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SYNTHESIS OF *N*-(3-CYANO-7-ETHOXY-1,4-DIHYDRO-4-OXOQUINOLIN-6-YL)ACETAMIDE

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Abstract – New route for the preparation of *N*-(3-cyano-7-ethoxy-1,4-dihydro-4-oxoquinolin-6-yl)acetamide (**1**), a key intermediate for the synthesis of selective EGFR kinase inhibitors, was described.

4(1*H*)-Quinolones are a series of important intermediates for the synthesis of anticancer,[1] antimalarial,[2] antidiabetic,[3] antiviral[4] agents and reversible (H^+/K^+) ATPase inhibitors.[5] *N*-(3-Cyano-7-ethoxy-1,4-dihydro-4-oxoquinolin-6-yl)acetamide (**1**, Figure 1) was a key intermediate for either EKB-569 (**2**) or neratinib (**3**) , both of which were developed as dual irreversible inhibitors of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (EGFR-2) protein tyrosine kinases.[6]

In the previous reports, **1** was prepared using 2-amino-5-nitrophenol (**4**) as starting material.[7] **5** was synthesized by acelytion, ethylation and reduction of **4** (Scheme 1), and then reacted with ethyl (*E*)-2-cyano-3-ethoxypropenoate to furnish **6**. In the following thermal cyclization, the reaction mixture was heated at 260 °C for 20 h to give **1** with 35% yield.

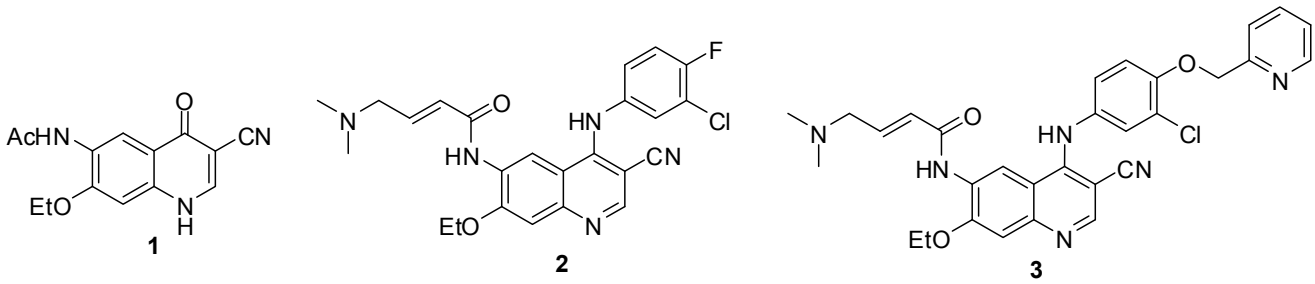
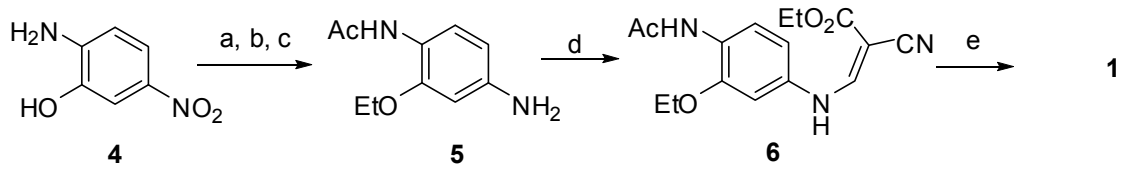


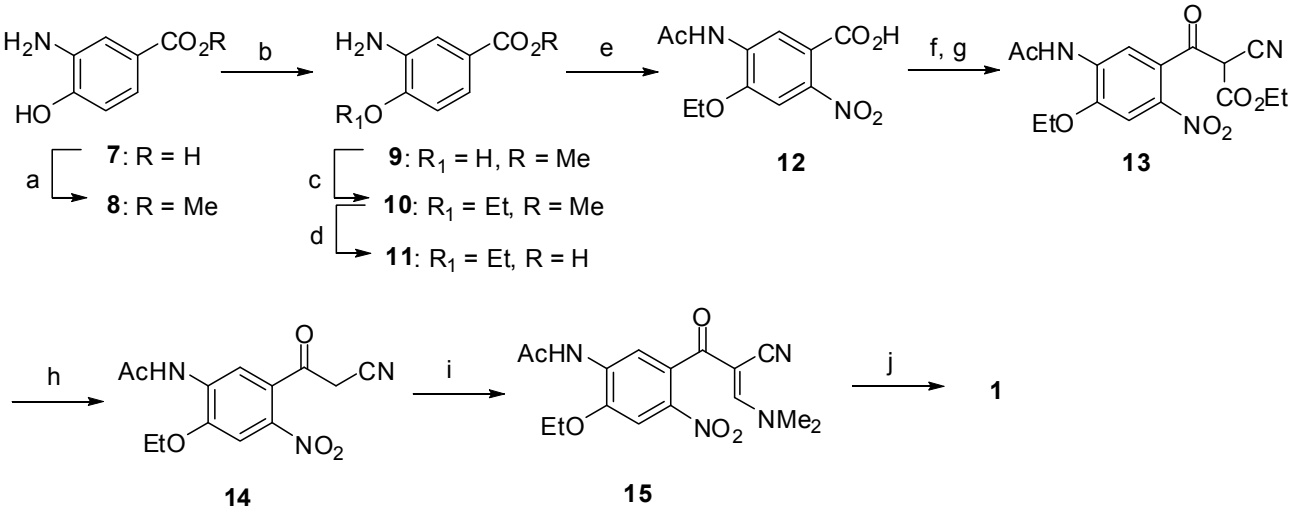
Figure 1. Chemical structures of **1**, EKB-569 (**2**) and neratinib (**3**)



Scheme 1. Reagents and conditions: (a) AcOH, Ac_2O, 60 ºC; (b) C_2H_5Br, K_2CO_3, DMF, 60 ºC; (c) H_2, Pd-C, THF, 71% (3 steps); (d) ethyl 2-cyano-3-ethoxyacrylate, toluene, 90 ºC, 16 h, 90%; (e) Dowtherm A, 260 ºC, 20 h, 35%

An efficient and mild synthesis for **1** is needed in the process for **2** and **3**. To address this issue, we conceived an alternative strategy using compound **7** as starting material. Herein, we wish to report this approach as a new mild promising method for the preparation of compound **1.**

We noted that Atkins[8] and Tois[9] had reported the preparation of 3,8-disubstatuted 4-hydroxyquinolines and 6,7-disubstitued 4-hydroxyquinolines, respectively, by condensation of *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) with the corresponding substituted *o*-nitrophenylethanones to afford nitroenamine intermediates. Intermediates were in turn subjected to hydrogenation conditions over palladium-on-carbon to give the corresponding substituted 4(1*H*)-quinolones. These convenient routes possessed the advantage of avoiding thermal cyclization at high temperature. Enlightened by the noticeable merit of this approach in the preparation of 4-hydroxyquinolines, we wondered if this strategy could be applied in the synthesis of compound **1**. Therefore, a new synthetic route using reductive cyclization method was designed and examined (**Scheme 2**).



Scheme 2. Reagents and conditions: (a) $SOCl_2$, MeOH, 65−70 ºC, 95%; (b) AcOH, Ac_2O, 60 ºC, 92%; (c) C_2H_5Br, K_2CO_3, DMF, 60 °C, 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, 70−80 ºC, 85%.

The key intermediate **12** can be readily prepared from 3-amino-4-hydroxybenzoic acid according to the well-established chemistry.[11] Esterfication of **7** followed by acetylation gave **9** in 87% yield. Ethylation of **9** followed by hydrolysis afforded the substituted benzoic acid **11**, whose treatment with fuming nitric acid produced compound **12**. By treating **12** with $SOCl_2$ and following reaction with ethyl cyanoacetate, the synthesis of compound **13** was achieved in excellent yield (90%) by two steps. Treatment of **13** in DMSO/H_2O provided the compound **14** in 84% yield. Condensation of **14** with DMF-DMA gave compound **15**. The next reductive cyclization of **15** was achieved with zinc-acetic acid-ethanol system to give **1** in good yield. Because the sodium salt form of **1** can dissolve in the mixture of ethanol and water, it is ready to give **1** in satisfying HPLC purity (99.20%) by simple alkalization, acidification and filtration. Finally, the overall yield of this reductive cyclization process was about 31% (from **7**) over ten steps.

EXPERIMENTAL

All commercially available materials and solvents were used as received products without 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 spectrometer at 400 MHz using TMS as an internal standard. Infrared spectra were recorded using a Thermo-Nicolet MAGNA-IR 750. The mass spectra were (LRMS and HRMS) obtained from a Finnigan MAT-95/711 spectrometer. All MS experiments were performed using electrospray ionization (ESI) in positive or negative ion mode. Melting points were measured on a Buchi-510 melting point apparatus, which are uncorrected. Elemental analyses were carried out in the Analytical Laboratories of Shanghai Institute of Meteria Medica.

Methyl 3-amino-4-hydroxybenzoate (8)

To a solution of **7** (3.1 kg, 20 mol) in MeOH (25 L) was added $SOCl_2$ (1.5 L, 21 mol) at 5 ^{o}C with stirring and allowed to reflux at 65 ^{o}C for 8 h. Excess MeOH and $SOCl_2$ were distilled off, and the crude products were dissolved in EtOAc (8 L). The organic layer was washed with 5% aqueous $NaHCO_3$ solution, water, brine and dried. Filtration followed by evaporation of the solvent *in vacuo* afforded 3.2 kg of **8** as a pale solid, yield 95%, mp 110 ^{o}C. ^{1}H NMR (300MHz, DMSO-d_6): δ 3.75 (s, 3H), 4.78 (br s, 2H), 6.72 (d, J = 8.2 Hz, 1H), 7.10 (dd, J = 2.1, 8.2 Hz, 1H), 7.25 (d, J = 2.1 Hz, 1H), 11.70 (br s, 1H). ESI-MS (m/z) 168 $[M + H]^+$.

Methyl 3-acetamido-4-hydroxybenzoate (9)

To a stirred solution of **8** (3 kg, 18 mol) in AcOH (15 L) was added acetic anhydride (2.6 L, 27 mol) at 60 ^{o}C, and the mixture was stirred at this temperature for 3 h. The mixture was poured to chilled water (35 L) over 1h. The resulting white solid was filtered, washed with water and dried to give 3.5 kg of pure product **9** as a white powder, yield 92%, mp 181-183 ^{o}C. ^{1}H NMR (300 MHZ, DMSO-d_6): δ 2.10 (s, 3H), 3.78 (s, 3H), 6.91 (d, J = 8.3 Hz, 1H), 7.58 (dd, J = 2.0, 8.4 Hz, 1H), 8.45 (s, 1H), 9.35 (s, 1H), 10.82 (s,

1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.7, 51.5, 114.9, 120.0, 123.3, 126.5, 126.6, 152.3, 166.0, 169.2. ESI-MS (*m*/*z*) 210 $[M + H]^+$.

Methyl 3-acetamido-4-ethoxybenzoate (10)

To a stirred suspension of **9** (3.5 kg, 16.7 mol) and K_2CO_3 (3.5 kg, 25 mol) in DMF (25 L) was added bromoethane (1.9 L, 25 mol) at 60 °C, and the mixture was stirred at this temperature for 6 h. The mixture was poured to chilled water (40 L). The resulting white solid was filtered, washed with water and dried to provide 3.8 kg of **10** as a white powder, yield 96%, mp 153-155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (t, J = 6.9 Hz, 3H), 2.20 (s, 3H), 3.90 (s, 3H), 4.25 (q, J = 6.9 Hz, 2H), 6.95 (d, J = 8.4 Hz, 1H), 7.75 (br s, 1H), 7.80 (dd, J = 2.0, 8.4 Hz, 1H), 9.05 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.7, 24.8, 51.8, 64.3, 109.8, 120.7, 122.6, 126.0, 127.1, 150.8, 166.6, 168.1. ESI-MS (*m*/*z*) 238 $[M + H]^+$.

3-Acetamido-4-ethoxybenzoic acid (11)

To a stirred solution of **10** (3.8 kg, 16 mol) in MeOH (30 L) was added aqueous NaOH solution (1 M, 16 L, 16 mol) at room temperature, and the resulting solution was stirred at this temperature for 5 h. Excess MeOH was distilled off, and the residue was dissolved in water, acidified with conc. HCl (1.3 L) to pH 2-3 at room temperature. The resulting precipitate was collected by suction filtration, washed with water, dried under reduced pressure to yield 3.4 kg of **11** as a white powder, yield 96%, mp 188-190 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.50 (t, J = 7.3 Hz, 3H), 2.15 (s, 3H), 4.20 (q, J = 7.3 Hz, 2H), 7.10 (d, J = 8.6 Hz, 1H), 7.65 (dd, J = 1.4, 8.5 Hz, 1H), 8.55 (s, 1H), 9.10 (s, 1H), 12.65 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.4, 23.8, 64.2, 111.6, 122.4, 123.0, 126.0, 127.1, 152.2, 166.9, 168.4. ESI-MS (*m*/*z*) 222 $[M - H]^-$.

5-Acetamido-4-ethoxy-2-nitrobenzoic acid (12)

To a stirred solution of **11** (3.3 kg, 15 mol) in AcOH (18 L) was added fuming nitric acid (1.8 L, 39 mol) at 25-35 °C. The resulting solution was stirred at this temperature for 6 h and diluted with chilled water (45 L). The resulting precipitate was collected by suction filtration, washed with water, dried under reduced pressure to provide 3.4 kg of **12** as a slightly brown solid, yield 85%, mp 234-236 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.40 (t, J = 6.9 Hz, 3H), 2.15 (s, 3H), 4.25 (q, J = 6.9 Hz, 2H), 7.60 (s, 1H), 8.55 (s, 1H), 9.40 (s, 1H), 13.25 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.1, 24.1, 65.3, 107.4, 119.0, 120.9, 131.1, 144.2, 149.6, 165.6, 169.5. ESI-MS (*m*/*z*) 267 $[M - H]^-$. Anal. Calcd for $C_{11}H_{12}N_2O_6$: C, 49.26; H, 4.51; N, 10.44. Found: C, 49.25; H, 4.58; N, 10.54.

Ethyl 3-(5-acetamido-4-ethoxy-2-nitrophenyl)-2-cyano-3-oxopropanoate (13)

A mixture of **12** (3.5 kg, 13.0 mol) and $SOCl_2$ (15 L) was stirred and heated at around 50 °C for 1 h to form a homogeneous solution. The solvent was recovered and the residue was azeotroped once with 5 L CH_2Cl_2 to provide 5-acetamido-4-ethoxy-2-nitrobenzoyl chloride. A suspension of NaOMe (0.75 kg, 11.0 mol) in MeOH (20 L) was stirred at 40–50 °C for 1 h to get a solution firstly, and ethyl cyanoacetate (1.4

L, 13.1 mol) was added dropwise over 1 h. The resulting white suspension was cooled below 0°C in an ice-salt bath and treated with 5-acetamido-4-ethoxy-2-nitrobenzoyl chloride (2.8 kg, 10.4mol) in THF (12 L) over 2 h, keeping the reaction temperature below 8 °C. To the mixture was then added chilled water (80 L), acidified to pH 2–3 with conc. HCl. The resulting solid was collected by suction filtration, washed with water, and dried under reduced pressure to give 3.2 kg of **13** as pale powders, yield 89% (from **12**), mp 169–171 °C. ^{1}H NMR (300 MHZ, DMSO-d_6): δ 0.98 (t, J = 6.9 Hz, 3H), 1.44 (t, J = 6.9 Hz, 3H), 2.19 (s, 3H), 3.85 (q, J = 6.9 Hz, 2H), 4.30 (q, J = 6.9 Hz, 2H), 7.77 (s, 1H), 8.15 (s, 1H), 9.50 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.9, 14.2, 24.3, 59.7, 65.2, 80.1, 107.2, 116.7, 118.9, 125.7, 133.5, 140.1, 147.8, 163.5, 169.8, 181.6. ESI-MS (*m*/*z*) 362 [M – H]$^-$. Anal. Calcd for $C_{16}H_{17}N_3O_7$: C, 52.89; H, 4.72; N, 11.57. Found: C, 52.86; H, 4.74; N, 11.73.

***N*-[5-(2-Cyanoacetyl)-2-ethoxy-4-nitrophenyl]acetamide (14)**

A mixture of **13** (3.0 kg, 8.2 mol), DMSO (15 L) and water (0.3 L) was heated at 100–110 °C for 30 min. Then the solution was cooled to around 50 °C and diluted with chilled water (60 L). The resulting precipitate was collected by suction filtration, washed with EtOAc, dried under reduced pressure to provide 1.9 kg of **14** as a pale yellow solid, yield 84%, mp 171–175 °C (dec.). IR: 3320, 2273, 1720, 1500 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (t, J = 5.4 Hz, 3H), 2.28 (s, 3H), 3.86 (s, 2H), 4.28 (q, J = 5.4 Hz, 2H), 7.88 (s, 1H), 8.01 (br s, 1H), 8.58 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.1, 24.2, 32.3, 65.4, 107.4, 115.3, 118.5, 126.9, 133.4, 140.5, 149.2, 169.7, 191.3. ESI-MS (*m*/*z*) 290 [M – H]$^-$. HRMS (ESI): Calcd for $C_{13}H_{13}N_3O_5Na$: 314.0753. Found: 314.0773. Anal. Calcd for $C_{13}H_{13}N_3O_5$: C, 53.61; H, 4.50; N, 14.43. Found: C, 53.35; H, 4.52; N, 14.20.

***N*-{5-[2-Cyano-3-(*N*,*N*-dimethylamino)acryloyl]-2-ethoxy-4-nitrophenyl}acetamide (15)**

To a stirred suspension of **14** (0.7 kg, 2.0 mol) in DME (6 L) was added DMF-DMA (0.4 L, 3.0 mol). The mixture was stirred at room temperature for 1 h. The resulting solid was collected by suction filtration, washed with EtOAc, and dried under reduced pressure to give 0.63 kg of **15** as a bright-yellow powder, yield 91%, mp 258–260 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.43 (t, J = 6.9 Hz, 3H), 2.19 (s, 3H), 3.28 (br s, 3H), 3.32 (s, 3H), 4.29 (q, J = 6.9 Hz, 2H), 7.73 (s, 1H), 7.88 (br s, 1H), 8.26 (s, 1H), 9.51 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 24.3, 38.7, 47.5, 65.1, 107.3, 118.3, 133.4, 140.2, 147.6, 157.8, 169.8. ESI-MS (*m*/*z*): 345 [M – H]$^-$. Anal. Calcd for $C_{16}H_{18}N_4O_5$: C, 55.49; H, 5.24; N, 16.18. Found: C, 55.20; H, 5.12; N, 15.93.

***N*-(3-Cyano-7-ethoxy-4-oxo-1,4-dihydroquinolin-6-yl)acetamide (1)**

To a mixture of **15** (0.52 kg, 1.5 mol) and zinc powder (0.6 kg, 9.0 mol) in water (5 L) and EtOH (5 L) was added AcOH (0.13 L, 2.3 mol). The suspension was refluxed with stirring for 12 h. The mixture was cooled to about 40 °C, then NaOH (0.18 kg, 4.5mol) was added and the solution was stirred at 40–50 °C for another 30 min. The resulting solution was filtered, and the filtrate was acidified with conc. HCl to pH

2–3 at 40–50 °C. The resulting precipitate was collected by suction filtration, washed with EtOH, dried under reduced pressure to give 0.35 kg of **1** as a pale solid, yield 85%, mp > 300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.45 (t, J = 6.6 Hz, 3H), 2.14 (s, 3H), 4.20 (q, J = 6.6 Hz, 2H), 7.05 (s, 1H), 8.59 (d, J = 6.3 Hz, 1H), 8.70 (s, 1H), 9.18 (s, 1H), 12.52 (d, J = 6.3 Hz, 1H). ESI-MS (m/z) 270 $[M - H]^-$.

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