CLAIMS

1. A process for preparing N-(5-(4-(4-((dimethylamino)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide or a pharmaceutically acceptable salt thereof, the process comprising

(a) reacting N-(5-(4-(4-formyl-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide with dimethylamine or an acid addition salt thereof in the presences of a reducing agent and a base to form N-(5-(4-(4-((dimethylamino)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide; and

(b) isolating the N-(5-(4-(4-((dimethylamino)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide from the reaction mixture of Step (a).

2. The process according to claim 1, wherein the reducing agent is one or more selected from the group consisting of sodium triacetoxyborohydride, sodium cyanoborohydride, and sodium borohydride.

3. The process according to claim 1, wherein the reducing agent is used in a ratio ranging from 1 to 5 equivalent(s) per 1 equivalent of N-(5-(4-(4-formyl-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide.

4. The process according to claim 1, wherein the base is one or more selected from the group consisting of sodium carbonate, sodium bicarbonate, potassium carbonate, potassium phosphate, sodium phosphate, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,4-diazabicyclo[2.2.2]octane, 1,5-diazabicyclo[4.3.0]non-5-ene, pyridine, triethylamine, diisopropylamine and diisopropylethylamine.

5. The process according to claim 1, wherein the reacting of Step (a) is carried out in the one or more solvent(s) selected from the group consisting of dimethylacetamide, dimethylformamide, dichloromethane, tetrahydrofuran, acetonitrile and ethyl acetate.

6. The process according to claim 1, wherein the isolating of Step (b) is carried out by crystallization through adding an antisolvent to the reaction mixture of Step (a).

7. The process according to claim 6, wherein the antisolvent is C_1~C_5 alcohol, water, or a mixture thereof.

8. The process according to claim 1, wherein the N-(5-(4-(4-formyl-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide is obtained by reacting N-(5-formamido-4-methoxy-2-morpholinophenyl)acrylamide with 1-(2-(methylsulfonyl)pyrimidin-4-yl)-3-phenyl-1H-pyrazole-4-carbaldehyde.

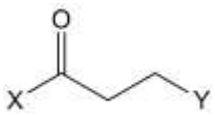
9. The process according to claim 8, wherein the reacting is carried out in the presence of one or more base(s) selected from the group consisting of sodium hydride, sodium C_1~C_6 alkoxide, potassium C_1~C_6 alkoxide, sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate, sodium bicarbonate, potassium bicarbonate, potassium phosphate, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,4-diazabicyclo[2.2.2]octane, 1,5-diazabicyclo[4.3.0]non-5-ene, pyridine, dimethylaminopyridine, and triethylamine.

10. The process according to claim 8, wherein the N-(5-formamido-4-methoxy-2-morpholinophenyl)acrylamide is obtained by a process comprising

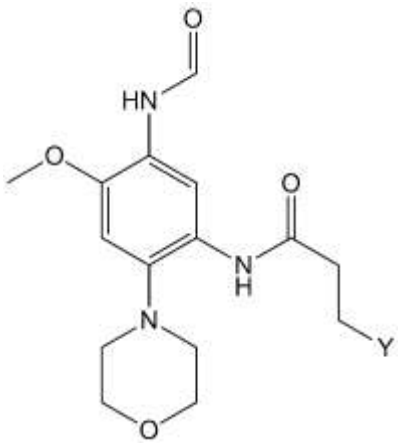
(i) reacting N-(5-amino-2-methoxy-4-morpholinophenyl)formamide with a compound of Formula 14 to form a compound of Formula 5; and

(ii) reacting the compound of Formula 5 with a base to obtain N-(5-formamido-4-methoxy-2-morpholinophenyl)acrylamide:

<Formula 14>



<Formula 5>



wherein, X and Y are, independently of each other, halogen.

11. The process according to claim 10, wherein Step (i) and Step (ii) are carried out in a one-pot reaction without isolating the compound of Formula 5.

12. The process according to claim 10, wherein the reacting of Step (i) is carried out in the presence of one or more base(s) selected from the group consisting of potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium hydride, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium phosphate, sodium phosphate, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,4-diazabicyclo[2.2.2]octane, 1,5-diazabicyclo[4.3.0]non-5-ene, pyridine, triethylamine, diisopropylamine and diisopropylethylamine.

13. The process according to claim 10, wherein the base used in Step (ii) is one or more selected from the group consisting of potassium tert-butoxide, sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium hydride, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium phosphate, sodium phosphate, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,4-diazabicyclo[2.2.2]octane, 1,5-diazabicyclo[4.3.0]non-5-ene, pyridine, triethylamine, diisopropylamine and diisopropylethylamine.

14. The process according to claim 10, wherein the N-(5-amino-2-methoxy-4-morpholinophenyl)formamide is obtained by performing a reduction of N-(2-methoxy-4-morpholino-5-nitrophenyl)formamide.

15. The process according to claim 14, wherein the reduction is carried out with a reducing agent selected from the group consisting of formic acid and ammonium formate.

16. The process according to claim 14, wherein the reduction is carried out in the presence of a catalyst selected from the group consisting of palladium, palladium/carbon, zinc, copper, magnesium, and platinum.

17. The process according to claim 14, wherein the N-(2-methoxy-4-morpholino-5-nitrophenyl)formamide is obtained by performing a formylation of 2-methoxy-4-morpholino-5-nitroaniline.

18. The process according to claim 17, wherein the formylation is carried out with a mixture of acetic acid and formic acid.

19. The process according to claim 8, wherein the 1-(2-(methylsulfonyl)pyrimidin-4-yl)-3-phenyl-1H-pyrazole-4-carbaldehyde is obtained by reacting 1-(2-(methylthio)pyrimidin-4-yl)-3-phenyl-1H-pyrazole-4-carbaldehyde with an oxidizing agent.

20. The process according to claim 19, wherein the oxidizing agent is one or more selected from the group consisting of potassium permanganate, chromic acid, oxygen, hydrogen peroxide and 3-chloroperbenzoic acid.

21. The process according to claim 19, wherein the reacting is carried out in the presence of one or more solvent(s) selected from the group consisting of C_1~C_5 alcohol, carbon tetrachloride, chloroform, dichloromethane, acetone, methyl ethyl ketone, methyl isobutyl ketone, cyclohexanone, pentane, hexane, heptane, octane, nonane, decane, undecane, dodecane, cyclohexane, petroleum ether, kerosene, toluene, xylene, mesitylene and benzene.

22. The process according to claim 19, wherein the 1-(2-(methylthio)pyrimidin-4-yl)-3-phenyl-1H-pyrazole-4-carbaldehyde is obtained by reacting 4-chloro-2-(methylthio)pyrimidine with 3-phenyl-1H-pyrazole-4-carbaldehyde.

23. The process according to claim 22, wherein the reacting is carried out in the presence of one or more base(s) selected from the group consisting of potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium hydride, sodium carbonate, potassium carbonate,

potassium phosphate, sodium phosphate, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,4-diazabicyclo[2.2.2]octane, 1,5-diazabicyclo[4.3.0]non-5-ene, pyridine, triethylamine, diisopropylamine and diisopropylethylamine.

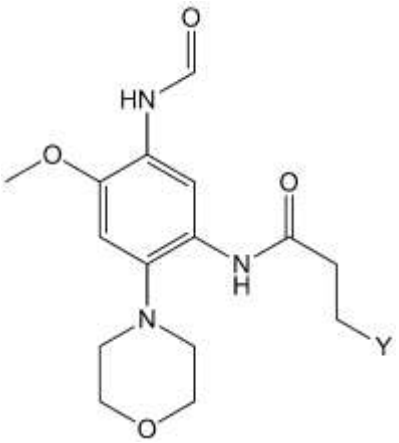
24. The process according to claim 22, wherein the reacting is carried out in the presence of one or more solvent(s) selected from the group consisting of dichloromethane, dichloroethane, dimethylformamide, dimethylacetamide, dimethyl sulfoxide, tetrahydrofuran, C_1~C_5 alcohol, ethyl acetate, acetone, methyl ethyl ketone, acetonitrile and toluene.

25. A compound, wherein said compound is N-(5-(4-(4-formyl-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide.

26. A compound, wherein said compound is N-(5-formamido-4-methoxy-2-morpholinophenyl)acrylamide.

27. A compound of Formula 5 or salt thereof:

<Formula 5>



wherein, Y is halogen.

28. A compound, wherein said compound is N-(5-amino-2-methoxy-4-morpholinophenyl)formamide.