

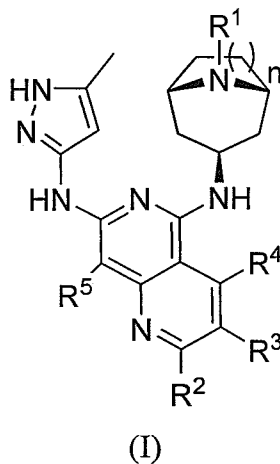
such as cell growth, differentiation and death (Clark et al., *J Med Chem*, **2014**, 57, 5023-5038).

Inhibition of the family of JAK enzymes could inhibit signaling of many key pro-inflammatory cytokines. Thus JAK inhibitors are likely to be useful in the treatment of ulcerative colitis and other inflammatory diseases such as Crohn's disease, allergic rhinitis, asthma, and chronic obstructive pulmonary disease (COPD). However, due to the modulating effect of the JAK/STAT pathway on the immune system, systemic exposure to JAK inhibitors may have an adverse systemic immunosuppressive effect. It would be desirable, therefore, to provide new JAK inhibitors which have their effect at the site of action without significant systemic effects. In particular, for the treatment of gastrointestinal inflammatory diseases, such as ulcerative colitis, it would be desirable to provide new JAK inhibitors which can be administered orally and achieve therapeutically relevant exposure in the gastrointestinal tract with minimal systemic exposure.

### SUMMARY OF THE INVENTION

The disclosure provides novel compounds having activity as JAK kinase inhibitors.

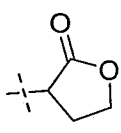
In one aspect, the disclosure provides a compound of formula (I):

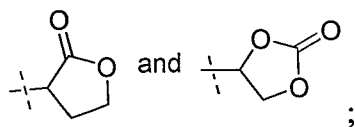


wherein

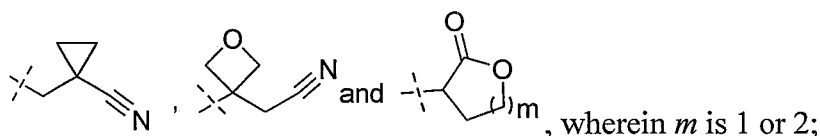
R<sup>1</sup> is selected from:

- (a) C<sub>1-4</sub>alkyl, wherein C<sub>1-4</sub>alkyl is optionally substituted with one, two, or three fluoro or with a substituent selected from -CN; -OC<sub>1-3</sub>alkyl; -C(O)OC<sub>1-4</sub>alkyl; phenyl, wherein phenyl is optionally substituted with -OH; pyridinyl, wherein pyridinyl is optionally substituted with -CN; tetrahydropyranyl; -C(O)NR<sup>a</sup>R<sup>b</sup>, wherein R<sup>a</sup> and R<sup>b</sup> are independently hydrogen

or C<sub>1-3</sub>alkyl or R<sup>a</sup> is hydrogen and R<sup>b</sup> is ; and a group selected from



(b) a group selected from

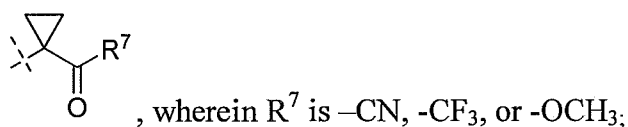


5 (c) -C(O)R<sup>6</sup>, wherein R<sup>6</sup> is selected from

C<sub>1-4</sub>alkyl, wherein C<sub>1-4</sub>alkyl is optionally substituted with one, two, or three fluoro or with a substituent selected from -OH, -CN, -OC<sub>1-4</sub>alkyl, phenyl, and -NR<sup>e</sup>R<sup>f</sup>, wherein R<sup>e</sup> and R<sup>f</sup> are independently hydrogen or C<sub>1-3</sub>alkyl;

10 C<sub>3-6</sub>cycloalkyl, wherein C<sub>3-6</sub>cycloalkyl is optionally substituted with C<sub>1-3</sub>alkyl;

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



15 (d) -C(O)OR<sup>8</sup>, wherein R<sup>8</sup> is selected from

C<sub>1-4</sub>alkyl, wherein C<sub>1-4</sub>alkyl is optionally substituted with -CN, C<sub>3-6</sub>cycloalkyl, tetrahydrofuranyl, or -OR<sup>m</sup>, wherein R<sup>m</sup> is hydrogen or C<sub>1-3</sub>alkyl; and

C<sub>1-4</sub>alkenyl; and

20 (e) -S(O)<sub>2</sub>R<sup>9</sup>, wherein R<sup>9</sup> is selected from

C<sub>1-4</sub>alkyl, wherein C<sub>1-4</sub>alkyl is optionally substituted with -CN, -OC<sub>1-3</sub>alkyl, phenyl, pyridinyl, or C<sub>3-6</sub>cycloalkyl,

C<sub>1-4</sub>alkenyl,

25 C<sub>3-6</sub>cycloalkyl, wherein C<sub>3-6</sub>cycloalkyl is optionally substituted with C<sub>1-3</sub>alkyl,

phenyl,

pyridinyl, wherein pyridinyl is optionally substituted with fluoro,

heterocycle containing 4 to 6 ring atoms including one nitrogen atom, wherein the heterocycle is optionally substituted with  $-\text{CN}$  or  $\text{C}_{1-3}\text{alkyl}$ , wherein  $\text{C}_{1-3}\text{alkyl}$  is optionally substituted with  $-\text{CN}$  or  $-\text{OC}_{1-3}\text{alkyl}$ ; and



$\text{R}^2$  is selected from hydrogen,  $-\text{OC}_{1-3}\text{alkyl}$ , and  $-\text{CH}_2\text{R}^{10}$ , wherein  $\text{R}^{10}$  is selected from  $-\text{OH}$ , morpholinyl, piperidinyl, wherein piperidinyl is optionally substituted with two fluoro, and piperazinyl, wherein piperazinyl is optionally substituted with methyl;

$\text{R}^3$  is selected from hydrogen,  $\text{C}_{1-3}\text{alkyl}$ ,  $-\text{OC}_{1-3}\text{alkyl}$ ,  $-\text{C}(\text{O})\text{OC}_{1-3}\text{alkyl}$ ,  
10  $-\text{S}(\text{O})_2\text{C}_{1-3}\text{alkyl}$ , and  $-\text{CH}_2\text{S}(\text{O})_2\text{C}_{1-3}\text{alkyl}$ ;

$\text{R}^4$  is hydrogen or  $-\text{OC}_{1-3}\text{alkyl}$ ;

$\text{R}^5$  is hydrogen or fluoro; and

$n$  is 1 or 2;

provided that

15 when  $\text{R}^3$  is  $-\text{OC}_{1-3}\text{alkyl}$  and  $\text{R}^2$ ,  $\text{R}^4$ , and  $\text{R}^5$  are each hydrogen,  $\text{R}^9$  is not phenyl;

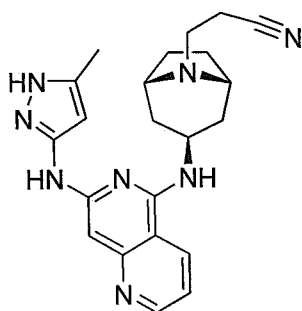
when  $\text{R}^5$  is fluoro,  $n$  is 1, and  $\text{R}^2$ ,  $\text{R}^3$ , and  $\text{R}^4$  are each hydrogen,  $\text{R}^9$  is not phenyl; and

20 when  $\text{R}^5$  is fluoro,  $\text{R}^3$  is methyl, and  $\text{R}^2$  and  $\text{R}^4$  are each hydrogen,  $\text{R}^1$  is not  $-\text{C}(\text{O})\text{OR}^8$ ;

or a pharmaceutically-acceptable salt or stereoisomer thereof.

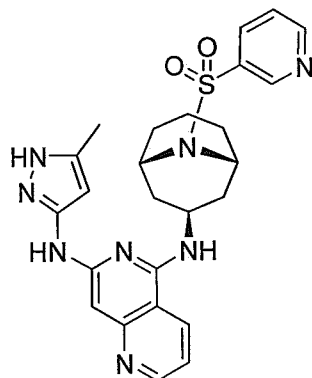
As used hereinafter, the phrase “compound of formula (I)” means a compound of formula (I) or a pharmaceutically acceptable salt thereof; i.e., this phrase means a compound of formula (I) in free base form or in a pharmaceutically acceptable salt form  
25 unless otherwise indicated.

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



or a pharmaceutically acceptable salt thereof.

In yet another aspect of the disclosure, there is also provided a compound of formula



or a pharmaceutically acceptable salt thereof.

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In another aspect, the disclosure provides a particular compound of formula (I) in crystalline free base form. Crystalline 3-((1*R*,3*s*,5*S*)-3-((7-((5-methyl-1*H*-pyrazol-3-yl)amino)-1,6-naphthyridin-5-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)propanenitrile wherein the crystalline form is characterized by a powder X-ray diffraction pattern comprising diffraction peaks at  $2\theta$  values of  $7.87 \pm 0.20$ ,  $12.78 \pm 0.20$ ,  $15.78 \pm 0.20$  and  $20.41 \pm 0.20$ , has been found to have a melting temperature in the range of about 243 °C to about 253 °C, typically between about 246 °C and about 250 °C, a decomposition onset at about 237 °C, and to exhibit weight changes of less than about 0.15 % when exposed to a range of

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relative humidity between about 5 % and about 90 % at room temperature.

In yet another aspect, the disclosure provides a crystalline solvate comprising 3-((1*R*,3*s*,5*S*)-3-((7-((5-methyl-1*H*-pyrazol-3-yl)amino)-1,6-naphthyridin-5-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)propanenitrile, methanol, N,N-dimethylformamide, and water, wherein the crystalline solvate is characterized by a powder X-ray diffraction pattern comprising diffraction peaks at  $2\theta$  values of  $9.76\pm 0.20$ ,  $15.06\pm 0.20$ ,  $16.61\pm 0.20$ ,  $20.40\pm 0.20$  and  $21.99\pm 0.20$ .

The disclosure also provides a method of treating gastrointestinal inflammatory disease, in particular, ulcerative colitis in a mammal, the method comprising administering to the mammal a therapeutically effective amount of a compound or of a pharmaceutical composition of the invention. In separate and distinct aspects, the disclosure also provides synthetic processes and intermediates described herein, which are useful for preparing compounds of the disclosure.

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

### BRIEF DESCRIPTION OF THE DRAWINGS

Various aspects of the present invention are illustrated by reference to the accompanying drawings.

Figure 1 shows a powder x-ray diffraction (PXRD) pattern of crystalline Form I 3-((1*R*,3*s*,5*S*)-3-((7-((5-methyl-1*H*-pyrazol-3-yl)amino)-1,6-naphthyridin-5-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)propanenitrile [hereinafter Form I].

Figure 2 shows a differential scanning calorimetry (DSC) thermogram of crystalline Form I.

Figure 3 shows a thermal gravimetric analysis (TGA) plot of crystalline Form I.

Figure 4 shows a dynamic moisture sorption (DMS) isotherm of crystalline Form I observed at a temperature of about 25 °C

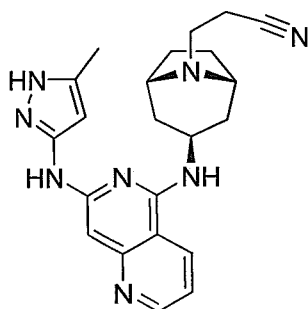
Figure 5 shows a powder X-ray diffraction (PXRD) pattern of the crystalline Form II solvate 3-((1*R*,3*s*,5*S*)-3-((7-((5-methyl-1*H*-pyrazol-3-yl)amino)-1,6-naphthyridin-5-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)propanenitrile.

## **DETAILED DESCRIPTION OF THE INVENTION**

Among other aspects, the invention provides JAK kinase inhibitors of formula (I), pharmaceutically-acceptable salts thereof, and intermediates for the preparation thereof. The following substituents and values are intended to provide representative examples of  
5 various aspects of this invention. These representative values are intended to further

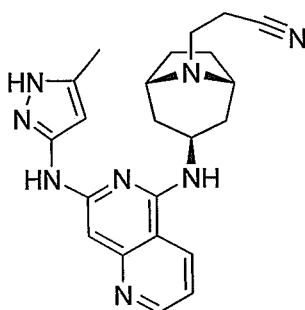
*N*<sup>7</sup>-(5-methyl-1*H*-pyrazol-3-yl)-*N*<sup>5</sup>-(((1*R*,3*s*,5*S*)-9-(pyridin-3-ylsulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-1,6-naphthyridine-5,7-diamine,  
 isobutyl (1*R*,3*s*,5*S*)-3-((2-(hydroxymethyl)-7-((5-methyl-1*H*-pyrazol-3-yl)amino)-1,6-naphthyridin-5-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate,  
*N*-methyl-2-((1*R*,3*s*,5*S*)-3-((7-((5-methyl-1*H*-pyrazol-3-yl)amino)-1,6-naphthyridin-5-yl)amino)-9-azabicyclo[3.3.1]nonan-9-yl)acetamide, and  
 pharmaceutically-acceptable salts thereof.

9. A compound of formula:

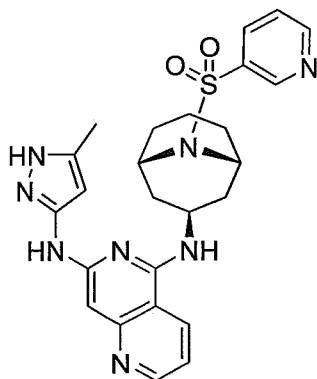


or a pharmaceutically-acceptable salt thereof.

10. A compound of formula:



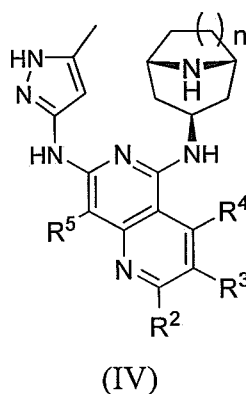
11. A compound of formula:



or a pharmaceutically-acceptable salt thereof.

12. A crystalline form of 3-((1*R*,3*s*,5*S*)-3-((7-((5-methyl-1*H*-pyrazol-3-yl)amino)-1,6-naphthyridin-5-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)propanenitrile

23. A compound of formula (IV):



wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and  $n$  are defined as in Claim 1.

24. The compound of Claim 23 wherein  $R^2$ ,  $R^3$ ,  $R^4$ , and  $R^5$  are each hydrogen.

25. A method of preparing the crystalline form of Claim 12, the method comprising:

- (a) forming a slurry of a crystalline solvate of 3-((1*R*,3*s*,5*S*)-3-((7-((5-methyl-1*H*-pyrazol-3-yl)amino)-1,6-naphthyridin-5-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)propanenitrile in a solvent selected from dioxane, toluene, butyl acetate, and acetone;
- (b) heating the slurry at a temperature between about 40 °C and about 110 °C for between about 4 hours and about 3 days; and
- (c) isolating the crystalline form from the slurry.

26. Use of a compound of any one of Claims 1 to 19 for the manufacture of a medicament for the treatment of a gastrointestinal inflammatory disease in a mammal.

27. The use of Claim 26 wherein the gastrointestinal inflammatory disease is ulcerative colitis.

28. The use of Claim 26 wherein the medicament further comprises one or more other therapeutic agents useful for treating a gastrointestinal inflammatory disease.

29. The use of Claim 27 wherein the ulcerative colitis is selected from proctosigmoiditis, pancolitis, ulcerative proctitis and left-sided colitis.

30. The use of Claim 26 wherein the gastrointestinal inflammatory disease is Crohn's disease.

31. The use of Claim 26 wherein the gastrointestinal inflammatory disease is selected from the group consisting of collagenous colitis, lymphocytic colitis, Behcet's disease, celiac disease, checkpoint cancer treatment-induced colitis, CTLA-4 inhibitor-induced colitis, ileitis, eosinophilic esophagitis, graft versus host disease-related colitis, and infected colitis.