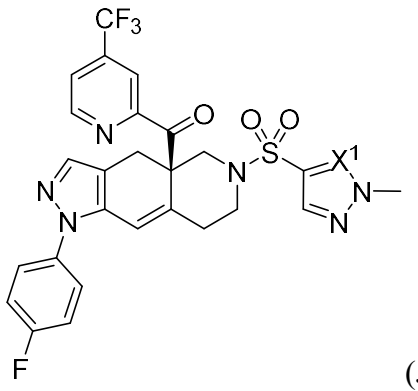
WHAT IS CLAIMED IS:

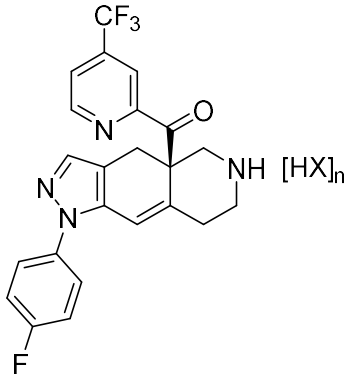
Claim 1. A method of preparing a compound of Formula J:



(J)

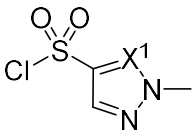
or a pharmaceutically acceptable salt thereof, comprising:

(a) forming a first reaction mixture comprising a compound of Formula IIb:



(IIb) , and

a sulfonyl chloride:



, to prepare the compound of Formula J in a yield of at least 60% and a purity of at least 98%,

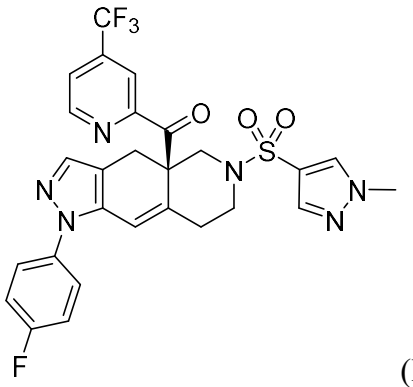
wherein

X^1 is –CH= or –N=;

HX is an acid solvate; and

subscript n is from 1 to 4.

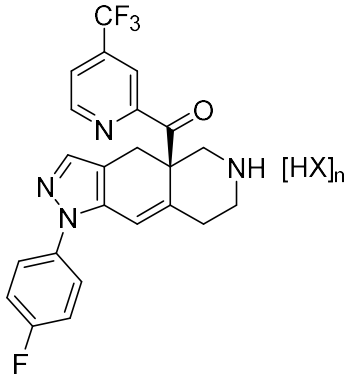
Claim 2. The method of claim 1, preparing the compound of Formula I:



(I)

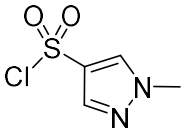
or a pharmaceutically acceptable salt thereof, comprising:

(a) forming the first reaction mixture comprising the compound of Formula IIb:



(IIb) , and

1-methyl-1H-pyrazole-4-sulfonyl chloride:



,

to prepare the compound of Formula I in a yield of at least 60% and a purity of at least 98%,

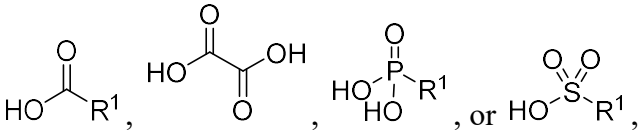
wherein

HX is the acid solvate; and

subscript n is from 1 to 4.

Claim 3. The method of claim 2, wherein

HX is HCl, HBr,

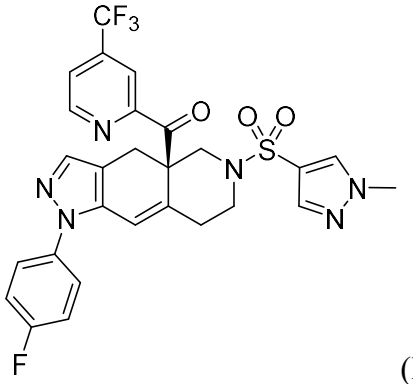


wherein

R^1 is C_{1-6} alkyl, C_{1-10} haloalkyl, phenyl, or 4-methylphenyl.

Claim 4. The method of any one of claims 1 to 3, wherein HX is HBr.

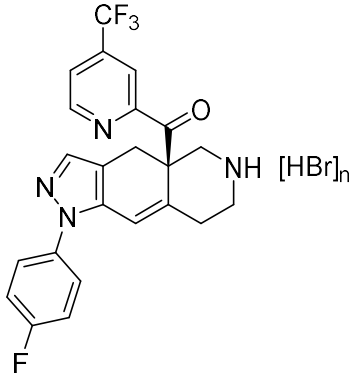
Claim 5. The method of claim 4, for preparing the compound of Formula I:



(I)

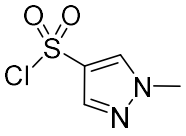
or a pharmaceutically acceptable salt thereof, comprising:

(a) forming the first reaction mixture comprising a compound of Formula IIb-1:



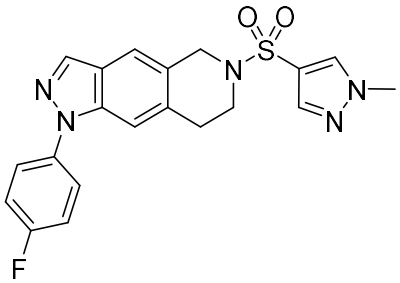
(IIb-1) , and

1-methyl-1H-pyrazole-4-sulfonyl chloride:



,

to prepare the compound of Formula I in a yield of at least 60% and a purity of at least 98%, wherein the compound of Formula I contains less than 1% (w/w) of a compound of Formula X-5:



(X-5) ,

and wherein subscript n is from 1 to 4.

Claim 6. The method of claim 5, wherein the first reaction mixture further comprises a non-nucleophilic amine base.

Claim 7. The method of claim 6, wherein the non-nucleophilic amine base comprises trimethyl amine, triethylamine, N,N-diisopropyl ethylamine (DIPEA), N,N-dimethyl isopropylamine (DIMPA), 1-ethylpiperidine, N-methylmorpholine, N-methylpyrrolidine, pyridine, N,N-dimethylaniline, N,N-diethylaniline, 2,6-lutidine, 2,4,6-collidine, 4-dimethyl aminopyridine (DMAP), quinuclidine, 4-pyrrolidinopyridine, 1,4-diazabicyclo[2.2.2]octane (DABCO), or mixtures thereof.

~~8. The method of claim 6 or 7, wherein the non-nucleophilic amine base comprises triethyl amine.~~

Claim 8~~9~~. The method of any one of claims 5 to 7~~8~~, wherein the sulfonyl chloride is present in a molar ratio of 1.2 to 2.3 to the compound of Formula IIb-1.

Claim 9~~10~~. The method of any one of claims 5 to 8~~9~~, further comprising after step (a):

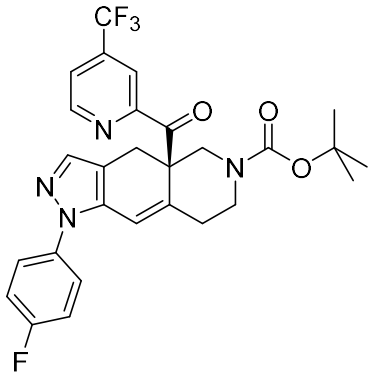
(a1) mixing the first reaction mixture with water having a pH of between 4 and 5 to form a first organic phase and a first aqueous phase;

(a2) mixing the first organic phase with water and sodium chloride wherein the water has a pH of between 5 and 6; and

(a3) mixing the first organic phase and silica gel.

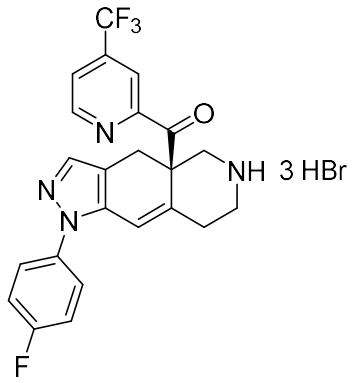
Claim 10~~11~~. The method of any one of claims 5 to 9~~10~~, wherein the compound of Formula IIb-1 is prepared by the step of:

(b) forming a second reaction mixture comprising a compound of Formula IIa:



(IIa) ,

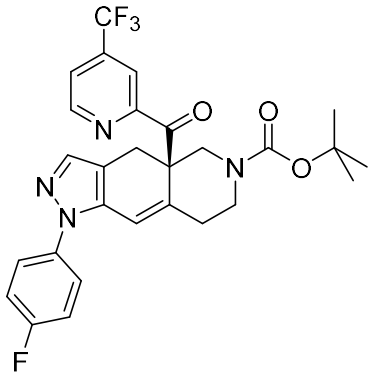
and gaseous HBr, to form the compound of Formula IIb-1 having the structure:



.

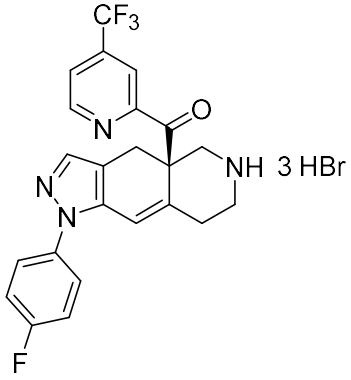
Claim 11~~12~~. The method of any one of claims 5 to 10~~11~~, wherein the compound of Formula I is prepared by the steps of:

(b) forming the second reaction mixture comprising a compound of Formula IIa:



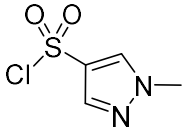
(IIa) ,

and gaseous HBr, to form the compound of Formula IIb-1 having the structure:



; and

(a) forming the first reaction mixture comprising the compound of Formula IIb-1: triethylamine, and 1-methyl-1H-pyrazole-4-sulfonyl chloride:



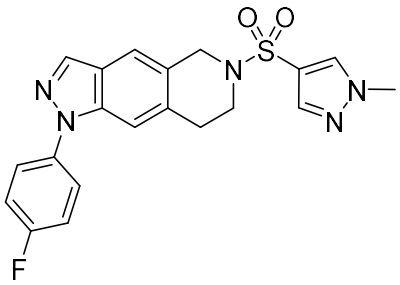
,

wherein the sulfonyl chloride is present in a molar ratio of about 1.2 to the compound of Formula IIb-1;

(a1) mixing the first reaction mixture with water having a pH of between 4 and 5 to form a first organic phase and a first aqueous phase;

(a2) mixing the first organic phase with water and sodium chloride wherein the water has a pH of between 5 and 6; and

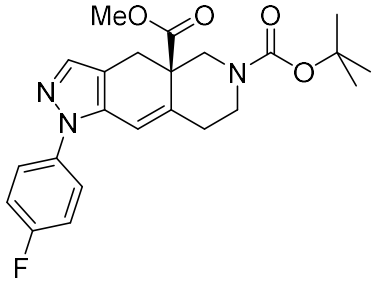
(a3) mixing the first organic phase and silica gel to prepare the compound of Formula I in a yield of at least 60% and a purity of at least 98%, wherein the compound of Formula I contains less than 1% (w/w) of the compound of Formula X-5:



(X-5) .

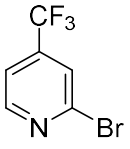
Claim 12~~13~~. The method of claim 10~~11~~ or 11~~12~~, wherein the compound of Formula IIa is prepared by:

(c) forming a third reaction mixture comprising a Grignard reagent, a compound of Formula III:



(III) , and

2-bromo-4-(trifluoromethyl)pyridine:



,

wherein the pyridine is present in a molar ratio of 1.0 to 1.5 to the compound of Formula III, and wherein the Grignard reagent is present in a molar ratio of 1.5 to 1.7 to the compound of Formula III, to prepare the compound of Formula IIa.

Claim 13~~14~~. The method of claim 12~~13~~, wherein the Grignard reagent comprises iPrMgCl or iPrMgBr.

~~15. The method of claim 13 or 14, wherein the Grignard reagent comprises iPrMgBr.~~

Claim 14~~16~~. The method of any one of claims 12~~13~~ to 13~~15~~, wherein the third reaction mixture further comprises a third solvent comprising tetrahydrofuran, 2-methyltetrahydrofuran, toluene or xylene.

Claim 15~~17~~. The method of claim 14~~16~~, wherein the third solvent comprises 2-methyltetrahydrofuran and toluene.

Claim 16~~18~~. The method of any one of claims 12~~13~~ to 15~~17~~, further comprising the steps of:

(c1) adding an acid and water to the third reaction mixture to form a workup mixture; and

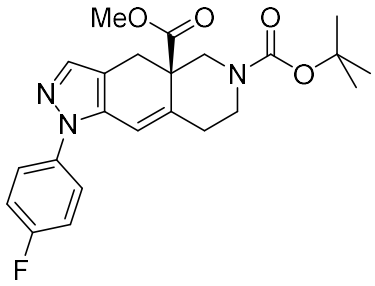
(c2) distilling the workup mixture to form an intermediate mixture comprising the compound of Formula IIa, 2-methyltetrahydrofuran in an amount of less than 100 ppm, and water in an amount of less than 0.5% (w/w).

Claim 17~~19~~. The method of claim 16~~18~~, wherein the acid comprises formic acid, acetic acid, propanoic acid, butyric acid, hexanoic acid, octanoic acid, trifluoroacetic acid, or mixtures thereof.

~~20. The method of claim 18 or 19, wherein the acid comprises acetic acid.~~

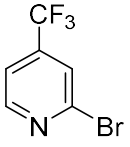
Claim 18~~21~~. The method of claim ~~20~~, wherein the method of preparing the compound of Formula I comprises:

(c) forming the third reaction mixture comprising iPrMgBr, 2-methyltetrahydrofuran, toluene, the compound of Formula III:



(III) , and

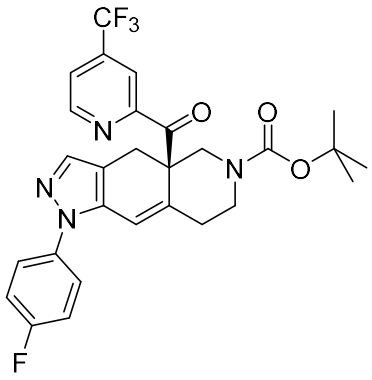
2-bromo-4-(trifluoromethyl)pyridine:



,

wherein the pyridine is present in the molar ratio of about 1.4 to the compound of Formula III, and wherein the Grignard reagent is present in the molar ratio

of about 1.65 to the compound of Formula III, to prepare the compound of Formula IIa:

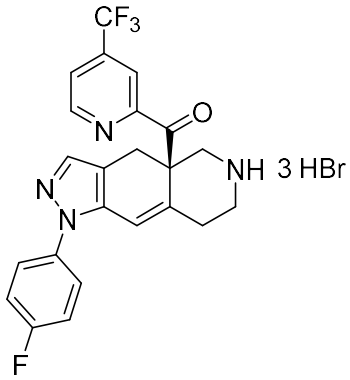


(IIa) ;

(c1) adding acetic acid and water to the third reaction mixture to form the workup mixture;

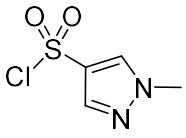
(c2) distilling the workup mixture to form an intermediate mixture comprising the compound of Formula IIa, 2-methyltetrahydrofuran in an amount of less than 100 ppm, and water in an amount of less than 0.5% (w/w);

(b) forming the second reaction mixture comprising the intermediate mixture and gaseous HBr, to form the compound of Formula IIb-1 having the structure:



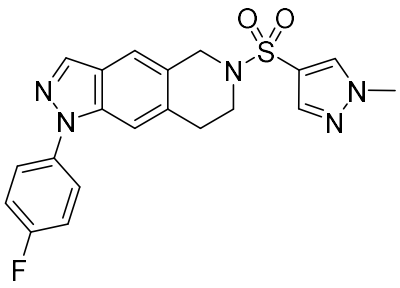
; and

(a) forming the first reaction mixture comprising the compound of Formula IIb-1, triethylamine, and 1-methyl-1H-pyrazole-4-sulfonyl chloride:



,

wherein the sulfonyl chloride is present in the molar ratio of about 1.2 to the compound of Formula IIb-1, to prepare the compound of Formula I in the yield of at least 60% and the purity of at least 98%, wherein the compound of Formula I contains less than 1% (w/w) of the compound of Formula X-5:



(X-5) .

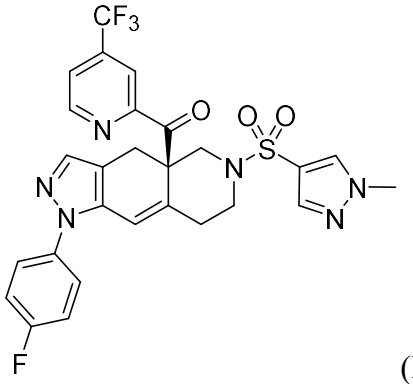
Claim 19~~22~~. The method of claim 18~~21~~, wherein the method further comprises following step (a):

(a1) mixing the first reaction mixture with water having the pH of between 4 and 5 to form the first organic phase and the first aqueous phase;

(a2) mixing the first organic phase with water and sodium chloride wherein the water has the pH of between 5 and 6; and

(a3) mixing the first organic phase and silica gel.

Claim 20~~23~~. A method of purifying a compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof, comprising:

(a) eluting the compound of Formula I through a High Pressure Liquid Chromatography C18 column using

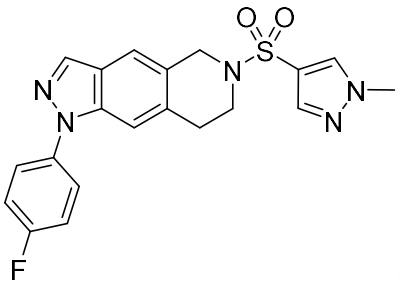
(i) a first mobile mixture comprising water in an amount of at least 95% (v/v), formic acid in an amount of 0.05 to 0.2% (v/v), and acetonitrile in an amount of 1 to 5% (v/v),

(ii) a second mobile mixture comprising water in an amount of 45 to 55% (v/v), formic acid in an amount of 0.01 to 0.1% (v/v), and acetonitrile in an amount of 45 to 55% (v/v), and

(iii) a third mobile phase comprising water in an amount of 5 to 15% (v/v), formic acid in an amount of 0.005 to 0.02% (v/v), and acetonitrile in an amount of at least 85% (v/v),

to form an eluted mixture comprising the compound of Formula I having a purity

of at least 98% and the compound of Formula X-5 in an amount of less than 0.75% (w/w):



(X-5) ;

(a1) extracting the compound of Formula I from the eluted mixture into ethyl acetate to form an extracted mixture;

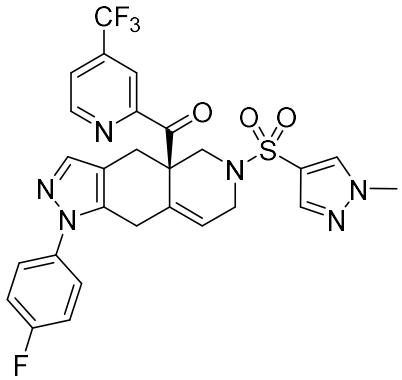
(a2) mixing the extracted mixture with methyl t-butyl ether (MTBE) under vacuum to form an MTBE mixture comprising less than 5% (v/v) ethyl acetate;

(d) filtering the MTBE mixture through a filter to form a filtered MTBE mixture comprising:

the compound of Formula I,

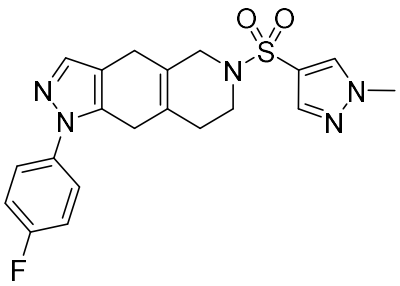
the compound of Formula X-5 in an amount of less than 0.5% (w/w),

a compound of Formula X-4 in an amount of less than 0.3% (w/w):



(X-4) , and

a compound of Formula X-6 in an amount of less than 0.25% (w/w):



(X-6) ;

(e) adding the filtered MTBE mixture to heptane to form a precipitated compound of Formula I, wherein the precipitated compound of Formula I comprises 1,4-dibromopentane in an amount of less than 20 ppm;

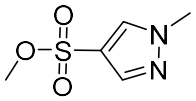
(f) dissolving the precipitated compound of Formula I in methanol to form a methanol mixture; and

(g) adding the methanol mixture to water to precipitate the purified compound of Formula I, wherein the purified compound of Formula I has a purity of at least 99%, and comprises

the compound of Formula X-5 in an amount of less than 0.5% (w/w),

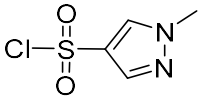
1,4-dibromopentane in an amount of less than 6 ppm,

methyl-1-methyl-1H-pyrazole-4-sulfonate in an amount of less than 6 ppm:



, and

1-methyl-1H-pyrazole-4-sulfonyl chloride in an amount of less than 6 ppm:



.

Claim 21~~24~~. The method of claim 20~~23~~, wherein the purified compound of Formula I has a purity of at least 99%, and comprises 1,4-dibromopentane in an amount of less than 8 ppm.

Claim 22~~25~~. The method of claim 20~~23~~, wherein the purified compound of Formula I has a purity of at least 99%, and further comprises

methyl bromide in an amount of less than 20 ppm, and

2-bromopropane in an amount of less than 20 ppm.

~~26. The method of claim 23, wherein the purified compound of Formula I has a purity of at least 99%, and comprises~~

~~methyl bromide in an amount of less than 8 ppm,~~

~~2-bromopropane in an amount of less than 8 ppm, and~~

~~1,4-dibromopentane in an amount of less than 8 ppm.~~

Claim 23~~27~~. The method of claim 20~~23 or 24~~, wherein the purified compound of Formula I has a purity of at least 99%, and comprises

the compound of Formula X-4 in an amount of less than 0.1% (w/w),

the compound of Formula X-5 in an amount of less than 0.2% (w/w),

the compound of Formula X-6 in an amount of less than 0.2% (w/w),

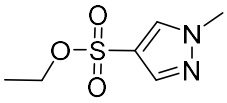
1,4-dibromopentane in an amount of less than 4 ppm,

1-methyl-1H-pyrazole-4-sulfonyl chloride in an amount of less than 4 ppm, and

methyl 1-methyl-1H-pyrazole-4-sulfonate in an amount of less than 4ppm.

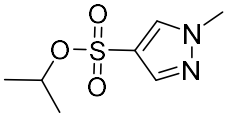
Claim 2428. The method of any one of claims 2023 to 2327, wherein the purified compound of Formula I has a purity of at least 99%, and further comprises

ethyl 1-methyl-1H-pyrazole-4-sulfonate in an amount of less than 6 ppm:



, and

isopropyl 1-methyl-1H-pyrazole-4-sulfonate in an amount of less than 6 ppm:



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Claim 2529. The method of ~~any one of~~ claim~~s~~ 2023 ~~to 28~~, wherein the purified compound of Formula I has a purity of at least 99%, and comprises

the compound of Formula X-4 in an amount of less than 0.1% (w/w),

the compound of Formula X-5 in an amount of less than 0.2% (w/w),

the compound of Formula X-6 in an amount of less than 0.2% (w/w),

methyl bromide in an amount of less than 4 ppm,

2-bromopropane in an amount of less than 4 ppm,

1,4-dibromopentane in an amount of less than 4 ppm,

1-methyl-1H-pyrazole-4-sulfonyl chloride in an amount of less than 4 ppm,

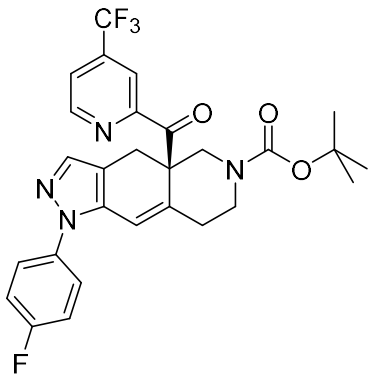
methyl 1-methyl-1H-pyrazole-4-sulfonate in an amount of less than 4ppm,

ethyl 1-methyl-1H-pyrazole-4-sulfonate in an amount of less than 4 ppm, and

isopropyl 1-methyl-1H-pyrazole-4-sulfonate in an amount of less than 4 ppm.

Claim 2630. The method of any one of claims 2023 to 2529, wherein the compound of Formula I is prepared by the method of any one of claims 5 to 1922.

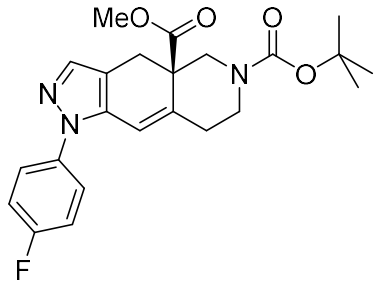
Claim 2731. A method of preparing a compound of Formula IIa:



(IIa) ,

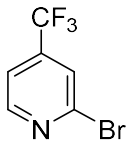
comprising the steps of:

(c) forming a third reaction mixture comprising a Grignard reagent, a compound of Formula III:



(III) , and

2-bromo-4-(trifluoromethyl)pyridine:



,

wherein the pyridine is present in a molar ratio of 1.0 to 1.5 to the compound of Formula III, and wherein the Grignard reagent is present in a molar ratio of 1.5 to 1.7 to the compound of Formula III, to prepare the compound of Formula IIa.

~~32. The method of claim 31, wherein the Grignard reagent comprises iPrMgCl or iPrMgBr.~~

~~33. The method of claim 31 or 32, wherein the Grignard reagent comprises iPrMgBr.~~

~~34. The method of any one of claims 31 to 33, wherein the third reaction mixture further comprises a third solvent comprising tetrahydrofuran, 2-methyltetrahydrofuran, toluene or xylene.~~

~~35. The method of claim 34, wherein the third solvent comprises 2-methyltetrahydrofuran and toluene.~~

~~36. The method of claim 35, further comprising~~

~~(c1) adding an acid and water to the third reaction mixture to form a workup mixture; and~~

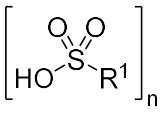
~~(c2) distilling the workup mixture to form an intermediate mixture comprising the compound of Formula IIa, 2-methyltetrahydrofuran in an amount of less than 200 ppm, and water in an amount of less than 0.5% (w/w).~~

~~37. The method of claim 36, wherein the acid comprises formic acid, acetic acid, propanoic acid, butyric acid, hexanoic acid, octanoic acid, trifluoroacetic acid, or mixtures thereof.~~

~~38. The method of claim 36 or 37, wherein the acid comprises acetic acid.~~

Claim 28~~39~~. The method of any one of claims 1 to 3, wherein

HX is



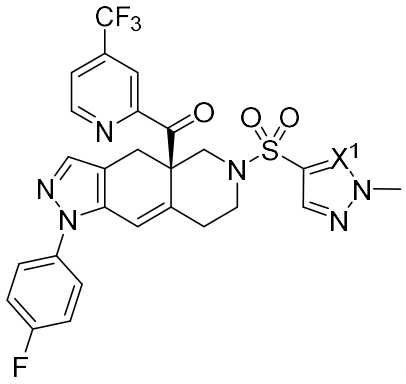
,

wherein

R^1 is C_{1-6} alkyl, C_{1-10} haloalkyl, phenyl, or 4-methylphenyl; and

subscript n is 1 to 4.

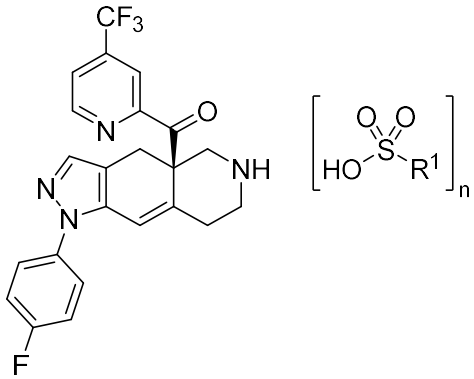
Claim 29~~40~~. The method of claim 28~~39~~, for preparing the compound of Formula J:



(J)

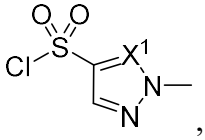
or a pharmaceutically acceptable salt thereof, comprises:

(a) forming a fourth reaction mixture comprising a compound of Formula IIb-2:



(IIb-2) ,

and the sulfonyl chloride:



,

to prepare the compound of Formula J in a yield of at least 75% and a purity of at least 98%,

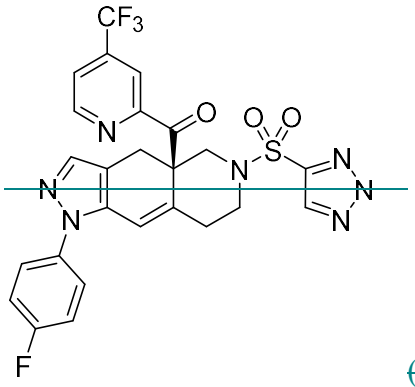
wherein

X^1 is –CH= or –N=;

R^1 is C_{1-6} alkyl, C_{1-10} haloalkyl, phenyl, or 4-methylphenyl; and

subscript n is 1 to 4.

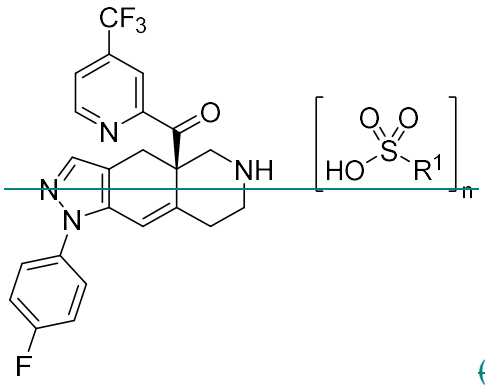
~~41. The method of claim 39 or 40, for preparing the compound of Formula Ia:~~



~~(Ia) ,~~

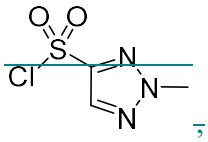
~~or a pharmaceutically acceptable salt thereof, comprises:~~

~~(a) forming the fourth reaction mixture comprising the compound of Formula IIb-2:~~



~~(IIb-2) ,~~

~~and 2-methyl-2H-1,2,3-triazole-4-sulfonyl chloride:~~



~~,~~

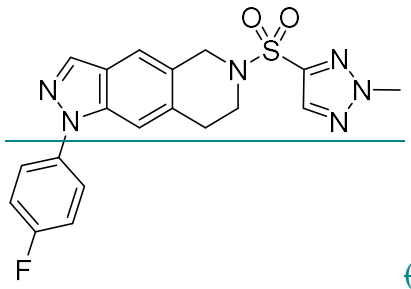
~~to prepare the compound of Formula Ia in a yield of at least 75% and a purity of at least 98%,~~

~~wherein~~

~~R^1 is C_{1-6} alkyl, C_{1-10} haloalkyl, phenyl, or 4-methylphenyl; and~~

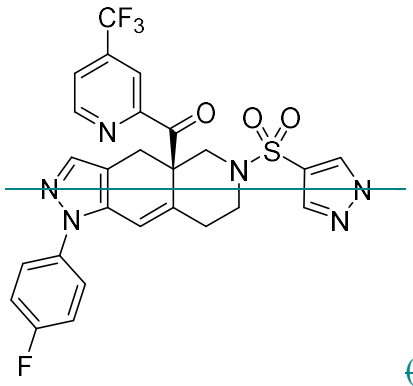
~~subscript n is 1 to 4.~~

42. The method of claim 41, wherein the compound of Formula Ia contains less than 1% (w/w) of the compound of Formula X-5a:



(X-5a).

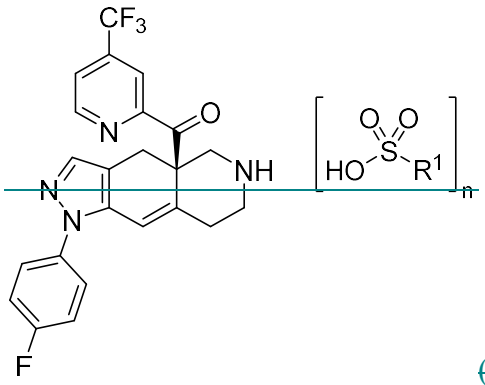
43. The method of claim 39 or 40, for preparing the compound of Formula I:



(I)

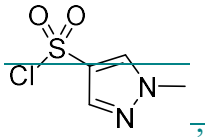
or a pharmaceutically acceptable salt thereof, comprising:

(a) forming a fourth reaction mixture comprising a compound of Formula IIb-2:



(IIb-2),

and 1-methyl-1H-pyrazole-4-sulfonyl chloride:



,

to prepare the compound of Formula I in a yield of at least 75% and a purity of at least 98%,

wherein

R^1 is C_{1-6} alkyl, C_{1-10} haloalkyl, phenyl, or 4-methylphenyl; and

subscript n is 1 to 4.

~~44. The method of any one of claims 40 to 43, wherein R^1 is C_{1-2} alkyl, C_{1-2} haloalkyl, phenyl, or 4-methylphenyl.~~

~~45. The method of any one of claims 40 to 44, wherein R^1 is methyl, ethyl, $-CF_3$, phenyl, or 4-methylphenyl.~~

~~46. The method of any one of claims 40 to 45, wherein R^1 is methyl.~~

~~47. The method of any one of claims 40 to 46, wherein n is 3.~~

~~48. The method of any one of claims 40 to 47, wherein the fourth reaction mixture further comprises a non-nucleophilic amine base.~~

~~49. The method of claim 48, wherein the non-nucleophilic amine base comprises trimethylamine, triethylamine, N,N-diisopropyl ethylamine (DIPEA), N,N-dimethyl isopropylamine (DIMPA), 1-ethylpiperidine, N-methylmorpholine, N-methylpyrrolidine, pyridine, N,N-dimethylaniline, N,N-diethylaniline, 2,6-lutidine, 2,4,6-collidine, 4-dimethyl aminopyridine (DMAP), quinuclidine, 4-pyrrolidinopyridine, 1,4-diazabicyclo[2.2.2]octane (DABCO), or mixtures thereof.~~

~~50. The method of claim 48 or 49, wherein the non-nucleophilic amine base comprises triethylamine.~~

~~51. The method of any one of claims 40 to 50, wherein the fourth reaction mixture further comprises a fourth solvent.~~

~~52. The method of claim 51, wherein the solvent comprises ethyl acetate, isopropyl acetate, or n-butyl acetate, or mixtures thereof.~~

~~53. The method of claim 51 or 52, wherein the fourth solvent comprises ethyl acetate.~~

~~54. The method of any one of claims 40 to 53, wherein the sulfonyl chloride is present in a ratio of about 1.0 to the compound of Formula IIb-2.~~

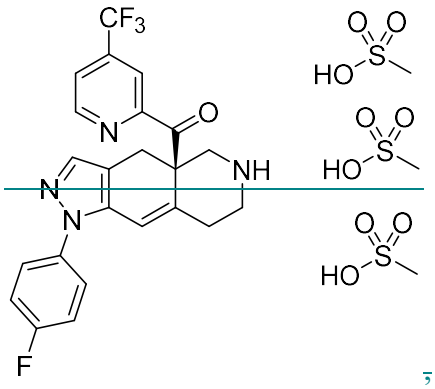
~~55. The method of any one of claims 40 to 54, further comprising the steps of:~~

~~(a1) adding methanol to the fourth reaction mixture; and~~

~~(a2) adding water to the fourth reaction mixture to precipitate the compound of Formula I.~~

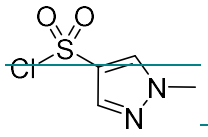
56. The method of any one of claims 43 to 55, comprising the steps of:

(a) forming the fourth reaction mixture comprising the compound of Formula IIb-2



,

triethylamine, ethyl acetate, and 1-methyl-1H-pyrazole-4-sulfonyl chloride:



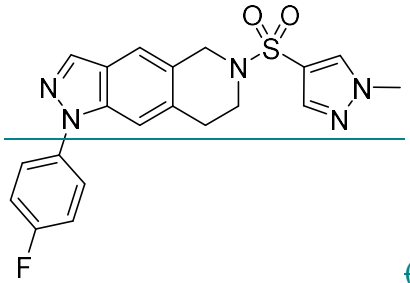
,

wherein the sulfonyl chloride is present in a ratio of about 1.0 to the compound of Formula IIb-2;

(a1) adding methanol to the fourth reaction mixture; and

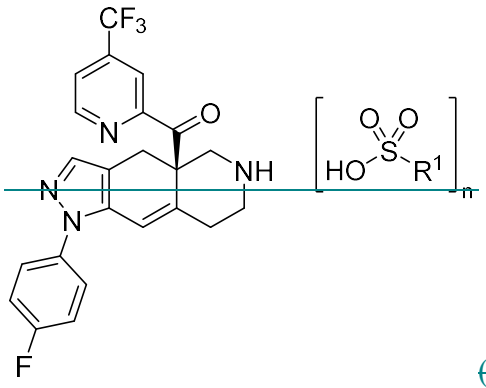
(a2) adding water to the fourth reaction mixture to precipitate the compound of Formula I in a yield of at least 75% and a purity of at least 98%.

57. The method of any one of claims 43 to 56, wherein the compound of Formula I contains less than 1% (w/w) of the compound of Formula X-5:



(X-5).

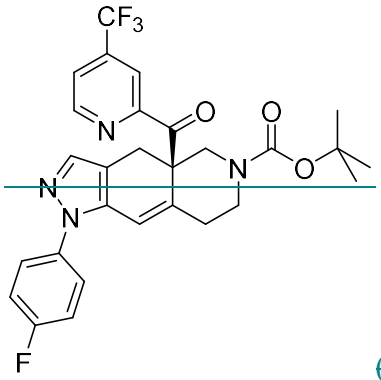
58. A method of preparing a compound of Formula IIb-2:



(IIb-2) ,

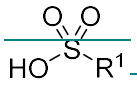
comprising:

(b) forming a fifth reaction mixture comprising a compound of Formula IIa:



(IIa) , and

a sulfonic acid of the formula:



,

to form the compound of Formula IIb-2,

wherein

R^1 is C_{1-6} alkyl, C_{1-10} haloalkyl, phenyl, or 4-methylphenyl; and

subscript n is 1 to 4.

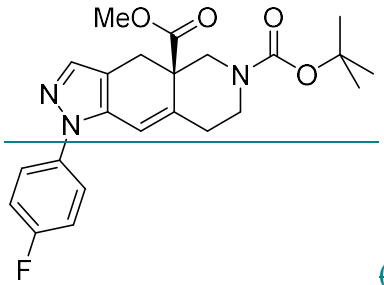
59. The method of claim 58, wherein the fifth reaction mixture further comprises a fifth solvent.

60. The method of claim 59, wherein the fifth solvent comprises acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, dimethylsulfoxide (DMSO), dimethylformamide (DMF), methanol, ethanol, diethyl ether, methyl-t-butyl ether (MTBE), toluene, or combinations thereof.

61. The method of claim 59 or 60, wherein the fifth solvent comprises acetonitrile.

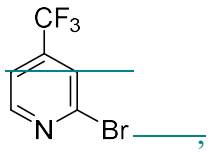
62. The method of any one of claims 58 to 61, wherein the compound of Formula IIa is prepared by the steps of:

(c) forming a sixth reaction mixture comprising a Grignard reagent, a compound of Formula III:



(III), and

2-bromo-4-(trifluoromethyl)pyridine:



,

wherein the pyridine is present in a molar ratio of 2.8 to 3.2 to the compound of Formula III, and wherein the Grignard reagent is present in a molar ratio of 2.8 to 3.3 to the compound of Formula III, to prepare the compound of Formula IIa.

63. The method of claim 62, wherein the Grignard reagent comprises iPrMgCl or iPrMgBr.

64. The method of claim 62 or 63, wherein the Grignard reagent comprises iPrMgCl.

65. The method of any one of claims 62 to 64, wherein the fifth reaction mixture further comprises a fifth solvent comprising tetrahydrofuran, 2-methyltetrahydrofuran, toluene or xylene.

66. The method of claim 65, wherein the fifth solvent comprises tetrahydrofuran and toluene.

67. The method of any one of claims 62 or 66, further comprising:

(c1) adding an acid and water to the sixth reaction mixture to form a workup mixture; and

(c2) distilling the workup mixture to form an intermediate mixture comprising the compound of Formula IIa.

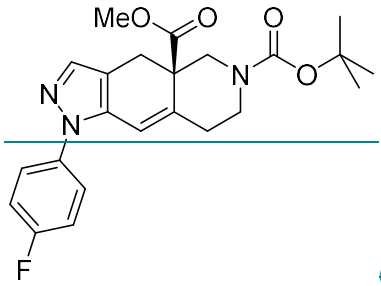
68. The method of claim 67, wherein the acid comprises formic acid, acetic acid, propanoic acid, butyric acid, hexanoic acid, octanoic acid, trifluoroacetic acid, or mixtures thereof.

69. The method of 67 or 68, wherein the acid comprises acetic acid.

70. The method of any one of claims 67 to 69, wherein the fifth reaction mixture further comprises the intermediate mixture comprising the compound of Formula IIa.

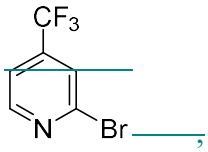
71. The method of any one of claims 62 to 70, comprising the steps of:

(c) forming the sixth reaction mixture comprising tetrahydrofuran, toluene, iPrMgCl, the compound of Formula III:



(III), and

2-bromo-4-(trifluoromethyl)pyridine:

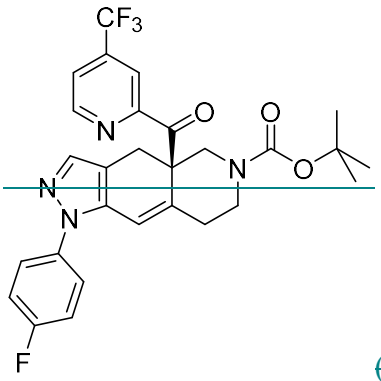


,

wherein the pyridine is present in the molar ratio of about 3.0 to the compound of Formula III, and wherein the Grignard reagent is present in the molar ratio of about 3.05 to the compound of Formula III;

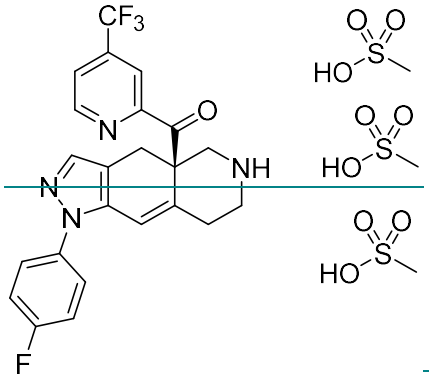
(c1) adding acetic acid and water to the sixth reaction mixture to form the workup mixture;

(c2) distilling the workup mixture to form the intermediate mixture comprising the compound of Formula IIa:



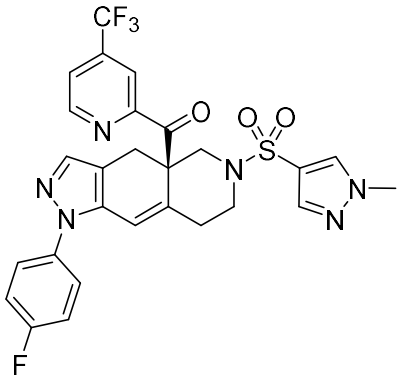
(IIa); and

~~(b) forming the fifth reaction mixture comprising the intermediate mixture, acetonitrile, and methanesulfonic acid, to form the compound of Formula IIb-2:~~



~~(IIb-2)~~ .

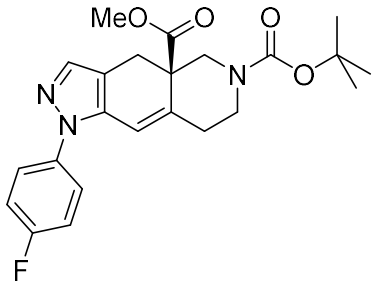
Claim 30~~72~~. A method of preparing a compound of Formula I:



(I)

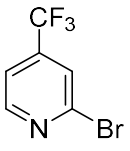
or a pharmaceutically acceptable salt thereof, comprising:

(c) forming a sixth reaction mixture comprising tetrahydrofuran, toluene, iPrMgCl, a compound of Formula III:



(III) , and

2-bromo-4-(trifluoromethyl)pyridine:

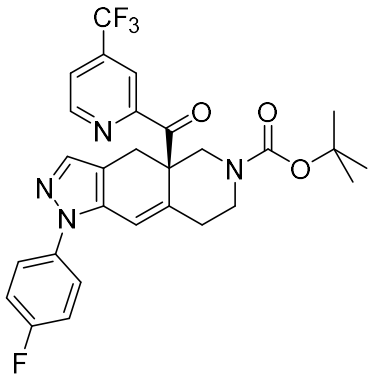


,

wherein the pyridine is present in a molar ratio of about 3.0 to the compound of Formula III, and wherein the Grignard reagent is present in a molar ratio of about 3.05 to the compound of Formula III;

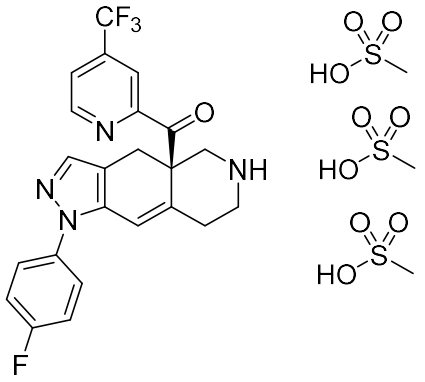
(c1) adding acetic acid and water to the sixth reaction mixture to form a workup mixture;

(c2) distilling the workup mixture to form an intermediate mixture comprising a compound of Formula IIa:



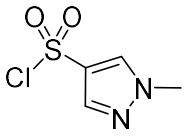
(IIa) ;

(b) forming a fifth reaction mixture comprising the intermediate mixture, acetonitrile, and methanesulfonic acid, to form a compound of Formula IIb-2:



(IIb-2) ;

(a) forming a fourth reaction mixture comprising the compound of Formula IIb-2, triethylamine, ethyl acetate, and 1-methyl-1H-pyrazole-4-sulfonyl chloride:



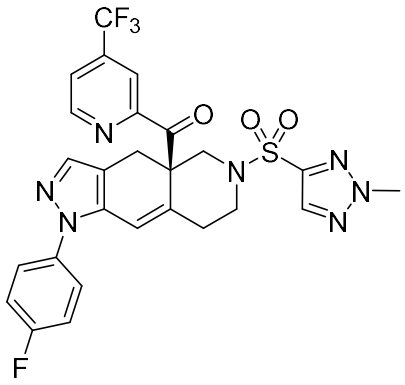
,

wherein the sulfonyl chloride is present in a ratio of about 1.0 to the compound of Formula IIb-2;

(a1) adding methanol to the fourth reaction mixture; and

(a2) adding water to the reaction mixture to precipitate the compound of Formula I in a yield of at least 75% and a purity of at least 98%.

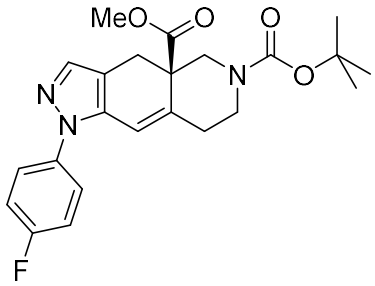
Claim 31~~73~~. A method of preparing a compound of Formula Ia:



(Ia) ,

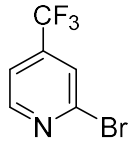
or a pharmaceutically acceptable salt thereof, comprising:

(c) forming a sixth reaction mixture comprising tetrahydrofuran, toluene, iPrMgCl, a compound of Formula III:



(III) , and

2-bromo-4-(trifluoromethyl)pyridine:

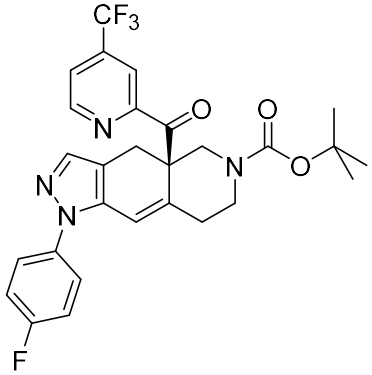


,

wherein the pyridine is present in a molar ratio of about 3.0 to the compound of Formula III, and wherein the Grignard reagent is present in a molar ratio of about 3.05 to the compound of Formula III;

(c1) adding acetic acid and water to the sixth reaction mixture to form a workup mixture;

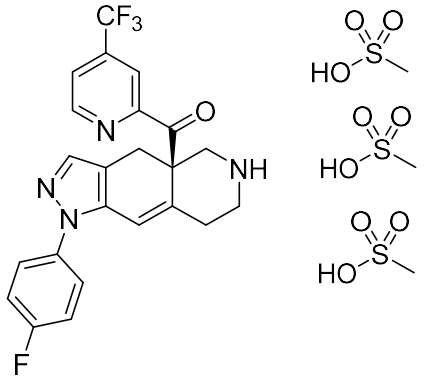
(c2) distilling the workup mixture to form an intermediate mixture comprising a compound of Formula IIa:



(IIa) ;

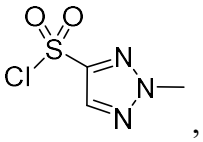
(b) forming a fifth reaction mixture comprising the intermediate mixture,

acetonitrile, and methanesulfonic acid, to form a compound of Formula IIb-2:



(IIb-2) ;

(a) forming a fourth reaction mixture comprising the compound of Formula IIb-2, triethylamine, ethyl acetate, and 2-methyl-2H-1,2,3-triazole-4-sulfonyl chloride:



,

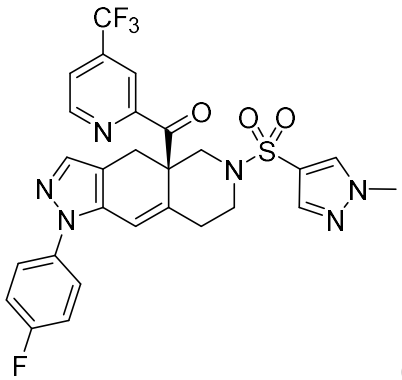
wherein the sulfonyl chloride is present in a ratio of about 1.0 to the compound of Formula IIb-2;

(a1) adding methanol to the fourth reaction mixture; and

(a2) adding water to the reaction mixture to precipitate the compound of Formula Ia in a yield of at least 75% and a purity of at least 98%.

3274. A composition comprising:

a compound of Formula I in an amount of at least 99% (w/w):

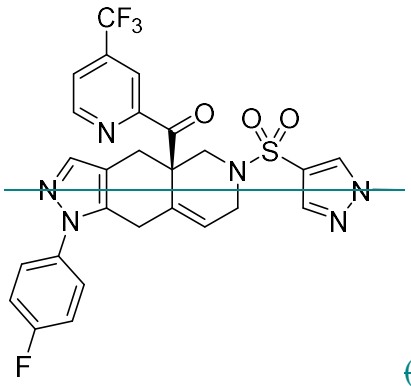


(I) ; and

one or more impurity in an amount of from 0.01 to 1% (w/w).

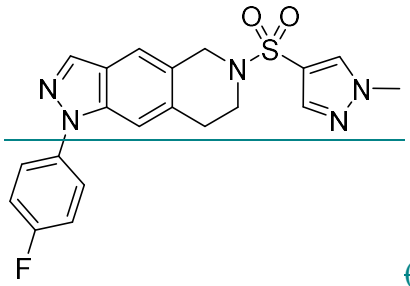
~~75. The composition of claim 74, wherein the impurity includes at least one of:~~

~~a compound of Formula X-4 in an amount of less than 0.5% (w/w):~~



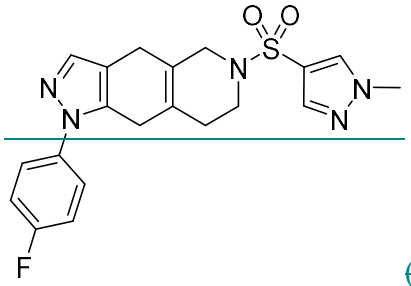
(X-4) ;

a compound of Formula X-5 in an amount of less than 0.2% (w/w):



(X-5) ; and

a compound of Formula X-6 in an amount of less than 0.1% (w/w):



(X-6) .

76. The composition of claim 74 or 75, wherein the impurity comprises:

the compound of Formula X-4 in an amount of less than 0.1% (w/w);

the compound of Formula X-5 in an amount of less than 0.15% (w/w); and

the compound of Formula X-6 in an amount of less than 0.1% (w/w).

77. The composition of any one of claims 74 to 76, wherein the impurity further comprises:

1-methyl-1H-pyrazole-4-sulfonyl chloride in an amount of less than 4 ppm; and

methyl 1-methyl-1H-pyrazole-4-sulfonate in an amount of less than 4ppm.

78. The composition of any one of claims 74 to 76, wherein the impurity further comprises:

1-methyl-1H-pyrazole-4-sulfonyl chloride in an amount of less than 4 ppm;

methyl 1-methyl-1H-pyrazole-4-sulfonate in an amount of less than 4ppm,

ethyl 1-methyl-1H-pyrazole-4-sulfonate in an amount of less than 4 ppm, and

~~isopropyl 1-methyl-1H-pyrazole-4-sulfonate in an amount of less than 4 ppm.~~

~~79. The composition of any one of claims 74 to 78, wherein the impurity further comprises:~~

~~1,4-dibromopentane in an amount of less than 4 ppm.~~

~~80. The composition of any one of claims 74 to 78, wherein the impurity further comprises:~~

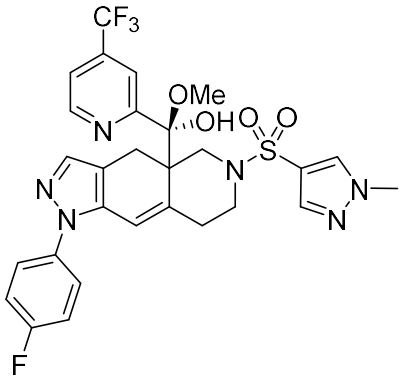
~~methylbromide,~~

~~2-bromopropane, and~~

~~1,4-dibromopentane in an amount of less than 4 ppm.~~

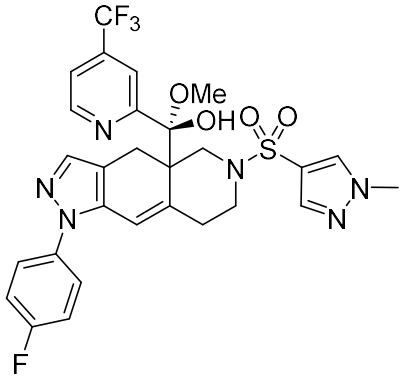
Claim 33~~81~~. The composition of ~~any one of~~ claim~~s~~ 32~~74 to 80~~, wherein the impurity further comprises:

a compound of Formula X-D in an amount of less than 0.40% (w/w)



(X-D); and

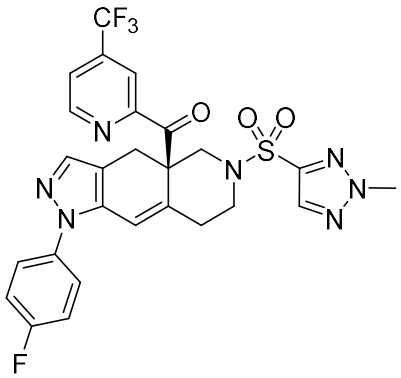
a compound of Formula X-E in an amount of less than 0.40% (w/w)



(X-E).

34~~82~~. A composition comprising:

a compound of Formula Ia in an amount of at least 99% (w/w):

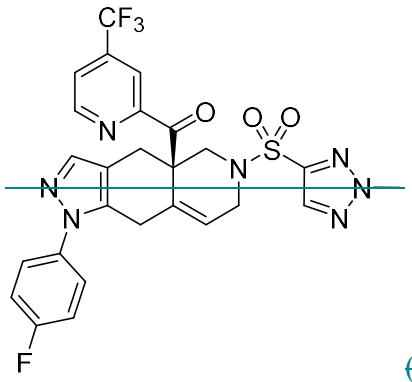


(Ia) ; and

one or more impurity in an amount of from 0.01 to 1% (w/w).

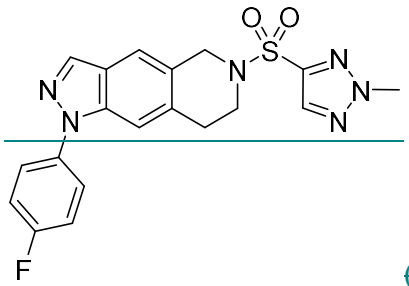
~~83. The composition of claim 82, wherein the impurity includes at least one of:~~

~~a compound of Formula X-4a in an amount of less than 0.5% (w/w):~~



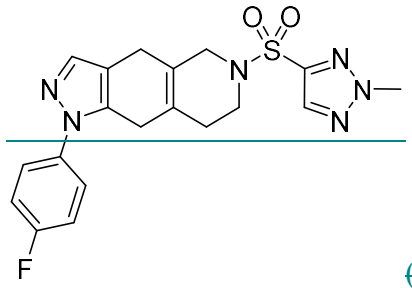
~~(X-4a) ;~~

~~a compound of Formula X-5a in an amount of less than 0.2% (w/w):~~



~~(X-5a) ; and~~

~~a compound of Formula X-6a in an amount of less than 0.1% (w/w):~~



~~(X-6a) .~~

~~84. The composition of claim 82 or 83, wherein the impurity comprises: the compound of Formula X-4a in an amount of less than 0.1% (w/w);~~

~~the compound of Formula X-5a in an amount of less than 0.15% (w/w); and~~

~~the compound of Formula X-6a in an amount of less than 0.1% (w/w).~~

~~85. The composition of any one of claims 82 to 84, wherein the impurity further comprises:~~

~~2-methyl-2H-1,2,3-triazole-4-sulfonyl chloride in an amount of less than 4 ppm;~~

~~methyl 2-methyl-2H-1,2,3-triazole-4-sulfonate in an amount of less than 4ppm;~~

~~ethyl 1-methyl-2H-1,2,3-triazole-4-sulfonate in an amount of less than 4 ppm; and~~

~~isopropyl 1-methyl-2H-1,2,3-triazole-4-sulfonate in an amount of less than 4 ppm.~~

~~86. The composition of any one of claims 82 to 85, wherein the impurity further comprises:~~

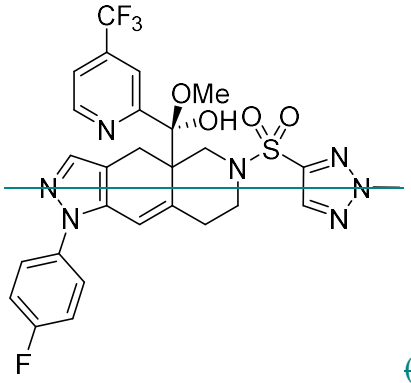
~~methyl bromide in an amount of less than 4 ppm,~~

~~2-bromopropane in an amount of less than 4 ppm, and~~

~~1,4-dibromopentane in an amount of less than 4 ppm.~~

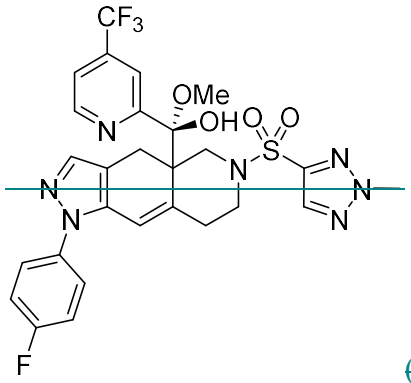
~~87. The composition of any one of claims 82 to 86, wherein the impurity further comprises:~~

~~a compound of Formula X-Da in an amount of less than 0.40% (w/w)~~



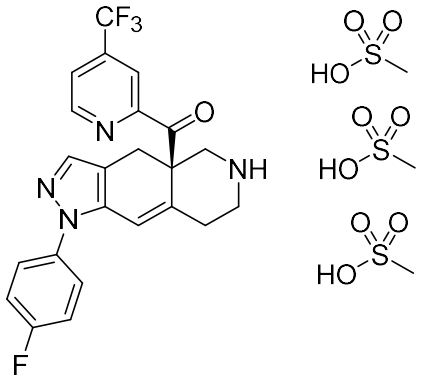
~~(X-Da) ; and~~

~~a compound of Formula X-Ea in an amount of less than 0.40% (w/w)~~



~~(X-Ea) .~~

Claim 3588. A crystalline form of (R)-(1-(4-fluorophenyl)-1,4,5,6,7,8-hexahydro-4aH-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone tris-methanesulfonic acid:



,

characterized by an X-ray powder diffraction (XRPD pattern having peaks at about 18.2°, 18.3°, and 19.7° 2-θ ± 0.2° 2-θ.

~~89. The crystalline form of claim 88, wherein the XRPD further comprises peaks at about 9.9°, 16.5°, and 17.6° 2-θ ± 0.2° 2-θ.~~

~~90. The crystalline form of claim 89, wherein the XRPD further comprises peaks at about 5.0°, 14.5°, 17.9°, 19.0°, 20.8°, 22.9°, 23.4°, and 25.3° 2-θ ± 0.2° 2-θ.~~

~~91. The crystalline form of claim 90, wherein the XRPD comprises peaks at about 5.0°, 9.9°, 14.5°, 16.5°, 17.6°, 17.9°, 18.2°, 18.3°, 19.0°, 19.7°, 20.8°, 22.9°, 23.4°, and 25.3° 2-θ ± 0.2° 2-θ.~~

~~92. The crystalline form of any one of claims 88 to 91, characterized by the XRPD pattern substantially as set forth in FIG. 2.~~

~~93. The crystalline form of any one of claims 88 to 92, characterized by a differential scanning calorimetry (DSC) thermogram having an endotherm with an onset of about 167°.~~

~~94. The crystalline form of claim 93, characterized by a DSC thermogram substantially as shown in FIG. 3.~~

Claim 3695. A pharmaceutical composition comprising a composition of any one of claims 3274 to 3381, and one or more pharmaceutically acceptable excipients.

~~96. The pharmaceutical composition of claim 95, further comprising one or more additional therapeutic agents.~~

Claim 37~~97~~. ~~A method of treating a disorder or condition through modulating a glucocorticoid receptor, comprising administering to a subject in need of such treatment, a therapeutically effective amount~~ Use of a composition of any one of claims 32~~74~~ to 33~~81~~, or a crystalline form according to claim 35 in the preparation of a medicament for treating a disorder or condition through modulating a glucocorticoid receptor.~~pharmaceutical composition of claims 95 or 96, thereby treating the disorder or condition.~~

Claim 38~~98~~. Use of a composition of any one of claims 32 to 33, or a crystalline form according to claim 35 in the preparation of a medicament for ~~A method of~~ treating a disorder or condition through antagonizing a glucocorticoid receptor~~, comprising administering to a subject in need of such treatment, a therapeutically effective amount of a composition of any one of claims 74 to 81, or a pharmaceutical composition of claims 95 or 96, thereby treating the disorder or condition.~~.

Claim 39~~99~~. Use of a composition of any one of claims 32 to 33, or a crystalline form according to claim 35 in the preparation of a medicament for ~~A method of~~ treating fatty liver disease~~, comprising administering to a subject in need thereof, a therapeutically effective amount of a composition of any one of claims 74 to 81, or a pharmaceutical composition of claims 95 or 96, thereby treating fatty liver disease~~.

~~100. The method of claim 99, wherein the fatty liver disease is alcohol related liver disease (ARLD) or nonalcoholic fatty liver disease (NAFLD).~~

~~101. The method of claim 100, wherein the alcohol related liver disease is alcohol fatty liver disease (AFL), alcoholic steatohepatitis (ASH) or alcoholic cirrhosis.~~

~~102. The method of claims 99 or 100, wherein the nonalcoholic fatty liver disease is nonalcoholic steatohepatitis (NASH) or nonalcoholic cirrhosis.~~

~~103. The method of claim 102, wherein the nonalcoholic fatty liver disease is nonalcoholic steatohepatitis.~~

Claim 40~~104~~. Use of a composition of any one of claims 32 to 33, or a crystalline form according to claim 35 in the preparation of a medicament for ~~A method of~~ treating antipsychotic induced weight gain~~, .~~ ~~comprising administering to a subject in need thereof, a therapeutically effective amount of the crystalline form of any one of claims 74 to 81, or a pharmaceutical composition of claims 95 or 96, thereby treating antipsychotic induced weight gain.~~