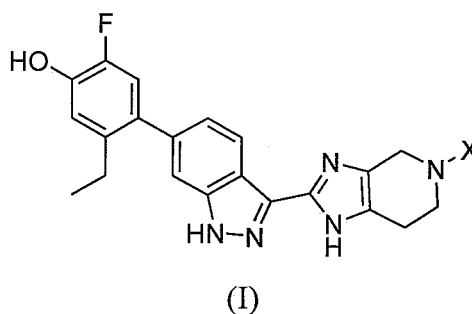


respiratory diseases in addition to asthma. Chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), pneumonitis, interstitial lung diseases (including idiopathic pulmonary fibrosis), acute lung injury, acute respiratory distress syndrome, bronchitis, emphysema, and bronchiolitis obliterans are also respiratory tract diseases in which the pathophysiology is believed to be related to JAK-signaling cytokines. Local administration of a JAK inhibitor to the lungs by inhalation offers the potential to be therapeutically efficacious by delivering a potent anti-cytokine agent directly to the site of action, limiting systemic exposure and therefore limiting the potential for adverse systemic immunosuppression. The need remains for a potent JAK inhibitor suitable for local administration to the lungs for treatment of respiratory disease.

SUMMARY OF THE DISCLOSURE

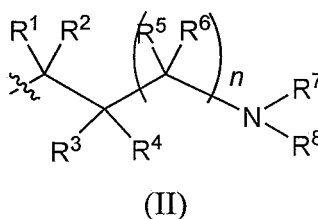
In one aspect, the disclosure provides novel compounds having activity as JAK kinase inhibitors.

Accordingly, the disclosure provides a compound of formula (I):



wherein:

X is a group of formula (II):



n is 0 or 1;

R¹ is hydrogen or C₁₋₃alkyl;

R² is hydrogen or C₁₋₃alkyl;

R³ is hydrogen or C₁₋₃alkyl;

or R² and R³ taken together form C₂₋₄alkylene;

or when n is 1 and R^2 and R^7 taken together form C_2 alkylene, R^4 and a substituent R^x on C_2 alkylene taken together form C_2 alkylene;

provided that two substituents R^x on the same carbon atom are not both fluoro, and

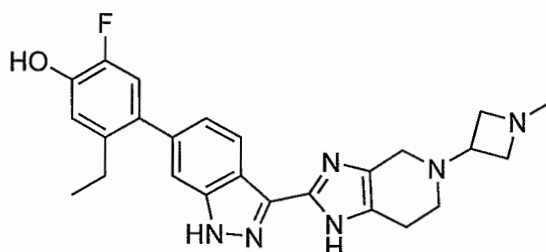
5 provided that when R^x is attached to a carbon atom adjacent to a nitrogen atom, R^x is not $-OH$, $-OC_{1-3}alkyl$, or halo;

or a pharmaceutically-acceptable salt 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

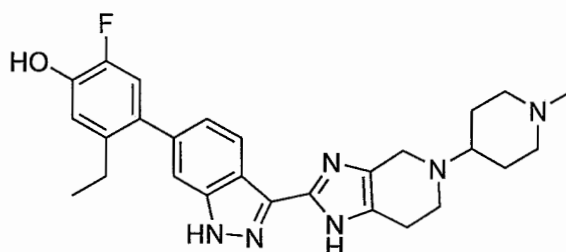
10 compound of formula (I) in free base form or in a pharmaceutically acceptable salt form unless otherwise indicated.

In another aspect, the disclosure provides a compound of formula



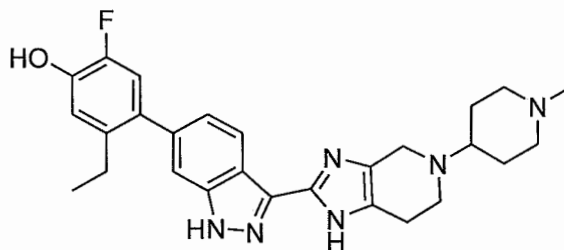
or a pharmaceutically acceptable salt thereof.

15 In another aspect, the disclosure provides a compound of formula



or a pharmaceutically acceptable salt thereof.

In another aspect, the disclosure provides a compound of formula

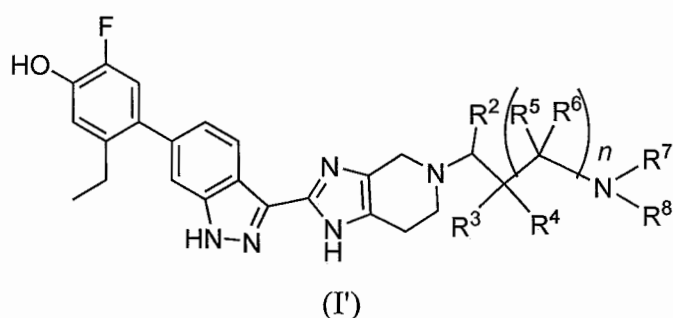


In another aspect, the disclosure provides a crystalline hydrate of 5-ethyl-2-fluoro-4-(3-(5-(1-methylpiperidin-4-yl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1*H*-indazol-6-yl)phenol wherein the crystalline form is characterized by a powder X-ray diffraction pattern comprising diffraction peaks at 2θ values of 6.20 ± 0.20 , 9.58 ± 0.20 , 17.53 ± 0.20 , 19.28 ± 0.20 , and 21.51 ± 0.2 .

In another aspect, the disclosure also provides a pharmaceutical composition comprising a compound as described herein and a pharmaceutically-acceptable carrier.

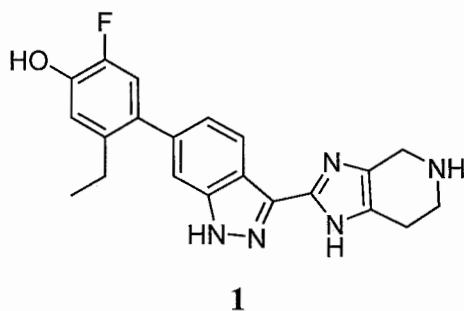
In one embodiment, the disclosure provides a particular compound of formula (I) as a crystalline free base hydrate. The crystalline hydrate of 5-ethyl-2-fluoro-4-(3-(5-(1-methylpiperidin-4-yl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1*H*-indazol-6-yl)phenol has been found to have a melting temperature in the range of about 206 °C to about 216 °C, typically between about 209 °C and about 214 °C, a decomposition onset at about 245 °C, and to exhibit weight changes of less than about 0.12 % when exposed to a range of relative humidity between about 5 % and about 90 % at room temperature.

In another aspect, the disclosure provides a process of preparing a compound of formula (I'):

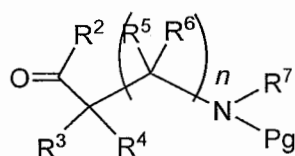


wherein R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and n are defined as described herein, or a pharmaceutically acceptable salt thereof, the process comprising:

(a) reacting a compound of formula 1:

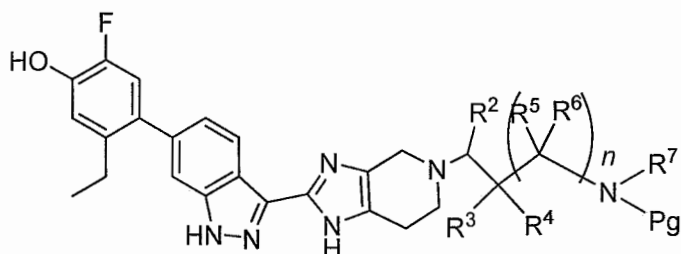


with a compound of formula 2:



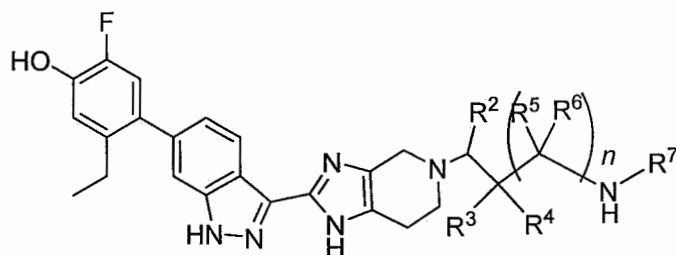
2

wherein Pg is an amino-protecting group to provide an intermediate of formula 3:



3;

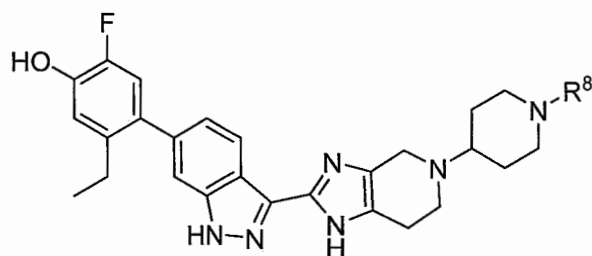
(b) deprotecting intermediate 3 to provide intermediate 4:



4;

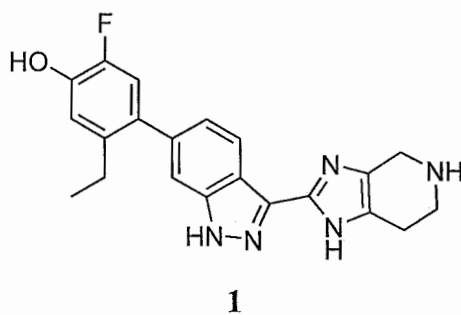
and (c) reacting intermediate 4 with $R^{8a}-C(=O)-R^{8b}$, wherein R^{8a} and R^{8b} are defined such that $R^{8a}-C(H)-R^{8b}$ is R^8 , to provide a compound of formula (I') or a pharmaceutically acceptable salt thereof.

In another aspect, the disclosure provides a process of preparing a compound of formula (IV):

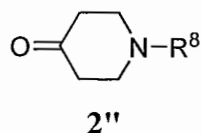


(IV)

or a pharmaceutically acceptable salt thereof, wherein R^8 is selected from hydrogen, methyl, C_{2-4} alkyl, and C_{3-4} cycloalkyl, the process comprising reacting a compound of formula 1:

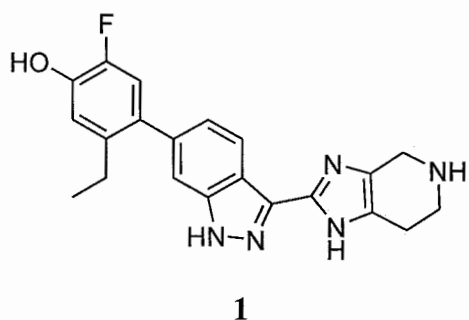


with a compound of formula **2''**:



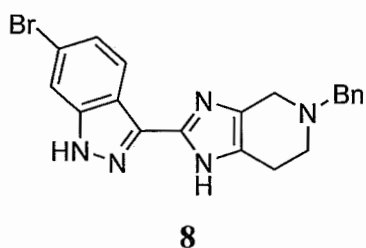
to provide a compound of formula (IV) or a pharmaceutically-acceptable salt thereof.

In another aspect, the disclosure provides a process of preparing a compound of formula **1**:

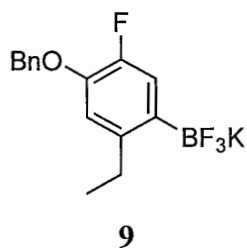


or a salt thereof, the process comprising:

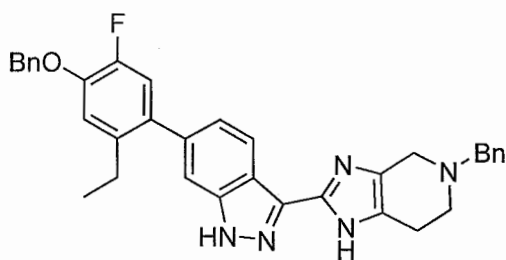
(a) reacting a compound of formula **8**;



wherein Bn represents a benzyl protecting group with a compound of formula **9**:



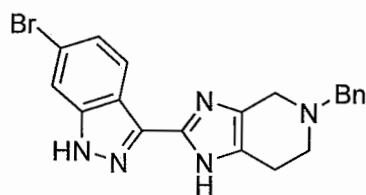
to form a compound of formula **10**:



10,

and (b) deprotecting the compound of formula **10**, to provide a compound of formula **1** or a salt thereof.

5 In another aspect, the disclosure provides a compound of formula **8**:



8

or a salt thereof.

10 In another aspect, the disclosure provides a method of preparing the crystalline hydrate of 5-ethyl-2-fluoro-4-(3-(5-(1-methylpiperidin-4-yl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-2-yl)-1H-indazol-6-yl)phenol, the method comprising:

(a) forming a slurry of 5-ethyl-2-fluoro-4-(3-(5-(1-methylpiperidin-4-yl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-2-yl)-1H-indazol-6-yl)phenol in solvate or amorphous form in a diluent including from about 1 to about 30 % v/v water along with
15 an organic solvent selected from methanol, tetrahydrofuran, *tert*-butyl alcohol, acetonitrile, isopropylacetate and acetone;

(b) heating the slurry at a temperature between about 40 °C and about 60 °C for between about 1 hour and about 2 days; and

(c) isolating the crystalline hydrate from the slurry.

20 In another aspect, the disclosure provides a compound as described herein for use in the treatment of a respiratory disease in a mammal.

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

In another embodiment, the disclosure also provides a method of treating respiratory disease, in particular, 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
5 invention also provides synthetic processes and intermediates described herein, which are useful for preparing compounds of the invention.

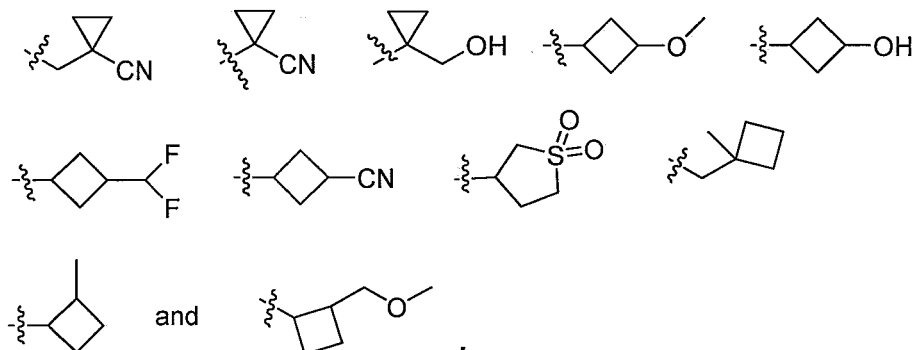
In another embodiment, the disclosure also provides a compound of the invention as described herein for use in medical therapy, as well as the use of a compound as described herein in the manufacture of a formulation or medicament for treating
10 respiratory disease in a mammal.

BRIEF DESCRIPTION OF THE DRAWINGS

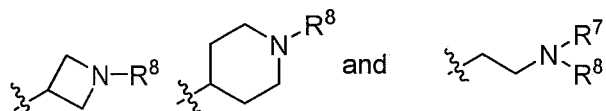
Various aspects of the present invention are illustrated by reference to the accompanying drawings.

- (a) hydrogen,
 (b) methyl, optionally substituted with C₃₋₆cycloalkyl,
 (c) C₂₋₄alkyl, wherein C₂₋₄alkyl is optionally substituted with one
 substituent selected from -OH, -OC₁₋₃alkyl, -CN, -SC₁₋₃alkyl, C₃₋₄cycloalkyl, and
 halo and optionally, in addition, with two substituents on a single carbon atom
 taken together to form C₂alkylene;
 (d) C₃₋₄cycloalkyl, wherein C₃₋₄cycloalkyl is optionally substituted
 with -OH, -CN, -OC₁₋₃alkyl, or C₁₋₃alkyl, wherein C₁₋₃alkyl is optionally
 substituted with -OC₁₋₃alkyl or with one or two halo,
 (e) oxetanyl,
 (f) tetrahydropyranyl, and
 (g) tetrahydrothiophenyl 1,1-dioxide.

6. The compound of Claim 5 wherein R⁸ is selected from hydrogen, -CH₃,
 -C₂H₅, isopropyl, cyclopropyl, cyclobutyl, -CH(CH₃)C₂H₅, -(CH₂)₂CN, -CH₂CH₂F
 -CH₂isopropyl, -CH₂cyclopropyl, -(CH₂)₂OH, (CH₂)₂₋₃OCH₃, -(CH₂)₂₋₃SCH₃,
 -(CH₂)₂CH(CH₃)SCH₃, tetrahydropyran-4-yl,

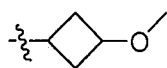


7. The compound of Claim 5 wherein X is selected from:



wherein:

R⁸ is selected from hydrogen, methyl, C₂₋₄alkyl, C₃₋₄cycloalkyl, and



4-(3-(5-(1-cyclopropylazetidin-3-yl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1*H*-indazol-6-yl)-5-ethyl-2-fluorophenol,

5-ethyl-2-fluoro-4-(3-(5-(1-methylpiperidin-4-yl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1*H*-indazol-6-yl)phenol,

5 4-(3-(5-(2-(dimethylamino)ethyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1*H*-indazol-6-yl)-5-ethyl-2-fluorophenol,

5-ethyl-2-fluoro-4-(3-(5-(2-((3-methoxycyclobutyl)amino)ethyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1*H*-indazol-6-yl)phenol,

10 5-ethyl-4-(3-(5-(2-(ethyl(methyl)amino)ethyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1*H*-indazol-6-yl)-2-fluorophenol,

4-(3-(5-(2-(*sec*-butyl(methyl)amino)ethyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1*H*-indazol-6-yl)-5-ethyl-2-fluorophenol,

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

15 4-(3-(5-(3-(dimethylamino)-2-fluoropropyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1*H*-indazol-6-yl)-5-ethyl-2-fluorophenol,

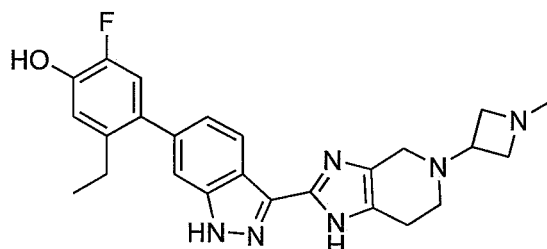
(*S*)-5-ethyl-2-fluoro-4-(3-(5-(morpholin-3-ylmethyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1*H*-indazol-6-yl)phenol,

20 (*R*)-5-ethyl-2-fluoro-4-(3-(5-(morpholin-3-ylmethyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1*H*-indazol-6-yl)phenol,

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

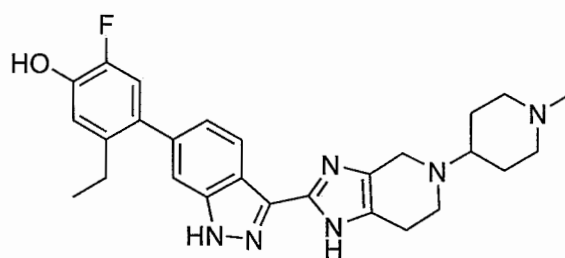
and pharmaceutically acceptable salts thereof.

25 14. A compound of formula



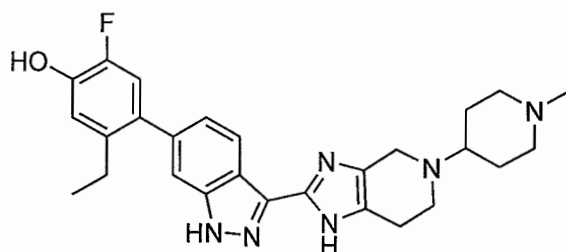
or a pharmaceutically acceptable salt thereof.

15. A compound of formula



or a pharmaceutically acceptable salt thereof.

5 16. A compound of formula

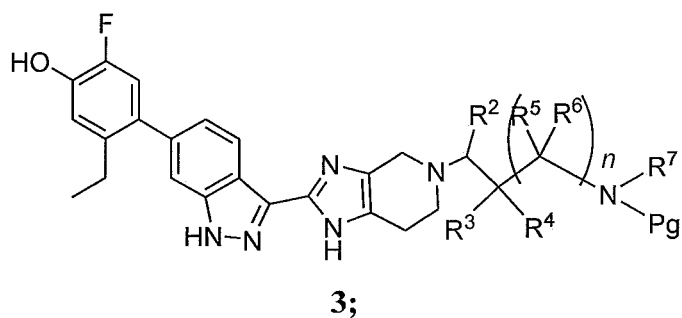


17. A crystalline hydrate of 5-ethyl-2-fluoro-4-(3-(5-(1-methylpiperidin-4-yl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-2-yl)-1H-indazol-6-yl)phenol wherein the
10 crystalline form is characterized by a powder X-ray diffraction pattern comprising diffraction peaks at 2θ values of 6.20 ± 0.20 , 9.58 ± 0.20 , 17.53 ± 0.20 , 19.28 ± 0.20 , and 21.51 ± 0.2 .

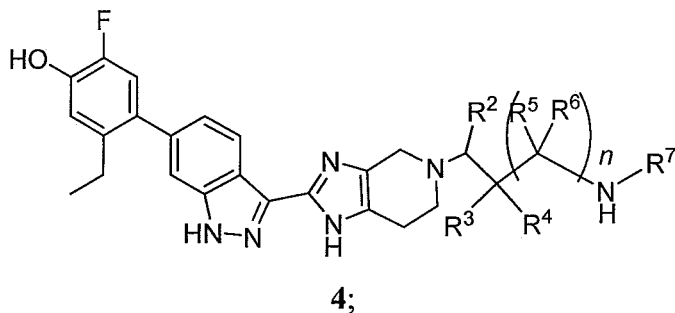
18. The crystalline hydrate of Claim 17 wherein the powder X-ray diffraction
15 pattern is further characterized by having two or more additional diffraction peaks at 2θ values selected from 10.34 ± 0.20 , 11.54 ± 0.20 , 12.77 ± 0.20 , 13.01 ± 0.20 , 16.94 ± 0.20 , 20.61 ± 0.20 , and 22.10 ± 0.20 .

19. The crystalline hydrate of Claim 17, wherein the crystalline form is
20 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.

20. The crystalline hydrate of Claim 17 wherein the crystalline form is
characterized by a differential scanning calorimetry trace recorded at a heating rate of
25 10°C per minute which shows a maximum in endothermic heat flow at a temperature between about 206°C and about 216°C .



(b) deprotecting intermediate **3** to provide intermediate **4**:

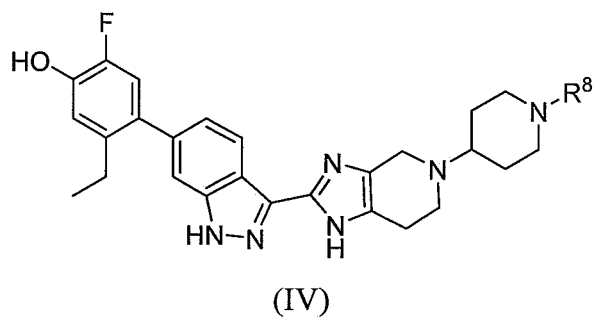


5

and (c) reacting intermediate **4** with $R^{8a}-C(=O)-R^{8b}$, wherein R^{8a} and R^{8b} are defined such that $R^{8a}-C(H)-R^{8b}$ is R^8 , to provide a compound of formula (I') or a pharmaceutically acceptable salt thereof.

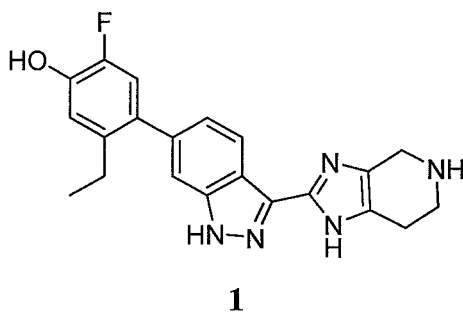
10

24. A process of preparing a compound of formula (IV):

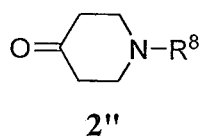


or a pharmaceutically acceptable salt thereof, wherein R^8 is selected from hydrogen, methyl, C_{2-4} alkyl, and C_{3-4} cycloalkyl, the process comprising reacting a compound of formula **1**:

15

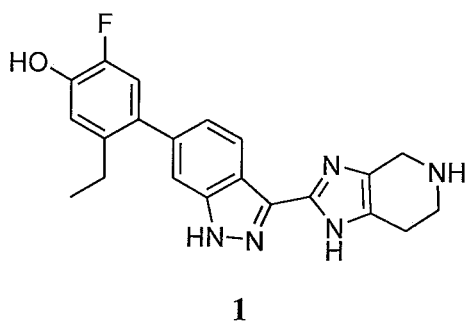


with a compound of formula **2''**:



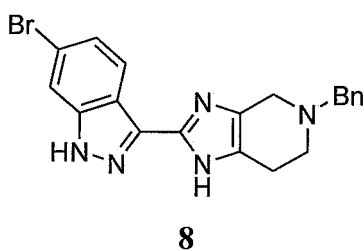
to provide a compound of formula (IV) or a pharmaceutically-acceptable salt thereof.

- 5 25. A process of preparing a compound of formula **1**:



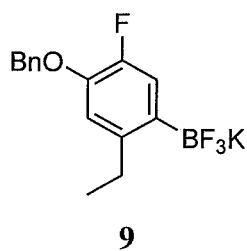
or a salt thereof, the process comprising:

- (a) reacting a compound of formula **8**;

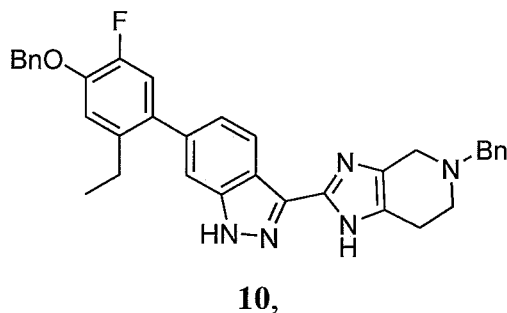


10

wherein Bn represents a benzyl protecting group with a compound of formula **9**:



- 15 to form a compound of formula **10**:



and (b) deprotecting the compound of formula **10**, to provide a compound of formula **1** or a salt thereof.

32. Use of a compound of any one of Claims 1 to 18 for the manufacture of a medicament for the treatment of a respiratory disease in a mammal.

5 33. The use of Claim 32 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 or bronchiolitis obliterans.

10 34. The use of Claim 33 wherein the respiratory disease is asthma or chronic obstructive pulmonary disease.

35. The compound of Claim 30 wherein the respiratory disease is asthma.

36. The use of Claim 33 wherein the respiratory disease is asthma.

15