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NEW SYNTHESIS OF *N*-(4-CHLORO-3-CYANO-7-ETHOXYQUINOLIN-6-YL)ACETAMIDE

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Abstract – New synthetic route of *N*-(4-chloro-3-cyano-7-ethoxyquinolin-6-yl)-acetamide (**1**) is described on a hectogram scale. The key steps include the intramolecular cyclization of 3-amino-2-(2-chlorobenzoyl)acrylonitrile **22** to give the 3-cyano-4-quinolone **7**, which was chlorinated by $POCl_3$ to give the final product **1** in 36.9% yield over 9 steps and 98.9% purity (HPLC). Purification methods of **7** and **1** were also given.

4-Chloroquinolines are the key synthetic precursors for anticancer,[1] anti-malarial,[2] antidiabetic,[3] antiviral[4] agents and reversible (H^+/K^+) ATPase inhibitors.[5] *N*-(4-Chloro-3-cyano-7-ethoxyquinolin-6-yl)acetamide (**1**, Figure 1) was developed as an important intermediate for the preparation of pelitinib (**2**) and neratinib (**3**), which were developed as irreversible inhibitors of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER-2) kinases.[6]

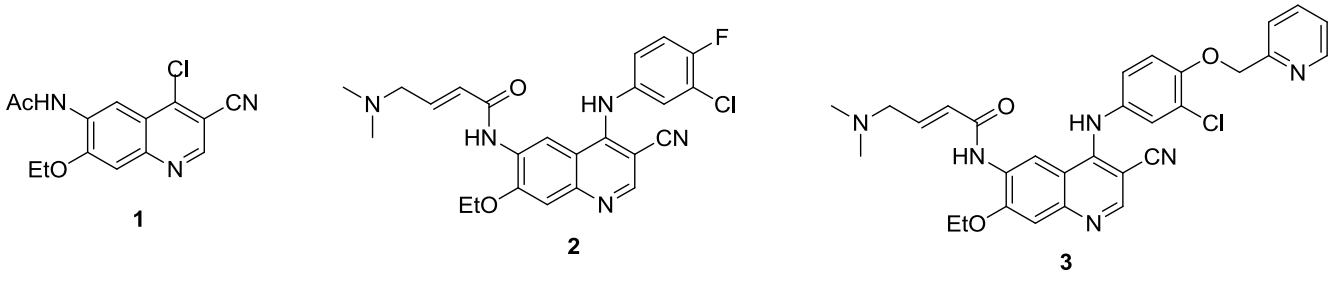
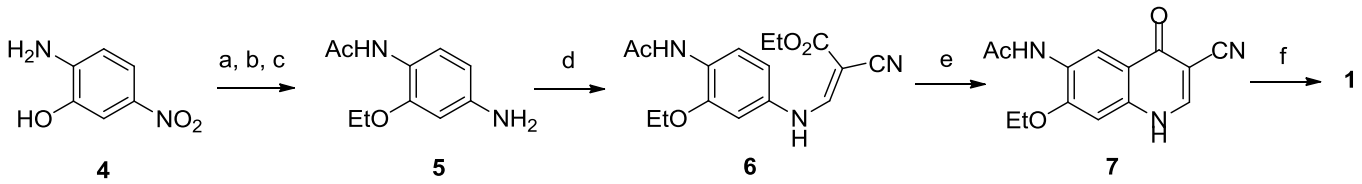


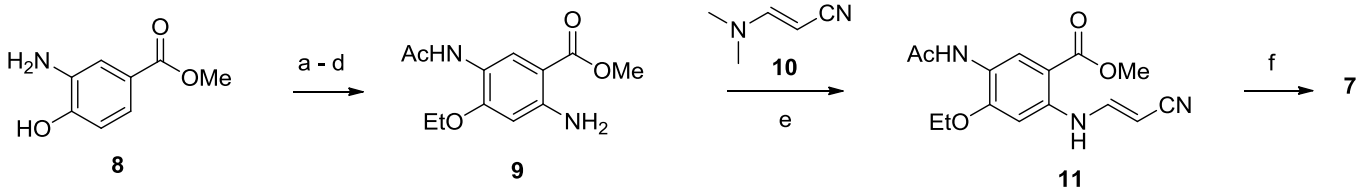
Figure 1. Chemical structures of **1**, pelitinib (**2**) and neratinib (**3**)

In the previous reports,[7] **1** was prepared based on Gould-Jacobs methodology using 2-amino-5-nitrophenol (**4**) as starting material (Scheme 1). **5** was then reacted with ethyl (*E*)-2-cyano-3-ethoxypropenoate to afford the corresponding ethyl cyanopropenoate **6**. 3-Cyano-4-quinolone **7** was obtained with ~ 40% yield through thermal cyclization at 260 ºC for 20 h in Dowtherm A. After chlorination with $POCl_3$ in diglyme, **1** was produced with 65% yield. This route was straightforward, while the high temperature required for cyclization of **6** to **7** on a kilogram scale was proved to be disadvantageous and so the overall yield is not good.

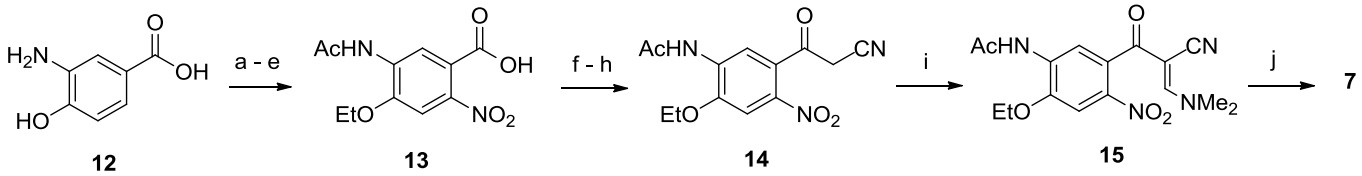


Scheme 1. Reagents and conditions: (a) AcOH, Ac_2O; (b) EtBr, K_2CO_3, DMF; (c) H_2, Pd-C, MeOH, 71% (3 steps); (d) ethyl 2-cyano-3-ethoxyacrylate, toluene, 90 ºC, 16 h, 90%; (e) Dowtherm A, 260 ºC, 20 h, 35−45%; (f) $POCl_3$, diglyme, 65%.

Recent years we developed a couple of new routes for synthesis of **7**,[8] as shown in Schemes 2 and 3. The key step in the first route is the basic cyclization of *o*-[(2-cyanovinyl)amino]benzoate (**11**) in *t*-BuONa/*t*-BuOH system to give the final product at kg scale. In the second, a reductive cyclization method was adopted, 3-(dimethylamino)-2-(2-nitrobenzoyl)acrylonitrile **15** was converted to **7**, while the overall yield is not attractive.

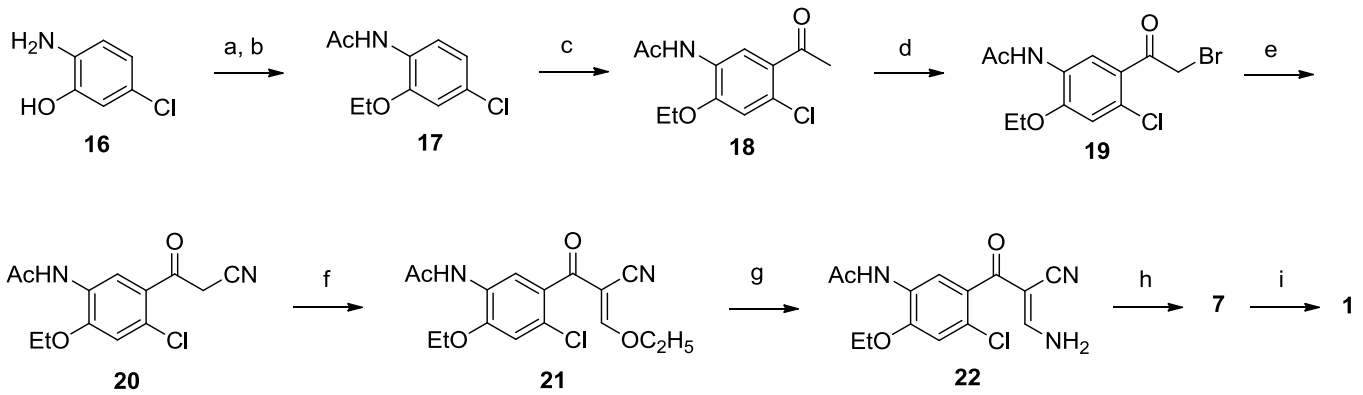


Scheme 2. Reagents and conditions: (a) AcOH, Ac_2O, 92%; (b) EtBr, K_2CO_3, DMF, 96%; (c) fuming HNO_3, $MeNO_2$, rt, 89%; (d) H_2, Raney Ni, 91%; (e) AcOH, rt, 4 h, 92%; (f) *t*-BuONa, *t*-BuOH, reflux, 3 h, 85%.



Scheme 3. Reagents and conditions: (a) $SOCl_2$, MeOH, 95%; (b) AcOH, Ac_2O, 92%; (c) EtBr, K_2CO_3, DMF, 96%; (d) 1M NaOH, MeOH, 96%; (e) AcOH, fuming HNO_3, 85%; (f) $SOCl_2$, CH_2Cl_2; (g) $CNCH_2CO_2Et$, NaOMe, MeOH, 89%; (h) DMSO/H_2O, 100−110 ºC, 84%; (i) DMF-DMA, DME, rt, 91%; (j) Zn, AcOH, EtOH-H_2O, 85%.

Here, we report a new synthetic method for compound **1** (Scheme 4). The cheap and easily available material 2-amino-5-chlorophenol (**16**) was converted to **17** through simple reactions with high yield.[6] Through a Friedel-Crafts acylation, compound **18** was obtained in 95% yield,[9] which was then treated with 1 eq. of Br_2 in CH_2Cl_2 to give **19**,[10] and followed by 1.1 eq. of NaCN in EtOH/DMSO at room temperature to afford **20** in 78% yield over two steps.[11] **20** was then condensed with $CH(OEt)_3$ and Ac_2O, substituted by NH_3 in EtOH to give the 3-amino-2-(2-chlorobenzoyl)acrylonitrile **22** in 84% yield.[12] The intramolecular cyclization of **22** was carried out in K_2CO_3/DMF condition to afford the 3-cyano-4-quinolone **7**,[13] which was purified by heating and stirring in 50% EtOH/EtOAc to give the compound with 73% overall yield and > 99% purity (HPLC). At the last step, 4-chloro-3-cyanoquinoline **1** was obtained by reaction with $POCl_3$ in EtOAc, catalyzed by 5 mol % DMAP. Purification of **1** was carried out by triturating and stirring in DMF at rt with 88% isolated yield and 98.9% purity (HPLC).



Scheme 4. Reagents and conditions: (a) AcOH, Ac_2O, 60 ºC, 96%; (b) EtBr, K_2CO_3, DMF, 60 ºC, 96%; (c) $AlCl_3$, CH_2Cl_2, AcCl, 0 ºC−rt, 95%; (d) Br_2, CH_2Cl_2, rt; (e) NaCN, EtOH/DMSO, 0 ºC−rt, 78% (2 steps); (f) Ac_2O, $CH(OEt)_3$, 120 ºC; (g) NH_3, EtOH, 0 ºC−rt, 84% (2 steps); (h) K_2CO_3, DMF, 120 ºC, 73%; (i) $POCl_3$, DMAP (cat.), EtOAc, reflux, 2 h, 88%.

In summary, we have developed a new synthetic route for 4-chloro-3-cyanoquinoline **1** on a hectogram scale. Starting from the easily available material 2-amino-5-chlorophenol (**16**), through the Friedel-Crafts acylation, substitution by -Br and -CN respectively, and the key intramolecular cyclization of 3-amino-2-(2-chlorobenzoyl)acrylonitrile **22** to give the 3-cyano-4-hydroxyquinoline **7**, which was chlorinated by $POCl_3$ in EtOAc to give the final product **1** in 36.9% yield over 9 steps and 98.9% purity (HPLC). Purification methods of **7** and **1** were also given.

ACKNOWLEDGMENT

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EXPERIMENTAL

All commercially available materials and solvents were used as received without any further purification. ^{1}H NMR spectra were recorded on a Varian Gemini 300 spectrometer and ^{13}C NMR spectra were obtained from a Bruker AMX 400/600 at 400 MHz using TMS as an internal standard. Infrared spectra were recorded using a Thermo-Nicolet MAGNA-IR 750. Mass spectra were obtained from a Finnigan MAT-95/711 spectrometer. Melting points were measured on a Buchi-510 melting point apparatus, which are uncorrected. The HPLC results were generated using a Waters 2487 UV/Visible Detector and Waters 515 Binary HPLC Pump.

***N*-(4-Chloro-2-ethoxyphenyl)acetamide (17).** To a stirred solution of 2-amino-5-chlorophenol **16** (300 g, 2.09 mol) in AcOH (1.5 kg) at 60 ºC was added Ac_2O (260 g, 2.55 mol) over 1 h, and the mixture was stirred at this temperature for 1 h. The mixture was poured into ice water (5 kg) over 20 min and stirred. The resulting tan solid was filtered, washed with water (500 g × 2) and dried at 50 ºC to give *N*-(4-chloro-2-hydroxyphenyl)acetamide (372 g, 95.8%) as a tan powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.06 (s, 3H), 6.78 (dd, J = 1.8, 6.9 Hz, 1H), 6.85 (d, J = 1.8 Hz, 1H), 7.74 (d, J = 6.9 Hz, 1H), 9.23 (s, 1H), 10.24 (s, 1H).

To a stirred suspension *N*-(4-chloro-2-hydroxyphenyl)acetamide (372 g, 2.01 mol) and K_2CO_3 (410 g, 2.96 mol) in DMF (1.9 kg) at 60 ºC was added EtBr (261 g, 2.4 mol) over 1 h, and the mixture was stirred at this temperature for 1 h. The mixture was poured into ice water (7 kg) and stirred for 30 min. The resulting grey solid was filtered, washed with water (500 g × 2) and dried at 50 ºC to provide **17** (410 g, 95.7%) as a grey powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (t, J = 5.4 Hz, 3H), 2.20 (s, 3H), 4.08 (q, J = 5.4 Hz, 2H), 6.83 (d, J = 1.8 Hz, 1H), 6.92 (dd, J = 1.8, 6.6 Hz, 1H), 7.68 (br s, 1H), 8.30 (d, J = 6.6 Hz, 1H).

***N*-(5-Acetyl-4-chloro-2-ethoxyphenyl)acetamide (18).** Anhydrous $AlCl_3$ (500 g, 3.74 mol) was suspended in CH_2Cl_2 (3 kg) under nitrogen and cooled to 0−5 ºC. AcCl (196 g, 2.5 mol) was added dropwise to the mixture over 1 h and stirred at 0−5 ºC for another 1 h. A solution of **17** (400 g, 1.87 mol) and AcCl (95 g, 1.2 mol) in CH_2Cl_2 (1.8 kg) was added dropwise to the previous $AlCl_3$ solution over 2 h and keep the reaction temperature below 20 ºC. A dark blue solution was obtained and stirred at rt for another 20 h. The reaction solution was then poured into chilled 10% hydrochloric acid (4 kg) and stirred for 1 h. The organic layer was separated and washed with water (2 kg × 3), dried over anhydrous Na_2SO_4. The solvent was recovered to give the **18** (454 g, 95.0%) as a tan solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (t, J = 5.1 Hz, 3H), 2.19 (s, 3H), 2.57 (s, 3H), 4.11 (q, J = 5.1 Hz, 2H), 6.82 (s, 1H), 7.69 (br s, 1H), 8.72 (s, 1H). ESI-MS (*m*/*z*) 254.0 (M – H), 255.9 (M + H).

***N*-(5-(2-Bromoacetyl)-4-chloro-2-ethoxyphenyl)acetamide (19).** Br_2 (32 g, 0.2 mol) was added to a stirred solution of **18** (440 g, 1.72 mol) in CH_2Cl_2 (5 kg). The reaction mixture was stirred at 20–25 ºC for 1 h. Another portion of Br_2 (243 g, 1.52 mol) was added and the reaction solution was stirred at 20–25 ºC for 12 h that the solution turned from red to faint yellow. The solvent was removed and **19** (580 g) was obtained as a faint red oil, which was used at the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49 (t, J = 7.5 Hz, 3H), 2.22 (s, 3H), 4.16 (q, J = 7.5 Hz, 2H), 4.48 (s, 2H), 6.88 (s, 1H), 7.68 (br s, 1H), 8.78 (s, 1H). ESI-MS (*m*/*z*) 333.9 (M – H), 335.9 (M + H).

***N*-(4-Chloro-5-(2-cyanoacetyl)-2-ethoxyphenyl)acetamide (20).** A solution of **19** (580 g, 1.72 mol) in DMSO (1 kg) and EtOH (2 kg) was cooled in an ice-water bath, then treated dropwise with NaCN (92.7 g, 1.89 mol) in H_2O (0.8 kg) over 1 h. The mixture was stirred for another 4 h at 20–25 ºC. The resulting solution was diluted with H_2O (5 kg), filtered, and the filtrate was acidified with 2 M HCl to pH = 4–5. The resulting solid was collected via suction filtration, washed with water (500 g × 2), and dried under reduced pressure to give **20** (376 g, 78%) as a pale solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (t, J = 7.5 Hz, 3H), 2.23 (s, 3H), 4.09 (s, 2H), 4.18 (q, J = 7.5 Hz, 2H), 6.92 (s, 1H), 7.67 (br s, 1H), 8.82 (s, 1H).

***N*-(5-(3-Amino-2-cyanoacryloyl)-4-chloro-2-ethoxyphenyl)acetamide (22).** A mixture of **20** (300 g, 1.07 mol), $CH(OEt)_3$ (311g, 2.1 mol) and Ac_2O (1.5 kg) was heated at 120 ºC for 2 h. The solvent was removed to give the *N*-(4-chloro-5-(2-cyano-3-ethoxyacryloyl)-2-ethoxyphenyl)acetamide **21** (370 g) as a red oil, which was used at the next step without purification.

21 (370 g, 1.07 mol) was dissolved in EtOH (2.5 kg) and cooled to ~10 ºC. NH_3 was then babbled to the solution till to saturated, and the reaction solution was stirred at 20 ºC for another 2 h. The resulting solid was collected by suction filtration, washed with 50% EtOH/H_2O, and dried under reduced pressure to give **22** (276 g, 84%) as a pale solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, J = 7.5 Hz, 3H), 2.10 (s, 3H), 4.16 (q, J = 7.5 Hz, 2H), 7.14 (s, 1H), 7.59 (br s, 2H), 7.95 (m, 1H), 9.18 (s, 1H). ESI-MS (*m*/*z*) 306.0 (M – H), 308.0 (M + H).

***N*-(3-Cyano-7-ethoxy-4-oxo-1,4-dihydroquinolin-6-yl)acetamide (7)**. **22** (250 g, 0.81 mol) and K_2CO_3 (134.0 g, 0.97 mol) were suspended in DMF (1.8 kg) under nitrogen. The reaction mixture was stirred and heated to 120 ºC for 3 h. Around 0.8 kg DMF was removed and the residue was poured into chilled water (3 kg), the resulting mixture was stirred at rt for 3 h. The resulting solid was filtered, washed with water, and dried to give the crude product **7** (175 g), which was suspended in 50% EtOH/EtOAc (700 g), stirred and heated to 70 ºC for 1 h. After cooled to rt, the resulting solid was collected by suction filtration,

washed by 50% EtOH/EtOAc (80 g × 2), dried at 50 ºC to give the pure product **7** (160 g, 73%) as a pale solid, mp > 300 ºC. ^{1}H NMR (DMSO-d_6, δ): 1.45 (t, 3H, J = 6.6 Hz), 2.14 (s, 3H), 4.20 (q, 2H, J = 6.6 Hz), 7.05 (s, 1H), 8.59 (d, 1H, J = 6.3 Hz), 8.70 (s, 1H), 9.18 (s, 1H), 12.52 (d, 1H, J = 6.3 Hz). ^{13}C NMR (DMSO-d_6, δ): 14.1, 23.9, 64.6, 93.0, 99.7, 116.3, 117.0, 118.7, 126.5, 136.5, 145.4, 152.9, 168.7, 173.5. ESI-MS (*m*/*z*): 270.2 (M – H), 272.2 (M + H). HPLC Conditions: Column: Phenomenex Prodigy ODS3, 150 mm × 4.6 mm × 5 μm; Detection: 230 nm; Flow rate: 1.0 mL/min; Temperature: 30 ºC; Injection load: 5 μL; Solvent: DMF; Concentration: 0.5 mg/mL; Run time: 60 min; Mobile phase A: water (0.1% H_3PO_4); Mobile phase B: acetonitrile; Gradient program: time (min): 0, 5, 45, 50, 52, 60; % of mobile phase A: 95, 95, 5, 5, 95, 95; % of mobile phase B: 5, 5, 95, 95, 5, 5, t_R: 15.546 min, purity: 99.1%.

***N*-(4-Chloro-3-cyano-7-ethoxyquinolin-6-yl)acetamide (1)**. Compound **7** (140 g, 0.51 mol), DMAP (3.0 g, 0.025 mol) were suspended in EtOAc (1.2 kg) and stirred at rt. $POCl_3$ (230 g, 1.5 mol) was added slowly to the mixture over 1 h, then heated to reflux for another 2 h to give a clear solution. After cooled to rt, the reaction solution was poured slowly into ice-water (2 kg) and stirred for 1 h. The resulting solid was filtered, washed with water (200 g × 2), and dried to give the crude product **1** (140 g), which was suspended in DMF (400 g), stirred at rt for 1 h. The solid was filtered, washed with EtOAc (80 g × 3), and dried at 50 ºC to give the pure product **1** (130 g, 88%) as a faint brown solid, mp 255 – 258 ºC. ^{1}H NMR (DMSO-d_6, δ): 1.50 (t, 3H, J = 6.3 Hz), 2.25 (s, 3H), 4.40 (q, 2H, J = 6.3 Hz), 7.60 (s, 1H), 9.01 (s, 1H), 9.17 (s, 1H), 9.54 (s, 1H). ESI-MS (*m*/*z*): 290.1 (M+H). Anal. Calcd for $C_{14}H_{12}ClN_3O_2$: C, 58.04; H, 4.17; N, 14.50. Found: C, 57.81; H, 4.07; N, 14.18. IR (KBr): 3334.4, 2993.0, 2235.1, 1689.4, 1618.0, 1521.6, 1427.1, 1348.0, 1259.3, 1161.0, 1037.5, 694.3. HPLC Conditions: Column: Phenomenex Prodigy ODS3, 150 mm × 4.6 mm × 5 μm; Detection: 230 nm; Flow rate: 1.0 mL/min; Temperature: 30 ºC; Injection load: 5 μL; Solvent: DMF; Concentration: 0.5 mg/mL; Run time: 60 min; Mobile phase A: water/acetonitrile/H_3PO_4 = 950/50/0.5; Mobile phase B: water/acetonitrile/H_3PO_4 = 50/950/0.5; Gradient program: time (min): 0, 5, 45, 50, 52, 60; % of mobile phase A: 100, 100, 0, 0, 100, 100; % of mobile phase B: 0, 0, 100, 100, 0, 0, t_R: 26.018 min, purity: 98.9%.

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