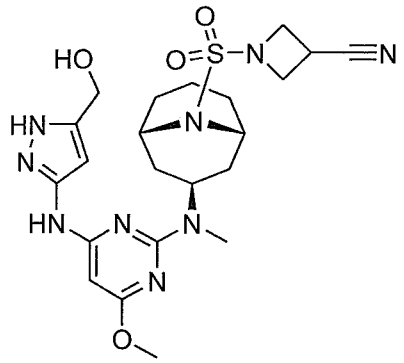
n is 1 or 2;

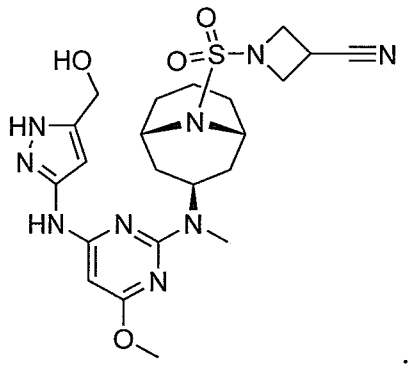
or a pharmaceutically-acceptable salt or stereoisomer thereof.

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



or a pharmaceutically-acceptable salt thereof.

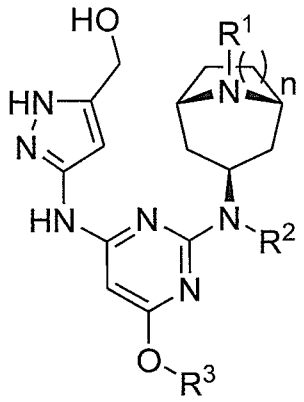
In another aspect, there is provided a compound of formula:



In another aspect, there is provided a crystalline form of 1-(((1*R*,3*s*,5*S*)-3-((4-((5-(hydroxymethyl)-1*H*-pyrazol-3-yl)amino)-6-methoxypyrimidin-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonan-9-yl)sulfonyl)azetidine-3-carbonitrile, wherein the crystalline form is characterized by a powder X-ray diffraction comprising diffraction peaks at 2θ values of 8.89±0.20, 12.99±0.20, 13.44±0.20, and 20.16±0.20.

In another aspect, there is provided a pharmaceutical composition comprising the compound or the crystalline form as described herein and a pharmaceutically-acceptable carrier.

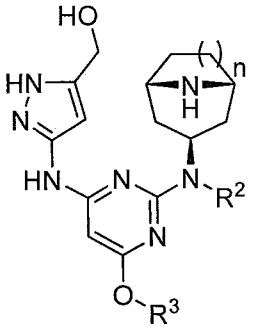
In another aspect, there is provided a process for preparing a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, and *n* are as defined herein, the process comprising:

(a) reacting a compound of formula (III):



(III)

wherein R^2, R^3, and *n* are as defined herein, with

(i) Cl-$S(O)_2R^4$, wherein R^4 is as defined herein;

(ii) a compound of formula L-R^A wherein L is a leaving group and R^A is C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with –CN, , or pyridinyl, wherein pyridinyl is optionally substituted with –CN;

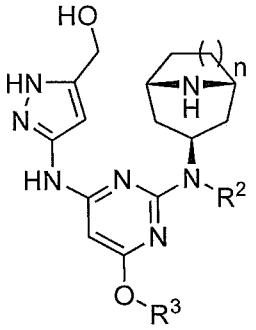
(iii) Cl-$C(O)R^5$, wherein R^5 is as defined herein; or

(iv) HO-$C(O)R^5$, wherein R^5 is as defined herein; and

(b) optionally forming a pharmaceutically acceptable salt

to provide a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound of formula (III):



(III)

wherein R^2, R^3, and n are as defined herein.

In another aspect, there is provided a method of preparing the crystalline form of 1-(((1*R*,3*s*,5*S*)-3-((4-((5-(hydroxymethyl)-1*H*-pyrazol-3-yl)amino)-6-methoxypyrimidin-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonan-9-yl)sulfonyl)azetidine-3-carbonitrile as defined herein, the method comprising:

(a) dissolving 1-(((1*R*,3*s*,5*S*)-3-((4-((5-(hydroxymethyl)-1*H*-pyrazol-3-yl)amino)-6-methoxypyrimidin-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonan-9-yl)sulfonyl)azetidine-3-carbonitrile in a diluent selected from *N*-methylpyrrolidone and dimethylformamide to form a reaction mixture;

(b) adding acetone and water to the reaction mixture; and

(c) isolating the crystalline form from the reaction mixture.

In another aspect, there is provided use of the compound or the crystalline form as described herein for the manufacture of a medicament for the treatment of a gastrointestinal inflammatory disease in a mammal.

In another aspect, there is provided use of the compound or the crystalline form as described herein for the manufacture of a medicament for the treatment of an inflammatory disease of the skin in a mammal.

As used hereinafter, the phrase "compound of formula (I)" means a compound of formula (I) or a pharmaceutically acceptable salt thereof; i.e., this phrase means a compound of formula (I) in free base form or in a pharmaceutically acceptable salt form unless otherwise indicated.

The invention also provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically-acceptable carrier.

In one embodiment, the invention provides a particular compound of formula (I) in crystalline free base form. Crystalline 1-(((1*R*,3*s*,5*S*)-3-((4-((5-(hydroxymethyl)-1*H*-pyrazol-3-yl)amino)-6-methoxypyrimidin-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonan-9-yl)sulfonyl)azetidine-3-carbonitrile has been found to have a melting temperature in the range of about 235 °C to about 245 °C, typically between about 237 °C and about 242 °C, and to exhibit weight changes of less than about 0.4 % when exposed to a range of relative humidity between about 5 % and about 90 % at room temperature.

The invention also provides a method of treating gastrointestinal inflammatory disease, in particular, ulcerative colitis, in a mammal, the method comprising administering to the mammal a compound or a pharmaceutical composition of the invention.

In yet another method embodiment, the invention provides a method of treating inflammatory diseases or disorders of the skin, in particular atopic dermatitis, in a mammal, the method comprising applying a compound or a pharmaceutical composition of the invention to the skin of the mammal.

In separate and distinct embodiments, the invention also provides synthetic processes and intermediates described herein, which are useful for preparing compounds of the invention.

The invention also provides a compound of the invention as described herein for use in medical therapy, as well as the use of a compound of the invention in the manufacture of a formulation or medicament for treating gastrointestinal inflammatory disease in a mammal. The invention further provides the use of a compound of the invention in the manufacture of a formulation or medicament for treating inflammatory diseases of the skin.

n is 1 or 2;
or a pharmaceutically-acceptable salt or stereoisomer thereof.

2. The compound of Claim 1, or a pharmaceutically-acceptable salt thereof, wherein R^3 is methyl.

3. The compound of Claim 1, or a pharmaceutically-acceptable salt thereof, wherein R^2 is methyl.

4. The compound of Claim 1, or a pharmaceutically-acceptable salt thereof, wherein *n* is 2.

5. The compound of Claim 1, or a pharmaceutically-acceptable salt thereof, wherein R^1 is selected from:

(a) $S(O)_2R^4$, wherein R^4 is selected from:

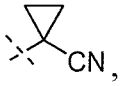
$C_{1\text{-}2}$alkyl, wherein $C_{1\text{-}2}$alkyl is optionally substituted with –CN, -OCH_3, or cyclopropyl,

azetidinyl or pyrrolidinyl, wherein azetidinyl is optionally substituted with -CN,

cyclopropyl,

pyridinyl, wherein pyridinyl is optionally substituted with fluoro, and

phenyl;

(b) $C_{1\text{-}4}$alkyl, wherein $C_{1\text{-}4}$alkyl is optionally substituted with –CN, , or

pyridinyl, wherein pyridinyl is optionally substituted with –CN; and

(c) $C(O)R^5$, wherein R^5 is selected from:

$C_{1\text{-}2}$alkyl, wherein $C_{1\text{-}2}$alkyl is optionally substituted with cyclopropyl, or with one or two fluoro,

-$OC_{1\text{-}4}$alkyl,

$C_{3\text{-}6}$cycloalkyl, and

morpholinyl.

6. The compound of Claim 1, wherein the compound is selected from:

1-(((1*R*,3*s*,5*S*)-3-((4-((5-(hydroxymethyl)-1*H*-pyrazol-3-yl)amino)-6-methoxypyrimidin-2-yl)(methyl)amino)-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)azetidine-3-carbonitrile,

isobutyl (1*R*,3*s*,5*S*)-3-((4-((5-(hydroxymethyl)-1*H*-pyrazol-3-yl)amino)-6-methoxypyrimidin-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate,

methyl (1*R*,3*s*,5*S*)-3-((4-((5-(hydroxymethyl)-1*H*-pyrazol-3-yl)amino)-6-methoxypyrimidin-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate,

((1*R*,3*s*,5*S*)-3-((4-((5-(hydroxymethyl)-1*H*-pyrazol-3-yl)amino)-6-methoxypyrimidin-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonan-9-yl)(morpholino)methanone,

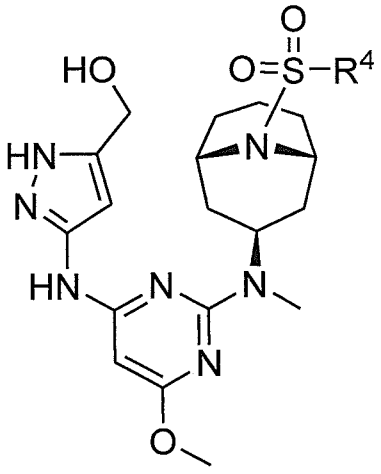
2-cyclopropyl-1-((1*R*,3*s*,5*S*)-3-((4-((5-(hydroxymethyl)-1*H*-pyrazol-3-yl)amino)-6-methoxypyrimidin-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonan-9-yl)ethan-1-one,

cyclopentyl((1*R*,3*s*,5*S*)-3-((4-((5-(hydroxymethyl)-1*H*-pyrazol-3-yl)amino)-6-methoxypyrimidin-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonan-9-yl)methanone, and

cyclobutyl((1*R*,3*s*,5*S*)-3-((4-((5-(hydroxymethyl)-1*H*-pyrazol-3-yl)amino)-6-methoxypyrimidin-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonan-9-yl)methanone,

and pharmaceutically acceptable salts thereof.

7. The compound of Claim 1, wherein the compound is a compound of formula (II):



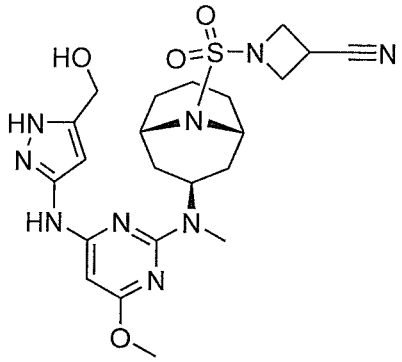
(II)

or a pharmaceutically-acceptable salt thereof.

8. The compound of Claim 7, or a pharmaceutically-acceptable salt thereof, wherein R^4 is methyl, ethyl, azetidinyl, pyrrolidinyl, cyclopropyl, pyridinyl, or phenyl, wherein ethyl is optionally substituted with methoxy, azetidinyl is optionally substituted with –CN, and pyridinyl is optionally substituted with fluoro.

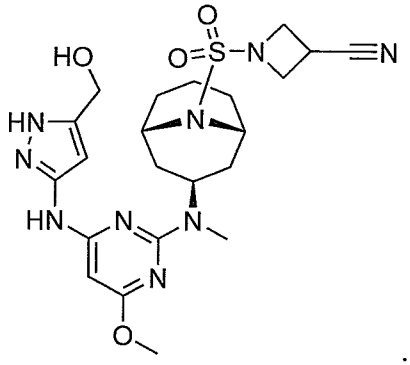
9. The compound of Claim 7, wherein the compound is selected from:

10. A compound of formula:



or a pharmaceutically-acceptable salt thereof.

11. A compound of formula:



12. A crystalline form of 1-(((1*R*,3*s*,5*S*)-3-((4-((5-(hydroxymethyl)-1*H*-pyrazol-3-yl)amino)-6-methoxypyrimidin-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonan-9-yl)sulfonyl)azetidine-3-carbonitrile, wherein the crystalline form is characterized by a powder X-ray diffraction comprising diffraction peaks at 2θ values of 8.89±0.20, 12.99±0.20, 13.44±0.20, and 20.16±0.20.

13. The crystalline form of Claim 12 wherein the powder X-ray diffraction pattern is further characterized by having two or more additional diffraction peaks at 2θ values selected from 10.64±0.20, 10.99±0.20, 15.02±0.20, 15.74±0.20, 16.47±0.20, 20.93±0.20, 22.22±0.20, and 26.25±0.20.

14. The crystalline form of Claim 12, wherein the crystalline form is characterized by a powder X-ray diffraction pattern in which the peak positions are substantially in accordance with the peak positions of the pattern shown in Figure 1.

15. The crystalline form of Claim 12 wherein the crystalline form is characterized by a differential scanning calorimetry trace recorded at a heating rate of

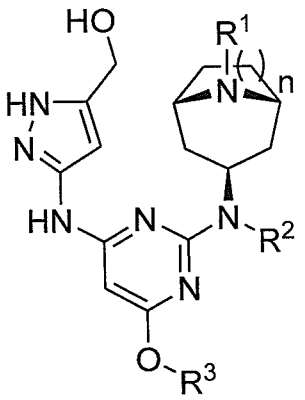
10 °C per minute which shows a maximum in endothermic heat flow at a temperature between about 235 °C and about 245 °C.

16. The crystalline form of Claim 15, wherein the crystalline form is characterized by a differential scanning calorimetry trace substantially in accordance with that shown in Figure 2.

17. A pharmaceutical composition comprising the compound of any one of Claims 1 to 11, or the crystalline form of any one of Claims 12 to 16 and a pharmaceutically-acceptable carrier.

18. The pharmaceutical composition of Claim 17 further comprising one or more other therapeutic agents useful for treating gastrointestinal inflammatory disease.

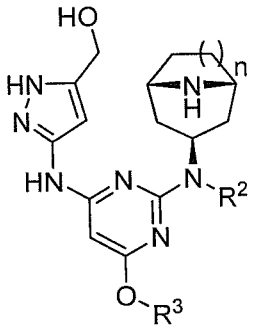
19. A process for preparing a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, and *n* are as defined in Claim 1, the process comprising:

(a) reacting a compound of formula (III):



(III)

wherein R^2, R^3, and *n* are as defined in Claim 1, with

23. Use of the compound of any one of Claims 1 to 11, or the crystalline form of any one of Claims 12 to 16 for the manufacture of a medicament for the treatment of a gastrointestinal inflammatory disease in a mammal.

24. The use of Claim 23 wherein the gastrointestinal inflammatory disease is ulcerative colitis.

25. The use of Claim 23 wherein the gastrointestinal inflammatory disease is Crohn's disease.

26. The use of Claim 23 wherein the gastrointestinal inflammatory disease is celiac disease.

27. The use of Claim 23 wherein the medicament is to be administered in combination with one or more other therapeutic agents useful for treating a gastrointestinal inflammatory disease.

28. Use of the compound of any one of Claims 1 to 11, or the crystalline form of any one of Claims 12 to 16 for the manufacture of a medicament for the treatment of an inflammatory disease of the skin in a mammal.

29. The use of Claim 28, wherein the inflammatory disease of the skin is atopic dermatitis.