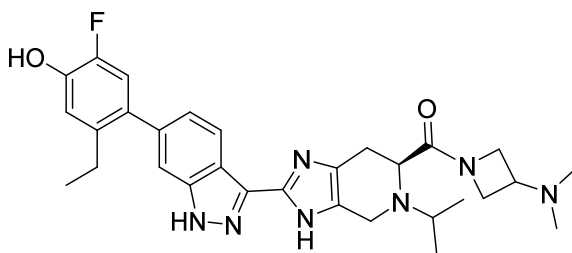


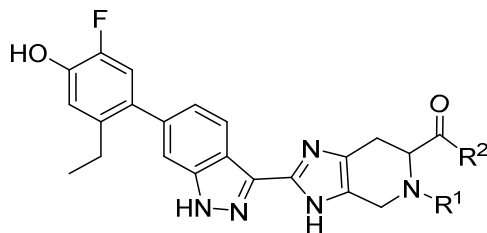
As used hereinafter, the phrase “compound of formula (I)” means a compound of formula (I) or a pharmaceutically acceptable salt thereof; i.e., this phrase means a compound of formula (I) in free base form or in a pharmaceutically acceptable salt form unless otherwise indicated.

In one aspect, there is provided a compound of the formula



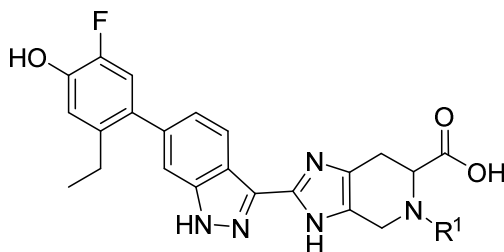
or a pharmaceutically-acceptable salt thereof.

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



(II)

wherein R^1 and R^2 are as defined herein, or a pharmaceutically-acceptable salt thereof, the process comprising reacting a compound of formula 1:



1

with a compound of formula 2:



2

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

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

The invention also provides a method of treating respiratory disease, in particular, asthma, in a mammal, the method comprising administering to the mammal a
5 therapeutically effective amount of a compound or of a pharmaceutical composition of the invention. In separate and distinct aspects, 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
10 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 respiratory disease in a mammal.

In one aspect, there is provided a compound as described herein for use in the treatment of a respiratory disease in a mammal.

15 In another aspect, there is provided a compound as described herein for use in the treatment of lung transplant rejection in a mammal.

In yet another aspect, there is provided a use of a compound as described herein for the manufacture of a medicament for the treatment of a respiratory disease in a mammal.

20 In a further aspect, there is provided a use of a compound as described herein for the manufacture of a medicament for the treatment of lung transplant rejection in a mammal.

DETAILED DESCRIPTION OF THE INVENTION

25 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 various aspects of this invention. These representative values are intended to further define such aspects and are not intended to exclude other values or limit the scope of the
30 invention.

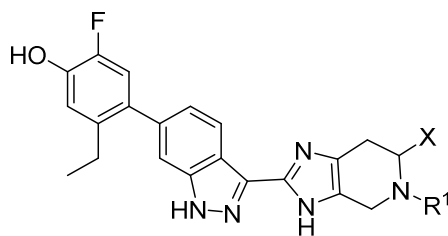
In a specific aspect, R¹ is selected from hydrogen, C₁₋₃alkyl, and C₃₋₆cycloalkyl.

In another specific aspect, R^1 is selected from hydrogen and C_{1-3} alkyl. In yet another specific aspect, R^1 is C_{1-3} alkyl.

Specific values of R^1 include, but are not limited to, methyl, ethyl, *n*-propyl, and isopropyl.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

wherein:

R¹ is selected from hydrogen, C₁₋₃alkyl, and C₃₋₆cycloalkyl, and X is -C(O)R² wherein

R² is -NR¹³R¹⁴, wherein

R¹³ and R¹⁴ are taken together with the nitrogen atom to which they are attached form a 4-membered heterocyclyl, wherein the heterocyclyl is optionally substituted with -NR⁵R⁶ and R⁷,

R⁵ and R⁶ are independently C₁₋₃alkyl or R⁵ and R⁶ taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclyl optionally including an oxygen atom,

R⁷ is C₁₋₃alkyl, optionally substituted with a 5- or 6-membered heterocyclyl containing one nitrogen atom,

or a pharmaceutically-acceptable salt thereof.

2. The compound of Claim 1, or a pharmaceutically-acceptable salt thereof, wherein R¹ is hydrogen or C₁₋₃alkyl.

3. The compound of Claim 2, or a pharmaceutically-acceptable salt thereof, wherein

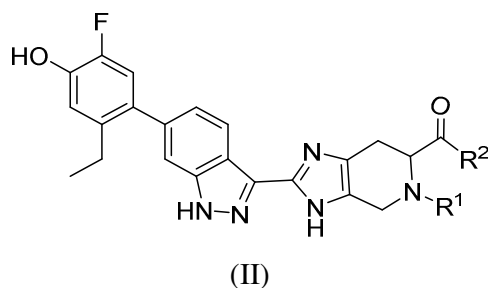
R¹³ and R¹⁴ taken together with the nitrogen atom to which they are attached form a 4-membered heterocyclyl, wherein the heterocyclyl is optionally substituted with -NR⁵R⁶ and R⁷, or

R⁵ and R⁶ are independently C₁₋₃alkyl or R⁵ and R⁶ taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclyl,

and

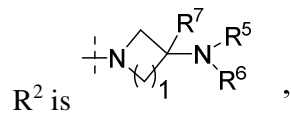
R⁷ is C₁₋₃alkyl, optionally substituted with pyrrolidinyl.

4. A compound of formula (II):



wherein:

5 R^1 is C_{1-3} alkyl;



wherein

R^5 and R^6 are independently C_{1-3} alkyl or R^5 and R^6 taken together form $-(CH_2)_{4-5}-$, R^7 is hydrogen or C_{1-3} alkyl,

10 or a pharmaceutically-acceptable salt thereof.

5. The compound of Claim 4, or a pharmaceutically-acceptable salt thereof, wherein R^5 and R^6 are C_{1-3} alkyl.

6. The compound of Claim 4, wherein the compound is (S)-(3-(dimethylamino)-3-methylazetidin-1-yl)(5-ethyl-2-(6-(2-ethyl-5-fluoro-4-hydroxyphenyl)-1H-indazol-3-yl)-4,5,6,7-tetrahydro-3H-imidazo[5,4-c]pyridin-6-yl)methanone, or a pharmaceutically-acceptable salt thereof.

7. The compound of Claim 4, wherein the compound is (S)-(3-(dimethylamino)azetidin-1-yl)(5-ethyl-2-(6-(2-ethyl-5-fluoro-4-hydroxyphenyl)-1H-indazol-3-yl)-4,5,6,7-tetrahydro-3H-imidazo[5,4-c]pyridin-6-yl)methanone, or a pharmaceutically-acceptable salt thereof.

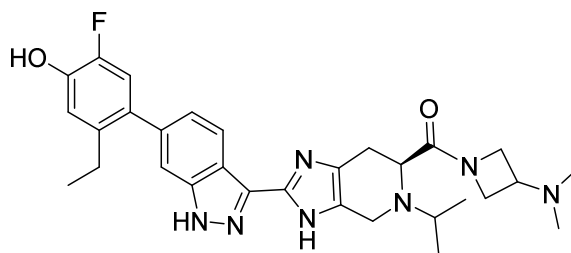
8. The compound of Claim 4, wherein the compound is selected from:
25 (S)-(3-(dimethylamino)azetidin-1-yl)(2-(6-(2-ethyl-5-fluoro-4-hydroxyphenyl)-1H-indazol-3-yl)-5-isopropyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-6-yl)methanone,

(S)-(3-(dimethylamino)azetidin-1-yl)(2-(6-(2-ethyl-5-fluoro-4-hydroxyphenyl)-1H-indazol-3-yl)-5-propyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-6-yl)methanone,

(*S*)-(3-(dimethylamino)-3-methylazetidin-1-yl)(2-(6-(2-ethyl-5-fluoro-4-hydroxyphenyl)-1*H*-indazol-3-yl)-5-propyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-6-yl)methanone,
and pharmaceutically-acceptable salts thereof.

5

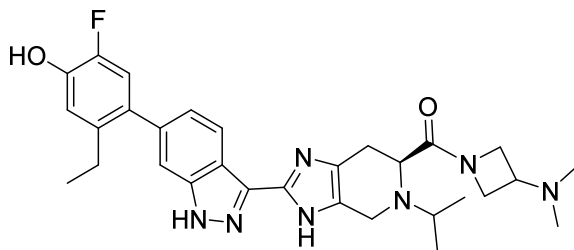
9. A compound of the formula



or a pharmaceutically-acceptable salt thereof.

10

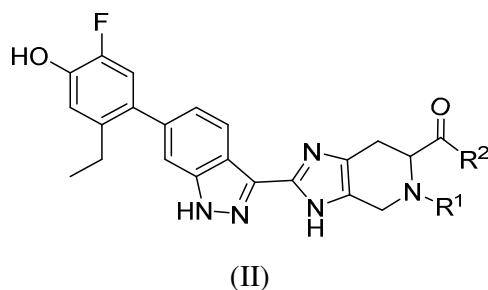
10. A compound of the formula



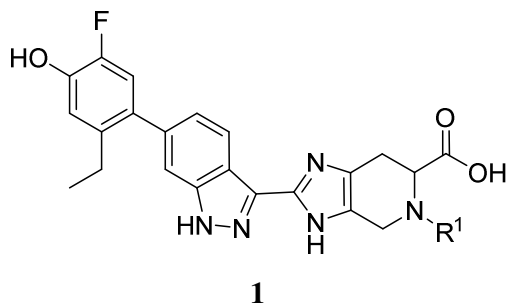
11. A pharmaceutical composition comprising a compound of any one of Claims 1 to 10 and a pharmaceutically-acceptable carrier.

15

12. A process of preparing a compound of formula (II):



wherein R¹ and R² are as defined in Claim 4, or a pharmaceutically-acceptable salt thereof, the process comprising reacting a compound of formula 1:



5 with a compound of formula 2:



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

10 13. A compound of any one of Claims 1 to 10 for use in the treatment of a respiratory disease in a mammal.

14. The compound of Claim 13 wherein the respiratory disease is asthma, chronic obstructive pulmonary disease, cystic fibrosis, pneumonitis, idiopathic pulmonary
15 fibrosis, acute lung injury, acute respiratory distress syndrome, bronchitis, emphysema, bronchiolitis obliterans, or sarcoidosis.

15. The compound of Claim 13 wherein the respiratory disease is asthma.

20 16. The compound of Claim 13 wherein the respiratory disease is an eosinophilic disease, a helminthic infection, pulmonary arterial hypertension, lymphangioleiomyomatosis, bronchiectasis, an infiltrative pulmonary disease, drug-induced pneumonitis, fungal induced pneumonitis, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonitis, eosinophilic granulomatosis with polyangiitis,
25 idiopathic acute eosinophilic pneumonia, idiopathic chronic eosinophilic pneumonia, hypereosinophilic syndrome, Löffler syndrome, bronchiolitis obliterans organizing pneumonia, lung graft-versus-host disease, or immune-checkpoint-inhibitor induced pneumonitis.

17. A compound of any one of Claims 1 to 10 for use in the treatment of lung transplant rejection in a mammal.

18. The compound of Claim 17 wherein the lung transplant rejection is
5 primary graft dysfunction, organizing pneumonia, acute rejection, lymphocytic bronchiolitis, or chronic lung allograft dysfunction.

19. The compound of Claim 17 wherein the lung transplant rejection is acute lung transplant rejection.
10

20. The compound of Claim 17 wherein the lung transplant rejection is chronic lung allograft dysfunction.

21. The compound of Claim 17 wherein the lung transplant rejection is
15 bronchiolitis obliterans, restrictive chronic lung allograft dysfunction, or neutrophilic allograft dysfunction.

22. Use of a compound of any one of Claims 1 to 10 for the manufacture of a medicament for the treatment of a respiratory disease in a mammal.
20

23. The use of Claim 22, wherein the respiratory disease is asthma, chronic obstructive pulmonary disease, cystic fibrosis, pneumonitis, idiopathic pulmonary fibrosis, acute lung injury, acute respiratory distress syndrome, bronchitis, emphysema, bronchiolitis obliterans, or sarcoidosis.
25

24. The use of Claim 23, wherein the respiratory disease is asthma.

25. The use of Claim 22, wherein the respiratory disease is an eosinophilic disease, a helminthic infection, pulmonary arterial hypertension,
30 lymphangioleiomyomatosis, bronchiectasis, an infiltrative pulmonary disease, drug-induced pneumonitis, fungal induced pneumonitis, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonitis, eosinophilic granulomatosis with polyangiitis, idiopathic acute eosinophilic pneumonia, idiopathic chronic eosinophilic pneumonia,

hypereosinophilic syndrome, Löffler syndrome, bronchiolitis obliterans organizing pneumonia, lung graft-versus-host disease, or immune-checkpoint-inhibitor induced pneumonitis.

5 26. Use of a compound of any one of Claims 1 to 10 for the manufacture of a medicament for the treatment of lung transplant rejection in a mammal.

 27. The use of Claim 26, wherein the lung transplant rejection is primary graft dysfunction, organizing pneumonia, acute rejection, lymphocytic bronchiolitis, or chronic
10 lung allograft dysfunction.

 28. The use of Claim 26, wherein the lung transplant rejection is acute lung transplant rejection.

15 29. The use of Claim 26, wherein the lung transplant rejection is chronic lung allograft dysfunction.

 30. The use of Claim 26, wherein the lung transplant rejection is bronchiolitis obliterans, restrictive chronic lung allograft dysfunction, or neutrophilic allograft
20 dysfunction.