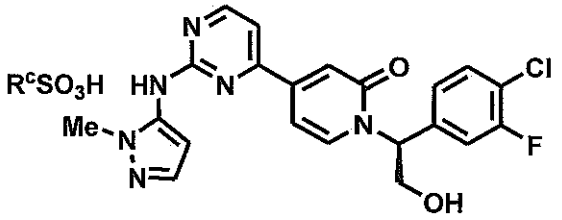
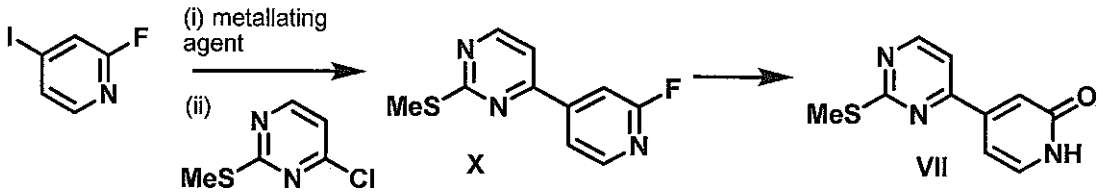
In embodiment 12, the present disclosure provides processes according to aspect 1 wherein the compound **VIII** from step h is contacted with a sulfonic acid in an organic solvent and water to afford a salt of **VIIIa** where $\mathbf{R^c}$ is an aryl sulfonic acid



(VIIIa).

In embodiment 13, the present disclosure provides processes according to embodiment 12 wherein $\mathbf{R^c}SO_3H$ is benzenesulfonic acid and the solvent is methyl ethyl ketone and water to afford the besylate salt **VIIIb**.

In aspect 2, the present invention provides processes for the preparation of 4-(2-(methylsulfonyl)pyrimidin-4-yl)pyridin-2(1H)-one (**VII**) comprising the steps of:



(*a*) contacting 2-fluoro-4-iodopyridine with a metallating agent in an aprotic organic solvent to afford an organomagnesium compound, which is reacted with 4-chloro-2(methylthio)pyrimidine in the presence of a palladium catalyst to afford 4-(2-fluoropyridin-4-yl)-2-(methylthio)pyrimidine (**X**);

(b) treating **X** with potassium *tert*-butoxide in THF and subsequently with an aqueous acid to afford 4-(2-(methylsulfonyl)pyrimidin-4-yl)pyridin-2(1H)-one (**VII**).

In embodiment 14, the present disclosure provides processes according to aspect 2 wherein the palladium catalyst is (1,3-diisopropylimidazol-2-ylidene)(3-chloropyridyl)palladium(II) dichloride, the metallating agent is *i*-PrMgCl and LiCl, and the aprotic solvent is THF.

The present disclosure provides the compound (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate.

The present disclosure provides pharmaceutical compositions comprising (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate and a pharmaceutically acceptable excipient.

In aspect 3, the present invention provides crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate.

In aspect 4, the present invention provides crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate having an X-ray powder diffraction pattern comprising peaks at 6.16 ± 0.2, 7.46 ± 0.2, 16.36 ± 0.2, 25.76 ± 0.2 and 25.98 ± 0.2 2Θ

In aspect 5, the present invention provides crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate having an X-ray powder diffraction pattern substantially as shown in Figure 1.

In aspect 6, the present invention provides crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate having an ^{13}C NMR pattern substantially as shown in Figure 19.

In aspect 7, the present invention provides crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate having an ^{19}F NMR pattern substantially as shown in Figure 20.

In aspect 8, the present invention provides crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate having an ^{13}C NMR pattern substantially as shown in Figure 19 and a ^{19}F NMR pattern substantially as shown in Figure 20.

In aspect 9, the present invention provides crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate having an ^{19}F NMR pattern comprising peaks at -111.1 ± 0.4 ppm and -115.4 ± 0.4 ppm relative to $CFCl_3$ (at 293 K).

In aspect 10, the present invention provides crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate having an ^{13}C NMR pattern comprising peaks at 157.7 ± 0.2 ppm, 129.6 ± 0.2 ppm, 125.8 ± 0.2 ppm, and 117.0 ± 0.2 ppm relative to tetramethylsilane (at 293 K).

In aspect 11, the present invention provides crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate having a DSC pattern substantially as shown in Figure 2.

In aspect 12, the present invention provides pharmaceutical compositions comprising crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate in accordance with any one of aspects 3 to 11 and a pharmaceutically acceptable excipient.

In embodiment 15, the present disclosure provides the compound (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one *p*-toluenesulfonic acid.

In embodiment 16, the present disclosure provides pharmaceutical compositions comprising (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one *p*-toluenesulfonic acid and a pharmaceutically acceptable excipient.

In embodiment 17, the present disclosure provides crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one *p*-toluenesulfonic acid.

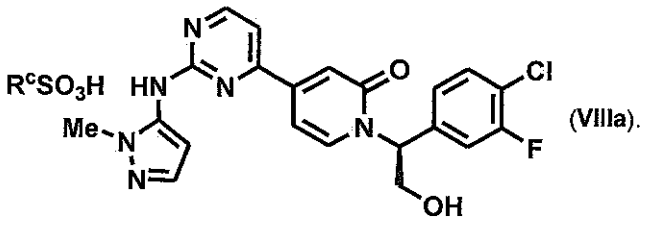
In embodiment 18, the present disclosure provides crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one *p*-toluenesulfonic acid Form A.

In embodiment 19, the present disclosure provides crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one *p*-toluenesulfonic acid Form A having an X-ray powder diffraction pattern comprising peaks at. 5.76 ± 0.2, 13.44 ± 0.2, 15.64± 0.2, 19.40± 0.2 2Θ.

In embodiment 20, the present disclosure provides crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one *p*-toluenesulfonic acid Form A having an X-ray powder diffraction pattern substantially as shown in Figure 12.

In embodiment 21, the present disclosure provides crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one *p*-toluenesulfonic acid Form A having a DSC pattern substantially as shown in Figure 13.

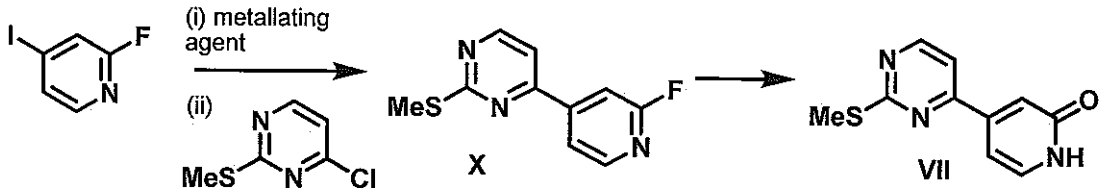
13. The process according to claim 1 wherein the compound **VIII** from step h is contacted with a sulfonicacid in an organic solvent and water to afford a salt of **VIIIa** where $\mathbf{R^c}$ is an aryl sulfonic acid



(VIIIa).

14. A process according to claim 13 wherein $\mathbf{R^c}SO_3H$ is benzenesulfonic acid and the solvent is methyl ethyl ketone and water to afford the besylate salt **VIIIb**.

15. A process for the preparation of 4-(2-(methylsulfonyl)pyrimidin-4-yl)pyridin-2(1H)-one (**VII**) comprising the steps of:



(*a*) contacting 2-fluoro-4-iodopyridine with a metallating agent in an aprotic organic solvent to afford an organomagnesium compound, which is reacted with 4-chloro-2(methylthio)pyrimidine in the presence of a palladium catalyst to afford 4-(2-fluoropyridin-4-yl)-2-(methylthio)pyrimidine (**X**);

(b) treating **X** with potassium *tert*-butoxide in THF and subsequently with an aqueous acid to afford 4-(2-(methylsulfonyl)pyrimidin-4-yl)pyridin-2(1H)-one (**VII**).

16. The process according to claim 15 wherein the palladium catalyst is (1,3-diisopropylimidazol-2-ylidene)(3-chloropyridyl)palladium(II) dichloride, the metallating agent is *i*-PrMgCl and LiCl, and the aprotic solvent is THF.

17. Crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate.

18. Crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate having an X-ray powder diffraction pattern comprising peaks at 6.16 ± 0.2, 7.46 ± 0.2, 16.36 ± 0.2, 25.76 ± 0.2 and 25.98 ± 0.2 2Θ

19. Crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate having an X-ray powder diffraction pattern substantially as shown in Figure 1.

20. Crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate having an ^{13}C NMR pattern substantially as shown in Figure 19.

21. Crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate having an ^{19}F NMR pattern substantially as shown in Figure 20.

22. Crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate having an ^{13}C NMR pattern substantially as shown in Figure 19 and a ^{19}F NMR pattern substantially as shown in Figure 20.

23. Crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate having an ^{19}F NMR pattern comprising peaks at -111.1 ± 0.4 ppm and -115.4 ± 0.4 ppm relative to $CFCl_3$ (at 293 K).

24. Crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate having an ^{13}C NMR pattern comprising peaks at 157.7 ± 0.2 ppm, 129.6 ± 0.2 ppm, 125.8 ± 0.2 ppm, and 117.0 ± 0.2 ppm relative to tetramethylsilane (at 293 K).

25. Crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate having a DSC pattern substantially as shown in Figure 2.

26. A pharmaceutical composition comprising crystalline (S)-1-(1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one benzenesulfonate in accordance with any one of claims 17 to 25 and a pharmaceutically acceptable excipient.