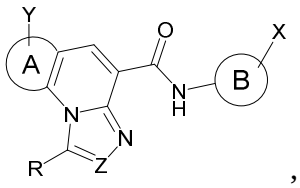
detoxification and metabolic clearance of PAHs, which reduces the probability of bioactivation, and DNA adduct formation. Several marketed drugs were found to activate AHR (thus upregulating CYP1A1, CYP1A2, and CYP1B1) after their FDA approval, yet their long-term use is not associated with dioxin-like toxicities (Ehrlich et al., *Curr. Opin. Toxicol.*, 2, 72-78 (2017)). As such, CYP induction is no longer viewed as a barrier to the adoption of AHR agonists in therapy (Ehrlich et al., *Curr. Opin. Toxicol.*, 2, 72-78 (2017)).

WO 2008/014307 discloses certain bicyclic heteroaryl amides as inhibitors of undecaprenyl pyrophosphate synthase. EP 0059698 discloses certain heterocyclic carboxamides, compositions containing these compounds and methods of treatment with these compositions.

The bacterial stilbenoid DMVT-505 (VTAMA® (tapinarof)) 1% cream, an aryl hydrocarbon receptor agonist, indicated for the topical treatment of plaque psoriasis in adults, has been approved by the U.S. Food and Drug Administration (FDA). Despite this, there remains a need for alternative novel, oral, selective, and/or potent AHR agonists for the treatment of IMDs.

Summary

In an aspect, there is provided a compound of formula:



,

wherein:

ring A is a 5-membered or 6-membered carbocycle;

ring B is a phenyl, or a 5-membered or 6-membered heteroaryl having 1 or 3 heteroatoms, wherein each heteroatom of the heteroaryl is independently selected from N, S, and O;

R is H or C_{1-3} alkyl;

X is H, halo, C_{1-3} alkyl optionally substituted with one or more halo, or a C_{1-3} alkoxyl;

Y is H, C_{1-4} alkyl, or C_{3-4} cycloalkyl, wherein the C_{1-4} alkyl is a primary or secondary alkyl; and

Z is CH or N,

a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

In another aspect, there is provided a compound selected from Table 2, 2A, and 3, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

In another aspect, there is provided a pharmaceutical composition, comprising a compound as described herein, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

In another aspect, there is provided use of a compound as described herein, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof, or the pharmaceutical composition as described herein in the manufacture of a medicament for treating an immune-mediated disease.

In another aspect, there is provided use of a compound as described herein, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof, or the pharmaceutical composition as described herein in the manufacture of a medicament for treating a disease or disorder selected from psoriasis, atopic dermatitis, ulcerative colitis, Crohn's disease, graft-versus-host disease, rheumatoid arthritis, and multiple sclerosis.

In another aspect, there is provided use of a compound as described herein, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof, for use in therapy.

In another aspect, there is provided use of a compound as described herein, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating psoriasis.

In another aspect, there is provided use of a compound as described herein, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating atopic dermatitis.

In another aspect, there is provided use of a compound as described herein, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating ulcerative colitis.

In another aspect, there is provided use of a compound as described herein, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Crohn's disease.

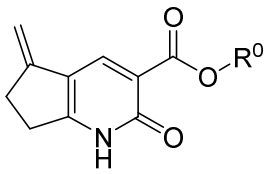
In another aspect, there is provided use of a compound as described herein, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating graft-versus-host disease.

In another aspect, there is provided use of a compound as described herein, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating rheumatoid arthritis.

In another aspect, there is provided use of a compound as described herein, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating multiple sclerosis.

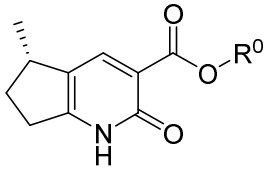
In another aspect, there is provided use of a compound as described herein, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating systemic lupus erythematosus (SLE).

In another aspect, there is provided a compound of the formula:



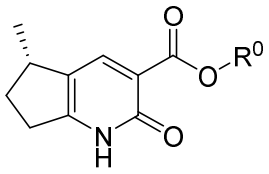
or a salt thereof, wherein R^0 is C_{1-3} alkyl.

In another aspect, there is provided a compound of the formula:

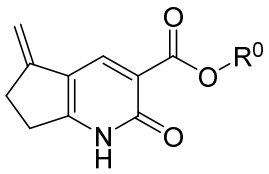


or a salt thereof, wherein R^0 is C_{1-3} alkyl.

In another aspect, there is provided a process for preparing a compound of the formula:



or a salt thereof, wherein R^0 is C_{1-3} alkyl, comprising contacting a compound of formula:



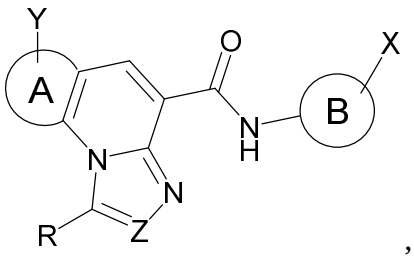
with molecular hydrogen under conditions sufficient to provide the compound.

Description

The present disclosure provides certain compounds that are agonists of AHR.

Accordingly, the present disclosure provides, for example, various embodiments as presented below. When a later embodiment refers to a previous "embodiment X", such reference also includes references to "embodiment XA", "embodiment XB", and so on, unless such later embodiment cannot be properly construed as a dependent embodiment (e.g. falling outside the scope of the referenced embodiment or having improper antecedent basis). For example, when "Embodiment 54" below refers to "embodiment 53", such reference also includes reference to "embodiment 53A", "embodiment 53B", "embodiment 53C", "embodiment 53D", and "embodiment 53E" among others.

Embodiment 1A. A compound of formula:



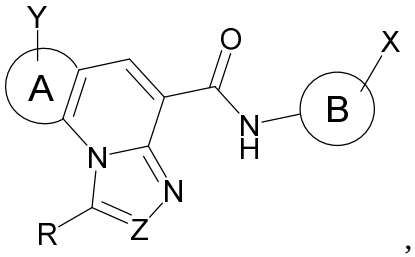
,

wherein:

ring A is a 5-membered or 6-membered carbocycle;

What is Claimed is:

1. A compound of formula:



,

wherein:

ring A is a 5-membered or 6-membered carbocycle;

ring B is a phenyl, or a 5-membered or 6-membered heteroaryl having 1 or 3 heteroatoms, wherein each heteroatom of the heteroaryl is independently selected from N, S, and O;

R is H or C_{1-3} alkyl;

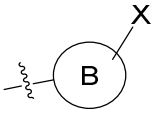
X is H, halo, C_{1-3} alkyl optionally substituted with one or more halo, or a C_{1-3} alkoxyl;

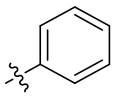
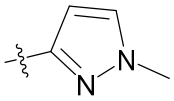
Y is H, C_{1-4} alkyl, or C_{3-4} cycloalkyl, wherein the C_{1-4} alkyl is a primary or secondary alkyl; and

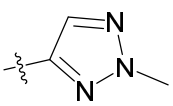
Z is CH or N,

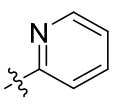
a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

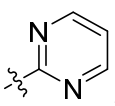
2. The compound of claim 1, wherein R is H, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

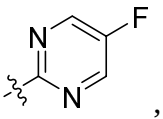
3. The compound of claim 1, wherein 

is selected from , 

, 

, 

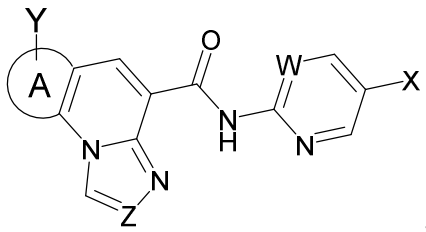
, 

, and 

,

a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

4. The compound of claim 1, having formula:



,

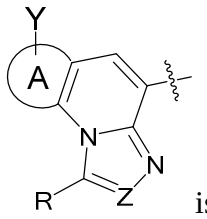
wherein:

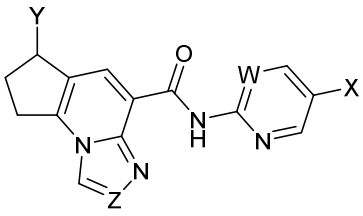
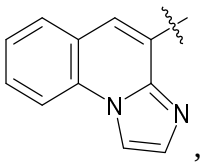
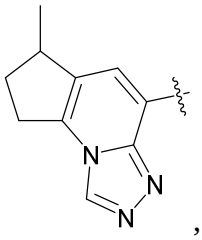
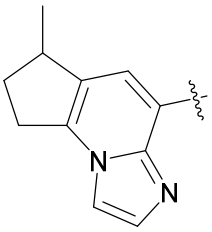
X is H or halo;

Y is H or C_{1-3} alkyl; and

W is CH or N,

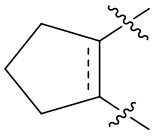
a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

5. The compound of any of claims 1-4, wherein  is selected from the group consisting of:

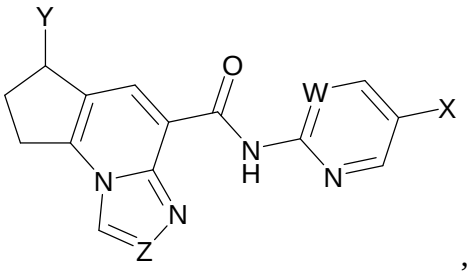
, , , and ,

a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

6. The compound of any of claims 1-4, wherein ring A is phenyl, or a pharmaceutically acceptable salt of each thereof.

7. The compound of any of claims 1-4, wherein ring A is , a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

8. The compound of claim 1, having the formula:



,

wherein:

X is H or halo;

Y is H or C_{1-3} alkyl; and

W is CH or N,

a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

9. The compound of any preceding claim, wherein Z is N, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

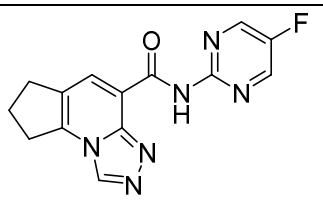
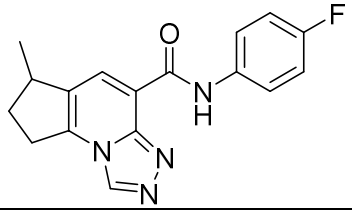
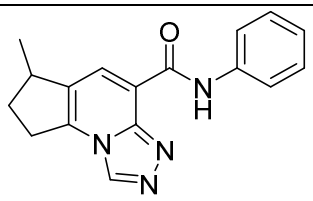
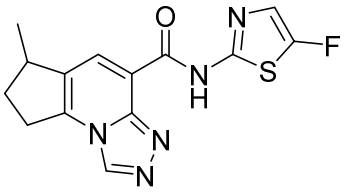
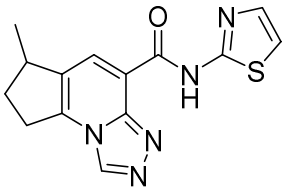
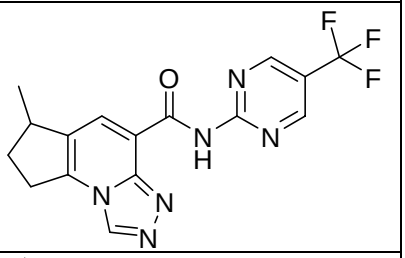
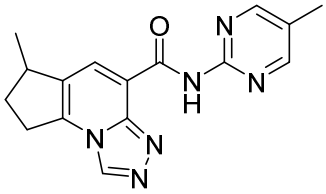
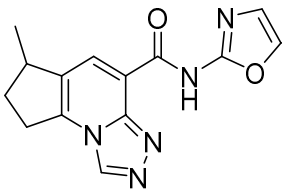
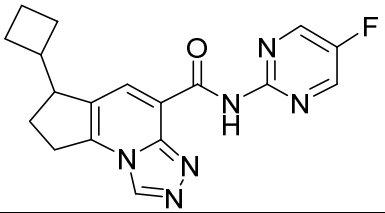
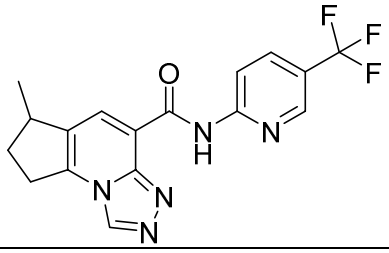
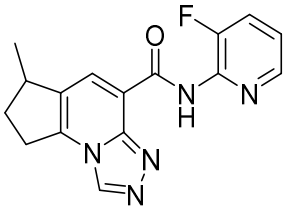
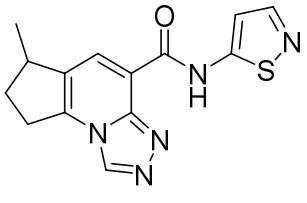
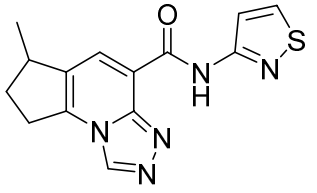
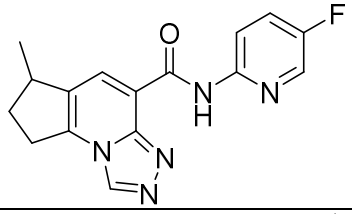
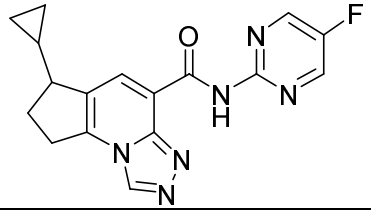
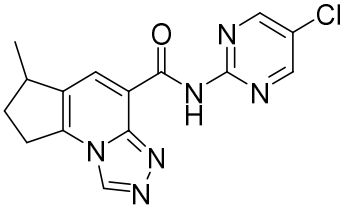
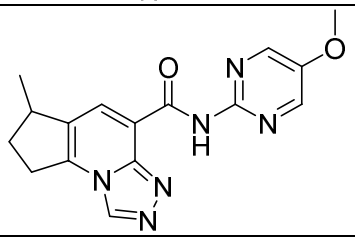
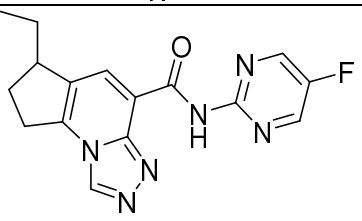
10. The compound of any of claims 1-8, wherein Z is CH, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

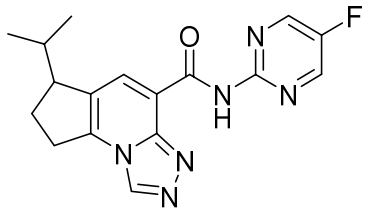
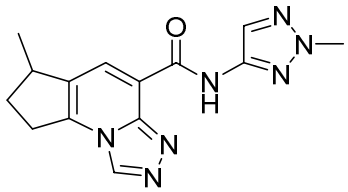
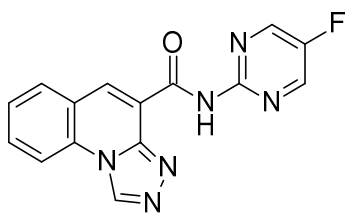
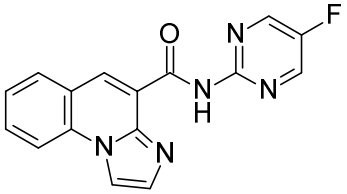
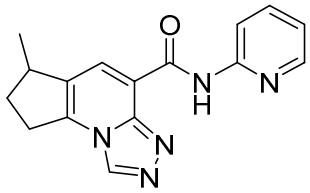
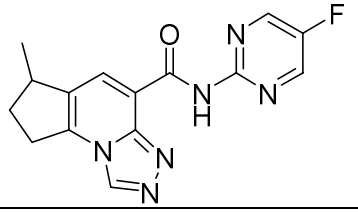
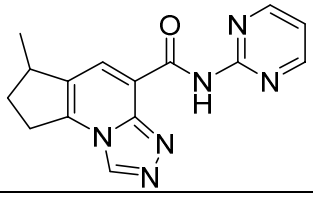
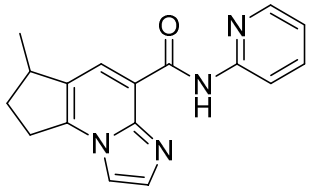
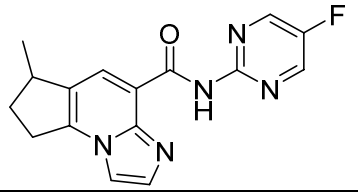
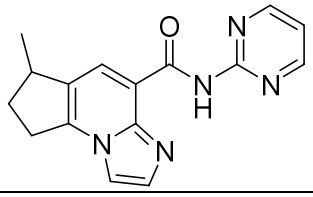
11. The compound of claim 4 or 8, wherein W is N, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

12. The compound of any of claims 1, 2, and 4-11, wherein X is F, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

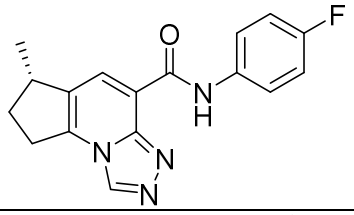
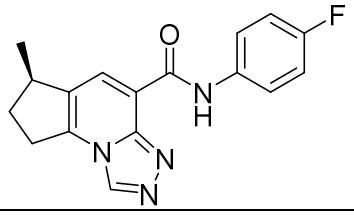
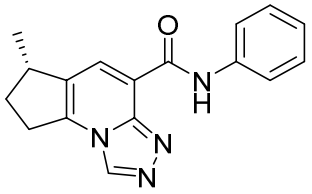
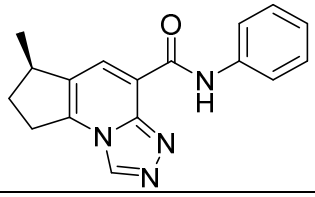
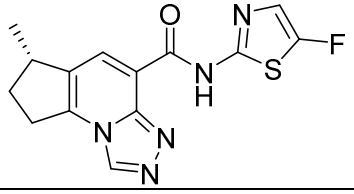
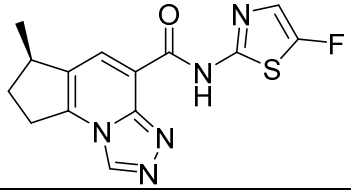
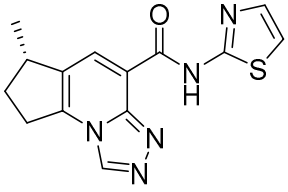
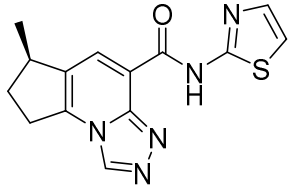
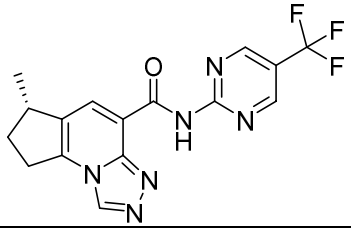
13. The compound of any of claims 1-4 and 6-12, wherein Y is methyl, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

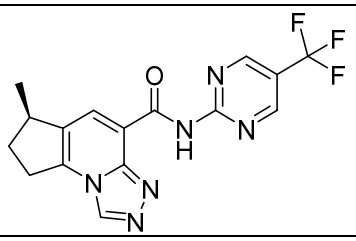
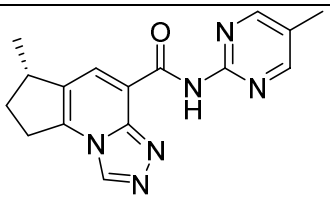
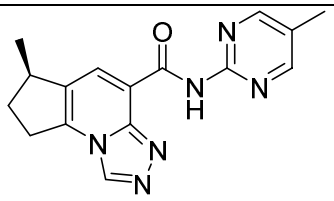
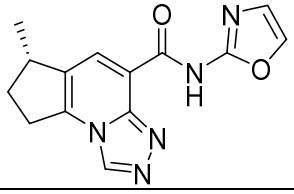
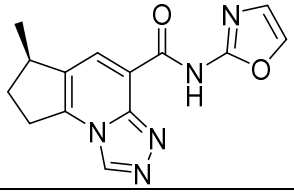
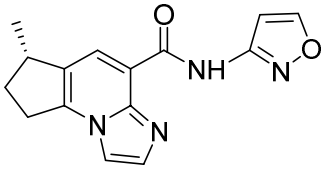
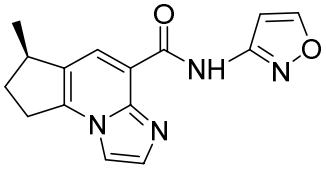
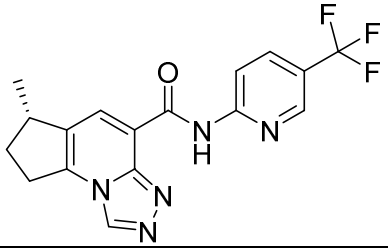
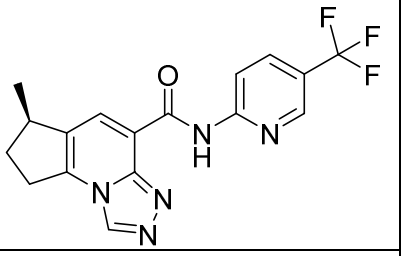
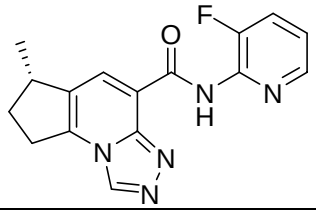
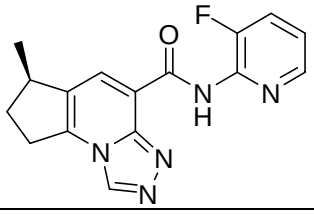
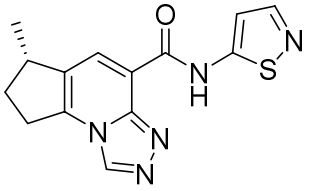
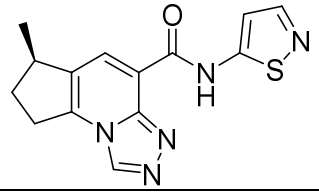
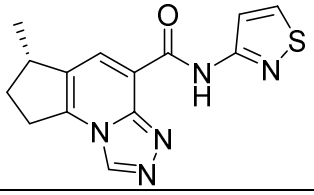
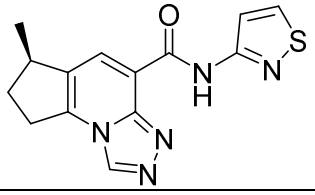
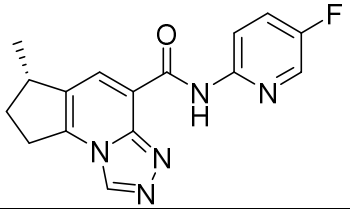
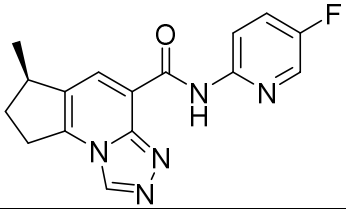
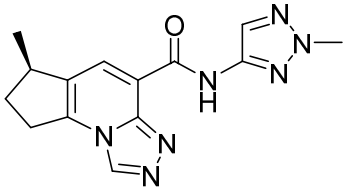
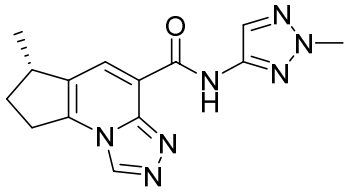
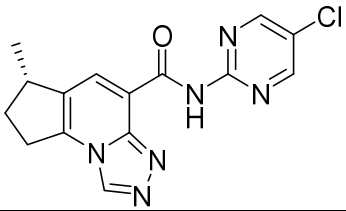
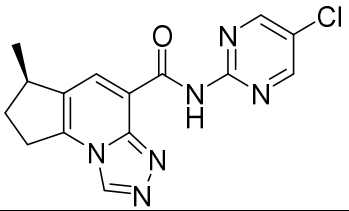
14. The compound of claim 1, selected from the table below, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof:

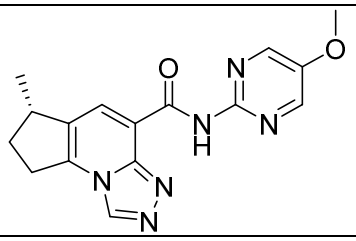
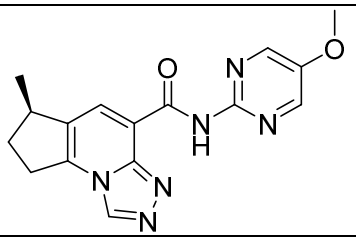
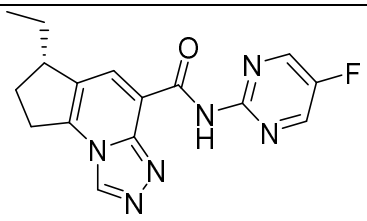
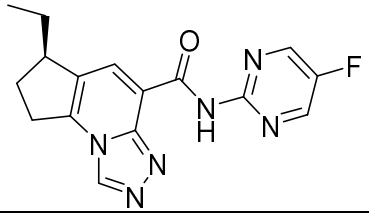
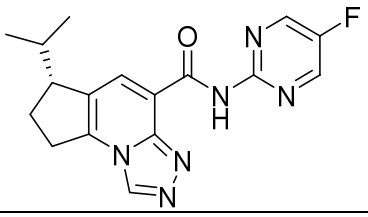
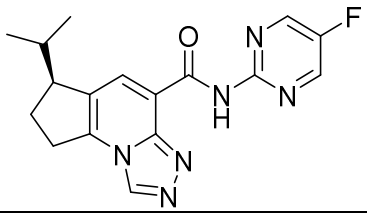
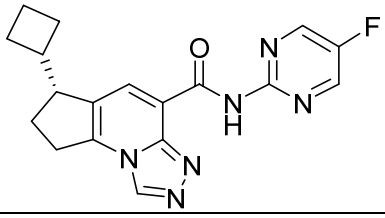
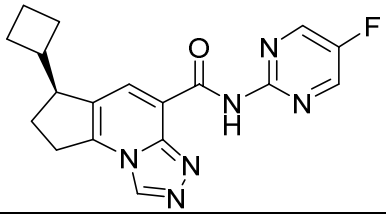
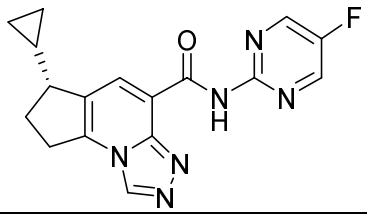
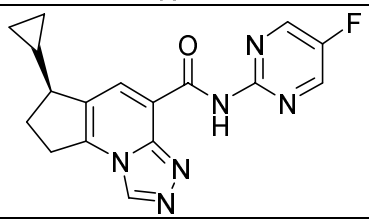
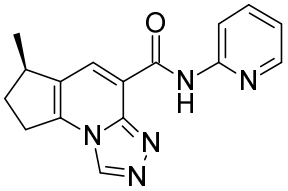
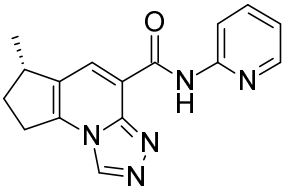
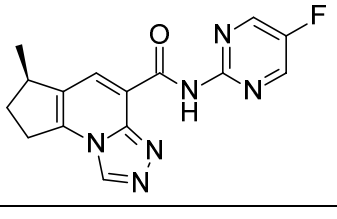
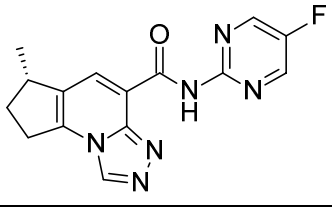
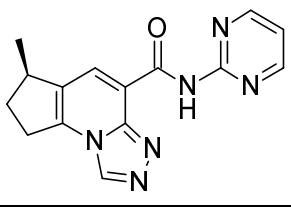
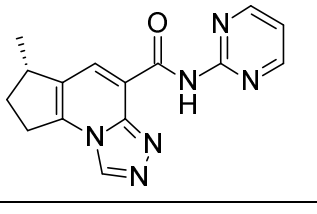
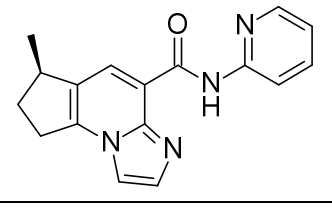
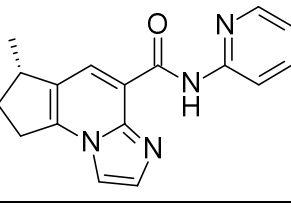
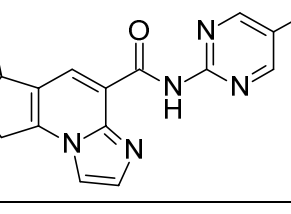
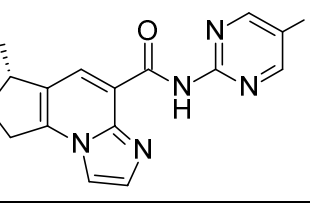
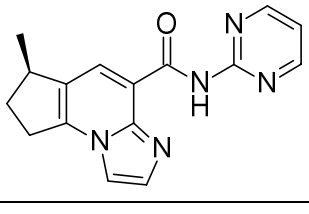
		
		
		
		
		
		

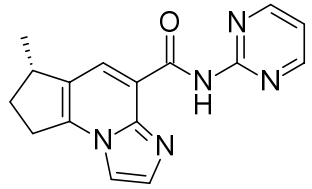
		
		
		
		

15. The compound of claim 1, selected from the following table, or a pharmaceutically acceptable salt thereof:

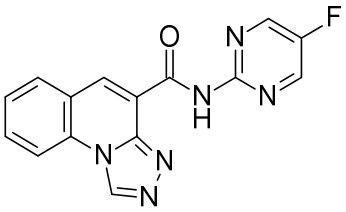
		
		
		

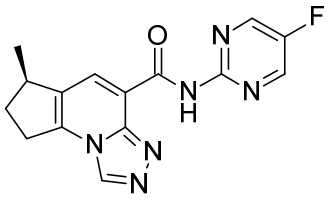
 .		

16. The compound of claim 1, having the formula of:

 ,

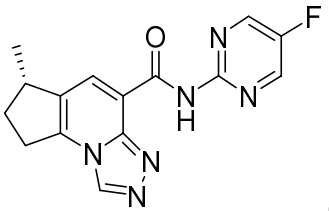
or a pharmaceutically acceptable salt thereof.

17. The compound of claim 1, having the formula of:

 ,

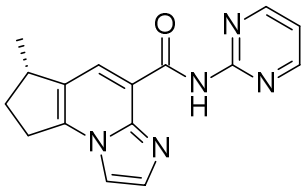
a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

18. The compound of claim 1, having the formula of:

 ,

or a pharmaceutically acceptable salt of each thereof.

19. The compound of claim 1, having the formula of:



,

a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

20. A compound selected from Table 2, 2A, and 3, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof.

21. A pharmaceutical composition, comprising a compound of any of claims 1 to 20, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

22. Use of a compound according to any one of claims 1 to 20, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof, or the pharmaceutical composition according to claim 21 in the manufacture of a medicament for treating an immune-mediated disease.

23. Use of a compound according to any one of claims 1 to 20, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof, or the pharmaceutical composition according to claim 21 in the manufacture of a medicament for treating a disease or disorder selected from psoriasis, atopic dermatitis, ulcerative colitis, Crohn’s disease, graft-versus-host disease, rheumatoid arthritis, and multiple sclerosis.

24. A compound according to any one of claims 1 to 20, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt of each thereof, for use in therapy.

25. Use of a compound according to any one of claims 1 to 20, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating psoriasis.

26. Use of a compound according to any one of claims 1 to 20, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating atopic dermatitis.

27. Use of a compound according to any one of claims 1 to 20, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating ulcerative colitis.

28. Use of a compound according to any one of claims 1 to 20, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Crohn’s disease.

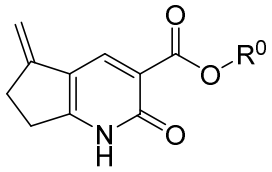
29. Use of a compound according to any one of claims 1 to 20, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating graft-versus-host disease.

30. Use of a compound according to any one of claims 1 to 20, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating rheumatoid arthritis.

31. Use of a compound according to any one of claims 1 to 20, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating multiple sclerosis.

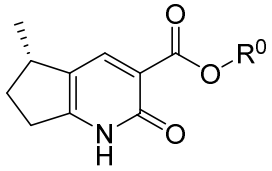
32. Use of a compound according to any one of claims 1 to 20, a stereoisomer or mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating systemic lupus erythematosus (SLE).

33. A compound of the formula:



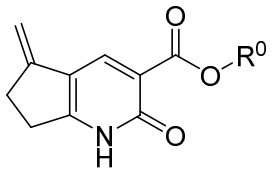
or a salt thereof, wherein R^0 is C_{1-3} alkyl.

34. A compound of the formula:



or a salt thereof, wherein R^0 is C_{1-3} alkyl.

35. A process for preparing a compound of claim 34, comprising contacting a compound of formula:



with molecular hydrogen under conditions sufficient to provide the compound of claim 34.