

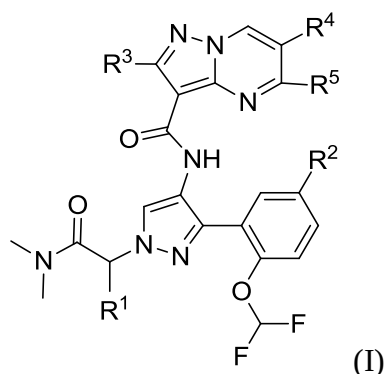
a need for potent compounds that demonstrate selectivity for one Janus kinase over other Janus kinases (e.g., selectivity for JAK1 over other Janus kinases). Kinases demonstrating selectivity for JAK1 could provide a therapeutic benefit, with fewer side effects, in conditions responsive to the inhibition of JAK1. Additionally there is currently a need for potent JAK1 inhibitors that possess other properties (e.g., melting point, pK, solubility, etc.) necessary for formulation and administration by inhalation. Such compounds would be particularly useful for treating conditions such as, for example, asthma.

There exists a need in the art for additional or alternative treatments of conditions mediated by JAK kinases, such as those described above.

SUMMARY

Provided herein are pyrazolopyrimidines that inhibit JAK kinase, such as selected from a compound of Formula (I) a stereoisomer or salt thereof, such as a pharmaceutically acceptable salt thereof. The JAK kinase may be JAK1.

One aspect of the disclosure provides a compound of Formula (I):



or a stereoisomer or salt (e.g., a pharmaceutically acceptable salt) thereof, wherein:

R¹ is hydrogen or CH₃;

R² is halogen, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, or -OR^a, wherein R² is optionally substituted by one or more groups independently selected from the group consisting of halogen, C₁-C₃alkyl, cyano, hydroxy and oxo;

R^a is C₁-C₆alkyl, -phenyl-COR^bR^c, -phenyl-(3-6-membered heterocyclyl), or 3-11-membered heterocyclyl, wherein R^a is optionally substituted by one or more groups independently selected from the group consisting of halogen, C₁-C₃alkyl, cyano, hydroxy and oxo;

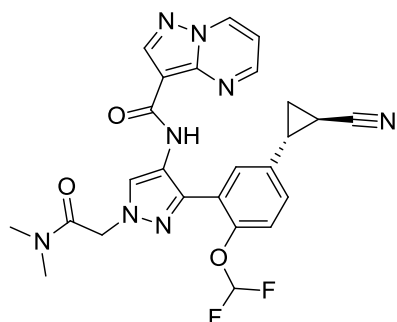
R^b and R^c are each independently hydrogen or CH_3 ;

R^3 is hydrogen or NH_2 ;

R^4 is hydrogen or CH_3 ; and

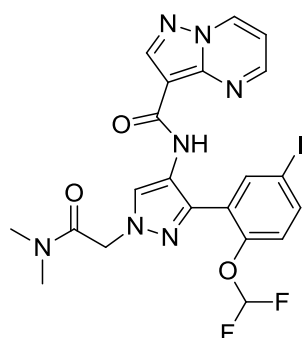
R^5 is hydrogen or NH_2 .

5 Another aspect of the disclosure provides a compound which is:



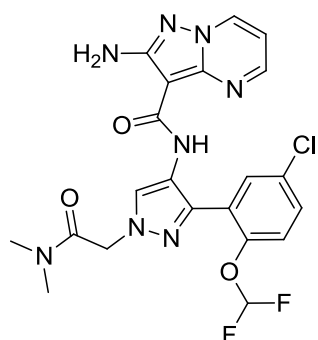
or a pharmaceutically acceptable salt thereof.

Another aspect of the disclosure provides a compound which is:



10 or a pharmaceutically acceptable salt thereof.

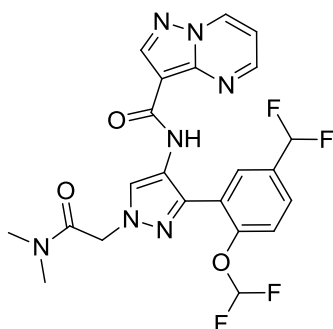
Another aspect of the disclosure provides a compound which is:



or a pharmaceutically acceptable salt thereof.

CN(C)C(=O)CN1C=NC2=C1C(=C(C=C2)C(=C3C=CC(=C3)OC(F)F)C(F)C)C(=O)N4C=CC5=C4N=CN=C5

Another aspect of the disclosure provides a compound which is:



or a pharmaceutically acceptable salt thereof.

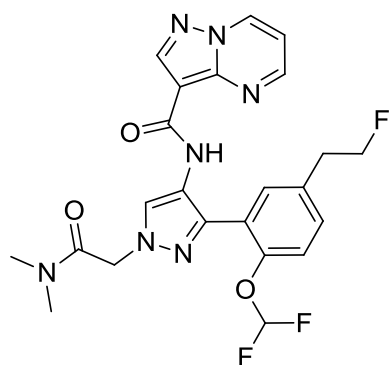
CN(C)C(=O)CC1=NN=C(C2=CC(OC(F)F)=CC(C2)C(=O)Nc3cc4nnccc4n3)C1

10

CN(C)C(=O)CC1=NC=C(C2=CC(OC(F)F)=CC(=C2)C(=N1)NC(=O)c3cnc4cccnc34)C5=CC(OC(=O)N6C=CC=C(C=C6)C(=O)N(C)C)=CC=C5

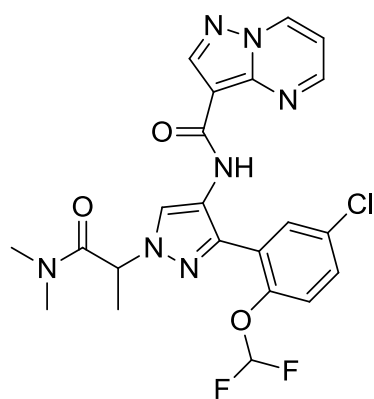
5a

Another aspect of the disclosure provides a compound which is:



or a pharmaceutically acceptable salt thereof.

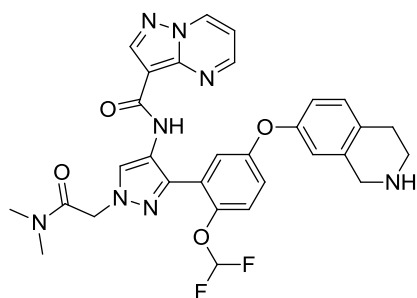
Another aspect of the disclosure provides a compound which is:



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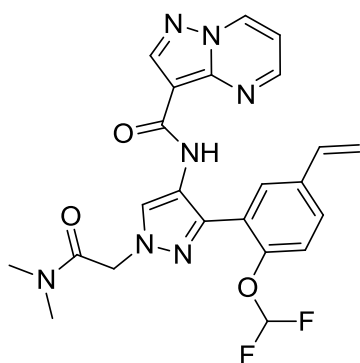
or a pharmaceutically acceptable salt or stereoisomer thereof.

Another aspect of the disclosure provides a compound which is:



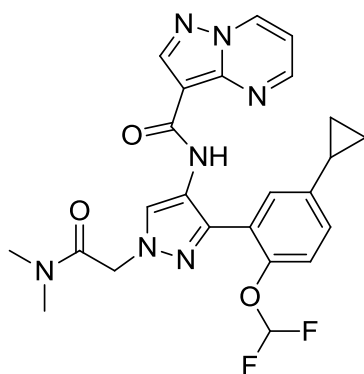
or a pharmaceutically acceptable salt or stereoisomer thereof.

Another aspect of the disclosure provides a compound which is:



or a pharmaceutically acceptable salt thereof.

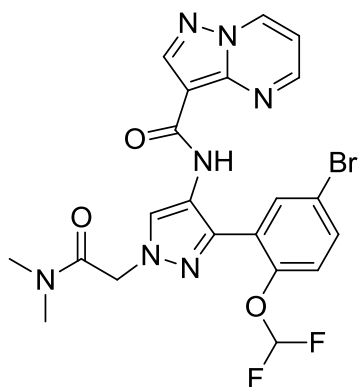
Another aspect of the disclosure provides a compound which is:



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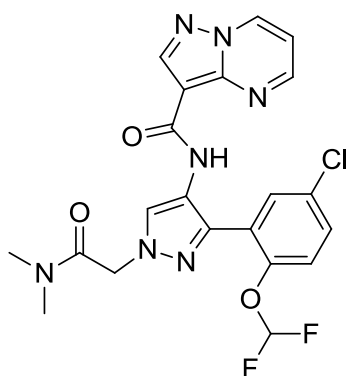
or a pharmaceutically acceptable salt thereof.

Another aspect of the disclosure provides a compound which is:



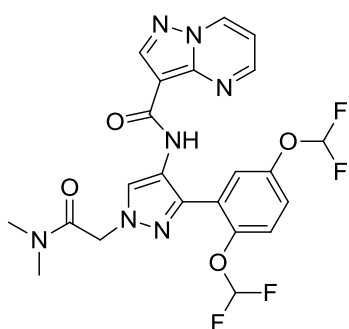
or a pharmaceutically acceptable salt thereof.

Another aspect of the disclosure provides a compound which is:



or a pharmaceutically acceptable salt thereof.

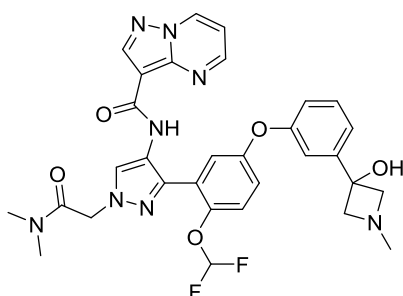
Another aspect of the disclosure provides a compound which is:



5

or a pharmaceutically acceptable salt thereof.

Another aspect of the disclosure provides a compound which is:



or a pharmaceutically acceptable salt thereof.

10 Also provided is a pharmaceutical composition comprising a JAK inhibitor as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient. Another aspect of the disclosure provides a pharmaceutical composition comprising a compound as defined herein or a pharmaceutically acceptable salt or stereoisomer thereof, and a
15 pharmaceutically acceptable carrier, diluent or excipient.

Also provided is the use of a JAK inhibitor as described herein, or a pharmaceutically acceptable salt thereof in therapy, such as in the treatment of an inflammatory disease (e.g., asthma). Also provided is the use of a JAK inhibitor as described herein or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of an inflammatory disease. Also provided is a method of preventing, treating or lessening the severity of a disease or condition responsive to the inhibition of a Janus kinase activity in a patient, comprising administering to the patient a therapeutically effective amount of a JAK inhibitor as described herein or a pharmaceutically acceptable salt thereof.

Another aspect of the disclosure provides a compound as defined herein or a pharmaceutically acceptable salt or stereoisomer thereof for use in therapy

Another aspect of the disclosure provides use of a compound as defined herein or a pharmaceutically acceptable salt or stereoisomer thereof, in the preparation of a medicament for the treatment of an inflammatory disease.

Another aspect of the disclosure provides a compound as defined herein or a pharmaceutically acceptable salt or stereoisomer thereof, for use in the treatment of an inflammatory disease.

Certain compounds or salts thereof (e.g., pharmaceutically acceptable salts thereof) described herein possess beneficial potency as inhibitors of one or more

Janus kinases (e.g., JAK1). Certain compounds or salts thereof (e.g., pharmaceutically acceptable salts thereof) are also a) selective for one Janus kinase over other kinases, b) selective for JAK1 over other Janus kinases, and/or c) possess other properties (e.g., melting point, pK, solubility, etc.) necessary for formulation and administration by inhalation. Certain compounds or salts thereof (e.g., pharmaceutically acceptable salts thereof) described herein may be particularly useful for treating conditions such as asthma.

DETAILED DESCRIPTION OF THE INVENTION

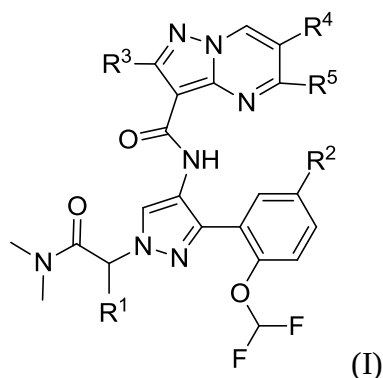
DEFINITIONS

“Halogen” or “halo” refers to F, Cl, Br or I. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl, wherein one or
5 more halogens replace a hydrogen(s) of an alkyl group.

The term "alkyl" refers to a saturated linear or branched-chain monovalent hydrocarbon radical, wherein the alkyl radical may be optionally substituted. In one

WHAT IS CLAIMED IS:

1. A compound of Formula (I)



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

- 5 R¹ is hydrogen or CH₃;

R² is halogen, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, or -OR^a, wherein R² is optionally substituted by one or more groups independently selected from the group consisting of halogen, C₁-C₃alkyl, cyano, hydroxy and oxo;

- 10 R^a is C₁-C₆alkyl, -phenyl-COR^bR^c, -phenyl-(3-6-membered heterocyclyl), or 3-11-membered heterocyclyl, wherein R^a is optionally substituted by one or more groups independently selected from the group consisting of halogen, C₁-C₃alkyl, cyano, hydroxy and oxo;

R^b and R^c are each independently hydrogen or CH₃;

R³ is hydrogen or NH₂;

- 15 R⁴ is hydrogen or CH₃; and

R⁵ is hydrogen or NH₂.

2. The compound of claim 1 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R¹ is hydrogen.

- 20 3. The compound of claim 1 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R¹ is CH₃.

4. The compound of any one of claims 1-3 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R³ is hydrogen.

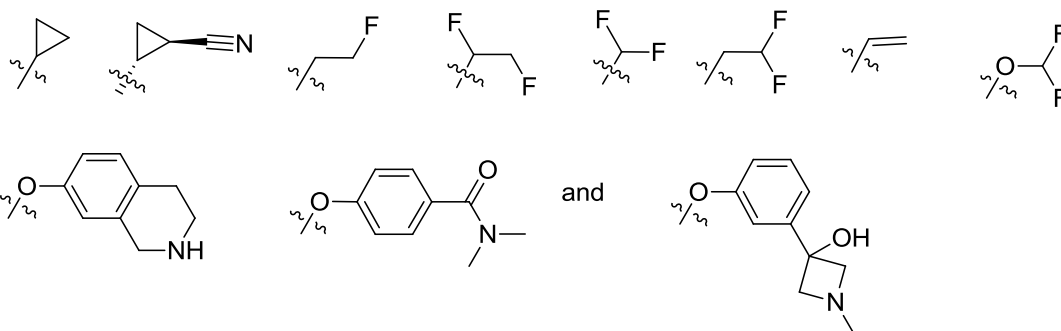
5. The compound of any one of claims 1-4 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R⁴ and R⁵ are each hydrogen.

6. The compound of claim 1 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R¹, R³, R⁴ and R⁵ are each hydrogen.

5 7. The compound of any one of claims 1-6 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R² is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, or -OR^a, wherein R² is optionally substituted by one or more groups independently selected from the group consisting of halogen, C₁-C₃alkyl, cyano, hydroxy and oxo.

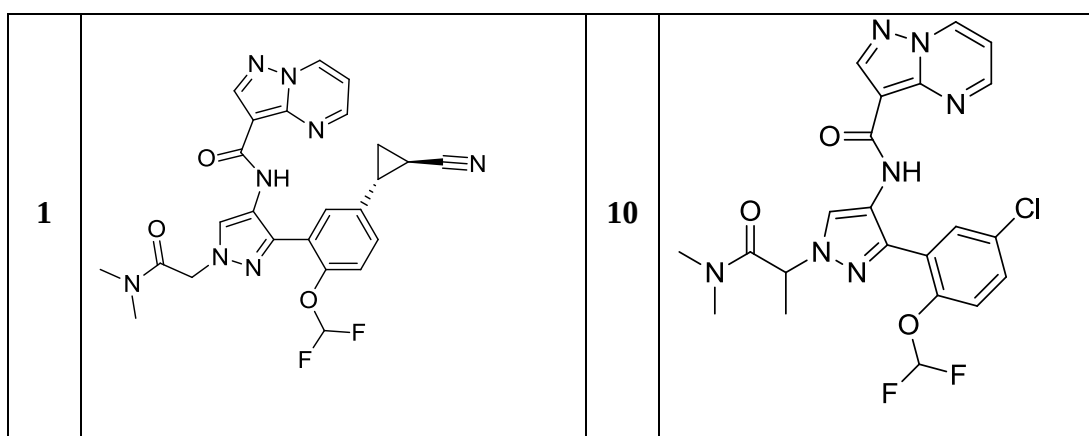
10 8. The compound of any one of claims 1-6 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R² is selected from the group consisting of halogen, C₁-C₆haloalkyl and C₁-C₆haloalkoxy.

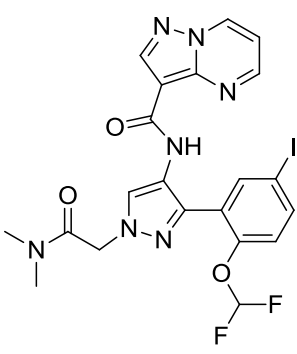
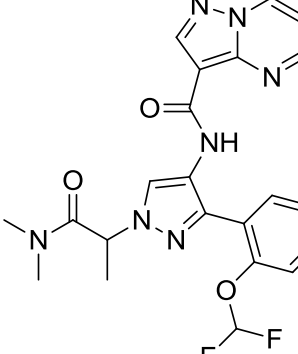
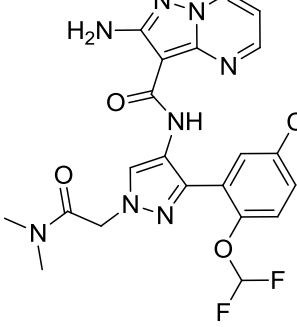
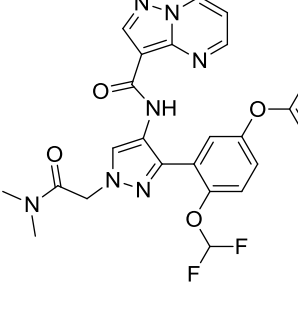
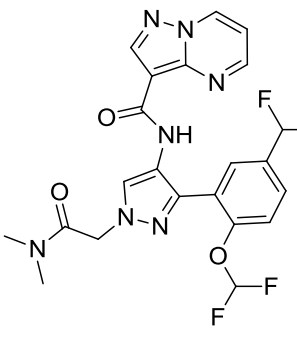
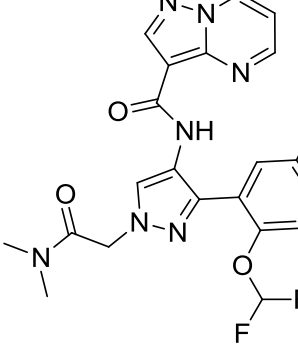
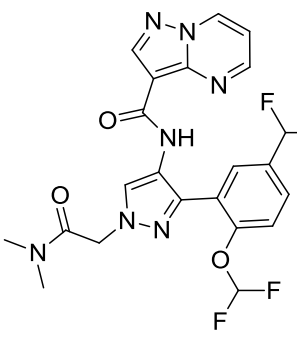
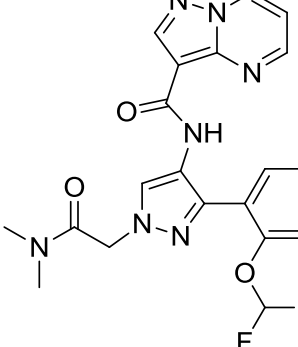
9. The compound of any of claims 1-8 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R² is selected from the group consisting of

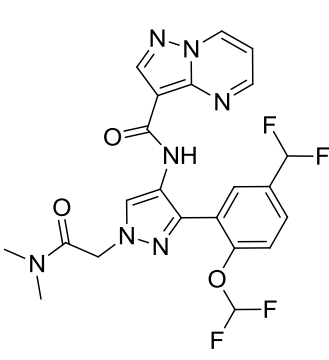
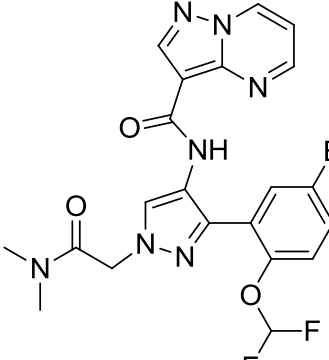
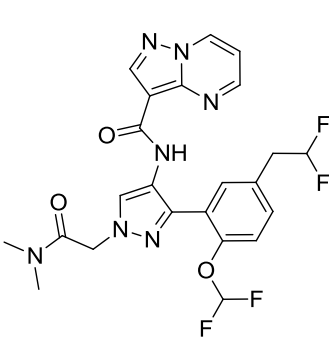
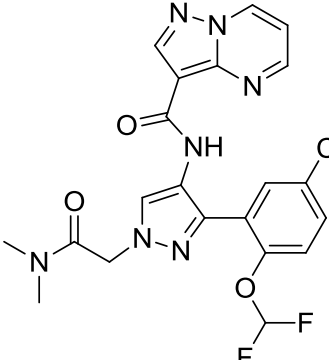
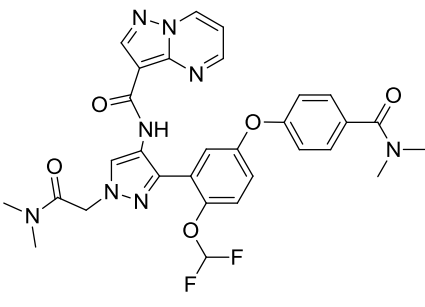
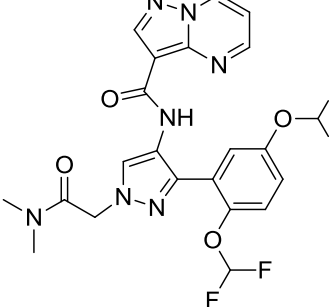
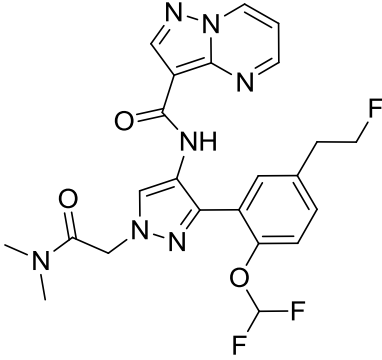
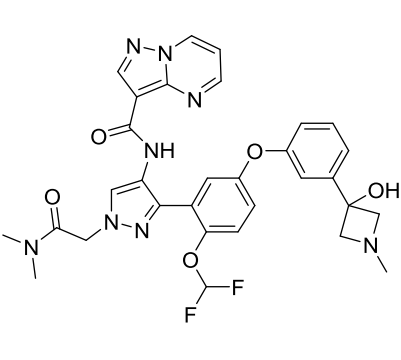


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10. A compound selected from the group consisting of 1-18 below:

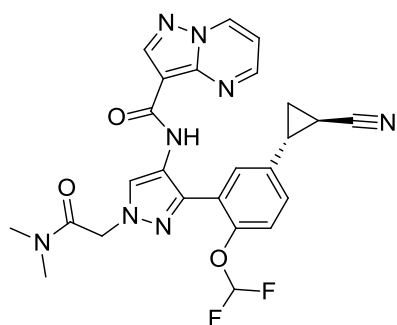


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9		18	

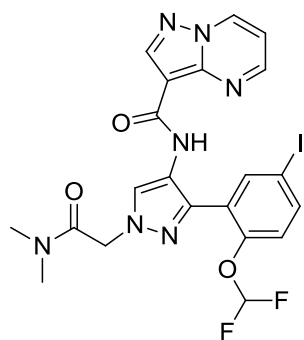
or a pharmaceutically acceptable salt or stereoisomer thereof.

11. A compound which is:



or a pharmaceutically acceptable salt thereof.

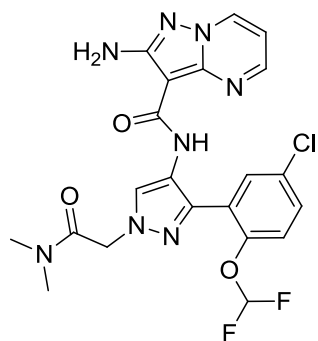
12. A compound which is:



5

or a pharmaceutically acceptable salt thereof.

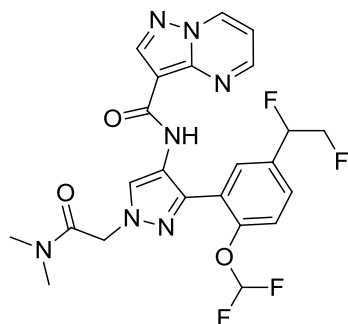
13. A compound which is:



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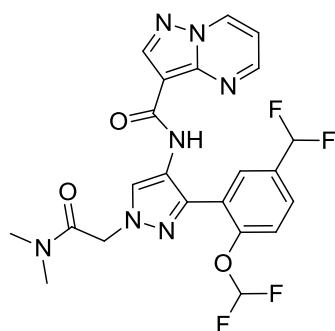
or a pharmaceutically acceptable salt thereof.

14. A compound which is:



or a pharmaceutically acceptable salt or stereoisomer thereof.

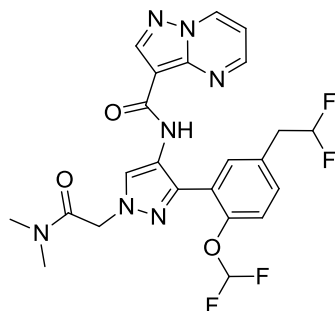
15. A compound which is:



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or a pharmaceutically acceptable salt thereof.

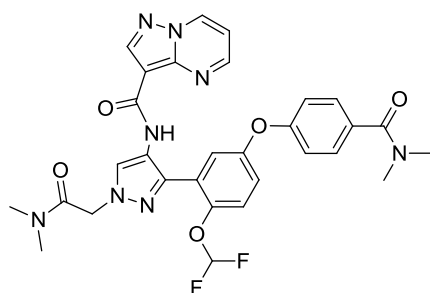
16. A compound which is:



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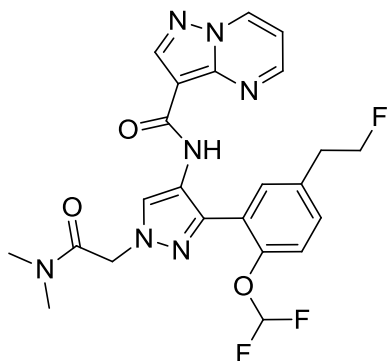
or a pharmaceutically acceptable salt or stereoisomer thereof.

17. A compound which is:



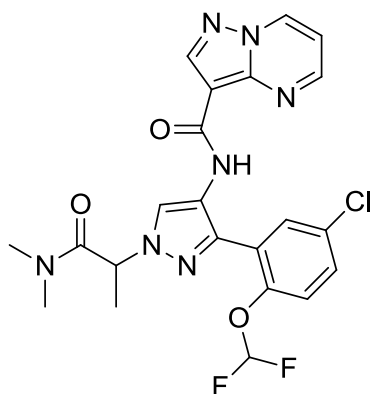
or a pharmaceutically acceptable salt thereof.

18. A compound which is:



5 or a pharmaceutically acceptable salt thereof.

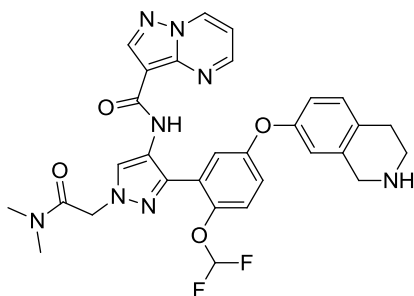
19. A compound which is:



or a pharmaceutically acceptable salt or stereoisomer thereof.

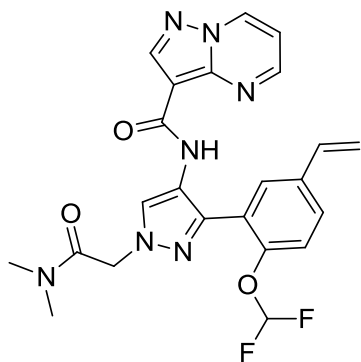
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20. A compound which is:



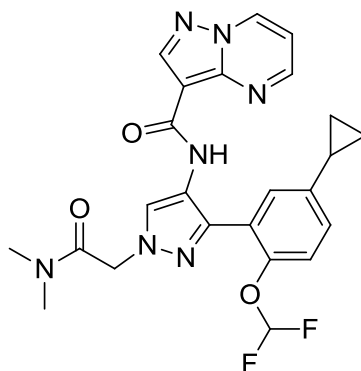
or a pharmaceutically acceptable salt or stereoisomer thereof.

15 21. A compound which is:



or a pharmaceutically acceptable salt thereof.

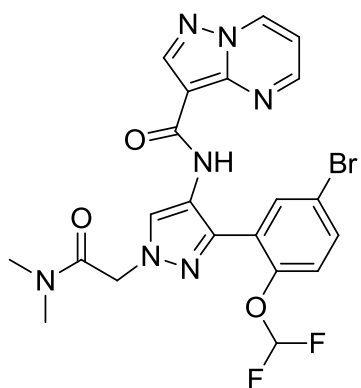
22. A compound which is:



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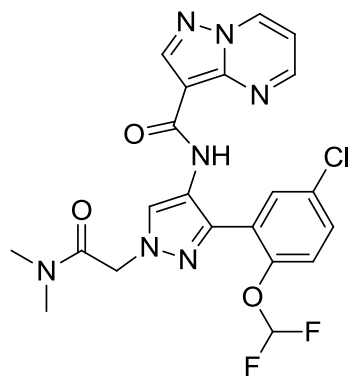
or a pharmaceutically acceptable salt thereof.

23. A compound which is:



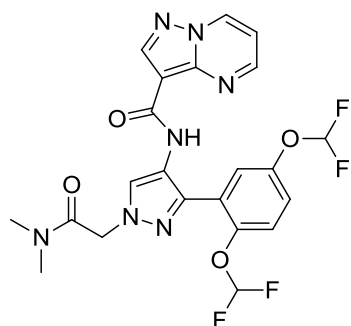
10 or a pharmaceutically acceptable salt thereof.

24. A compound which is:



or a pharmaceutically acceptable salt thereof.

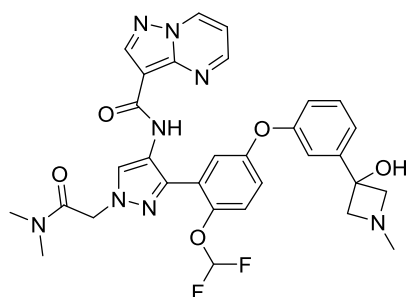
25. A compound which is:



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or a pharmaceutically acceptable salt thereof.

26. A compound which is:



10 or a pharmaceutically acceptable salt thereof.

27. A pharmaceutical composition comprising a compound of any of claims 1-26 or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

15 28. A compound of any of claims 1-26 or a pharmaceutically acceptable salt or stereoisomer thereof for use in therapy.

29. Use of a compound of any of claims 1-26 or a pharmaceutically acceptable salt or stereoisomer thereof, in the preparation of a medicament for the treatment of an inflammatory disease.
30. A compound of any of claims 1-26 or a pharmaceutically acceptable salt or stereoisomer thereof, for use in the treatment of an inflammatory disease.
- 5 31. The use of claim 29 or the compound or a pharmaceutically acceptable salt or stereoisomer thereof, for use of claim 30, wherein the inflammatory disease is asthma.