H).

To a solution of Example 305 (15 mg, 0.036 mmol) in DCM (2 mL) was added isobutyryl chloride (4.2 μL, 0.04 mmol) and pyridine (4.5 μL, 0.04 mmol). The reaction was stirred at rt for 30 min and then concentrated to provide a residue. The residue was purified by preparative HPLC. The product containing fraction was concentrated and lyophilized to give Example 309 as a yellow powder (10 mg, 57.4%). MS found: 484.3 (M + H).
A solution of (R)-2-amino-1-(4-(4-chlorophenyl)piperidine-1-yl)-3-methylbutan-1-one hydrochloride (40 mg, 0.136 mmol, 1 eq) and phthalic anhydride (20 mg, 0.136 mmol, 1 eq) were stirred at 25 °C in 3 mL of chloroform for 20 hours. After this time, the reaction was concentrated and purified by preparative HPLC to afford Example 310, yield = 55%. MS found: 443.30 (M+H)+.

EXAMPLE 311

Example 311 was prepared in a similar manner as described for the preparation of Example 310. MS found: 477.3 (M+H)+.

EXAMPLE 312

Example 312 was prepared in a similar manner as described for the preparation of Example 310. MS found: 493.2 (M + H)

EXAMPLE 313

Step 1: Methyl 2-((tert-butoxycarbonyl)aminomethyl)benzoate
Methyl 2-((aminomethyl)benzoate-hydrochloride (500 mg, 2.48 mmol, 1 eq) was dissolved in 10 mL of THF at 25 °C under nitrogen. Triethylamine (0.35 mL, 4.96 mmol, 2 eq) was added followed by BOC anhydride (541 mg, 2.48 mmol, 1 eq). The reaction was stirred for 20 hours. After this time, saturated NH₄Cl (10 mL) was added and the product was extracted 3 times with methylene chloride. The organic extracts were combined, dried over sodium sulfate and stripped to give methyl 2-((tert-butoxycarbonyl)aminomethyl)benzoate (650 mg) as a light-colored oil.

**Step 2: 2-((Tert-butoxycarbonyl)aminomethyl)benzoic acid**

Methyl 2-((tert-butoxycarbonyl)aminomethyl)benzoate (600 mg, 1.99 mmol, 1 eq) was dissolved in 5 mL of THF at 25 °C. 1 N NaOH (5.96 mL, 5.96 mmol, 3 eq) was added and the reaction stirred for 20 hours. After this time, 1.0 N HCl (5.86 mL) was added and the product was extracted 3 times with chloroform. The organic extracts were combined, dried over sodium sulfate and stripped to give 2-((tert-butoxycarbonyl)aminomethyl)benzoic acid (560 mg, 98% yield). MS (M+H-BOC)⁷ found: 152.3.

**Step 3: Example 313**

Example 313 was prepared in a similar manner as described for the preparation of Example 75. MS found: 429.3 (M - Boc)
EXAMPLE 314

[00230]  Example 314 was prepared in a similar manner as described for the preparation of Example 313 using methyl 3-(aminomethyl)benzoate-hydrochloride. MS found: 528.4 (M+H).

EXAMPLE 315

[00231]  Example 315 was prepared in a similar manner as described for the preparation of Steps 1 and 2 of Example 313 using 3-(piperazin-1-yl) benzoic acid. MS Found: 583.5 (M+H).

EXAMPLE 316

[00232]  Example 315 was deprotected utilizing either TFA in dichlormethane or HCl in dioxane to provide Example 316 after preparative HPLC. MS Found: 483.4 (M+H).
EXAMPLE 317

Example 317 was prepared in a similar manner as described for the preparation of Example 316 using 2-(piperazin-1-yl)benzoic acid. MS found 483.4 (M + H).

EXAMPLE 318

Example 318 was prepared in a similar manner as described for the preparation of Steps 1 and 2 of Example 314 using 3-(piperidin-1-yl) benzoic acid. MS found: 582.5 (M + H).

EXAMPLE 319

Example 318 was deprotected utilizing either TFA in dichloromethane or HCl in dioxane to provide Example 319 after preparative HPLC. MS found: 482.1 (M + H).
EXAMPLE 320

[00236] Example 320 was prepared in a similar manner as described for the preparation of Example 75 using trans-1,4-Cyclohexanedicarboxylic acid monomethyl ester. MS found: 463.4 (M + H).

EXAMPLE 321

[00237] Example 321 was prepared in a similar manner as described for the preparation of Example 290 using 3-phenylpyrazole. MS found: 479.4 (M+).

EXAMPLE 322

[00238] Example 322 was prepared in a similar manner as described for the preparation of Example 290 using 4-methoxy indole. MS found: 482.3 (M+).

EXAMPLE 323
[00239] To a solution of (R)-2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride (59 mg, 0.195 mmol) in THF (2 mL) was added phenyl 1,3,4-thiadiazol-2-ylcarbamate (45 mg, 0.2 mmol) and DIPEA (35 µL, 0.2 mmol), the mixture was stirred at 50 °C overnight and then concentrated to provide a residue. The residue was purified by prep-HPLC. The product containing fraction was concentrated and lyophilized to give Example 323 as a white powder (52 mg, 55 %). MS found: 422.3 (M+H).

EXAMPLE 324

[00240] To a solution of Example 317 (15 mg, 0.025 mmol) in pyridine (2 mL) was added acetic anhydride (7 µL, 0.075 mmol) and the reaction allowed to stir overnight. After this time, the mixture was purified by preparative HPLC and the product isolated by extracting NaOH neutralized product fractions to give Example 324 (17 mg) as a colorless film. MS found: 525.5 (M+).

EXAMPLE 325

[00241] Example 325 was prepared in a similar manner as described for the preparation of Example 75 using 3-benzoylbenzoic acid. MS found: 503.2 (M+H).
EXAMPLE 326

[00242] Example 326 was prepared by reacting a solution of Example 325 (50 mg, 0.1 mmol) in methanol (3 mL) with NaBH₄ (4 mg, 0.1 mmol) for 24 h. Aqueous workup followed by purification via silica gel provided Example 326 (40 mg, 80% yield) as an off-white solid. MS found: 505.3 (M+H).

EXAMPLE 327

N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide

Step 1: (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one hydrochloride

[00243] (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one hydrochloride was prepared in a similar manner as described in Preparation C with the exception that (S)-4-(4-chlorophenyl)-3,3-dimethylpiperidin-4-ol (WO 04/043965) was used instead of 4(4-chlorophenyl)piperidine.

Step 2: N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide
Example 327 was prepared in a similar manner as described in Example 75 from (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one hydrochloride and benzoic acid.

EXAMPLE 328

Example 328 was prepared in a similar manner as described for the preparation of Example 75 using (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one hydrochloride and quinoline-5-carboxylic acid. MS found: 443.3 (M+).

EXAMPLE 329

Example 329 was prepared in a similar manner as described for the preparation of Example 328 with the exception that 4-chlorobenzoic acid was used instead of benzoic acid. MS found 477.2 (M+).

EXAMPLE 330

(R)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2'-nitrobiphenyl-3-carboxamide
Step 1: (R)-3-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobut-2-ylcarbamoyl)phenylboronic acid.

(R)-3-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobut-2-ylcarbamoyl)phenylboronic acid was prepared in a similar manner as Example 75 using 3-carboxybenzeneboronic acid.

Step 2: (R)-3-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobut-2-ylcarbamoyl)phenylboronic acid

A solution of (R)-3-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobut-2-ylcarbamoyl)phenylboronic acid (100 mg, 2.26 mmol), 1-bromo-2-nitrobenzene (46 mg 2.26 mmol), Na₂CO₃ (72 mg, 0.67 mmol) and Pd(Ph₃P)₄ (13 mg) in toluene (5 mL) water (3 mL) and ethanol (3 mL) was heated at 100 °C for 30 min. After this time, the reaction mixture was cooled, filtered and then concentrated. Water was added and the resulting solution was extracted with ethyl acetate. The combined organic extracts were dried and concentrated to provide crude material. The crude material was purified via column chromatography (25% EtOAc/hexane to 50% EtOAc/hexane) to provide Example 330 as an off-white glass. MS found: 520.2 (M+H).
Step 1:

[00249] 3-Carboxyphenyl boronic acid (100 mg, 0.60 mmol), 2-bromophenyl urea (130 mg, 0.60 mmol), tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.030 mmol), sodium carbonate (192 mg, 1.81 mmol), toluene (5 mL), water (3 mL), and ethanol (3 mL) were mixed at 25 °C under nitrogen then heated in a microwave reactor for 30 minutes at 100 °C. Water (5 mL) was added followed by removal of the EtOH in vacuo. The aqueous layer was washed with diethyl ether (2x) and the pH was adjusted to 3 with 1N HCl. The aqueous layer was extracted with ethyl acetate (2x) and the combined were dried over sodium sulfate and then concentrated in vacuo to give 2'-ureidobiphenyl-3-carboxylic acid (150 mg, 0.58 mmol, 97% yield) as a tan glass. MS found: (M + H)^+ = 257.29

Step 2: Example 331

[00250] Example 331 was prepared in a similar manner as described for the preparation of Example 75 using 2'-ureidobiphenyl-3-carboxylic acid. MS found 533.4 (M+H).
EXAMPLE 332

TFA Salt

To a solution of Example 142 (30 mg, 0.05 mmol) in acetone was added KOH (6 mg 0.1 mmol) and iodomethane (10 μL, 0.16 mmol). The resulting mixture was stirred at room temperature for 48 h. After this time, EtOAc was added to the solution, and the resulting mixture was washed with water and brine. The organic layer was dried and concentrated to an oil. The oil was purified by preparative HPLC to provide Example 332 (18 mg). MS found: 453.4 (M+H).

EXAMPLE 333

Example 333 was prepared in a similar manner as described for the preparation of Example 323 with the exception that Example 305 was used in place of (R)-2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one hydrochloride. MS found: 541.3 (M+).

EXAMPLE 334

To a solution of Example 305 (31 mg, 0.075 mmol) in DCM (1 mL) was added methanesulfonyl chloride (6 μL, 0.075 mmol) and pyridine (8 μL, 075 mmol).
The reaction was stirred at rt for 30 min and and additional aliquots (1 equiv each) of pyridine and methanesulfonyl chloride was added. The reaction was stirred and then concentrated to yield a residue. The residue was purified by preparative HPLC. The product containing fraction was concentrated and lyophilized to give Example 334 as a white solid powder (21 mg). MS found: 492.2 (M+).

EXAMPLES 335 TO 404

Examples 335 to 404, as described in Table 13, were prepared in a similar manner as described for the preparation of Example 75. In the synthesis of Examples 344 to 404, the appropriate acid needed to produce the product listed was used in place of the benzoic acid used in Example 75. Examples 404, 398, 399, 401 and 403 were prepared from the corresponding esters of Examples 395, 396, 397, 400 and 402, respectively, via standard hydrolysis.

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EXAMPLES 405 TO 438

[00255] Examples 405 to 438, as described in Table 14, were prepared in a similar manner as described for the preparation of Example 294. In the synthesis of Examples 404 to 438, the boronic acid needed to produce the product listed was used in place of the 3-cyanophenylboronic acid used in Example 294.

**TABLE 14**

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</tr>
</tbody>
</table>

**EXAMPLE 439**

```
Step 1: Tert-butyl 4-(3,4-dichlorophenyl)-4-hydroxypiperidine-1-carboxylate
```

[00256] n-BuLi (2.5 M, 2 mL, 5.21 mmol) was added into a solution of 4-bromo-1,2-dichlorobenzene (1.07 g, 4.74 mmol) in dry THF (10 mL) at -78 °C. The mixture was stirred for 20 mins and then a solution of tert-butyl 4-oxopiperidine-1-carboxylate (0.95 g, 4.74 mmol) in THF (5 mL) was added. The mixture was further stirred at -78 °C for 1h. After this time, the reaction was quenched with NH₄Cl (aq., 15 mL), extracted with ethyl acetate (50 mL X 3), dried over Na₂SO₄ and concentrated to yield a residue. The residue was purified by flash chromatography using 10-30% ethyl acetate in hexanes as an eluent to provide tert-butyl 4-(3,4-
dichlorophenyl)-4-hydroxypiperidine-1-carboxylate (1.6 g, 90% purity, 88% yield) as a colorless oil. MS found: 346.3 (M⁺).

Step 2: 4-(3,4-Dichlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride

[00257] HCl (conc., 1.5 mL) was slowly added to a flask containing tert-butyl 4-(3,4-dichlorophenyl)-4-hydroxypiperidine-1-carboxylate (200 mg, 0.58 mmol). The mixture was stirred at rt for 30 mins, heated to 90 °C for 5h and then cooled overnight. The resulting precipitate was collected by filtration to give 4-(3,4-dichlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (107 mg, 70% yield). MS found: 215.6 (M⁺).

Step 3: 4-(3,4-Dichlorophenyl)piperidine hydrochloride

[00258] A balloon filled with hydrogen was charged into a solution of 4-(3,4-dichlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (107 mg, 0.41 mmol) in the presence of 5% Pd/C (5% mmol) after the system was degassed. The reaction was stirred at rt for 2h, filtered, rinsed with MeOH and then concentrated to give 4-(3,4-Dichlorophenyl)piperidine hydrochloride (79 mg, 72% yield) as an oil. MS found: 266.4 (M⁺).

Step 4: Example 439
Example 439 was prepared in a similar manner as described for the preparation of Example 75 by reacting 4-(3,4-dichlorophenyl)piperidine hydrochloride with N-Boc-D-valine, followed by Boc group removal and coupling with 3-hydroxy benzoic acid. MS found 449.2 (M+).

EXEMPLARY 440 TO 458

Examples 440 to 458, as described in Table 15, were prepared in a similar manner as described for the preparation of Example 439. In the synthesis of Examples 449 to 458, the appropriate acid and piperidine needed to produce the product listed was used in place of the benzoic acid used in Example 439.

<table>
<thead>
<tr>
<th>Example</th>
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<th>MS (M+)</th>
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<td>407.4 (M+H)</td>
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EXAMPLES 459 TO 497

[00261] Examples 459 to 497, as described in Table 16, were prepared in a similar manner as described for the preparation of Example 328. In the synthesis of Examples 459 to 496, the appropriate acid and piperidine needed to produce the product listed was used in place of the benzoic acid used in Example 328. Examples 463, 496 and 497 were prepared from the corresponding esters Examples 462, 494 and 495, respectively, via standard hydrolysis.

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**EXAMPLE 498**

Cl

![Structure 498](image)

[00262] Example 498 was prepared in a similar manner as described for the preparation of Example 309 with the exception that isopropyl isocyanate was used in place of isobutyryl chloride. MS found: 499.3 (M⁺).

**EXAMPLE 499**

Cl

![Structure 499](image)

[00263] Example 499 was prepared in a similar manner as described for the preparation of Example 309 with the exception that trifluoromethanesulfonic anhydride was used in place of isobutyryl chloride. MS found: 545.9 (M⁺).
Example 500 was prepared by reacting with methyl sulfonamide and Example 394 in a similar manner as described for the preparation of Example 1. MS found: 553.9 (M+).

Example 501

Step 1: 4-(4-Chlorophenyl)-3,3-dimethyl-1,2,3,6-tetrahydropyridine

(S)-4-(4-chlorophenyl)-3,3-dimethylpiperidin-4-ol was dehydrated under acidic conditions in a similar manner as described for the preparation of Example 439 to give 4-(4-chlorophenyl)-3,3-dimethyl-1,2,3,6-tetrahydropyridine.

Step 2: Example 501

4-(4-Chlorophenyl)-3,3-dimethyl-1,2,3,6-tetrahydropyridine was coupled with racemic N-benzyol valine in a similar manner as described for the preparation of Example 1 to give Example 501. MS found: 426.3 (M+).
Step 1: (R)-2-(4-aminophenyl)-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)acetamide

Example 382 was reduced under hydrogen balloon in a similar manner as described for the preparation of Example 305 to furnish the above amine.

Step 2: Example 502

The amine from Step 1 was treated with trifluoromethanesulfonic anhydride to furnish Example 502. MS found: 560.1 (M^+).

EXAMPLE 503

Step 1: Tert-butyl 4-(4-chlorophenyl)-2-methylpiperidine-1-carboxylate

A solution of N-Boc-4-chlorophenylpiperidine (6.0 g, 20.3 mmol) in ether (50 mL) was cooled to -78 °C and TMEDA (6.73 mL, 44.6 mmol) was added followed by sec-butyl lithium (17.4 mL, 24.3 mmol) while maintaining the temperature below -60 °C. After stirring for 5 h, iodomethane (1 eq) was added and the reaction was allowed to warm to rt. Once at the prescribed temperature, the reaction was quenched with water (50 mL) and the layers were separated. The aquesous layer was extracted with ether (50 mL) and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated to an oil. The oil was purified by HPLC to give tert-butyl 4-(4-chlorophenyl)-2-methylpiperidine-1-carboxylate (1.35 g, 22% yield) as an oil. MS found: 310.3 (M+H).
Step 2: 4-(4-Chlorophenyl)-2-methylpiperidine hydrochloride

4-(4-Chlorophenyl)-2-methylpiperidine hydrochloride was prepared from tert-butyl 4-(4-chlorophenyl)-2-methylpiperidine-1-carboxylate in a similar manner as described for the preparation of Step 2, Example 439.

Step 3: Example 503

4-(4-Chlorophenyl)-2-methylpiperidine hydrochloride was converted to Example 503 in a similar manner as described for the preparation of the 3-step sequence outlined in Preparation C and Example 75 (EDC/HOBt coupling with Boc-D-valine, Boc removal with HCl in dioxane, and finally EDC/HOBt coupling with 4-chloro benzoic acid). MS found: 447.2 (M+).

EXAMPLE 504

Example 504 was prepared in a similar manner as described for the preparation of Example 503 using (2R)-2-amino-1-(4-(4-chlorophenyl)-2-methylpiperidin-1-yl)-3-methylbutan-1-one hydrochloride with the exception that 3-chloro-5-(methoxycarbonyl)benzoic acid was used in place of 4-chloro benzoic acid in Step 3. MS found: 505.1 (M+).

EXAMPLE 505
Example 505 was prepared from 504 under standard ester hydrolysis (1 N NaOH, methanol) conditions. MS found: 491.2 (M+).

**EXAMPLE 506**

![Chemical Structure](image)

**Step 1:** (2R)-2-amino-1-(4-(4-chlorophenyl)-4-hydroxy-2-methylpiperidin-1-yl)-3-methylbutan-1-one hydrochloride

(2R)-2-amino-1-(4-(4-chlorophenyl)-4-hydroxy-2-methylpiperidin-1-yl)-3-methylbutan-1-one hydrochloride was prepared from tert-Butyl 2-methyl-4-oxopiperidine-1-carboxylate in a similar manner as described for the preparation of Example 439. MS found: 463.2.

**Step 2:** Example 506

4-Chlorobenzoic acid was coupled to (2R)-2-amino-1-(4-(4-chlorophenyl)-4-hydroxy-2-methylpiperidin-1-yl)-3-methylbutan-1-one hydrochloride in a similar manner as described for the preparation of Example 75. MS found: 463.2 (M+).

**EXAMPLE 507**

![Chemical Structure](image)

To a stirred solution of 2-(4-chloro-5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (see US 2004/0162282, 36.5 mg, 0.15 mmol), EDCi (32 mg, 0.17 mmol) and HOBT (22 mg, 0.17 mmol) in DMF (0.3 mL) was added 4-
chlorophenylpiperidine hydrochloride (42 mg, 0.18 mmol) and DIPEA (66 µL). Upon completion of addition, the reaction mixture was stirred for 18 h and then purified directly by HPLC to provide Example 507 (46.5 mg, 74%) as a white solid. MS found: 420.1 (M+).

EXEMPLARY 508

Example 508 was prepared in a similar manner as described for the preparation of Example 328 using (R)-4-(4-chlorophenyl)-3,3-dimethylpiperidin-4-ol. MS found: 443.3 (M+).

EXEMPLARY 509

Step 1: 1-(3'-hydroxybiphenyl-2-yl)urea

3-Hydroxy phenol and 2-bromophenyl urea were reacted under Suzuki cross coupling conditions in a similar manner as described for the preparation of Example 294 to provide 1-(3'-hydroxybiphenyl-2-yl)urea.

Step 2: Example 509
To a stirred solution of (R)-2-chloro-N-(1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methyl-1-oxobutan-2-yl)acetamide (40 mg, 0.14 mmol) and K₂CO₃ (39 mg, 0.28 mmol) in DMSO (2 mL) was added 1-(3'-hydroxybiphenyl-2-yl)urea (32 mg, 0.14 mmol). Upon completion of addition, the reaction mixture was stirred or 18 h. After this time, the reaction mixture was purified via preparative HPLC to provide Example 509 (36% yield). MS found: 563.2 (M+).

EXAMPLE 510

1-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-methylurea

A reaction tube was charged with methyl isocyanate (3 μL), (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one hydrochloride (20 mg) and THF (2 mL). Triethylamine (7.4 μL) was added and the reaction mixture was shaken overnight at rt. After this time, the resulting solution was concentrated and purified by preparative silica gel chromatography (100% EtOAc to 20% MeOH/CH₂Cl₂) to provide Example 510. MS found: (M + H)⁺ = 396.3.

EXAMPLE 511

1-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-cyclopentylurea

A reaction tube was charged with cyclopentyl isocyanate (9 μL), (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one hydrochloride (30 mg) and THF (2 mL). Triethylamine (11 μL) was added and the reaction mixture was shaken overnight at rt. After this time, the
resulting solution concentrated and purified by preparative silica gel chromatography (100% EtOAc to 20% MeOH/CH₂Cl₂) to provide Example 511. MS found: (M + H)⁺ = 450.2.

**EXAMPLE 512**

(R)-N-(1-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)cyclopentane-carboxamide

**Step 1:** (R)-tert-butyl 1-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

N-Boc-D-valine (2.22g, 10.2 mmol), EDC (1.96 g, 10.2 mmol), HOBT (1.38 g, 10.2 mmol) was dissolved in dichloromethane (40 mL). DIPEA (4.0 mL, 23.3 mmol) and 4-hydroxy-(4-chlorophenyl)piperidine (1.98 g, 9.34 mmol) was added and the solution was stirred at rt for 2h. The reaction was concentrated and the resulting oily residue partitioned between EtOAc (150 mL) and water (50 mL), shaken and then separated. The organic layer was then washed with aq NaHCO₃ (50 mL) and brine and the combined organic fractions were dried over solid sodium sulfate. The solution was filtered and concentrated by to give (R)-tert-butyl 1-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (3.9 g) as a white foam. MS found: (M⁺)⁺ = 411.1.

**Step 2:** (R)-2-amino-1-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-3-methylbutan-1-one hydrochloride
[00283] A 4M solution of HCl in dioxane (10 mL) was added to (R)-tert-butyl 1-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (2.0 g) and the resulting solution was allowed to stir at rt. for 1 h. After this time, the solvent was removed by rotary evaporation to provide an oil. The oil was dried overnight in vacuo to provide (R)-2-amino-1-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-3-methylbutan-1-one hydrochloride as a white foam.

Step 3: Example 512

[00284] To a solution of (R)-2-amino-1-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-3-methylbutan-1-one hydrochloride (31.1 mg, 0.09 mmol) and cyclopentane carbonyl chloride (12 μL, 0.09 mmol) in dichloromethane (0.5 mL) was added DIPEA (34.3 μL, 0.2 mmol) and the reaction solution was allowed to stir at rt for 1h. The solvents were removed and the residue was partitioned between EtOAc (3 mL) and water (1.5 mL). the layers were separated, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified via column chromatography (33% EtOAc/heptane) to afford Example 512 (29.1 mg, 80% yield) as a white solid. MS found 407.04 (M+)+; HPLC rt 3.66 min.

EXAMPLE 513

(N-((2R)-1-(4-(4-chloro-3-methoxyphenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)cyclopentanecarboxamide

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Step 1: tert-butyl 4-(4-chloro-3-methoxyphenyl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate

To a solution of 5-bromo-2-chloro-anisole (1.613 g, 7.3 mmol) in THF (15 mL) at -78 °C was added n-butyl lithium (4.75 mL, 7.6 mmol, 1.6 M) dropwise over 15 min and the resulting solution was allowed to stir at -78 °C for 1 h. A solution of tert-butyl 3,3-dimethyl-4-oxopiperidine-1-carboxylate (prepared in the manner described in International Patent Application WO 04/043965, 754 mg, 3.32 mmol) in THF (5 mL) was added dropwise via canula. The reaction was stirred for 2 h at -78 °C then allowed to warm to rt slowly over 30 min at which time the mixture was heated at 50 °C for 30 min. The reaction was cooled to rt, quenched by the addition of aq NH₄Cl, diluted with water and extracted into EtOAc. The combined organic extracts were dried over magnesium sulfate, filtered and concentrated. The residue was purified via column chromatography (15% to 33% to 50% EtOAc/heptane to afford tert-butyl 4-(4-chloro-3-methoxyphenyl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (728 mg, 60% yield).

Step 2: 4-(4-chloro-3-methoxyphenyl)-3,3-dimethylpiperidin-4-ol hydrochloride

tert-Butyl 4-(4-chloro-3-methoxyphenyl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (1.36 g, 2.39 mmol) was added 4N HCl in dioxane (10 mL) and stirred for 30 min. The solvents were removed in vacuo and the resulting solids were dried azeotropically with toluene and then further dried under high vacuum to afford 4-(4-chloro-3-methoxyphenyl)-3,3-dimethylpiperidin-4-ol hydrochloride as a white solid.
Step 3: tert-butyl (2R)-1-(4-(4-chloro-3-methoxyphenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

[00287] N-Boc-D-valine (85 mg, 0.39 mmol), EDC (75 mg, 0.39 mmol), HOBT (53 mg, 0.39 mmol) was dissolved in dichloromethane (2 mL). 4-(4-Chloro-3-methoxyphenyl)-3,3-dimethylpiperidin-4-ol hydrochloride (100 mg, 0.33 mmol) was added followed by DIPEA (136 µL, 0.78 mmol) and the solution was stirred at rt for 10 min. The reaction was concentrated and the resulting oily residue was purified via column chromatography (10% to 50% EtOAc/heptane) to furnish tert-butyl (2R)-1-(4-(4-chloro-3-methoxyphenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (153 mg, 99% yield) MS found: (M-Boc)$^+$ = 396.3.

Step 4: (2R)-2-amino-1-(4-(4-chloro-3-methoxyphenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one hydrochloride

[00288] tert-Butyl (2R)-1-(4-(4-chloro-3-methoxyphenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (153 mg, 0.33 mmol) was added 4N HCl in dioxane (2 mL) and stirred for 60 min. The solvents were removed in vacuo and the resulting solids were dried azeotropically with toluene and then further dried under high vacuum to afford (2R)-2-amino-1-(4-(4-chloro-3-methoxyphenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one hydrochloride as a white solid.

Step 5: Example 513
[00289] To a solution of (2R)-2-amino-1-(4-(4-chloro-3-methoxyphenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one hydrochloride (20 mg, 0.05 mmol) and cyclopentane carbonyl chloride (7.4 μL, 0.06 mmol) in dichloromethane (0.3 mL) was added DIPEA (22 μL, 0.13 mmol) and the reaction solution was allowed to stir at rt for 16h. The solvents were removed and the residue was purified preparative HPLC to afford Example 513 (14.5 mg, 60% yield) as a white solid. MS found 465.3 (M+)⁺; HPLC rt 3.89 min.

EXAMPLE 514

N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-5-guanidino-1-oxopentan-2-yl)cyclopentane-carboxamide

Step 1:

[00290] To a solution of Boc-D-ORN(Cbz)-OH (336 mg, 0.92 mmol), EDC (176 mg, 0.92 mmol) and HOBT (124 mg, 0.92 mmol) in dichloromethane (5 mL) was added (S)-4(4-chlorophenyl)-3,3-dimethylpiperidin-4-ol (200 mg, 0.83 mmol) followed by DIPEA (0.16 mL, 0.92 mmol). The solution was stirred for 2 h then poured into EtOAc and washed successively with water, aq. NaHCO₃, and brine. The organic layer was dried over magnesium sulfate, concentrated and dried under high vacuum to afford the crude solid which was used without further purification. MS found 588.4 (M+)⁺.
Step 2: Benzyl (R)-4-amino-5-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-5-oxopentylcarbamate hydrochloride

[00291] The product of step 1, above was deprotected in 4N HCl in dioxane (5 mL) to furnish benzyl (R)-4-amino-5-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-5-oxopentylcarbamate hydrochloride (463 mg, crude product).

Step 3: benzyl (R)-5-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-4-(cyclopentanecarboxamido)-5-oxopentylcarbamate

[00292] Benzyl (R)-4-amino-5-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-5-oxopentylcarbamate hydrochloride (50.5 mg, 0.096 mmol) was dissolved in dichloromethane (0.5 mL) and added cyclopentane carbonylchloride (14 µL, 0.12 mmol) followed by DIPEA (42 µL, 0.24 mmol). The solution was stirred for 2 h, concentrated, and partitioned between EtOAc (2 mL) and aq NaHCO₃ (0.5 mL). The EtOAc layer was separated, dried over magnesium sulfate, and concentrated to give benzyl (R)-5-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-4-(cyclopentanecarboxamido)-5-oxopentylcarbamate which was used without further purification.
Step 4: N-((R)-5-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-1-oxopentan-2-yl)cyclopentanecarboxamide 2,2,2-trifluoroacetate

5

[00293] Benzyl (R)-5-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-4-(cyclopentanecarboxamido)-5-oxopentylcarbamate (0.096 mmol from step 3) was added HBr in acetic acid (0.5 mL) and the resulting solution was stirred for 1 h. Ether (15 mL) was added and stirring continued for an additional hour. The ether was removed via pipet and the gummy solids were washed again with ether. The residue was dissolved in MeOH, added solid potassium carbonate then filtered. The crude solution was purified via preparative HPLC to afford N-((R)-5-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-1-oxopentan-2-yl)cyclopentanecarboxamide 2,2,2-trifluoroacetate (20.6 mg, 38% yield). MS found 450.29 (M+)⁺.

Step 5: Example 514

[00294] To a mixture of afford N-((R)-5-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-1-oxopentan-2-yl)cyclopentanecarboxamide 2,2,2-trifluoroacetate (10.6 mg, 0.019 mmol) and 1H-pyrazole-1-carboxamidine hydrochloride (3.03 mg, 0.021 mmol) in DMF was added DIPEA (13.1 µl, 0.075 mmol). The reaction mixture was stirred for 3 h at room temperature. The crude reaction mixture was diluted with MeOH and purified directly by preparative HPLC to give Example 514 (8.1 mg, 60% yield) as a white solid. MS found : 492.23 (M+)⁺.

EXAMPLE 515

2-(3-(3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)phenyl)ureido)acetic acid
Step 1: 3-(3-(2-ethoxy-2-oxoethyl)ureido)benzoic acid

[00295] To a solution of 3-aminobenzoic acid (140 mg, 1 mmol) in THF (5 mL) at 0 °C was added ethyl isocyanato acetate (150 μL, 1.3 mmol). The reaction solution was allowed to warm to room temperature and stir for 18h. The mixture was then poured into EtOAc (40 mL) and washed successively with water (15 mL) and brine (15 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated to an oil which was used without further purification. MS found 267.17 (M+)⁺.

Step 2: ethyl 2-(3-(3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)phenyl)ureido)acetate
[00296] To a resealable vial was added (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl, (24.1 mg, 0.064 mmol), 3-(2-ethoxy-2-oxoethyl)ureido)benzoic acid (17.10 mg, 0.064 mmol), and benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate(BOP) (28.4 mg, 0.064 mmol). The solids were then added DMF (0.25 ml) followed by DIPEA (0.022 mL, 0.126 mmol). After stirring for 1 h, water (1.25 mL) was added to the reaction mixture and the precipitated solids stirred rapidly for several hours. The solids were collected by filtration and washed with water (2x0.5 mL) to give ethyl 2-(3-(3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)phenyl)ureido)acetate (34.8 mg, 90% yield) a white solid. MS found: 587.26 (M+)^+.

Step 3: Example 515

[00297] To a solution of ethyl 2-(3-(3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)phenyl)ureido)acetate, (34 mg, 0.058 mmol) in THF (0.2 mL) and methanol (0.2 mL) was added aqueous NaOH (1N) (60 μL, 0.058 mmol). HPLC/LCMS at 1 h indicates complete consumption of starting material and conversion to product (559.26, M+). The reaction was then neutralized with 1 N HCl (0.06 mL), diluted with water (0.2 mL) and concentrated to remove organic solvents. The resulting oily suspension was dissolved in methanol and purified directly by preparative HPLC. The product containing fraction was concentrated and the solids dried under high vacuum to give Example 515 (27.7 mg, 71% yield) as a white solid.

MS found: 559.27 (M+)^+.

EXAMPLE 516

Sodium 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)phenyl)methanesulfonate

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Step 1: 3-(Chloromethyl)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide

[00298] To an ice cooled solution of R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl, (30.3 mg, 0.089 mmol), in CH₂Cl₂ (0.8 mL) was added 3-(chloromethyl)benzoyl chloride (14 μL, 0.098 mmol) followed by DIPEA (34.4 μL, 0.197 mmol). The reaction was stirred overnight then partitioned between EtOAc and dilute aq. NaHCO₃. The aqueous layer was further extracted with EtOAc then dried over Na₂SO₄. Filter, strip, and flash to purify (20% EtOAc/heptane to 60% EtOAc/heptane) to afford 3-(chloromethyl)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide (33 mg, 75% yield). MS found: 491.20 (M+)⁺.

Step 2: Example 516

[00299] To a solution of 3-(chloromethyl)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide, (33 mg, 0.067 mmol) in Ethanol (0.25 mL)/Water (0.25 mL) was added Sodium Sulfite (0.016 mL, 0.336 mmol) and the reaction vessel heated at reflux overnight. The reaction was
cooled to room temperature then concentrated on a rotovap. The remaining suspension was loaded onto a 1 gram C18 cartridge (pre-wetted with water) and eluted sequentially with water, 10% MeCN/water, 20% MeCN/water then 50% MeCN/water. The product containing fractions were combined, concentrated, and lyophilized to give Example 516 (27.0 mg, 72% yield), which was isolated as a white solid. MS found: 537.22 (M+)⁺.

**EXAMPLE 517**

(R)-2-(benzo[d]oxazol-2-ylamino)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one

[00300] To an solution of (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl, (23.7 mg, 0.07 mmol), ) in EtOH (300 μL) was added 2-chlorobenzoxazole (8 μL, 0.070 mmol) and TEA (19.50 μL, 0.140 mmol). The reaction solution was heated at 150 °C for 45 min. The reaction was purified directly by preparative HPLC to furnish Example 517 (21 mg, 53% yield). MS found: 456.3 (M+)⁺.

**EXAMPLE 518**

3-acetyl-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide

[00301] To a solution of 3-acetylbenzoic acid (10.4 mg, 0.063 mmol), (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one (21.6 mg, 0.058 mmol), EDC (12.14 mg, 0.063 mmol), and HOBT
(9.69 mg, 0.063 mmol) in DMF (250 µL) was added DIPEA (11.06 µL, 0.063 mmol) after stirring for ~20 min. The reaction mixture was stirred for 30 min then added water (1 mL). The precipitated solids were stirred for 45 min, filtered, and rinsed with water to afford Example 518 (24 mg, 86 % yield) as a white solid. HPLC purity: >95%, rt 3.85 min; MS found 485.19 (M+)<sup>+</sup>.

**EXAMPLE 519**

N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-(1H-pyrazol-5-yl)benzamidine, TFA

![Chemical Structure](image)

**Step 1:** N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-((E)-3-(dimethylamino)acyrloyl)benzamide

![Chemical Structure](image)

[00302] 3-Acetyl-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide was added DMF-DMA (0.3 mL) and the reaction mixture heated at 105 °C for ~5 h. The residual DMF-DMA was removed on a rotovap and the crude product was dried on house high vac for ~3 h to afford N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-((E)-3-(dimethylamino)acyrloyl)benzamide.

**Step 2:** Example 519
To a solution of N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-((E)-3-(dimethylamino)acryloyl)benzamide, (11 mg, 0.020 mmol) in ethanol (0.3 mL) was added hydrazine hydrate (20 μL, 0.411 mmol). The reaction was stirred overnight and the crude reaction purified directly via preparative HPLC to give Example 519 (10.0 mg, 0.016 mmol, 79 % yield), as a white solid. HPLC purity >99%, rt 3.92 min; MS found: 509.30 (M+)⁺.

**EXAMPLE 520**

Methyl 2-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)thiazol-4-yl)acetate

![Chemical structure](image)

**Step 1:** 1-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)thiourea

![Chemical structure](image)

To a solution of (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl (141.6 mg, 0.377 mmol) in CHCl₃ (2 mL) at 0 °C was added DIPEA (0.066 mL, 0.377 mmol) followed by the dropwise addition of benzoyl isothiocyanate (0.051 mL, 0.377 mmol). The reaction was stirred for 1 h then concentrated on a rotovap and added MeOH (2 mL). 5 N NaOH (0.080 mL) was added and the resulting mixture was stirred for 1 h then at 65 °C for 1 h. Cool to rt and concentrate. Add water (1 mL) and stir rapidly over the weekend. Extract into EtOAc (3 X 25 mL), dry over Na₂SO₄, filter, strip. Purify via column chromatography (50% EA/heptane to 75% EA/heptane) to afford 1-((R)-1-((S)-4-(4-
chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)thiourea (135 mg, 90 % yield) as a white solid. HPLC purity: 98.6%, rt 3.64 min; MS found: 420.24 (M+Na)^+.

5 Step 2: Example 520

[00305] To a solution of 1-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)thiourea (21.4 mg, 0.054 mmol) in EtOH (0.3 mL) was added methyl 4-chloroacetoacetate (7.4 μL, 0.065 mmol) and the reaction mixture heated at 80 °C overnight. The reaction mixture was concentrated and purified via column chromatography (33% EA/heptane to 50% EA/heptane) to afford Example 520 (13.7 mg, 51.6 % yield) as a clear glass. HPLC purity: 96.7%, rt 3.41 min; MS found: 494.25 (M+)^+.

15 EXAMPLE 521

N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-(sulfamoylmethyl)benzamide

[00306] To a suspension of sodium (3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamoyl)phenyl)methanesulphonate (19.9 mg, 0.036 mmol) in CH₂Cl₂ (1 mL) was added phosphorus pentachloride (0.012 mL, 0.089 mmol) in one portion. The reaction mixture was stirred for 2 h then quenched with water (1 mL) and stirred rapidly for 30 min. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 X 10 mL). The combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated. CH₂Cl₂ (0.6 mL) was added and the solution cooled to 0 °C upon which aq. NH₄OH (0.5 mL) was added drop wise with rapid stirring. The mixture was stirred rapidly while gradually reaching room temperature.
The reaction was diluted with CH₂Cl₂ (~15 mL) and water (3 mL), the layers separated and the aq. layer further extracted with CH₂Cl₂ (15 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The crude product was purified via column chromatography (50% EA/heptane to 100% EA) to furnish Example 521 (14.1 mg, 74 % yield) which was lyophilized to a white powder overnight. HPLC purity: >99%, rt 3.59 min; LCMS: 536.18 (M+)⁺.

**EXAMPLE 522**

(R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-2-(4-(hydroxymethyl)thiazol-2-ylamino)-3-methylbutan-1-one, TFA Salt

Step 1: (R)-2-(4-(chloromethyl)thiazol-2-ylamino)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one

[00307] To a suspension of 1-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)thiourea (29 mg, 0.073 mmol) in acetone (300 µL) was added 1,3-dichloropropan-2-one (14 mg, 0.105 mmol) and the reaction mixture was stirred overnight at rt. The solvents were removed and the residue purified via column chromatography (SiO₂, 25% EtOAc/hep then 50% EtOAc/hep then 10% EtOAc with 0.06% DIPEA). (R)-2-(4-(chloromethyl)thiazol-2-ylamino)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one (35 mg, >95 % yield) was isolated as a clear glass. HPLC purity: >99%, rt 3.87 min; MS found: 470.22 (M+)⁺.

Step 2: Example 522
[00308] A solution of (R)-2-(4-(chloromethyl)thiazol-2-ylamino)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one (30 mg, 0.064 mmol) and Sodium Sulfite (40.2 mg, 0.319 mmol) in EtOH (0.6 mL)/Water (0.3 mL) was stirred at 80 °C. The mixture was heated for 2 h, cooled and purified directly via preparative HPLC to give Example 522 (4.8 mg, 13.3% yield). HPLC purity >97, tr 3.12 min; MS found 452.31 (M+)⁺.

EXAMPLE 523

(R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-2-(4-ethoxymethyl)thiazol-2-ylamino)-3-methylbutan-1-one, HCl

[00309] An additional product, Example 523 (12.5 mg, 33% yield), was isolated from Step #2, Example 522: ~95% pure, rt 3.55 min; MS found 480.34 (M+)⁺.

EXAMPLE 524

Ethyl 2-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)thiazole-4-carboxylate

[00310] 1-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)thiourea (67.5 mg, 0.170 mmol) and ethyl bromopyruvate (0.026 mL, 0.187 mmol) in EtOH (0.6 mL) were heated at ~65 °C overnight. The
reaction was neutralized with 2 equiv TEA in CH₂Cl₂, concentrated, and purified via column chromatography (20% to 40% EtOAc/heptane) to afford Example 524 (74.9 mg, 89% yield) as a clear glass. HPLC purity: 99.5%, 4.00 min; LCMS: 494.28 (M+)+.

5

EXAMPLE 525

2-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)thiazole-4-carboxylic acid

[00311] To a solution of ethyl 2-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)thiazole-4-carboxylate (69 mg, 0.140 mmol) in MeOH (0.28 ml)/THF (0.280 ml) was added NaOH, 1N (0.140 ml, 0.140 mmol) and the reaction stirred at room temperature. The reaction was stirred for 8 h and then neutralized with 1 N HCL. The solvents were removed and water (~1 mL) was added. The resulting solids were stirred and sonicated briefly, filtered and rinsed with water. HPLC purity of crude solids, ~90%; MS found: 466.26 (M+)+.

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EXAMPLE 526

(R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-2-(4-(morpholine-4-carbonyl)thiazol-2-ylamino)butan-1-one, TFA

[00312] To a vial containing 2-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)thiazole-4-carboxylic acid (14.4 mg, 0.031 mmol), HOBT (5.68 mg, 0.037 mmol), and EDC (7.11 mg, 0.037
mmol) was added DMF (0.2 mL). The reaction mixture was stirred for ~30 min
followed by addition of morpholine (8.08 µL, 0.093 mmol). The reaction was stirred
overnight and the product was purified directly by preparative HPLC and lyophilized
to a solid. HPLC purity: 97.8%, Tₚ 3.70 min; LCMS: 535.31 (M+)⁺.

EXAMPLE 527

(S)-2-amino-N-[(R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-
1-yl)-3-methyl-1-oxobutan-2-yl)propanamide 2,2,2-trifluoroacetate

[00313] To a solution of (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-
dimethylpiperidin-1-yl)-3-methylbutan-1-one hydrochloride (30.1 mg, 0.080 mmol),
(R)-2-(tert-butoxycarbonylamino)propanoic acid (16.69 mg, 0.088 mmol), HOBt
(13.51 mg, 0.088 mmol), and EDC (16.91 mg, 0.088 mmol) in DMF was added
DIPEA (0.031 mL, 0.176 mmol). The reaction mixture was stirred for 2 h then added
water (1 mL) slowly. The precipitated solids were stirred for 2h, filtered and dried
under high vacuum. The dried white solids were dissolved in CH₂Cl₂ (0.25 mL),
added TFA (0.1 mL) and stirred for 4h. The solvents were removed via N₂ sweep and
the product purified by preparative HPLC to afford Example 527 (25.2 mg, 0.048
mmol, 60.0 % yield) as a white solid. HPLC purity: >99.5%, 3.12 min; LCMS:
410.28 (M+).

EXAMPLE 528

(R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-2-
(phenylamino)butan-1-one, TFA
[00314] A solution of (R)-3-methyl-2-(phenylamino)butanoic acid (20 mg, 0.103 mmol), EDC (21.8 mg, 0.114 mmol), and HOBT (17.4 mg, 0.114 mmol) in dichloromethane (414 µL) was added (S)-4-(4-chlorophenyl)-3,3-dimethylpiperidin-4-ol (24.8 mg, 0.103 mmol) then DIPEA (19.89 µL, 0.114 mmol). The reaction was stirred for 30 min, the solvents removed and the residue purified directly by preparative HPLC to afford Example 528 (24.8 mg, 45 % yield) as a white solid. HPLC purity: >98%, Tr 4.03 min; MS found: 415.20 (M+)⁺.

EXAMPLE 529
(R)-2-acetamido-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-phenylacetamide

Step 1: (R)-2-amino-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-phenylacetamide

[00315] To a solution of (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one hydrochloride (30.0 mg, 0.080 mmol),
Boc-D-phenyl glycine (22.1 mg, 0.088 mmol), HOBT (13.5 mg, 0.088 mmol), and EDC (16.9 mg, 0.088 mmol) in DMF was added DIPEA (0.031 mL, 0.176 mmol). The reaction mixture was stirred for 2 h then added water (1 mL) slowly. The precipitated solids were stirred for 2 h, filtered, and dried under high vacuum. The dried white solids were dissolved in CH₂Cl₂ (0.25 mL), added TFA (0.1 mL) and stirred for 4 h.

The solvents were removed via N₂ sweep and the product purified by preparative HPLC to afford (R)-2-amino-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-phenylacetamide, TFA (21.7 mg, 46% yield) as a white solid. HPLC purity: 95.2%, 3.14 min; MS found: 410.27 (M+)+.

**Step 2: Example 529**

To a solution of (R)-2-amino-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-phenylacetamide, TFA, (6.9 mg, 0.012 mmol) in CH₂Cl₂ (0.2 mL) was added Ac₂O (1.3 μL, 0.014 mmol) followed by DIPEA (4.1 μL, 0.024 mmol). The reaction was concentrated and purified via prep TLC to afford Example 529 (4 mg, 66.1% yield) after drying. HPLC purity: >99%, tr 3.67 min; MS found: 514.21 (M+)+.

**Example 530**

Methyl 3′-[(R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl]biphenyl-2-carboxylate

![Methyl 3′-[(R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl]biphenyl-2-carboxylate](image)

(R)-2-Amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl (25 mg, 0.067 mmol) was stirred in THF (2 mL) and methylene chloride (2 mL) at 25 °C then triethylamine (0.019 mL, 0.13 mmol) was added followed by phenyl isocyanate (0.015 mL, 0.13 mmol). The reaction was...
stirred overnight then purified over silica gel (3:1 to 1:1 hexanes/EtOAc to 100% THF) to obtain Example 530 (9.0 mg, 0.020 mmol, 29.5 % yield). MS found: (M + H)⁺ = 458.28.

Example 531

3′-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)biphenyl-2-carboxylic acid

Step 1: Methyl 3′-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)biphenyl-2-carboxylate

[00318] (R)-2-Amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one (40 mg, 0.107 mmol), 2′-(methoxycarbonyl)biphenyl-3-carboxylic acid (33 mg, 0.128 mmol), HOBT (20 mg, 0.128 mmol), EDC (25 mg, 0.128 mmol) and triethylamine (0.030 mL, 0.213 mmol) were mixed in methylene chloride (3 mL) at 25 °C with stirring. The reaction was stirred for 20 hours then worked up by adding methylene chloride and washing with sat'd sodium bicarbonate. The methylene chloride layer was dried over sodium sulfate and concentrated in vacuo to give a white glass which was purified over silica gel (3:1 to 1:1 Hexanes/EtOAc) to obtain methyl 3′-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)biphenyl-2-carboxylate (40 mg, 0.069 mmol, 65.0 % yield) as a white glass. MS found: (M + H)⁺ = 577.31.
Step 2: Example 531

Methyl 3'-(((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)biphenyl-2-carboxylate (35 mg, 0.061 mmol) was dissolved in MeOH (3 mL) and added 1N NaOH (0.12 mL, 0.12 mmol) and stirred at 25 °C overnight. The MeOH was removed in vacuo and the aqueous was washed 2 times with diethyl ether. The basic aqueous was acidified to pH = 3 with 1N HCl, then extracted 2 times with methylene chloride to give Example 531 (30 mg, 0.053 mmol, 88.0 % yield) as a white glass product. MS found: (M + H)^+ = 563.30.

Example 532

N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-N-methylcyclopentanecarboxamide

Step 1: tert-butyl (R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl(methyl)carbamate

(S)-4-(4-chlorophenyl)-3,3-dimethylpiperidin-4-ol (100 mg, 0.417 mmol), (R)-2-(tert-butoxycarbonyl(methyl)amino)-3-methylbutanoic acid (116 mg, 0.501 mmol), HOBT (77 mg, 0.501 mmol), EDC (96 mg, 0.501 mmol) and triethylamine (0.116 mL, 0.834 mmol) were mixed in methylene chloride (3 mL) at 25 °C with stirring. The reaction was stirred for 20 hours then washed with sat'd sodium bicarbonate. The methylene chloride layer was dried over sodium sulfate and
concentrated in vacuo to give a white glass which was purified over silica gel (9:1 to 3:1 to 1:1 Hexanes/EtOAc) to obtain tert-butyl (R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl-(methyl)carbamate (190 mg, 0.417 mmol, 100 % yield) as a white glass. MS found: (M + H)^+ = 453.15.

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Step 2: (R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-2-(methylamino)butan-1-one

![Chemical Structure]

[00321] tert-Butyl (R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl-(methyl)carbamate (190 mg, 0.42 mmol) was dissolved in dioxane (3 mL) at 25 °C with stirring then 4N HCl in dioxane (0.524 mL, 2.10 mmol) was added. The reaction was stirred for 20 then concentrated to obtain (R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-2-(methylamino)butan-1-one, HCl (150 mg, 0.39 mmol, 92 % yield) as a white solid. MS found: (M + H)^+ = 353.22.

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Step 3: Example 532

[00322] (R)-1-((S)-4-(4-Chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-2-(methylamino)butan-1-one, HCl (30 mg, 0.077 mmol), cyclopentane carboxylic acid (11 mg, 0.092 mmol), HOBT (15 mg, 0.092 mmol), EDC (18 mg, 0.092 mmol) and triethylamine (0.021 mL, 0.154 mmol) were mixed in methylene chloride (3 mL) at 25 °C with stirring. The reaction was stirred for 20 hours then washed with sat’d sodium bicarbonate. The methylene chloride layer was dried over sodium sulfate and concentrated in vacuo to give a white glass which was purified over silica gel (3:1 to 1:1 Hexanes/EtOAc) to obtain Example 532 (25 mg, 0.056 mmol, 72.3 % yield) as a white glass. MS found: (M + H)^+ = 449.20.

Examples 533A and 533B
(1R,3S)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-(1-methyl-1H-tetrazol-5-yl)cyclohexanecarboxamide and (1S,3R)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-(1-methyl-1H-tetrazol-5-yl)cyclohexanecarboxamide

Step 1: (±)-cis-methyl 3-(methylcarbamoyl)cyclohexanecarboxylate

[00323] (±)-cis-3-(Methoxycarbonyl)cyclohexanecarboxylic acid (500 mg, 2.69 mmol), methylamine, HCl (218 mg, 3.22 mmol), HOBT (493 mg, 3.22 mmol), EDC (618 mg, 3.22 mmol) and triethylamine (0.75 mL, 5.37 mmol) were mixed and stirred in methylene chloride (10mL) at 25 °C. The reaction was stirred overnight then washed with 1N HCl, sat’d sodium bicarbonate, and brine. The organic layer was dried over sodium sulfate and concentrated in vacuo to give (±)-cis-3-(methyl 3-(methylcarbamoyl) cyclohexanecarboxylate (460 mg, 2.309 mmol, 86 % yield) as a white glass. MS found: (M + H)^+ = 200.10.

Step 2: (±)-cis-Methyl 3-(1-methyl-1H-tetrazol-5-yl)cyclohexanecarboxylate

[00324] (±)-cis-Methyl 3-(methylcarbamoyl)cyclohexanecarboxylate (460 mg, 2.309 mmol) was dissolved in Acetonitrile (5 mL) at 25 °C under nitrogen with stirring, then sodium azide (150 mg, 2.309 mmol) was added. Cooled to 0 °C then added trifluoromethanesulfonic anhydride (0.390 mL, 2.309 mmol) dropwise over
minutes. The reaction was a colorless solution. Stirred for 20 hours then added sat'd sodium bicarbonate and stirred for 15 minutes, then added a little EtOAc and concentrated in vacuo the acetonitrile. Added more EtOAc and separated the layers. The EtOAc layer was rinsed again with sat'd sodium bicarbonate then 1 time with brine. The EtOAc layer was dried over sodium sulfate and stripped to give of a colorless oil. Obtained (±)- cis-methyl 3-(1-methyl-1H-tetrazol-5-yl)cyclohexanecarboxylate (350 mg, 1.561 mmol, 68 % yield) as a colorless oil for product. MS found: (M + H)^+ = 225.00.

Step 3: (±)- cis-3-(1-methyl-1H-tetrazol-5-yl)cyclohexanecarboxylic acid

![Chemical structure](image)

[00325] (±)- cis-Methyl 3-(1-methyl-1H-tetrazol-5-yl)cyclohexanecarboxylate (350 mg, 1.56 mmol) was dissolved in MeOH (3 mL) at 25 °C with stirring then 1.000 N NaOH (3.12 mL, 3.12 mmol) was added. Stirred for 3 hours then worked up by adding a little water then concentrating in vacuo the methanol. The pH was adjusted to = 3 with conc. HCl. No solids formed. The acidic aqueous was extracted 3 times with methylene chloride. The methylene chloride extracts were combined, dried (sodium sulfate) and concentrated in vacuo to give (±)- cis-3-(1-methyl-1H-tetrazol-5-yl)cyclohexanecarboxylic (230 mg, 1.094 mmol, 70 % yield) of a white solid as product. MS found: (M + H)^+ = 211.10.

Step 4: (±)- cis-(±)- cis-3-(1-methyl-1H-tetrazol-5-yl)cyclohexanecarboxylic

![Chemical structure](image)

[00326] (R)-2-Amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one (25 mg, 0.067 mmol), (±)- cis-3-(1-methyl-1H-tetrazol-5-yl)cyclohexanecarboxylic acid (17 mg, 0.080 mmol), HOBT (12 mg, 0.080 mmol),
EDC (15 mg, 0.080 mmol) and triethylamine (0.019 mL, 0.133 mmol) were mixed in methylene chloride (3 mL) at 25 °C with stirring. The reaction was stirred for 20 hours then washed with sat'd sodium bicarbonate. The methylene chloride layer was dried over sodium sulfate and concentrated in vacuo to give a white glass which was purified over silica gel (1:1 Hexanes/EtOAc to 100% EtOAc to 4:1 methylene chloride) to obtain (±)-cis-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-(1-methyl-1H-tetrazol-5-yl)cyclohexanecarboxamide (35 mg, 0.066 mmol, 99 % yield) as a white glass. MS found: (M + H)^+ = 531.46.

Step 5: Examples 533A and 533B

(±)-cis-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-(1-methyl-1H-tetrazol-5-yl)cyclohexanecarboxamide was separated by SFC HPLC to give Example 533A (4.0 mg, 7.53 μmol), white solids for product, MS found: (M + H)^+ = 531.43 and Example 533B (4.0 mg, 7.53 μmol), white solids for product. MS found: (M + H)^+ = 531.43.

Example 534

2-(2-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2-oxoethoxy)benzoic acid

Step 1: 2-chloro-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)acetamide
(R)-2-Amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl (100 mg, 0.266 mmol), triethylamine (0.074 mL, 0.533 mmol) and methylene chloride (5 mL) were mixed and stirred at 25 °C then 2-chloroacetyl chloride (0.021 mL, 0.266 mmol) in 1 mL of methylene chloride was added dropwise. The reaction was stirred for 1 hour then concentrated in vacuo to give 2-chloro-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)acetamide (90 mg, 0.218 mmol, 82 % yield) as a tan solid. MS found: (M + H)^+ = 415.46. The product was used without further purification.

**Step 2: methyl 2-((2-(R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2-oxoethoxy)benzoate**

2-Chloro-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)acetamide (35 mg, 0.084 mmol), potassium carbonate (35 mg, 0.253 mmol), methyl 2-hydroxybenzoate (13 mg, 0.084 mmol) and DMSO (3 mL) were mixed with stirring at 25 °C. The reaction was stirred for 20 hours, diluted with EtOAc, and then rinsed 4 times with water. The organic layer was dried over sodium sulfate and concentrated in vacuo to give an amber oil which was purified over silica gel in (3:1 to 1:1 hexanes/EtOAc to 100% EtOAc) to obtain methyl 2-((2-(R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2-oxoethoxy)benzoate (18 mg, 0.034 mmol, 40 % yield) as a white glass. MS found: (M + H)^+ = 531.21.
Step 3: Example 534

Methyl 2-(2-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2-oxoethoxy)benzoate (18 mg, 0.034 mmol) was dissolved in Methanol (2 mL) at 25 °C with stirring then 1.0 N NaOH (0.068 mL, 0.068 mmol) was added. The reaction was stirred 20 hours, added water, then concentrated to remove the MeOH. The basic aqueous was acidified to pH = 3 with 1N HCl, then extracted with methylene chloride. The organic layers were combined, dried over sodium sulfate and concentrated in vacuo to give Example 534 (11 mg, 0.021 mmol, 62 % yield) as a white solid. MS found: (M + H)^+ = 517.35.

Example 535

(R)-1-(4-amino-4-oxobutanoyl)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)piperidine-3-carboxamide

Step 1: (R)-tert-buty1 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)piperidine-1-carboxylate

(R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl (100 mg, 0.266 mmol), (R)-1-((tert-butoxycarbonyl)piperidine-3-carboxylic acid (73 mg, 0.320 mmol), HOBT (49 mg, 0.320 mmol), EDC (61 mg, 0.320 mmol) and triethylamine (0.074 mL, 0.533 mmol)
were mixed in methylene chloride (3 mL) at 25 °C with stirring. The reaction was stirred for 20 hours then washed with sat'd sodium bicarbonate. The methylene chloride layer was dried over sodium sulfate and concentrated in vacuo to give a white glass which was purified over silica gel (1:1 Hexanes/EtOAc to 100% EtOAc to 4:1 methylene chloride/MeOH) to obtain (R)-tert-butyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)piperidine-1-carboxylate (125 mg, 227 mmol, 85% yield) as a white solid. MS found: (M + H)^+ = 550.52.

Step 2: (R)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)piperidine-3-carboxamide, HCl

![Chemical Structure](image)

(R)-tert-butyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)piperidine-1-carboxylate (125 mg, 0.23 mmol) was stirred in Dioxane (2) at 25 °C under nitrogen then 4N HCl in dioxane (0.284 mL, 1.14 mmol) added. The reaction was stirred for 3 hours then concentrated to obtain (R)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)piperidine-3-carboxamide, HCl (100 mg, 0.206 mmol, 90 % yield) as a white glass. MS found: (M + H)^+ = 450.23.

Step 3: Example 535

(R)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)piperidine-3-carboxamide, HCl (30 mg, 0.062 mmol), 4-amino-4-oxobutanoic acid (9 mg, 0.074 mmol), HOBT (11 mg, 0.074 mmol), EDC (14 mg, 0.074 mmol) and triethylamine (0.017 mL, 0.124 mmol) were mixed in methylene chloride (3 mL) at 25 °C with stirring. The reaction was stirred for 20 hours then washed with sat'd sodium bicarbonate. The methylene chloride layer was
dried over sodium sulfate and concentrated in vacuo to give a white glass which was purified over silica gel (100% EtOAc to 4:1 methylene chloride) to obtain Example 535 (24 mg, 0.044 mmol, 70 % yield) as a white glass. MS found: (M + H)^+ = 549.48.

Example 536

1-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-((1S,3S)-3-hydroxycyclopentyl)urea

Step 1: Phenyl (R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

[R][0033] (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one (500 mg, 1.33 mmol), triethylamine (0.371 mL, 2.66 mmol) and methylene chloride (10 mL) were mixed at 0 °C under nitrogen then a methylene chloride solution of phenyl carbonochloridate (209 mg, 1.33 mmol) was added dropwise via an addition funnel. The reaction was stirred for 1 hour, diluted with EtOAc, and washed consecutively with 1N HCl and sat'd sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated in vacuo to give a white glass which was purified over silica gel (3:1 to 1:1 hexanes/EtOAc) to obtain phenyl (R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (365 mg, 0.795 mmol, 59 % yield) as a white glass. MS found: (M + H)^+ = 459.32.

Step 2: Example 536
Phenyl (R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (30 mg, 0.065 mmol), (1S,3S)-3-amino cyclopentanol (7 mg, 0.065 mmol) and triethylamine (0.018 mL, 0.131 mmol) were mixed in acetonitrile (3 mL) at 25 °C then heated in a microwave reactor at 150 °C for 30 minutes. The solvent was concentrated in vacuo then the residue purified over silica gel (1:1 hexanes/EtOAc to 100% EtOAc to 1:1 methylene chloride/MeOH) to obtain Example 536 (20 mg, 0.043 mmol, 65% yield) as a white glass. MS found: (M + H)^+ = 466.37.

Example 537

N1-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-4,4-dimethylpentanediamide

Step 1: 5-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2,2-dimethyl-5-oxopentanoic acid

(R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl (50 mg, 0.133 mmol), 3,3-dimethyldihydro-2H-pyran-2,6(3H)-dione (19 mg, 0.133 mmol) and triethylamine (0.037 mL, 0.266 mmol) were mixed in methylene chloride (3 mL) at 25 °C with stirring. The reaction was stirred for 20 hours, concentrated in vacuo, and purified over silica gel (1:1 hexanes/EtOAc to 100% EtOAc to 4:1 methylene chloride/MeOH) to obtain 5-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-
oxobutan-2-ylamino)-2,2-dimethyl-5-oxopentanoic acid (50 mg, 0.104 mmol, 78 \% yield) as a white glass. MS found: (M + H)\(^+\) = 481.34.

**Step 2: Example 537**

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\(\text{[00337] 5-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpipерidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2,2-dimethyl-5-oxopentanoic acid (25 mg, 0.052 mmol), ammonium chloride (14 mg, 0.260 mmol), HOBT (10 mg, 0.062 mmol), EDC (12 mg, 0.062 mmol) and triethylamine (7.24 \mu l, 0.052 mmol) were mixed in acetonitrile (2 mL) at 25 °C with stirring. The reaction was stirred for 20 hours, concentrated, and then methylene chloride was added. The methylene chloride layer was washed with sat'd sodium bicarbonate, dried over sodium sulfate, and concentrated in vacuo to give a white glass which was purified over silica gel (1:1 Hexanes/EtOAc to 100\% EtOAc to 4:1 methylene chloride/Methanol) to obtain Example 537 (22 mg, 0.046 mmol, 88 \% yield) as a white glass. MS found: (M + H)\(^+\) = 480.29.**

**Example 538**

\(\text{(R)-N\textsubscript{3}-(R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpipерidin-1-yl)-3-methyl-1-oxobutan-2-yl)pyrroldidine-1,3-dicarboxamide}\)

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**Step 1: (R)- tert-butyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpipерidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyle)pyrroldidine-1-carboxylate**
Followed the procedure of Example 535, Step 1, using (R)-1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid (0.69 g, 3.20 mmol), (R)-tert-butyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamoyl]pyrrolidine-1-carboxylate (1.1 g, 2.05 mmol, 77% yield) was obtained as a white glass. MS found: (M + H)$^+$ = 436.43.

**Step 2: (R)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)pyrrolidine-3-carboxamide, HCl**

Followed the procedure of Example 535, Step 2, using (R)-tert-butyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamoyl]pyrrolidine-1-carboxylate (1.1 g, 2.052 mmol), (R)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)pyrrolidine-3-carboxamide, HCl (1.0 g, 2.12 mmol, 100% yield) was obtained as a white solid. MS found: (M + H)$^+$ = 436.28.

**Step 3: Example 538**

(R)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)pyrrolidine-3-carboxamide, HCl (40 mg, 0.085 mmol) was stirred in acetic acid (3 mL) at 25 °C for 2 hours, the reaction was heated at 50 °C for 20 hours. After stirring for 2 hours, the reaction was heated at 50 °C for 20 hours. The pH was adjusted to pH = 7–8 with 1N NaOH and the aqueous was then extracted with EtOAc. The EtOAc layers were combined, washed with sat'd sodium
bicarbonate, dried (sodium sulfate) and concentrated in vacuo to give a tan glass which was purified over silica gel (1:1 hexanes/EtOAc to 100% EtOAc to 4:1 methylene chloride/MeOH) to obtain Example 538 (10 mg, 0.021 mmol, 24% yield) as a white solid. MS found: (M + H)^+ = 479.37.

Example 539

1,4-Diacetyl-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)piperazine-2-carboxamide

Step 1: 1,4-Diacetyl piperazine-2-carboxylic acid

Piperazine-2-carboxylic acid, 2HCl (200 mg, 0.985 mmol), triethylamine (0.137 mL, 0.985 mmol) and acetic anhydride (0.093 mL, 0.985 mmol) were mixed in methylene chloride (3 mL) at 25 °C with stirring. Added 1 mL of 4N HCl in dioxane, then concentrated in vacuo 3 times from methylene chloride/MeOH to give of white solids. MS found: (M + H)^+ = 215.24. The product was used without further purification.

Step 2: Example 539

(R)-2-Amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one (30 mg, 0.080 mmol), 1,4-diace tyl piperazine-2-carboxylic acid (21 mg, 0.096 mmol), HOBT (15 mg, 0.096 mmol), EDC (18 mg, 0.096 mmol) and triethylamine (0.022 mL, 0.160 mmol) were mixed in methylene chloride (3 mL) at 25 °C with stirring. The reaction was stirred for 20 hours then washed with sat'd
sodium bicarbonate. The methylene chloride layer was dried over sodium sulfate and concentrated in vacuo to give a white glass which was purified over silica gel (1:1 Hexanes/EtOAc to 100% EtOAc to 4:1 methylene chloride/MeOH) to obtain Example 539 (40 mg, 0.075 mmol, 94 % yield) as a white solid. MS found: (M + H)^+ = 535.45.

Example 540

2-(4-acetypiperazin-1-yl)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)acetamide

Step 1: Tert-butyl 4-((2-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2-oxoethyl)piperazine-1-carboxylate

[00343] Following the procedure of Example 535, Step 1, using 2-(4-((tert-butoxycarbonyl)piperazin-1-yl)acetic acid (47 mg, 0.192 mmol), tert-butyl 4-((2-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2-oxoethyl)piperazine-1-carboxylate (47 mg, 0.083 mmol, 52% yield) was obtained as a white glass. MS found: (M + H)^+ = 565.38.

Step 2: N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-(piperazin-1-yl)acetamide, HCl
Follow the procedure of Example 535, Step 2, using tert-butyl 4-(2-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2-oxoethyl)piperazine-1-carboxylate (70 mg, 0.124 mmol), N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-(piperazin-1-yl)acetamide, HCl (60 mg, 0.120 mmol, 97% yield) was obtained as a white solid. MS found: (M + H)^+ = 465.44.

Step 3: Example 540

N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-(piperazin-1-yl)acetamide, HCl (30 mg, 0.060 mmol), triethylamine (0.042 mL, 0.299 mmol), and acetic anhydride (0.028 ml, 0.299 mmol) were mixed in methylene chloride (3 mL) at 25 °C with stirring. The reaction was stirred for 3 hours, concentrated in vacuo, and the residue purified over silica gel (1:1 hexanes/EtOAc to 100% EtOAc to 4:1 methylene chloride/MeOH) to afford Example 540 (21 mg, 0.041 mmol, 69% yield) as a colorless oil. MS found: (M + H)^+ = 507.46.

Example 541

N5-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-N1,2,2-trimethylpentanediamide

5-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2,2-dimethyl-5-oxopentanoic acid (from Example 537, Step 1) (25 mg, 0.052 mmol), methylamine hydrochloride (4 mg, 0.062 mmol),
HOBT (10 mg, 0.062 mmol), EDC (12 mg, 0.062 mmol) and triethylamine (0.014 mL, 0.104 mmol) were mixed in methylene chloride (3 mL) at 25 °C with stirring. The reaction was stirred for 20 hours then washed with sat'd sodium bicarbonate. The methylene chloride layer was dried over sodium sulfate and concentrated in vacuo to give a white glass which was purified over silica gel (1:1 Hexanes/EtOAc to 100% EtOAc to 4:1 methylene chloride) to obtain Example 541 (25 mg, 0.051 mmol, 97 % yield) as a white glass. MS found: (M + H)^+ = 494.47.

**Example 542**

N5-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-N1,N1,2,2-tetramethylpentanediamide

5-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2,2-dimethyl-5-oxopentanoic acid (from Example 537, Step 1) (25 mg, 0.052 mmol), 2.0 M dimethylamine in THF (0.031 mL, 0.062 mmol), HOBT (10 mg, 0.062 mmol), EDC (12 mg, 0.062 mmol) and triethylamine (0.014 mL, 0.104 mmol) were mixed in methylene chloride (3 mL) at 25 °C with stirring. The reaction was stirred for 20 hours then washed with sat'd sodium bicarbonate. The methylene chloride layer was dried over sodium sulfate and concentrated in vacuo to give a white glass which was purified over silica gel (1:1 Hexanes/EtOAc to 100% EtOAc to 4:1 methylene chloride) to obtain Example 542 (10 mg, 0.020 mmol, 38%) as a white glass. MS found: (M + H)^+ = 508.49.

**Example 543**

N1-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-N5-methylglutaramide
Step 1: 5-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-5-oxopentanoic acid

Following the procedure of Example 537, Step 1, using dihydro-2H-pyran-2,6(3H)-dione (18 mg, 0.160 mmol). The solvent was evaporated then the residue purified over silica gel (1:1 hexanes/EtOAc to 100% EtOAc to 4:1 methylene chloride/MeOH) to obtain 5-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-5-oxopentanoic acid (56 mg, 0.124 mmol, 77% yield) as a white glass. MS found: (M + H)^+ = 453.35.

Step 2: Example 543

[00349] 5-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-5-oxopentanoic acid (25 mg, 0.055 mmol), methylamine hydrochloride (5 mg, 0.066 mmol), HOBT (10 mg, 0.066 mmol), EDC (13 mg, 0.066 mmol) and triethylamine (0.015 mL, 0.110 mmol) were mixed in methylene chloride (3 mL) at 25 °C with stirring. The reaction was stirred for 20 hours then washed with sat’d sodium bicarbonate. The methylene chloride layer was dried over sodium sulfate and concentrated in vacuo to give a white glass which was purified over silica gel (1:1 Hexanes/EtOAc to 100% EtOAc to 4:1 methylene chloride) to obtain Example 543 (23 mg, 0.049 mmol, 89% yield) as a white glass. MS found: (M + H)^+ = 466.41.

Example 544
N1-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-N5,N5-dimethylglutaramide

[00350] 5-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-5-oxopentanoic acid (from Example 543, Step 1) (25 mg, 0.055 mmol), 2.0 M dimethylamine in THF (0.033 mL, 0.066 mmol), HOBT (10 mg, 0.066 mmol), EDC (13 mg, 0.066 mmol) and triethylamine (0.015 mL, 0.110 mmol) were mixed in methylene chloride (3 mL) at 25 °C with stirring. The reaction was stirred for 20 hours then washed with sat’d sodium bicarbonate. The methylene chloride layer was dried over sodium sulfate and concentrated in vacuo to give a white glass which was purified over silica gel (1:1 Hexanes/EtOAc to 100% EtOAc to 4:1 methylene chloride) to obtain Example 544 (16 mg, 0.033 mmol, 60% yield) as a white glass. MS found: (M + H)^+ = 480.44.

Example 545

6-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-6-oxohexanoic acid

[00351] (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one (50 mg, 0.133 mmol), oxepane-2,7-dione (20 mg, 0.160 mmol), HOBT (24 mg, 0.160 mmol), EDC (31 mg, 0.160 mmol) and triethylamine (0.037 mL, 0.266 mmol) were mixed in methylene chloride (3 mL) at 25 °C with stirring. The reaction was stirred for 20 hours and then the solvent was evaporated. The resulting residue was purified over silica gel (100% EtOAc to 4:1 methylene chloride/MeOH) to obtain Example 545 (50 mg, 0.107 mmol, 80 % yield) as a white glass. MS found: (M + H)^+ = 467.38.
Example 546

1-acetyl-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)azetidine-3-carboxamid, TFA

Step 1: Tert-butyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)azetidine-1-carboxylate

Following the procedure of Example 535, Step 1, using 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid (32 mg, 0.160 mmol), tert-butyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)azetidine-1-carboxylate (50 mg, 0.096 mmol, 71 % yield) was obtained as a white glass. MS found: (M + H)$^+$ = 522.39.

Step 2: N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)azetidine-3-carboxamide, HCl

Following the procedure of Example 535, Step 2, using tert-butyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)azetidine-1-carboxylate (45 mg, 0.086 mmol), N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)azetidine-3-carboxamide (38 mg, 0.083 mmol, 95 % yield) was obtained as a white solid. MS found: (M + H)$^+$ = 539.25.
oxobutan-2-yl)azetidine-3-carboxamide, HCl (39 mg, 0.085 mmol, 99 % yield) was obtained as a white glass. MS found: (M + H)^+ = 422.32.

Step 3: Example 546

Following the procedure of Example 539, Step 1 using acetic anhydride (0.036 mL, 0.382 mmol), Example 546 (6.0 mg, 10.38 μmol, 13 % yield) was obtained as a white solid after purification by LCMS HPLC. MS found: (M + H)^+ = 464.29.

Example 547

3-(N-acetylsulfamoyl)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide

Step 1: N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-sulfamoylbenzamide

(R)-2-Amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one (200 mg, 0.533 mmol), 3-sulfamoylbenzoic acid (129 mg, 0.639 mmol), HOBT (98 mg, 0.639 mmol), EDC (123 mg, 0.639 mmol) and triethylamine (0.149 mL, 1.066 mmol) were mixed in methylene chloride (3 mL) at 25 °C with stirring. The reaction was stirred for 20 hours then washed with sat'd sodium bicarbonate. The methylene chloride layer was dried over sodium sulfate and concentrated in vacuo to give a white glass which was purified over silica gel (1:1
Hexanes/EtOAc to 100% EtOAc) to obtain N-((R)-1-((S)-4-(4-chlorophenyl)-4- hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3- sulfamoylbenzamide (197 mg, 0.377 mmol, 70% yield) as a white glass. MS found: (M + H)$^+$ = 522.32.

Step 2: Example 547

N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-sulfamoylbenzamide (40 mg, 0.077 mmol), acetic acid (5.70 µL, 0.100 mmol), DMAP (12 mg, 0.100 mmol), EDC (19 mg, 0.100 mmol) and triethylamine (0.021 mL, 0.153 mmol) were mixed and stirred in methylene chloride (3 mL). The reaction was stirred for 20 hours then washed with 1N HCl (2x) and brine. The organic layer was dried over sodium sulfate and concentrated in vacuo and purified over silica gel (1:1 hexanes/EtOAc to 100% EtOAc) to obtain Example 547 (27 mg, 0.048 mmol, 62% yield) as a white glass. MS found: (M + H)$^+$ = 564.36.

Example 548

N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3- methyl-1-oxobutan-2-yl)-3-(N-propionylsulfamoyl)benzamide

Following the procedure of Example 547, Step 2, using propionic acid (7.38 mg, 0.100 mmol), Example 548 (25 mg, 0.043 mmol, 56% yield) was obtained as a white glass. MS found: (M + H)$^+$ = 578.38.

Example 549
3-(N-benzyloxy)sulfamoyl)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide

[00358] Following the procedure of Example 547, Step 2, using benzoic acid (12 mg, 0.100 mmol), Example 549 (35 mg, 0.056 mmol, 73.0 % yield) was obtained as a white glass. MS found: \((M + H)^+ = 626.40\).

Example 550

2-((S)-1-acetylpyrrolidin-3-yl)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)acetamide

Step 1: (S)-tert-butyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2-oxoethyl)pyrrolidine-1-carboxylate

[00359] Following the procedure of Example 535, Step 1, using (S)-2-((tert-butoxycarbonyl)pyrrolidin-3-yl)acetic acid (37 mg, 0.160 mmol), (S)-tert-butyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2-oxoethyl)pyrrolidine-1-carboxylate (60 mg, 0.109 mmol, 82 % yield) was obtained as a white glass. MS found: \((M + H)^+ = 550.48\).
Step 2: N-\((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)2-((S)-pyrrolidin-3-yl)acetamide, HCl

Following the procedure of Example 535, Step 2, using (S)-tert-butyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2-oxoethyl)pyrrolidine-1-carboxylate (55 mg, 0.100 mmol), N-\((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)2-((S)-pyrrolidin-3-yl)acetamide, HCl (45 mg, 0.093 mmol, 93% yield) was obtained as a white solid. MS found: \((M + H)^+ = 450.35\).

Step 3: Example 550

Following the procedure of Example 537, Step 1 using acetic anhydride (0.039 ml, 0.411 mmol), Example 550 (40 mg, 0.081 mmol, 99% yield) was obtained as a white glass. MS found: \((M + H)^+ = 492.39\).

Example 551

2-((R)-1-acetylpyrrolidin-3-yl)-N-\((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)acetamide

Step 1: (R)-tert-butyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2-oxoethyl)pyrrolidine-1-carboxylate
[00362] Following the procedure of Example 535, Step 1, using (R)-2-((1-tert-butoxycarbonyl)pyrrolidin-3-yl)acetic acid (37 mg, 0.160 mmol), (R)-tert-butyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2-oxoethyl)pyrrolidine-1-carboxylate (60 mg, 0.109 mmol, 82 % yield) was obtained as a white glass. MS found: (M + H)$^+$ = 550.42.

Step 2: N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-((R)-pyrrolidin-3-yl)acetamide, HCl

[00363] Following the procedure of Example 535, Step 2, using (R)-tert-butyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2-oxoethyl)pyrrolidine-1-carboxylate (55 mg, 0.100 mmol), N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2-((R)-pyrrolidin-3-yl)acetamide, HCl (45 mg, 0.093 mmol, 93 % yield) was obtained as a white solid. MS found: (M + H)$^+$ = 450.37.

Step 3: Example 551

[00364] Following the procedure of Example 537, Step 1 using acetic anhydride (0.039 ml, 0.411 mmol), Example 551 (40 mg, 0.081 mmol, 99 % yield) was obtained as a white glass. MS found: (M + H)$^+$ = 492.39.

Example 552
2-((S)-1-acetylpseudin-2-yl)-N-((R)-4-(4-chlorophenyl)-4-hydroxy-3,3-
dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)acetamide

5 Step 1: (S)-tert-butyl 2-(2-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-
dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylamino)-2-oxoethyl)pyrroloidine-
1-carboxylate

[00365] Following the procedure of Example 535, Step 1, using (S)-2-(1-(tert-
butoxycarbonyl)pyrroloidin-2-yl)acetic acid (37 mg, 0.160 mmol), (S)-tert-butyl 2-(2-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-
oxobutan-2-ylamino)-2-oxoethyl)pyrroloidine-1-carboxylate (60 mg, 0.109 mmol, 82
% yield) was obtained as a white glass. MS found: (M + H)⁺ = 550.42.

15 Step 2: N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-
3-methyl-1-oxobutan-2-yl)-2-((S)-pyrroloidin-2-yl)acetamide, HCl

[00366] Following the procedure of Example 535, Step 2, using (S)-tert-butyl 2-(2-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-
oxobutan-2-ylamino)-2-oxoethyl)pyrroloidine-1-carboxylate (55 mg, 0.100 mmol), N-
(1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-
-222-
oxobutan-2-yl)-2-((S)-pyrrolidin-2-yl)acetamide, HCl (48 mg, 0.099 mmol, 99 % yield) was obtained as a white glass. MS found: (M + H)^+ = 450.39.

Step 3: Example 552

Following the procedure of Example 537, Step 1 using acetic anhydride (0.024 ml, 0.257 mmol), Example 552 (20 mg, 0.041 mmol, 79 % yield) was obtained as a white glass. MS found: (M + H)^+ = 492.40.

Example 553

N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2'-ureidobiphenyl-3-carboxamide

(R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl (30 mg, 0.080 mmol), 2'-ureidobiphenyl-3-carboxylic acid (25 mg, 0.096 mmol), HOBT (15 mg, 0.096 mmol), EDC (18 mg, 0.096 mmol) and triethylamine (0.022 mL, 0.160 mmol) were mixed in methylene chloride (3 mL) at 25 °C with stirring. The reaction was stirred for 20 hours then washed with sat'd sodium bicarbonate. The methylene chloride layer was washed over sodium sulfate and concentrated in vacuo to give a white glass which was purified over silica gel (1:1 Hexanes/EtOAc to 100% EtOAc to 4:1 methylene chloride/MeOH) to obtain Example 553 (40 mg, 0.069 mmol, 87 % yield) as a tan solid. MS found: (M + H)^+ = 577.39.

Example 554

3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)-5-(pyridin-2-yl)benzoic acid
Step 1: Methyl 3-bromo-5-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)benzoate

[00369] (R)-2-Amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl (100 mg, 0.266 mmol), 3-bromo-5-(methoxycarbonyl)benzoic acid (83 mg, 0.320 mmol), HOBT (49 mg, 0.320 mmol), EDC (61 mg, 0.320 mmol) and triethylamine (0.074 mL, 0.533 mmol) were mixed in methylene chloride (5 mL) at 25 °C with stirring. The reaction was stirred for 20 hours then washed with sat'd sodium bicarbonate. The methylene chloride layer was dried over sodium sulfate and concentrated in vacuo to give a white glass which was purified over silica gel (3:1 to 1:1 Hexanes/ EtOAc to 100% EtOAc) to obtain methyl 3-bromo-5-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)benzoate (120 mg, 0.207 mmol, 78 % yield) as a white glass. MS found: (M + H)^+ = 579.10/581.13.

Step 2: Methyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)-5-(pyridin-2-yl)benzoate
[00370] Methyl 3-bromo-5-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)benzoate (40 mg, 0.069 mmol) was dissolved in toluene (3 mL) at 25 °C then 2-(tributylstannyl)pyridine (76 mg, 0.207 mmol) was added. The reaction was degassed then placed under nitrogen. Tetrakis(triphenylphosphine)palladium(0) (4 mg, 3.45 μmol) was added and the reaction heated at reflux for 2 hours. The reaction was concentrated in vacuo to give a dark residue which was then dissolved in MeOH, filtered to remove insoluble material, then purified by LCMS HPLC. The obtained colorless oil was dissolved in EtOAc, dried over sodium sulfate and concentrated in vacuo to give methyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)-5-(pyridin-2-yl)benzoate (30 mg, 0.052 mmol, 75% yield) as a white glass. MS found: \((M + H)^+ = 578.34\).

**Step 3: Example 554**

[00371] Methyl 3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)-5-(pyridin-2-yl)benzoate (25 mg, 0.043 mmol) was dissolved in MeOH (2 mL) at 25 °C then 1N NaOH (0.086 mL, 0.086 mmol) added with stirring. The reaction was stirred for 2 hours, diluted with water and concentrated to remove MeOH. The aqueous was acidified to pH = 3 with 1N HCl and the formed solids were extracted into methylene chloride. The organic layers were combined, dried (sodium sulfate) and concentrated in vacuo to give Example 554 (12 mg, 0.021 mmol, 49% yield) as a white solid. MS found: \((M + H)^+ = 564.33\).

**Example 555**

- 225 -
tert-butyl 2-(3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)ureido)-2-methylpropanoate

Step 1: tert-Butyl 2-methyl-2-(phenoxy carbonylamino)propanoate

[00372] tert-Butyl 2-amino-2-methylpropanoate, HCl (66 mg, 0.337 mmol) and triethylamine (0.047 mL, 0.337 mmol) were mixed and stirred in THF (10 mL) at 25 °C then cooled to 0 °C and added a THF solution of phenyl carbonochloridate (53 mg, 0.337 mmol). The reaction was stirred for 20 hours, diluted with EtOAc, and washed with 1N HCl and brine. The organic layer was dried (sodium sulfate) and concentrated in vacuo to give tert-butyl 2-methyl-2-(phenoxy carbonylamino)propanoate (90 mg, 0.322 mmol, 96% yield) of a white glass as product. MS found: (M + H)^+ = 280.30.

Step 2: Example 555

[00373] (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl (40 mg, 0.107 mmol), tert-butyl 2-methyl-2-(phenoxy carbonylamino)propanoate (30 mg, 0.107 mmol) and triethylamine (0.030 mL, 0.213 mmol) were mixed in acetonitrile (3 mL) at 25 °C then heated at 150 °C for 60 minutes in a microwave reactor. The reaction was concentrated in vacuo then purified over silica gel (3:1 to 1:1 hexanes/EtOAc to 100% EtOAc) to obtain Example 555 (40 mg, 0.076 mmol, 72% yield) as a white glass. MS found: (M + H)^+ = 524.35.

Example 556
3'-(R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)biphenyl-4-carboxylic acid

5 Step 1: 3-Bromo-N-(R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide

[00374] (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl (100 mg, 0.266 mmol), 3-bromobenzoic acid (64 mg, 0.320 mmol), HOBT (49 mg, 0.320 mmol), EDC (61 mg, 0.320 mmol) and triethylamine (0.074 mL, 0.533 mmol) were mixed in methylene chloride (5 mL) at 25 °C with stirring. The reaction was stirred for 20 hours then washed with sat'd sodium bicarbonate. The methylene chloride layer was dried over sodium sulfate and concentrated in vacuo to give a white glass which was purified over silica gel (3:1 to 1:1 Hexanes/EtOAc to 100% EtOAc) to obtain 3-bromo-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide (100 mg, 0.192 mmol, 72 % yield) as a white solid. MS found: (M + H)^+ = 521.1/523.1.

20 Step 2: Methyl 3'-(R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)biphenyl-4-carboxylate
[00375] 3-Bromo-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-
dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide (50 mg, 0.096 mmol), 4-(methoxycarbonyl) phenylboronic acid (17 mg, 0.096 mmol), 1.5M cesium carbonate (0.192 ml, 0.287 mmol) and palladium(II) acetate (1.08 mg, 4.79 μmol) were dissolved in DMF (3 mL) in a microwave tube at 25 °C then heated at 60 °C for 30 minutes. The reaction was diluted with EtOAc then washed with water (4x). The organic layer was dried (sodium sulfate) and concentrated in vacuo to give methyl 3'-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)biphenyl-4-carboxylate (44 mg, 0.076 mmol, 80% yield) as a white solid. MS found: (M + H)^+ = 577.32.

Step 3: Example 556

[00376] Methyl 3'-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-
dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)biphenyl-4-carboxylate (40 mg, 0.069 mmol) was dissolved in MeOH (3 ml) and added 1N NaOH (0.14 mL, 0.14 mmol) at 25 °C and stirred over the weekend. The MeOH was removed in vacuo and the aqueous was acidified to pH = 3 with 1N HCl. The formed solids were extracted 2 times with methylene chloride. The organic layers were combined, dried (sodium sulfate) and concentrated in vacuo to give Example 556 (30 mg, 0.053 mmol, 77 % yield) of white solids as product. MS found: (M + H)^+ = 563.32.

Example 557

3-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-1-methyl-1-phenylurea
(R)-2-Amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl (25 mg, 0.067 mmol) and methyl(phenyl)carbamic chloride (11 mg, 0.067 mmol) were stirred in acetonitrile (2 ml) at 25 °C, then heated for 20 hours at 60 °C. The reaction was cooled to rt, concentrated and purified over silica gel (3:1 hexanes / EtOAc to 1:1 hexanes / EtOAc to 100% EtOAc) to obtain Example 557 (30 mg, 0.064 mmol, 95% yield) as a white solid. MS found: (M + H)^+ = 472.28.

Example 558

N1-(R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-N3-(methylsulfonyl)isophthalamide

Step 1: Methyl 3-(methylsulfonylcarbamoyl)benzoate

[00378] 3-(Methoxycarbonyl)benzoic acid (500 mg, 2.78 mmol), methyl sulfonamide (264 mg, 2.78 mmol), HATU (1.06 g, 2.78 mmol), and diisopropylethylamine (1.45 mL, 8.33 mmol) were mixed in methylene chloride (20 mL) with stirring. The reaction was stirred for 20 hours, added sat’d ammonium chloride, and extracted with methylene chloride. The organic extracts were combined, dried over sodium sulfate and concentrated to give an amber oil which was purified over silica gel (1:1 hexanes/ethyl acetate to 100% ethyl acetate to 4:1
methylene chloride/methanol) to obtain methyl 3-(methylsulfonylcarbamoyl)benzoate (700 mg, 2.72 mmol, 97% yield). MS found: (M + H)^+ = 258.07.

**Step 2: 3-(Methylsulfonylcarbamoyl)benzoic acid**

5

[00379] Methyl 3-(methylsulfonylcarbamoyl)benzoate (700 mg, 2.72 mmol) was dissolved in methanol at 25 °C with stirring then 1.0 N NaOH (5.56 mL, 5.56 mmol) was added. The reaction mixture was stirred for 20 hours, diluted with water, and the methanol removed in vacuo. The aqueous was washed with diethyl ether (2x) then acidified to pH = 3 with 1N HCl. The resulting solution was extracted with ethyl acetate to give 3-(methylsulfonylcarbamoyl)benzoic acid (285 mg, 1.12 mmol, 42% yield). MS found: (M + H)^+ = 244.00.

**Step 3: N1-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-N3-(methylsulfonyl)isophthalamide**

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[00380] (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl (20 mg, 0.053 mmol), 3-(methylsulfonylcarbamoyl)benzoic acid (17 mg, 0.069 mmol), DMAP (8 mg, 0.069 mmol), EDC (13 mg, 0.069 mmol) and triethylamine (8 μL, 0.053 mmol) were mixed in methylene chloride (3 mL) with stirring. The reaction was stirred for 20 hours, diluted with methylene chloride (10 mL) then washed with 1N HCl (2 x 5 mL). The organic layer was dried over sodium sulfate then concentrated in vacuo to give a solid which was purified over silica gel (100% ethylacetate to 4:1 methylene chloride/methanol) to obtain Example 558 (15 mg, 2.66 mmol, 50% yield) as a white solids. MS found: (M + H)^+ = 564.26.

**Example 559**

N-(1-(4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide, TFA
1-Bromo-4-chlorobenzene (17 mg, 0.091 mmol) and N-(1-(3,3-dimethyl-4-oxopiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide (0.11 mL, 0.18 mmol) were dissolved in THF (5 mL) at 25 °C under nitrogen then the reaction was cooled to -70 °C with stirring, then 1.6 M n-butyllithium in hexanes was added dropwise via an addition funnel. The reaction was stirred at -70 °C for 2 hours then quenched with sat’d ammonium chloride (5 mL). The reaction was extracted 3 times with ethyl acetate and the combined organic extracts were dried over sodium sulfate then concentrated in vacuo to give a colorless oil which was purified by LCMS HPLC to give Example 559 (7 mg, 1.58 mmol, 17% yield). MS found: (M + H)^+ = 443.20.

Example 560
(S)-4-(4-chlorophenyl)-3,3-dimethyl-1-((R)-3-methyl-2-(3-methylureido)butanoyl)piperidin-4-yl acetate, TFA

Step 1: 1-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-methylurea

(R)-2-Amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl (20 mg, 0.053 mmol) and triethylamine (7.4 μL, 0.053 mmol) were mixed in THF (2 mL) at 25 °C with stirring. Methyl isocyanate (6
μg, 0.11 mmol) was added. After 1 hour, additional methyl isocyanate (30 μg, 0.55 mmol) was added and the reaction heated at 100 °C for 30 minutes in a microwave reactor. The reaction was cooled, diluted with methylene chloride and washed with water (5 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo to give an oil which was purified over silica gel (100% ethyl acetate to 4:1 methylene chloride/methanol) to give 1-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-methylurea (18 mg, 45 mmol, 86% yield) as an off-white solid. MS found: (M + H)^+ = 396.19.

Step 2: Example 560

1-(((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-methylurea (18 mg, 45 mmol) and triethylamine (6 μL) were mixed in THF (2 mL) at 25 °C with stirring then acetyl chloride (3 μL, 45 mmol) was added. Stirred for 20 hours then added additional acetyl chloride (15 μL, 225 mmol). Stirred stirring was continued for 6 hours and then the reaction mixture was filtered, diluted with water (3 mL) and extracted into methylene chloride. The organic extracts were combined, dried over sodium sulfate and concentrated in vacuo to give a colorless oil which was purified by HPLC to give Example 560 (3 mg, 5.4 mmol, 12% yield) as a white solid. MS found: (M + H)^+ = 438.37.

Example 561

(R)-1-(4-(4-chlorophenyl)piperidin-1-yl)-2-(7-chloroquinazolin-4-ylamino)-3-methylbutan-1-one

[R0384] (R)-2-amino-1-(4-(4-chlorophenyl)piperidin-1-yl)-3-methylbutan-1-one, HCl (25 mg, 0.085 mmol), 4,7-dichloroquinazoline (20 mg, 0.10 mmol) and triethylamine (47 μL) were mixed in isopropanol (2 mL) at 25 °C then heated at 100 °C for 30 minutes in a microwave reactor. The reaction was concentrated in vacuo
and purified over silica gel (9:1 to 1:1 hexanes/ethyl acetate) to obtain Example 561 (31 mg, 68 mmol, 80% yield) as a white solid. MS found: \((M + H)^+ = 457.03\).

**EXAMPLES 562 and 563**

(R)-1-((S)-4-(4-Chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-2-(2-chloropyrimidin-4-ylamino)-3-methylbutan-1-one and (R)-1-((S)-4-(4-Chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-2-(4-chloropyrimidin-2-ylamino)-3-methylbutan-1-one

\[\text{Structure Image}\]

**[00385]** A reaction vessel was charged with 2,4-dichloropyrimidine (21.5 mg, 0.144 mmole, 1 eq), (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one (54.0 mg, 0.144 mmol, 1 eq), triethylamine (0.024 mL, 0.144 mmol, 1 eq) and DMF (2 mL) The reaction mixture was stirred overnight at rt. At the conclusion of this period, the resulting solution was evaporated, diluted with MeOH and purified by preparative LC-MS. The resulting fractions were lyophilized to provide 35.5 mg of Example 562 and 8.4 mg of Example 563. Example 562, MS found: \((M + H)^+ = 451.37\). Example 563, MS found: \((M + H)^+ = 451.27\).

**EXAMPLE 564**

\[N-(1-(4-(2,4-dichlorophenyl)-4-hydroxypiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide\]
[00386] A reaction vessel was charged with N-(3-methyl-1-oxo-1-(4-oxopiperidin-1-yl)butan-2-yl)benzamide (68.4 mg, 0.23 mmol, 1.0 eq), 1-bromo-2,4-dichlorobenzene (112.4 mg, 0.50 mmol, 2.2 eq), and THF (20 mL). The stirred reaction mixture was cooled to -78 °C. 1.6 M n-BuLi in hexanes (0.31 mL, 0.50 mmol, 1.0 eq) was added dropwise thereto via syringe (Caution: exotherm). The mixture was allowed to warm to rt in 2 hours. The mixture was quenched with water. Ethyl acetate was added thereto and the layers were separated. The organic layer was consecutively washed with 1N NaOH (3x) and 1N HCl (1x). The organic layer was dried (MgSO₄) and the solvent removed in vacuo. The residue was dissolved in MeOH and purified by preparative LC-MS. The collected fractions were evaporated and the residue dissolved in methylene chloride, dried (MgSO₄) and the solvent removed in vacuo to provide 30 mg of Example 564 as a white solid. MS found: (M + H)^+ = 449.03.

Example 565

(1R,3R)-N-((R)-1-(8-(4-chlorophenyl)-8-hydroxy-5-azaspiro[2.5]octan-5-yl)-3-methyl-1-oxobutan-2-yl)-3-hydroxycyclopentanecarboxamide

Step 1: (2-Chloroethyl)dimethylsulfonium iodide

[00387] A mixture of (2-chloroethyl)(methyl)sulfane (24.73 g, 224 mmol) and iodomethane (100 mL, 1600 mmol) was stirred for two days at room temperature,
during which a solid precipitated. The reaction was diluted with 300 mL diethyl ether, and the suspension was stirred for 2 h. The solids were collected by filtration, rinsed with diethyl ether, and dried under vacuum to yield 27.2 g of a dark amber, sticky solid. This was stirred in 100 mL of 9:1 diethyl ether/methanol. The solids were collected by filtration, rinsed with diethyl ether, and dried under vacuum to yield the title compound (23.7 g, 94 mmol, 42.0 % yield) as a pale yellow powder. Used as-is in the next step.

**Step 2: tert-Butyl 8-oxo-5-azaspiro[2.5]octane-5-carboxylate**

![Chemical Structure](attachment:image)

[00388] A solution of potassium tert-butoxide (3.26 g, 27.6 mmol) in tert-butanol (40 mL) was treated with tert-butyl 4-oxopiperidine-1-carboxylate (5 g, 25.09 mmol), causing the reaction to turn bright orange. The mixture was stirred for 1 h, then treated with (2-chloroethyl)dimethylsulfonium iodide (5.70 g, 22.59 mmol), added in three portions at 10 minute intervals. This addition caused the color of the reaction to gradually fade to pale yellow. The mixture was stirred for 2 hours, then diluted with tert-butanol (10 mL), treated with potassium tert-butoxide (2.96 g, 25.09 mmol), and stirred overnight at room temperature. The reaction was poured into water (100 mL) and extracted 3 x with 100 mL ethyl acetate. The combined organic phases were washed with water and brine, then dried over sodium sulfate and concentrated in vacuo. The residue was purified over a 5 x 15 cm silica gel column, eluting with ethyl acetate/hexanes (10% - 15% - 20% - 25% EtOAc, 1 L at each concentration), to yield the title compound (1.15 g, 5.10 mmol, 20.34 % yield) as a colorless oil.

**Step 3: tert-Butyl 8-(4-chlorophenyl)-8-hydroxy-5-azaspiro[2.5]octane-5-carboxylate**

![Chemical Structure](attachment:image)
[00389] In a flame-dried 100 mL three necked flask, a solution of 1-bromo-4-chlorobenzene (3.51 g, 18.36 mmol) in THF (20 mL) was cooled to -78 °C and treated with the dropwise addition of 1.6 M BuLi in hexanes (12.00 mL, 19.19 mmol) at a rate which did not allow the temperature to exceed -60 °C. The mixture was stirred at -78 °C for 1 h, during which time a white precipitate was observed. The mixture was treated with the dropwise addition of a solution of tert-butyl 8-oxo-5-azaspiro[2.5]octane-5-carboxylate (1.88g, 8.35 mmol) in THF (5 mL), at a rate which did not allow the temperature to exceed -60 °C. The mixture was stirred for 3 h, then allowed to warm to -20 °C and quenched with saturated ammonium chloride solution. The mixture was extracted 3 x with ethyl acetate, the combined organic phases were washed with water followed by brine, then dried over sodium sulfate and concentrated in-vacuo. The residue was purified over a 5 x 15 cm silica gel column, eluting with ethyl acetate/hexanes (5% - 10% - 15% - 20% ethyl acetate, to yield the title compound (1.81g, 5.36 mmol, 64.2 % yield) as a colorless powder. MS (ESI+) = 264.27, (M-tBuO)+, 220 (M-H2O-Boc)+.

Step 4: 8-(4-Chlorophenyl)-5-azaspiro[2.5]octan-8-ol

[00390] A solution of tert-butyl 8-(4-chlorophenyl)-8-hydroxy-5-azaspiro[2.5]octane-5-carboxylate (1.81 g, 5.36 mmol) in dioxane (2 mL) was treated with 4.0 M HCl in dioxane (7 mL, 28.0 mmol), and the reaction was stirred for 30 minutes at room temperature. The mixture was concentrated in-vacuo then concentrated 2 x from methylene chloride to remove residual HCl. The residue was dissolved in water and washed 2 x with diethyl ether. The aqueous phase was treated with sodium bicarbonate until the mixture was basic, then washed 2 x with 10 mL diethyl ether. The aqueous phase was treated with solid sodium hydroxide until the pH was > 13, and the mixture was extracted 5 x with ethyl acetate. The combined ethyl acetate extracts were dried over sodium sulfate and concentrated in vacuo to

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yield (±)-8-(4-chlorophenyl)-5-azaspiro[2.5]octan-8-ol as a colorless powder (1.1 g, 87% yield). MS (ESI+) = 238.1, (M+H)^+. The isomers were separated via chiral super critical fluid chromatography to yield 463 mg of isomer A and 522 mg of isomer B.

5

Step 5: (R)-3-methyl-2-((2-(trimethylsilyl)ethoxy)carbonylamino) butanoic acid

[00391] A mixture of (R)-2-amino-3-methylbutanoic acid (2.01 g, 17.16 mmol) and 2,5-dioxopyrrolidin-1-yl 2-(trimethylsilyl)ethyl carbonate (4.89 g, 18.87 mmol) in 1:1 dioxane/water (40 mL) was treated with triethylamine (3.59 mL, 25.7 mmol), and the mixture was stirred for two days at room temperature. The mixture was acidified with saturated sodium hydrogen sulfate and extracted 3 x with ethyl acetate. The combined organic phases were washed with saturated sodium hydrogen sulfate, water, and brine, then dried over sodium sulfate and concentrated in-vacuo to yield the title compound (4.17 g, 15.96 mmol, 93 % yield) as an amber oil.

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Step 6: (2R)-1-(8-(4-chlorophenyl)-8-hydroxy-5-azaspiro[2.5]octan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamate

[00392] A solution of 8-(4-chlorophenyl)-5-azaspiro[2.5]octan-8-ol, isomer A (463 mg, 1.948 mmol), (R)-3-methyl-2-((2-(trimethylsilyl)ethoxy)carbonylamino)butanoic acid (560 mg, 2.142 mmol), EDC (821 mg, 4.28 mmol), and HOBT (656 mg, 4.28 mmol) in methylene chloride (10 mL) was stirred at room temperature for 30 minutes, the mixture was treated with triethylamine (1.086 mL, 7.79 mmol), and the reaction was stirred for an additional 30 minutes at room temperature. The reaction was concentrated in vacuo, and the residue was taken up in ethyl acetate. The organic phase was washed 3 x with 1 N NaOH, 3 x with 1 N HCl, and once with brine, then dried over sodium sulfate and concentrated in-vacuo. The residue was purified over
silica gel eluting with ethyl acetate/hexanes (25 - 50% EtOAc) to yield the title compound (754 mg, 1.567 mmol, 80 % yield) as a colorless, viscous oil.

**Step 7:** (2R)-2-amino-1-(8-(4-chlorophenyl)-8-hydroxy-5-azaspiro[2.5]octan-5-y1)-3-methylbutan-1-one

![Chemical Structure](image)

A solution of 2-(trimethylsilyl)ethyl (2R)-1-(8-(4-chlorophenyl)-8-hydroxy-5-azaspiro[2.5]octan-5-yl)-3-methyl-1-oxobutan-2-yl carbamate (754 mg, 1.567 mmol) in THF (10 mL) was treated with TBAF (1.0 M in THF) (6.27 mL, 6.27 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated in-vacuo, and the residue was partitioned between EtOAc and saturated sodium bicarbonate. The layers were separated, and the organic phase was washed 2 x with saturate sodium bicarbonate, once with water, and once with brine. The combined aqueous phases were extracted once with ethyl acetate, and the combined organic phases were washed with water and brine, then dried over sodium sulfate and concentrated in-vacuo. The residue was taken up in acetonitrile (100 mL), and washed 3 x with 20 mL of hexanes. The acetonitrile phase was concentrated in vacuo to yield the title compound (420 mg, 1.247 mmol, 80 % yield) as a colorless glass. MS (ESI+) = 337.4, (M+H)^+.

**Step 8: Example 565**

A mixture of (R)-2-amino-1-(8-(4-chlorophenyl)-8-hydroxy-5-azaspiro[2.5]octan-5-yl)-3-methylbutan-1-one, HCl (41.7 mg, 0.112 mmol), (1R,3R)-3-hydroxycyclopentanecarboxylic acid (16 mg, 0.123 mmol), HOBT (37.7 mg, 0.246 mmol), and triethylamine (78 μL, 0.559 mmol) in methylene chloride was treated with EDC (47.1 mg, 0.246 mmol), and the reaction was allowed to stir overnight at room temperature. The mixture was concentrated in vacuo, and the residue was taken
up in ethyl acetate. The organic phase was washed 3 X with saturated sodium carbonate, 3 X with 1M HCl, and once with brine, dried over sodium sulfate, and concentrated in-vacuo. The residue was purified over a 12 g silica gel column via ISCO, eluting at 30 mL/min with a 0-10% MeOH/EtOAc gradient over 35 minutes to yield Example 565 (33mg, 0.073 mmol, 65.8 % yield) as a colorless glass. MS (ESI+) = 431.13, (M+H-H2O)+.

The following examples in Table 17 were prepared using the procedures described in Example 565, substituting the appropriate carboxylic acid for (1R,3R)-3-hydroxycyclopentanecarboxylic acid in Step 8.

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<th>Example</th>
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<th>Structure</th>
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<td>Carboxylic Acid</td>
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**Example 571**

3-((2R)-1-(8-(4-chlorophenyl)-8-hydroxy-5-azaspiro[2.5]octan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamoyl)benzoic acid

![Structure](image3.png)

**[00396]** A mixture of (2R)-2-amino-1-(8-(4-chlorophenyl)-8-hydroxy-5-azaspiro[2.5]octan-5-yl)-3-methylbutan-1-one (21mg, 0.062 mmol), 3-(methoxycarbonyl)benzoic acid (12.35 mg, 0.069 mmol), HOBT (21.00 mg, 0.137 mmol), and triethylamine (35 µl, 0.251 mmol) in CH2Cl2 (2 mL) was treated with EDC (26.3 mg, 0.137 mmol), and the mixture was stirred for three days at room temperature. The mixture was concentrated in-vacuo, and the residue was taken up in ethyl acetate. The organic phase was washed 3X with saturated sodium carbonate, 3X with 1M HCl, and once with saturated sodium chloride, dried over sodium sulfate, and concentrated in-vacuo. The residue was taken up in THF (1 mL), treated with 0.5 M LiOH (aq) (187 µl, 0.094 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with 1:1 acetonitrile/water, and injected directly onto the prep HPLC for purification to yield Example 571 (9.2mg, 0.019 mmol, 30.4 % yield). MS (ESI+) = 485.29, (M+H)^+.
Example 572

\[(1R,3R)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-hydroxycyclopentanecarboxamide\]

Step 1. tert-Butyl (R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

[00397] A solution of (S)-4-(4-chlorophenyl)-3,3-dimethylpiperidin-4-ol (6.3 g, 26.3 mmol), Boc-D-Val-OH (6.28 g, 28.9 mmol), EDC (11.08 g, 57.8 mmol), and HOBT (8.85 g, 57.8 mmol) in methylene chloride (250 mL) was stirred at room temperature for 30 minutes, treated with triethylamine (14.65 mL, 105 mmol), and stirred at room temperature for 3 hours. The solution was washed 3 X with saturated sodium carbonate, 3 X with 1M HCl, once with water, and once with brine, dried over sodium sulfate, and concentrated in-vacuo. The residue was purified over a 330 g silica gel column via ISCO, eluting at 100 mL/min with a 0-100% ethyl acetate/hexanes gradient over 40 minutes to yield the title compound (11.0 g, 25.06 mmol, 95% yield) as a colorless glass. MS (ESI+) = 439.18, (M+H)^+.

Step 2. (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl

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A solution of tert-butyl (R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (11 g, 25.06 mmol) in 4 M HCl in dioxane (100 mL, 400 mmol) was stirred at room temperature for 2 h. The mixture was concentrated in vacuo, then concentrated 3 x from methanol and 3 x from methylene chloride to remove residual HCl, to yield the title compound (9.3 g, 24.78 mmol, 99% yield) as a colorless powder. MS (ESI+) = 339, (M+H)^+.

Step 3. Example 572

A mixture of (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl (5.77 g, 15.37 mmol), (1R,3R)-3-hydroxycyclopentanecarboxylic acid (2 g, 15.37 mmol), HOBT (5.18 g, 33.8 mmol), and triethylamine (10.71 mL, 77 mmol) in methylene chloride (100 mL) was treated with EDC (6.48 g, 33.8 mmol), and the reaction was allowed to stir overnight at room temperature. The mixture was concentrated in vacuo, and the residue was taken up in ethyl acetate. The organic phase was washed 3 X with saturated sodium carbonate, 3 X with 1M HCl, and once with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified over a 330 g silica gel column via ISCO, eluting at 100 mL/min with ethyl acetate for 10 minutes followed by a 0-10% methanol/ethyl acetate gradient over 35 minutes to yield 3.2 g of (1R,3R)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-hydroxycyclopentanecarboxamide as a colorless solid. Another 1.7 g of desired product which contained a small amount of impurity was also isolated. This material was subjected to the chromatography conditions described above, substituting an 80 g silica column and a 60 mL/minute flow rate, to yield an additional 800 mg of (1R,3R)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-hydroxycyclopentanecarboxamide as a colorless solid.
oxobut-2-yl)-3-hydroxycyclopentanecarboxamide as a colorless solid, and 700 mg of material which was 88.6% pure by HPLC. The three lots of material were combined and purified by chiral super-critical fluid chromatography to yield Example 572 (3.7 g, 53% yield). An analytical sample was crystallized by dissolving 400 mg in 2 mL of acetone, adding water until the solution became hazy (3 mL), heating the mixture until a clear solution was observed, and allowing the mixture to stand uncovered at room temperature overnight. The resulting solids were collected by filtration and dried under vacuum at 60°C to yield 265 mg of crystalline powder.

Examples 572A and 572B

(1R,3S,4S)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobut-2-yl)-3-hydroxy-4-methylcyclopentanecarboxamide, and

(1S,3R,4R)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobut-2-yl)-3-hydroxy-4-methylcyclopentanecarboxamide

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with 25 mL saturated sodium carbonate, once with water, and once with brine, then
dried over sodium sulfate and concentrated in-vacuo. The residue was purified over a
8 x 10 cm silica gel column, eluting with ethyl acetate/hexanes (5% - 10% - 15% -
20% ethyl acetate), to yield the title compound (4.54 g, 22.45 mmol, 48.4 % yield) as
a colorless oil.

Step 2. Trans-benzyl 6-oxabicyclo[3.1.0]hexane-3-carboxylate and cis-benzyl 6-
oxabicyclo[3.1.0]hexane-3-carboxylate

![Structural formulas](image)

[00401] The titled compounds were prepared via the method of Lizotte, et. al.; J.
Org. Chem.; 1983; 48(20); 3594-3597. A solution of benzyl cyclopent-3-encarboxylate
(4.54 g, 22.45 mmol) in methylene chloride (50 mL) was cooled to 0 °C and treated
with the dropwise addition of a solution of m-CPBA (7.04 g, 31.4 mmol) in
methylene chloride (50.0 mL) over 40 minutes. The resulting suspension was
allowed to come to room temperature and stirred overnight. The mixture was treated
with 20 mL of saturated sodium sulfite and stirred for 20 minutes. The solids were
removed by filtration, rinsed with methylene chloride, and the layers of the filtrate
were separated. The organic phase was washed with saturated sodium sulfite, 3 x
with saturated sodium bicarbonate, once with water, and once with brine, then dried
over sodium sulfate and concentrated in-vacuo to 3.6 g of an amber oil. The residue
was purified over a 5 x 15 cm silica gel column, eluting with ethyl acetate/hexanes
(15% EtOAc), to yield trans-benzyl 6-oxabicyclo[3.1.0]hexane-3-carboxylate (3.4 g,
64% yield) and cis-benzyl 6-oxabicyclo[3.1.0]hexane-3-carboxylate (1.2 g, 24.5%
yield) as colorless oils.

Step 3. Racemic mixture of (1R,3R,4R)-benzyl 3-hydroxy-4-
methylecypentanecarboxylate and (1S,3S,4S)-benzyl 3-hydroxy-4-
methylecypentanecarboxylate
A 50 mL three neck round bottom flask equipped with a magnetic stirrer and two addition funnels, which had been flame dried under argon, charged with COPPER(I) CYANIDE (226 mg, 2.52 mmol), and evacuated under high vacuum overnight, was charged with THF (5 mL), and the suspension was cooled to -78 °C. The mixture was treated with the dropwise addition of methyllithium (1.6 M in diethylether) (3.15 mL, 5.04 mmol). When the addition was complete, the cooling bath was removed, and the suspension was allowed to slowly warm, until a homogeneous solution was observed. The solution was cooled to -78 °C, then treated with the slow dropwise addition of a solution of trans-benzyl 6-oxabicyclo[3.1.0]hexane-3-carboxylate (250mg, 1.145 mmol) in THF (5 mL) followed by boron trifluoride etherate (0.581 mL, 4.58 mmol) in one portion. The mixture was stirred at -78 °C for 2 h, at which point a precipitate was observed, and the color quickly changed to bright yellow. The reaction was allowed to slowly come to room temperature, during which the color began to turn grey. The reaction was quenched with 30 mL of a 9:1 aqueous solution of saturated NH₄Cl and 10% NH₄OH, and the mixture was stirred for 30 minutes. The resulting deep blue mixture was filtered to remove a small amount of precipitate, and extracted 3x with ethyl acetate.

The combined organic phases were washed with water followed by brine, then dried over sodium sulfate and concentrated in-vacuo. The residue was purified over a 2 x 15 cm silica gel column, eluting with ethyl acetate/hexanes (25% - 50% EtOAc), to yield a racemic mixture of (1R,3R,4R)-benzyl 3-hydroxy-4-methylcyclopentanecarboxylate and (1S,3S,4S)-benzyl 3-hydroxy-4-methylcyclopentanecarboxylate (225mg, 0.480 mmol, 84% yield) as a colorless oil.

**Step 4. Racemic mixture of (1R,3R,4R)-3-hydroxy-4-methylcyclopentanecarboxylic acid and (1S,3S,4S)-3-hydroxy-4-methylcyclopentanecarboxylic acid**
[00403] A racemic mixture of (1R,3R,4R)-benzyl 3-hydroxy-4-methylcyclopentanecarboxylate and (1S,3S,4S)-benzyl 3-hydroxy-4-methylcyclopentanecarboxylate (217 mg, 0.463 mmol) and palladium hydroxide on carbon (65.0 mg, 0.463 mmol) in methanol (10 mL) was degassed under vacuum/nitrogen, and the mixture was hydrogenated overnight at 50 psi. The catalyst was removed by filtration and rinsed with methanol. The filtrates were combined and concentrated in-vacuo to yield a racemic mixture of (1R,3R,4R)-3-hydroxy-4-methylcyclopentanecarboxylic acid and (1S,3S,4S)-3-hydroxy-4-methylcyclopentanecarboxylic acid (131 mg, 0.454 mmol, 98% yield) as a colorless oil which solidified upon standing overnight.

Step 5. Examples 572A and 572B

[00404] A mixture of (R)-2-amino-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methylbutan-1-one, HCl (56.0 mg, 0.149 mmol), (±)-[(1R,3R,4R)-3-hydroxy-4-methylcyclopentanecarboxylic acid, (1S,3S,4S)-3-hydroxy-4-methylcyclopentanecarboxylic acid (47.3 mg, 0.164 mmol)], HOBT (50.2 mg, 0.328 mmol), and triethylamine (0.104 mL, 0.745 mmol) in methylene chloride (2 mL) was treated with EDC (62.9 mg, 0.328 mmol), and the reaction was allowed to stir overnight at room temperature. The mixture was concentrated in-vacuo, and the residue was taken up in ethyl acetate. The organic phase was washed 3 X with 1M NaOH, 3 X with 1M HCl, and once with brine, dried over sodium sulfate, and concentrated in-vacuo. The residue was purified over a 2 x 10 cm silica gel column, eluting with 50 - 100% EtOAc/Hexanes then 5% MeOH/EtOAc to yield 47 mg of a mixture of the two titled compounds. The two diastereomers were separated via chiral super-critical fluid chromatography to yield 20.0 mg of Example 572A, and 15.2 mg of Example 572B. MS (ESI+) = 465.2, M+ for both isomers.
Examples 572C and 572D

(1R,3S,4S)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-hydroxy-4-methylcyclopentanecarboxamide

and

(1R,3S,4S)-N-((R)-1-((S)-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-hydroxy-4-methylcyclopentanecarboxamide

[00405] Examples 572C and 572D were prepared using the procedures described in Examples 572A and 572B, substituting cis-benzyl 6-oxabicyclo[3.1.0]hexane-3-carboxylate for trans-benzyl 6-oxabicyclo[3.1.0]hexane-3-carboxylate in Step 3. MS (ESI+) = 465.2, M+ for both isomers.

Example 573

N-((R)-1-((4R,5S)-4-(4-chlorophenyl)-4,5-dihydroxy-3,3-dimethylpiperidin-1-yl)-3-methyl-1-oxobutan-2-yl)cyclopentanecarboxamide

Step 1: 4-(4-Chlorophenyl)-3,3-dimethyl-1,2,3,6-tetrahydropyridine

[00406] A suspension of (R)-4-(4-chlorophenyl)-3,3-dimethylpiperidin-4-ol, D(-)-Tartaric Acid (6.2 g, 15.90 mmol) in concentrated hydrochloric acid (150 mL) was refluxed for 27 hours, during which time a clear solution was observed. The solution was cooled to 0°C, which caused a white solid to precipitate, and the pH was
adjusted to \(-13\) with the slow, careful addition of solid sodium hydroxide. The aqueous was extracted with EtOAc (3 x 300 mL), the combined organic layers were washed with 1N NaOH (3 x 100 mL), once with brine (100 mL), then dried over sodium sulfate and concentrated in-vacuo to yield the title compound (3.46 g, 15.60 mmol, 98% yield) as a pale yellow oil. MS (ESI+) = 222/224, (M+H)+.

**Step 2. tert-Butyl 4-(4-chlorophenyl)-5,5-dimethyl-5,6-dihydropyridine-1(2H)-carboxylate**

![Chemical Structure]

[00407] A solution of 4-(4-chlorophenyl)-3,3-dimethyl-1,2,3,6-tetrahydropyridine (3.46 g, 15.60 mmol) in THF (50 mL) was treated di-tert-butyl dicarbonate (3.99 mL, 17.17 mmol), causing a color change to amber, and the mixture was stirred overnight at room temperature. The solution was concentrated in-vacuo, and the residue was purified by flushing through silica gel, eluting with hexanes/ethyl acetate (10%-15% EtOAc), to yield the title compound (5.0 g, 15.54 mmol, 100% yield) as a colorless oil. MS (ESI+) = 266, (M+H-t-Bu)+.

**Step 3. (4R,5S)-tert-butyl 4-(4-chlorophenyl)-4,5-dihydroxy-3,3-dimethylpiperidine-1-carboxylate**

![Chemical Structure]

[00408] The title compound was prepared via the method of Sharpless, et. al., J. Org. Chem. 57, 1992, 2768. A stirring suspension of AD-MIX-alpha (2.3 g, 1.554 mmol) and methanesulfonamide (148 mg, 1.554 mmol) in 1:1 tert-butanol/water (16 mL) was cooled to 0 °C, then treated with tert-butyl 4-(4-chlorophenyl)-5,5-dimethyl-5,6-dihydropyridine-1(2H)-carboxylate (500 mg, 1.554 mmol). The mixture was
DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME _1_ DE _2_

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME _1_ OF _2_

NOTE: For additional volumes please contact the Canadian Patent Office.
Claims

1. A compound of Formula (Ib):

![formula image]

(Ib)

or stereoisomers or pharmaceutically acceptable salt forms thereof, wherein:

- \( T \) is \( \text{O} \) or \( \text{C} - \text{N}^+ \);
- \( R_1 \) is \((C_1-C_6)\)alkyl, phenyl or \((C_3-C_6)\)cycloalkyl, all of which may be optionally substituted with 0-5 \( R_{1b} \);
- \( R_{1b} \), at each occurrence, is independently \((C_1-C_6)\)alkyl, \((C_1-C_6)\)haloalkyl, \((C_6-C_{10})\)aryl, halo, -C(=O)OH, -C(=O)O(CR_8R_8)R_{10} or -OH, wherein the aryl, may be optionally substituted with 0-3 \( R_{1b} \);
- \( R_{1b} \), at each occurrence, is alkyl, or -OH;
- \( R_2 \) is alkyl, wherein the alkyl may be optionally substituted with -OH;
- \( R_4 \), at each occurrence, is \( F \), -OH or \((C_1-C_6)\)alkyl;
- \( W \) is \( F \), -OH, -CN or -NH_2;
- \( R_5 \) is halo, -CN or -Oalkyl;
- \( R_8 \), at each occurrence, is independently hydrogen or \((C_1-C_6)\)alkyl;
- \( R_{10} \) is \((C_1-C_6)\)alkyl;
- \( m \), at each occurrence, is 0-2; and
- \( r \) is 0-5.

2. A compound of formula (Ib'):
or pharmaceutically acceptable salt forms thereof, wherein:

$$T = \begin{array}{c}
\text{O} \\
\text{C} \\
\text{N} \\
\text{C} \\
\end{array}
\text{ or } \begin{array}{c}
\text{R}_8 \\
\end{array}$$

$R_1$ is $(C_1-C_6)$alkyl, phenyl or $(C_3-C_{10})$cycloalkyl, all of which may be optionally substituted with 0-5 $R_{1a}$:

$R_{1a}$, at each occurrence, is independently $(C_1-C_6)$alkyl, haloalkyl, $(C_6-C_{10})$aryl, halo, $-C(=O)OH$, $-C(=O)O(CR_8R_3)R_{10}$, or $-OH$, wherein the aryl may be optionally substituted with 0-3 $R_{1b}$;

$R_{1b}$, at each occurrence, is alkyl, or $-OH$;

$R_2$ is alkyl, wherein the alkyl may be optionally substituted with $-OH$;

$R_4$, at each occurrence, is $F$, $-OH$ or alkyl;

$W$ is $-OH$;

$R_5$ is halo, $-CN$ or $-Oalkyl$;

$R_8$, at each occurrence, is independently hydrogen or alkyl;

$R_{10}$, is alkyl;

m, at each occurrence, is 0-2; and

r is 0-5.

3. The compound of claim 2, wherein $R_2$ is isopropyl or sec-butyl; $R_4$ is methyl or $OH$; $R_5$ is Cl, F or Br; and $R_1$ is $(C_1-C_6)$alkyl, phenyl or $(C_3-C_6)$cycloalkyl, all of which may be optionally substituted with 0-5 $R_{1a}$.

4. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one compound of claim 2.

5. A compound of claim 2 for use in treating a disorder, wherein said disorder is osteoarthritis, aneurysm, fever, cardiovascular effects, Crohn’s disease, congestive heart failure, autoimmune diseases, HIV-infection, HIV-associated dementia, psoriasis, idiopathic pulmonary...
fibrosis, transplant arteriosclerosis, physically- or chemically-induced brain trauma, inflammatory bowel disease, alveolitis, colitis, systemic lupus erythematosus, nephrototoxic serum nephritis, glomerulonephritis, asthma, multiple sclerosis, arteriosclerosis, rheumatoid arthritis, restinosis, organ transplantation, psoriatic arthritis, multiple myeloma, allergies, hepatocellular carcinoma, osteoporosis, renal fibrosis or cancer.

6. Use of a compound of claim 2 for treating a disorder, wherein said disorder is osteoarthritis, aneurysm, fever, cardiovascular effects, Crohn’s disease, congestive heart failure, autoimmune diseases, HIV-infection, HIV-associated dementia, psoriasis, idiopathic pulmonary fibrosis, transplant arteriosclerosis, physically- or chemically-induced brain trauma, inflammatory bowel disease, alveolitis, colitis, systemic lupus erythematosus, nephrototoxic serum nephritis, glomerulonephritis, asthma, multiple sclerosis, arteriosclerosis, rheumatoid arthritis, restinosis, organ transplantation, psoriatic arthritis, multiple myeloma, allergies, hepatocellular carcinoma, osteoporosis, renal fibrosis or cancer.

7. Use of a compound of claim 2 in the manufacture of a medicament for treating a disorder, wherein said disorder is osteoarthritis, aneurysm, fever, cardiovascular effects, Crohn’s disease, congestive heart failure, autoimmune diseases, HIV-infection, HIV-associated dementia, psoriasis, idiopathic pulmonary fibrosis, transplant arteriosclerosis, physically- or chemically-induced brain trauma, inflammatory bowel disease, alveolitis, colitis, systemic lupus erythematosus, nephrototoxic serum nephritis, glomerulonephritis, asthma, multiple sclerosis, arteriosclerosis, rheumatoid arthritis, restinosis, organ transplantation, psoriatic arthritis, multiple myeloma, allergies, hepatocellular carcinoma, osteoporosis, renal fibrosis or cancer.