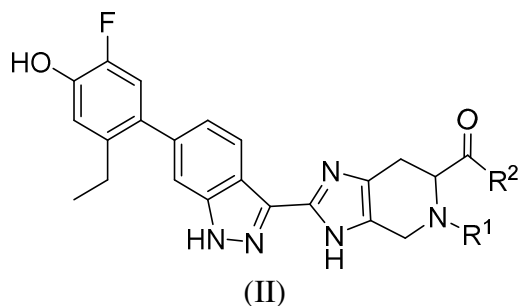


As used hereinafter, the phrase “compound of formula (I)” means a compound of formula (I) or a pharmaceutically acceptable salt thereof; i.e., this phrase means a compound of formula (I) in free base form or in a pharmaceutically acceptable salt form unless otherwise indicated.

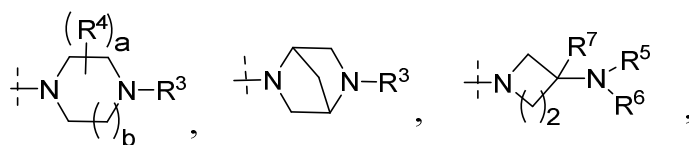
5 In one aspect, there is provided a compound of formula (II):



wherein:

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

10 R^2 is a group selected from:



and $-NR^8R^9$,

wherein

R^3 is hydrogen or C_{1-3} alkyl, wherein C_{1-3} alkyl is optionally substituted with $-OH$,

a is 0, 1, or 2,

b is 1 or 2,

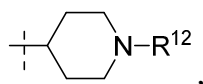
R^4 , when present, is C_{1-3} alkyl,

provided that when a is 0, R^3 is C_{1-3} alkyl, wherein C_{1-3} alkyl is optionally substituted with $-OH$,

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,

R^8 is $-CH_3$,

R^9 is $-(CH_2)_2NR^{10}R^{11}$ or

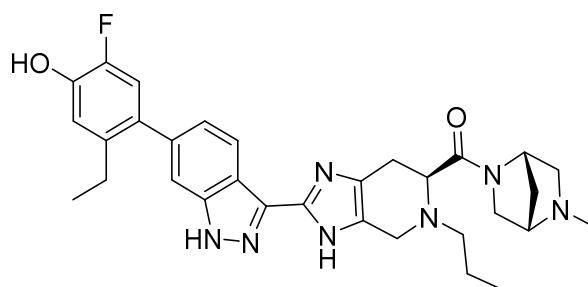


R^{10} and R^{11} are independently C_{1-3} alkyl, and

R^{12} is C_{1-3} alkyl;

or a pharmaceutically-acceptable salt thereof

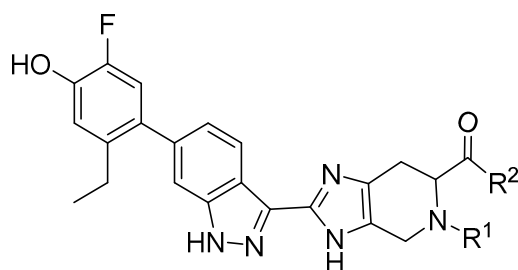
In another aspect, there is provided a compound of the formula



or a pharmaceutically-acceptable salt thereof.

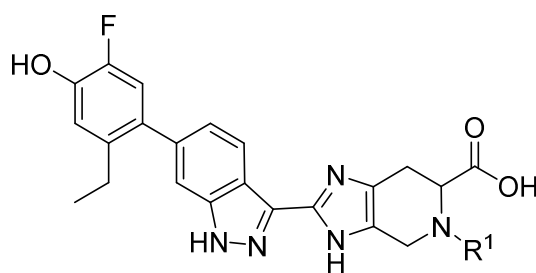
The invention also provides a pharmaceutical composition comprising a
5 compound of the invention and a pharmaceutically-acceptable carrier.

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



(II)

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



1

with a compound of formula **2**:

15 $H-R^2$
2

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

The invention also provides a method of treating respiratory disease, in particular,
20 asthma, 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 invention also provides synthetic processes and intermediates described herein, which are useful for preparing compounds of the invention.

5 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 respiratory disease in a mammal.

10 In a further aspect, there is provided the 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

15 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 invention.

20 In a specific aspect, R^1 is selected from hydrogen, C_{1-3} alkyl, and C_{3-6} cycloalkyl.

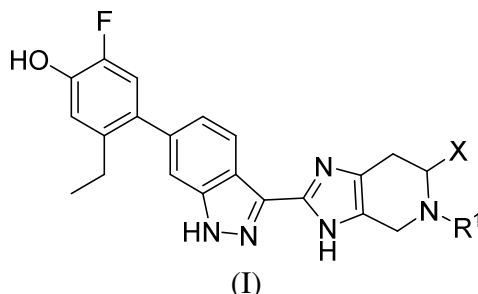
 In another specific aspect, R^1 is selected from hydrogen and C_{1-3} alkyl. In yet another specific aspect, R^1 is C_{1-3} alkyl.

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

25 In a specific aspect, R^1 is selected from hydrogen and C_{1-3} alkyl and X is $-C(O)R^2$, wherein R^2 is $-NR^{13}R^{14}$, wherein R^{13} and R^{14} taken together with the nitrogen atom to which they are attached form a 6- or 7-membered monocyclic or bicyclic heterocyclyl containing one additional nitrogen atom, wherein the additional nitrogen atom is substituted with R^3 and the heterocyclyl is optionally substituted with one or two R^4 ; R^3 is

WHAT IS CLAIMED IS:

1. A compound of formula (I):



wherein:

R^1 is selected from hydrogen, C_{1-3} alkyl, and C_{3-6} cycloalkyl, and X is selected from $-C(O)R^2$ and $-CH_2R^{16}$, or

R^1 is selected from $-(CH_2)_2NR^{20}R^{21}$ and a 4- to 6-membered heterocyclyl containing one nitrogen atom, wherein the nitrogen atom is optionally substituted with R^{22} , and X is selected from $-CH_2OR^{23}$ and $-C(O)OR^{24}$,

wherein

R^2 is selected from $-NR^{13}R^{14}$ and $-OR^{15}$,

R^{13} and R^{14} taken together with the nitrogen atom to which they are attached form a 6- or 7-membered monocyclic or bicyclic heterocyclyl containing one additional nitrogen atom, wherein the additional nitrogen atom is substituted with R^3 and the heterocyclyl is optionally substituted with one or two R^4 , or

R^{13} and R^{14} taken together with the nitrogen atom to which they are attached form a 5- to 6-membered heterocyclyl, wherein the heterocyclyl is optionally substituted with $-NR^5R^6$ and R^7 , or

R^{13} and R^{14} taken together with the nitrogen atom to which they are attached form morpholinyl, or

R^{13} is R^8 and R^{14} is R^9 ,

R^3 is selected from hydrogen, C_{3-6} cycloalkyl, and C_{1-3} alkyl, wherein C_{1-3} alkyl is optionally substituted with $-OH$ or $-OC_{1-3}$ alkyl,

R^4 is C_{1-3} alkyl, wherein C_{1-3} alkyl is optionally substituted with $-OH$,

R^5 and R^6 are independently C_{1-3} alkyl or R^5 and R^6 taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclyl optionally including an oxygen atom,

R^7 is C_{1-3} alkyl, optionally substituted with a 5- or 6-membered heterocyclyl containing one nitrogen atom,

R^8 is hydrogen or C_{1-3} alkyl,

R^9 is $-(CH_2)_2NR^{10}R^{11}$ or a 4- to 6-membered heterocyclyl containing one nitrogen atom, wherein the nitrogen atom is substituted with R^{12} ,

R^{10} and R^{11} are independently C_{1-3} alkyl or R^{10} and R^{11} taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclyl,

R^{12} is C_{1-3} alkyl or C_{3-6} cycloalkyl, wherein C_{1-3} alkyl is optionally substituted with $-OH$,

R^{15} is selected from C_{1-3} alkyl, C_{3-6} cycloalkyl, and a 5- or 6-membered heterocyclyl including one heteroatom selected from nitrogen and oxygen, wherein C_{1-3} alkyl is optionally substituted with $-OH$ or $-N(C_{1-3}alkyl)_2$, and a 5- or 6-membered heterocyclyl is optionally substituted with C_{1-3} alkyl,

R^{16} is selected from $-NR^{17}R^{18}$ and $-OR^{19}$,

R^{17} and R^{18} are independently C_{1-4} alkyl or C_{3-5} cycloalkyl or R^{17} and R^{18} taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclyl optionally including an oxygen atom, wherein the heterocyclyl is optionally substituted with C_{1-3} alkyl,

R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , and R^{24} are independently selected from hydrogen and C_{1-3} alkyl,

or a pharmaceutically-acceptable salt thereof.

2. The compound of Claim 1, or a pharmaceutically-acceptable salt thereof, wherein R^1 is selected from hydrogen and C_{1-3} alkyl, and X is selected from $-C(O)R^2$ and $-CH_2R^{16}$.

3. The compound of Claim 2, or a pharmaceutically-acceptable salt thereof, wherein R^{13} and R^{14} taken together with the nitrogen atom to which they are attached form a 6- or 7-membered monocyclic or bicyclic heterocyclyl containing one additional nitrogen atom, wherein the additional nitrogen atom is substituted with R^3 and the heterocyclyl is optionally substituted with one or two R^4 , or

R^{13} and R^{14} taken together with the nitrogen atom to which they are attached form a 5- to 6-membered heterocyclyl, wherein the heterocyclyl is optionally substituted with $-NR^5R^6$ and R^7 , or

R^{13} is R^8 and R^{14} is R^9 ,

R^3 is selected from hydrogen and C_{1-3} alkyl, wherein C_{1-3} alkyl is optionally substituted with $-OH$,

R^5 and R^6 are independently C_{1-3} alkyl or R^5 and R^6 taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclyl,

R^7 is C_{1-3} alkyl, optionally substituted with pyrrolidinyl,

R^8 is C_{1-3} alkyl,

R^9 is $-(CH_2)_2NR^{10}R^{11}$ or piperidinyl, wherein piperidinyl is substituted at the nitrogen atom with R^{12} ,

R^{10} and R^{11} are independently C_{1-3} alkyl,

R^{12} is C_{1-3} alkyl or C_{3-6} cycloalkyl, wherein C_{1-3} alkyl is optionally substituted with $-OH$,

R^{15} is selected from C_{1-3} alkyl, C_{3-6} cycloalkyl, and a 5- or 6-membered heterocyclyl including one heteroatom selected from nitrogen and oxygen, wherein C_{1-3} alkyl is optionally substituted with $-OH$, and a 5- or 6-membered heterocyclyl is optionally substituted with C_{1-3} alkyl,

R^{16} is selected from $-NR^{17}R^{18}$, and

R^{17} and R^{18} are independently C_{1-4} alkyl or C_{3-5} cycloalkyl or R^{17} and R^{18} taken together with the nitrogen atom to which they are attached form morpholinyl or a 5- or 6-membered heterocyclyl, wherein the heterocyclyl is optionally substituted with C_{1-3} alkyl.

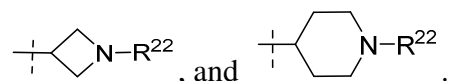
4. The compound of Claim 3, or a pharmaceutically-acceptable salt thereof, wherein X is $-C(O)R^2$, wherein R^2 is $-NR^{13}R^{14}$.

5. The compound of Claim 3, or a pharmaceutically-acceptable salt thereof, wherein X is $-C(O)R^2$, wherein R^2 is $-OR^{15}$.

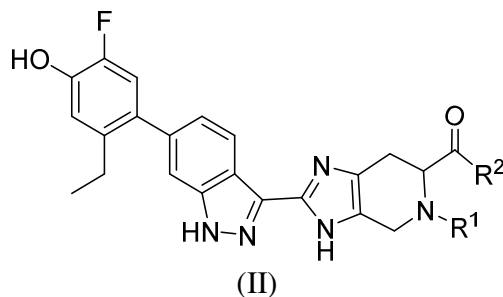
6. The compound of Claim 3, or a pharmaceutically-acceptable salt thereof, wherein X is $-CH_2R^{16}$.

7. The compound of Claim 1, or a pharmaceutically-acceptable salt thereof, wherein R^1 is selected from $-(CH_2)_2NR^{20}R^{21}$ and a 4- to 6-membered heterocyclyl containing one nitrogen atom, wherein the nitrogen atom is optionally substituted with R^{22} and X is selected from $-CH_2OR^{23}$ and $-C(O)OR^{24}$.

8. The compound of Claim 7, or a pharmaceutically-acceptable salt thereof, wherein R^1 is selected from $-(CH_2)_2NR^{20}R^{21}$,



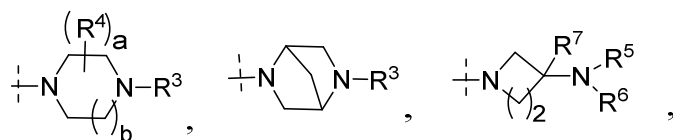
9. A compound of formula (II):



wherein:

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

R^2 is a group selected from:



and $-NR^8R^9$,

wherein

R^3 is hydrogen or C_{1-3} alkyl, wherein C_{1-3} alkyl is optionally substituted with $-OH$,

a is 0, 1, or 2,

b is 1 or 2,

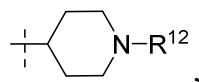
R^4 , when present, is C_{1-3} alkyl,

provided that when a is 0, R^3 is C_{1-3} alkyl, wherein C_{1-3} alkyl is optionally substituted with $-OH$,

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,

R^8 is $-CH_3$,

R^9 is $-(CH_2)_2NR^{10}R^{11}$ or

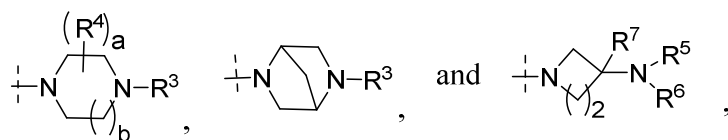


R^{10} and R^{11} are independently C_{1-3} alkyl, and

R^{12} is C_{1-3} alkyl;

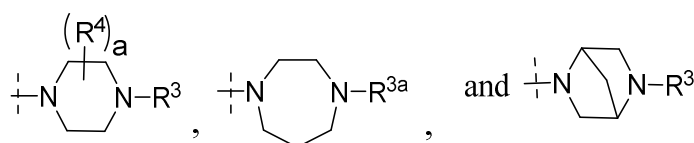
or a pharmaceutically-acceptable salt thereof.

10. The compound of Claim 9, or a pharmaceutically-acceptable salt thereof, wherein R^2 is a group selected from:



wherein R^5 and R^6 are C_{1-3} alkyl.

11. The compound of Claim 10, or a pharmaceutically-acceptable salt thereof, wherein R^2 is a group selected from

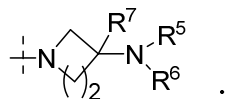


wherein

R^3 is C_{1-3} alkyl or $-(CH_2)_2OH$, and

R^{3a} is C_{1-3} alkyl.

12. The compound of Claim 10, or a pharmaceutically-acceptable salt thereof, wherein R^2 is



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

((*S*)-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)((1*S*,4*S*)-5-methyl-2,5-diazabicyclo-[2.2.1]heptan-2-yl)methanone,

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

(*S*)-(2-(6-(2-ethyl-5-fluoro-4-hydroxyphenyl)-1*H*-indazol-3-yl)-5-isopropyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-6-yl)(4-methyl-1,4-diazepan-1-yl)methanone,

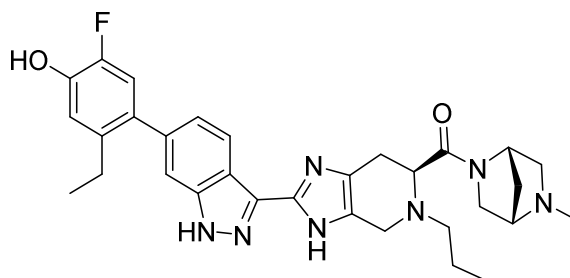
((*S*)-2-(6-(2-ethyl-5-fluoro-4-hydroxyphenyl)-1*H*-indazol-3-yl)-5-methyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-6-yl)((*R*)-4-(2-hydroxyethyl)-2-methyl-piperazin-1-yl)methanone,

(*S*)-(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)(4-(2-hydroxyethyl)piperazin-1-yl)methanone, and pharmaceutically-acceptable salts thereof.

14. The compound of Claim 9, wherein the compound is ((*S*)-2,4-dimethylpiperazin-1-yl)((*S*)-2-(6-(2-ethyl-5-fluoro-4-hydroxyphenyl)-1*H*-indazol-3-yl)-5-methyl-4,5,6,7-tetrahydro-3*H*-imidazo[5,4-*c*]pyridin-6-yl)methanone, or a pharmaceutically-acceptable salt thereof.

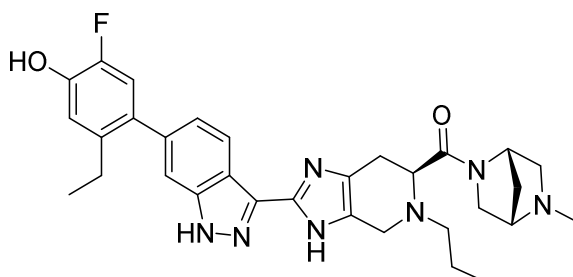
15. The compound of Claim 9, wherein the compound is (*R*)-*N*-(2-(diethylamino)ethyl)-5-ethyl-2-(6-(2-ethyl-5-fluoro-4-hydroxyphenyl)-1*H*-indazol-3-yl)-*N*-methyl-4,5,6,7-tetrahydro-3*H*-imidazo[5,4-*c*]pyridine-6-carboxamide, or a pharmaceutically-acceptable salt thereof.

16. A compound of the formula



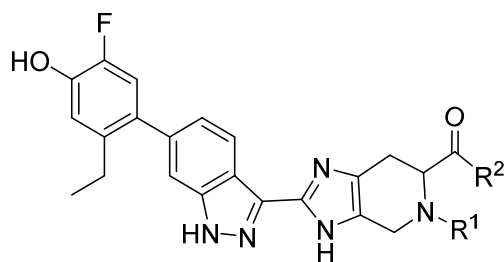
or a pharmaceutically-acceptable salt thereof.

17. A compound of the formula



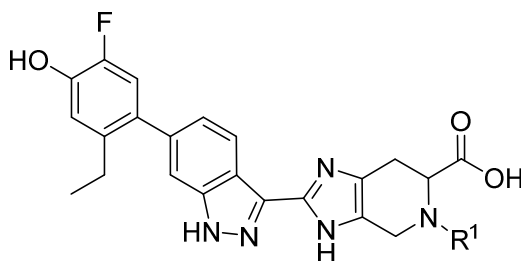
18. A pharmaceutical composition comprising a compound of any one of Claims 1 to 17 and a pharmaceutically-acceptable carrier.

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



(II)

wherein R¹ and R² are as defined in Claim 9, 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.

20. Use of a compound of any one of Claims 1 to 17 for the manufacture of a medicament for the treatment of a respiratory disease in a mammal.

21. The use of Claim 20, 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.

22. The use of Claim 21, wherein the respiratory disease is asthma.
23. The use of Claim 20, 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, 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.
24. Use of a compound of any one of Claims 1 to 17 for the manufacture of a medicament for the treatment of lung transplant rejection in a mammal.
25. The use of Claim 24, wherein the lung transplant rejection is primary graft dysfunction, organizing pneumonia, acute rejection, lymphocytic bronchiolitis, or chronic lung allograft dysfunction.
26. The use of Claim 24, wherein the lung transplant rejection is acute lung transplant rejection.
27. The use of Claim 24, wherein the lung transplant rejection is chronic lung allograft dysfunction.
28. The use of Claim 24, wherein the lung transplant rejection is bronchiolitis obliterans, restrictive chronic lung allograft dysfunction, or neutrophilic allograft dysfunction.