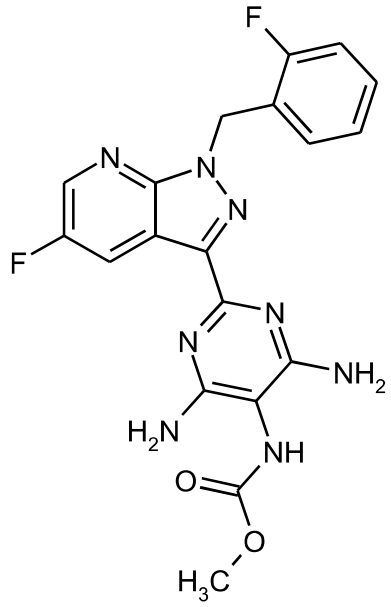
Claims

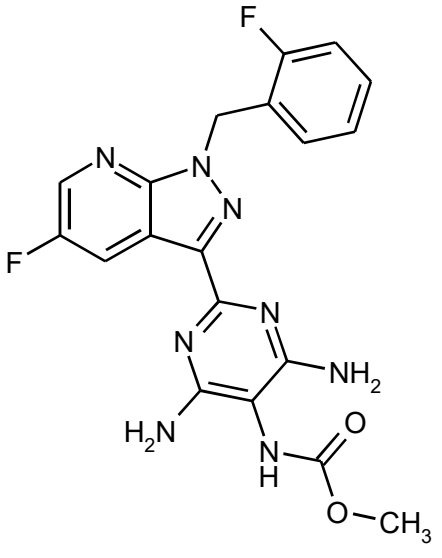
1. Process for preparing methyl {4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}carbamate of the formula (I)



(I),

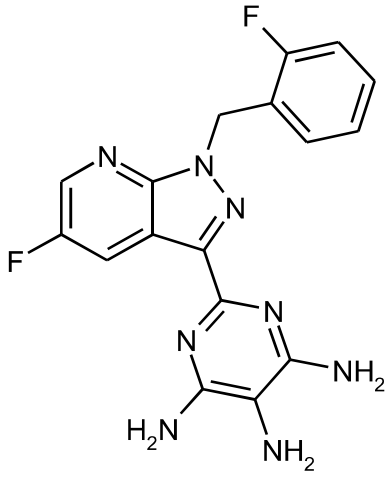
in the crystalline form of modification I, wherein the x-ray diffractogram of the compound of the formula (I) in modification I exhibits peak maxima of the 2 theta angle at 5.9, 6.9, 22.7,

wherein the hydrochloride of the compound of the formula (I)



x HCl (I),

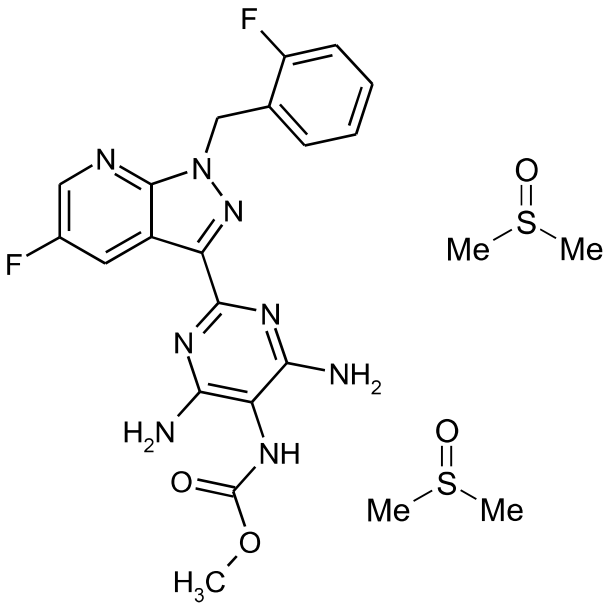
is prepared by heating the compound of the formula (IX)



(IX)

in tetrahydrofuran as solvent, adding 1.0 eq. to 1.2 eq. methyl chloroformate, stirring within a reaction time of 1h to 10h, and isolating the hydrochloride of the compound of the formula (I),

subsequently the di-DMSO solvate of the compound of the formula (I)



(I), di-DMSO solvate

is prepared by dissolving the hydrochloride of the compound of the formula (I) in DMSO, adding tri-n-butylamine and activated carbon, removing the activated carbon, crystallising the di-DMSO solvate by cooling and adding ethyl acetate, isolating the di-DMSO in crystallized form, and washing with a mixture of DMSO and ethyl acetate,

subsequently the compound of the formula (I) in the crystalline form of modification I is prepared, wherein

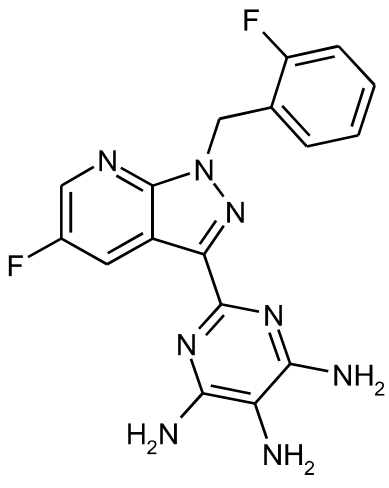
1.1 the di-DMSO solvate of the compound of the formula (I) is dissolved in DMSO, and ethanol is added in a ratio of DMSO to ethanol of 2:1 to 6:1 w/w,

1.2 the dissolved compound of the formula (I) is subsequently crystallized out of the solution by addition of water;

1.3 the suspension formed is subsequently cooled to a temperature of 5°C to 50°C and

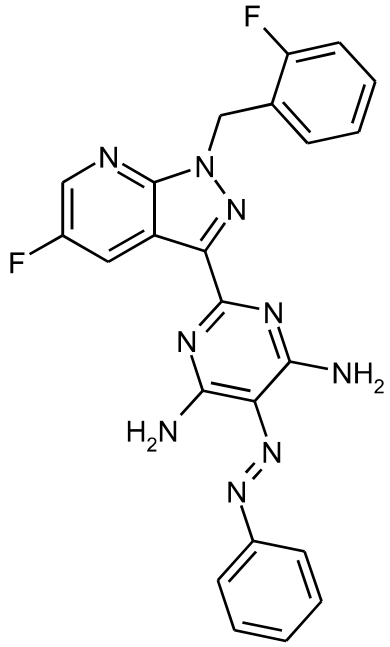
1.4 the crystals formed in step 1.2 are subsequently agglomerated to afford active compound product by addition of isopropyl acetate, wherein the ratio of the mass of isopropyl acetate to the sum of the mass of the compound of the formula (I) plus the mass of ethanol is 0.3 to 2.0.

2. Process according to claim 1, wherein the compound of the formula (IX)



(IX)

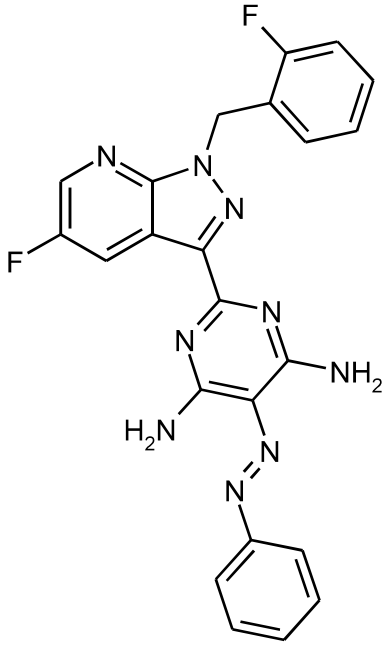
is prepared by hydrogenating the compound of the formula (VIII)



(VIII),

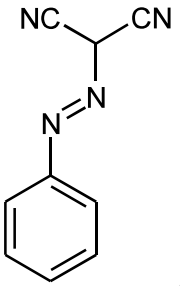
in NMP as solvent in the presence of hydrogen, catalysed by a catalyst selected from the group consisting of palladium on activated carbon, platinum on carbon, palladium hydroxide and Raney nickel, crystallizing by addition of water, and isolating to give the compound of the formula (IX).

3. Process according to claim 2, wherein the compound of the formula (VIII)



(VIII),

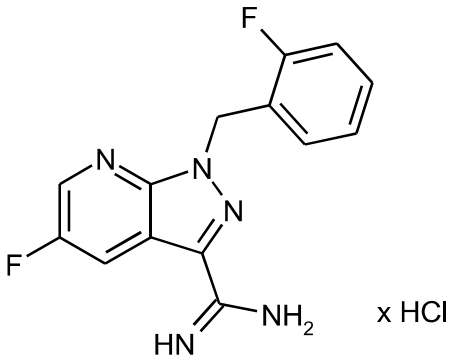
is prepared by initially preparing the compound of the formula (VIIIa)



(VIIIa)

by adding conc. hydrochloric acid in water to aniline in water, then sequentially adding a solution of sodium nitrite in water, a solution of sodium acetate in water, and a solution of malononitrile in ethanol, isolating the solids, and washing with water and isopropanol to obtain the compound of the formula (VIIIa);

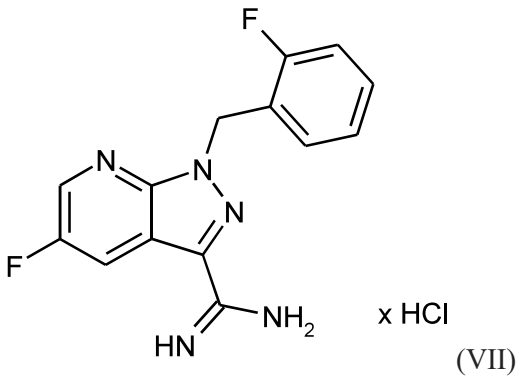
subsequently heating the compound of the formula (VII)



(VII)

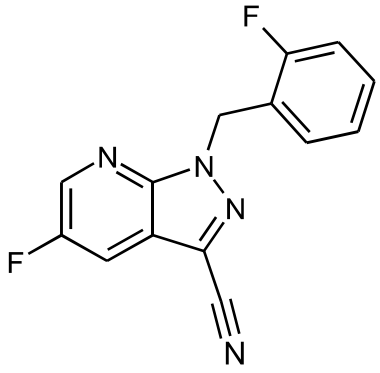
in DMF, adding the compound of the formula (VIIIa), dissolved in DMF, and 1.2 eq. to 1.7 eq. triethylamine, related to the compound of the formula (VII), adding methanol and isolating the compound of the formula (VIII).

4. Process according to claim 3, wherein the compound of the formula (VII)



(VII)

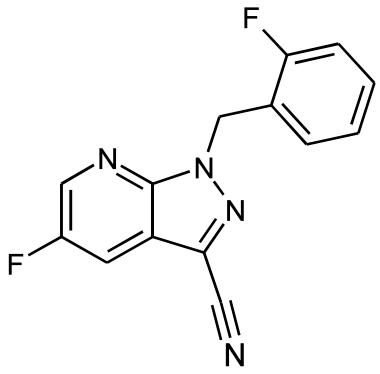
is prepared by suspending the compound of the formula (VI)



(VI)

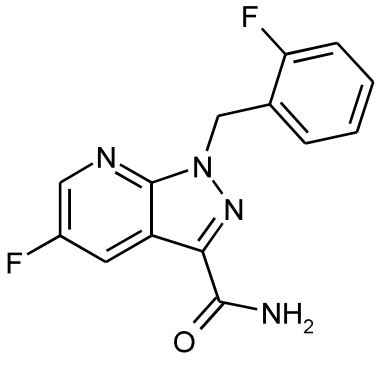
in methanol, adding sodium methoxide in methanol, adding methanol and ammonium chloride, filtering using a filter aid, concentrating and adding ethyl acetate, adding ethanol, and isolating, to obtain the compound of the formula (VII).

5. Process according to claim 4, wherein the compound of the formula (VI)



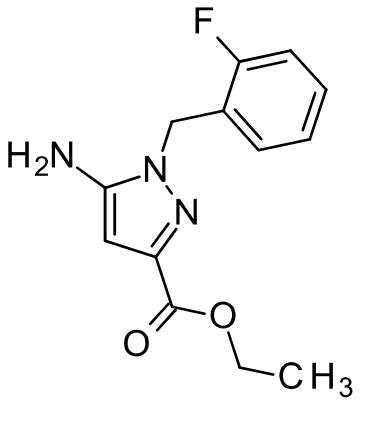
(VI)

is prepared by first preparing the compound of the formula (V)



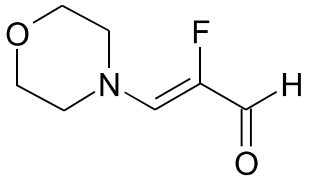
(V)

by initially charging the compound of the formula (II)



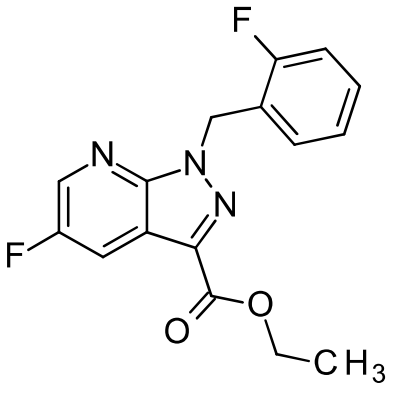
(II)

and lithium chloride in ethanol, charging the compound of the formula (III),



(III),

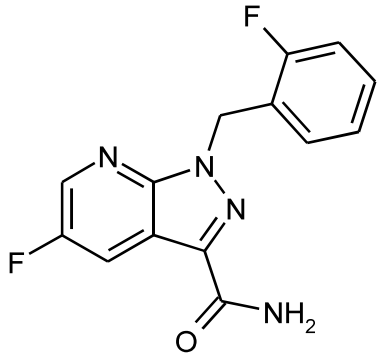
and chlorotrimethylsilane, and heating to give the compound of the formula (IV)



(IV),

or alternatively changing the order of charging of any of the input materials,

adding formamide and sodium methoxide in methanol, distilling off low boilers, while refilling the distilled off volume with formamide, cooling, adding water, isolating the solids, washing and drying to give the compound of the formula (V),

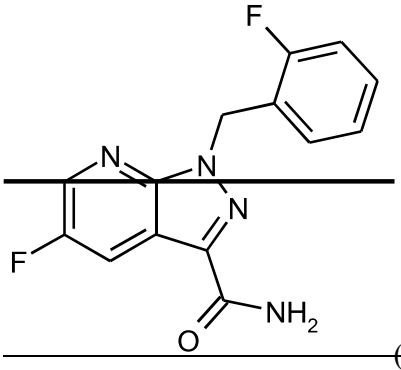


(V)

subsequently dehydrating the compound of the formula (V) by heating in sulfolane, acetonitrile, and phosphoryl chloride, adding acetonitrile and water under appropriate agitation and at a good pace and under cooling, keeping an internal temperature of 20°C to 50°C, adding ammonia in water, and isolating to give the compound of the formula (VI).

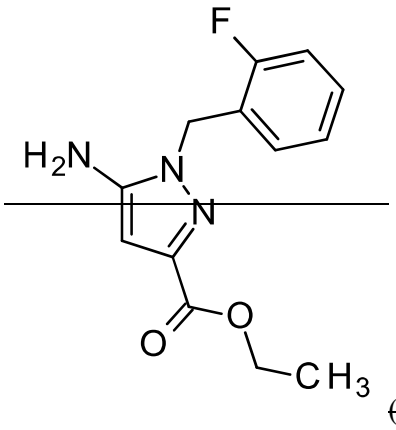
6. Process according to any of claims 1 to 5, wherein the compound of the formula (I) in the crystalline form of modification I is obtained in a purity of 99.90% (as measured by HPLC area%) or more.

~~7. Process for preparing the compound of the formula (V)~~



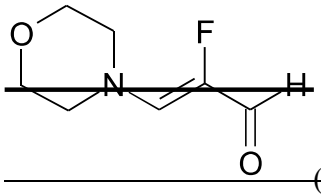
~~(V)~~

~~wherein the compound of the formula (II)~~



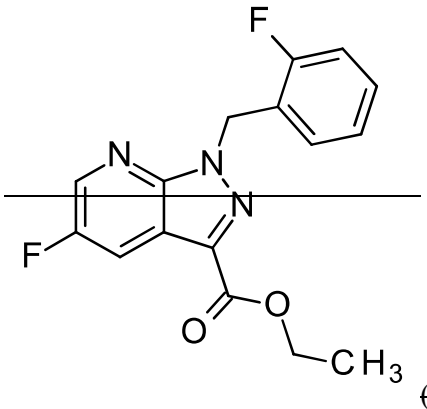
(II)

and lithium chloride are initially charged in ethanol, charging the compound of the formula (III),



(III),

and chlorotrimethylsilane, and heating to give the compound of the formula (IV)

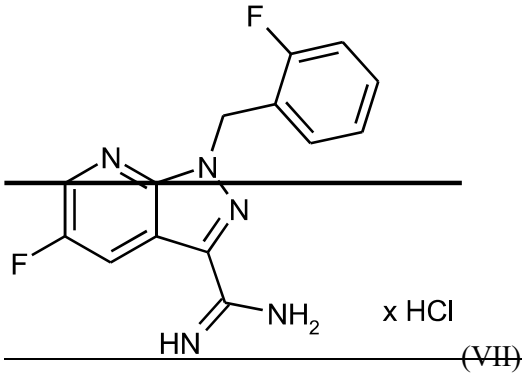


(IV),

or alternatively changing the order of charging of any of the input materials,

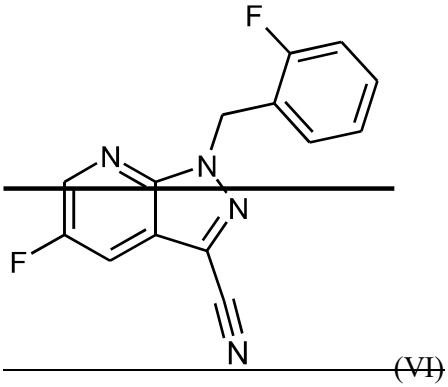
adding formamide and sodium methoxide in methanol, distilling off low boilers, while refilling the distilled off volume with formamide, cooling, adding water, isolating the solids, washing and drying to give the compound of the formula (V).

8. Process for preparing the compound of the formula (VII)



~~(VII)~~

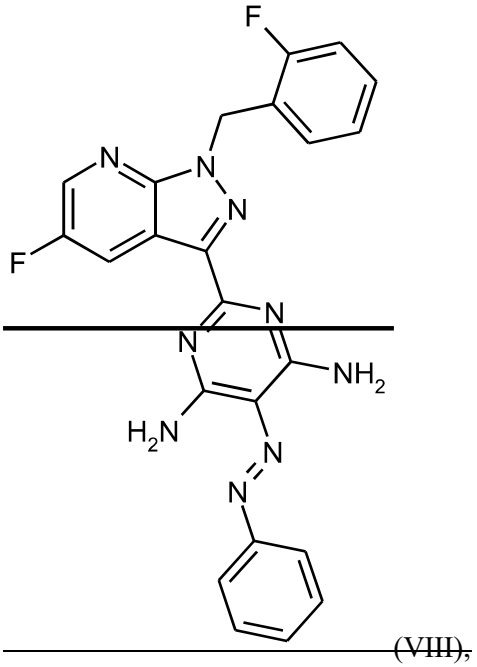
~~wherein the compound of the formula (VI)~~



~~(VI)~~

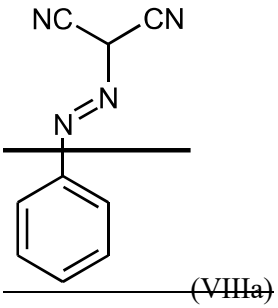
~~is suspended in methanol, adding sodium methoxide in methanol, adding methanol and ammonium chloride, filtering using a filter aid, concentrating and adding ethyl acetate, adding ethanol, and isolating to obtain the compound of the formula (VII).~~

~~9. Process for preparing the compound of the formula (VIII)~~



~~(VIII),~~

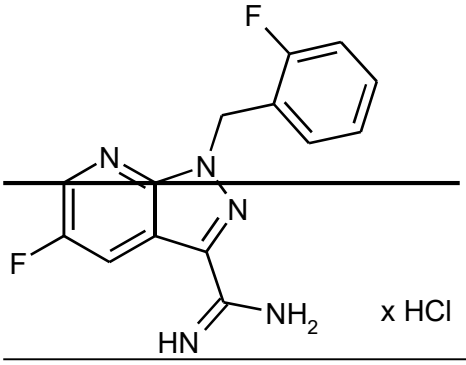
~~wherein the compound of the formula (VIIIa)~~



~~(VIIIa)~~

~~is initially prepared by adding conc. hydrochloric acid in water to aniline in water, then sequentially adding a solution of sodium nitrite in water, a solution of sodium acetate in water, and a solution of malononitrile in ethanol, isolating the solids, and washing with water and isopropanol to obtain the compound of the formula (VIIIa);~~

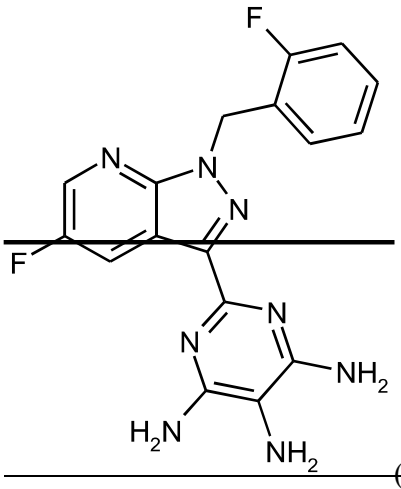
~~subsequently heating the compound of the formula (VII)~~



~~(VII)~~

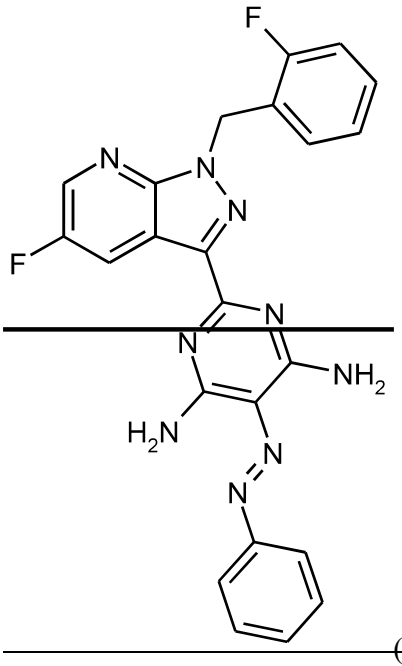
~~in DMF, adding the compound of the formula (VIIIa), dissolved in DMF and 1.2 eq. to 1.7 eq. triethylamine, related to the compound of the formula (VII), , adding methanol and isolating the compound of the formula (VIII).~~

~~10. Process for preparing the compound of the formula (IX)~~



~~(IX),~~

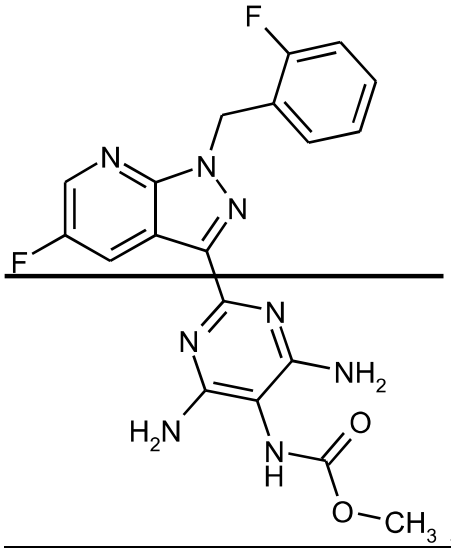
~~wherein the compound of the formula (VIII)~~



~~(VIII),~~

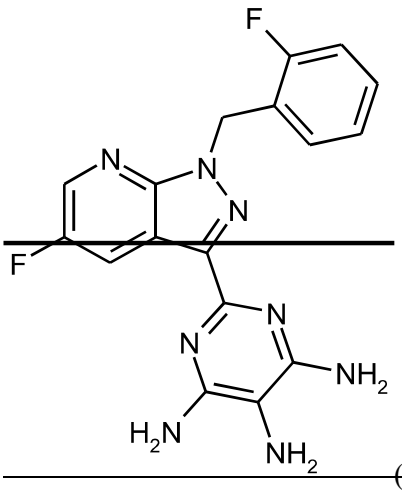
~~is hydrogenated in NMP as solvent in the presence of hydrogen, catalysed by a catalyst selected from palladium on activated carbon, platinum on carbon, palladium hydroxide and Raney nickel, crystallizating by addition of water, and isolating to give the compound of the formula (IX).~~

~~11. Process for preparing the hydrochloride of the compound of the formula (I)~~



x HCl (I),

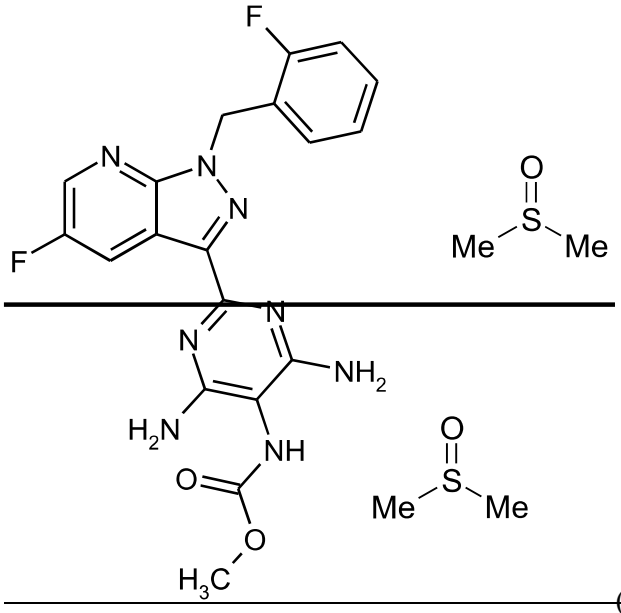
wherein the compound of the formula (IX)



(IX)

is heated in tetrahydrofuran as solvent, adding 1.0 eq. to 1.2 eq. methyl chloroformate stirring within a reaction time of 1h to 10h, isolating the hydrochloride of the compound of the formula (I).

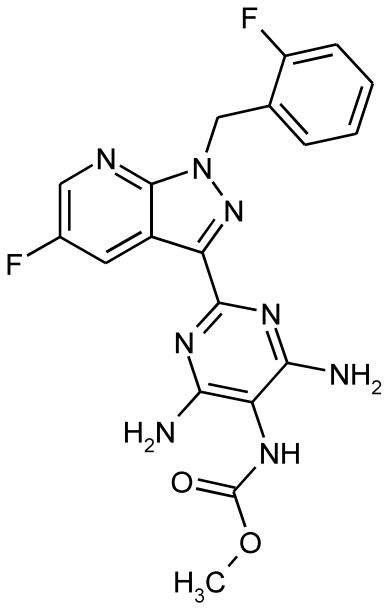
12. Process for preparing the di-dimethylsulfoxide solvate of the compound of the formula (I),



~~(I), di-DMSO solvate~~

~~wherein the hydrochloride of the compound of the formula (I) is is dissolved in DMSO, adding tri-n-butylamine and activated carbon, crystallising the di-DMSO solvate by cooling and adding ethyl acetate, isolating the di-DMSO in crystallized form, and washing with a mixture of DMSO and ethyl acetate.~~

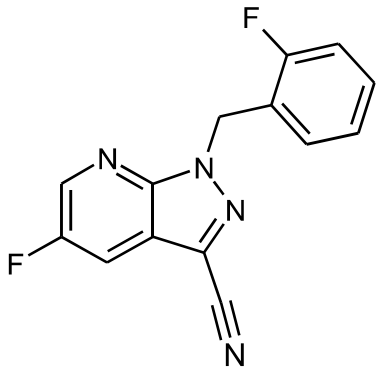
~~13.~~7. Process for preparing methyl {4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}carbamate of the formula (I) in the crystalline form of modification I according to claim 1



(I),

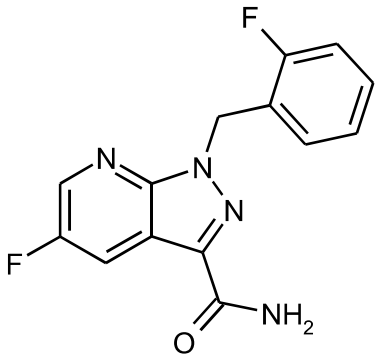
wherein the x-ray diffractogram of the compound of the formula (I) in modification I exhibits peak maxima of the 2 theta angle at 5.9, 6.9, 22.7 and

wherein the compound of the formula (VI)



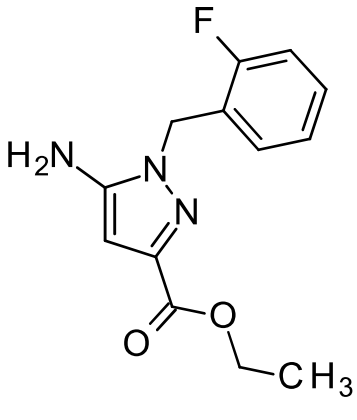
(VI)

is prepared by first preparing the compound of the formula (V)



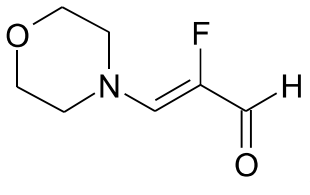
(V)

by initially charging the compound of the formula (II)



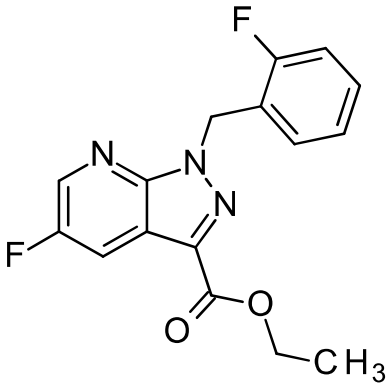
(II)

and lithium chloride in ethanol, charging the compound of the formula (III),



(III),

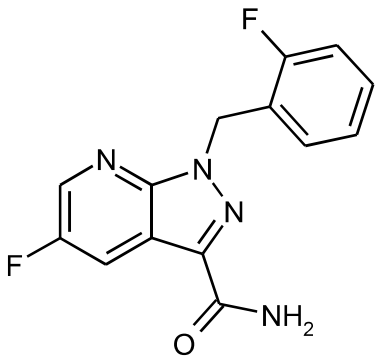
and chlorotrimethylsilane, and heating to give the compound of the formula (IV)



(IV),

or alternatively changing the order of charging of any of the input materials,

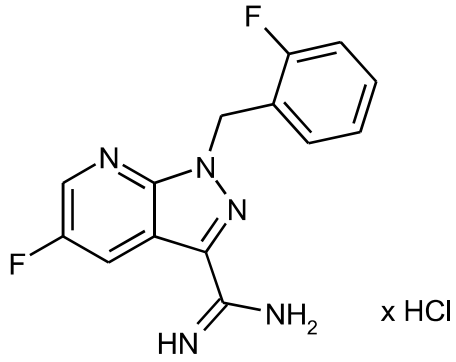
adding formamide and sodium methoxide in methanol, distilling off low boilers, while refilling the distilled off volume with formamide, cooling, adding water, isolating the solids, washing and drying to give the compound of the formula (V),



(V)

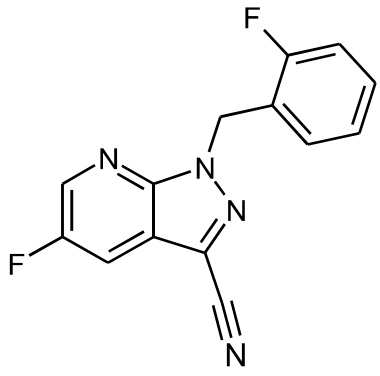
subsequently dehydrating the compound of the formula (V) by heating in sulfolane, acetonitrile, and phosphoryl chloride, adding acetonitrile and water under appropriate agitation and at a good pace and under cooling, keeping an internal temperature of 20°C to 50°C, adding ammonia in water, and isolating to give the compound of the formula (VI);

subsequently, the compound of the formula (VII)



(VII)

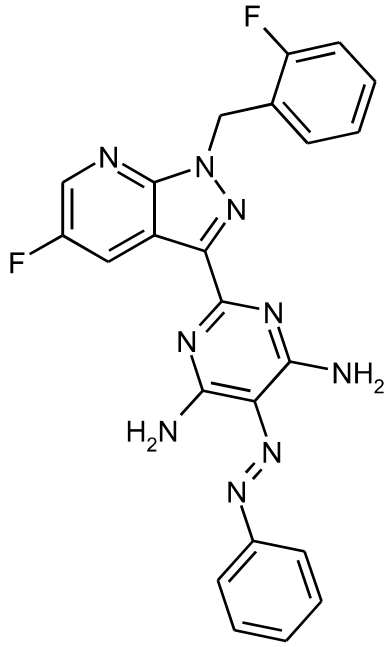
is prepared by suspending the compound of the formula (VI)



(VI)

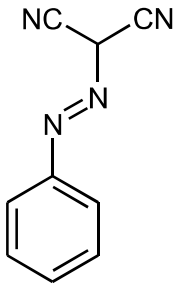
in methanol, adding sodium methoxide in methanol, adding methanol and ammonium chloride, filtering using a filter aid, concentrating and adding ethyl acetate, adding ethanol, and isolating to obtain the compound of the formula (VII);

subsequently, the compound of the formula (VIII)



(VIII),

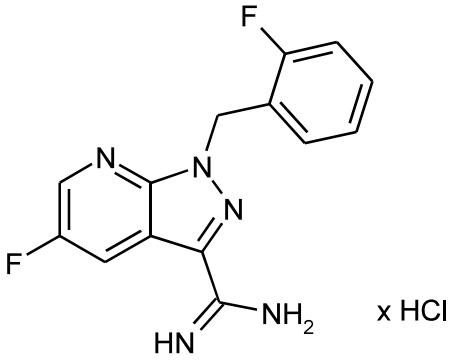
is prepared by initially preparing the compound of the formula (VIIIa)



(VIIIa)

by adding conc. hydrochloric acid in water to aniline in water, then sequentially adding a solution of sodium nitrite in water, a solution of sodium acetate in water, and a solution of malononitrile in ethanol, isolating the solids, and washing with water and isopropanol to obtain the compound of the formula (VIIIa);

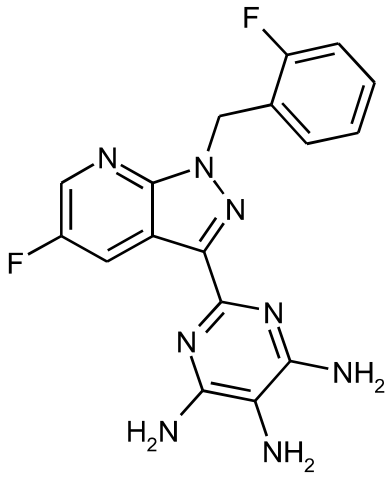
subsequently heating the compound of the formula (VII)



(VII)

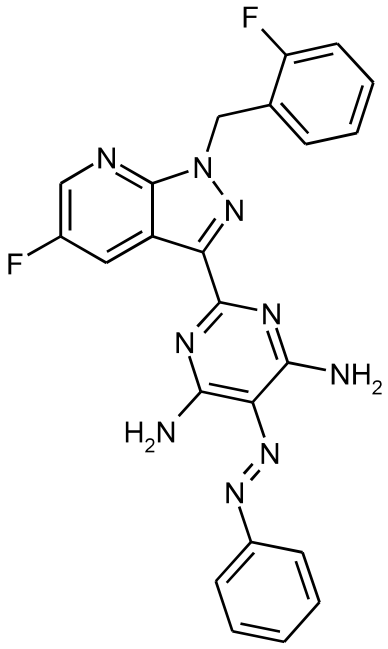
in DMF, adding the compound of the formula (VIIIa), dissolved in DMF and 1.2 eq. to 1.7 eq. triethylamine, related to the compound of the formula (VII), adding methanol and isolating the compound of the formula (VIII);

subsequently, the compound of the formula (IX)



(IX)

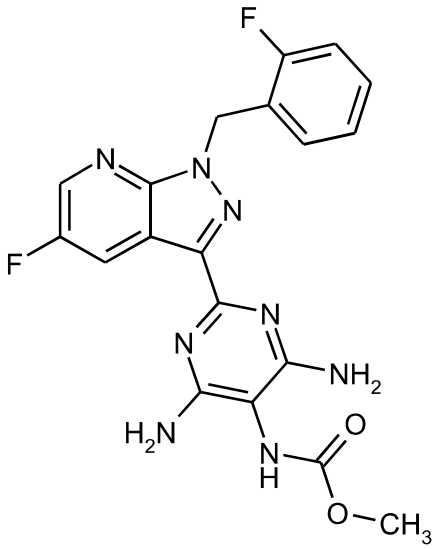
is prepared by hydrogenating the compound of the formula (VIII)



(VIII),

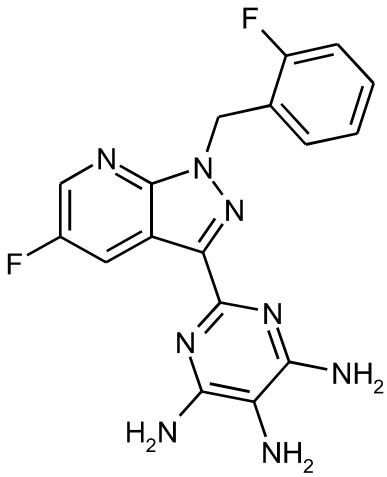
in NMP as solvent in the presence of hydrogen, catalysed by a catalyst selected from the group consisting of palladium on activated carbon, platinum on carbon, palladium hydroxide and Raney nickel, crystallizing by addition of water, and isolating to give the compound of the formula (IX);

subsequently, the hydrochloride of the compound of the formula (I)



x HCl (I),

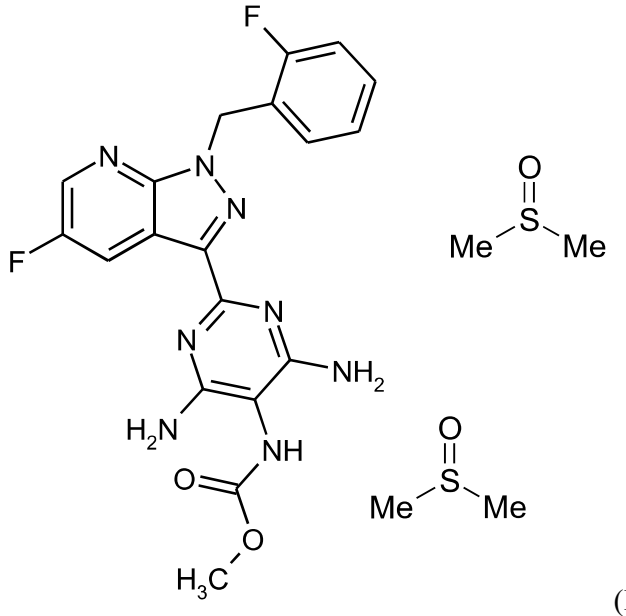
is prepared by heating the compound of the formula (IX)



(IX)

in tetrahydrofuran as solvent adding 1.0 eq. to 1.2 eq. methyl chloroformate, stirring within a reaction time of 1h to 10h, and isolating the hydrochloride of the compound of the formula (I),

subsequently the di-DMSO solvate of the compound of the formula (I)



(I), di-DMSO solvate

is prepared by dissolving the hydrochloride of the compound of the formula (I) in DMSO, adding tri-n-butylamine and activated carbon, removing the activated carbon, cooling and adding ethyl acetate, isolating the di-DMSO in crystallized form, washing with a mixture of DMSO and ethyl acetate,

finally the compound of the formula (I) in the crystalline form of modification I is prepared, wherein

1.1 the di-DMSO solvate of the compound of the formula (I) is dissolved in DMSO and ethanol in a ratio of DMSO to ethanol of 2:1 to 6:1 w/w,

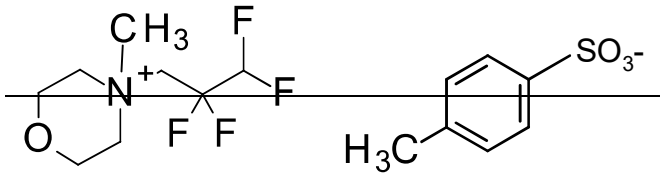
1.2 the dissolved compound of the formula (I) is subsequently crystallized out of the solution by addition of water;

1.3 the suspension formed is subsequently cooled to a temperature of 5°C to 50°C and

1.4 the crystals formed in step 1.2 are subsequently agglomerated to afford active compound product by addition of isopropyl acetate, wherein the ratio of the mass of isopropyl acetate to the sum of the mass of the compound of the formula (I) plus the mass of ethanol is 0.3 to 2.0.

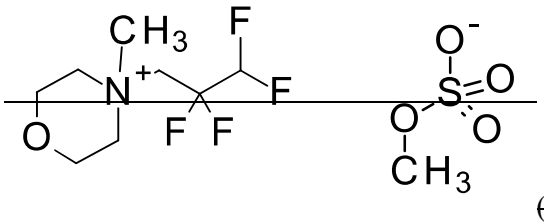
~~14.~~8. Process according to claim ~~13~~7, wherein the compound of the formula (I) in the crystalline form of modification I is obtained in a purity of 99.90% (as measured by HPLC area%) or more.

~~15. Compound selected from the group consisting of the compound of the formula (X)~~



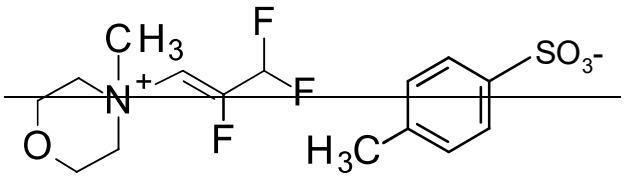
~~(X),~~

~~the compound of the formula (XI)~~



~~(XI), and~~

~~the compound of the formula (XII)~~



~~(XII).~~