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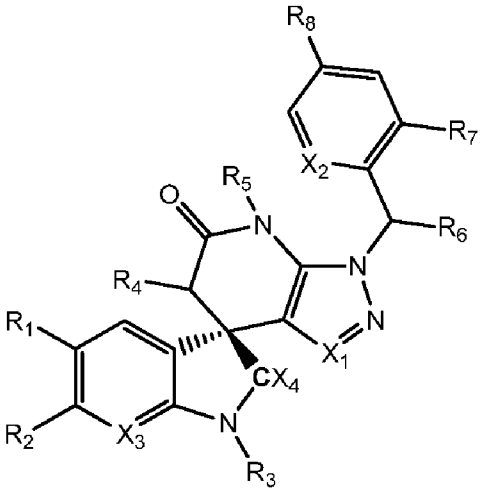
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(54) Title: SPIROPYRAZOLOPYRIDINE DERIVATIVES AND USES THEREOF FOR THE TREATMENT OF VIRAL INFECTIONS

(57) Abstract: A compound of Formula (I) is provided that has been shown to be useful for treating a disease caused by a viral infection: (I) wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $X_1$, $X_2$, $X_3$ and $X_4$, are as defined herein.




(I)

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# SPIROPYRAZOLOPYRIDINE DERIVATIVES AND USES THEREOF FOR THE TREATMENT OF VIRAL INFECTIONS

This application claims priority to foreign Singapore Patent Application No. 201302813-9, filed April 11, 2013, the contents of which are incorporated herein by reference in their entirety.

## FIELD OF THE INVENTION

The present disclosure relates to spiropyrazolopyridine derivatives, pharmaceutical formulations thereof, and their use for the treatment of viral infections, in particular viral infections caused by dengue virus.

## BACKGROUND

Dengue fever is a febrile disease caused by one of the four dengue virus serotypes DEN-1, DEN-2, DEN-3 and DEN-4, which belong to the family *Flaviviridae*. The virus is transmitted to humans primarily by *Aedes aegypti*, a mosquito that feeds on humans.

Infections produce a range of clinical manifestations, from milder flu-like symptoms to the more severe and sometimes fatal haemorrhagic disease. Typical symptoms include fever, severe headache, muscle and joint pains and rashes. The more severe forms of the disease are dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). According to the WHO, there are four major clinical manifestations of DHF: (1) high fever (2) haemorrhagic phenomena (3) thrombocytopenia and (4) leakage of plasma. DSS is defined as DHF plus weak rapid pulse, and narrow pulse pressure or hypotension with cold, clammy skin and restlessness. The severity of DHF can be reduced with early detection and intervention, but subjects in shock are at high risk of death.

Dengue is endemic in tropical regions, particularly in Asia, Africa and Latin America, and an estimated 2.5 billion people live in areas where they are at risk of infection. There are around 40 million cases of dengue fever and several hundred thousand cases of DHF each year. In Singapore, an epidemic in 2005 resulted in more than 12000 cases of dengue fever.

Despite regular outbreaks, previously infected people remain susceptible to infection because there are four different serotypes of the dengue virus and infection with one of these serotypes provides immunity to only that serotype. It is believed that DHF is more likely to occur

in subjects who have secondary dengue infections. Efficient treatments for dengue fever, DHF and DSS are being sought.

The flaviviral genome is a single-stranded, positive-sense RNA about 11 kb in length. It contains 5' and 3' untranslated regions (UTR) flanking a single open reading frame. The open reading frame encodes a long polyprotein that is co- and post- translationally processed by viral and cellular proteases into three structural proteins (capsid [C], pre-membrane [prM], and envelope [E]) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). Structural proteins are involved in virus entry and assembly. Non-structural proteins are involved in viral RNA replication, evasion of innate immune response, and virus assembly.

The glycoprotein NS1 plays a role in viral RNA replication at an early step of viral RNA replication. NS3 acts as a viral serine protease with the cofactor NS2B, an RNA triphosphatase, and an RNA helicase. NS5 functions as a methyl transferase and an RNA-dependent RNA polymerase (RdRp). Regarding the small hydrophobic proteins NS2A, NS4A, and NS4B, these transmembrane proteins anchor the viral replication complex to the endoplasmic reticulum (ER) membrane.

Yellow fever virus (YFV), West Nile virus (WNV), Japanese encephalitis virus (JEV), Powassan virus (POWV),tick-borne encephalitis virus, Kunjin virus, Murray Valley encephalitis, St Louis encephalitis, Omsk hemorrhagic fever virus, bovine viral diarrhea virus, Zika virus and Hepatitis C virus (HCV) also belong to the family *Flaviviridae*.

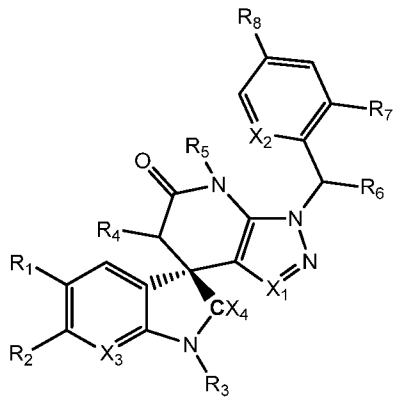
WNV can be asymptomatic, or it can cause flu-like symptoms in some individuals. In some cases it causes neurological disorders, encephalitis, and in severe cases can result in death. WNV is also transmitted by mosquitos. YFV is another mosquito-borne virus, which can cause severe symptoms in infected individuals. JEV is also transmitted by mosquitoes, and is either asymptomatic or causes flu-like symptoms, with some cases developing into encephalitis. The acute encephalitis stage of the disease is characterized by convulsions, neck stiffness and other symptoms. HCV is a blood-borne virus that is transmitted by blood-to-blood contact. In the initial (acute) stage of the disease, most subjects will not show any symptoms. Even during the chronic stage (i.e. where the disease persists for more than 6 months), severity of symptoms can vary from subject to subject. In the long term, some infected persons can progress to cirrhosis and liver cancer. The current treatment for HCV involves a combination of interferon alpha and ribavirin, an anti-viral drug. Efficient treatments for infections caused by these *Flaviviridae* viruses are being sought as well.

It has now surprisingly been found that spiropyrazolopyridine derivatives as presently disclosed are useful for the treatment of viral infections such as those caused by a virus of the family *Flaviviridae*, especially dengue virus and yellow fever virus.

## SUMMARY

The compounds described herein have been shown to be useful in the prevention and/or treatment of viral infections.

One aspect of the present disclosure provides compounds of Formula (I)



(I)

Wherein

$R_1$ is F, Cl, Br, $CF_3$, $OCH_3$, ($C_1$-$C_6$)alkyl or cycloalkyl;

$R_2$ is H, F, Cl, Br, ($C_1$-$C_6$)alkyl or cycloalkyl; or $R_1$ and $R_2$ taken together with the aromatic carbon atoms to which they are attached form a fused 1,3-dioxolo group;

$R_3$ is H,($C_1$-$C_6$)alkyl or cycloalkyl;

$R_4$ is H,($C_1$-$C_6$)alkyl, cycloalkyl or -C(=O)-$NH_2$;

$R_5$ is H,($C_1$-$C_6$)alkyl, cycloalkyl or benzyl;

$R_6$ is H,($C_1$-$C_6$)alkyl or cycloalkyl;

$R_7$ is H,F, Cl or $OCH_3$;

$R_8$ is F, Cl, Br,$CF_3$, -$OCHF_2$, $OCF_3$, $OCH_3$ or ($C_1$-$C_6$)alkyl;

$X_1$ is CH or N;

$X_2$ is CH or N;

$X_3$ is CH or N;

$X_4$ is =O or $H_2$;

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, and $R_8$ are each optionally independently substituted with one or more independent $R_{300}$ substituents;

$R_{300}$ is selected from the group consisting of H, ($C_1$-$C_6$)alkyl, cycloalkyl, hydroxy, amino, F, Cl, Br, phenyl, heterocycle and heteroaryl;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, whereinR$_1$ is Cl. In another embodiment, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R_2$ is Cl or F. In still another embodiment, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R_3$ is H or cyclopropyl.

In another embodiment, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R_4$ is H. In still another embodiment, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R_5$ is H, methyl or *i*-propyl. In still another embodiment, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R_6$ is H or methyl.

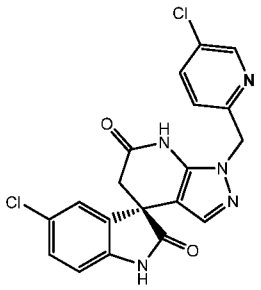
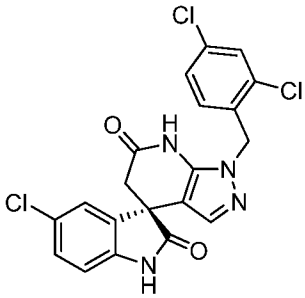
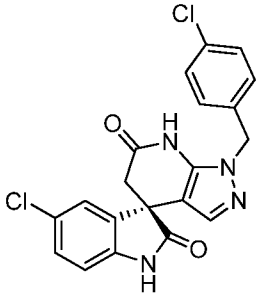
In another embodiment, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R_7$ is H or Cl. In still another embodiment, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, $R_8$ is Cl, methyl, *i*-propyl or *t*-butyl.

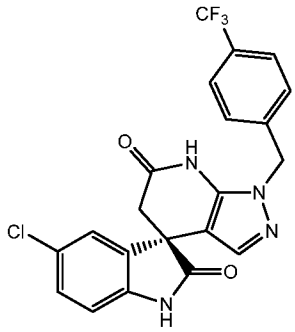
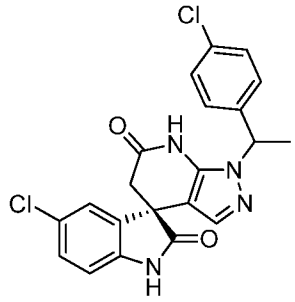
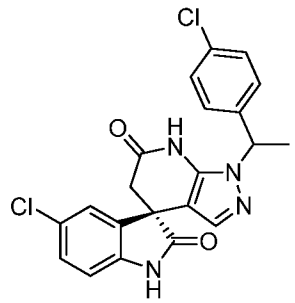
In another embodiment, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $X_1$ is CH. In still another embodiment, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $X_2$ is N. In still another embodiment, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $X_3$ is CH. In

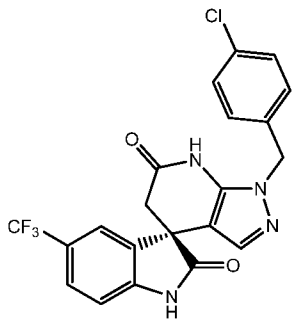
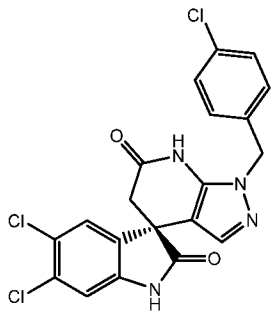
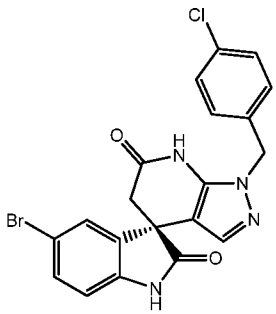
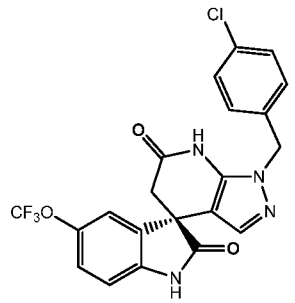
still another embodiment, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $X_4$ is =O.

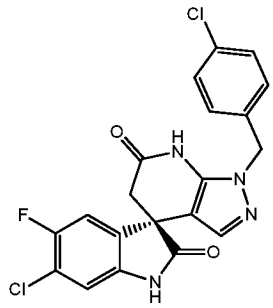
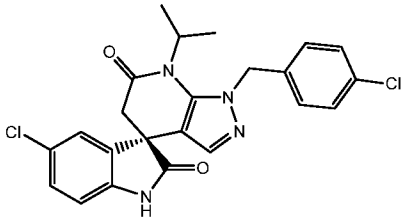
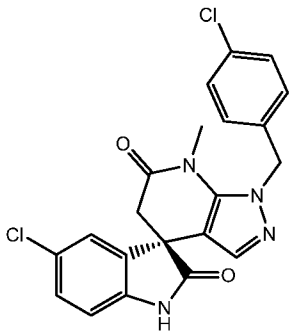
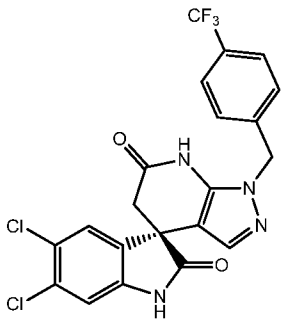
Representative compounds of Formula (I), or a pharmaceutically acceptable salt thereof, are present in the following Table 1:

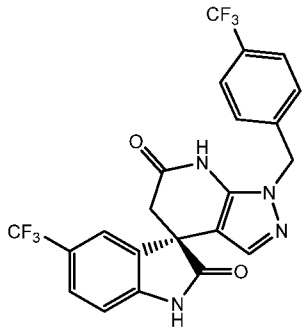
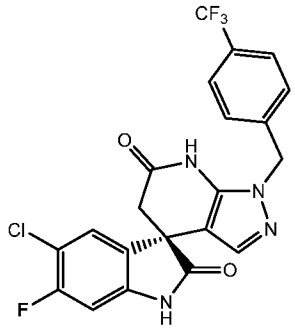
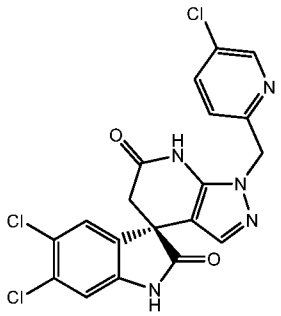
**Table 1**

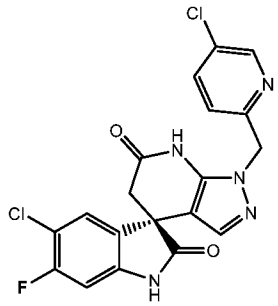
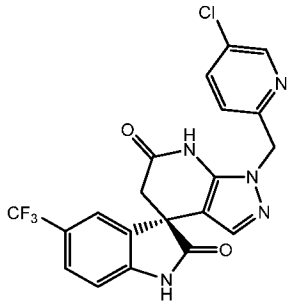
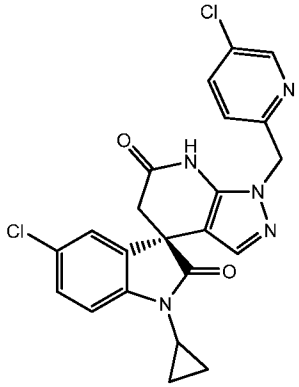
| Example No. | Compound Structure | Compound Chemical Name |
|---|---|---|
| 1 |  | (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 2 |  | (R)-5-chloro-1'-(2,4-dichlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 3-1 |  | (R)-5-chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

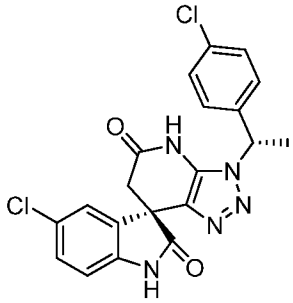
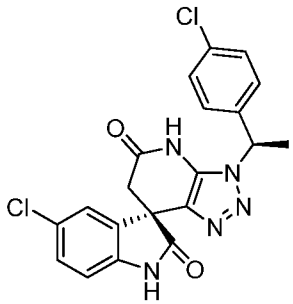
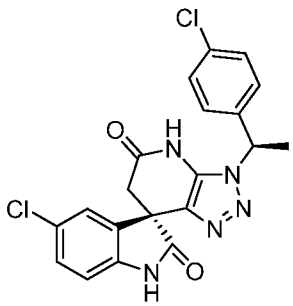
| | | |
|---|---|---|
| 3-2 |  | (R)-5-chloro-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 3-3-1 |  | (R)-5-chloro-1'-(1-(4-chlorophenyl)ethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, Isomer 1 |
| 3-3-2 |  | (S)-5-chloro-1'-(1-(4-chlorophenyl)ethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, Isomer 1 |

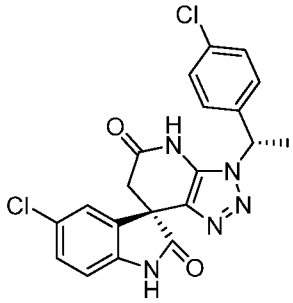
| | | |
|---|---|---|
| 3-4 |  | (R)-1'-(4-chlorobenzyl)-5-(trifluoromethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 3-5 |  | (R)-5,6-dichloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 3-6 |  | (R)-5-bromo-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 3-7 |  | (R)-1'-(4-chlorobenzyl)-5-(trifluoromethoxy)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

| | | |
|---|---|---|
| 3-8 |  | (R)-6-chloro-1'-(4-chlorobenzyl)-5-fluoro-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 3-9 |  | (R)-5-chloro-1'-(4-chlorobenzyl)-7'-isopropyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 3-10 |  | (R)-5-chloro-1'-(4-chlorobenzyl)-7'-methyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 3-11 |  | (R)-5,6-dichloro-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

| | | |
|---|---|---|
| 3-12 |  | (R)-5-(trifluoromethyl)-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 3-13 |  | (R)-5-chloro-6-fluoro-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 3-14 |  | (R)-5,6-dichloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

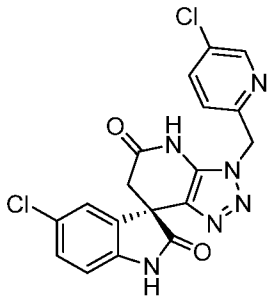
| | | |
|---|---|---|
| 3-15 |  | (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-6-fluoro-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 3-16 |  | (R)-1'-((5-chloropyridin-2-yl)methyl)-5-(trifluoromethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 3-17 |  | (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-1-cyclopropyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

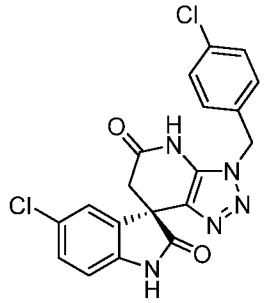
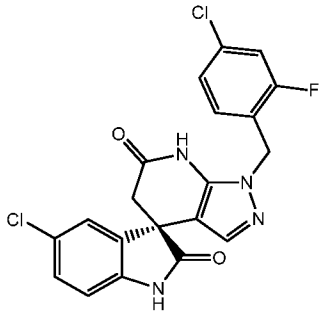
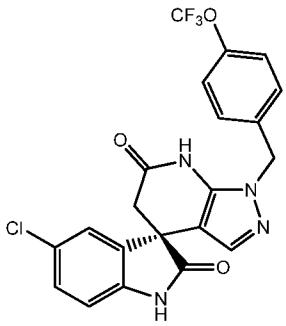
| | | |
|---|---|---|
| 4-1 |  | (R)-5'-chloro-3-((S)-1-(4-chlorophenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione, |
| 4-2 |  | (R)-5'-chloro-3-((R)-1-(4-chlorophenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione' |
| 4-3 |  | (S)-5'-chloro-3-((R)-1-(4-chlorophenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione |

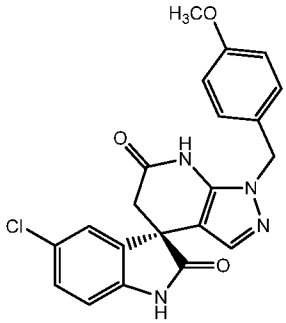
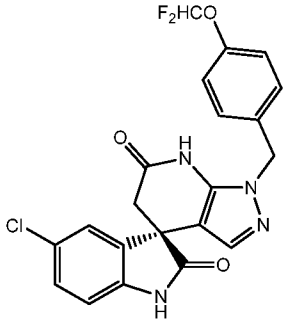
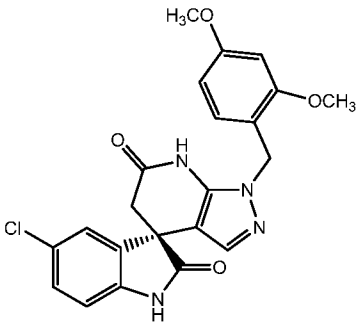
| | | |
|---|---|---|
| 4-4 |  | (S)-5'-chloro-3-((S)-1-(4-chlorophenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione |

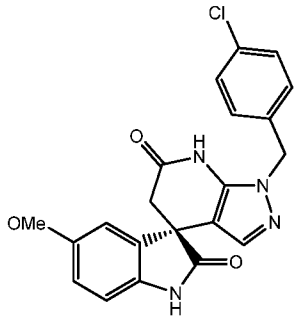
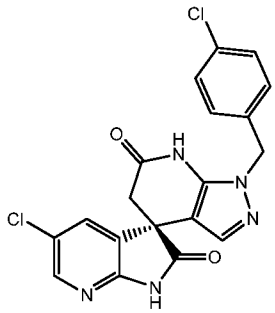
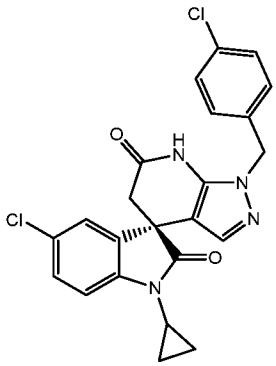
Additional representative compounds of Formula (I), or a pharmaceutically acceptable salt thereof, are present in the following Table 2:

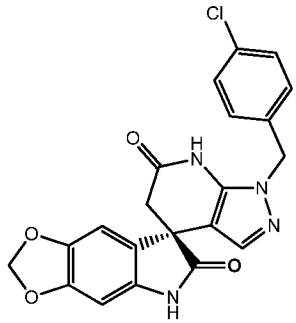
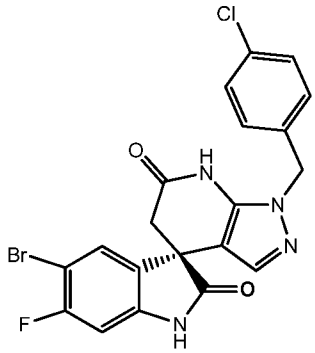
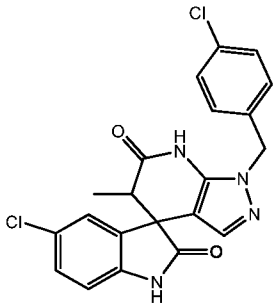
**Table 2**

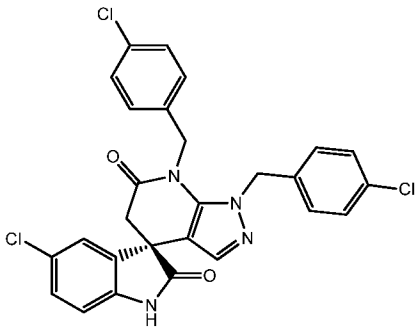
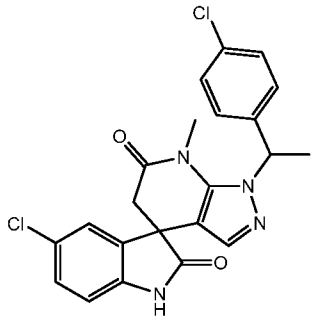
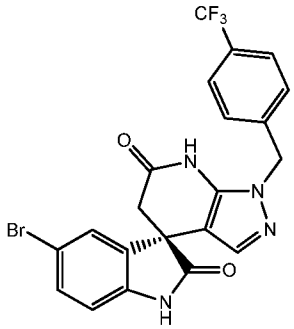
| Example No. | Compound Structure | Compound Chemical Name |
|---|---|---|
| 5 |  | (R)-5'-chloro-3-((5-chloropyridin-2-yl)methyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione, |

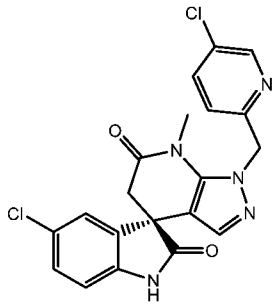
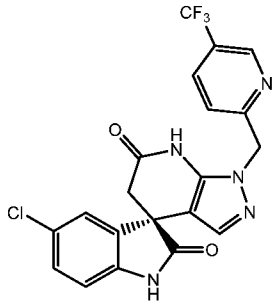
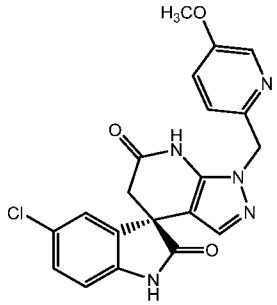
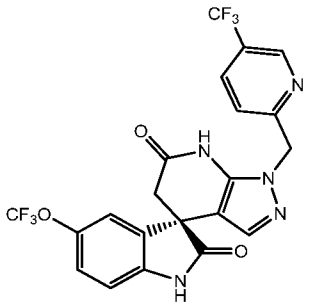
| | | |
|---|---|---|
| 6 |  | (R)-5'-chloro-3-(4-chlorobenzyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione, |
| 7-1 |  | (R)-5-chloro-1'-(4-chloro-2-fluorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 7-2 |  | (R)-5-chloro-1'-(4-(trifluoromethoxy)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

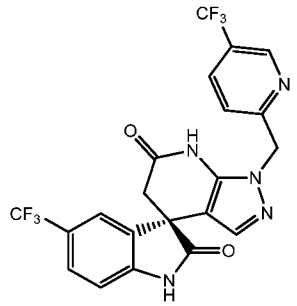
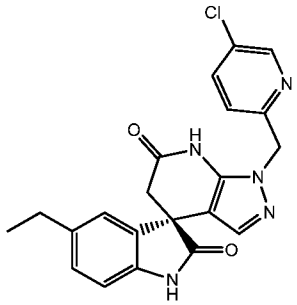
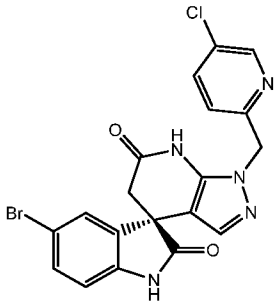
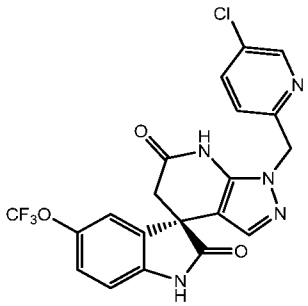
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|---|---|---|
| 7-3 |  | (R)-5-chloro-1'-(4-methoxybenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 7-4 |  | (R)-5-chloro-1'-(4-(difluoromethoxy)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 7-5 |  | (R)-5-chloro-1'-(2,4-dimethoxybenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

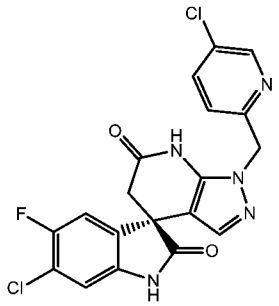
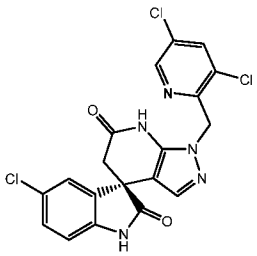
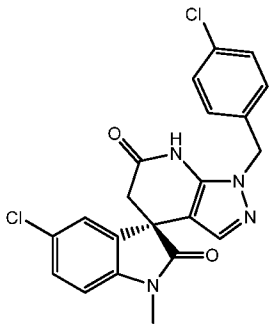
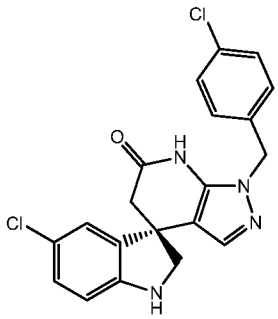
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| 7-6 |  | (R)-1'-(4-chlorobenzyl)-5-methoxy-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 7-7 |  | (S)-5'-chloro-1-(4-chlorobenzyl)-5,7-dihydrospiro[pyrazolo[3,4-b]pyridine-4,3'-pyrrolo[2,3-b]pyridine]-2',6(1H,1'H)-dione, |
| 7-8 |  | (R)-5-chloro-1'-(4-chlorobenzyl)-1-cyclopropyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

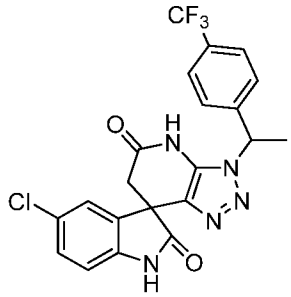
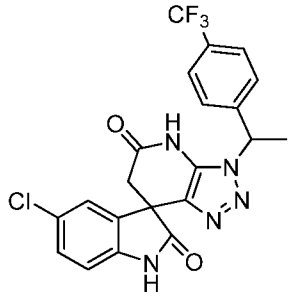
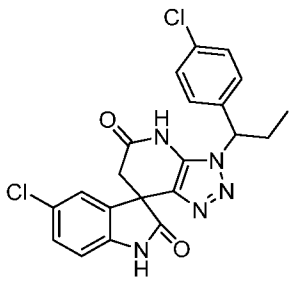
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| 7-9 |  | (R)-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[[1,3]dioxolo[4,5-f]indole-7,4'-pyrazolo[3,4-b]pyridine]-6,6'(1'H,5H)-dione, |
| 7-10 |  | (R)-5-bromo-1'-(4-chlorobenzyl)-6-fluoro-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione |
| 7-11 |  Racemic mixture of (R,R) and (S,S); or Racemic mixture of (R,S) and (S,R) | Racemic (R,R) and (S,S) or Racemic (R,S) and (S,R) of 5-chloro-1'-(4-chlorobenzyl)-5'-methyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

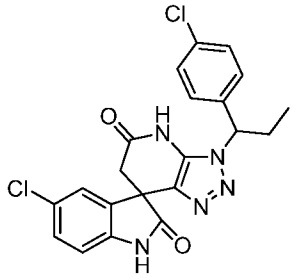
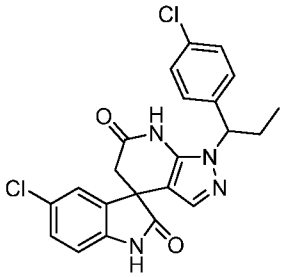
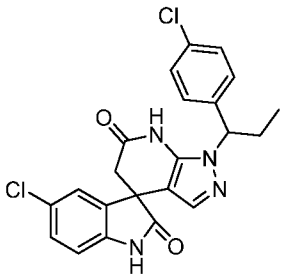
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| 7-12 |  | (R)-5-chloro-1',7'-bis(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 7-13 | <br>Racemic mixture of (R,R) and (S,S); or<br>Racemic mixture of (R,S) and (S,R) | Racemic (R,R) and (S,S) or<br>Racemic (R,S) and (S,R) of 5-chloro-1'-(1-(4-chlorophenyl)ethyl)-7'-methyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 7-14 |  | (R)-5-bromo-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

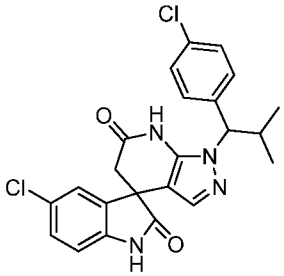
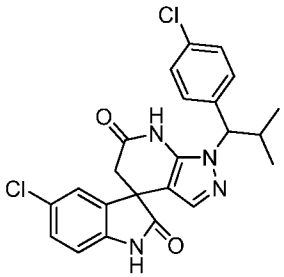
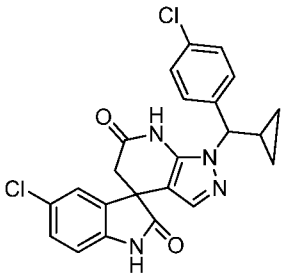
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|---|---|---|
| 7-15 |  | (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-7'-methyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 7-16 |  | (R)-5-chloro-1'-((5-(trifluoromethyl)pyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 7-17 |  | (R)-5-chloro-1'-((5-methoxypyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 7-18 |  | (R)-5-(trifluoromethoxy)-1'-((5-(trifluoromethyl)pyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

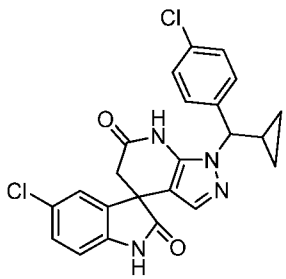
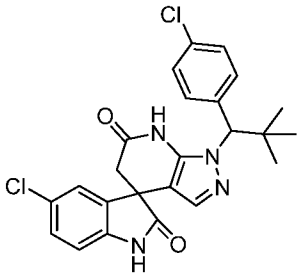
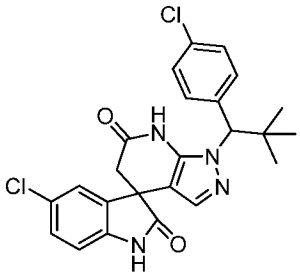
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| 7-19 |  | (R)-5-(trifluoromethyl)-1'-((5-(trifluoromethyl)pyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 7-20 |  | (R)-1'-((5-chloropyridin-2-yl)methyl)-5-ethyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 7-21 |  | (R)-5-bromo-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 7-22 |  | (R)-1'-((5-chloropyridin-2-yl)methyl)-5-(trifluoromethoxy)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

| | | |
|---|---|---|
| 7-23 |  | (R)-6-chloro-1'-((5-chloropyridin-2-yl)methyl)-5-fluoro-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 7-24 |  | (R)-5-chloro-1'-((3,5-dichloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 7-25 |  | (R)-5-chloro-1'-(4-chlorobenzyl)-1-methyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, and |
| 7-26 |  | (R)-5-chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridin]-6'(1'H)-one. |
| | | |

| | | |
|---|---|---|
| 8-1 | <br>Racemic mixture of (R,R) and (S,S); or<br>Racemic mixture of (R,S) and (S,R) | Racemic (R,R) and (S,S) or<br>Racemic (R,S) and (S,R) of 5'-Chloro-3-(1-(4-(trifluoromethyl)phenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione |
| 8-2 | <br>Racemic mixture of (R,S) and (S,R); or<br>Racemic mixture of (R,R) and (S,S) | Racemic (R,S) and (S,R) or<br>Racemic (R,R) and (S,S) of 5'-Chloro-3-(1-(4-(trifluoromethyl)phenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione |
| 8-3 | <br>Racemic mixture of (R,R) and (S,S); or<br>Racemic mixture of (R,S) and (S,R) | Racemic (R,R) and (S,S) or<br>Racemic (R,S) and (S,R) of (5'-chloro-3-(1-(4-chlorophenyl)propyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione |

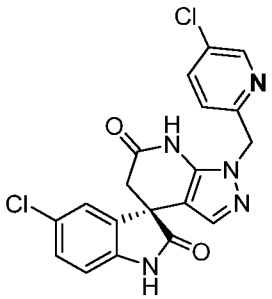
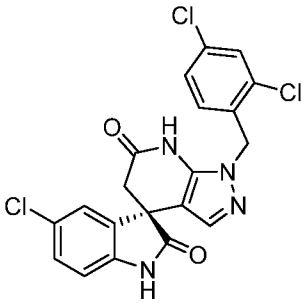
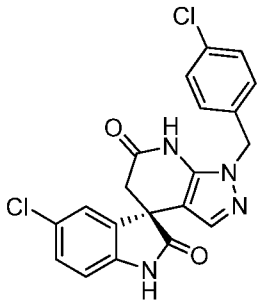
| | | |
|---|---|---|
| 8-4 |  Racemic mixture of (R,S) and (S,R); or Racemic mixture of (R,R) and (S,S) | Racemic (R,S) and (S,R) or Racemic (R,R) and (S,S) of (5'-chloro-3-(1-(4-chlorophenyl)propyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione |
| 8-5 |  Racemic mixture of (R,R) and (S,S); or Racemic mixture of (R,S) and (S,R) | Racemic (R,R) and (S,S) or Racemic (R,S) and (S,R) of 5-chloro-1'-(1-(4-chlorophenyl)propyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione |
| 8-6 |  Racemic mixture of (R,S) and (S,R); or Racemic mixture of (R,R) and (S,S) | Racemic (R,S) and (S,R) or Racemic (R,R) and (S,S) of 5-chloro-1'-(1-(4-chlorophenyl)propyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione |

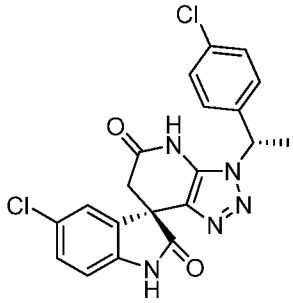
| | | |
|---|---|---|
| 8-7 | <br>Racemic mixture of (R,R) and (S,S); or<br>Racemic mixture of (R,S) and (S,R) | Racemic (R,R) and (S,S) or Racemic (R,S) and (S,R) of 5-chloro-1'-(1-(4-chlorophenyl)-2-methylpropyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione |
| 8-8 | <br>Racemic mixture of (R,S) and (S,R); or<br>Racemic mixture of (R,R) and (S,S) | Racemic (R,S) and (S,R) or Racemic (R,R) and (S,S) of 5-chloro-1'-(1-(4-chlorophenyl)-2-methylpropyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione |
| 8-9 | <br>Racemic mixture of (R,R) and (S,S); or<br>Racemic mixture of (R,S) and (S,R) | Racemic (R,R) and (S,S) or Racemic (R,S) and (S,R) of 5-chloro-1'-((4-chlorophenyl)(cyclopropyl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione |

| | | |
|---|---|---|
| 8-10 | <br>Racemic mixture of (R,S) and (S,R); or<br>Racemic mixture of (R,R) and (S,S) | Racemic (R,S) and (S,R) or Racemic (R,R) and (S,S) of 5-chloro-1'-((4-chlorophenyl)(cyclopropyl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione |
| 8-11 | <br>Racemic mixture of (R,R) and (S,S); or<br>Racemic mixture of (R,S) and (S,R) | Racemic (R,R) and (S,S) or Racemic (R,S) and (S,R) of 5-chloro-1'-(1-(4-chlorophenyl)-2,2-dimethylpropyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione |
| 8-12 | <br>Racemic mixture of (R,S) and (S,R); or<br>Racemic mixture of (R,R) and (S,S) | Racemic (R,S) and (S,R) or Racemic (R,R) and (S,S) of 5-chloro-1'-(1-(4-chlorophenyl)-2,2-dimethylpropyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione |

Compounds of particular interest, or a pharmaceutically acceptable salt thereof, are present in the following Table 3:

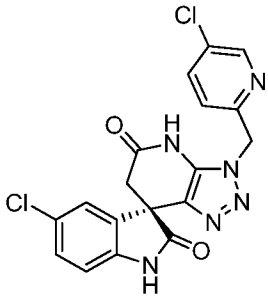
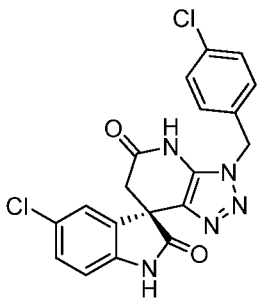
**Table 3**

| Example No. | Compound Structure | Compound Chemical Name |
|---|---|---|
| 1 |  | (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
| 2 |  | (R)-5-chloro-1'-(2,4-dichlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, and |
| 3-1 |  | (R)-5-chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione. |

| | | |
|---|---|---|
| 4-1 |  | (R)-5'-chloro-3-((S)-1-(4-chlorophenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione, Isomer 1 |

Additional compounds of particular interest, or a pharmaceutically acceptable salt thereof, are present in the following Table 4:

**Table 4**

| Compound No. | Compound Structure | Compound Chemical Name |
|---|---|---|
| 5 |  | (R)-5'-chloro-3-((5-chloropyridin-2-yl)methyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione,and |
| 6 |  | (R)-5'-chloro-3-(4-chlorobenzyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione. |

Another aspect of the present disclosure includes a pharmaceutical composition comprising a compound of Formula (I) comprising any one of the embodiments described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient. The pharmaceutical composition may further comprise at least one additional pharmaceutical agent. Examples of the additional pharmaceutical agent include, but are not limited to, Celgosivir.

In yet another aspect of the present disclosure, a method is provided for treating a disease caused by a viral infection comprising the step of administering to a subject (in particular, a human) in need thereof, a therapeutically effective amount of a compound of Formula(I) including any of the embodiments described herein, or a pharmaceutically acceptable salt thereof. In a particular useful embodiment, the viral infection is caused by a virus selected from the group consisting of dengue virus and yellow fever virus. In a more particular useful embodiment, the viral infection is caused by dengue virus. The compound may be administered as a pharmaceutical composition described herein.

Another aspect of the present disclosure includes a compound of Formula (I) comprising any one of the embodiments described above, or a pharmaceutically acceptable salt thereof, for use as a medicament (e.g., the use of a compound of Formula(I) comprising any one of the embodiments described above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease caused by a viral infection).In a particular useful embodiment, the viral infection is caused by a virus selected from the group consisting of dengue virus and yellow fever virus. In a more particular useful embodiment, the viral infection is caused by dengue virus. Another aspect of the present disclosure includes a compound of Formula (I) comprising any one of the embodiments described above, or a pharmaceutically acceptable salt thereof, where the compound is a NS4B inhibitor.

## BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate an embodiment and together with the description illustrate the disclosed compounds, compositions, methods and uses.

Figure 1 shows an *in vivo* mouse efficacy study of a representative compound of the present disclosure under various dosages.

Figure 2 shows a representative compound of the present disclosure inhibits viral RNA synthesis.

Figure 3 shows effects of I64V substitution in DENV-1 NS4B on the activity of a representative compound of the present disclosure.

***Definitions***

The phrase "therapeutically effective amount" means an amount of a compound of the present disclosure that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

As used herein, a subject is “in need of” a treatment if such subject would benefit biologically, medically or in quality of life from such treatment (preferably, a human).

As used herein, the term “inhibit”, "inhibition" or “inhibiting” refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term “subject” refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

As used herein, the term “treat”, “treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment “treat”, "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the subject. In yet another embodiment, “treat”, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. In yet another embodiment, “treat”, "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

The term "compounds of the present disclosure" (unless specifically identified otherwise) refer to compounds of Formula (I) and salts thereof, as well as all stereoisomers (including diastereoisomers and enantiomers), rotamers, tautomers and isotopically labelled compounds (including deuterium substitutions), as well as inherently formed moieties (e.g., polymorphs, solvates and/or hydrates). For purposes of this disclosure, solvates and hydrates are generally considered compositions.

The term "a," "an," "the" and similar terms used in the context of the present disclosure (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

As used herein, the terms "alkyl" refers to a hydrocarbon radical of the general formula $C_nH_{2n+1}$. The alkane radical may be straight or branched. For example, the term "($C_1$-$C_6$)alkyl" refers to a monovalent, straight, or branched aliphatic group containing 1 to 6 carbon atoms (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neo-pentyl, 3,3-dimethylpropyl, hexyl, 2-methylpentyl, and the like). Similarly, the alkyl portion (i.e., alkyl moiety) of an alkoxy, acyl (e.g., alkanoyl), alkylamino, dialkylamino, and alkylthio group has the same definition as above.

The term"cycloalkyl" refers to a nonaromatic carbocyclic ring that is fully hydrogenated and exists as a monocyclic ring. Unless specified otherwise, the carbocyclic ring is generally a 3- to 8-membered ring. For example, a fully saturated cycloalkyl include groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

The term "heteroaryl" refers to an aromatic ring structure containing from 5 to 14 ring atoms in which at least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as triazolyl, imidazolyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered

fused rings such as quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and 1,4-benzoxazinyl. In a group that has a heteroaryl substituent, the ring atom of the heteroaryl substituent that is bound to the group may be the at least one heteroatom, or it may be a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. Similarly, if the heteroaryl substituent is in turn substituted with a group or substituent, the group or substituent may be bound to the at least one heteroatom, or it may be bound to a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. The term "heteroaryl" also includes pyridyl N-oxides and groups containing a pyridine N-oxide ring.

Examples of single-ring heteroaryls include furanyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl (also known as "thiofuranyl"), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiadiazolyl, oxathiazolyl, oxadiazolyl (including oxadiazolyl, 1,2,4-oxadiazolyl (also known as "azoximyl"), 1,2,5-oxadiazolyl (also known as "furazanyl"), or 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl or 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, or 1,3,4-dioxazolyl), oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl (including 1,2-pyranyl or 1,4-pyranyl), dihydropyranyl, pyridinyl (also known as "azinyl"), piperidinyl, diazinyl (including pyridazinyl (also known as "1,2-diazinyl"), pyrimidinyl (also known as "1,3-diazinyl" or "pyrimidyl"), or pyrazinyl (also known as "1,4-diazinyl")), piperazinyl, triazinyl (including s-triazinyl (also known as "1,3,5-triazinyl"), as-triazinyl (also known 1,2,4-triazinyl), and v-triazinyl (also known as "1,2,3-triazinyl")), oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl (also known as "pentoxazolyl"), 1,2,6-oxazinyl, or 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl or p-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl or 1,2,6-oxathiazinyl), oxadiazinyl (including 1,4,2-oxadiazinyl or 1,3,5,2-oxadiazinyl), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

Examples of 2-fused-ring heteroaryls include, indolizinyl, pyridinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, or pyrido[4,3-b]-pyridinyl), and pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl,

benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, and tetrahydroisoquinolinyl.

Examples of 3-fused-ring heteroaryls or heterocycloalkyls include 5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline, 4,5-dihydroimidazo[4,5,1-hi]indole, 4,5,6,7-tetrahydroimidazo[4,5,1-jk][1]benzazepine, and dibenzofuranyl.

Other examples of fused-ring heteroarylsincludebenzo-fused heteroaryls such as indolyl, isoindolyl (also known as “isobenzazolyl” or “pseudoisoindolyl”), indoleninyl (also known as “pseudoindolyl”), isoindazolyl (also known as “benzpyrazolyl”), benzazinyl (including quinolinyl (also known as “1-benzazinyl”) or isoquinolinyl (also known as “2-benzazinyl”)), phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl (including cinnolinyl (also known as “1,2-benzodiazinyl”) or quinazolinyl (also known as “1,3-benzodiazinyl”)), benzopyranyl (including “chromanyl” or “isochromanyl”), benzothiopyranyl (also known as “thiochromanyl”), benzoxazolyl, indoxazinyl (also known as “benzisoxazolyl”), anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl (also known as “coumaronyl”), isobenzofuranyl, benzothienyl (also known as “benzothiophenyl,” “thionaphthenyl,” or “benzothiofuranyl”), isobenzothienyl (also known as “isobenzothiophenyl,” “isothionaphthenyl,” or “isobenzothiofuranyl”), benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl (including 1,3,2-benzoxazinyl , 1,4,2-benzoxazinyl , 2,3,1-benzoxazinyl , or 3,1,4-benzoxazinyl ), benzisoxazinyl (including 1,2-benzisoxazinyl or 1,4-benzisoxazinyl), tetrahydroisoquinolinyl , carbazolyl, xanthenyl, and acridinyl.

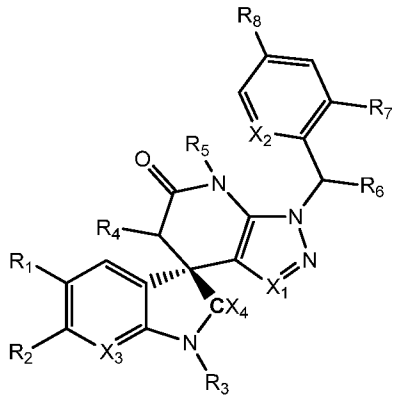
The term “heterocycle” refers to a saturated or partially saturated ring structure containing a total of 3 to 14 ring atoms. At least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heterocycle alternatively may comprise 2 or 3 rings fused together, wherein at least one such ring contains a heteroatom as a ring atom (e.g., nitrogen, oxygen, or sulfur). In a group that has a heterocycle substituent, the ring atom of the heterocycle substituent that is bound to the group may be the at least one heteroatom, or it may be a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. Similarly, if the heterocycle substituent is in turn substituted with a group or substituent, the group or substituent may be bound to the at least one heteroatom, or it may be bound to a ring carbon atom, where the ring carbon atom may be in

the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom.

## *DETAILED DESCRIPTION*

The present disclosure provides compounds and pharmaceutical compositions thereof that are useful in treating a disease caused by a viral infection, in particular viral infection caused by dengue virus. The following enumerated embodiments are included within the invention.

1. A compound of Formula (I)



(I)

wherein

$R_1$ is F, Cl, Br, $CF_3$, $OCH_3$, ($C_1$-$C_6$)alkyl or cycloalkyl;

$R_2$ is H, F, Cl, Br, ($C_1$-$C_6$)alkyl or cycloalkyl; or $R_1$ and $R_2$ taken together with the aromatic carbon atoms to which they are attached form a fused 1,3-dioxolo group;

$R_3$ is H, ($C_1$-$C_6$)alkyl or cycloalkyl;

$R_4$ is H, ($C_1$-$C_6$)alkyl, cycloalkyl or -C(=O)-$NH_2$;

$R_5$ is H, ($C_1$-$C_6$)alkyl, cycloalkyl or benzyl;

$R_6$ is H, ($C_1$-$C_6$)alkyl or cycloalkyl;

$R_7$ is H, F, Cl or $OCH_3$;

$R_8$ is F, Cl, Br, $CF_3$, $-OCHF_2$, $OCF_3$, $OCH_3$ or $(C_1$-$C_6)$alkyl;

$X_1$ is CH or N;

$X_2$ is CH or N;

$X_3$ is CH or N;

$X_4$ is =O or $H_2$;

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, and $R_8$ are each optionally independently substituted with one or more independent $R_{300}$ substituents;

$R_{300}$ is selected from the group consisting of H, $(C_1$-$C_6)$alkyl, cycloalkyl, hydroxy, amino, F, Cl, Br, phenyl, heterocycle and heteroaryl;

or a pharmaceutically acceptable salt thereof.

2. The compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein $R_1$ is Cl.

3. The compound of embodiment 1 or embodiment 2, or a pharmaceutically acceptable salt thereof, wherein $R_2$ is Cl or F.

4. The compound of any one of the foregoing embodiments, or a pharmaceutically acceptable salt thereof, wherein $R_3$ is H or cyclopropyl.

5. The compound of any one of the foregoing embodiments, or a pharmaceutically acceptable salt thereof, wherein $R_4$ is H.

6. The compound of any one of the foregoing embodiments, or a pharmaceutically acceptable salt thereof, wherein $R_5$ is H, methyl or *i*-propyl.

7. The compound of any one of the foregoing embodiments, or a pharmaceutically acceptable salt thereof, wherein $R_6$ is H or methyl.

8. The compound of any one of the foregoing embodiments, or a pharmaceutically acceptable salt thereof, wherein $R_7$ is H or Cl.

9. The compound of any one of the foregoing embodiments, or a pharmaceutically acceptable salt thereof, wherein $R_8$ is Cl, methyl, *i*-propyl or *t*-butyl.

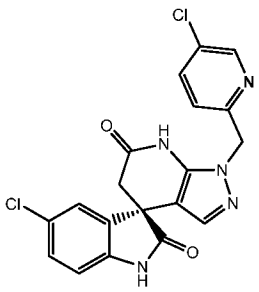
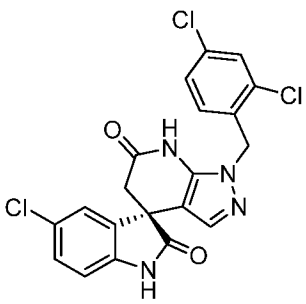
10. The compound of any one of the foregoing embodiments, or a pharmaceutically acceptable salt thereof, wherein $X_1$ is CH.

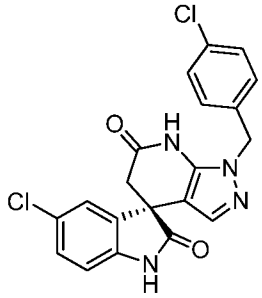
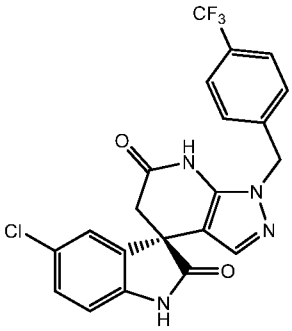
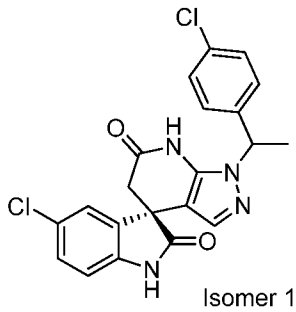
11. The compound of any one of the foregoing embodiments, or a pharmaceutically acceptable salt thereof, wherein $X_2$ is N.

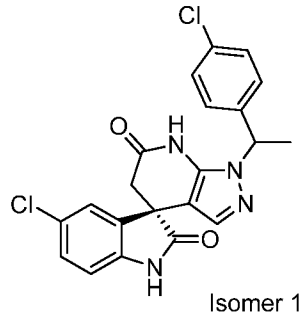
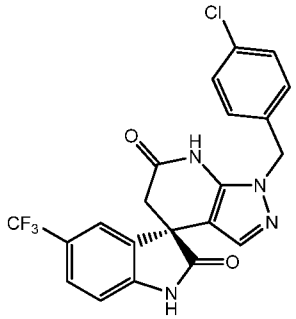
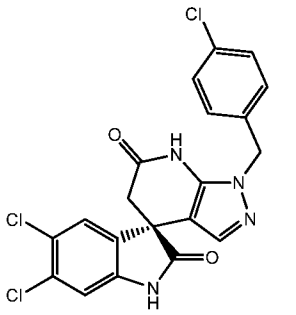
12. The compound of any one of the foregoing embodiments, or a pharmaceutically acceptable salt thereof, wherein $X_3$ is CH.

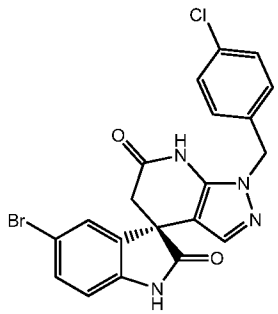
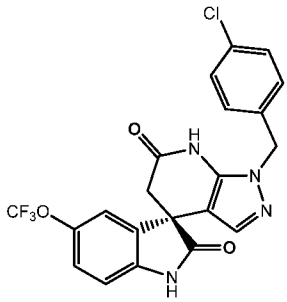
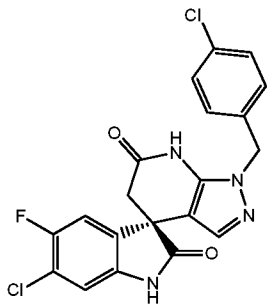
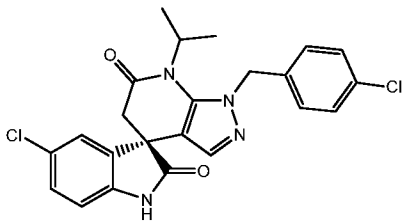
13. The compound of any one of the foregoing embodiments, or a pharmaceutically acceptable salt thereof, wherein $X_4$ is =O.

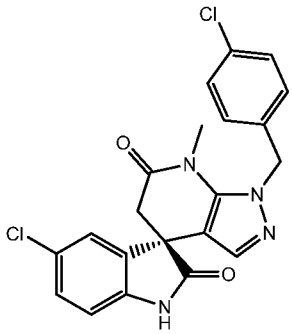
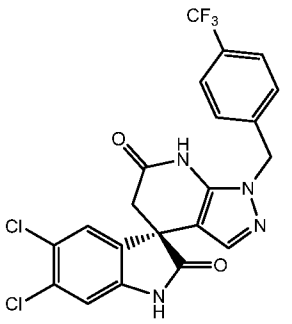
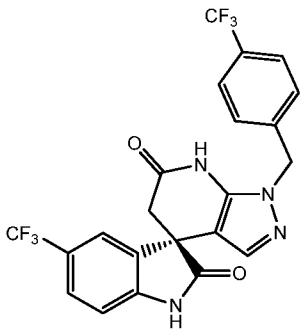
14. The compound of any one of the foregoing embodiments, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

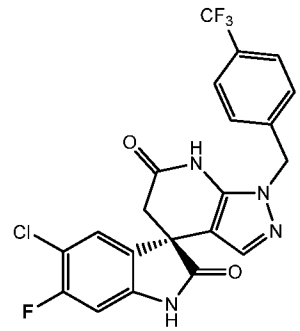
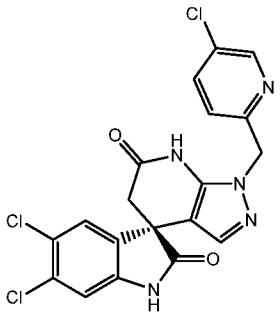
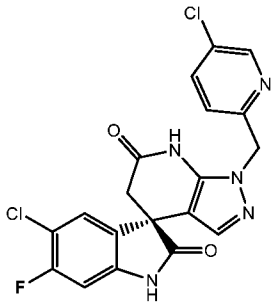
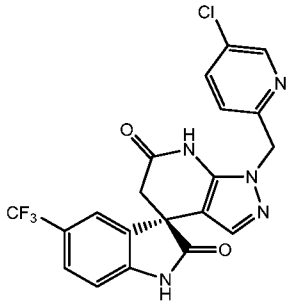
| | |
|---|---|
|  | (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5-chloro-1'-(2,4-dichlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

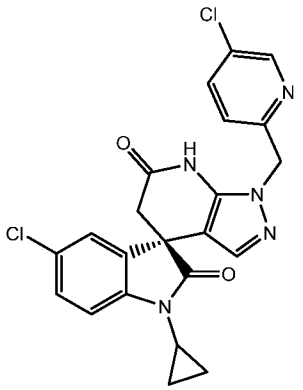
| | |
|---|---|
|  | (R)-5-chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5-chloro-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  Isomer 1 | ((R)-5-chloro-1'-(1-(4-chlorophenyl)ethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, Isomer 1, |

| | |
|---|---|
|  Isomer 1 | ((S)-5-chloro-1'-(1-(4-chlorophenyl)ethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, Isomer 1, |
|  | (R)-1'-(4-chlorobenzyl)-5-(trifluoromethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5,6-dichloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

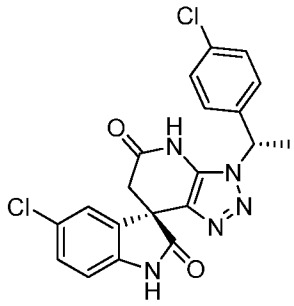
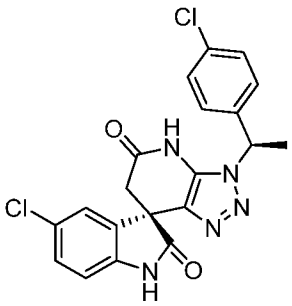
| | |
|---|---|
|  | (R)-5-bromo-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-1'-(4-chlorobenzyl)-5-(trifluoromethoxy)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-6-chloro-1'-(4-chlorobenzyl)-5-fluoro-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5-chloro-1'-(4-chlorobenzyl)-7'-isopropyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

| | |
|---|---|
|  | (R)-5-chloro-1'-(4-chlorobenzyl)-7'-methyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5,6-dichloro-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5-(trifluoromethyl)-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

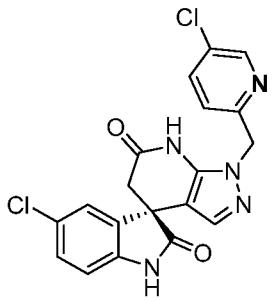
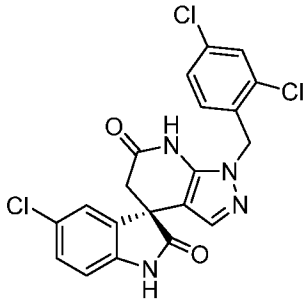
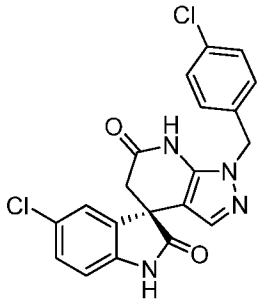
| | |
|---|---|
|  | (R)-5-chloro-6-fluoro-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5,6-dichloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-6-fluoro-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-1'-((5-chloropyridin-2-yl)methyl)-5-(trifluoromethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, and |

| | |
|---|---|
|  | (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-1-cyclopropyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione. |

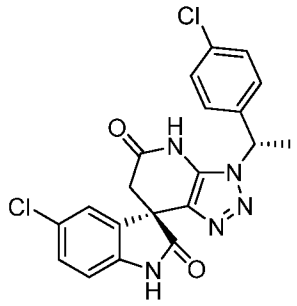
15. The compound of any one of the foregoing embodiments, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

| | |
|---|---|
|  | (R)-5'-chloro-3-((S)-1-(4-chlorophenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione; and |
|  | (R)-5'-chloro-3-((R)-1-(4-chlorophenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione. |

16. The compound of any one of the foregoing embodiments, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

| | |
|---|---|
|  | (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5-chloro-1'-(2,4-dichlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, and |
|  | (R)-5-chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione. |

17. The compound of any one of the foregoing embodiments, or a pharmaceutically acceptable salt thereof, is (R)-5'-chloro-3-((S)-1-(4-chlorophenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione



18. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of the Claims 1-17, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

19. The pharmaceutical composition of embodiment 18 further comprising at least one additional pharmaceutical agent.

20. The pharmaceutical composition of embodiment 18 or embodiment 19 wherein said at least one additional pharmaceutical agent is Celgosivir.

21. A method for treating a disease caused by a viral infection comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of the embodiments 1-17, or a pharmaceutically acceptable salt thereof.

22. The method of embodiment 21 wherein said subject is human.

23. The method of embodiment 21 or embodiment 22, wherein said viral infection is caused by dengue virus.

24. The compound as claimed in any one of the embodiments 1-17, or a pharmaceutically acceptable salt thereof, for use as a medicament.

25. The use of a compound as claimed in any one of embodiments 1 to 17, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease caused by a viral infection.

26. The use of embodiment 25 wherein said viral infection is caused by dengue virus.

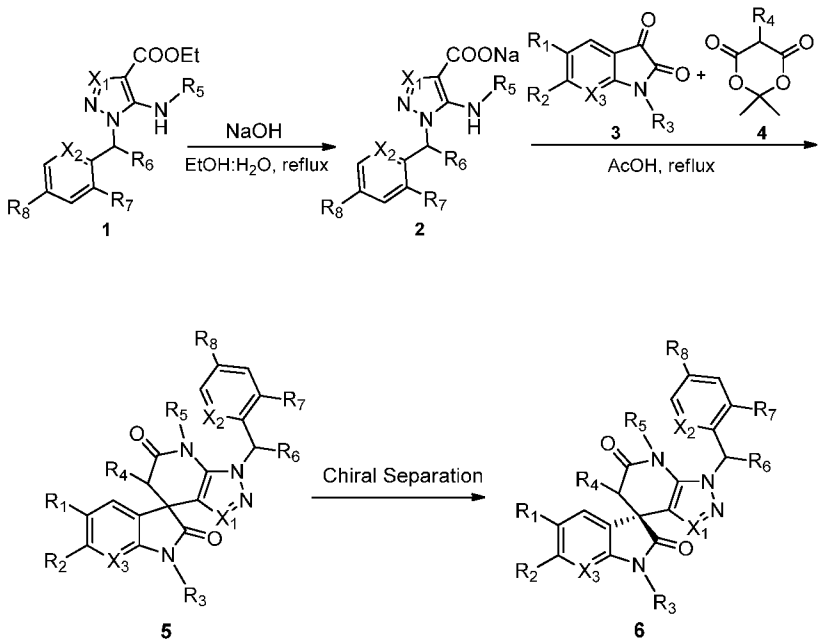
27. The compound as claimed in any one of the embodiments 1-17, or a pharmaceutically acceptable salt thereof, is a NS4B inhibitor.

Compounds of the present disclosure may be synthesized by synthetic routes that include processes analogous to those well-known to those of skill in the art, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wis.) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-19, Wiley, New York (1967-1999 ed.), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present disclosure as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

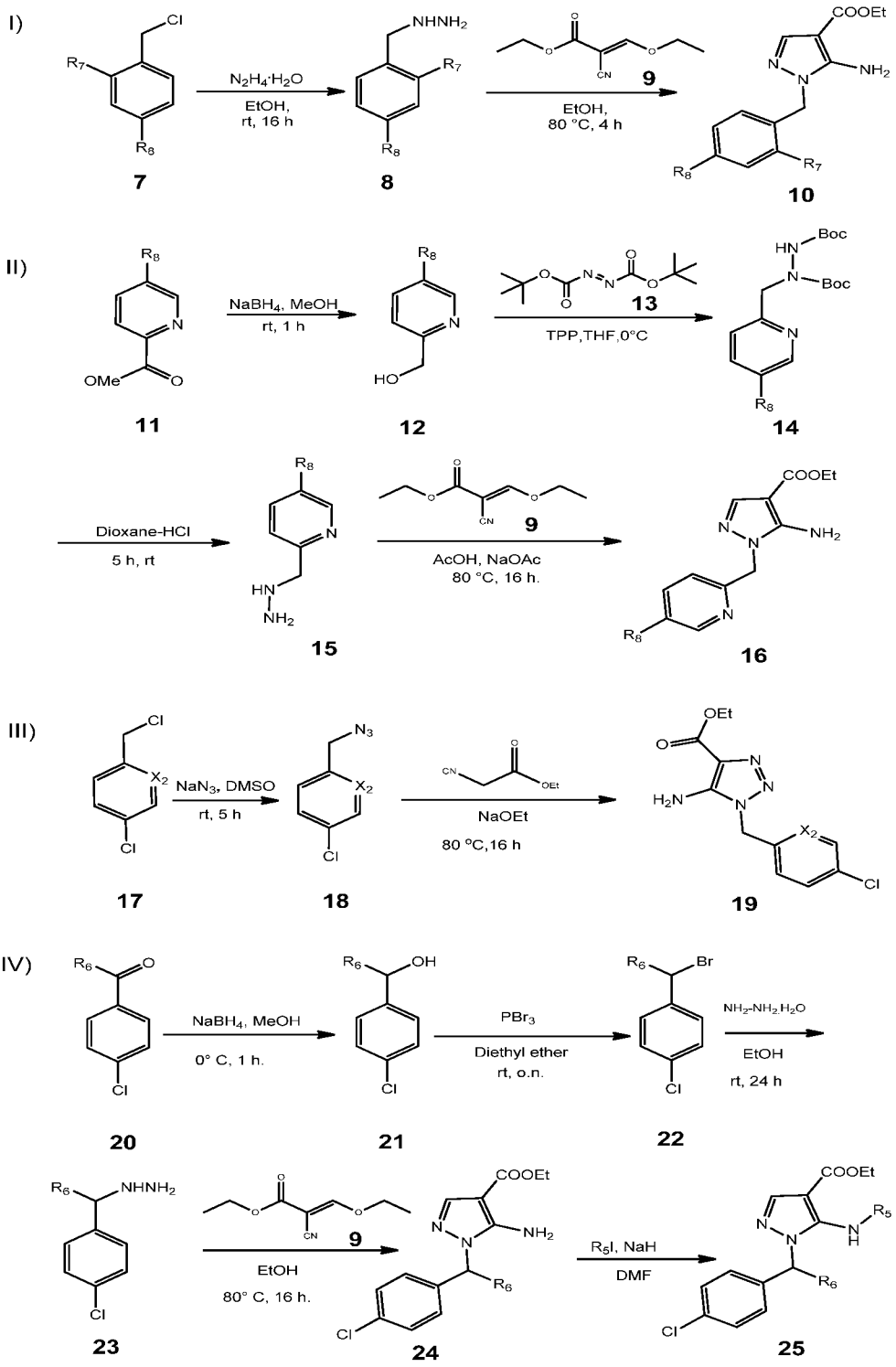
In the preparation of compounds of the present disclosure, protection of remote functionality of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

Schemes1-3 (below) describe potential routes for producing compounds of Formula (I). Compounds of Formula (I) can be made substantially optically pure by either using substantially optically pure starting material or by separation chromatography, recrystallization or other separation techniques well-known in the art. For a more detailed description, see the Example section below.



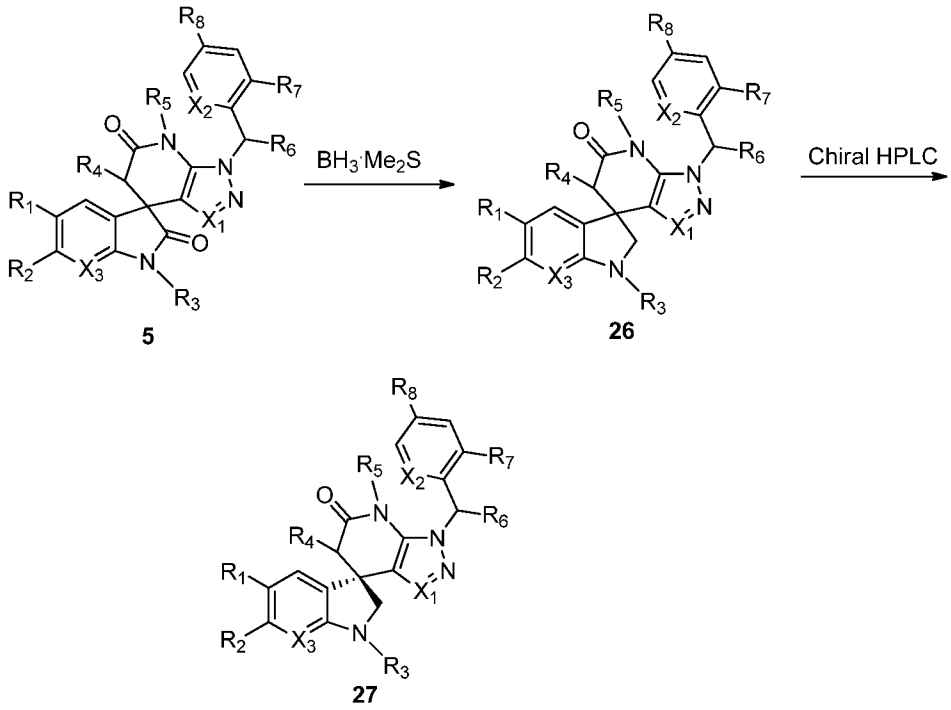

**Scheme 1**

Under Scheme 1, amino-ester **1**, made via various routes shown in Scheme 2 below, was hydrolyzed under basic conditions to afford corresponding acid **2**. Three-component-condensation of acid **2**, substituted isatins **3**, and Meldrum's acid derivative **4** in the presence of acetic acid afforded condensation product **5**, which was further purified by chiral HPLC to give the *R*-spiro-enantiomer product **6**.


I)
Cl
R7
R8
7
N2H4·H2O
EtOH,
rt, 16 h
NHNH2
R7
R8
8
9
EtOH,
80 °C, 4 h
COOEt
NH2
N
N
R8
R7
10
II)
R8
N
OMe
O
11
NaBH4, MeOH
rt, 1 h
R8
N
HO
12
13
TPP,THF,0°C
HN
Boc
N
Boc
N
R8
14
Dioxane-HCl
5 h, rt
R8
N
HN
NH2
15
9
AcOH, NaOAc
80 °C, 16 h.
COOEt
NH2
N
N
N
R8
16
III)
Cl
X2
Cl
17
NaN3, DMSO
rt, 5 h
N3
X2
Cl
18
CN
OEt
NaOEt
80 °C,16 h
OEt
O
H2N
N
N
N
X2
Cl
19
IV)
R6
O
Cl
20
NaBH4, MeOH
0° C, 1 h.
R6
OH
Cl
21
PBr3
Diethyl ether
rt, o.n.
R6
Br
Cl
22
NH2-NH2.H2O
EtOH
rt, 24 h
R6
NHNH2
Cl
23
9
EtOH
80° C, 16 h.
COOEt
NH2
N
N
R6
Cl
24
R5I, NaH
DMF
COOEt
N
N
N
H
R5
R6
Cl
25

**Scheme 2**

Scheme 2 shows that amino-ester **1** was made by four synthetic routes. Under route I), starting material **7** was converted to hydrazine **8**, which then underwent condensation reaction with (*E*)-ethyl 2-cyano-3-ethoxyacrylate **9** to afford amino-carboxylate **10**. Under route II), starting material **11** was converted to alcohol **12**, then Mitsunobu reaction of alcohol **12** with diazene **13** afforded intermediate **14**, which was then deprotected in the presence of HCl to afford hydrazine **15**. Hydrazine **15** was condensed with **9** to give compound **16**. Under route III), starting material **17** was converted to azide **18**, then underwent condensation reaction with ethyl 2-cyanoacetate to afford amino-triazole **19**.Under route IV), ketone **20** was reduced to alcohol **21**, which was converted to intermediate **22**. **22**was then converted to hydrazine **23**, which then underwent condensation reaction with **9** to give **24**. Capping of amine **24** afforded the compound **25**.




5 **26** **27**

**Scheme 3**

Under Scheme 3, reduction of oxindole **5** (as prepared according to Scheme 1) in the presence of $BH_3{\cdot}Me_2S$ afforded compound **26**, which was then purified by chiral HPLC to give the desired R-isomer **27**.

The compounds and intermediates may be isolated and used as the compound *per se* or as its salt. As used herein, the terms "salt" or "salts" refers to an acid addition or base addition salt of a compound of the present disclosure or intermediate. "Salts" include in particular "pharmaceutical acceptable salts". The term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compounds of this disclosure and, which typically are not biologically or otherwise undesirable.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfornate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate and trifluoroacetate salts.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

The pharmaceutically acceptable salts of the present disclosure can be synthesized from a parent compound, a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labelled forms of the compounds. Isotopically labelled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the present disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as $^{2}H$, $^{3}H$, $^{11}C$, $^{13}C$, $^{14}C$, $^{15}N$, $^{18}F$ $^{31}P$, $^{32}P$, $^{35}S$, $^{36}Cl$, $^{125}I$ respectively. The present disclosure includes various isotopically labelled compounds as defined herein, for example those into which radioactive isotopes, such as $^{3}H$, $^{13}C$, and $^{14}C$ , are present. Such isotopically labelled compounds are useful in metabolic studies (with $^{14}C$), reaction kinetic studies (with, for example $^{2}H$ or $^{3}H$), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an $^{18}F$ or labelled compound may be particularly desirable for PET or SPECT studies. Isotopically labelled compounds of this present disclosure can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

Further, substitution with heavier isotopes, particularly deuterium (i.e., $^{2}H$ or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life, reduced dosage requirements, reduced Cyp450 inhibition (competitive or time dependent) or an improvement in therapeutic index. For example, substitution with deuterium may modulate undesirable side effects of the undeuterated

compound, such as competitive Cyp450 inhibition, time dependent Cyp450 inactivation, etc. It is understood that deuterium in this context is regarded as a substituent in compounds of the present disclosure (including both the monomeric and linker moieties of the dimer). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this disclosure is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Isotopically-labelled compounds of the present disclosure can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labelled reagents in place of the non-labelled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the present disclosure include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* $D_2O$, $d_6$-acetone, $d_6$-DMSO.

It will be recognized by those skilled in the art that the compounds of the present disclosure may contain chiral centers and as such may exist in different isomeric forms. As used herein, the term “isomers” refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Also as used herein, the term “an optical isomer” or “a stereoisomer” refers to any of the various stereo isomeric configurations which may exist for a given compound of the present disclosure and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. Therefore, the present disclosure includes enantiomers, diastereomers or racemates of the compound.

"Enantiomers" are a pair of stereoisomers that are non- superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (–) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Alternatively, the resolved compounds can be defined by the respective retention times for the corresponding enantiomers/diastereomers via chiral HPLC.

Certain of the compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. Unless specified otherwise, the compounds of the present invention are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques (e.g., separated on chiral SFC or HPLC chromatography columns, such as CHIRALPAK® and CHIRALCEL® available from DAICEL Corp. using the appropriate solvent or mixture of solvents to achieve good separation). If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

Compounds of the present disclosure that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of the present disclosure by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of the present disclosure with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the present disclosure further provides co-crystals comprising a compound of the present disclosure.

The compounds of the present disclosure are typically used as a pharmaceutical composition (e.g., a compound of the present disclosure and at least one pharmaceutically

acceptable carrier). As used herein, the term "pharmaceutically acceptable carrier" includes generally recognized as safe (GRAS) solvents, dispersion media, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, salts, preservatives, drug stabilizers, buffering agents (e.g., maleic acid, tartaric acid, lactic acid, citric acid, acetic acid, sodium bicarbonate, sodium phosphate, and the like), and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289-1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated. For purposes of this present disclosure, solvates and hydrates are considered pharmaceutical compositions comprising a compound of the present disclosure and a solvent (i.e., solvate) or water (i.e., hydrate).

The formulations may be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (i.e., compound of the present disclosure or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent)) is dissolved in a suitable solvent in the presence of one or more of the excipients described above. The compound of the present disclosure is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to give the patient an elegant and easily handleable product.

The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers are well-known to those skilled in the art and include materials such as bottles (plastic and glass), ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

In certain instances, it may be advantageous to administer the compound of the present disclosure in combination with at least one additional pharmaceutical (or therapeutic) agent. The compound of the present disclosure may be administered either simultaneously with, or before or after, one or more other therapeutic agent(s). Alternatively, the compound of the

present disclosure may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition as the other agent(s).

Suitable additional pharmaceutical agents include, but not limited to, interferons, ribavirin and ribavirin analogs, cyclophilin binder, HCV NS3 protease inhibitors, HCV NS5a inhibitors, P7 inhibitor, entry inhibitor, NS4b inhibitor, alpha-glucosidase inhibitors, host protease inhibitors, immune modulators, kinase inhibitors which induce cytokines or chemokines for severe dengue, symptomatic relief agents such as for plasma leakage etc., surface receptors such as CLEC5A and DC-SIGN, nucleoside and non-nucleoside NS5b inhibitors.

The compound of the present disclosure or pharmaceutical composition thereof for use in humans is typically administered orally at a therapeutic dose.

It will be appreciated that the dosage range of a compound of the present disclosure to be employed for treating a viral infection depends upon factors known to the person skilled in the art, including host, nature and severity of the condition to be treated, the mode of administration and the particular substance to be employed.

The daily dosage of the compound of the present disclosure will vary with the compound employed, the mode of administration, the treatment desired and the disease indicated, as well as other factors such as a subject's age, body weight, general health, condition, prior medical history and sex, and like factors known in the medical arts. For example, a compound of the present disclosure is administered at a daily dosage in the range from about 0.1mg/kg body weight to about20mg/kg body weight, e.g. in the range from about 1 mg/kg body weight to about 10 mg/kg body weight. Typically, satisfactory results can be obtained when the compound of the present disclosure is administered at a daily dosage from about 0.001 g to about 10 g, e.g. not exceeding about 1 gram, e.g. from about 0.1 g to about 0.5 g for a 70 kg human, given up to 4 times daily.

Furthermore, several divided dosages, as well as staggered dosages, can be administered daily or sequentially, or the dose can be continuously infused, or can be a bolus injection. Further, the dosages of the compounds of the present disclosure can be proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.

In general, the therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body

weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, pharmacist, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

Another aspect of the present disclosure is a product comprising a compound of the present disclosure and at least one other therapeutic agent (or pharmaceutical agent) as a combined preparation for simultaneous, separate or sequential use in therapy to treat a subject having a disease caused by viral infection.

In the combination therapies of the present disclosure, the compound of the present disclosure and the other therapeutic agent may be manufactured and/or formulated by the same or different manufacturers. Moreover, the compound of the present disclosure and the other therapeutic (or pharmaceutical agent) may be brought together into a combination therapy: (i) prior to release of the combination product to physicians (*e.g.* in the case of a kit comprising the compound of the present disclosure and the other therapeutic agent or fixed dose composition); (ii) by the physician themselves (or under the guidance of the physician) shortly before administration; (iii) in the patient themselves, *e.g.* during sequential administration of the compound of the present disclosure and the other therapeutic agent.

It is especially advantageous to formulate the pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

Daily dosages with respect to the other therapeutic agent used will vary depending upon, for example, the compound employed, the host, the mode of administration and the severity of the condition to be treated. Because of the diverse types of the other therapeutic agent that may be used, the amounts can vary greatly, and can be determined by routine experimentation, as described above.

The compound of the present disclosure and at least one other therapeutic (or pharmaceutical) agent may be administered by any conventional route, in particular enterally,

e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions.

Embodiments of the present disclosure are illustrated by the following Examples. It is to be understood, however, that the embodiments of the present disclosure are not limited to the specific details of these Examples, as other variations thereof will be known, or apparent in light of the instant disclosure, to one of ordinary skill in the art.

Throughout this disclosure, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this disclosure in order to more fully describe the state of the art to which this pertains.

***EXAMPLES***

Unless specified otherwise, starting materials are generally available from a non-excluding commercial sources such as TCI Fine Chemicals (Japan), Shanghai Chemhere Co., Ltd.(Shanghai, China), Aurora Fine Chemicals LLC (San Diego, CA), FCH Group (Ukraine), Aldrich Chemicals Co. (Milwaukee, Wis.), Lancaster Synthesis, Inc. (Windham, N.H.), Acros Organics (Fairlawn, N.J.), Maybridge Chemical Company, Ltd. (Cornwall, England), Tyger Scientific (Princeton, N.J.), AstraZeneca Pharmaceuticals (London, England), Chembridge Corporation (USA), Matrix Scientific (USA), Conier Chem & Pharm Co., Ltd (China), Enamine Ltd (Ukraine), Combi-Blocks, Inc. (San Diego, USA), Oakwood Products, Inc. (USA), Apollo Scientific Ltd. (UK), Allichem LLC. (USA) and Ukrorgsyntez Ltd (Latvia).

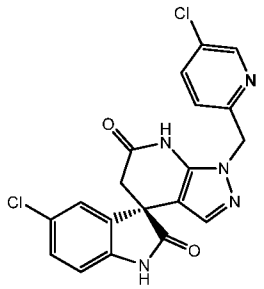
The following abbreviations used herein below have the corresponding meanings:

| | |
|---|---|
| h | hour(s) |
| min | minute(s) |
| DCM | dichloromethane |
| NMR | nuclear magnetic resonance |
| TLC | thin layer chromatography |
| MS | mass spectrometry |
| LC-MS | liquid chromatography-mass spectrometry |
| HPLC | high performance liquid chromatography |
| DMSO | dimethylsulfoxide |
| TEA | triethylamine |
| DMF | dimethylformamide |
| THF | tetrahydrofuran |

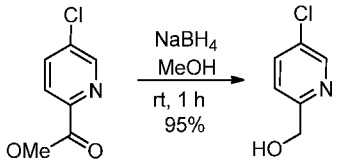
| | |
|---|---|
| $Na_2SO_4$ | sodium sulphate |
| HCl | hydrochloric acid |
| EA | ethyl acetate |
| ACN | acetonitrile |
| t-Bu | tert-butyl |
| rt | room temperature |
| ee | enantiomeric excess |

***Example 1***

Preparation of (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



Step 1: Preparation of (5-Chloropyridin-2-yl) methanol

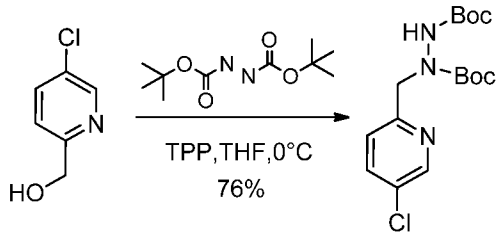



A solution of methyl 5-chloropicolinate (2 g, 11.7 mmol) in MeOH (20 ml) and sodium borohydride (0.89 g, 23.3 mmol) was stirred at rt for 1 h. After reaction was completed, solvent was evaporated. Distilled water was added and the aqueous layer was extracted with dichloromethane (3 x 30 ml). The combined organic layer was washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to afford 1.6 g (95% yield) of (5-Chloropyridin-2-yl) methanol as colourless liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ ppm 3.29 (br s, 1H), 4.75 (br s, 2H), 7.25 (1H, merged with $CDCl_3$), 7.67 (d, *J* = 7.0 Hz, 1H), 8.52 (s, 1H).

LC-MS: m/z 144.0 $(M+H)^+$.

Step 2: Preparation of di-tert-butyl 1-((5-chloropyridin-2-yl) methyl) hydrazine-1, 2-dicarboxylate

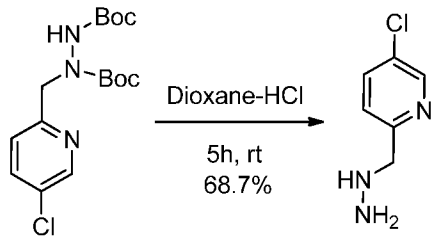



To a solution of (5-Chloropyridin-2-yl) methanol (1.6 g, 11.2 mmol) in THF at 0 °C was added triphenylphosphine (1.6 g, 11.188 mmol) and di-tert-butylcarbazate (4.4 g, 16.79 mmol) and the reaction mixture was stirred at rt for 16 h. The solvent was removed under vacuum and purified by column chromatography using 100-200 silica gel mesh eluting with 20% EtOAc/Pet-ether, to give 3.5 g of Di-tert-butyl 1-((5-chloropyridin-2-yl) methyl) hydrazine-1, 2-dicarboxylate (76% yield) as a pale yellow liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ ppm 1.46 (br s, 18H), 4.74 (br s, 2H), 7.26 (1H, merged with $CDCl_3$), 7.60-7.65 (m, 1H), 8.49 (d, *J* = 2.2 Hz, 1H).

LC-MS: m/z 358.1 $(M+H)^+$.

Step 3: Preparation of 5-Chloro-2-(hydrazinylmethyl) pyridine hydrochloride



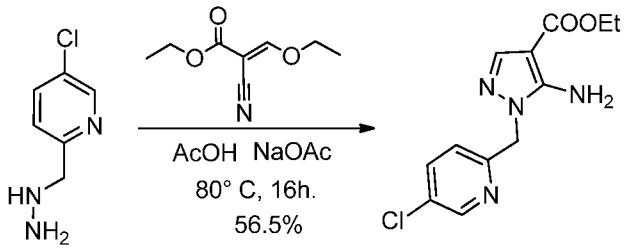

To a solution of Di-tert-butyl 1-((5-chloropyridin-2-yl) methyl) hydrazine-1, 2-dicarboxylate (3.5 g, 9.8 mmol) in dioxane (20 mL) was added dioxane-HCl (35 mL) followed by 2 drops of water at 0

°C. The reaction mixture was stirred at rt for 3 h till the reaction was completed, and the solvent was removed under vacuum and triturated with diethyl ether to afford 1.3 g of 5-chloro-2-(hydrazinylmethyl)pyridine hydrochloride (69% yield) as an off-white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 4.18 (br s, 2H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.95-8.0 (m, 1H), 8.62 (d, *J* = 2.2 Hz, 1H).

LC-MS:m/z 158.0 $(M+H)^+$.

Step 4: Preparation of ethyl 5-amino-1-((5-chloropyridin-2-yl) methyl)-1H-pyrazole-4-carboxylate

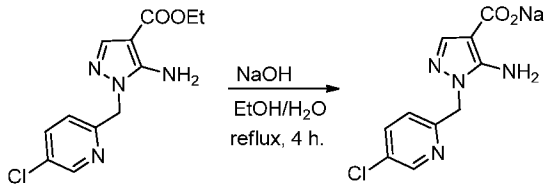



To a solution of 5-chloro-2-(hydrazinylmethyl) pyridine hydrochloride (1.3 g, 8.4 mmol) and (*E*)-ethyl 2-cyano-3-ethoxyacrylate (1.4 g, 8.4 mmol) in acetic acid (6.5 ml) was added water (1.3 ml) followed by sodium acetate (1.49 g, 18.2 mmol) at rt and the resulting reaction mixture was maintained at 110 °C for 16 h. The reaction mixture was cooled to rt and solvent was removed under reduced pressure and purified by column chromatography using 100-200 silica gel mesh. The product was eluted in 20% EtOAc/Pet-ether, to give 800 mg of Ethyl 5-amino-1-((5-chloropyridin-2-yl) methyl)-1H-pyrazole-4-carboxylate (57% yield) as an off white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ ppm 1.32 (t, *J* = 7.0 Hz, 3H), 4.25 (q, *J* = 7.1 Hz, 2H), 5.18 (s, 2H), 5.73 (br s, 2H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.60 (s, 1H), 7.65-7.70 (m, 1H), 8.51 (d, *J* = 2.2 Hz, 1H).

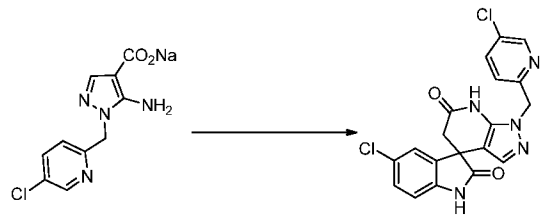
LC-MS:m/z 281.1 $(M+H)^+$.

Step 5: preparation of sodium 5-amino-1-((5-chloropyridin-2-yl) methyl)-1H-pyrazole-4-carboxylate




To a solution of Ethyl 5-amino-1-((5-chloropyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (800 mg, 2.86 mmol) in ethanol (8 mL) was added water (8 mL) followed by sodium hydroxide (228 mg, 5.7mmol) at rt and the resulting reaction mixture was maintained at 90 °C for 4 h. The resulting reaction mixture was cooled to rt and concentrated to dryness to get Sodium 5-amino-1-(3-chlorobenzyl)-1H-pyrazole-4-carboxylate, which was used for next step without further purification.

Step 6: Preparation of 6-Chloro-1'-((5-chloropyridin-2-yl) methyl)-5', 7'-dihydrospiro [indoline-3, 4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



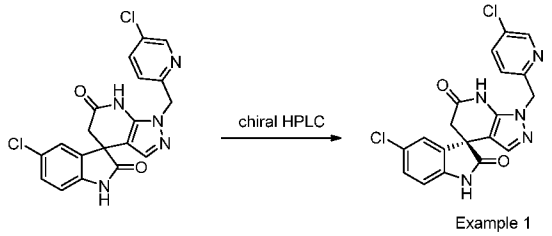

To a solution of above sodium 5-amino-1-(3-chlorobenzyl)-1H-pyrazole-4-carboxylate in acetic acid was added 5-chloro-isatin (73 mg, 0.365 mmol) and Meldrum's acid (52.6 mg, 0.365 mmol) at rt and refluxed for 3h. The reaction mixture was cooled to rt and solvent was removed under reduced pressure. Water was added to the reaction mixture and stirred at rt for 15 min. The solid obtained through filtration was washed with water (2 x 15 ml) and dried under vacuum The resultant solid was purified by column chromatography over silica gel (100-200 mesh) using a solvent gradient of 8% methanol in dichloromethane as eluent to afford 200 mg of 6-Chloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione (17% yield for two steps) as an off white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$):δ ppm 2.54 (d, *J* = 16.2 Hz, 1H, partially overlap with DMSO peak), 3.12 (d, *J* = 16.2 HZ, 1H), 5.35 (q, *J* = 16.2 Hz, 2H), 6.82 (s, 1H), 6.92(d, *J* = 8.3 HZ, 1H),

7.00 (d, *J* = 8.3 HZ, 1H), 7.33-7.30 (m, 2H), 7.90 (d, *J* = 8.3 HZ, 1H), 8.60 (br, s, 1H), 10.60 (br, s, 1H), 11.10 (br, s, 1H).

LC-MS: 414.0 $(M+H)^+$.

Step 7: Preparation of (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione (Example 1)




Example 1

500 mg of 6-Chloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione was subjected to chiral preparativeHPLC (Column: Chiralpak AS-H (4.6x250 mm) 5µ; Mobile phase: Hexane : EtOH : Isopropyl amine (60 : 40 : 0.1); Flow: 1.0 mL/min; Diluent: Mobile phase; UV: 258 nm) to afford two enantiomers: 250 mg of (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione (Example 1) (Peak-1, 6.17 min in chiral HPLC, 100% ee) and 155 mg of (*S*)- 5-chloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione(Peak-2, 10.48 min in chiral HPLC, 99.1% ee) as white solid. The characterization data of Example 1 is shown below:

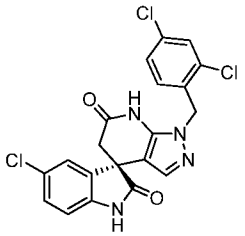
$[\alpha]^{25.8}_{D}$ : -99.1 (c = 0.53, $CHCl_3$).

$^1$H NMR (400 MHz, DMSO-$d_6$):δ ppm 2.54 (d, *J* = 16.2 Hz, 1H, partially overlap with DMSO peak), 3.12 (d, *J* = 16.2 HZ, 1H), 5.35 (q, *J* = 16.2 Hz, 2H), 6.82 (s, 1H), 6.92(d, *J* = 8.3 HZ, 1H), 7.00 (d, *J* = 8.3 HZ, 1H), 7.33-7.30 (m, 2H), 7.90 (d, *J* = 8.3 HZ, 1H), 8.60 (br, s, 1H), 10.60 (br, s, 1H), 11.10 (br, s, 1H).

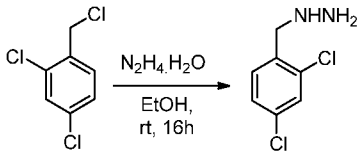
LC-MS: 414.0 $(M+H)^+$.

***Example 2***

Preparation of (R)-5-chloro-1'-(2,4-dichlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



Step 1: Preparation of (2,4-Dichlorobenzyl)hydrazine

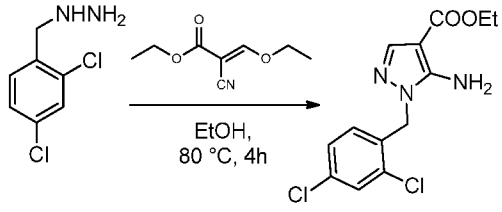



To a solution of hydrazine hydrate (25.2 g, 503.8 mmol) in ethanol (80 mL) was added a solution of 2,4-dichloro-1-(chloromethyl)benzene (10 g, 50.4 mmol) in ethanol (50 mL) at rt, the resulting reaction mass was stirred for 14 h. After the reaction was completed, the solvent was evaporated under reduced pressure. The residue was taken in 50% of sodium hydroxide in water (50 mL), aqueous solution was extracted with diethyl ether (3 x 100 mL). The combined organic layer was washed with water(100mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure to afford of *(2,4-Dichlorobenzyl)hydrazine* (7 g, 72% yield) as a colourless liquid.

$^1$H-NMR ($CDCl_3$): H-NMR ($CDCl_3$ 400 MHz, $CDCl_3$): δ ppm 2.8-3.5 (br s, 3H), 3.99 (s, 2H), 7.3-7.2 (m, 1H), 7.45-7.34 (m, 2H).

MS: m/z 191.0 $(M+H)^+$.

Step 2: Preparation of ethyl 5-amino-1-(2,4-dichlorobenzyl)-1H-pyrazole-4-carboxylate

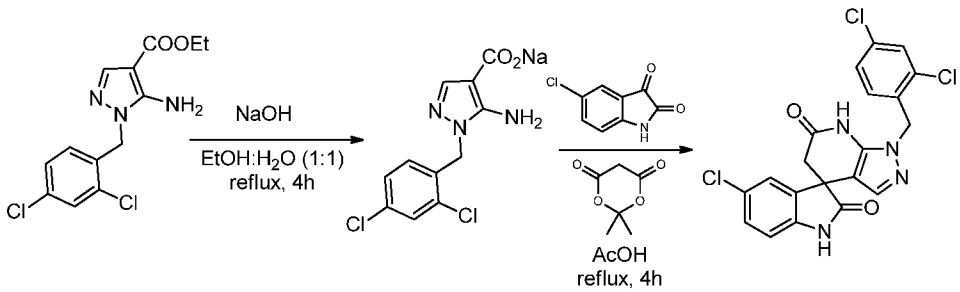



To a stirred solution of (2,4-Dichlorobenzyl)hydrazine (7 g, 36.65 mmol) in ethanol (80 mL) was added (E)-ethyl 2-cyano-3-ethoxyacrylate (6.2 g, 36.65 mmol) at rt. The resulting reaction mixture was maintained at 80 °C for 4 h. The reaction mixture was cooled to rt, solvent was removed under reduced pressure. The crude compound was purified by column chromatography over silica gel (100-200 mesh) using a solvent gradient of 20-25% ethyl acetate in pet-ether as eluent to afford 7 g (60.8% yield) of *ethyl 5-amino-1-(2,4-dichlorobenzyl)-1H-pyrazole-4-carboxylate* as a pale yellow gum.

$^1$H NMR (400 MHz, DMSO-*d6*): δ ppm 1.26 (t, *J* = 7.0 Hz, 3H) 4.18 (q, *J* = 7.0 Hz, 2H), 5.22 (s, 2H), 6.47 (br s, 2H), 6.64 (d, *J* = 8.3 Hz, 1H), 7.41 (d, *J* = 2.2 Hz, 1H), 7.55 (s, 1H), 7.67 (d, *J* = 1.7 Hz, 1H).

MS: m/z 314.0 $(M+H)^+$.

Step 3: Preparation of 5-Chloro-1'-(2,4-dichlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



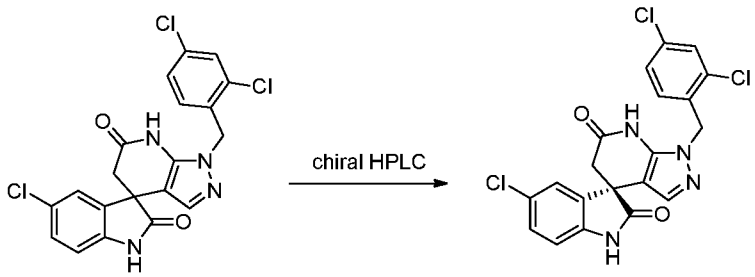

To a solution of *ethyl 5-amino-1-(2,4-dichlorobenzyl)-1H-pyrazole-4-carboxylate* (3 g, 9.6 mmol) in ethanol (15 mL) was added water (15 mL) followed by sodium hydroxide (1.15 g, 28.75 mmol) at rt and resulting reaction mixture was maintained at 80 °C for 4 h. The reaction mixture was cooled to rt and concentrated to dryness to get *sodium 5-amino-1-(2,4-dichlorobenzyl)-1H-*

*pyrazole-4-carboxylate*. To the resultant salt in acetic acid (15mL) was added 5-chloroindoline-2,3-dione (1.74 g, 9.585 mmol), and Meldrum's acid (1.4 g, 9.585 mmol) at rt and maintained at 100 °C for 4 h. The reaction mixture was cooled to rt and solvent was removed under reduced pressure. Ice water was added to the reaction mixture and stirred at rt for 15 min. The solid obtained through filtration was washed with water (2 x 15 mL) and dried under vacuum. The resultant solid was purified by washing with acetone (2 x 20 mL) to afford 3 g (71.4%) of *5-Chloro-1'-(2,4-dichlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione* as a white solid.

$^1$H NMR (400 MHz, DMSO-*d6*): δ ppm 2.55 (d, *J* = 15.8 Hz, 1H), 3.14 (d, *J* = 15.8 Hz, 1H), 5.36 (q, *J* = 16.7 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.85 (s, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 7.32 (dd, *J* = 1.7, 6.2 Hz, 1H), 7.35 (s, 1H), 7.46 (dd, *J* = 1.8, 6.5 Hz, 1H), 7.68 (d, *J* = 1.8 Hz, 1H), 10.64 (s, 1H), 11.10 (s, 1H).

MS = 447.0 $(M+H)^+$.

Step 4: Preparation of (R)-5-Chloro-1'-(2,4-dichlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione




Example 2

2 g of 5-Chloro-1'-(2,4-dichlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione was subjected to chiral preparative HPLC (Column: Chiralpak IA (4.6x250 mm) 5µ; Mobile phase: Hexane :EtOH: $CHCl_3$ :TFA (70:15 :15:0.1); Flow: 1.0 mL/min; Diluent: Mobile phase; UV: 255 nm) to afford two enantiomers: 208 mg of (R)-5-Chloro-1'-(2,4-dichlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione (Example 2) (Peak-1, 8.43 min in chiral HPLC, 98.8% ee) and 180 mg of (S)-5-Chloro-1'-(2,4-dichlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione (Peak-2, 12.63 min in chiral HPLC, 99% ee) as white solid. The characterization data of Example 2 is shown below:

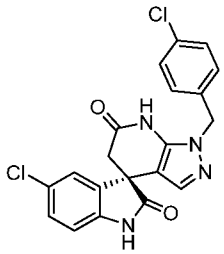
$[\alpha]^{27.5}_{D}$ : -123.1 (c = 0.56, DMSO).

$^1$H NMR (400 MHz, DMSO-*d6*): δ ppm 2.55 (d, *J* = 15.8.0 Hz, 1H), 3.14 (d, *J* = 15.8 Hz, 1H), 5.36 (q, *J* = 16.7 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.85 (s, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 7.32 (dd, *J* = 1.7, 6.2 Hz, 1H), 7.35 (s, 1H), 7.46 (dd, *J* = 1.8, 6.5 Hz, 1H), 7.68 (d, *J* = 1.8 Hz, 1H), 10.64 (s, 1H), 11.10 (s, 1H).

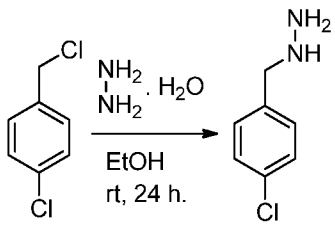
MS = 447.0 $(M+H)^+$.

***Example 3-1***

Preparation of (R)-5-chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



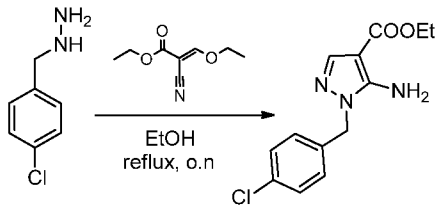
Step 1: Preparation of (4-Chlorobenzyl)hydrazine




A solution of 1-chloro-4-(chloromethyl)benzene (6 g, 37.0 mmol) in ethanol (30 mL) was added drop wise to a solution of hydrazine hydrate (18.5 g, 370 mmol) in ethanol (40 mL) and stirred at rt for 24 h. After completion of reaction, excess of ethanol and hydrazine was evaporated. A solution of 50% solution of sodium hydroxide (50 mL) in water was added to the above reaction mixture. The aqueous solution was extracted with diethyl ether (3 x 40 mL). The combined

organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to afford *(4-chlorobenzyl) hydrazine* as a colourless liquid, which was used in the next step without any further purification.

Step 2: Preparation of ethyl 5-amino-1-(4-chlorobenzyl)-1H-pyrazole-4-carboxylate

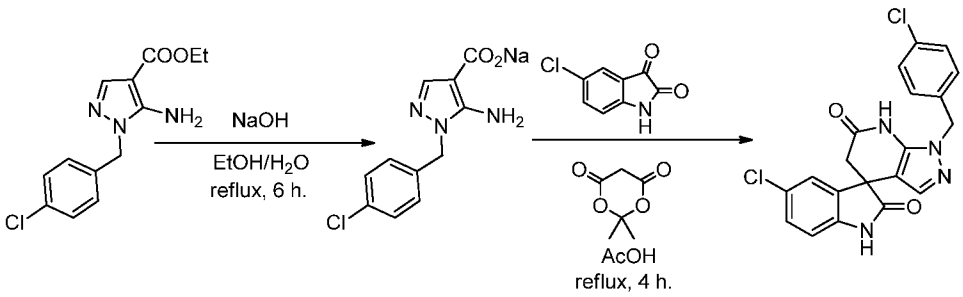



A solution of (E)-ethyl2-cyano-3-ethoxyacrylate (1.64 g, 9.708 mmol) and (4-chlorobenzyl) hydrazine (2 g, 9.708 mmol) in ethanol was stirred at 80° C for overnight. The solvent was removed under reduced pressure. The crude compound was purified by column chromatography over silica gel (100-200 mesh) using a solvent gradient of 20% ethyl acetate in pet-ether as eluent to afford 400 mg (11%) of *ethyl 5-amino-1-(4-chlorobenzyl)-1H-pyrazole-4-carboxylate* as an off-white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$): 1.24 (t, *J* = 7.0 Hz, 3H), 4.16 (q, *J* = 7.0 Hz, 2H), 5.17 (s, 2H), 6.41 (br s, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.50 (s, 1H).

LC-MS: m/z 280.1 $(M+H)^+$.

Step 3: Preparation of 5-Chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione

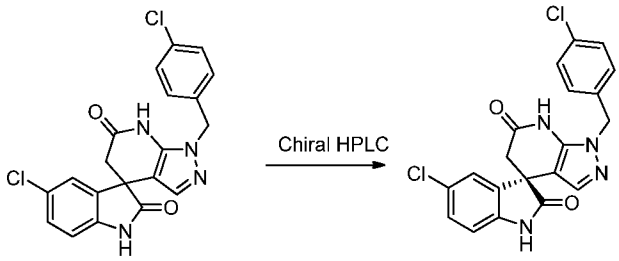


To a solution of ethyl 5-amino-1-(4-chlorobenzyl)-1H-pyrazole-4-carboxylate (400 mg, 1.433 mmol) in ethanol (5 mL) was added water (5 mL) followed by sodium hydroxide (150 mg, 2.867 mmol) at rt and resulting reaction mixture was maintained at 90 °C for 6h. The resulting reaction mixture was cooled to rt and concentrated to dryness to get sodium 5-amino-1-(4-chlorobenzyl)-1H-pyrazole-4-carboxylate. The resultant salt in acetic acid was added 5-chloroindoline-2,3-dione (240 mg, 1.576 mmol) and Meldrum's acid (237 mg, 1.648 mmol) at rt and stirred at 100° C for 3 h. The reaction mixture was cooled to rt and solvent was removed under reduced pressure. Water was added to the reaction mixture and stirred at rt for 15 min. The solid obtained through filtration was washed with water (2 x 15 mL) and dried under vacuum. The resultant solid was washed with acetone to get pure 5-Chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione 550 mg (92%).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 2.51 (d, *J* = 13.6 Hz, 1H), 3.12 (d, *J* = 15.8 Hz, 1H), 5.28 (q, *J* = 15.4 Hz, 10.6 Hz, 2H), 6.79 (s, 1H), 6.9 (d, *J* = 7.9 Hz, 1H), 7.35-7.2 (m, 4H), 7.42 (d, *J* = *8.3* Hz, 2H), 10.59 (br s, 1H), 11.08 (br s, 1H).

LC-MS: m/z 413.0 $(M+H)^+$.

Step 4: Preparation of (R)-5-chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione




Example 3-1

500 mg of 5-Chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione was subjected to chiral prepare HPLC (Column: Chiralpak IA (4.6x250 mm) 5µ; Mobile phase: Hexane : EtOH : DEA (60 : 40 : 0.1); Flow: 1.0 mL/min; UV: 255 nm) to afford two enantiomers: 110 mg of (R)-5-chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione (Example 3-1) (Peak-1, 6.87 min in chiral HPLC, 99.9% ee) and 150 mg of (S)-5-chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-

b]pyridine]-2,6'(1'H)-dione (Peak-2, 8.16 min in chiral HPLC, 99% ee) as white solid. The characterization data of Example 3-1 is shown below:

$[\alpha]^{25.4}_{D}$ : -121.7 (c = 0.25, MeOH).

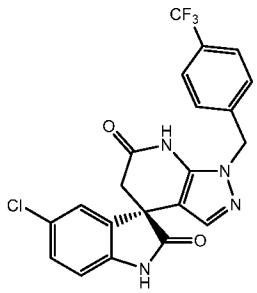
$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 2.51 (d, *J* = 13.6 Hz, 1H), 3.12 (d, *J* = 15.8 Hz, 1H), 5.28 (q, *J* = 15.4 Hz, 10.6 Hz, 2H), 6.79 (s, 1H), 6.9 (d, *J* = 7.9 Hz, 1H), 7.35-7.2 (m, 4H), 7.42 (d, *J* = *8.3* Hz, 2H), 10.59 (br s, 1H), 11.08 (br s, 1H).

LC-MS: m/z 413.0 $(M+H)^+$.

The following compounds were prepared using the general procedures as well as the procedures from the examples described above with the appropriate starting materials.

***Example 3-2***

(R)-5-chloro-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione

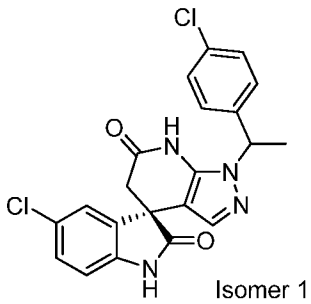



$^1$H-NMR (DMSO-$d_6$): δ ppm 2.66 (d, 1H, merged with DMSO). 3.12-3.16 (d, *J* = 15.8 Hz, 1H), 5.40 (q, *J* = 16.2 Hz, 2H), 6.82 (s, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 7.29-7.33 (m, 2H), 7.42 (d, *J* = 7.92 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 2H), 10.62 (s, 1H), 11.14 (br s, 1H).

MS:m/z 445.0 $(M-H)^-$.

***Example 3-3-1***

(R)-5-chloro-1'-(1-(4-chlorophenyl)ethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, Isomer 1.



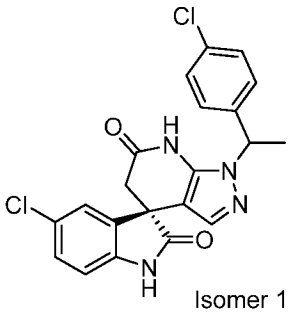

Isomer 1

$^1$H NMR (400 MHz, DMSO-*d6*): δ ppm 1.72 (d, *J* = 7.0 Hz, 3H), 2.52 (d, *J* = 16.3 Hz, 1H),3.07 (d, *J* = 16.6 Hz, 1H), 5.66 (d, *J* = 7.0 Hz, 1H), 6.83 (s, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 7.28-7.42 (m, 6H), 10.59 (s, 1H), 11.05 (br s, 1H).

MS: m/z 427.0 $(M+H)^+$.

***Example 3-3-2***

(S)-5-chloro-1'-(1-(4-chlorophenyl)ethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, Isomer 1.




Isomer 1

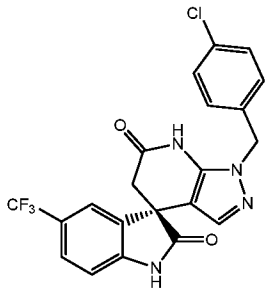
$^1$H NMR (400 MHz, DMSO-*d6*): δ ppm 1.72 (d, *J* = 7.0 Hz, 3H), 2.52 (d, *J* = 16.3 Hz, 1H),3.07 (d, *J* = 16.6 Hz, 1H), 5.66 (d, *J* = 7.0 Hz, 1H), 6.83 (s, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 7.28-7.42 (m, 6H), 10.59 (s, 1H), 11.05 (br s, 1H).

MS: m/z 427.0 $(M+H)^+$.

Examples 3-3-1 and 3-3-2 were resolved by chiral HPLC (Column: Acquity;UPLC;BEH; C18; 100×2.1mm, 1.7 µ; Mobile phase: 0.025% TFA in Aqueous and 0.025% TFA in ACN; Flow: 0.4 ml/min; Diluent: ACN; UV: 214 nm, 254 nm) from a racemic mixture of 5-chloro-1'-(1-(4-chlorophenyl)ethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, respectively.

***Example 3-4***

(R)-1'-(4-chlorobenzyl)-5-(trifluoromethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione

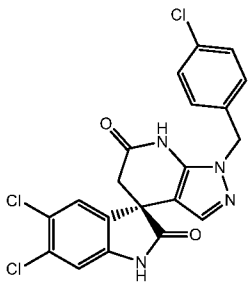


$^1$H-NMR (DMSO-$d_6$): δ ppm 2.57 (d, 1H, merged with DMSO), 3.23 (d, *J* = 16.0 Hz, 1H), 5.27 (q, *J* = 16.0 Hz, 2H), 6.77 (s, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 9.6 Hz, 2H), 10.8 (s, 1H), 11.1 (br s,1H).

MS: m/z 447.0 $(M+H)^+$.

***Example 3-5***

(R)-5,6-dichloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione

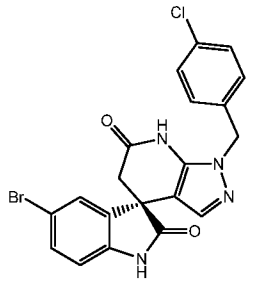


$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 11.09 (s, 1H), 10.72 (s, 1H), 7.55 (s, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.08 (s, 1H), 6.85 (s, 1H), 5.27 (q, *J* = 14.6 Hz, 2H), 3.18 (d, *J* = 16.0 Hz, 1H), 2.54 (d, *J* = 16.0 Hz, 1H).

MS: m/z 449.0 $(M+H)^+$.

***Example 3-6***

(R)-5-bromo-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione

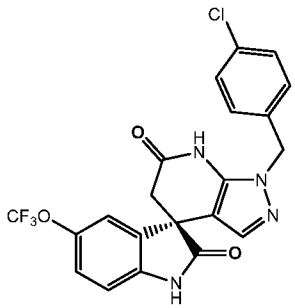



$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 2.52 (d, *J* = 14.1 Hz, 1H), 3.12 (d, *J* = 15.8 Hz, 1H), 5.27 (q, *J* = 15.8 Hz, 2H), 6.79 (s, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.43-7.41 (m, 4H), 10.59 (s, 1H), 11.00 (br s, 1H).

MS: m/z 457.0 $(M+H)^+$.

***Example 3-7***

(R)-1'-(4-chlorobenzyl)-5-(trifluoromethoxy)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione

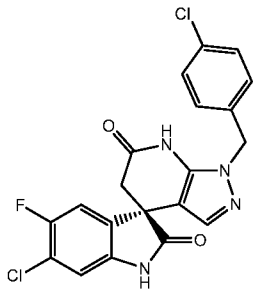


$^1$H-NMR (DMSO-$d_6$): δ ppm 2.56 (d, 1H, merged with DMSO) 3.16 (d, *J* = 15.8 Hz, 1H), 5.27 (q, *J* = 15.9 Hz, 2H), 6.76 (s, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.31 (s, 2H),7.43 (d, *J* = 8.4 Hz, 1H), 10.66 (s, 1H), 11.11 (br s, 1H).

MS m/z: 463.3 $(M+H)^+$.

***Example 3-8***

(R)-6-chloro-1'-(4-chlorobenzyl)-5-fluoro-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione

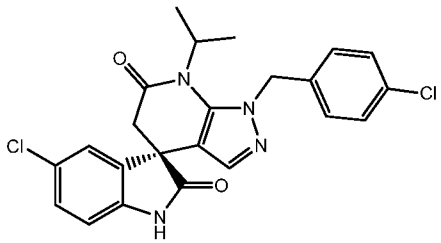



$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 11.10 (s, 1H), 10.60 (s, 1H), 7.42 (m, 3H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 6 Hz, 1H), 6.83 (s, 1H), 5.27 (q, *J* = 14.2 Hz, 2H), 3.15 (d, *J* = 16.0 Hz, 1H), 2.55 (d, 1H, merged with DMSO).

MS: m/z 432.0 $(M+H)^+$.

***Example 3-9***

(R)-5-chloro-1'-(4-chlorobenzyl)-7'-isopropyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione

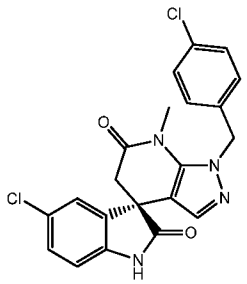


$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm1.39 (m, 6H), 2.5 (d, merged with DMSO, 1H), 3.21 (d, *J* = 15.6 Hz, 1H), 3.92 (m, 1H), 5.43 (q, *J* = 17.2 Hz, 2H), 6.91-6.93 (m, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.34-7.31 (m, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 10.66 (s, 1H).

MS: m/z 455.1 $(M+H)^+$.

***Example 3-10***

(R)-5-chloro-1'-(4-chlorobenzyl)-7'-methyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione

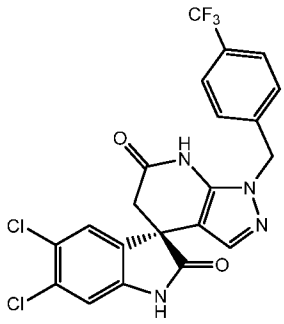


$^1$H NMR (400 MHz, DMSO-$d_6$):$\delta$ ppm2.63 (d, *J* = 15.8 Hz, 1H), 3.21 (d, *J* = 15.4 Hz, 1H), 3.26 (s, 3H), 5.54 (s, 2H), 6.95-6.90 (m, 2H), 7.17 (d, *J* = 7.5 Hz, 2H), 7.35-7.31 (m, 2H), 7.44 (d, *J* = 7.9 Hz, 2H), 10.68 (s, 1H).

MS: m/z 427.1 $(M+H)^+$.

***Example 3-11***

(R)-5,6-dichloro-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



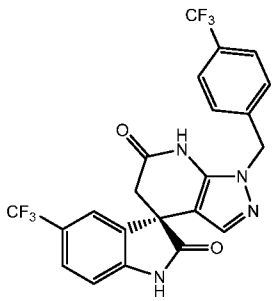
$[\alpha]^{25.9}_{D}$ : -104.9 (c = 0.54, $CHCl_3$).

$^1$H-NMR (400 MHz, DMSO-$d_6$): δ ppm 2.44 (d, 1H, merged with DMSO), 3.19 (d, *J* = 15.6 Hz, 1H), 5.38 (q, *J* = 16.0 Hz, 2H), 6.88 (s, 1H), 7.09 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.57 (s,1H),7.74 (d, *J* = 8.4 Hz, 2H), 10.74 (s, 1H), 11.13 (br s, 1H).

MS: m/z 479.0 $(M-H)^-$.

***Example 3-12***

(R)-5-(trifluoromethyl)-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



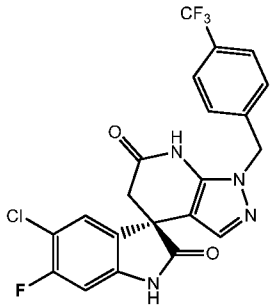
$[\alpha]^{25.0}_{D}$ : -109.2 (c = 0.5, DMSO).

$^1$H-NMR (400 MHz, DMSO-$d_6$): δ ppm 2.46 (d, 1H, merged with DMSO), 3.24 (d, *J* = 15.6 Hz and , 1H), 5.41 (q, *J* = 16.4 Hz, 2H), 6.81 (s, 1H),7.08 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz), 7.627-7.647 (m, 2H), 10.88 (s, 1H), 11.14 (br s, 1H).

MS: m/z 481.1 $(M+H)^+$.

***Example 3-13***

(R)-5-chloro-6-fluoro-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



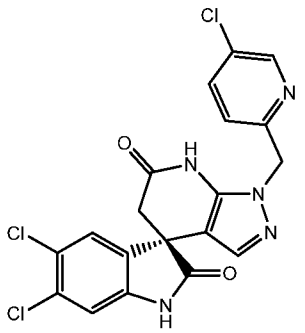

$[\alpha]^{28.3}_D$ : -103.2 (c = 0.53, MeOH:$CHCl_3$=1:1).

$^1$H-NMR (400 MHz, DMSO-$d_6$): δ ppm 2.59 (d, 1H, merged with DMSO). 3.18 (d, *J* = 16.4 Hz, 1H), 5.38 (q, *J* = 16.4 Hz, 2H), 6.85 (s, 1H), 6.93 (d, *J* = 9.6 Hz, 1H), 748 (m, 3H), 7.74 (d, *J* = 8.4 Hz, 2H), 10.74 (s, 1H), 11.11 (br s, 1H).

MS: m/z 465.1 $(M+H)^+$.

***Example 3-14***

(R)-5,6-dichloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione

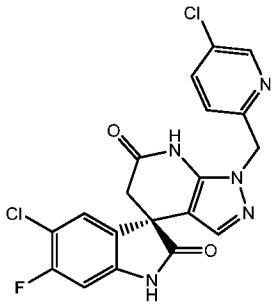


$^1$H NMR (400 MHz, DMSO-$d_6$):δ ppm,2.56 (d, 1H, merged with DMSO), 3.19 (d, *J* = 15.9 Hz, 1H), 5.40 (q, *J* = 16.3 Hz, 2H), 6.87 (s, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 7.10 (s, 1H), 7.57 (s, 1H), 7.94 (dd, *J* = 2.6, 8.3 Hz, 1H), 8.6 (d, *J* = 1.8 Hz, 1H), 10.7 (s, 1H), 11.07 (br s, 1H).

MS: m/z 448.0 $(M+H)^+$.

***Example 3-15***

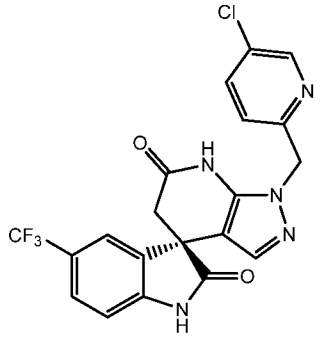
(R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-6-fluoro-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



$^1$H NMR (400 MHz, DMSO-$d_6$) d ppm 11.06 (s, 1H), 10.77 (s, 1H), 8.62 (d, *J* = 2.4 Hz, 1H), 7.94 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.94 (d, *J* = 9.2 Hz, 1 H), 6.85 (s, 1H), 5.40 (q, *J* = 14.8 Hz, 2H), 3.18 (d, *J* = 16 Hz, 1H), 2.55 (d, overlap with DMSO solvent peak).

***Example 3-16***

(R)-1'-((5-chloropyridin-2-yl)methyl)-5-(trifluoromethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione

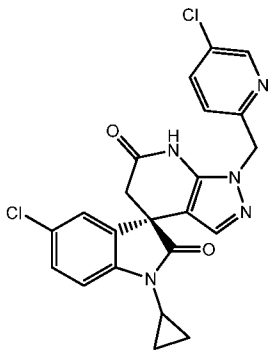


$^1$H NMR (400 MHz, DMSO-$d_6$):δ ppm 2.58 (d, 1H, merged with DMSO), 3.22 (d, *J* = 15.8 Hz, 1H), 5.42 (q, *J* = 16.4 Hz,2H), 6.80 (s, 1H), 7.08 (d, *J* = 7.9 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 2.8 Hz, 1H), 8.61 (br, s, 1H), 10.89 (br, s, 1H), δ 11.07 (br, s, 1H).

MS: m/z 448.1 $(M+H)^+$.

***Example 3-17***

(R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-1-cyclopropyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



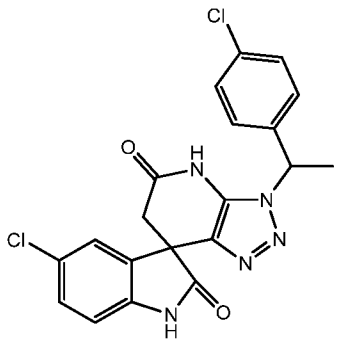
$^1$H NMR (400 MHz, DMSO-$d_6$):δ ppm 0.7-0.84 (m, 2H), 0.87-0.99 (m, 2H), 2.57 (d, 1H, merged with DMSO), 2.70 (m,1H), 3.10 (d, *J* = 16.4Hz, 1H), 5.35 (q, *J* = 9.6 Hz, 2H), 6.78 ( s, 1H), 7.05

(d, *J* = 8.4Hz, 1H), 7.18 (d, *J* = 8.4Hz, 1H), 7.35 (d, *J* = 1.8 Hz, 1H), 7.41-7.45 (m, 2H),7.92-7.94 (dd, *J* = 2.0, 1.2 Hz, 1H) 8.60 (s, 1H), δ 11.05 (br s, 1H).

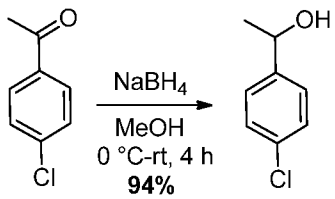
MS: m/z 454.1 $(M+H)^+$.

***Examples 4-1, 4-2, 4-3 and 4-4***

Preparations of the four isomers of 5'-chloro-3-(1-(4-chlorophenyl)ethyl)-4,6-dihydrospiro[ [1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione.



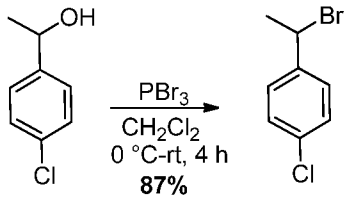
Step 1: Preparation of 1-(4-Chlorophenyl)ethanol




To a cold solution of 4'-chloroacetophenone (20 g, 129.37mmol) in methanol (250 mL) was added $NaBH_4$ (5.87 g, 155.24 mmol) in small portions at 0 °C and the resulting mixture was stirred at rt for 4 h. The reaction mixture was quenched with 1N HCl (100 mL) and extracted with $CH_2Cl_2$ (3 ×200 mL). The combined organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to afford 19 g of *1-(4-Chlorophenyl)ethanol* **1** as a colourless liquid (94% yield).

$^1$H-NMR (400 MHz, $CDCl_3$); *δ* 7.31 (s, 4H), 4.85-4.92 (m, 1H), 1.79 (br s, 1H), 1.47 (d, *J* = 6.8 Hz, 3H).

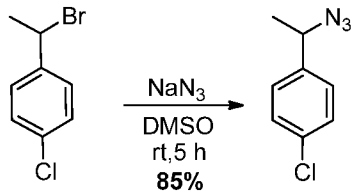
Step 2: Preparation of 1-(1-Bromoethyl)-4-chlorobenzene




To a cold solution of *1-(4-Chlorophenyl)ethanol* (19 g, 121.33mmol) in $CH_2Cl_2$ (200 mL) was added phosphorus tribromide (13.8 mL, 145.59mmol) slowly at 0 °C and the resulting mixture was allowed to stir at rt for 4 h. The reaction mass was diluted with $CH_2Cl_2$ (500 mL) and washed with water, saturated $NaHCO_3$ followed by water and brine. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to afford 23.4 g (87%) of *1-(1-Bromoethyl)-4-chlorobenzene* as a colourless liquid.

$^1$H-NMR (400 MHz, DMSO-$d_6$); $\delta$ 7.52-7.55 (m, 2H), 7.45-7.39 (m, 2H), 5.51 (q, $J$ = 6.9 Hz, 1H), 1.97 (d, $J$ = 6.8 Hz, 3H).

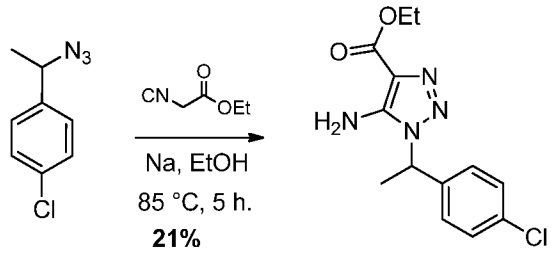
Step 3: Preparation of 1-(1-Azidoethyl)-4-chlorobenzene




To a solution of *1-(1-Bromoethyl)-4-chlorobenzene* (23.4 g, 106.6mmol) in DMSO (250 mL) was added sodium azide (6.93 g, 266.5mmol) and the resulting mixture was stirred at rt for 5 h. The reaction mixture was quenched with water and extracted with ethyl acetate (3 ×300 mL). The combined organic layer was washed with water, brine, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to afford 16.5 g (85%) of *1-(1-Azidoethyl)-4-chlorobenzene* as a colourless liquid.

$^1$H-NMR (400 MHz, DMSO-$d_6$); $\delta$ 7.38-7.48 (m, 4H), 4.87 (q, $J$ = 6.5 Hz, 1H), 1.44 (d, $J$ = 6.8 Hz, 3H).

Step 4: Preparation of Ethyl 5-amino-1-(1-(4-chlorophenyl)ethyl)-1H-1,2,3-triazole-4-carboxylate

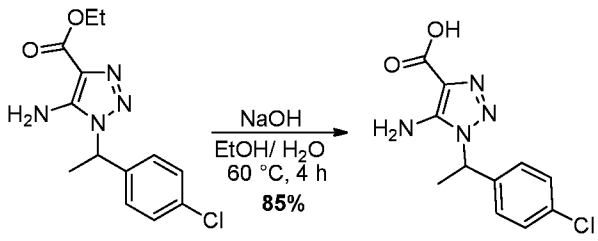



To a cold solution of *1-(1-Azidoethyl)-4-chlorobenzene* (1 g, 5,51mmol) and ethyl cyanoacetate (0.88 mL, 8.26 mmol) in ethanol (10 mL) was added sodium ethoxide (21% in ethanol) (4.1 mL, 12.66mmol) and the resulting mixture was stirred at reflux temperature for 5 h. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The combined organic layer was dried over anhydrous $Na_2SO_4$ and concentrated. The crude product was purified by column chromatography over silica gel (100-200 mesh)using a solvent gradient of 40-45% EtOAc in pet-ether as eluent to afford 350 mg (21%) of *Ethyl 5-amino-1-(1-(4-chlorophenyl)ethyl)-1H-1,2,3-triazole-4-carboxylate* as a yellow solid.

$^1$H-NMR (400 MHz, DMSO-$d_6$); $\delta$ 7.42 (d, $J$ = 8.8 Hz, 2H), 7.26 (d, $J$ = 8.8 Hz, 2H), 6.5 (s, 2H), 5.72 (q, $J$ = 7.0 Hz, 1H), 4.25 (q, $J$ = 7.2 Hz, 2H), 1.84 (d, $J$ = 7.2 Hz, 3H), 1.27 (t, $J$ = 7.0 Hz, 3H);

MS: m/z 295.0 $[M+H]^+$.

Step 5: Preparation of 5-Amino-1-(1-(4-chlorophenyl)ethyl)-1H-1,2,3-triazole-4-carboxylic acid



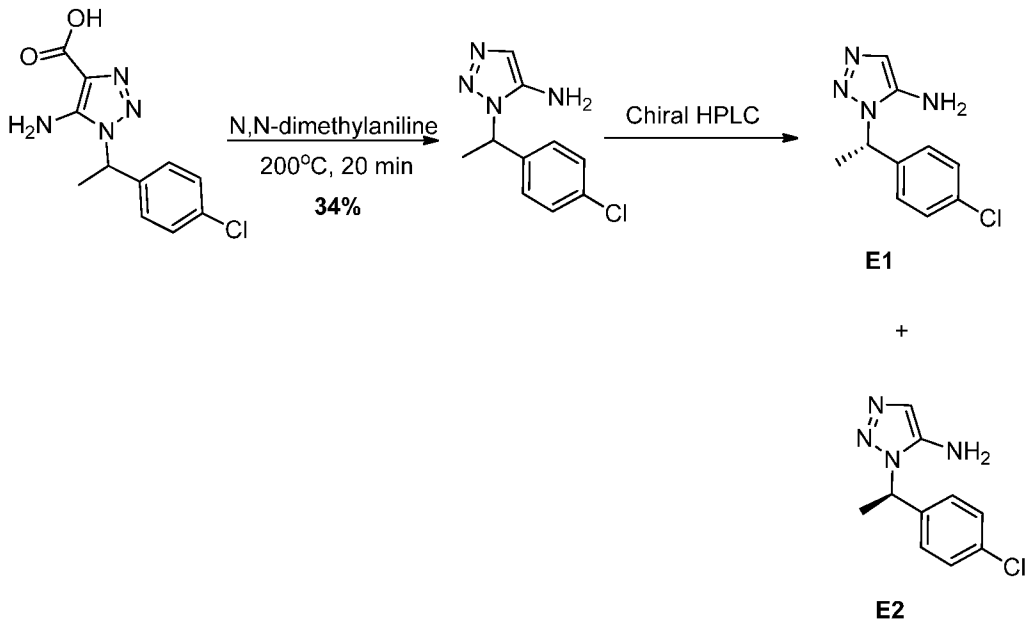

To a solution of *Ethyl 5-amino-1-(1-(4-chlorophenyl)ethyl)-1H-1,2,3-triazole-4-carboxylate* (320 mg, 1.08mmol) in ethanol (3 mL) was added a solution of NaOH (130 mg, 3.26 mmol) in water

(2 mL) and the resulting mixture was stirred at 60 °C for 4 h. The reaction mixture was concentrated under reduced pressure and residue was taken into cold-water (10 mL) and acidified with saturated sodium hydrogen sulphate to pH ~6. The resultant solid was collected by filtration, washed with water followed by hexane and dried under reduced pressure to afford 290 mg (85%) of *5-Amino-1-(1-(4-chlorophenyl)ethyl)-1H-1,2,3-triazole-4-carboxylic acid* as an off white solid.

$^1$H-NMR (400 MHz, DMSO-$d_6$); $\delta$ 12.38 (brs, 1H), 7.42 (d, $J$ = 8.4 Hz, 2H), 7.27 (d, $J$ = 8.4 Hz, 2H), 6.42 (s, 2H), 5.71 (q, $J$ = 7.2 Hz, 1H), 1.83 (d, $J$ = 7.2 Hz, 3H);

MS: *m/z* 267.0 $[M+H]^+$.

Step 6: Preparation of two enantiomers, **E1** and E2, of 1-(1-(4-Chlorophenyl)ethyl)-1H-1,2,3-triazol-5-amine



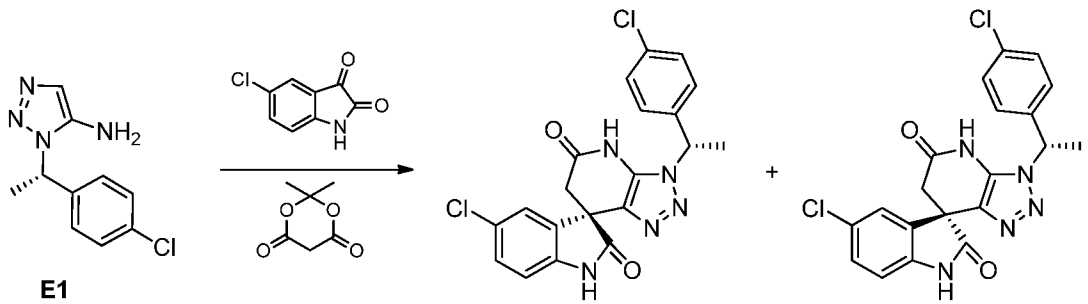

A mixture of *5-Amino-1-(1-(4-chlorophenyl)ethyl)-1H-1,2,3-triazole-4-carboxylic acid* (1.5 g, 5.62mmol) and N,N-dimethyl aniline (8 mL) was stirred in a pre-heated oil bath at 200 °C for 15 min. The combined reaction mass was directly purified by column chromatography over silica gel (100-200 mesh)using a solvent gradient of 100% EtOAc in pet-ether as eluent to afford 850

mg (34%) of *1-(1-(4-Chlorophenyl)ethyl)-1H-1,2,3-triazol-5-amine* as an off white solid, which was purified by chiral prep-HPLC and separated two enantiomers, **E1** and **E2**.

**(S)-1-(1-(4-chlorophenyl)ethyl)-1H-1,2,3-triazol-5-amine (E1)** $^1$H-NMR (400 MHz, DMSO-$d_6$); $\delta$ 7.39 (d, $J$ = 8.4 Hz, 2H), 7.23 (d, $J$ = 8.4 Hz, 2H), 6.8 (s, 1H), 5.60 (q, $J$ = 6.8 Hz, 1H), 5.47 (s, 2H), 1.81 (d, $J$ = 6.8 Hz, 3H); LCMS (ESI): *m/z* 223.1 $[M+H]^+$; Chiral HPLC retention time: 10.54 min

**(R)-1-(1-(4-chlorophenyl)ethyl)-1H-1,2,3-triazol-5-amine (E2)** $^1$H-NMR (400 MHz, DMSO-$d_6$); $\delta$ 7.39 (d, $J$ = 8.4 Hz, 2H), 7.23 (d, $J$ = 8.4 Hz, 2H), 6.8 (s, 1H), 5.60 (q, $J$ = 6.8 Hz, 1H), 5.47 (s, 2H), 1.81 (d, $J$ = 6.8 Hz, 3H); LCMS (ESI): *m/z* 223.1 $[M+H]^+$; Chiral HPLC retention time: 12.37 min

Step 7: Preparation of Examples 4-1 and 4-4




A mixture of *1-(1-(4-Chlorophenyl)ethyl)-1H-1,2,3-triazol-5-amine* **E1** (1 g, 4.49mmol), 5-chloroisatin (0.816 g, 4.49mmol) and Meldrum's acid (0.647 g, 4.49mmol) in acetic acid (30 mL) was stirred in a pre-heated oil bath at 100 °C for 4 h. The reaction mass was concentrated and water added to the residue. The resultant solid was collected by filtration, washed with water followed by hexane and dried under reduced pressure. The crude compound (mixture of diastereomers was purified by column chromatography over silica gel (100-200 mesh) using a solvent gradient of 35-50% EtOAc in pet-ether to get 140 mg (7%) of Example 4-4 and with 60-100% EtOAc in pet-ether as eluent gave 220 mg (11%) Example 4-1 as off-white solids.

The characterization data of **Example 4-1** is shown below:

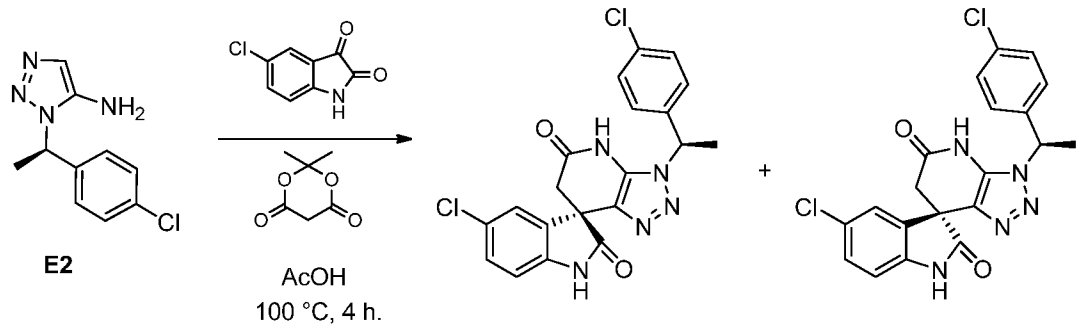
$[\alpha]^{25}_D$: -102.7 (c = 0.15, MeOH).

$^1$H-NMR (400 MHz, DMSO-$d_6$); $\delta$ 11.20 (s, 1H), 10.69 (s, 1H), 7.46 (d, $J$ = 8.4 Hz, 2H), 7.36 (d, $J$ = 8.4 Hz, 2H), 7.32 (dd, $J$ = 2.4 Hz, 6.0 Hz, 2H), 6.92 (d, $J$ = 8.4 Hz, 1H), 5.85 (q, $J$ = 6.9 Hz, 1H), 3.33 (d, $J$ = 16.4 Hz, 1H), 2.62 (d, $J$ = 16.4 Hz, 1H), 1.87 (d, $J$ = 7.2 Hz, 3H); LCMS (ESI): *m/z* 427.9 $[M+H]^+$; r.t. = 3.488; HPLC Purity: 97.82 at 254 nm; Chiral HPLC Purity: 97.14 at 254 nm.

The characterization data of **Example 4-4** is shown below:

$[\alpha]^{25}_D$ : +31.2 (c = 0.16, MeOH).

$^1$H-NMR (400 MHz, DMSO-$d_6$); $\delta$ 11.29 (s, 1H), 10.73 (s, 1H), 7.46 (d, $J$ = 8.8 Hz, 2H), 7.38 (d, $J$ = 8.8 Hz, 2H), 7.32 (dd, $J$ = 2.0 Hz, 7.2 Hz, 2H), 6.93 (d, $J$ = 8.8 Hz, 1H), 5.80 (q, $J$= 6.8 Hz, 1H), 3.23 (d, $J$ = 16.4 Hz, 1H), 2.73 (d, $J$ = 16.0 Hz, 1H), 1.87 (d, $J$ = 7.2 Hz, 3H); LCMS (ESI): *m/z* 426 $[M-H]^-$; r.t. = 1.94; HPLC Purity: 95.98 at 254 nm.




Using the procedures similar to step 7, Example 4-2 and Example 4-3 were synthesized and isolated.

The characterization data of Example 4-2 is shown below:

$[\alpha]^{25}_D$ : -24.0 (c = 0.30, MeOH).

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ ppm 1.86 (d, $J$ = 6.8Hz, 3H), 2.72 (d, $J$ = 16.4Hz, 1H), 3.21 (d, $J$ = 16.4Hz, 1H), 5.80 (q, $J$ = 6.8Hz, 1H), 6.93 (d, $J$ = 9.2Hz, 1H), 7.33-7.31 (m, 2H), 7.38 (d, $J$ = 8.4Hz, 2H), 7.45 (d, $J$ = 8.4Hz, 2H), 10.71 (s, 1H), 11.27 (s, 1H).MS:m/z 428.1 $(M+H)^+$.

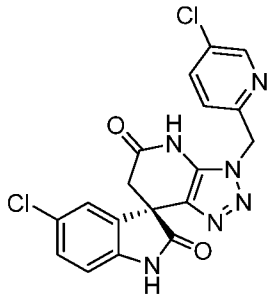
The characterization data of Example 4-3 is shown below:

$[\alpha]^{25}_{D}$ : +102.7 (c = 0.30, MeOH).

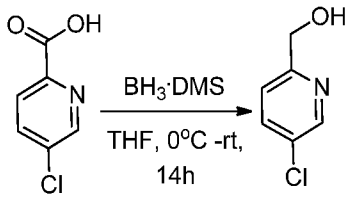
$^{1}$H-NMR (400 MHz, DMSO-$d_6$); $\delta$ 11.2 (s, 1H), 10.69 (s, 1H), 7.46 (d, $J$ = 8.4 Hz, 2H), 7.36 (d, $J$ = 8.4 Hz, 2H), 7.32 (dd, $J$ = 2.4 Hz, 6.0 Hz, 2H), 6.92 (d, $J$ = 8.4 Hz, 1H), 5.85 (q, $J$ = 6.9 Hz, 1H), 3.33 (d, $J$ = 16.4 Hz, 1H), 2.62 (d, $J$ = 16.4 Hz, 1H), 1.87 (d, $J$ = 7.2 Hz, 3H); LCMS (ESI): $m/z$ 427.9 $[M+H]^{+}$

***Example 5***

Preparation of (R)-5'-chloro-3-((5-chloropyridin-2-yl)methyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione



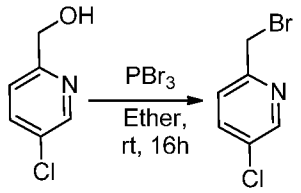
Step 1: Preparation of (5-Chloropyridin-2-yl)methanol




To a solution of 5-chloropicolinic acid (5 g, 31.7 mmol) in tetrahydrofuran (50 mL) was added borane-dimethylsulfide complex (10 mL) at 0°C and resulting reaction mixture was maintained at rt for 16 h. Cooled the reaction mass to 0°C, excess borane-dimethylsulfide complex was quenched with methanol (15 mL), refluxed for 1h, concentrated the reaction, diluted in ethyl acetate (150 mL), washed with water (2 x 50 mL), brine (50 mL), dried over anhydrous sodium sulfate and concentrated to afford 3 g (66.6% yield) of (5-Chloropyridin-2-yl)methanol as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ ppm 3.75 (br.s, 1H), 4.75 (s, 2H), 7.25 (d, *J* = 8.8 Hz, 1H), 7.67 (dd, *J* = 2.2, 6.1 Hz 1H), 8.53 (d, *J* = 8.8 Hz, 1H).

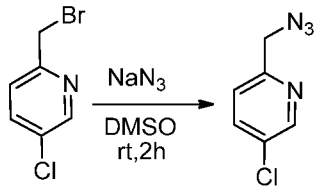
Step 2: Preparation of 2-(Bromomethyl)-5-chloropyridine




To a solution of (5-Chloropyridin-2-yl)methanol (1.5 g, 10.45 mmol) in ether (20 mL) was added a solution of tribromophosphine (2.83 g, 10.45 mmol) in ether at 0 °C. The resulting reaction mixture was stirred at room temperature for 16 h. The reaction mixture was poured in ice cooled water (50 mL) basified to ph-7 using solid sodium bi carbonate, extracted in ether (2 x 75 mL) combined the organic layers washed with water (2 x 70 mL), brine (30 mL), dried over anhydrous $Na_2SO_4$ and concentrated to afford 1.6 g (76% yield) 2-(Bromomethyl)-5-chloropyridine as pink liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ ppm 4.52 (s, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.67 (dd, *J* = 2.2, 6.1 Hz 1H), 8.53 (d, *J* = 2.7 Hz, 1H).

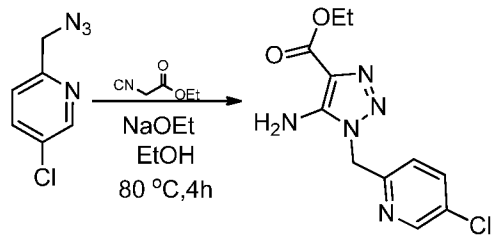
Step 3: Preparation of 2-(Azidomethyl)-5-chloropyridine




To a solution of 2-(Bromomethyl)-5-chloropyridine (750 mg, 3.64 mmol) in dimethyl sulfoxide (8 mL) was added sodium azide (590 mg, 9.10 mmol) at rt and stirred for 2 h at the same temperature. The reaction mixture was diluted with ether (50 mL) washed with water (2 x 40 mL), brine (30 mL) dried over anhydrous $Na_2SO_4$ and concentrated to afford 0.5 g (82% yield) of 2-(Azidomethyl)-5-chloropyridine as a colourless liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ ppm 4.48 (s, 2H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.71 (dd, *J* = 2.2, 6.2 Hz, 1H), 8.56 (d, *J* = 2.6 Hz, 1H).

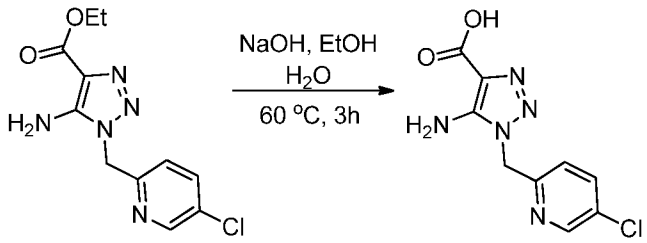
Step 4: Preparation of ethyl 5-amino-1-((5-chloropyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate




To a solution of 2-(Azidomethyl)-5-chloropyridine (1.3 g, 7.71 mmol) in ethanol was added ethylcyano acetate (1.31 g, 11.57 mmol) and sodium ethoxide solution (6.6 mL, 17.71 mmol) at rt. The resulting reaction mixture was maintained at 80 °C for 4 h. The reaction mixture was cooled to rt, concentrated, diluted in ethyl acetate(150 mL), washed with water (2 x 50 mL) and brine (50 mL), dried over anhydrous $Na_2SO_4$ and concentrated. The resulting solid was purified by column chromatography over silica gel (100-200 mesh) using a solvent gradient of 30% ethyl acetate in pet ether as eluent to afford 600 mg (77.9% yield) ethyl 5-amino-1-((5-chloropyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 1.24 (t, *J* = 8.0 Hz, 3H), 4.26 (q, *J* = 6.8 Hz, 2H), 5.56 (s, 2H), 6.58 (br s, 2H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.95 (dd, *J* = 2.4, 6.0 Hz, 1H), 8.58 (d, *J* = 1.7 Hz, 1H).

Step 5: Preparation of 5-Amino-1-((5-chloropyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid

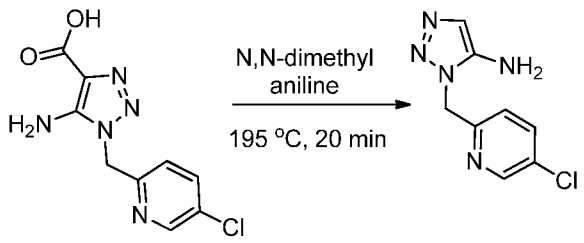


To a solution of Ethyl 5-amino-1-((5-chloropyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (600 mg, 2.14 mmol) in ethanol (3 mL) was added water (3 mL) followed by sodium hydroxide (256 mg, 6.41 mmol) at rt and resulting reaction mixture was maintained at 60 °C for 3 h. The resulting reaction mixture was cooled to rt, concentrated to remove ethanol, acidified to pH 6 using saturated sodium hydrogen sulfate, the solid obtained through filtration was washed with water (2 x 15 mL) and dried under vacuum to obtain 350 mg (64.8% yield) of 5-Amino-1-((5-chloropyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid as white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$): 5.55 (s, 2H), 6.52 (br s, 2H), 7.20 (d, *J* = 8.3 Hz, 1H), 7.95 (dd, *J* = 1.8, 6.6 Hz, 1H), 8.59 (d, *J* = 2.2 Hz, 1H), 12.48 (s, 1H).

MS: m/z 254.3 $(M+H)^+$.

Step 6: Preparation of 1-((5-chloropyridin-2-yl)methyl)-1H-1,2,3-triazol-5-amine

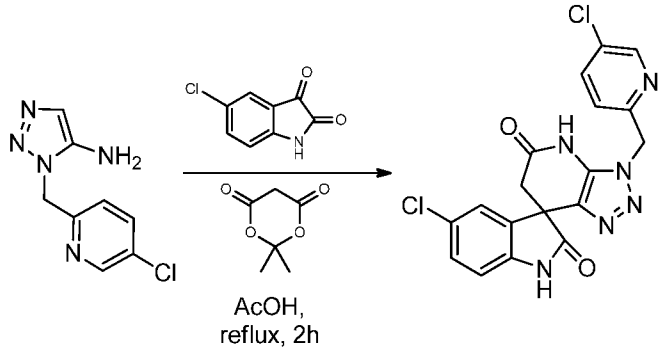



A suspension of 5-Amino-1-((5-chloropyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (300 mg, 1.19 mmol) in *N*,*N*-dimethyl aniline (2 mL) was maintained at 200 °C for 20 min. The reaction mass was cooled to rt and washed with petrol ether to remove *N*,*N*-dimethyl aniline. The resultant solid was purified by column chromatography over silica gel (100-200 mesh) using a solvent gradient of 50% ethyl acetate in pet ether as eluent to afford 110 mg (44% yield) of 1-((5-chloropyridin-2-yl)methyl)-1H-1,2,3-triazol-5-amine as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$): 5.46 (s, 2H), 5.62 (br s, 2H), 6.85 (s, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 7.94 (dd, *J* = 2.2, 6.1 Hz, 1H), 8.6 (d, *J* = 2.7 Hz, 1H).

MS: m/z 210.3 $(M+H)^+$.

Step 7: Preparation of 5'-Chloro-3-((5-chloropyridin-2-yl)methyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione

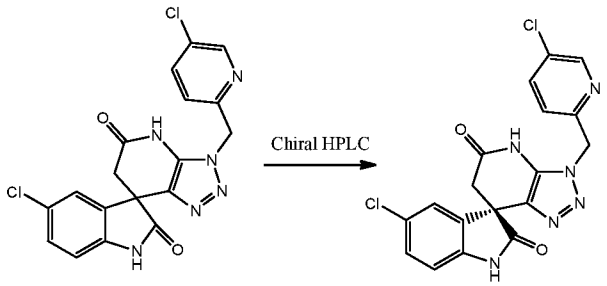



To a solution of 1-((5-chloropyridin-2-yl)methyl)-1H-1,2,3-triazol-5-amine (110 mg, 0.53 mmol) in acetic acid was added 5-chloroindoline-2,3-dione (95.6 mg, 0.53 mmol), Meldrum's acid (75.7 mg, 0.53 mmol) at rt and maintained at 100 °C for 2 h. The reaction mixture was cooled to rt and solvent was removed under reduced pressure. Ice water was added to the reaction mixture and stirred at rt for 15 min. The solid obtained through filtration was washed with water (2 x 5 mL) and dried under *vacuum*. The resultant solid was purified by column chromatography over silica gel (100-200 mesh) using a solvent gradient of 10% MeOH in DCM as eluent to afford 32 mg (16% yield) of 5'-Chloro-3-((5-chloropyridin-2-yl)methyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione as a pale yellow solid.

$^1$H NMR (400 MHz, DMSO-*d6*): δ ppm 2.73 (d, *J* = 16.3 Hz, 1H), 3.30 (d, *J* = 16.3 Hz, 1H), 5.66 (s, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 7.30-7.40 (m, 3H), 8.00 (dd, *J* = 2.7 Hz and 5.7 Hz, 1H), 8.63 (d, *J* = 2.2 Hz, 1H), 10.77 (s, 1H), 11.29 (br s, 1H).

MS: m/z 415.0 $(M+H)^+$.

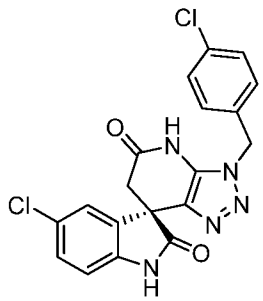
Step 8: Preparation of (R)-5'-chloro-3-((5-chloropyridin-2-yl)methyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione



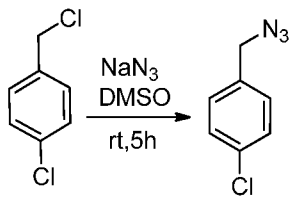
Example 5, (R)-5'-chloro-3-((5-chloropyridin-2-yl)methyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione, can be prepared by isolating 5'-Chloro-3-((5-chloropyridin-2-yl)methyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione using the procedures from the examples described above, e.g., chiral prepare HPLC.

***Example 6***

Preparation of (R)-5'-chloro-3-(4-chlorobenzyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione



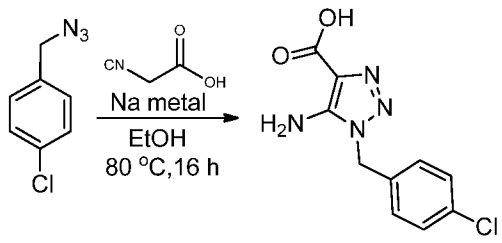
Step 1: Preparation of 1-(Azidomethyl)-4-chlorobenzene




To a solution of 1-chloro-4-(chloromethyl)benzene (5 g, 31.05 mmol) in dimethyl sulfoxide (40 mL) was added sodium azide (5.06 g, 77.63 mmol) at rt and stirred for 5 h at the same temperature. The reaction mixture was diluted with ethyl acetate (100 mL) washed with water (2 x 70 mL), brine (30 mL) dried over anhydrous sodium sulfate and concentrated to afford 4.5 g (86% yield ) of *1-(azidomethyl)-4-chlorobenzene* as a colourless liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ ppm 4.32 (s, 2H), 7.25-7.26 (d, 2H, merged with $CDCl_3$), 7.36 (d, *J* = 8.4 Hz, 2H).

Step 2: Preparation of 5-Amino-1-(4-chlorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid

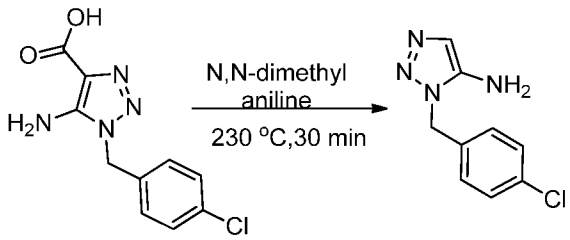



To a solution of sodium (550 mg, 23.88 mmol) in ethanol was added 2-cyanoacetic acid (1.01 g, 11.94 mmol) and 1-(azidomethyl)-4-chlorobenzene (2 g, 11.94 mmol) at rt. The resulting reaction mixture was maintained at 80 °C for 16 h. The reaction mixture was cooled to 0 °C; ice water was added to the reaction mixture and stirred at rt for 15 min, acidified to pH 1 with aq. HCl. The solid obtained through filtration was washed with water (2 x 15 mL), diethyl ether (2 x 10 mL) and dried under vacuum to afford 720 mg (25% yield) of *5-amino-1-(4-chlorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid* as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 5.42 (s, 2H), 6.55 (br s, 2H), 7.22 (d, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 7.1 Hz, 2H), 12.49 (br s, 1H).

MS: m/z 253.3 $(M+H)^+$.

Step 3: Preparation of 1-(4-Chlorobenzyl)-1H-1,2,3-triazol-5-amine

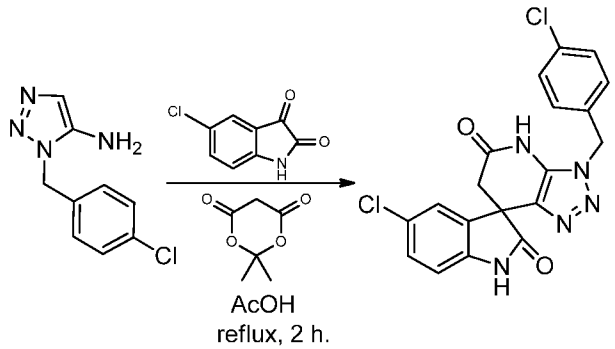



A suspension of 5-amino-1-(4-chlorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid (500 mg, 1.98 mmol) in *N,N*-dimethyl aniline was maintained at 230 °C for 30 min. The reaction mass was cooled to rt and washed with petrol ether to remove *N,N*-dimethyl aniline The resultant solid was purified by column chromatography over silica gel (100-200 mesh) using a solvent gradient of

50% ethyl acetate in petrol ether as eluent to afford 130 mg (31% yield) of *1-(4-chlorobenzyl)-1H-1,2,3-triazol-5-amine* as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 5.32 (s, 2H), 6.16 (br s, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H).

Step 4: Preparation of 5'-Chloro-3-(4-chlorobenzyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b] pyridine-7,3'-indoline]-2',5(3H)-dione

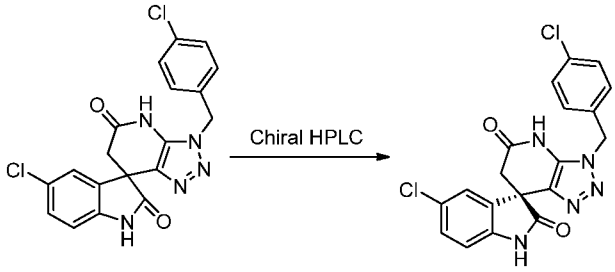



To a solution of 1-(4-chlorobenzyl)-1H-1,2,3-triazol-5-amine (130 mg, 0.625 mmol) in acetic acid was added 5-chloroindoline-2,3-dione (113 mg, 0.625 mmol), Meldrum's acid (90 mg, 0.625 mmol) at rt and maintained at 100 °C for 2 h. The reaction mixture was cooled to rt and solvent was removed under reduced pressure. Ice water was added to the reaction mixture and stirred at rt for 15 min. The solid obtained through filtration was washed with water (2 x 5 mL) and dried under vacuum. The resultant solid was washed with acetone to afford 80 mg (31% yield) of *5'-chloro-3-(4-chlorobenzyl)-4,6-dihhydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione* as a pale yellow solid.

$^1$H-NMR (DMSO-$d_6$): $^1$H NMR (400 MHz, DMSO-*d6*): δ ppm 2.68 (d, *J* = 16.3 Hz, 1H), 3.30 (d, merged with moisture, 1H), 5.53 (s, 2H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.30-7.42 (m, 4H), 7.48 (d, *J* = 8.3 Hz, 2H), 10.75 (s, 1H), 11.38 (s, 1H).

LC/MS:m/z: 414.0 $(M+H)^+$.

Step 5: Preparation of (R)-5'-chloro-3-(4-chlorobenzyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione



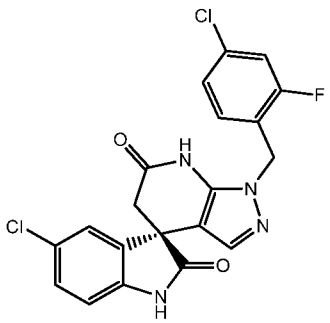

Example **6**, (R)-5'-chloro-3-(4-chlorobenzyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione, can be prepared by isolating

5'-Chloro-3-(4-chlorobenzyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b] pyridine-7,3'-indoline]-2',5(3H)-dione using the procedures from the examples described above, e.g., chiral preparative HPLC.

The following compounds can be prepared using the general procedures as well as the procedures from the examples described above with the appropriate starting materials.

***Example 7-1***

(R)-5-chloro-1'-(4-chloro-2-fluorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione




The racemate of the above title compound, which is 5-chloro-1'-(4-chloro-2-fluorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

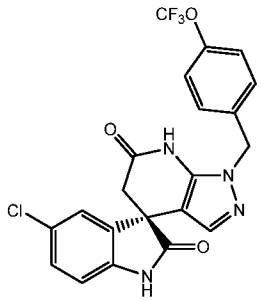
$^1$H NMR (400 MHz, DMSO-$d_6$):δ ppm 2.53 (d, *J* = 20.7 Hz, 1H), 3.12 (d, *J* = 15.9 Hz, 1H), 5.33 (q, *J* = 15.9 Hz, 2H), 6.91 (d, *J* = 7.8 Hz 1H), 6.80 (s, 1H), 7.07 (t, *J* = 8.4 Hz 1H), 7.27-7.33 (m, 3H), 7.47 (dd, *J* = 1.7,1.7 Hz, 1H), 10.6 (s, 1H), 11.08 (br s, 1H).

MS: m/z 431.0 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above

***Example 7-2***

(R)-5-chloro-1'-(4-(trifluoromethoxy)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione




The racemate of the above title compound, which is 5-chloro-1'-(4-(trifluoromethoxy)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

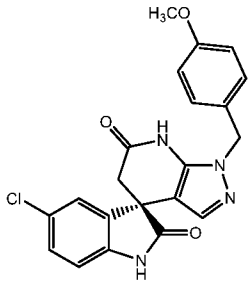
$^1$H NMR (400 MHz, DMSO-*d6*): δ ppm 2.54 (d, *J* = 16.5 Hz, 1H), 3.15 (d, *J* = 16.3 Hz, 1H), 5.35 (ABq, *J* = 15.8 Hz, 2H), 6.80 (s, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 7.35 (m, 6H), 10.60 (s, 1H), 11.1 (br s, 1H).

MS: m/z 463.1 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-3***

(R)-5-chloro-1'-(4-methoxybenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione




The racemate of the above title compound, which is 5-chloro-1'-(4-methoxybenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

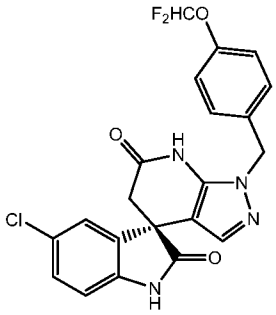
$^1$H NMR (400 MHz, DMSO-*d6*): δ ppm 2.56 (s,1H, merged in DMSO), 3.08 (d, *J* = 16.2 Hz, 1H), 3.73 (s, 3H), 5.20 (ABq, *J* = 15.0 Hz, 2H), 6.74 (s, 1H), 6.90 (d, *J* = 6.6 Hz, 1H), 7.2-7.3 (m, 4H), 10.58 (br, s, 1H), 11.08 (br, s, 1H).

MS: m/z 407.1 $(M-H)^-$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-4***

(R)-5-chloro-1'-(4-(difluoromethoxy)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione




The racemate of the above title compound, which is 5-chloro-1'-(4-(difluoromethoxy)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

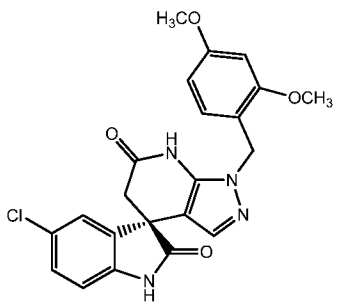
$^1$H-NMR (400 MHz, DMSO-$d_6$): δ ppm 2.53 (d, 1H, merged with DMSO), 3.13 (d, *J* = 16.3 Hz, 1H), 5.27 (ABq, *J* = 15.8 Hz, 2H), 6.78 (s, 1H), 6.91 (d, *J* = 8.30 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.21 (t, *J* = 74.2 Hz, 1H), 7.28 -7.34 (m, 4H), 10.60 (s, 1H), 11.10 (br s, 1H).

MS: m/z 445.1 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-5***

(R)-5-chloro-1'-(2,4-dimethoxybenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



The racemate of the above title compound, which is 5-chloro-1'-(2,4-dimethoxybenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

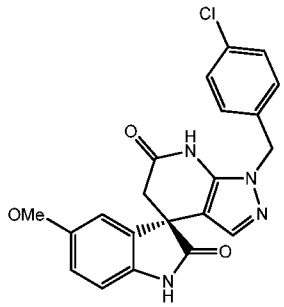
$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.56 (d, *J* = 15.97 Hz, 1 H), 3.11 (d, *J* = 15.97 Hz, 1 H), 3.63 (s, 3 H). 3.76 (s, 3 H), 5.15-5.27 (m, 2 H), 6.23 (d, *J* = 3.00 Hz, 1 H), 6.79 (s, 1 H), 6.82 (dd, *J* = 3.08, 3.04 Hz, 1 H), 6.93 (t, *J* = 9.10, 2 H), 7.29 (s, 1 H), 7.31 (d, *J* = 2.16 Hz, 1 H), 10.62 (s, 1 H), 10.95 (s, 1 H).

ES-MS: 439.1 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-6***

(R)-1'-(4-chlorobenzyl)-5-methoxy-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione




The racemate of the above title compound, which is 1'-(4-chlorobenzyl)-5-methoxy-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

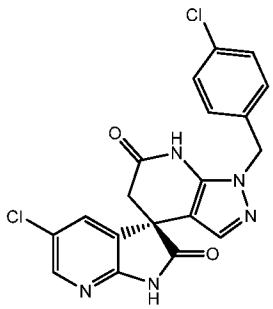
$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm2.50 (d, proton merged with DMSO, 1H), 3.06 (d, *J* = 15.8 Hz, 1H), 5.27 (ABq, *J* = 15.8 Hz, 2H), 5.30 (d, *J* = 15.8 Hz, 1H), 6.75 (s, 1H), 6.81 (s, 2H), 6.86 (s, 1H), 7.27 (d, *J* = 7.9 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 10.28 (s, 1H), 11.05 (br s, 1H).

MS: m/z 409.1 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-7***

(S)-5'-chloro-1-(4-chlorobenzyl)-5,7-dihydrospiro[pyrazolo[3,4-b]pyridine-4,3'-pyrrolo[2,3-b]pyridine]-2',6(1H,1'H)-dione



The racemate of the above title compound, which is 5'-chloro-1-(4-chlorobenzyl)-5,7-dihydrospiro[pyrazolo[3,4-b]pyridine-4,3'-pyrrolo[2,3-b]pyridine]-2',6(1H,1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

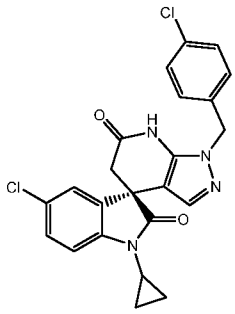
$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 2.61 (d, *J* = 16.2 Hz, 1H). 3.21 (d, *J* = 15.8 Hz, 1H), 5.28 (ABq, *J* = 15.8 Hz, 2H), 6.91 (s, 1H), 7.26 (dd, *J* = 8.4 Hz, 2H), 7.43 (dd, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 1.7 Hz, 1H), 8.20 (d, *J* = 1.8 Hz, 1H), 11.15 (s, 1H),11.31 (br s, 1H),

MS:m/z 414.0 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-8***

(R)-5-chloro-1'-(4-chlorobenzyl)-1-cyclopropyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



The racemate of the above title compound, which is 5-chloro-1'-(4-chlorobenzyl)-1-cyclopropyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

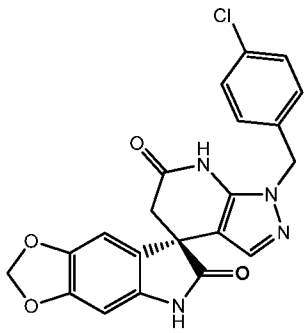
$^1$H NMR (400 MHz, DMSO-$d_6$):δ ppm 0.77 (d, *J* = 18.0 Hz, 2H), 0.97 (d, *J* = 6.2 Hz, 2H), 2.55 (d, 1H, merged with DMSO), 2.67-2.70 (m, 1H), 3.12 (d, *J* = 16.3 Hz, 1H), 5.27 (ABq, *J* = 15.9 Hz, 2H), 6.75 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 1.6 Hz, 1H), 7.42-7.44 (m, 3H), 11.12 (br s, 1H).

MS:m/z 453.0 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-9***

(R)-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[[1,3]dioxolo[4,5-f]indole-7,4'-pyrazolo[3,4-b]pyridine]-6,6'(1'H,5H)-dione



The racemate of the above title compound, which is 1'-(4-chlorobenzyl)-5',7'-dihydrospiro[[1,3]dioxolo[4,5-f]indole-7,4'-pyrazolo[3,4-b]pyridine]-6,6'(1'H,5H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

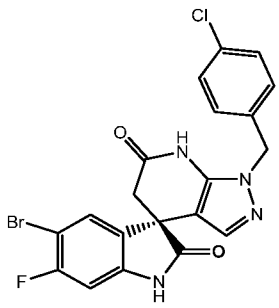
$^1$H NMR (400 MHz, DMSO-$d_6$) d ppm 2.42 (d, $J$ = 15.8 Hz, 1 H), 3.05 (d, $J$ = 15.8 Hz, 1 H), 5.27 (d, $J$ = 10.8 Hz, 2H), 5.90-6.02 (m, 2H), 6.55 (s, 1H), 6.78 (s, 1H), 6.88 (s, 1H), 7.27 (d, $J$ = 8.5 Hz, 2 H), 7.38-7.48 (m, 2 H), 10.26 (s, 1 H), 11.03 (s, 1 H).

MS:m/z 423.1 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-10***

(R)-5-bromo-1'-(4-chlorobenzyl)-6-fluoro-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione




The racemate of the above title compound, which is 5-bromo-6-chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

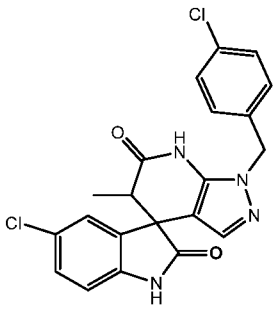
$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 2.52 (d, $J$ = 15.97 Hz, 1H), 3.15 (d, $J$ = 15.97 Hz, 1H), 5.22-5.33 (m, 2H), 6.82 (s, 1H), 6.92 (d, $J$ = 8.92 Hz, 1H), 7.26 (d, $J$ = 8.44, 2H), 7.42 (d, $J$ = 8.44, 2H), 7.57 (d, $J$ = 6.88, 1H), 10.77 (s, 1H), 11.04 (s, 1H).

ES-MS: m/z 476.9 $(M+H^+)$

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-11***

Racemic (R,R) and (S,S) or racemic (R,S) and (S,R) of 5-chloro-1'-(4-chlorobenzyl)-5'-methyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



Racemic (R,R) and (S,S) or racemic (R,S) and (S,R) of 5-chloro-1'-(4-chlorobenzyl)-5'-methyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

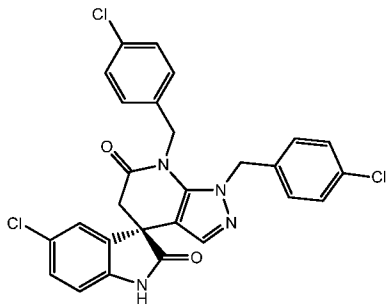
$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 0.75 (d, *J*=6.6 Hz, 3H), 3.0(d, *J*=6.6 Hz, 1H), 5.28 (q, *J*=16.2 Hz, 2H), 6.85 (s, 1H), 6.93 (d, *J*=8.3 Hz, 1H), 6.97 (s, 1H), 7.22 (d, *J*=7.9 Hz, 2H), 7.28(d, *J*=8.4 Hz, 2H), 7.41(d, *J*=7.9 Hz, 1H), 10.89 (s, 1H), 11.19 (s, 1H).

MS:m/z 427.0 $(M+H)^+$.

The individual (R,R), (S,S), (R,S) and (S,R) enantiomer can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-12***

(R)-5-chloro-1',7'-bis(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



The racemate of the above title compound, which is 5-chloro-1',7'-bis(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

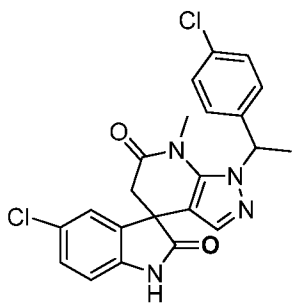
$^1$H NMR (400 MHz, DMSO-*d6*): δ ppm 2.77 (d, *J* = 15.4 Hz, 1H), 3.47 (d, *J* = 15.4 Hz, 1H), 4.92 (d, *J* = 17.6 Hz, 1H), 5.13 (d, *J* = 17.6 Hz, 1H), 5.19 (s, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.94 (s, 1H), 6.96 (s, 1H), 7.27-7.4 (m, 7H), 10.75 (s, 1H).

MS:m/z 537.1 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-13***

Racemic (R,R) and (S,S) or racemic (R,S) and (S,R) of 5-chloro-1'-(1-(4-chlorophenyl)ethyl)-7'-methyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



Racemic (R,R) and (S,S) or racemic (R,S) and (S,R) of 5-chloro-1'-(1-(4-chlorophenyl)ethyl)-7'-methyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

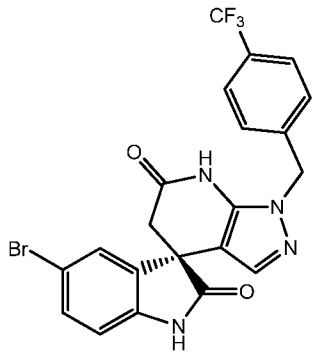
H-NMR (400 MHz, DMSO-$d_6$): δ ppm 1.81 (d, *J* = 6.6 Hz, 3H), 2.61 (d, *J* = 14.9 Hz, 1H), 3.14 (d, *J* = 15.3 Hz, 1H), 3.36 (s, 3H), 5.90 (m, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.93 (s, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.27 (s, 1H), 7.32 (d, *J* = 9.2 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 10.7 (s, 1H).

MS: m/z 441.0 $(M+H)^+$.

The individual (R,R), (S,S), (R,S) and (S,R) enantiomer of the racemic mixture, can be prepared by the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-14***

(R)-5-bromo-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione




The racemate of the above title compound, which is 5-bromo-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

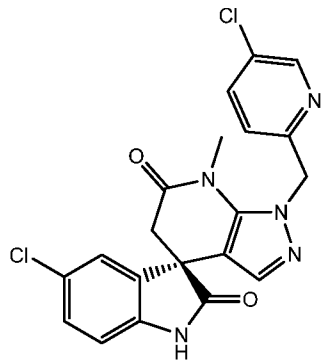
$^1$H-NMR (400 MHz, DMSO-$d_6$): δ ppm 2.54 (d, 1H, merged with DMSO), 3.14 (d, *J* = 16.3 Hz, 1H), 5.39 (ABq, *J* = 15.9 Hz, 2H), 6.82 (s, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 7.50-7.40 (m, 4H), 7.74 (d, *J* = 8.4 Hz, 2H), 10.62 (s, 1H), 11.10 (br s, 1H).

MS m/z: 491.0 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-15***

(R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-7'-methyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione




The racemate of the above title compound, which is 5-chloro-1'-((5-chloropyridin-2-yl)methyl)-7'-methyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

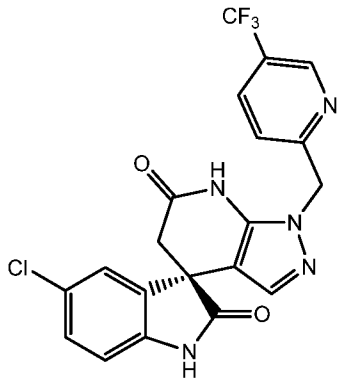
$^1$H NMR (400 MHz, $CD_3OD$): δ ppm 2.74 (d, *J* = 15.4Hz, 1H). 3.20 (d, *J* = 15.8Hz, 1H), 3.45 (s, 3H), 5.63 (s, 2H), 6.96 (s, 1H), 6.97 (d, *J* = 5.7Hz, 1H), 7.19 (d, *J* = 8.8Hz, 1H), 7.28 (s, 1H), 7.31 (d, *J* = 8.3Hz, 1H), 7.85 (d, *J* = 6.6Hz, 1H), 8.55 (s, 1H).

MS:m/z 428.0 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above

***Example 7-16***

(R)-5-chloro-1'-((5-(trifluoromethyl)pyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione




The racemate of the above title compound, which is 5-chloro-1'-((5-(trifluoromethyl)pyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

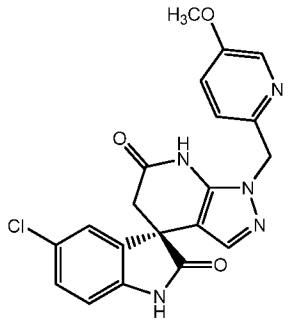
$^1$H-NMR (400 MHz, DMSO-$d_6$): δ ppm 2.51 (d, merged with DMSO), 1H), 3.13 (d, *J* = 16.0 Hz, 1H), 5.52 (ABq, *J* = 16.8, 2H), 6.85 (s, 1H), 6.92 (d, *J* = 7.6 Hz,1H), 7.19-7.34 (m, 3H), 8.23 (d, *J* = 6.4 Hz, 1H), 8.971 (s, 1H), 10.638 (s, 1H), 11.06 (br s, 1H).

MS: m/z 448.0 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-17***

(R)-5-chloro-1'-((5-methoxypyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



The racemate of the above title compound, which is 5-chloro-1'-((5-methoxypyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

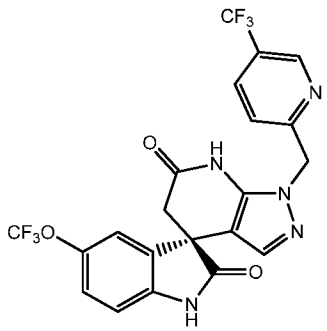
$^1$H NMR (400 MHz, DMSO-*d6*): δ ppm 3.12 (d, *J* = 15.8 Hz, 1H), 3.56 (br s, 1H), 3.81 (s, 3H), 5.32 (ABq, *J* = 15.9 Hz, 2H), 6.77 (s, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 7.29-7.42 (m, 3H), 8.26 (d, *J* = 2.7 Hz, 1H), 10.62 (s, 1H), 11.03 (br s, 1H).

MS: m/z 410.1 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-18***

(R)-5-(trifluoromethoxy)-1'-((5-(trifluoromethyl)pyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



The racemate of the above title compound, which is 5-(trifluoromethoxy)-1'-((5-(trifluoromethyl)pyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

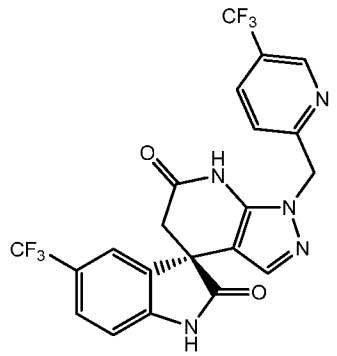
$^1$H-NMR (400 MHz, DMSO-$d_6$): δ ppm 2.67 (d, *J* = 20.6 Hz, 1H), 3.30 (d, *J* = 15.8 Hz, 1H), 5.52 (d, *J* = 6.6 Hz, 2H), 6.81 (s, 1H), 6.9 (s, 1H), 7.00 (s, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.31 (s, 2H), 8.21 (dd, *J* = 2.2 Hz and 2.2 Hz, 1H), 8.96 (s, 1H), 10.60 (s, 1H), 11.07 (br s, 1H).

MS: m/z 498.0 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-19***

(R)-5-(trifluoromethyl)-1'-((5-(trifluoromethyl)pyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione




The racemate of the above title compound, which is 5-(trifluoromethyl)-1'-((5-(trifluoromethyl)pyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

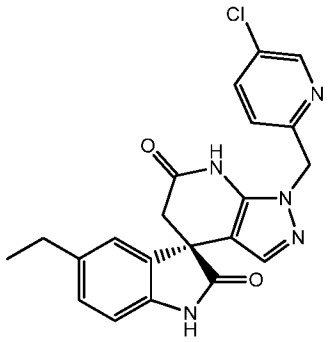
$^1$H-NMR (400 MHz, DMSO-$d_6$): δ ppm 2.61 (d, *J* = 16.4 Hz,1H), 3.22 (d, *J* = 16.4 Hz, 1H), 5.53 (ABq, *J* = 16.4 Hz, 2H), 6.83 (s, 1H), 7.09 (d, *J* = 7.6 Hz,1H), 7.23 (d, *J* = 8.4 Hz,1H), 7.641 (m, 2H), 8.23 (d, *J* = 7.6 Hz, 1H), 8.96 (s, 1H), 10.91 (s, 1H), 11.09 (br s, 1H).

MS: m/z 480.1 $(M-H)^-$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-20***

(R)-1'-((5-chloropyridin-2-yl)methyl)-5-ethyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



The racemate of the above title compound, which is 1'-((5-chloropyridin-2-yl)methyl)-5-ethyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

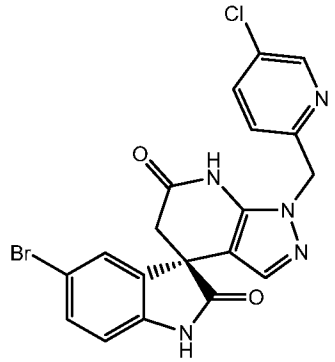
$^1$H NMR (400 MHz, DMSO-$d_6$):δ ppm1.14 (t, *J* = 7.6, 3H), 2.5 (m,3H, merged with DMSO), 2.98 (d, *J* = 15.6Hz, 1H), 5.40 (ABq, *J* = 16.4 Hz, 2H), 6.7 (s,1H), 6.819 (d, *J* = 7.5Hz, 1H), 7.07 (m,3H), 7.94 (t, 1H, *J* = 1.6Hz,), 8.62 (s,1H), 10.42 (s, 1H), 11.03 (br s, 1H).

MS: m/z 408.0 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-21***

(R)-5-bromo-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione




The racemate of the above title compound, which is 5-bromo-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

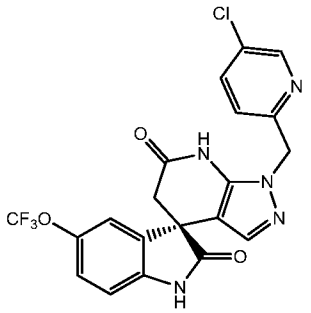
$^1$H-NMR (400 MHz, DMSO-$d_6$): δ ppm 2.56 (d, 1H, merged with DMSO), 3.12 (d, *J* = 6.4 Hz, 1H), 5.42 (ABq, *J* = 16.4 Hz, 2H), 6.82 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 7.06 (d, *J* = 8.4, 1H),7.43 (d, *J* = 6.8 Hz), 7.93 (dd, *J* = 2.4, 2.0 Hz, 1H),8.61 (s, 1H), 10.63 (s, 1H), 11.03 (br s, 1H).

MS: m/z 458.0 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-22***

(R)-1'-((5-chloropyridin-2-yl)methyl)-5-(trifluoromethoxy)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



The racemate of the above title compound, which is 1'-((5-chloropyridin-2-yl)methyl)-5-(trifluoromethoxy)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

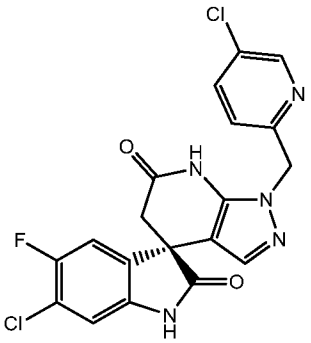
$^1$H-NMR (400 MHz, DMSO-$d_6$): δ 2.50 (d, *J* = 1.6 Hz, 1H), 3.157 (d, *J* = 6.2 Hz, 1H), 5.40 (ABq, *J* = 16.3 Hz, 2H), 6.78 (s, 1H), 6.98 (d *J* = 8.4 Hz, 1H) 7.07 (d *J* = 8.40 Hz 1H),7.28 (m, 2H), 7.93 (dd *J* = 10.8 Hz, 1H), 8.615 (d, *J* = 2.4 Hz,1H), 10.32 (s, 1H), 11.09 (br s, 1H),

MS: m/z 464.2 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-23***

(R)-6-chloro-1'-((5-chloropyridin-2-yl)methyl)-5-fluoro-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



The racemate of the above title compound, which is 6-chloro-1'-((5-chloropyridin-2-yl)methyl)-5-fluoro-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

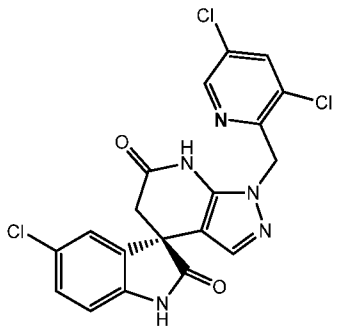
$^1$H-NMR (400 MHz, DMSO-$d_6$): δ ppm 2. 54 (d, 1H, merged with DMSO). 3.16 (d, *J* = 16.2Hz, 1H), 5.40 (d, *J* = 11.0 Hz, 2H), 6.85 (s, 1H), 7.01-7.17 (m, 2H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.93 (dd, *J* = 2.6, 2.7 Hz, 1H), 8.61 (d, *J* = 2.2Hz, 1H), 10.61 (br s, 1H), 11.04 (br s, 1H).

MS: m/z 432.0 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-24***

(R)-5-chloro-1'-((3,5-dichloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione




The racemate of the above title compound, which is 5-chloro-1'-((3,5-dichloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

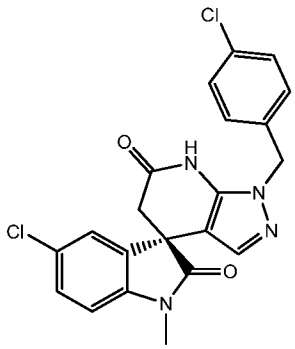
$^1$H-NMR (400 MHz, DMSO-$d_6$): δ ppm 2.55 (d, 1H, merged with DMSO), 3.01 (d, *J* = 15.6 Hz, 1H), 5.46 (s, 2H), 6.74 (s, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 7.23-7.26 (m, 2H), 8.26 (s, 1H), 8.53 (s, 1H), 10.6 (s, 1H), 10.99 (br s, 1H).

MS m/z: 446.2 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-25***

(R)-5-chloro-1'-(4-chlorobenzyl)-1-methyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



The racemate of the above title compound, which is 5-chloro-1'-(4-chlorobenzyl)-1-methyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

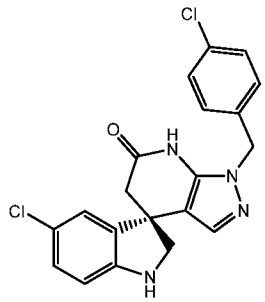
$^1$H NMR (400 MHz, DMSO-*d6*): δ ppm 2.54 (d, peak merged with DMSO, 1H), 3.10-3.20 (m, 4H), 5.28 (ABq, *J* = 15.9 Hz, 2H), 6.77 (s, 1H), 7.1 (d, *J* = 8.3 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 2H), 7.35-7.45 (m, 4H), 11.11 (br s, 1H).

MS: m/z 427.0 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

***Example 7-26***

(R)-5-chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridin]-6'(1'H)-one



The racemate of the above title compound, which is 5-chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridin]-6'(1'H)-one, was prepared using the general procedures as well as the procedures from the examples described above, and the characterization data is:

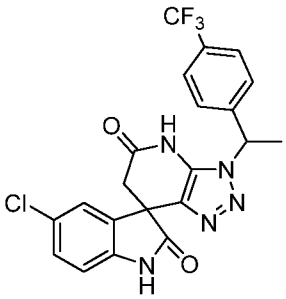
$^1$H NMR (400 MHz, $CD_3OD$): δ 2.78 (AB q, *J* = 16.4 Hz, 2H), 3.50 (AB q, *J* = 9.2 Hz, 2H), 5.28 (s, 2H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 7.02 (dd, *J* = 2.0 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.23 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 2H).

MS: m/z 399.0 $(M+H)^+$.

The title compound can be prepared from the racemate via chiral resolution using similar procedures to the examples described above.

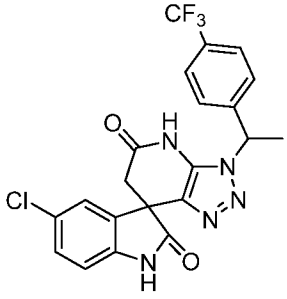
***Example 8-1 and Example 8-2***

Preparation of racemic mixture of (R,R) and (S,S) or racemic mixture of (R,S) and (S,R) of 5'-chloro-3-(1-(4-(trifluoromethyl)phenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione (Example 8-1); and preparation of racemic mixture of (R,S) and (S,R) or racemic mixture of (R,R) and (S,S) of 5'-chloro-3-(1-(4-(trifluoromethyl)phenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione (Example 8-2)



Racemic (R,R) and (S,S) or
Racemic (R,S) and (S,R)

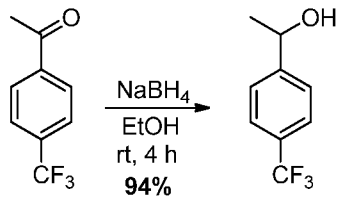
Example 8-1



Racemic (R,S) and (S,R) or
Racemic (R,R) and (S,S);

Example 8-2

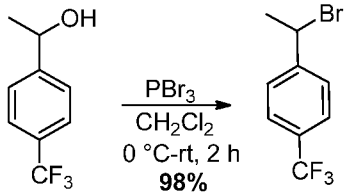
Step 1: preparation of 1-(4-(Trifluoromethyl)phenyl)ethanol




To a cold solution of 4'-(trifluoromethyl)acetophenone (10 g, 53.15 mmol) in ethanol (55 mL) was added $NaBH_4$ in small portions at 0 °C and the resulting mixture was stirred at rt for 4 h. The reaction mixture was quenched with 1N HCl (50 mL) and extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layer was washed with saturated $NaHCO_3$, brine, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to afford 9.5 g (94%) of *1-(4-(Trifluoromethyl)phenyl)ethanol* as a pale yellow liquid.

$^1$H-NMR (400 MHz, $CDCl_3$); $\delta$ 7.6 (d, $J$ = 8.0 Hz, 2H), 7.49 (d, $J$ = 8.4 Hz, 2H), 4.94-5.0 (m, 1H), 1.86 (s, 1H), 1.51 (d, $J$ = 6.8 Hz, 3H).

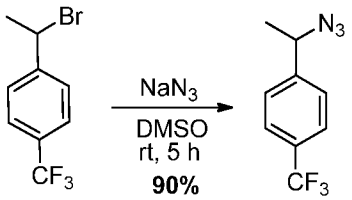
Step 2: preparation of 1-(1-Bromoethyl)-4-(trifluoromethyl)benzene




To a cold solution of *1-(4-(Trifluoromethyl)phenyl)ethanol* (2 g, 10.52 mmol) in $CH_2Cl_2$ (30 mL) was added phosphorus tribromide (1.1 mL, 11.58 mmol) slowly at 0 °C and the resulting mixture was allowed to stir at rt for 2 h. The reaction mass was diluted with $CH_2Cl_2$ (100 mL) and washed with water, saturated $NaHCO_3$, water and brine. The resultant organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to afford 2.6 g (98%) of *1-(1-Bromoethyl)-4-(trifluoromethyl)benzene* as a pale yellow liquid.

$^1$H-NMR (400 MHz, $CDCl_3$); $\delta$ 7.6 (d, $J$ = 8.4 Hz, 2H), 7.55 (d, $J$ = 8.4 Hz, 2H), 5.19 (q, $J$ = 6.9 Hz, 1H), 2.05 (d, $J$ = 6.8 Hz, 3H).

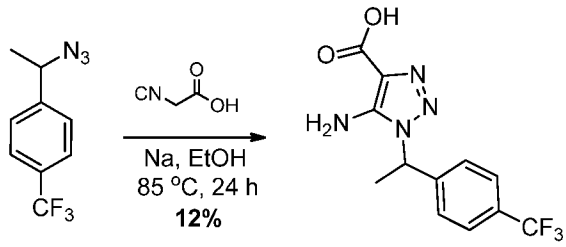
Step 3: preparation of 1-(1-Azidoethyl)-4-(trifluoromethyl)benzene




To a solution of *1-(1-Bromoethyl)-4-(trifluoromethyl)benzene* (13 g, 51.37 mmol) in DMSO (130 mL) was added sodium azide (3.34 g, 128.46 mmol) and the resulting mixture was stirred at rt for 5 h. The reaction mass was quenched with water and extracted with ethyl acetate (3 × 200 mL). The combined organic layer was washed with water, brine, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to afford 10 g (90%) of *1-(1-Azidoethyl)-4-(trifluoromethyl)benzene* as a colourless liquid.

$^1$H-NMR (400 MHz, $CDCl_3$); $\delta$ 7.64 (d, $J$ = 8.0 Hz, 2H), 7.44 (d, $J$ = 8.4 Hz, 2H), 4.68 (q, $J$ = 6.8 Hz, 1H), 1.55 (d, $J$ = 6.4 Hz, 3H).

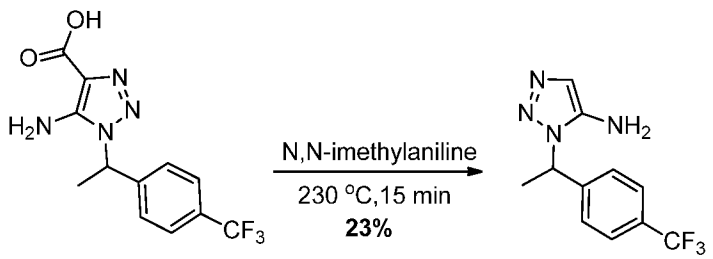
Step 4: preparation of 5-Amino-1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-1,2,3-triazole-4-carboxylic acid




To a clear solution of Na (0.214 g, 9.29 mmol) in ethanol (15 mL) cooled to 0 °C were added cyanoacetic acid (0.395 g, 4.65 mmol), *1-(1-Azidoethyl)-4-(trifluoromethyl)benzene* (1 g, 4.65 mmol) and the resulting mixture was stirred at reflux temperature for 24 h. The reaction mixture was quenched with ice and solvent was distilled off under reduced pressure. The residue was dissolved in water and the solution was acidified with con. HCl. The resultant solid was collected by filtration, washed with diethyl ether and dried under reduced pressure to afford 200 mg (12% based on LCMS~ 85%) of *5-Amino-1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-1,2,3-triazole-4-carboxylic acid* as an off white solid.

$^1$H-NMR (400 MHz, DMSO-$d_6$); $\delta$ 12.25 (br s, 1H), 7.73 (d, $J$ = 8.4 Hz, 2H), 7.45 (d, $J$ = 8.0 Hz, 2H), 6.46 (s, 2H), 5.81 (q, $J$ = 7.2 Hz, 1H), 1.88 (d, $J$ = 6.8 Hz, 3H); LCMS (ESI): *m/z* 301.0 $[M+H]^+$.

Step 5: preparation of 1-(1-(4-(Trifluoromethyl)phenyl)ethyl)-1H-1,2,3-triazol-5-amine

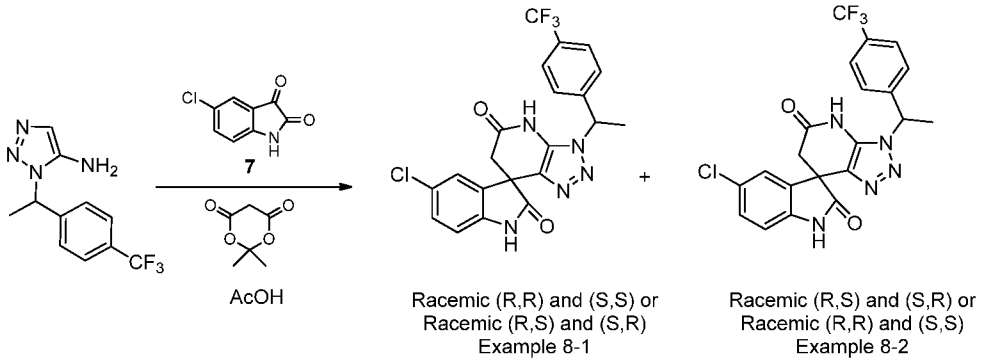



A mixture of *5-Amino-1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-1,2,3-triazole-4-carboxylic acid* (1 g, 3.33 mmol) and *N,N*-dimethyl aniline (7 mL) was stirred in a pre-heated oil bath at 200 °C for 15 min. The reaction mass was directly purified by column chromatography over silica gel

(100-200 mesh) using a solvent gradient of 35-50% EtOAc in pet-ether as eluent to afford 200 mg (23%) of *1-(1-(4-(Trifluoromethyl)phenyl)ethyl)-1H-1,2,3-triazol-5-amine* as an off white solid.

$^1$H-NMR (400 MHz, DMSO-$d_6$); $\delta$ 7.71 (d, $J$ = 8.0 Hz, 2H), 7.41 (d, $J$ = 8.0 Hz, 2H), 6.83 (s, 1H), 5.71 (q, $J$ = 6.9 Hz, 1H), 5.51 (s, 2H), 1.85 (d, $J$ = 7.2 Hz, 3H); LCMS (ESI): *m/z* 257.0 $[M+H]^+$.

Step 6: preparation of 5'-Chloro-3-(1-(4-(trifluoromethyl)phenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione




A mixture of *1-(1-(4-(Trifluoromethyl)phenyl)ethyl)-1H-1,2,3-triazol-5-amine* (200 mg, 0.78 mmol), 5-chloroisatin (142 mg, 0.78 mmol) and Meldrum's acid (112 mg, 0.78 mmol) in acetic acid (10 mL) was stirred in a pre-heated oil bath at 100 °C for 4 h. The reaction mass was concentrated and water was added to the residue. The resultant solid was collected by filtration, washed with water followed by hexane and dried under reduced pressure. The diastereomers were separated by column chromatography over silica gel (100-200 mesh) using a solvent gradient of 40-50% EtOAc in pet-ether for D1 and 60-80% EtOAc in pet-ether for D2 as eluent. Further D1 was washed with $CH_2Cl_2$/pentane and D2 was washed with methanol to afford 30 mg of 5'-Chloro-3-(1-(4-(trifluoromethyl)phenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione (Example 8-1) as a red solid and 35 mg of *5'-Chloro-3-(1-(4-(trifluoromethyl)phenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione* (Example 8-2) as an off white solid.

Characterization data of Example 8-1 is shown below:

$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 1.91 (d, *J* = 6.8Hz, 3H), 2.61 (d, *J* = 16.0Hz, 1H), 3.35 (d, 1H, merged with DMSO-water), 5.95 (q, *J* = 6.8Hz, 1H), 6.93 (d, *J* = 8.0Hz, 1H), 7.36-7.31 (m, 2H), 7.54 (d, *J* = 8.4Hz, 2H), 7.78 (d, *J* = 8.4Hz, 2H), 10.70 (s, 1H), 11.22 (s, 1H).

MS: m/z 462.0 $(M+H)^+$.

The individual (R,R), (S,S), (R,S) and (S,R) enantiomer of Example 8-1, can be prepared by isolating the racemic mixture using the procedures from the examples described above.

Characterization data of Example 8-2 is shown below:

$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 1.90 (d, *J* = 7.2Hz, 3H), 2.72 (d, *J* = 16.0Hz, 1H), 3.19 (d, *J* = 17.6Hz, 1H), 5.90 (q, *J* = 7.2Hz, 1H), 6.93 (d, *J* = 8.8Hz, 1H), 7.34-7.32 (m, 2H), 7.56 (d, *J* = 8.4Hz, 2H), 7.77 (d, *J* = 8.0Hz, 2H), 10.71 (s, 1H), 11.30 (s, 1H).

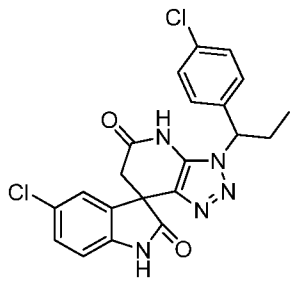
MS: m/z 462.0 $(M+H)^+$.

The individual (R,S), (S,R), (R,R) and (S,S) enantiomer of Example 8-2, can be prepared by isolating the racemic mixture using the procedures from the examples described above.

The following compounds were prepared using the general procedures as well as the procedures from the examples described above with the appropriate starting materials.

***Example 8-3***

Racemic mixture of (R,R) and (S,S) or Racemic mixture of (R,S) and (S,R) of (5'-chloro-3-(1-(4-chlorophenyl)propyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione



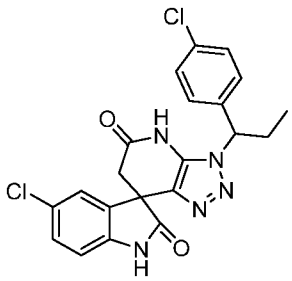

Racemic (R,R) and (S,S) or Racemic (R,S) and (S,R)

$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 0.81 (t, *J* = 7.6Hz, 3H), 2.24-2.16 (m, 1H), 2.43-2.32 (m, 1H), 2.60 (d, *J* = 16.0Hz, 1H), 3.33 (d, *J* = 16.8Hz, 1H), 5.58 (t, *J* = 7.6Hz, 1H), 6.92 (d, *J* = 8.4Hz, 1H), 7.34-7.30 (m, 2H), 7.49-7.43 (m, 4H), 10.68 (s, 1H), 11.22 (s, 1H).

MS: m/z 442.0 $(M+H)^+$.

***Example 8-4***

Racemic mixture of (R,S) and (S,R) or Racemic mixture of (R,R) and (S,S) of (5'-chloro-3-(1-(4-chlorophenyl)propyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione



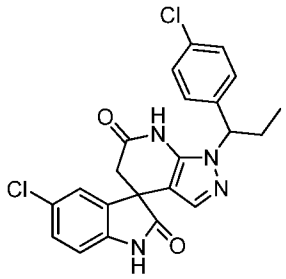
Racemic (R,S) and (S,R) or Racemic (R,R) and (S,S)

$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 0.83 (t, *J* = 7.6Hz, 3H), 2.24-2.16 (m, 1H), 2.40-2.32 (m, 1H), 2.71 (d, *J* = 16.8Hz, 1H), 3.27 (d, *J* = 16.8Hz, 1H), 5.52 (t, *J* = 7.6Hz, 1H), 6.93 (d, *J* = 8.0Hz, 1H), 7.34-7.30 (m, 2H), 7.49-7.43 (m, 4H), 10.70 (s, 1H), 11.30 (s, 1H).

MS:m/z 442.0 $(M+H)^+$.

***Example 8-5***

Racemic mixture of (R,R) and (S,S) or Racemic mixture of (R,S) and (S,R) of 5-chloro-1'-(1-(4-chlorophenyl)propyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



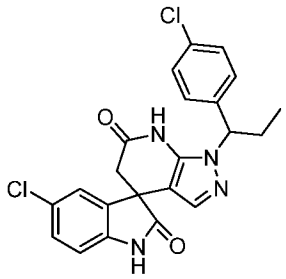
Racemic (R,R) and (S,S) or Racemic (R,S) and (S,R)

$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 0.78 (t, *J* = 7.6Hz, 3H), 2.05-2.00 (m, 1H), 2.30-2.24 (m, 1H), 2.44 (d, *J* = 15.6Hz, 1H), 3.12 (d, *J* = 16.0Hz, 1H), 5.47-5.41 (m, 1H), 6.82 (s, 1H), 6.91-6.89 (m, 1H), 7.30-7.26 (m, 2H), 7.44-7.38 (m, 4H), 10.54 (s, 1H), 10.97 (s, 1H).

MS: m/z 441.3 $(M+H)^+$.

***Example 8-6***

Racemic mixture of (R,S) and (S,R) or Racemic mixture of (R,R) and (S,S) of 5-chloro-1'-(1-(4-chlorophenyl)propyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



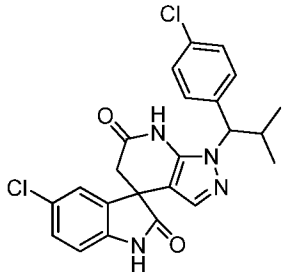
Racemic (R,S) and (S,R) or Racemic (R,R) and (S,S)

$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 0.78 (t, *J* = 7.6Hz, 3H), 2.00-2.08 (m, 1H), 2.26-2.19 (m, 1H), 2.54 (d, *J* = 16.4Hz, 1H), 3.08 (d, *J* = 16.4Hz, 1H), 5.39-5.34 (m, 1H), 6.84 (s, 1H), 6.90 (d, *J* = 8.8Hz, 1H), 7.32-7.28 (m, 2H), 7.40 (d, *J* = 8.4Hz, 2H), 7.47 (d, *J*=8.4Hz, 2H), 10.57 (s, 1H), 11.05 (s, 1H).

MS: m/z 441.3 $(M+H)^+$.

***Example 8-7***

Racemic mixture of (R,R) and (S,S) or Racemic mixture of (R,S) and (S,R) of 5-chloro-1'-(1-(4-chlorophenyl)-2-methylpropyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



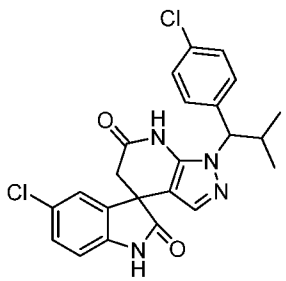
Racemic (R,R) and (S,S) or Racemic (R,S) and (S,R)

$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 0.74 (t, *J* = 6.8Hz, 6H), 2.43 (*J* = 16.0Hz, 1H), 2.61-2.55 (m, 1H), 3.12 (d, *J* = 16.0Hz, 1H), 5.12 (d, *J* = 10.4Hz, 1H), 6.80 (s, 1H), 6.90-6.88 (m, 1H), 7.29-7.26 (m, 2H), 7.43 (d, *J* = 8.4Hz, 2H), 7.55 (d, *J* = 8.4Hz, 2H), 10.52 (s, 1H), 11.0 (s, 1H).

MS: m/z 454.9 $(M+H)^+$.

***Example 8-8***

Racemic mixture of (R,S) and (S,R) or Racemic mixture of (R,R) and (S,S) of 5-chloro-1'-(1-(4-chlorophenyl)-2-methylpropyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



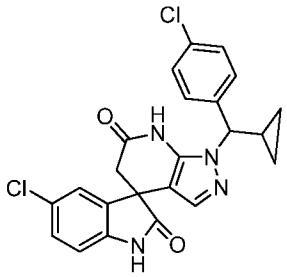
Racemic (R,S) and (S,R) or Racemic (R,R) and (S,S)

$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 0.75 (t, *J* = 7.2Hz, 6H), 2.62-2.54 (m, 2H), 3.07 (d, *J* = 15.6Hz, 1H), 5.02 (d, *J* = 10.0Hz, 1H), 6.82 (s, 1H), 6.89 (d, *J* = 8.4Hz,1H), 7.32-7.26 (m, 1H), 7.42 (d, *J* = 8.4Hz, 2H), 7.65 (d, *J* = 8.0Hz, 2H), 10.56 (s, 1H), 11.08 (s, 1H).

MS: m/z 454.9 $(M+H)^+$.

***Example 8-9***

Racemic mixture of (R,R) and (S,S) or Racemic mixture of (R,S) and (S,R) of 5-chloro-1'-((4-chlorophenyl)(cyclopropyl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



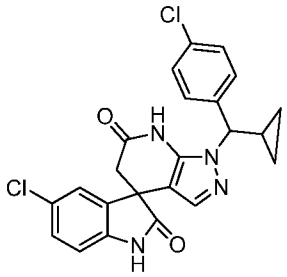

Racemic (R,R) and (S,S) or Racemic (R,S) and (S,R)

$^1$H NMR (400 MHz, DMSO-d6) δ 10.88 (br. s., 1H), 10.60 (br. s., 1H), 7.37-7.52 (m, 4H), 7.22-7.36 (m, 2H), 6.87-6.97 (m, 1H), 6.81 (s, 1H), 4.82 (d, *J* = 9.54 Hz, 1H), 3.14 (d, *J* = 15.89 Hz, 1H), 2.45 (s, 1H), 1.69-1.94 (m, 1H), 0.52-0.83 (m, 2H), 0.28-0.49 (m, 2H);

MS: m/z 454.0 $(M+H)^+$.

***Example 8-10***

Racemic mixture of (R,S) and (S,R) or Racemic mixture of (R,R) and (S,S) of 5-chloro-1'-((4-chlorophenyl)(cyclopropyl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



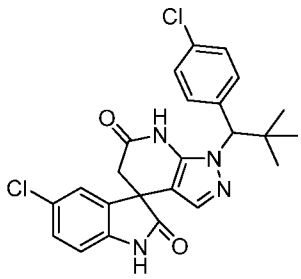
Racemic (R,S) and (S,R) or Racemic (R,R) and (S,S)

$^1$H NMR (400 MHz, DMSO-d6) δ 10.94 (br. s., 1H), 10.59 (br. s., 1H), 7.39-7.53 (m, 4H), 7.28-7.37 (m, 2H), 6.91 (d, *J* = 8.31 Hz, 1H), 6.83 (s, 1H), 4.81 (d, *J* = 9.54 Hz, 1H), 3.13 (d, *J* = 16.14 Hz, 1H), 2.57 (s, 1H), 1.68-1.84 (m, 1H), 0.52-0.78 (m, 2H), 0.24-0.50 (m, 2H)

MS: m/z 453.9 $(M+H)^+$.

***Example 8-11***

Racemic mixture of (R,R) and (S,S) or Racemic mixture of (R,S) and (S,R) of 5-chloro-1'-(1-(4-chlorophenyl)-2,2-dimethylpropyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



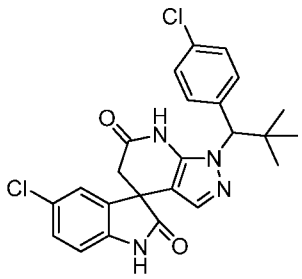
Racemic (R,R) and (S,S) or Racemic (R,S) and (S,R)

$^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.01 (s, 1H), 10.55 (s, 1H), 7.70–7.63 (m, 2H), 7.47–7.40 (m, 2H), 7.31–7.26 (m, 2H), 6.94–6.88 (m, 1H), 6.85 (s, 1H), 5.36 (s, 1H), 3.12 (d, *J* = 16.0 Hz, 1H), 2.44 (d, *J* = 16.0 Hz, 1H), 1.23 (s, 2H), 0.93 (s, 10H).

MS: m/z 470.0 $(M+H)^+$.

***Example 8-12***

Racemic mixture of (R,S) and (S,R) or Racemic mixture of (R,R) and (S,S) of 5-chloro-1'-(1-(4-chlorophenyl)-2,2-dimethylpropyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione



Racemic (R,S) and (S,R) or Racemic (R,R) and (S,S)

Off-white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.07 (s, 1H), 10.59 (s, 1H), 7.80–7.71 (m, 2H), 7.46–7.38 (m, 2H), 7.30 (dd, *J* = 8.2, 2.2 Hz, 2H), 7.27 (d, *J* = 2.3 Hz, 2H), 6.91 (d, *J* = 8.3 Hz, 2H), 6.87 (s, 1H), 5.31 (s, 1H), 3.06 (d, *J* = 16.0 Hz, 1H), 2.55 (s, 1H), 1.23 (s, 1H), 0.93 (s, 10H).

MS: m/z 470.0 $(M+H)^+$.

For Examples 8-3 to 8-12, the individual (R,R), (S,S), (R,S), (S,R) enantiomer of the racemic mixture can be prepared by isolating the racemic mixture using the procedures from the examples described above.

**PHARMACOLOGICAL DATA**

The utility of the compounds of the present disclosure may be evidenced by using any one of the assays described herein below.

**Dengue virus $EC_{50}$ determination by the replicon assay**

BHK21 DENV-2 replicon cells were seeded at a density of 10,000 cells per well in a 96-well microplate. After incubating at 37°C with 5% CO2 overnight, cells were treated with compounds.

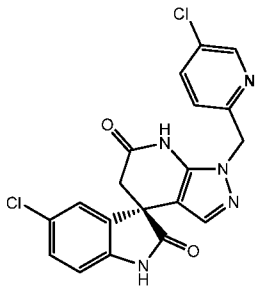
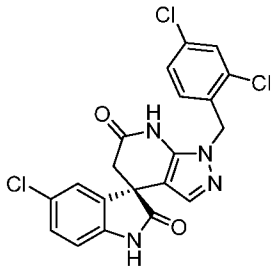
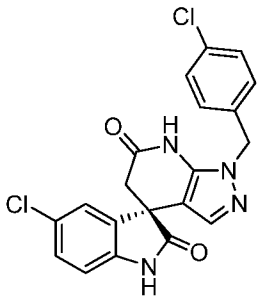
Luciferase activities were measured after 48 h incubation using Promega's EndurRen live cell substrate. Following luciferase activity measurement, Promega's CellTiter-Glo reagent was added to each well to determine the cytotoxicity of the compounds. The plate was read in a Clarity luminescence microplate reader (BioTek). Dose response curves were plotted from the mean light units versus the log of the concentration of test compounds. 50% effective concentration ($EC_{50}$), the concentration of the test compound that decreases the luciferase activity by 50%, was calculated by nonlinear regression analysis.

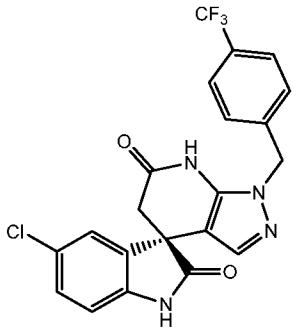
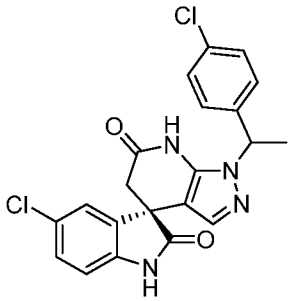
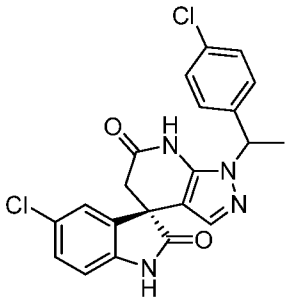
**Dengue virus $EC_{50}$ determination by the CFI assay**

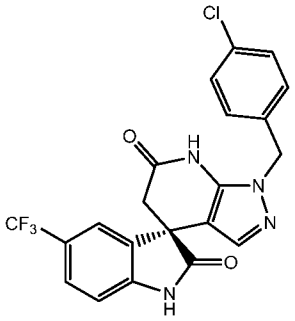
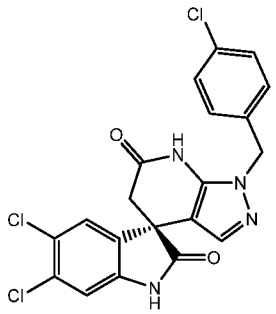
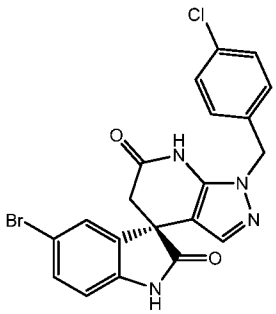
BHK21 cells were trypsinized and diluted to a concentration of $2x10^5$ cells/ml in culture media containing 2% FBS. A 100µl of cell suspension ($2x10^4$cells) was dispensed per well into one 96-well tissue culture plate (Nunc, 96-well clear flat bottom, sterile, Nunclone Δ surface). Cells were grown overnight in culture medium at 37°C, 5% CO2, and then infected with dengue virus at an MOI (multiplicity of infection) = 0.3 in the presence of different concentrations of test compounds for 1h at 37°C ,5% CO2. The virus inoculum was removed, replaced with fresh medium containing test compounds, and incubated at 37°C, 5% CO2 for 48h. The cells were washed once with PBS, and fixed with cold methanol for 10min. After washing twice with PBS, the fixed cells were blocked with PBS containing 1% FBS and 0.05% Tween-20 for 1h at room temperature. Then primary antibody (4G2) solution was added, and incubated for 3h. The cells were washed three times with PBS followed by 1h incubation with horseradish peroxidase (HRP)-conjugated anti-mouse IgG. After washing three times with PBS, 3,3',5,5'-tetramethylbenzidine (TMB) substrate solution was added to each well, and the reaction was stopped by adding 0.5M sulfuric acid. The plate was read in Tecan Safire II plate reader at 450 nM for viral antigen quantification. Dose response curves were plotted from the mean absorbance versus the log of the concentration of test compounds. 50% effective concentration ($EC_{50}$), the concentration of the test compound that decreases the viral E protein production by 50%, was calculated by nonlinear regression analysis.

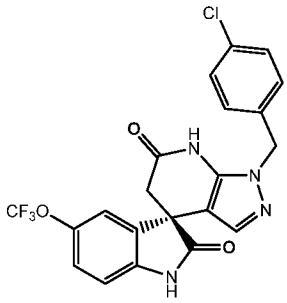
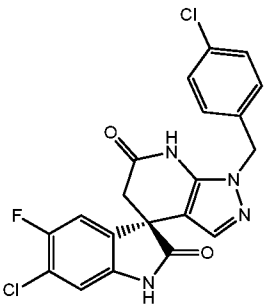
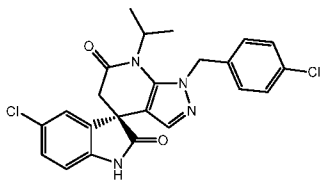
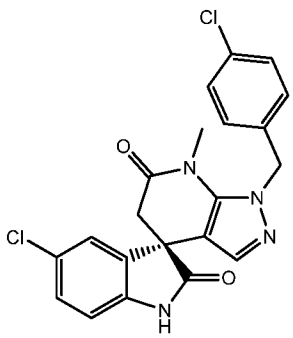
Dengue $EC_{50}$ Data of some representative compounds of the present disclosure are shown in Table 5 below.

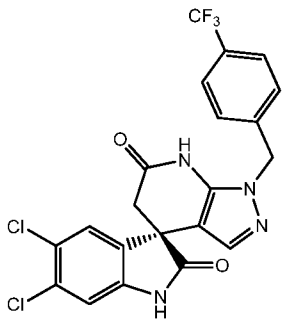
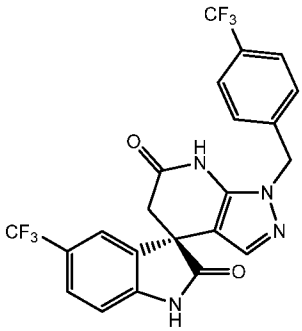
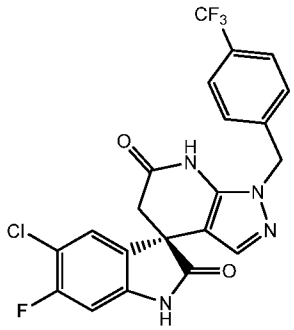
**Table 5**

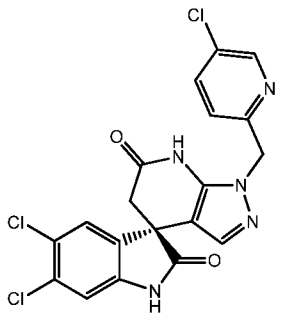
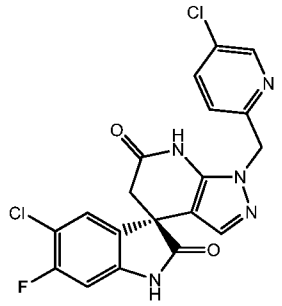
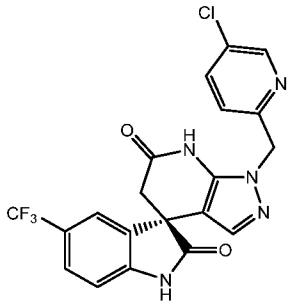
| Example No. | Compound Structure | Dengue-2 Replicon $EC_{50}$ (μM) | Dengue-2 CFI $EC_{50}$ (μM) | Dengue-3 CFI $EC_{50}$ (μM) |
|---|---|---|---|---|
| 1 |  | 0.23 | 0.51 | 0.12 |
| 2 |  | 0.021 | 0.029 | 0.022 |
| 3-1 |  | 0.11 | 0.12 | 0.02 |

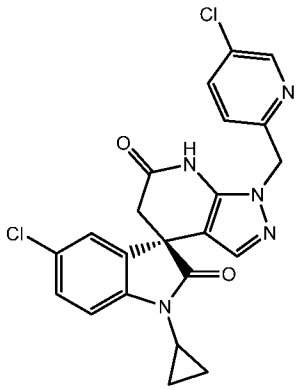
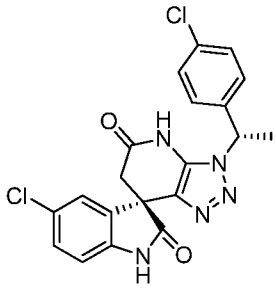
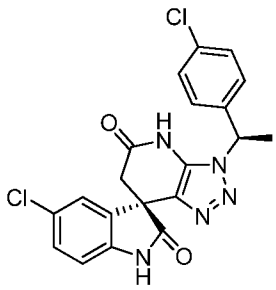
| | | | | |
|---|---|---|---|---|
| 3-2 |  | 0.015 | 0.046 | 0.05 |
| 3-3-1 |  | 0.076 | 0.125 | 0.016 |
| 3-3-2 |  | 2.3 | 9.9 | 5.0 |

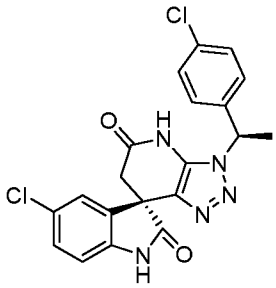
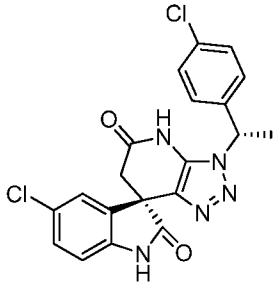
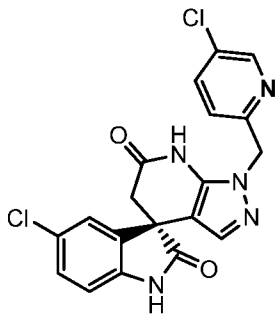
| | | | | |
|---|---|---|---|---|
| 3-4 |  | 0.13 | 1.3 | 3.7 |
| 3-5 |  | <0.09 | 2.0 | 0.12 |
| 3-6 |  | 0.1 | 0.046 | 0.015 |

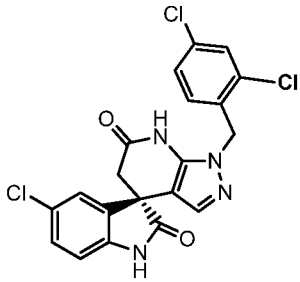
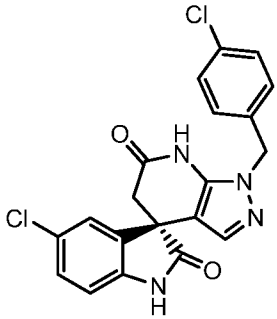
| | | | | |
|---|---|---|---|---|
| 3-7 |  | 0.3 | 4.4 | |
| 3-8 |  | 0.36 | 1.3 | 0.25 |
| 3-9 |  | 1.1 | 3.5 | |
| 3-10 |  | 0.04 | 0.4 | 0.05 |

| | | | | |
|---|---|---|---|---|
| 3-11 |  | 0.10 | 5.45 | 9.9 |
| 3-12 |  | 0.056 | 2.8 | |
| 3-13 |  | 0.02 | 3.5 | 5.3 |

| | | | | |
|---|---|---|---|---|
| 3-14 |  | 0.64 | 3.7 | 0.2 |
| 3-15 |  | 0.105 | 6.4 | |
| 3-16 |  | 0.31 | 23.7 | 0.27 |

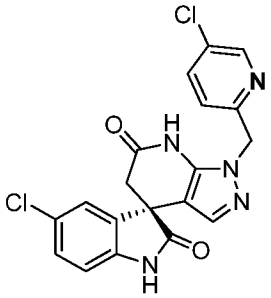
| | | | | |
|---|---|---|---|---|
| 3-17 |  | 0.05 | 0.17 | 0.168 |
| 4-1 |  | | 0.014 | 0.0025 |
| 4-2 |  | | 0.84 | 0.49 |

| | | | | |
|---|---|---|---|---|
| 4-3 |  | | 3.77 | 7.4 |
| 4-4 |  | | 21.9 | 17.4 |
| Comparative Example #1 |  (comparator) | | 11 | |

| | | | | |
|---|---|---|---|---|
| Comparative Example #2 |  (comparator) | | 2.5 | |
| Comparative Example #3 |  (comparator) | | 8.75 | |

The above data demonstrates that compounds of the present disclosure are active against the Dengue virus.

***In vivo* Mouse efficacy Study of (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione (Example 1)**



AG129 mice (lacking IFN-α/β and IFN-γ receptors) were obtained from B&K Universal. Mice were housed in individually ventilated cages (TechniPlast) and used between 7 and 9 weeks of age. Mice were injected intraperitoneally $2\times10^6$ PFU of DENV-2 (strain TSV01) on day 0 (6 animals per group). Immediately after infection, orally dosing of infected mice with either vehicle or the above title compound at 50 and 100 mg/kg body weight twice daily or 100mg/kg body weight once a day for 3 days. On day 3 post-infection, blood samples were obtained by retro-orbital puncture under ketamine and xylazine anaesthesia. Blood samples were collected in tubes that contained sodium citrate to a final concentration of 0.4% and were immediately centrifuged for 3 min at 6000 g to obtain plasma. Then, 20 µL of plasma was diluted in 780 µL of RPMI 1640 medium and snap frozen in liquid nitrogen for plaque assay analysis. In brief, BHK-21 cells were seeded in 24-well plates (Nunc) and grown to confluency. Cell layers were incubated with serially diluted virus samples for 1 h and overlaid with 0.8% methylcellulose. Plates were incubated for 5 days at 37°C, fixed in 10% formaldehyde, and stained with 1% crystal violet in water for 20 min. Plaques were counted visually. Statistical analysis comparing average values of differently treated groups of mice with the vehicle control group was done using the one-way ANOVA Tukey-Kramer test.

The result of the *in vivo* efficacy study of the above title compound is presented in Figure 1. It clearly shows that this title compound demonstrates significant viremia reduction when administered to mouse under various dosages, e.g., 50mg/Kg, or 100 mg/Kg twice a day, or 100mg/kg once a day.

**Cytotoxicity Determination**

The cytotoxicity of representative compounds of the present disclosure can be determined using the following general protocol.

***CCK8 Cytotoxicity Assay in HepG2 Cells***

HepG2 cells were trypsinized, washed, counted and diluted to 1.6 $x10^4$ cells/ml in DMEM-W/O Glucose, supplemented with 10% Fetal bovine serum (FBS), 1% Penicillin/ Streptomycin, 2mM HEPES, 1mM Sodium Pyruvate, 10mM Galactose & 2mM Glutamine. 25µl of the media containing 400 cells per well were dispensed in clear 384-well tissue culture plate and incubated at room temperature for 30 minutes. The plate was then transferred and placed at 37°C, 5% $CO_2$ humidified incubator overnight. On the next day, serial-diluted compound plates were prepared and 125nl of compounds at various concentrations were then dispensed into the tissue culture well (200 × dilution). The plates were then transferred to 37°C, 5%

$CO_2$humidified incubator for additional 96 hours. Cytotoxicity was measured by CCK-8 assay. Briefly, CCK-8 was thawed on bench top and diluted 2.5 × with the growth media. 35ul of the pre-diluted CCK-8 was then introduced into each well and the plates were then further incubated in 37°C, 5% $CO_2$ humidified incubator for 3 h. The absorbance was read by Envision at 450nm. Dose response curves were calculated as in the previous section. The $CC_{50}$ is estimated as the concentration of the compound which will inhibit 50% of the signal. A positive control (puromycin) was used to ensure the quality of the data.

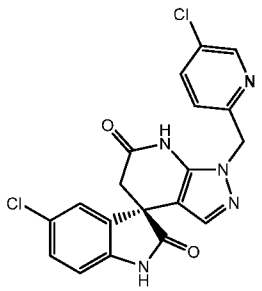
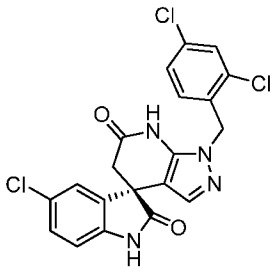
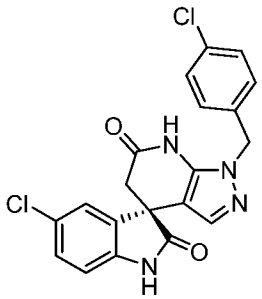
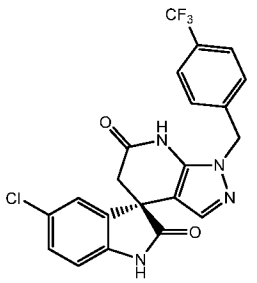
***CCK8 Cytotoxicity Assay in THP-1 Cells***

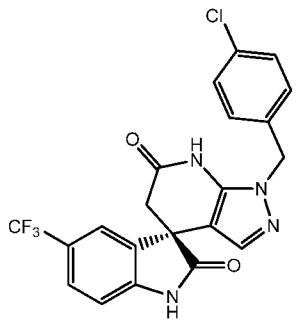
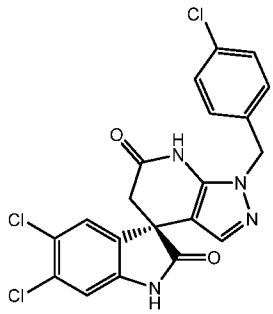
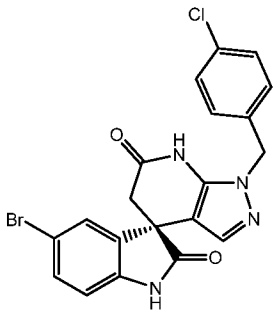
4 day cytotoxicity assay using THP-1 cells: THP-1 cells grown in suspension were counted and diluted to 8 × $10^4$ cells/ml in RPMI-1640 media supplemented with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin. 25ul of the THP-1 containing media consisting of 2000 cells were dispensed in 384-well tissue culture plate and pre-incubated at room temperature for 30 minutes, followed by 37°C, 5% $CO_2$ overnight in the humidified incubator. On the next day, serial-diluted compound plates were prepared and 125nl of compounds at various concentrations were then dispensed into the tissue culture well (200 × dilution). The plates were then transferred to 37°C, 5% $CO_2$ humidified incubator for additional 96 hours. The plates were then transferred to 37°C, 5% $CO_2$ humidified incubator for additional 96 hours. Cytotoxicity was measured by CCK-8 assay. Briefly, CCK-8 was thawed on bench top and diluted 2.5 × with the growth media. 35ul of the pre-diluted CCK-8 was then introduced into each well and the plates were then further incubated in 37°C, 5% $CO_2$ humidified incubator for 3 hours. The absorbance was read by Envision at 450nm. Dose response curves were calculated as in the previous section (n=2). The $CC_{50}$ is estimated as the concentration of the compound which will inhibit 50% of the signal. A positive control (puromycin) was used to ensure the quality of the data.

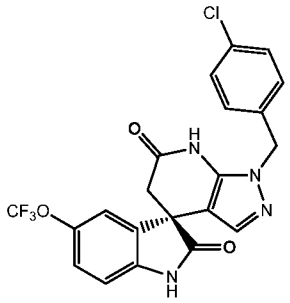
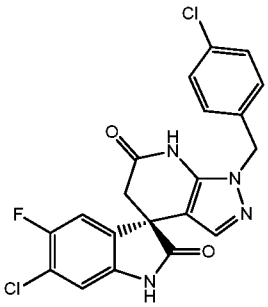
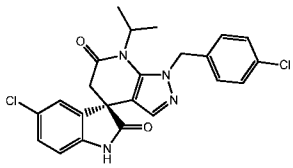
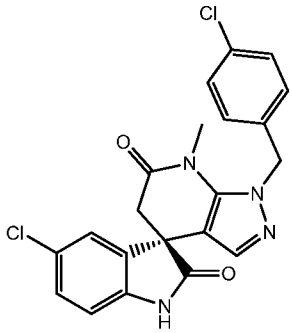
Cytotoxicity Data of some representative compounds are shown in Table 6 below. The data indicates that compounds of the present disclosure have good selectivity, because while they are active against cells infected by dengue, they are not toxic to normal cells.

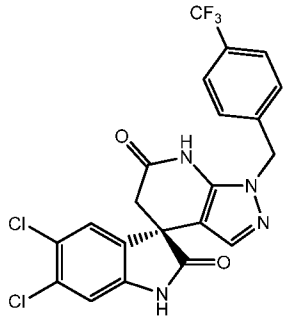
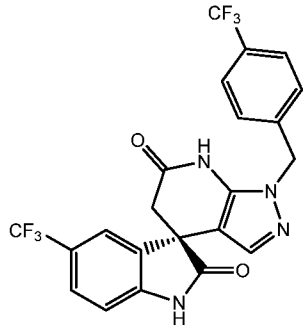
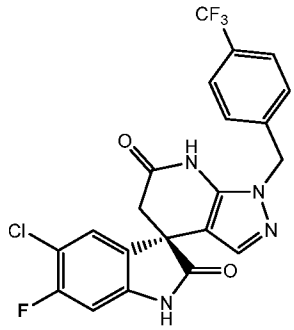
**Table 6**

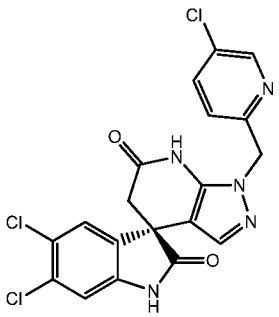
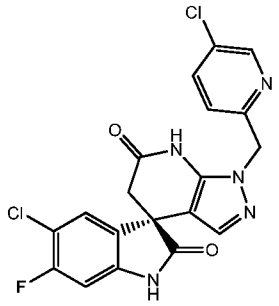
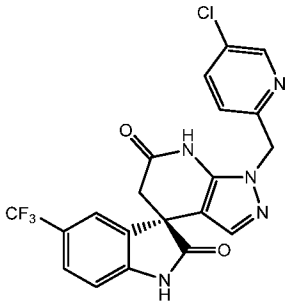
| Example No. | Compound Structure | HepG2 $CC_{50}$ (μM) | THP-1 $CC_{50}$ (μM) |
|---|---|---|---|

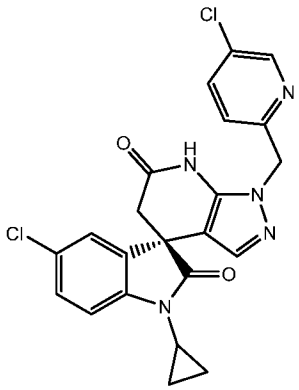
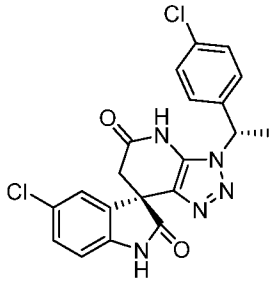
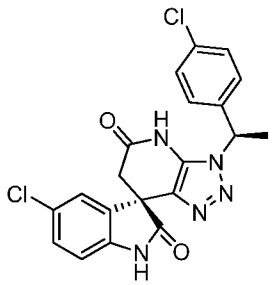
| | | | |
|---|---|---|---|
| 1 |  | 30.4 | >50 |
| 2 |  | 29.1 | 33.6 |
| 3-1 |  | 37.6 | >50 |
| 3-2 |  | 19.73 | 27.58 |

| | | | |
|---|---|---|---|
| 3-4 |  | 20.4 | 19.3 |
| 3-5 |  | 19.2 | 18.0 |
| 3-6 |  | >10 | >10 |

| | | | |
|---|---|---|---|
| 3-7 |  | 27.7 | 31.4 |
| 3-8 |  | 18.9 | >50 |
| 3-9 |  | 7.2 | 31.1 |
| 3-10 |  | 10.5 | 33.7 |

| | | | |
|---|---|---|---|
| 3-11 |  | 29.0 | 31.1 |
| 3-12 |  | 23.1 | 22.6 |
| 3-13 |  | 18.6 | 26.9 |

| | | | |
|---|---|---|---|
| 3-14 |  | 33.4 | >50 |
| 3-15 |  | 41.9 | >50 |
| 3-16 |  | 11.3 | >50 |

| | | | |
|---|---|---|---|
| 3-17 |  | >50 | >50 |
| 4-1 |  | 40 | >50 |
| 4-2 |  | >50 | >50 |

**In-vivo Pharmacokinetic (PK) study**

The pharmacokinetic profile was determined in CD-1 female mice following intravenous (i.v.) and oral (p.o.) administration of representative compound of the present invention at the dosage of 5 and 25 mg/kg, respectively. The formulations used for i.v. and p.o. were the following: solution in NMP: plasma (10:90 v/v) and suspension in methylcellulose (0.5% w/v) Tween80 (0.5% v/v) in phosphate buffer pH 6.8, respectively. Blood samples were collected at 0.02 (only intravenous dose) 0.08 (only oral dose), 0.25, 0.75, 1.5, 3, 8 and 24 h after dosing. Plasma concentrations of tested compounds were measured by LC/MS/MS. Pharmacokinetic parameters were calculated by a non-compartmental approach using the WinNonLin software (Pharsight) and shown in below Table 7.

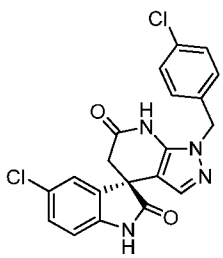
**Table 7**

| **Administration** | | **Example 3-1** | **Example 1** |
|---|---|---|---|
| PO | Cmax (µg/mL) | 0.8 | 3.9 |
| | $AUC_{0-24}$ (ng*h/mL) | 9459 | 13762 |
| | F (%) | 33 | 63 |

Cmax: maximum concentration of the tested compound in plasma
$AUC_{0-24}$: area under the curve extrapolated to infinity
F%: oral bioavailability

**Mechanism of action (MoA)**:

An representative compound of the present disclosure, (R)-5-chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione ("the testing compound"), structure shown below, was used to study the mechanism of the action against the dengue virus.



In order to determine whether the testing compound inhibits viral translation and/or RNA synthesis, a transient transfection assay using a luciferase-reporting replicon of DENV-2 was performed. The replicon was in vitro transcribed and transfected into BHK21 cells followed by treatment with the testing compound at indicated concentrations or DMSO (see Fig. 2). Luciferase activities were monitored at various time points post-transfection. In the DMSO-treated cells (as a control), luciferase activity peaked within 4 h p.t. and gradually diminished afterwards. At 16 h p.t., the luciferase activity increased again and peaked at 33 h post-transfection. The 4-h peak of the luciferase signal represented translation of the input replicon RNA, whereas the 33-h peak represented RNA synthesis. In the testing compound-treated cells, the testing compound showed no effect on luciferase signals at 2 and 4 h after transfection, whereas it suppressed the luciferase activities in a dose-responsive manner at 24 and 33 h after transfection (see Figure 2). The results suggest that the testing compound inhibits viral RNA synthesis.

To identify antiviral target(s), the testing compound-resistant DENV was selected by culturing wild-type (WT) virus in the presence of increasing concentrations of the testing compound. Six independent selections were performed. For each selection, a total of 11 passages was carried out, with the first 3 passages (P1-P3) selected at 27 nM of the testing compound, the next 4 passages (P4-P7) selected at 80 nM of the testing compound, and the last 4 passages (P8-P11) selected at 150 nM of the testing compound. Viruses from each passage were assayed for their resistance, through comparison of viral titers from mock-treated infection with viral titers from the testing compound-treated infection (harvested at 72 h p.i.). P11 virus capable of growing in the presence of 150 nM of the testing compound (corresponding to a ~20-fold higher $EC_{50}$) was isolated, propagated, and examined for compound sensitivity. The complete genomes of P11 viruses from the six independent selections were sequenced to identify potential resistance mutation(s). All selections had accumulated a nucleotide change at position 7012 and/or 7013, resulting in an amino acid substitution from Val to Ala, Leu, Met, Ser, or Thr at position 63 in the NS4B protein (see Table 8: Resistant profile of selected mutant viruses).

**Table 8**

| Selection | NS4B mutation recovered | The testing compound potency ($EC_{50}$ μM) |
|---|---|---|
| I | V63A, V63M, & V63T mixture | >1 |

| | | |
|---|---|---|
| II | V63L & V63M mixture | >1 |
| III | V63A, V63L, & V63S mixture | >1 |
| IV | V63L & V63M mixture | >1 |
| V | V63M | >1 |
| VI | V63M | >1 |

To confirm that amino acid substitution at V63 is responsible for conferring resistance to the testing compound, each of the mutations in the NS4B region was individually engineered into an infectious cDNA clone of DENV. Infectious virus recovered from the engineered cDNA clone showed resistant to the testing compound treatment, similar to the parental resistant isolates (see Table 9: effects of amino acid substitution at residue 63 in NS4B on the testing compound potency against DENV-2).

**Table 9**

| **V63 substitution** | **$EC_{50}$ (μM)** | **Fold resistance** |
|---|---|---|
| None (WT) | 0.008 | 1 |
| V63A | 0.13 | 16.5 |
| V63I | >1 | >125 |
| V63L | >1 | >125 |
| V63M | >1 | >125 |
| V63S | >1 | >125 |
| V63T | >1 | >125 |

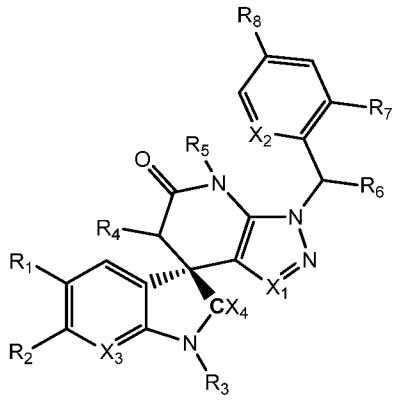
Sequence alignment of NS4B showed that V63 is absolutely conserved among DENV-2 and -3, but is different among DENV-1 and -4 and other flaviviruses. Notably, the mutated 63 Ile residue exists as the WT amino acid in the DENV-1; the mutated 63Leu residue exists as the WT amino acid in the DENV-4, TBEV, and YFV NS4B proteins; and the mutated 63Thr residue exists as the WT amino acid in the JEV and WNV NS4B proteins. Such differences at amino acid 63 of NS4B may account for the selectivity of the testing compound in inhibiting DENV-2 and -3. Engineering the I64 residue of DENV-1 NS4B protein into Val was performed, and the change in resistance phenotype of DENV-1 to the testing compound was examined. As shown in Figure 3, the I64V mutation increased the susceptibility of DENV-1 to the testing compound treatment. These results indicate that mutations at residue V63 of NS4B is responsible for the testing compound resistance.

In summary, mutational and genetic analyses as described in the above suggest that the testing compound inhibits DENV replication by interacting with the NS4B protein. As a result, the compounds of the present disclosure are NS4B inhibitors.

CLAIMS

What is claimed is:

1. A compound of Formula (I)



(I)

wherein

$R_1$ is F, Cl, Br, $CF_3$, $OCH_3$, $(C_1$-$C_6)$alkyl or cycloalkyl;

$R_2$ is H, F, Cl, Br, $(C_1$-$C_6)$alkyl or cycloalkyl; or $R_1$ and $R_2$ taken together with the aromatic carbon atoms to which they are attached form a fused 1,3-dioxolo group;

$R_3$ is H, $(C_1$-$C_6)$alkyl or cycloalkyl;

$R_4$ is H, $(C_1$-$C_6)$alkyl, cycloalkyl or -C(=O)-$NH_2$;

$R_5$ is H, $(C_1$-$C_6)$alkyl, cycloalkyl or benzyl;

$R_6$ is H, $(C_1$-$C_6)$alkyl or cycloalkyl;

$R_7$ is H, F, Cl or $OCH_3$;

$R_8$ is F, Cl, Br, $CF_3$, -$OCHF_2$, $OCF_3$, $OCH_3$ or $(C_1$-$C_6)$alkyl;

$X_1$ is CH or N;

$X_2$ is CH or N;

$X_3$ is CH or N;

$X_4$ is =O or $H_2$;

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, and $R_8$ are each optionally independently substituted with one or more independent $R_{300}$ substituents;

$R_{300}$ is selected from the group consisting of H, ($C_1$-$C_6$)alkyl, cycloalkyl, hydroxy, amino, F, Cl, Br, phenyl, heterocycle and heteroaryl;

or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein $R_1$ is Cl.

3. The compound of Claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein $R_2$ is Cl or F.

4. The compound of any one of Claims 1-3, or a pharmaceutically acceptable salt thereof, wherein $R_3$ is H or cyclopropyl.

5. The compound of any one of Claims 1-4, or a pharmaceutically acceptable salt thereof, wherein $R_4$ is H.

6. The compound of any one of Claims 1-5, or a pharmaceutically acceptable salt thereof, wherein $R_5$ is H, methyl or *i*-propyl.

7. The compound of any one of Claims 1-6, or a pharmaceutically acceptable salt thereof, wherein $R_6$ is H or methyl.

8. The compound of any one of Claims 1-7, or a pharmaceutically acceptable salt thereof, wherein $R_7$ is H or Cl.

9. The compound of any one of Claims 1-8, or a pharmaceutically acceptable salt thereof, wherein $R_8$ is Cl, methyl, *i*-propyl or *t*-butyl.

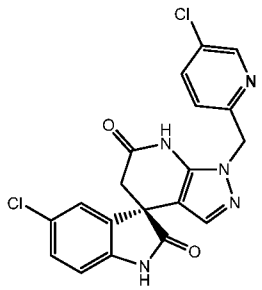
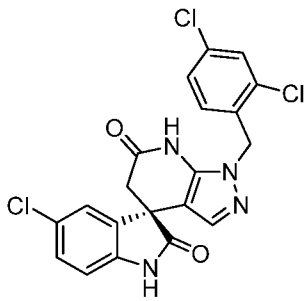
10. The compound of any one of Claims 1-9, or a pharmaceutically acceptable salt thereof, wherein $X_1$ is CH.

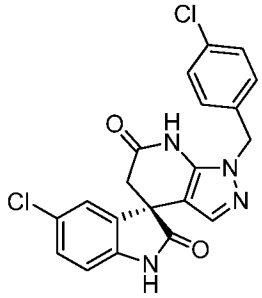
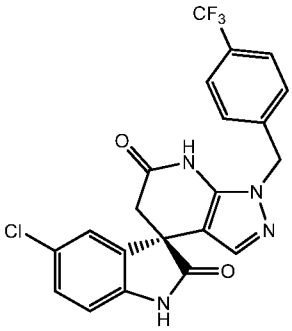
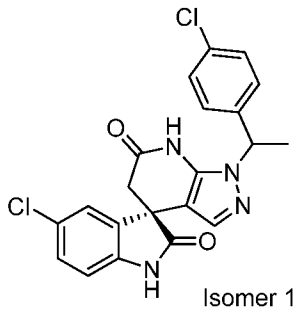
11. The compound of any one of Claims 1-10, or a pharmaceutically acceptable salt thereof, wherein $X_2$ is N.

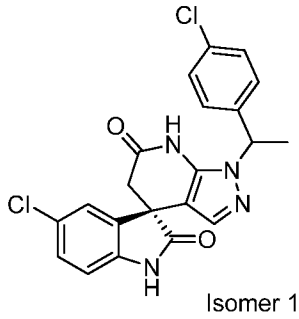
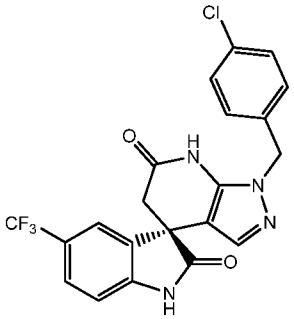
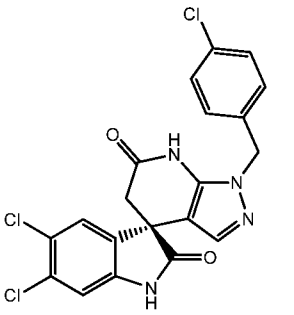
12. The compound of any one of Claims 1-11, or a pharmaceutically acceptable salt thereof, wherein $X_3$ is CH.

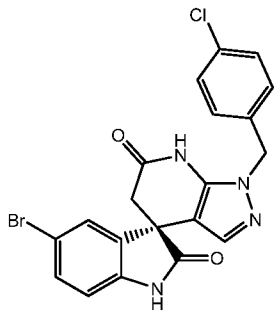
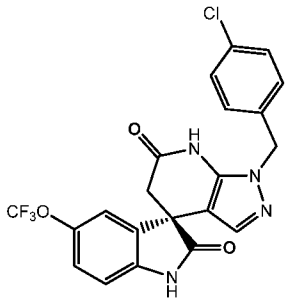
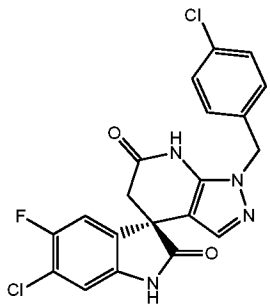
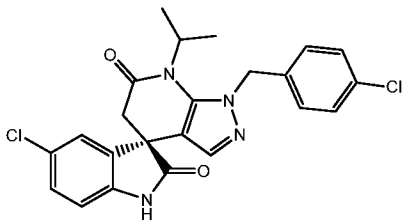
13. The compound of any one of Claims 1-12, or a pharmaceutically acceptable salt thereof, wherein $X_4$ is =O.

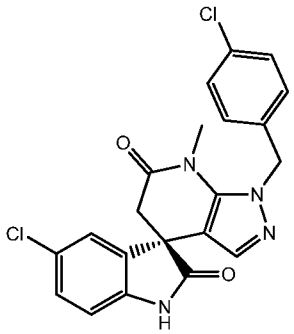
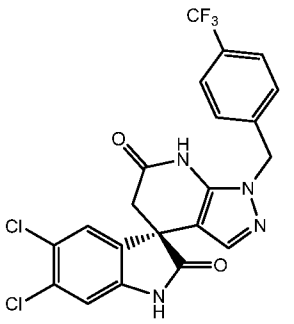
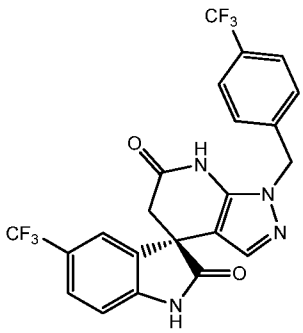
14. The compound of any one of Claims 1-13, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

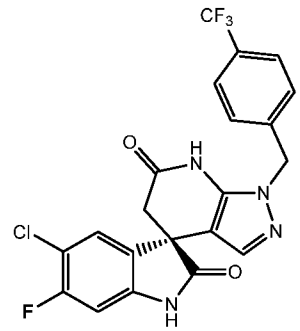
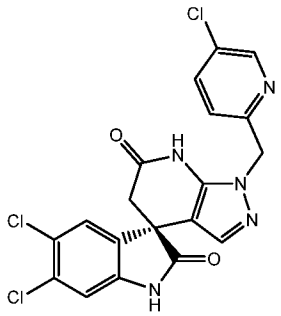
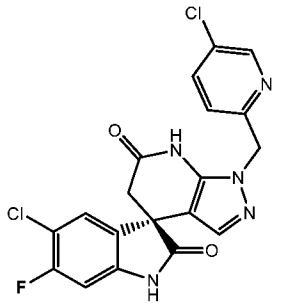
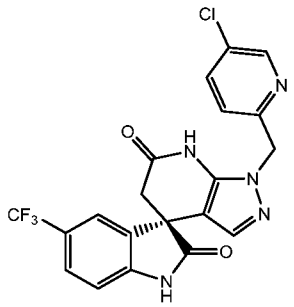
| | |
|---|---|
|  | (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5-chloro-1'-(2,4-dichlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

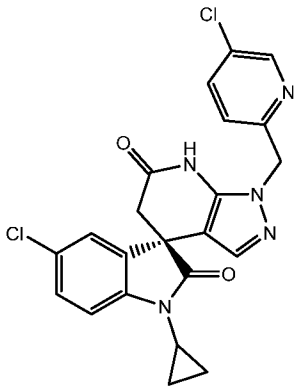
| | |
|---|---|
|  | (R)-5-chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5-chloro-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  Isomer 1 | (R)-5-chloro-1'-(1-(4-chlorophenyl)ethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, Isomer 1, |

| | |
|---|---|
|  Isomer 1 | (S)-5-chloro-1'-(1-(4-chlorophenyl)ethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, Isomer 1, |
|  | (R)-1'-(4-chlorobenzyl)-5-(trifluoromethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5,6-dichloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

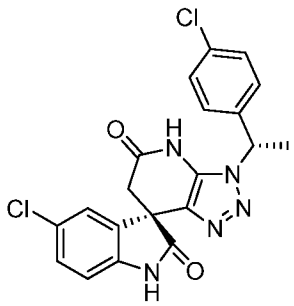
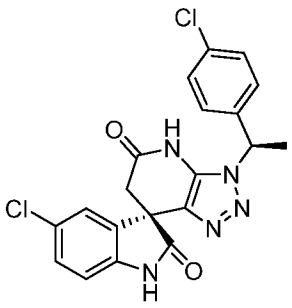
| | |
|---|---|
|  | (R)-5-bromo-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-1'-(4-chlorobenzyl)-5-(trifluoromethoxy)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-6-chloro-1'-(4-chlorobenzyl)-5-fluoro-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5-chloro-1'-(4-chlorobenzyl)-7'-isopropyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

| | |
|---|---|
|  | (R)-5-chloro-1'-(4-chlorobenzyl)-7'-methyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5,6-dichloro-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5-(trifluoromethyl)-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |

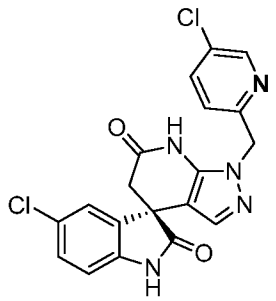
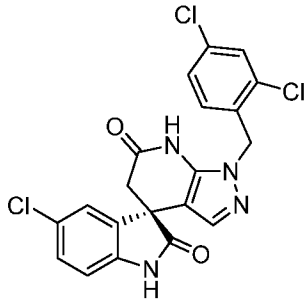
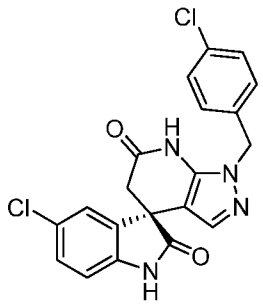
| | |
|---|---|
|  | (R)-5-chloro-6-fluoro-1'-(4-(trifluoromethyl)benzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5,6-dichloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-6-fluoro-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-1'-((5-chloropyridin-2-yl)methyl)-5-(trifluoromethyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, and |

| | |
|---|---|
|  | (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-1-cyclopropyl-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione. |

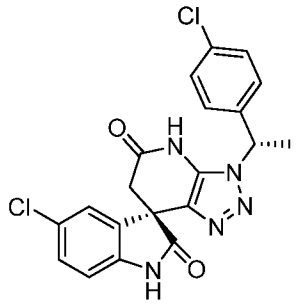
15. The compound of any one of Claims 1-14, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

| | |
|---|---|
|  | (R)-5'-chloro-3-((S)-1-(4-chlorophenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione; and |
|  | (R)-5'-chloro-3-((R)-1-(4-chlorophenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione. |

16. The compound of any one of Claims 1-15, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

| | |
|---|---|
|  | (R)-5-chloro-1'-((5-chloropyridin-2-yl)methyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, |
|  | (R)-5-chloro-1'-(2,4-dichlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione, and |
|  | (R)-5-chloro-1'-(4-chlorobenzyl)-5',7'-dihydrospiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'(1'H)-dione. |

17. The compound of any one of Claims 1-16, or a pharmaceutically acceptable salt thereof, is (R)-5'-chloro-3-((S)-1-(4-chlorophenyl)ethyl)-4,6-dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione



18. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of the Claims 1-17, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

19. The pharmaceutical composition of Claim 18 further comprising at least one additional pharmaceutical agent.

20. The pharmaceutical composition of Claim 18 or Claim 19 wherein said at least one additional pharmaceutical agent is Celgosivir.

21. A method for treating a disease caused by a viral infection comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of the Claims 1-17, or a pharmaceutically acceptable salt thereof.

22. The method of Claim 21 wherein said subject is human.

23. The method of Claim 21 or Claim 22, wherein said viral infection is caused by dengue virus.

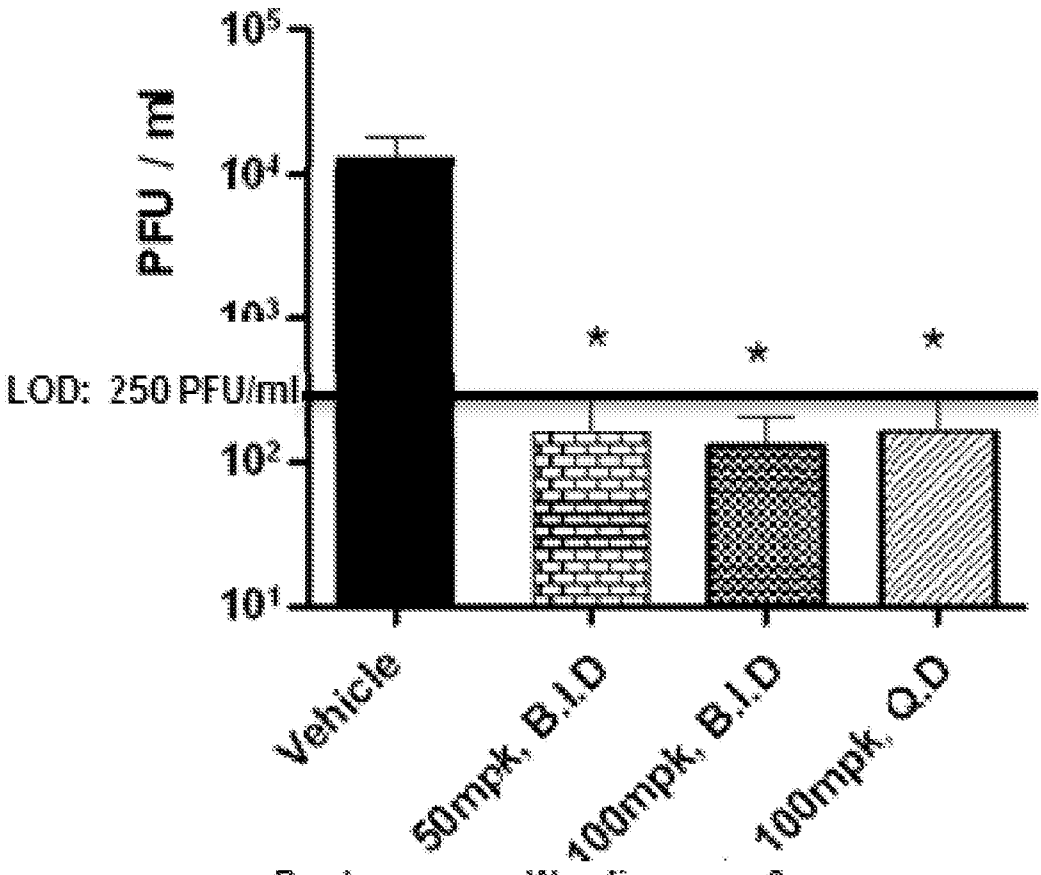
24. The compound as claimed in any one of the Claims 1-17, or a pharmaceutically acceptable salt thereof, for use as a medicament.

25. The use of a compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease caused by a viral infection.

26. The use of Claim 25 wherein said viral infection is caused by dengue virus.

27. The compound as claimed in any one of the Claims 1-17, or a pharmaceutically acceptable salt thereof, is a NS4B inhibitor.

Figure 1




| P value | Wording | Summary |
|---|---|---|
| < 0.001 | Extremely significant | *** |
| 0.001 to 0.01 | Very significant | ** |
| 0.01 to 0.05 | Significant | * |
| >0.05 | Not significant | ns |

* LOD: limit of detection

Figure 2

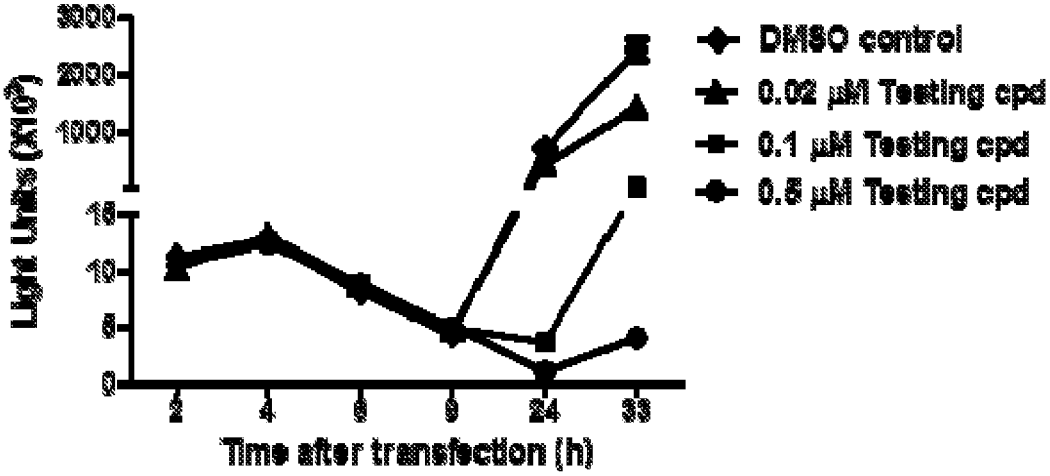
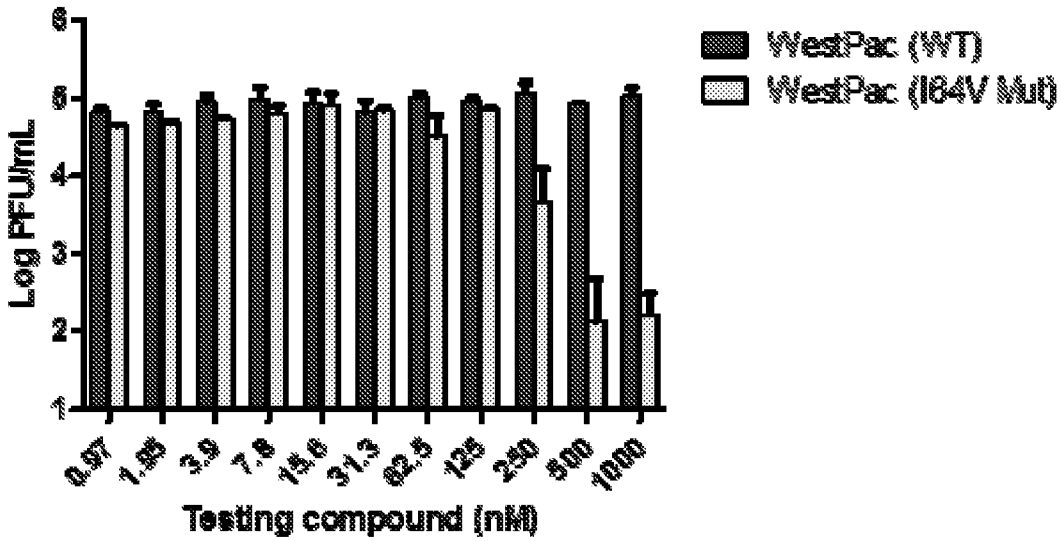

Light Units (X10³)
3000
2000
1000
15
10
5
0
2
4
8
9
24
33
Time after transfection (h)
DMSO control
0.02 µM Testing cpd
0.1 µM Testing cpd
0.5 µM Testing cpd

Figure 3


WestPac (WT)
WestPac (I84V Mut)
Log PFU/mL
6
5
4
3
2
1
0.97
1.95
3.9
7.8
15.6
31.3
62.5
125
250
500
1000
Testing compound (nM)

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/060628

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/20 A61K31/438 A61P31/12
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | LEYSSEN P ET AL: "PERSPECTIVES FOR THE TREATMENT OF INFECTIONS WITH FLAVIVIRIDAE", CLINICAL MICROBIOLOGY REVIEWS, vol. 13, no. 1, 1 January 2000 (2000-01-01), pages 67-82, XP000971418, WASHINGTON, DC, US ISSN: 0893-8512 the whole document | 1-27 |
| | ----- | |
| A | WO 02/48165 A2 (PHARMASSET LTD [US]; STUYVER LIEVEN [US]; PANKIEWICZ KRYSZTOF W [US];) 20 June 2002 (2002-06-20) claims; | 1-27 |
| | ----- | |
| | -/-- | |

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 12 June 2014 | 04/07/2014 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Schuemacher, Anne |

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | YANG, LI-MIN ET AL: "One-pot three-component synthesis of spiro[pyrazolo[3,4-b]pyridine-4,3'-indolin e] derivatives catalyzed by melamine trisulfonic acid", JOURNAL OF THE CHINESE CHEMICAL SOCIETY, vol. 59, no. 12, 13 July 2012 (2012-07-13) , pages 1500-1503, XP002725667, (WEINHEIM, GERMANY) ISSN: 0009-4536, DOI: 10.1002/JCCS.201200046 scheme II, compound 4; ----- | 1-17 |
| A | Andrea Baier: "5 Flaviviral Infections and Potential Targets for Antiviral Therapy", , 30 September 2011 (2011-09-30), XP055122868, Retrieved from the Internet: URL:http://www.intechopen.com/source/pdfs/ 20864/InTech-Flaviviral_infections_and_pot ential_targets_for_antiviral_therapy.pdf [retrieved on 2014-06-12] the whole document ----- | 1-27 |
| X | DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 30 July 2009 (2009-07-30), XP002725626, retrieved from STN Database accession no. 1170395-25-1 abstract ----- | 1,4-10, 12,13 |
| X | DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 31 July 2009 (2009-07-31), XP002725627, Database accession no. 1170898-52-8 abstract ----- | 1,2, 5-10,12, 13 |
| X | DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2 August 2009 (2009-08-02), XP002725628, retrieved from STN Database accession no. 1171807-41-2 CAS Registry Numbers: 1171715-14-2, 1171608-17-5 ----- | 1,2, 4-10,12, 13 |

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# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/060628

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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