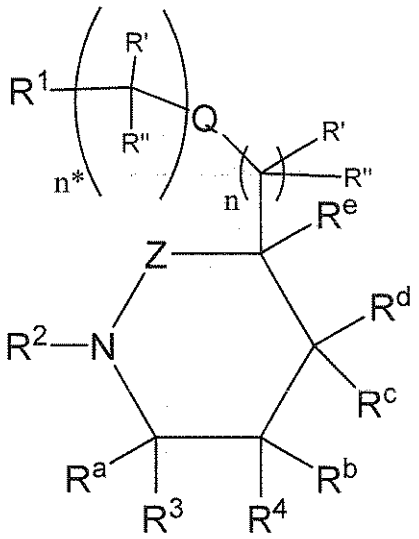
vitro and in vivo. Further, in patients with p53-inactivated tumors, stabilization of wildtype p53 in normal tissues by MDM2 inhibition might allow selective protection of normal tissues from mitotic poisons.

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

SUMMARY OF THE INVENTION

The present disclosure~~invention~~ relates to piperidinone derivatives of Formula I.



I

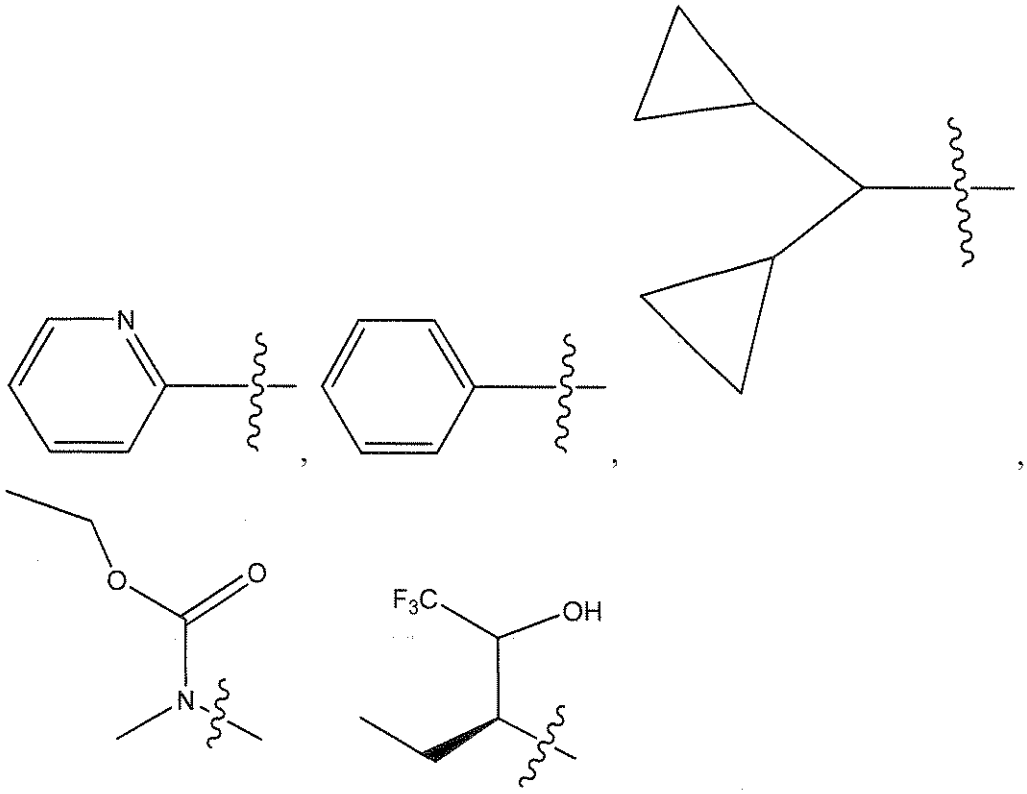
enantiomers, diastereomers and pharmaceutically acceptable salts thereof,

wherein

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

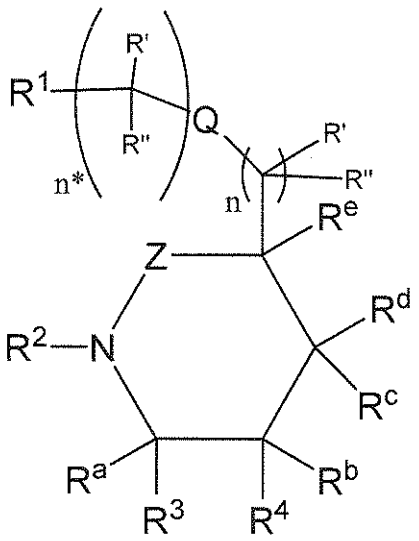
Z is C=O or $S(=O)_2$

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



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

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



I

or a pharmaceutically acceptable salt thereof, wherein:

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

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

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

m is 1, 2 or 3;

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

p is 0, 1, 2 or 3;

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

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

In another exampleaspect, exampleaspect AA, the present disclosureinvention provides compounds of Formula I:

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

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

m is 1, 2 or 3;

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

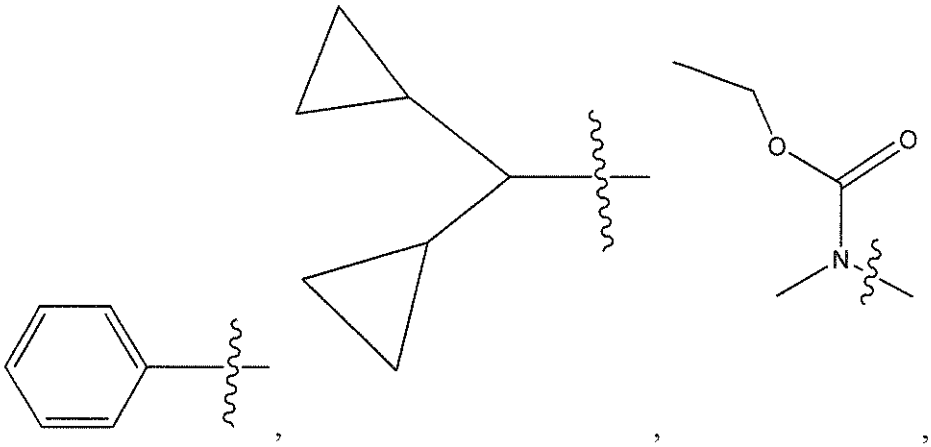
p is 0, 1, 2 or 3;

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

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

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

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



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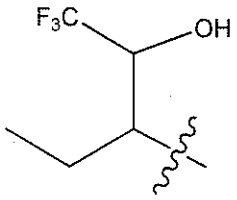
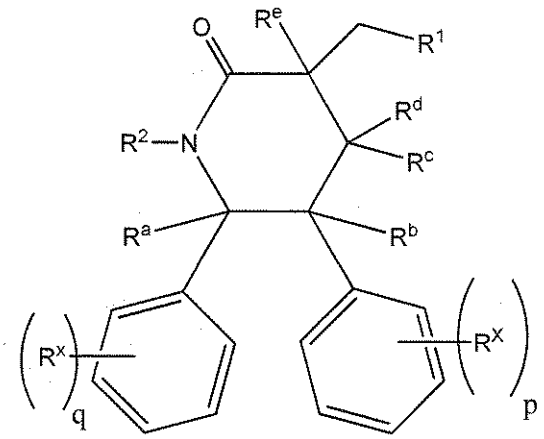


, any of which may be optionally substituted with one or more R^x groups as allowed by valence.

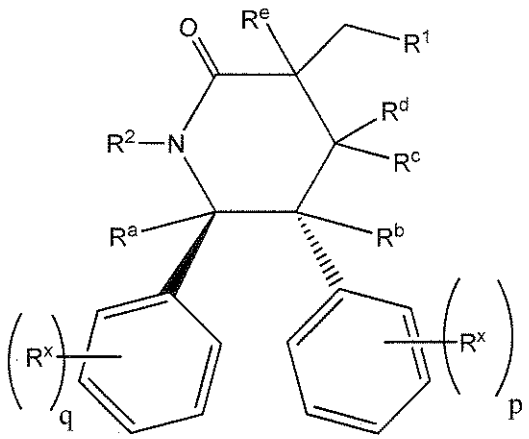
In another ~~example~~embodiment, ~~embodiment~~ 4, the compounds of ~~Example~~Aspect A or AA have the structure of Formula IA



IA

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

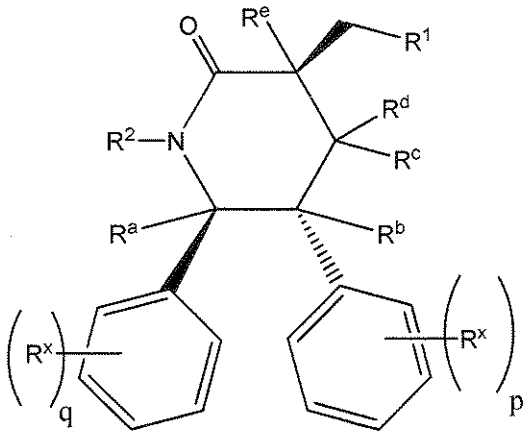
In another ~~example~~embodiment, ~~embodiment 5~~, the compounds of ~~Example~~Aspect A or AA have the structure of Formula IB



IB

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

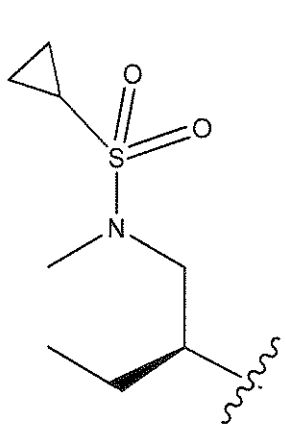
In another ~~example~~embodiment, ~~embodiment 6~~, the compounds of ~~Example~~Aspect A or AA have the structure of Formula IC



IC

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

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



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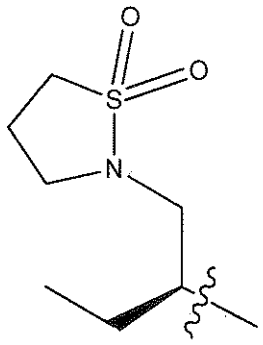

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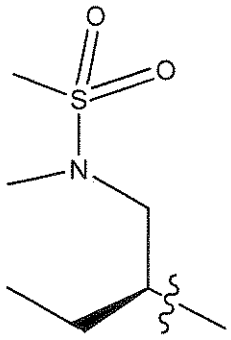

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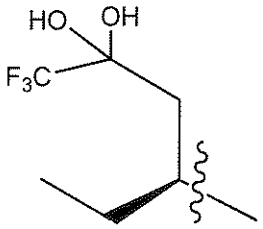

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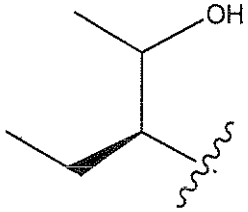

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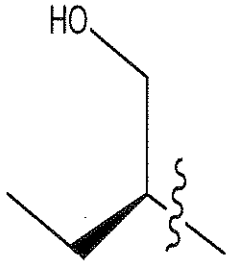

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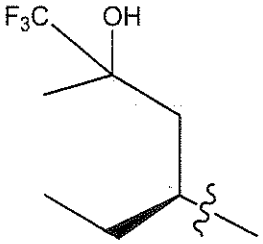

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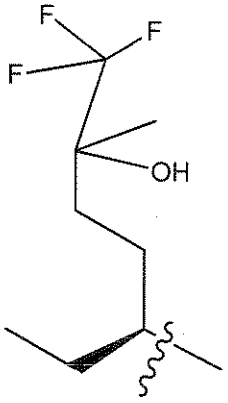

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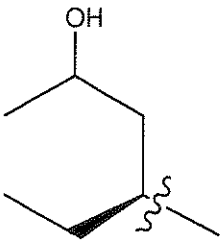

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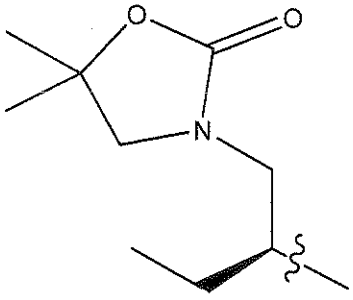

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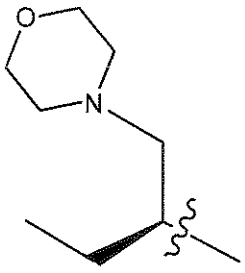

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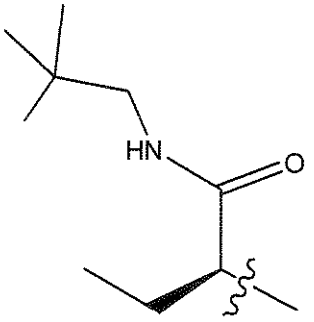

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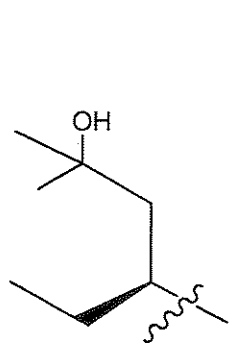
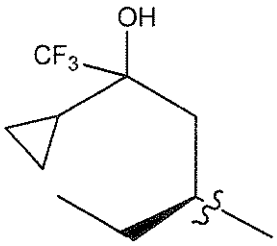
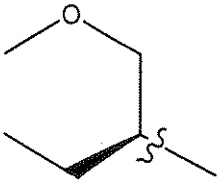
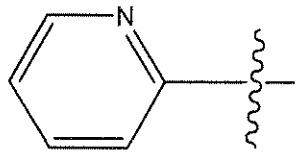
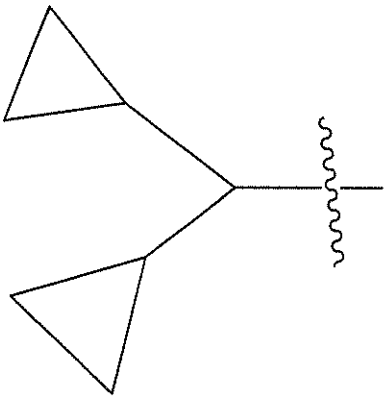
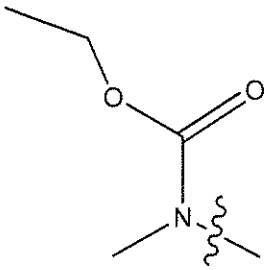
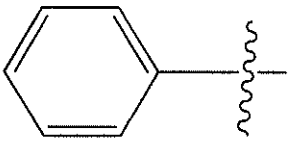
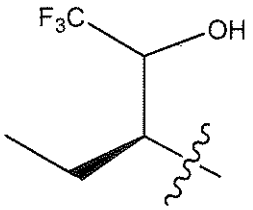
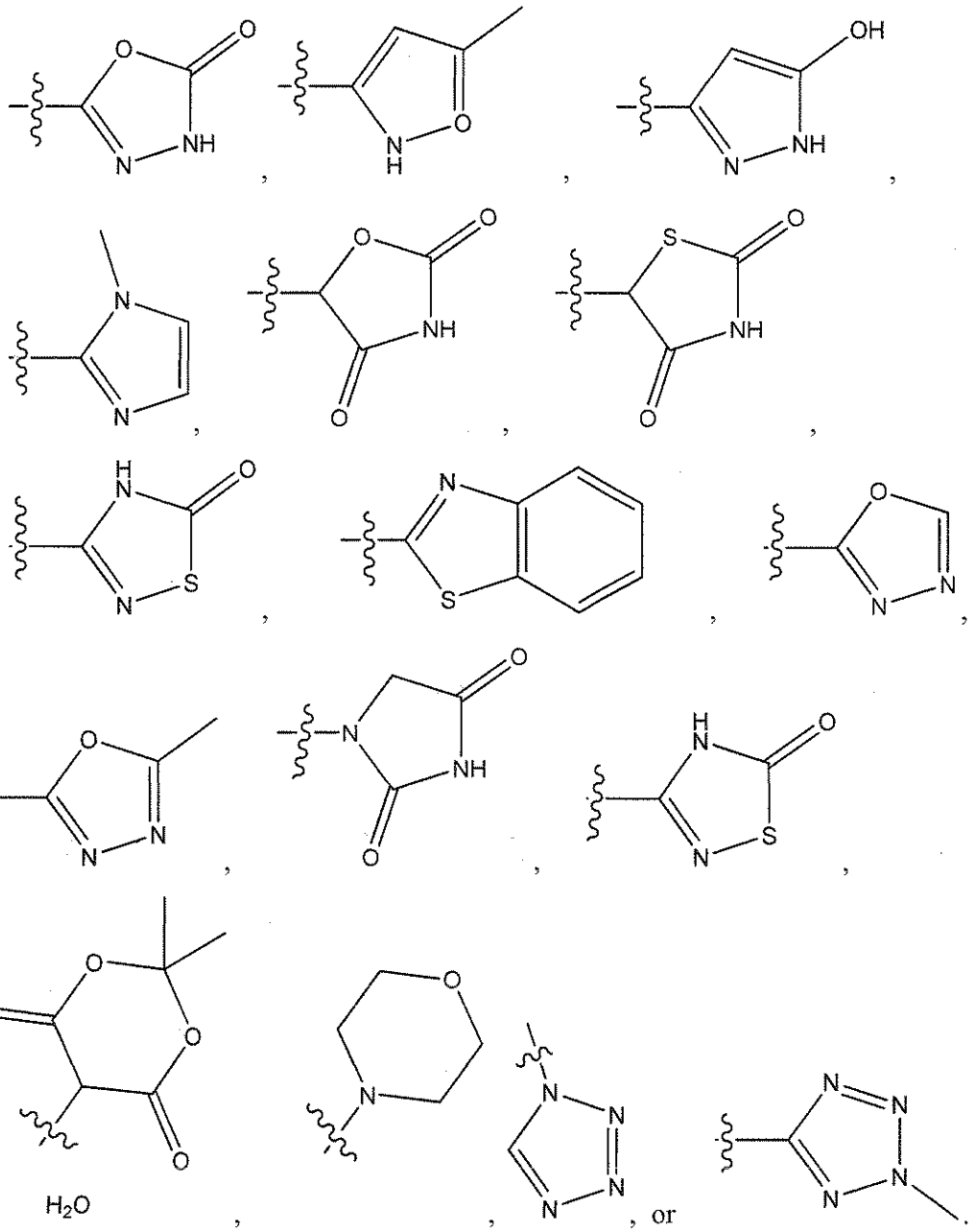









, any of which may be optionally substituted with one or more R^x groups as allowed by valence.

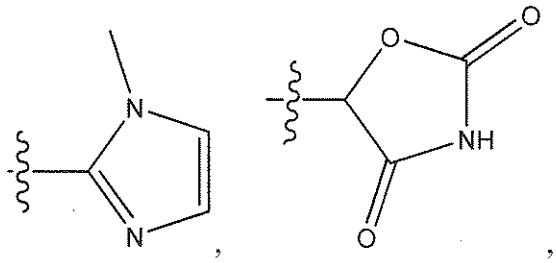
In another example~~aspect of embodiment 6 (embodiment 8) or the pharmaceutically acceptable salts thereof~~,

R^2 is selected from



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

R^2 is selected from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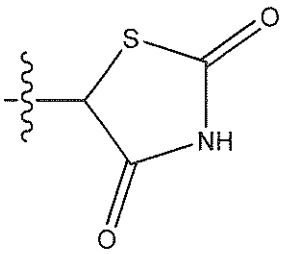
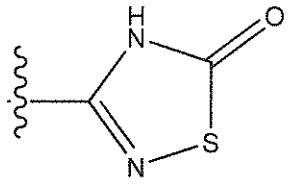
, 
or 
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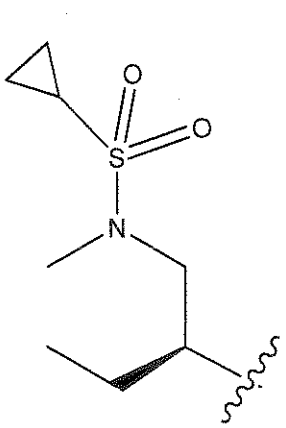
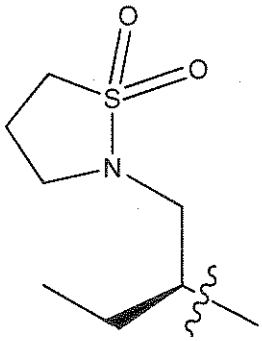
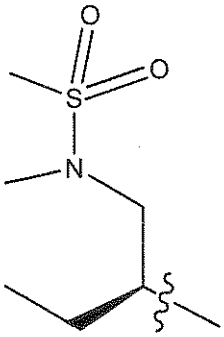
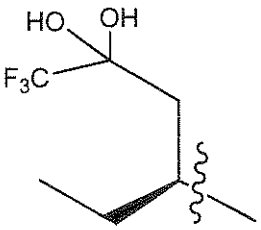
In another example~~aspect of embodiment 6 (embodiment 10), or the pharmaceutically acceptable salts thereof~~,

R^2 is selected from


, 
, 
, 
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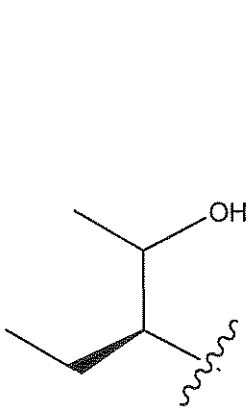
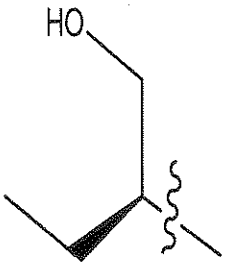
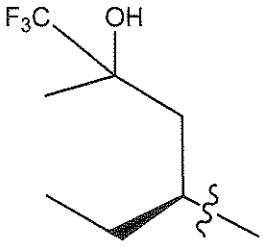
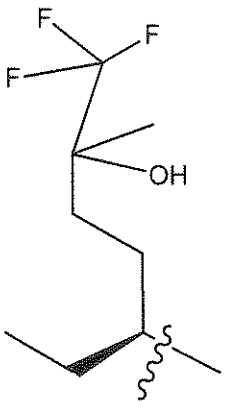

, 
, 
, 
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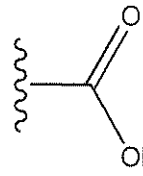
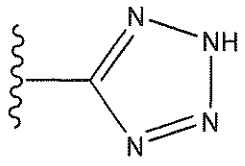


, or a heteroaryl or heterocycle selected from



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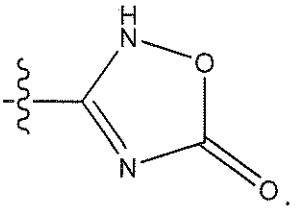

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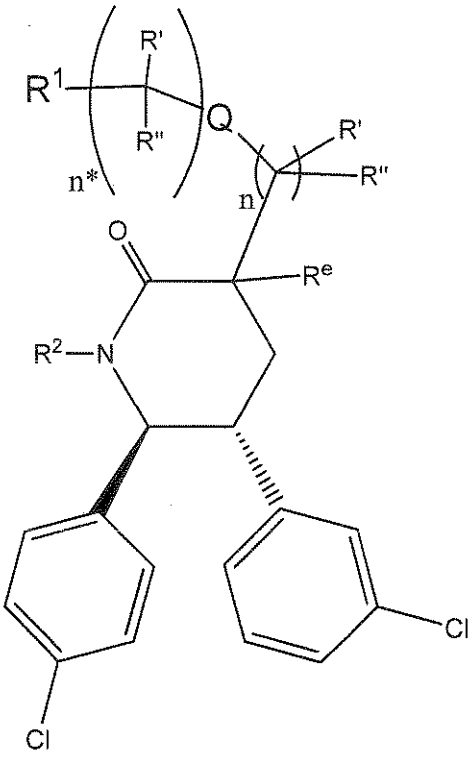
In another example~~embodiment, embodiment 11~~, the compounds of Example~~Aspect~~ A have the structure of Formula ID

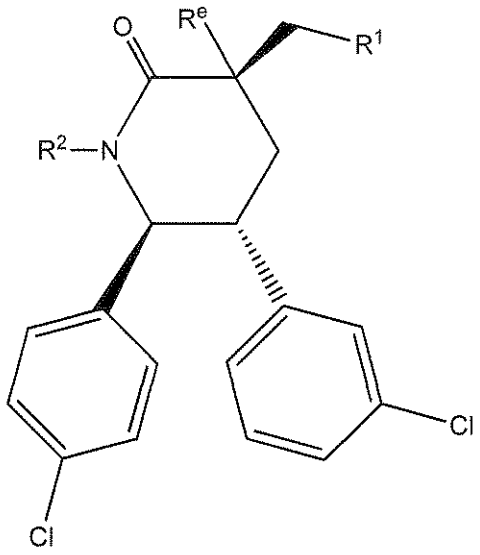


ID

or a pharmaceutically acceptable salt thereof.

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

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



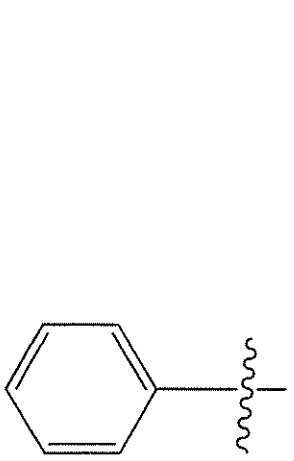
IE

or the pharmaceutically acceptable salts thereof.

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

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

R^2 is selected from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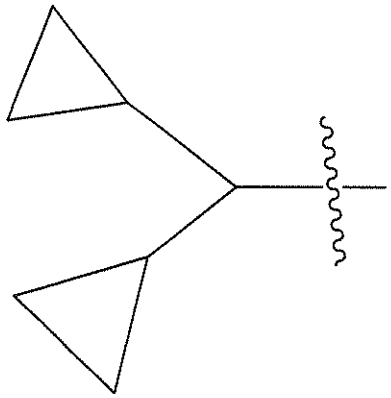
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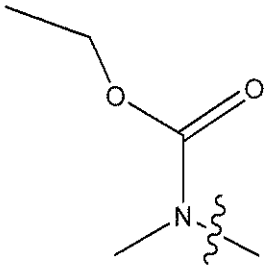
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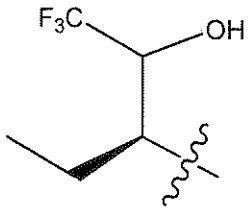
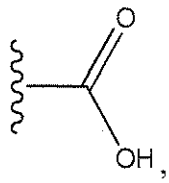
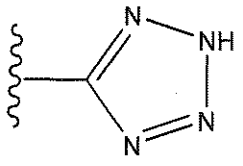


, any of which may be optionally substituted with one or more R^x groups as allowed by valence; and

R^1 is


, or a heteroaryl or heterocycle selected from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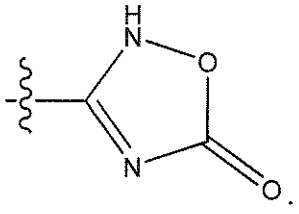
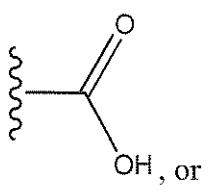

.

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

R^1 is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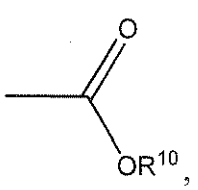
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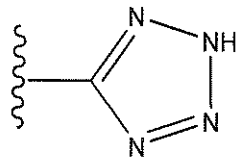
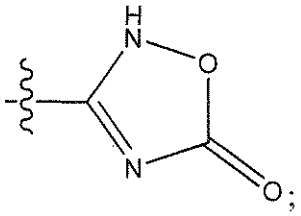
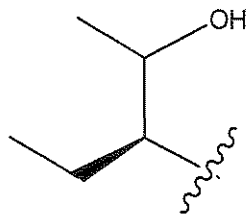
or a heteroaryl or heterocycle selected from

 or  ;

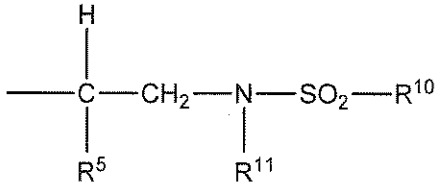
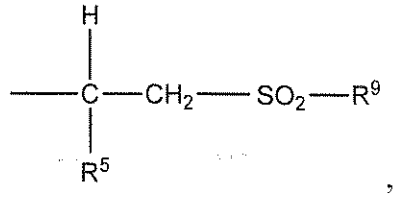
R^2 is

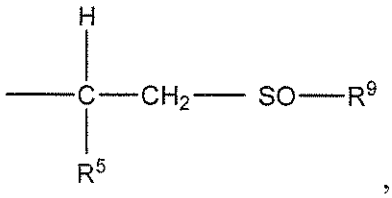
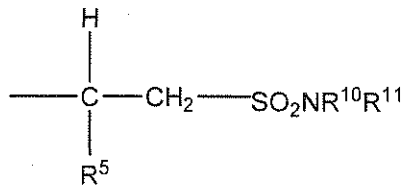
 ; and

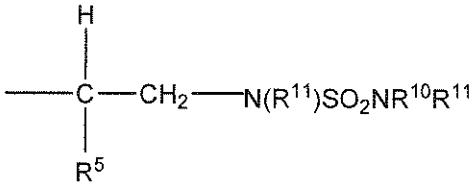
R^e is methyl.

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

R^2 is

 ,  ,

 ,  , or

 ;

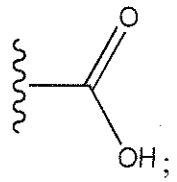
R^5 is cyclopropyl, or C_{1-6}alkyl;

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

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

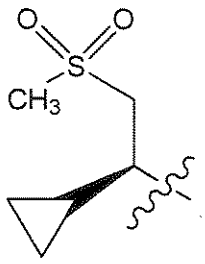
In another example~~aspect of embodiment 13 (embodiment 18), or a pharmaceutically acceptable salt thereof~~,

R^1 is



;

R^2 is



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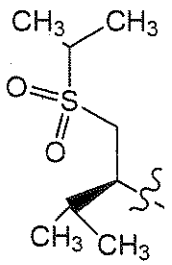

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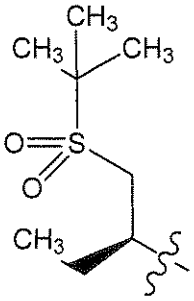

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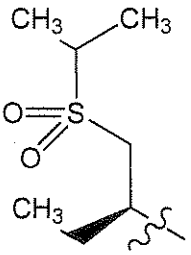

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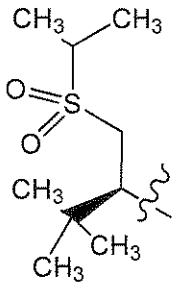

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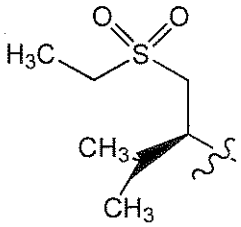

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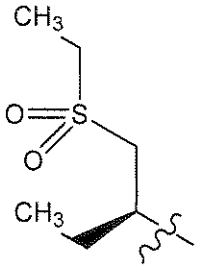

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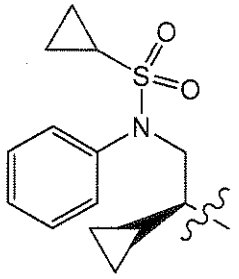

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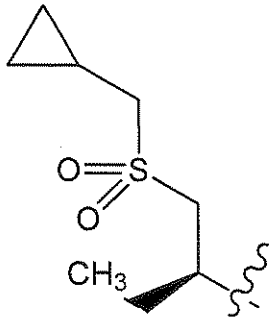

;

and R^e is methyl.

In one aspect, the present invention provides the compound of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid.

In another aspect, the present invention provides the compound of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In a further aspect, the present invention provides a pharmaceutical composition comprising 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid together with a pharmaceutically acceptable excipient, diluent or carrier.

In yet another aspect, there is provided a pharmaceutical composition comprising 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient, diluent or carrier.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-cyclopropyl-2-(ethylsulfonyl)ethyl)-3-(3-hydroxy-2-oxopropyl)-3-methylpiperidin-2-one;

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

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

(2S,3S,5S,6R,7aR,10aS)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-ethyl-2,7a-dimethylhexahydrofuro[2,3-b]oxazolo[3,2-a]pyridin-9(5H)-one.

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

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

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

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

2-(1-(2-(5-Chloro-N-methylthiophene-2-sulfonamido)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

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

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

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

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

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

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

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

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

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

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

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

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

(5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-(1-cyclopropyl-2-(ethylsulfonyl)ethyl)-3-(3-hydroxy-2-oxopropyl)-3-methylpiperidin-2-one;

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

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

6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-ethyl-2,7a-dimethylhexahydrofuro[2,3-b]oxazolo[3,2-a]pyridin-9(5H)-one.

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

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

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

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

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

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

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

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

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

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

In another example~~aspect~~, the present disclosure~~invention~~ provides a compound, or a pharmaceutically acceptable salt thereof, selected from:
2-(-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-(-1-cyclopropyl-2-(methylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid;

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

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

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

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

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

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

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

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

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

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

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

The present disclosure~~invention~~ provides pharmaceutical compositions comprising a compound of any one of the above aspects or example~~embodiment~~s, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient, diluent or carrier.

The present disclosure~~invention~~ also provides method of treating cancer in a subject in need of said treatment, the method comprising administering to the subject an effective dosage amount of a compound according to any one of the above aspects or example~~embodiment~~s, or a pharmaceutically acceptable salt thereof.