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NEW AND CONVERGENT SYNTHESIS OF MOMELOTINIB DIHYDROCHLORIDE

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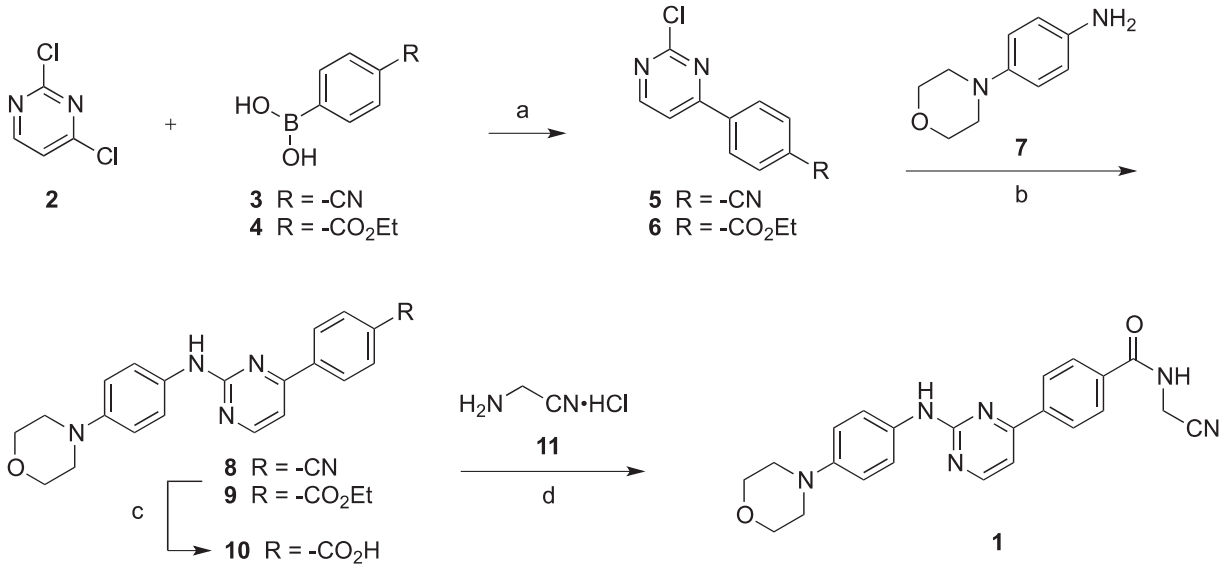
Abstract – A new and convergent synthesis of Momelotinib dihydrochloride, a new anticancer drug, is described in this article. The key step is cyclization of 1-(4-morpholinophenyl)guanidine (**12**) with *N*-(cyanomethyl)-4-(3-(dimethylamino)acryloyl)benzamide (**17**) to give Momelotinib under mild condition in 77% yield. The title product is obtained in 52.5% yield over 4 steps and 99.1% purity (HPLC).

Momelotinib (**1**, CYT-387, GS-0387, Scheme 1) is an ATP-competitive inhibitor of JAK1/JAK2 with IC_{50} values of 11 and 18 nM.[1] Its indications include myelofibrosis, myeloproliferative neoplasms, and cancer.[2] It is developed by Gilead Sciences and now in phase III clinical study.[3]

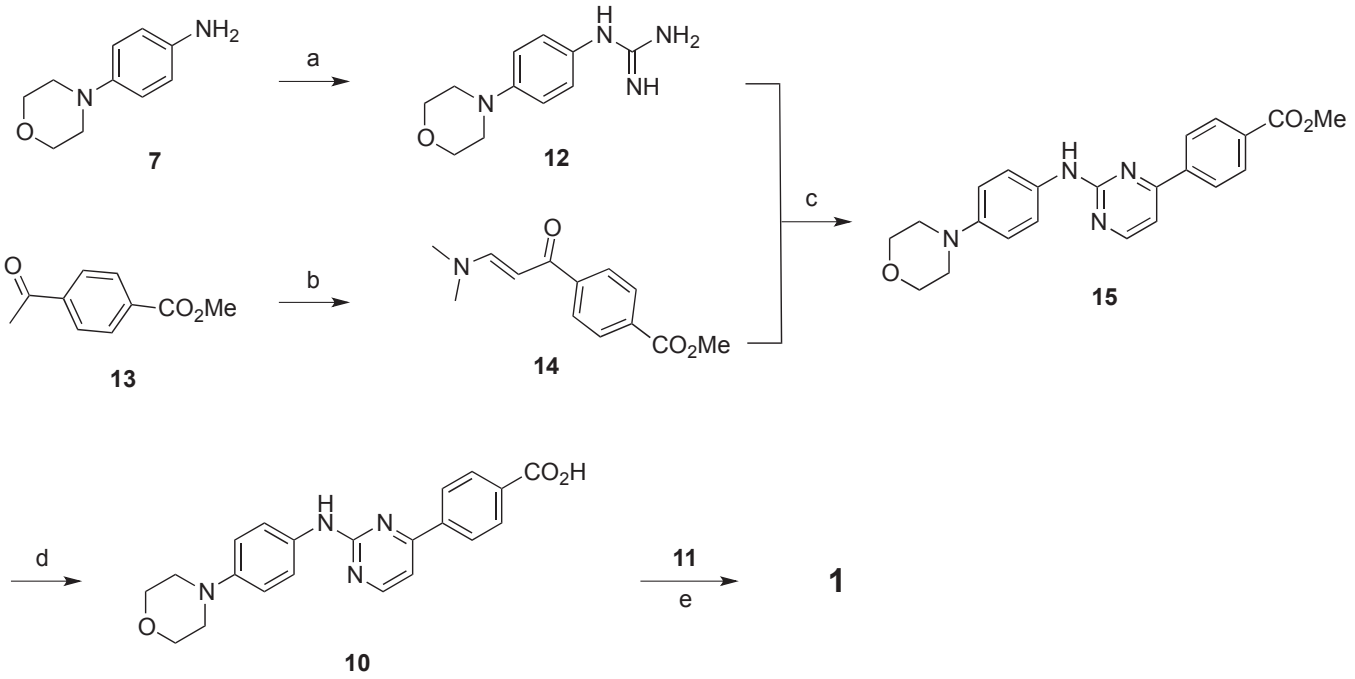
At present, the following two methods are mainly used for the preparation of Momelotinib. The first route was reported by YM BioSciences Corporation,[4] which is based on the preparation of 2-chloro-4-phenylpyrimidine intermediates (**5** or **6**) by the coupling of 4-phenylboronic acid materials (**3** or **4**) and dichloropyrimidine (**2**) under Pd catalyst in around 50–60% yield, as shown in Scheme 1. Momelotinib (**1**) was obtained through the subsequent procedure containing substitution, ester hydrolysis and condensation in 22–36% yield over 4 steps.[5] Expensive palladium catalysts and phosphine ligands are adopted in this original synthetic route which enhances the overall cost. In addition, removal of heavy metal residues is also difficult and the by-products are complicated. In some extent, these defects restrict the industrial production of Momelotinib.

In recent year, our group also reported a new method to synthesis of Momelotinib,[6] as shown in Scheme 2. The key step was cyclization of 1-(4-morpholinophenyl)guanidine (**12**) and methyl 4-(3-(dimethylamino)-acryloyl)benzoate (**14**) to give the key intermediate methyl 4-(2-((4-morpholinophenyl)amino)-

pyrimidin-4-yl)benzoate (**15**). Avoid using Pd to make this procedure, more practical and simpler than the first route. Sodium hydroxide is used for ester hydrolysis[7] at the end, and the total yield of 5 steps is not high.

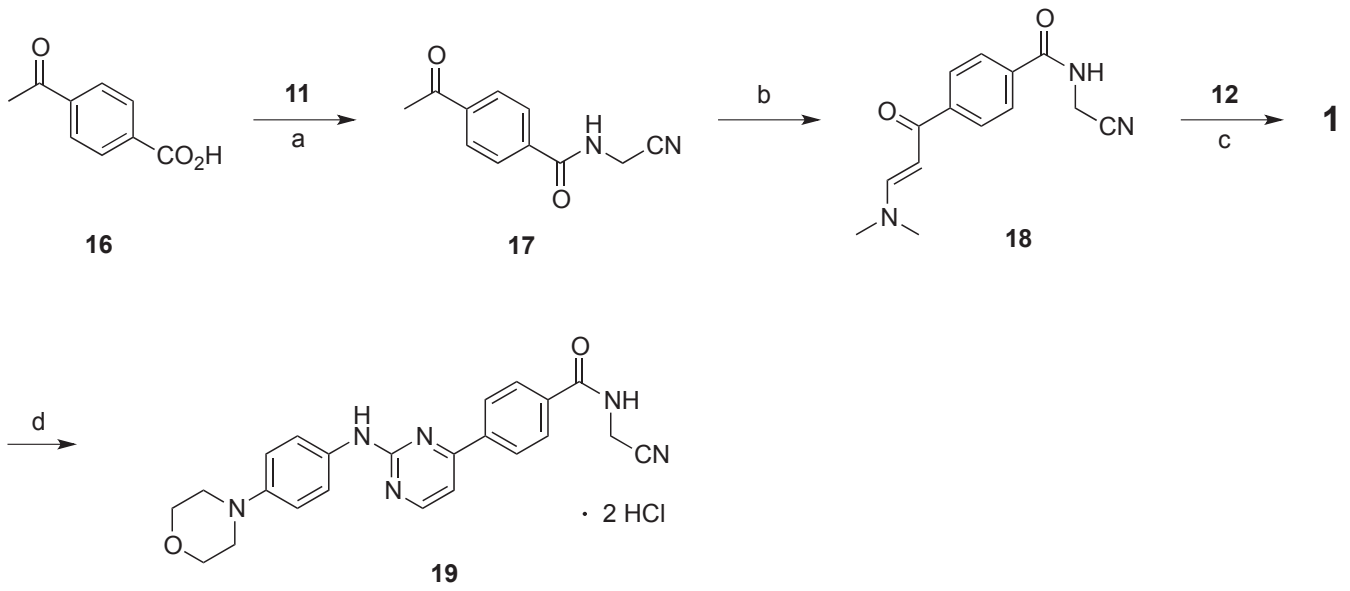


Scheme 1. Reagents and conditions: (a) $(dppf)_2PdCl_2$, Na_2CO_3, toluene, 100 °C, 50% for **3** and 60% for **4**; (b) *p*-TsOH, dioxane, reflux, 66% for **5** and 80% for **6**; (c) LiOH, H_2O, THF, reflux, 85% for **8** and 92% for **9**; (d) EDC·HCl, HOBt, TEA, DMF, rt, 80%.



Scheme 2. Reagents and conditions: (a) NH_2CN, EtOH, HCl, H_2O, 50 ºC, 12 h, 78%; (b) DMF-DMA, toluene, reflux, 6 h, 82%; (c) MeCN, reflux, 10 h, 81%; (d) H_2O, NaOH, MeOH, reflux, 2 h, 96%; (e) HOBt, EDC·HCl, TEA, DMF, rt, 10 h, 87%.

In order to develop a practical and commercial method for preparing of Momelotinib (**1**) and its dihydrochloride product **19**, a new, efficient and convergent synthetic route was developed successfully, as shown in Scheme 3.



Scheme 3. Reagents and conditions: (a) HOBt, EDC·HCl, TEA, DMF, rt, 4 h, 95%; (b) DMF-DMA, toluene, reflux, 24 h, 79%; (c) MeCN, reflux, 48 h, 77%; (d) HCl, MTBE, 91%.

4-Acetylbenzoic acid (**16**) and aminoacetonitrile hydrochloride (**11**) were used as the starting materials, and 4-acetyl-*N*-(cyanomethyl)benzamide (**17**) was obtained under the amide condensation condition in 95% isolated yield with >99% purity (HPLC).[8] Compound **17** reacted with *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) in toluene to give the key intermediate *N*-(cyanomethyl)-4-(3-(dimethylamino)acryloyl)benzamide (**18**) in around 80% isolated yield with >98% purity (HPLC).[9] 1-(4-Morpholinophenyl)guanidine intermediate (**12**) was prepared using the reported method.[6] Momelotinib (**1**) was obtained directly by refluxing **12** and **18** in acetonitrile for 48 h in 77% yield and >98% purity. At the last step, Momelotinib was salified by 2 equivalents concentrated hydrochloric acid in methyl *t*-butyl ether (MTBE) to give the final product **19** in around 90% yield and >99% purity.

In summary, an effective synthetic route of Momelotinib dihydrochloride is developed successfully. The key step is adopting a convergent synthesis technology to prepare Momelotinib by cyclization of *N*-(cyanomethyl)-4-(3-(dimethylamino)acryloyl)benzamide (**18**) and 1-(4-morpholinophenyl)guanidine (**12**) in high yields and mild conditions. With commercially available materials including 4-acetylbenzoic acid, aminoacetonitrile hydrochloride, 4-morpholinoaniline and so on, Momelotinib dihydrochloride was obtained through 4 steps in 52.5% yield and 99.1% purity. Purification methods of the intermediates and

the final product involved in the route were developed, which make it as a process of cost effective, environmental friendly, and feasible for scale-up operation.

EXPERIMENTAL

All commercially available chemicals and solvents were used as received without any further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker UltraShield 400 or 500 Plus spectrometer using TMS as an internal standard. Mass spectra were obtained from a Finnigan MAT-95/711 spectrometer. Melting points were measured on a Shenguang WRS-1B melting point apparatus and uncorrected. The HPLC data were acquired using a Waters 2487 UV/Visible Detector and Waters 515 Binary HPLC Pump. The purity of the compounds was based on the areas of HPLC UV.

4-Acetyl-*N*-(cyanomethyl)benzamide (17). Triethylamine (18 mL, 0.133 mol) and 1-hydroxybenzotriazole (HOBt) (9.7 g, 0.071 mol) were added to a stirred solution of 4-acetylbenzoic acid (**16**) (10 g, 0.061 mol) in DMF (100 mL) at room temperature and the reaction solution was stirred for 30 min. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) (13.8 g, 0.071 mol) was then added and the reaction solution was stirred at room temperature for another 30 min. Aminoacetonitrile hydrochloride (6.16 g, 0.067 mol) was added and the reaction mixture was stirred at room temperature for 4 h. The resulting suspension was poured into cooled 5% hydrochloric acid (300 mL) and was stirred for 30 min. The resulting solid was collected by suction filtration, washed with H_2O (50 mL × 2), dried at 40 ºC for 6 h to afford **16** (11.7 g, 95%) as a colorless solid; mp 140.2–142.5 ºC. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.64 (s, 3H), 4.36 (d, J = 5.4 Hz, 2H), 8.00 (d, J = 8.3 Hz, 2H), 8.07 (d, J = 8.3 Hz, 2H), 9.40 (t, J = 5.3 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.5, 28.3, 118.0, 128.2, 128.8, 137.0, 139.7, 166.4, 198.2. MS (ESI): m/z = 203.1 $[M + H]^+$.

HPLC Conditions: Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 254 nm; Flow rate: 0.8 mL/min; Temperature: 35 °C; Injection load: 1 μL; Solvent: MeOH; Run time: 20 min; Mobile phase: MeOH/H_2O = 70/30, t_R: 3.921 min, purity: 99.97%.

***N*-(Cyanomethyl)-4-(3-(dimethylamino)acryloyl)benzamide (18).** *N,N*-Dimethylformamide dimethyl acetal (DMF-DMA) (26.2 g, 0.22 mmol) was added to a stirred suspension of 4-acetyl-*N*-(cyanomethyl)benzamide (**17**) (10.1 g, 0.05 mol) in toluene (50 mL). The mixture was stirred and heated to reflux for 24 h, then cooled to room temperature. The resulting solid was collected by suction filtration, washed with toluene (30 mL × 2), and dried at 40 ºC for 4 h to give **18** (10.2 g, 79%) as a light yellow solid; mp 179.1–181.2 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.92 (s, 3H), 3.17 (s, 3H), 4.34 (d, J = 5.2 Hz, 2H), 5.87 (d, J = 12.1 Hz, 1H), 7.76 (d, J = 12.1 Hz, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 8.0 Hz, 2H), 9.30 (t, J = 4.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 28.3, 37.7, 45.1, 91.6, 118.1, 127.7,

127.8, 134.9, 143.6, 155.2, 166.7. MS (ESI): *m/z* = 258.2 $[M + H]^+$.

HPLC Conditions: Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 254 nm; Flow rate: 0.8 mL/min; Temperature: 35 °C; Injection load: 1 μL; Solvent: MeOH; Run time: 20 min; Mobile phase: MeOH/H_2O = 70/30, t_R: 3.764 min, purity: 98.27%.

Momelotinib (1). A stirred mixture of 1-(4-morpholinophenyl)guanidine (**12**) (6.8 g, 0.031 mol) and *N*-(cyanomethyl)-4-(3-(dimethylamino)acryloyl)benzamide (**18**) (8.0 g, 0.031 mol) in MeCN (50 mL) was heated to reflux for 48 h. The reaction mixture was cooled to room temperature and the resulting solid was collected by suction filtration, dried at 45 ºC for 4 h to give the crude product **1** (11.7 g, 91%), which was stirred and heated with 1:2 (v/v) EtOH/EtOAc (30 mL) to reflux for 1 h then cooled to room temperature overnight, the resulting solid was filtered and washed with 1:2 (v/v) EtOH/EtOAc (10 mL × 2), dried at 45 ºC for 5 h to afford **1** (9.9 g, 77%) as an off-white solid; mp 240.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.06 (t, 4H), 3.75 (t, 4H), 4.36 (d, J = 5.3 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 5.1 Hz, 1H), 7.67 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.3 Hz, 2H), 8.27 (d, J = 8.3 Hz, 2H), 8.54 (d, J = 5.1 Hz, 1H), 9.34 (t, J = 5.6 Hz, 1H), 9.48 (s, 1H).

Momelotinib dihydrochloride (19). 37% Hydrochloric acid (3.3 mL, 0.04 mol) was added to a suspension of **1** (8.28 g, 0.02 mol) in methyl *t*-butyl ether (MTBE) (60 mL) and the mixture was stirred at room temperature for 1 h. The resulting solid was collected by suction filtration, washed with MTBE (20 mL × 2), and dried at 45 ºC for 4 h to give **19** (8.8 g, 91%) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.49 (s, 4H), 4.03 (s, 4H), 4.36 (d, J = 5.4 Hz, 2H), 7.55 (d, J = 5.2 Hz, 1H), 7.65 (s, 2H), 7.93 (d, J = 8.5 Hz, 2H), 8.07 (d, J = 8.5 Hz, 2H), 8.30 (d, J = 8.5 Hz, 2H), 8.64 (d, J = 5.2 Hz, 1H), 9.46 (t, J = 5.4 Hz, 1H), 10.00 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.3, 49.8, 66.7, 108.1, 116.1, 118.0, 120.9, 127.4, 128.4, 133.3, 135.0, 140.5, 146.8, 159.7, 160.9, 163.0, 166.7. MS (ESI): *m/z* = 415.2 $[M + H]^+$.

HPLC Conditions: Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 220 nm; Flow rate: 0.8 mL/min; Temperature: 30 °C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Run time: 15 min; Mobile phase: MeOH/H_2O = 80/20, t_R: 3.787 min, purity: 99.16%.

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