Supporting Information
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Development of a Scalable Synthesis of a VEGFR Inhibitor

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Supporting Information

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**General Information**

Reactions were carried out under an atmosphere of dry nitrogen. All reagents were purchased from suppliers and used as received unless noted otherwise. $^1$H NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in ppm with dimethyl-d6 sulfoxide, 99.9 atom %D. Data are reported as follows: chemical shift, multiplicity ($s =$ singlet, $d =$ doublet, $t =$ triplet, $q =$ quartet, $br =$ broad, $m =$ multiplet), coupling constants (Hz) and integration. $^{13}$C NMR spectra were recorded on a 100 MHz spectrometer with complete proton decoupling. Melting points are uncorrected. Mass spectra analyses were measured by means of electrospary ionization (ESI).
Experiment Procedure:

7-Nitro-1,2-dihydroisoquinoline (11):

Sulfuric acid (360 ml, 6.5 mol) was added very slowly into the oily 1,2-dihydroisoquinoline (10)(90.4g, 689 mmol). Addition was exothermic and temperature was controlled below 40°C. The mixture was cooled to room temperature after addition. Potassium nitrate (76.6 g, 758 mmol) was added in portion over 1 hr. Addition was exothermic and temperature was controlled below 40°C. The mixture was stirred at room temperature until the reaction was completed in 2 hrs. The reaction was quenched via slow addition of H2O (500 mL) followed by slow addition of NH4OH (1 L, 13 mol) to pH 8-9. The quenching was exothermic and the temperature was kept below 30°C. The mixture was stirred for 20 min at room temperature. Extraction was carried out with dichloromethane (2 x 2L). The combined extracts were concentrated to about 500 mL. To the above dichloromethane solution was added a solution of TsOH monohydrate (132 g, 689 mmol) in IPA (600 mL) slowly at rt. The addition was not exothermic. Precipitation took place during the addition. The mixture was subjected to a vacuum distillation to remove about 500 mL of solvents. The mixture was then stirred at room temperature for 5 hrs. Filtration gave the wet cake. The wet cake was dried in vacuum oven at 50°C until the constant weight to produce the redish solid product (72% yield). The solid was suspended in dichloromethane (1 L). To the suspension was added 3 N NaOH (460 mL, 2.8 mol). The addition was slightly exothermic. The two phases were separated. The organic phase was washed with 3 N NaOH (1 x 460 mL) and
H₂O (1 x 460 mL). The organic phase was concentrated to dryness to give a brownish solid (11) (84.7 g, overall 70% yield, >99% purity by HPLC). m.p. (DSC): 92.4 °C. MS: [M+H]⁺: 177.0. ¹H NMR (400 MHz, DMSO-d₆): δ 8.50 (1H, s), 8.28 (1H, d, J = 2.0 Hz), 8.21, (1H, dd, J = 2.4, 8.2 Hz), 7.51 (1H, d, J = 8.2 Hz), 3.72 (2H, t, J = 7.8 Hz), 2.82 (2H, t, J = 7.84 Hz). ¹³C NMR (100 MHz, DMSO-d₆): δ 157.79, 146.58, 143.82, 128.87, 128.48, 125.46, 121.61, 46.21, 24.30.

7-Nitroisoquinoline (8):

A mixture of 7-nitro-1,2-dihydroisoquinoline (11) (40 g, 224.0 mmol) and MnO₂ (78.0 g, 900 mmol) in PhCF₃ (1000 mL) was heated at 103 °C for 18 hrs. The mixture was cooled to room temperature. The reaction mixture was filtered through a bed of celite followed rinsing with dichloromethane (3 x 200 mL) afforded an organic solution. After remove solvent under vacuum, the product was obtained as a brownish solid (8) (29.3 g, 75% yield). The crude product was used in the next step without further purification. m.p. (DSC): 179.1 °C. MS: [M+H]⁺: 175.0. ¹H NMR (400 MHz, DMSO-d₆): δ 9.63 (1H, s), 9.17 (1H, s), 8.72 (1H, d, J = 5.8 Hz), 8.46 (1H, dd, J = 1.9, 9.0 Hz), 8.22 (1H, d, J = 9.0 Hz), 8.01 (1H, d, J = 5.9 Hz). ¹³C NMR (100 MHz, DMSO-d₆): δ 154.53, 146.21, 145.73, 137.68, 128.81, 126.79, 124.70, 123.58, 120.29.

7-Aminoisoquinoline (3):

![7-Aminoisoquinoline (3)]
To a solution of 7-nitroisoquinoline (8) (29.0 g, 167 mmol) in EtOH (500 mL) was added 10% Pd/C (7.5 g) under nitrogen. The reaction mixture was exposed to a balloon with H₂. The reaction was completed in 5 hrs. The organic phase was concentrated to dryness to afford light brown solid product (3) (23.0 g, >98%A, 95% yield). m.p. (DSC): 202.4 °C. MS: [M+H]+: 145.0.

¹H NMR (400 MHz, DMSO-d₆): δ 8.90 (1H, s), 8.11 (1H, d, J = 5.5 Hz), 7.64 (1H, d, J = 8.8 Hz), 7.52 (1H, d, J = 5.5 Hz), 7.18(1H, dd, J = 2.1, 8.6 Hz), 6.93 (1H, d, J = 1.8 Hz), 5.70 (2H, s).

¹³C NMR (100 MHz, DMSO-d₆): δ 149.51, 147.94, 138.34, 130.50, 128.10, 127.20, 122.62, 120.10, 104.23.

2-Chloro-N-(4-isopropyl-3-methyl-phenyl)-nicotinamide (14):

![Structure of 14](image)

To a solution of 4-isopropyl 3-methyl phenylamine HCl salt (1172 g, 6.1 mol) at 0 °C was added slowly triethylamine (1.9 L, 13.5 mol) over 30 minutes. A suspension of 2-chloro-nicotinoyl chloride (1) (1209 g, 6.7 mol) in DCM (8.2 L) was added into the reaction mixture slowly while keeping the temperature below 10 °C. After addition, the reaction was stirred at 10 °C for 30 min. The reaction was quenched with 10% Na₂CO₃ solution (12 L) by slow addition. The two phases were separated. Solvent switching from DCM to MTBE was carried out by distillation until final volume (2L) was reached. Heptanes (6 L) was slowly added to induce the crystallization. The slurry was aged for 2 hrs at room temperature. Filtration afforded the wet cake. The wet cake was dried further in the oven at 70 °C under vacuum until the weight was constant to give the
product (14) (1.8 kg, 98% yield, >99 % purity by HPLC). m.p. (DSC): 111.4 °C. MS: [M+H]+: 289.0. $^1$H NMR (400 MHz, DMSO-d$_6$): 10.47 (1H, s), 8.53 (1H, dd, J = 1.1, 4.7 Hz), 8.04 (1H, dd, J = 1.1, 7.5 Hz), 7.56 (1H, dd, J = 4.9, 7.4 Hz), 7.46-7.46 (2H, m), 7.20-7.23 (1H, m). $^{13}$C NMR (100 MHz, DMSO-d$_6$): 163.29, 150.37, 146.45, 142.26, 138.09, 136.02, 134.98, 133.32, 124.94, 123.15, 121.17, 117.64, 28.33, 23.16, 19.10.

N-(4-Isopropyl-3-methyl-phenyl)-2-(isoquinolin-7-ylamino)nicotinamide (15):

To a solution of 2-chloro-N-(4-isopropyl-3-methyl-phenyl)-nicotinamide (14) (100 g, 346 mmol) in THF (100 mL) was slowly added LiHMDS solution (1N in THF, 1.1 L, 1.1 mol) while keeping the temperature below 40 °C. The resulted solution was degassed with nitrogen to be free of oxygen. 7-Aminoisoquinoline (3)(52.4 g, 364 mmol) was added as powder. The reaction was heated to 70 °C and was completed in 7 hrs. The reaction mixture was cooled to room temperature. The reaction was quenched with water (500 mL) by slow addition. MeOH (500 mL) was added to the reaction mixture over 30 minutes. The mixture was filtered through a pad of celite to remove any insoluble materials. Portion of solvents (about 1.1 L) were removed by distillation. The crystallization was formed during the distillation. Another portion of MeOH (1 L) was added. More crystalline solid was formed over 1 hr under vigorous stirring. Filtration followed by washing cake with MeOH/H$_2$O (1:4) (2 x 1 L) afforded the wet cake. The wet cake
was dried under vacuum at 80 °C until the weight was constant to give the product (15) (109 g, 79% yield, 99%A). m.p. (DSC): 153.6 °C. MS: [M+H]+: 397.0. ¹H NMR (400 MHz, DMSO-d₆): δ 10.80 (1H, S), 10.39 (1H, s), 9.20 (1H, s), 8.66 (1H, s), 8.48, (1H, dd, J = 1.4, 4.7 Hz), 8.36 (1H, d, J = 5.6 Hz), 8.31 (1H, dd, J = 1.6, 7.6 Hz), 7.89-7.94 (2H, m), 7.73 (1H, d, J = 4.7 Hz), 7.51-7.53 (2H, m), 7.25 (1H, d, J = 9.0 Hz), 7.04 (1H, dd, J = 4.9, 7.7 Hz), 3.10 (1H, q, J = 6.8 Hz), 2.32 (1H, s), 1.20 (6H, d, J = 6.8 Hz). ¹³C NMR (100 MHz, DMSO-d₆): δ 166.32, 154.14, 151.30, 150.68, 142.55, 140.96, 138.95, 137.74, 135.67, 134.74, 131.05, 129.27, 126.97, 125.57, 124.74, 122.86, 119.96, 119.26, 114.29, 113.17, 112.68, 28.37, 23.15, 19.08.

**Compound A:**

A suspension of compound (15) (936 g, 2.4 mol) in EtOH (20 L) was heated to 78 °C until a homogenous solution was formed. The seeds (19 g) were added. H₃PO₄ (1.1 equiv) was slowly added over 30 minutes. The mixture was cooled to room temperature over 5 hrs. Filtration afforded the wet cake. The wet cake was dried in the oven at 100 °C under vacuum until the weight was constant to produce Compound (A) (1 kg, 86% yield, >99% purity by HPLC). m.p. (DSC): 217.0 °C. MS: [M+H]+: 397.0. ¹H NMR (400 MHz, DMSO-d₆): δ 10.80 (1H, S), 10.41 (1H, s), 9.21 (1H, s), 8.67 (1H, s), 8.37, (1H, dd, J = 1.4, 4.7 Hz), 8.35 (1H, d, J = 5.6 Hz), 8.30
(1H, dd, J = 1.6, 7.6 Hz), 7.89-7.92 (2H, m), 7.74 (1H, d, J = 4.7 Hz), 7.51-7.53 (2H, m), 7.25
(1H, d, J = 9.0 Hz), 7.04 (1H, dd, J = 4.9, 7.7 Hz), 3.10 (1H, q, J = 6.8 Hz), 2.32 (1H, s), 1.20
(6H, d, J = 6.8 Hz). $^{13}$C NMR (100 MHz, DMSO-d$_6$): δ 166.32, 154.10, 151.23, 150.70, 142.56,
140.96, 138.97, 137.74, 135.67, 134.75, 131.08, 129.27, 127.02, 125.57, 124.74, 122.85, 119.96,
119.25, 114.35, 113.15, 112.71, 28.38, 23.17, 19.11.