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Technical Note

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A New and Improved Process for *N*-(4-Chloro-3-cyano-7-ethoxyquinolin-6-yl)acetamide

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ABSTRACT: A new and improved synthetic route to *N*-(4-chloro-3-cyano-7-ethoxyquinolin-6-yl)acetamide (**1**) is described on a kilogram scale. The key step is the basic cyclization of *o*-[(2-cyanovinyl)amino]benzoate (**14**) in ^{t}BuONa/^{t}BuOH system to give the 3-cyano-4-hydroxyquinoline (**7**). The final product **1** is obtained with 49% overall yield (seven steps) and 98.9% purity (HPLC), which makes it a cost-effective and commercially friendly process for scale-up operations.

INTRODUCTION

4-Chloroquinolines are important precursors to a number of anticancer,[1] antimalarial,[2] antidiabetic,[3] and 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 EKB-569 (**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]

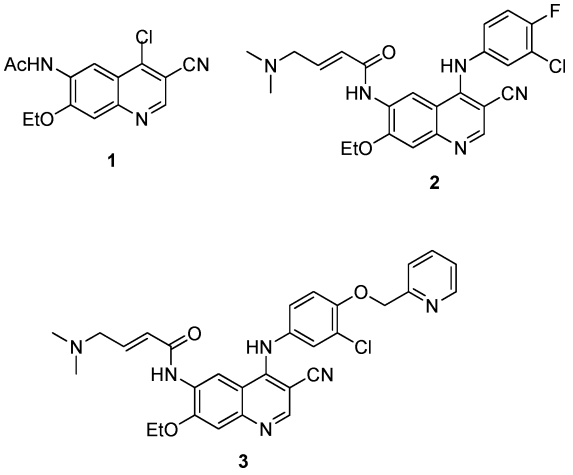
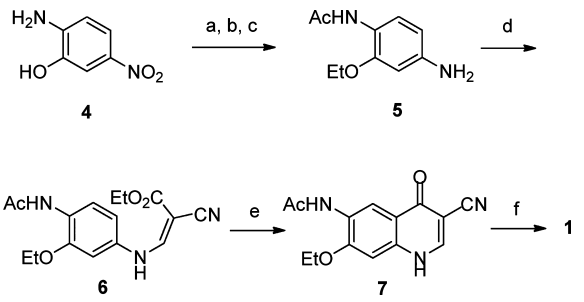


Figure 1. Chemical structures of **1**, EKB-569 (**2**), and HKI-272 (**3**).

The earlier work to prepare *N*-(4-chloro-3-cyano-7-ethoxyquinolin-6-yl)acetamide (**1**) (Scheme 1)[7] was based on Gould–Jacobs methodology and involved the reaction of cyanopropenoate **6** in through thermal cyclization at 250 °C for 20 h in Dowtherm A, which led to a messy and tedious operation, and too much material was destroyed in the reaction producing a tar or resin, which resulted in difficulties for purification; thus, the overall yield was reduced dramatically (only 35–45% was reached from **6** to **7**). What's more, Dowtherm A and diphenyl ether are high-boiling point solvents which are difficult to recover; they are harmful to the environment and also cause allergic reactions in the operation people based on our own experience. It only gave 16.6% yield over six steps.

Scheme 1. Reported large-scale synthesis of 1[a]



[a]Reagents and conditions: (a) AcOH, Ac_2O, 60 °C; (b) C_2H_5Br, K_2CO_3, DMF, 60 °C; (c) H_2, Pd–C, MeOH, 71% (three steps); (d) ethyl 2-cyano-3-ethoxyacrylate, toluene, 90 °C, 16 h, 90%; (e) Dowtherm A, 260 °C, 20 h, 35–45%; (f) diglyme, $POCl_3$, 100 °C, 1 h, 65%.

In order to develop a practical and commercial process of preparing compound **1**, a couple of synthetic routes were designed and studied by us.[8] The most efficient method[9] was based on the cyclization of the *o*-[(2-cyanovinyl)amino]-benzoate (**14**) under strongly basic conditions to form the 3-cyano-4-hydroxyquinoline (**7**). The target product **1** was obtained in $POCl_3$/EtOAc system with ~90% isolated yield, which is depicted in Scheme 2.

RESULTS AND DISCUSSION

Starting from methyl 3-amino-4-hydroxybenzoate (**8**), benzoate **10** was prepared by adopting the method described by Wissner,[10] with 88% overall yield (2 steps) and >99% purity (HPLC) without extra purification operation. Nitration of **10** to **11** was carried out in good yield by using yhe fuming HNO_3/

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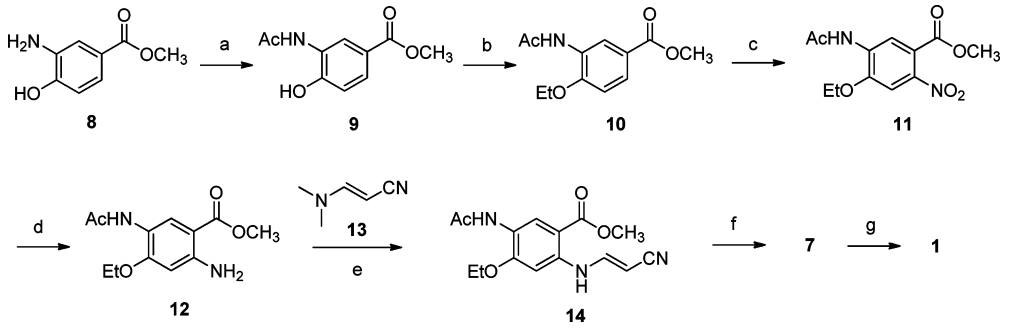
Scheme 2. Improved synthetic route of 1[a]



[a]Reagents and conditions: (a) AcOH, Ac_2O, 60 °C, 3 h, 92%; (b) C_2H_5Br, K_2CO_3, DMF, 60 °C, 6 h, 96%; (c) fuming HNO_3, CH_3NO_2, rt, 6 h, 89%; (d) H_2, Raney Ni, 1 atm, rt, 12 h, 91%; (e) AcOH, rt, 4 h, 92%; (f) ^{t}BuONa, ^{t}BuOH, reflux, 3 h, 85%; (g) $POCl_3$, DMAP (cat.), EtOAc, reflux, 2 h, 88%.

CH_3NO_2 system.[11] The crude **11** was purified by triturating in warm water to give the product with >97% purity (HPLC). Other nitration conditions had been studied also, including fuming HNO_3/CH_2Cl_2, 65% HNO_3, and HNO_3/H_2SO_4 mixed acid, most of which gave lower yield and purity. The aniline **12** was obtained through catalytic hydrogenation of **11** under H_2/Raney Ni/MeOH condition, under 1 atm at room temperature. The crude **12** was purified by heating and stirring in EtOAc, giving 91% overall yield and >96% purity (HPLC). 3-(Dimethylamino)acrylonitrile (**13**) was produced by condensation of cyanoacetic acid with *N,N*-dimethylformamide dimethylacetal (DMF-DMA) in good yield based on Kraus's method.[12] The key intermediate **14** was afforded in HOAc at room temperature by condensation of aniline **12** with acrylonitrile **13** in high yield,[13] which contained both cis and trans isomers as confirmed by HPLC and MS results. The two isomers of **14** could both be converted to 4-hydroxyquinoline compound **7** under strongly basic conditions. The crude **14** was purified by suspending and stirring in 50% EtOH/H_2O at room temperature to obtain the product in 92% yield and >97% purity (HPLC). Compound 3-cyano-4-hydroxyquinoline (**7**) was produced by cyclization of **14** under strongly basic conditions.[14] The ^{t}BuONa/^{t}BuOH system was selected as the reaction condition for the scale-up. Other conditions had also been studied by us in detail. The experimental results showed that NaOH/EtOH, NaOMe/MeOH, or NaOEt/EtOH system gave more impurities. Although NaOEt/EtOH (produced by metallic sodium and anhydrous ethanol) or DBU/MeCN condition produced good results, the safety or cost factor limited their application on a scale-up operation. The crude **7** was purified by heating and stirring in 50% EtOH/EtOAc to give the compound with 85% overall yield and 99% purity (HPLC). In 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).

CONCLUSIONS

In this article, we developed a new and kilogram scale of a synthetic process for *N*-(4-chloro-3-cyano-7-ethoxyquinolin-6-yl)acetamide (**1**). In the new synthetic route, common and inexpensive regents and mild reaction conditions were used in order to simplify the operation, enhance the overall yield, and decrease the preparation cost, which made it as an efficient, practical, and commercial manufacture process of the title compound **1**, which gave 49% yield over 7 steps.

EXPERIMENTAL SECTION

Materials and Instruments. 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 100 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. The purity measurements are on the basis of HPLC UV Area%.

Methyl 3-Acetamido-4-hydroxybenzoate (9). To a stirred solution of methyl 3-amino-4-hydroxybenzoate **8** (3.0 kg, 17.9 mol) in AcOH (15 L) at 60 °C was added Ac_2O (2.6 L, 27.5 mol) over 30 min, and the mixture was stirred at this temperature for 3 h. The mixture was poured into chilled water (~10 °C, 40 L) over 1 h and stirred. The resulting white solid was filtered, washed with water (2 × 4 L), and dried at ordinary pressure (50 °C, 6 h) to give product **9** (3.5 kg, 92%) as a white powder, mp 181−183 °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): 210.1 (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, 25.3 mol) in DMF (25 L) at 60 °C was added C_2H_5Br (1.5 L, 19.9 mol) over 1 h, and the mixture was stirred at this temperature for 6 h. The mixture was poured into chilled water (~10 °C, 50 L) and stirred for 1 h at rt. The resulting white solid was filtered, washed with water (2 × 4 L), and dried at ordinary pressure (50 °C, 6 h) to provide **10** (3.8 kg, 96%) as a white powder, 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): 238.1 (M + H), 260.1 (M + Na). HPLC conditions: Column: ZORBAX SB-

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C18, 150 mm × 4.6 mm × 5 μm; Detection: 254 nm; Flow rate: 1.0 mL/min; Temperature: 30 °C; Injection load: 10 μL; Solvent: acetonitrile; Concentration: 0.5 mg/mL; Run time: 25 min; Mobile phase A: water (0.1% H_3PO_4); Mobile phase B: acetonitrile; Gradient program: time (min): 0, 10, 20, 25; % of mobile phase A: 80, 60, 10, 10; % of mobile phase B: 20, 40, 90, 90, t_R: 10.754 min. Purity: 99.3%.

Methyl 5-Acetamido-4-ethoxy-2-nitrobenzoate (11). To a stirred solution of compound **10** (3.6 kg, 15.2 mol) in $MeNO_2$ (40 L) at rt was added 95% fuming HNO_3 (0.20 L, 4.6 mol) over 20 min. After the mixture was stirred at rt for 1 h, another portion of 95% fuming HNO_3 (1.2 L, 27.6 mol) was added over 1 h, so that the reaction temperature stayed under 35 °C; the reaction solution was then stirred for another 6 h at rt. Then the reaction solution was poured into cooled water (~10 °C, 40 L) and stirred for 1 h. The organic layer was separated and washed by water (2 × 20 L). The solvent was distilled off to give the crude **11** (4.1 kg) as a brown solid, which was added to water (20 L) and stirred rapidly at rt for 1 h. The resulting solid was collected by suction filtration, washed with water (2 × 4 L), and dried at ordinary pressure (50 °C, 8 h) to give product **11** (3.8 kg, 89%) as a light-yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.52 (t, J = 7.2 Hz, 3H), 2.25 (s, 3H), 3.89 (s, 3H), 4.23 (q, J = 7.2 Hz, 2H), 7.44 (s, 1H), 7.91 (br, 1H), 8.74 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.6, 24.6, 53.4, 65.9, 108.1, 118.7, 120.8, 132.1, 144.1, 150.2, 165.4, 170.1. ESI-MS (m/z): 281.0 (M − H), 282.9 (M + H), 305.0 (M + Na). HPLC conditions: Column: ShinoChrom ODS-BP, 250 mm × 4.6 mm × 5 μm; Detection: 230 nm; Flow rate: 1.0 mL/min; Temperature: 30 °C; Injection load: 5 μL; Solvent: 60% acetonitrile/water; Concentration: 0.5 mg/mL; Run time: 50 min; Mobile phase A: water (0.1% H_3PO_4); Mobile phase B: acetonitrile; Gradient program: time (min): 0, 5, 45, 50; % of mobile phase A: 90, 90, 0, 0; % of mobile phase B: 10, 10, 100, 100, t_R: 27.441 min. Purity: 97.7%.

Methyl 5-Acetamido-2-amino-4-ethoxybenzoate (12). Compound **11** (3.2 kg, 11.3 mol) and RTH-311 Raney-Ni (wet, 0.30 kg) were added to MeOH (40 L), and the mixture stirred for 12 h at rt under 1 atm hydrogen atmosphere. The reaction mixture was then filtered through a Celite pad, and then the filter cake was washed by methanol (2 × 3 L). The combined filtrates were concentrated to give the crude aniline product **12** (3.0 kg) as a brown solid, which was suspended in EtOAc (8 L) and heated to reflux for 1 h. After cooling to rt, the resulting solid was collected by suction filtration, washed with EtOAc (2 × 1 L), and dried at ordinary pressure (50 °C, 4 h) to give product **12** (2.6 kg, 91%) as a light-tan solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.45 (t, J = 7.2 Hz, 3H), 2.16 (s, 3H), 3.82 (s, 3H), 4.06 (q, J = 7.2 Hz, 2H), 5.71 (br, 2H), 6.09 (s, 1H), 7.35 (br, 1H), 8.68 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.8, 23.9, 51.5, 64.1, 98.6, 101.0, 116.7, 126.3, 150.9, 155.9, 167.9, 168.5. ESI-MS (m/z): 252.9 (M + H). Using HPLC conditions the same as those for compound **11**, t_R: 20.267 min. Purity: 96.3%.

Methyl 5-Acetamido-2-[(2-cyanovinyl)amino]-4-ethoxybenzoate (14). Compound **12** (2.5 kg, 9.9 mol) was dissolved in glacial HOAc (18 L) at rt. 3-(Dimethylamino)-acrylonitrile **13** (1.1 kg, 11.4 mol) was added over 1 h and stirred at rt for another 4 h. A large amount of grey solid was generated gradually. The mixture was poured into chilled water (~10 °C, 40 L) over 1 h and stirred. The resulting solid was filtered, washed with water (2 × 2 L), and dried to give crude product **14** (3.0 kg) as a grey powder, which was added to 50% EtOH/H_2O (10 L) and stirred at rt for 1 h. The resulting solid was collected by suction filtration, washed by 50% EtOH/H_2O (2 × 2 L), and dried at 10−20 mmHg (50 °C, 4 h) to give product **14** (2.8 kg, 92%) as a white solid, which contained both cis and trans isomers as confirmed by LC−MS results. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.39 (t, J = 6.9 Hz, 3H), 2.06 (s, 3H), 3.82 (s, 3H), 4.25 (q, J = 6.9 Hz, 2H), 5.14 (d, J = 13.2 Hz, 1H), 7.05 (s, 1H), 8.21 (t, J = 13.2 Hz, 1H), 8.41 (s, 1H), 9.02 (s, 1H), 10.41 (d, J = 13.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.6, 23.9, 52.3, 65.1, 72.0, 98.1, 104.6, 120.9, 121.4, 125.2, 141.2, 146.3, 155.4, 167.9, 168.9. ESI-MS (m/z): 303.9 (M + H), 326.0 (M + Na). HPLC conditions: Column: ShinoChrom ODS-BP, 250 mm × 4.6 mm × 5 μm; Detection: 254 nm; Flow rate: 1.0 mL/min; Temperature: 30 °C; Injection load: 5 μL; Solvent: 60% acetonitrile/water; Concentration: 10 mg/mL; Run time: 35 min; Mobile phase A: 0.02 M aqueous KH_2PO_4; Mobile phase B: acetonitrile; Gradient program: time (min): 0, 5, 15, 35; % of mobile phase A: 60, 60, 30, 30; % of mobile phase B: 40, 40, 70, 70, t_R: 12.355 min (59.9%), t_R: 12.564 (37.7%), Combined purity: 97.6%.

***N*-(3-Cyano-7-ethoxy-4-oxo-1,4-dihydroquinolin-6-yl)acetamide (7).** The benzoate **14** (2.0 kg, 6.6 mol) and ^{t}BuONa (1.3 kg, 13.5 mol) were added to ^{t}BuOH (20 L, warmed to liquid if needed). The reaction mixture was stirred and heated to reflux for 3 h. The clear reaction solution was cooled to ~40 °C, concentrated to ~8 L, and then diluted with water (15 L). The pH was then adjusted to ~4 with concentrated HCl. The resulting suspension was stirred at 40−50 °C for another 1 h. The resulting solid was filtered, washed with water, and dried to give the crude product **7** (1.7 kg), which was suspended in 50% EtOH/EtOAc (8 L) and stirred and heated to 70 °C for 1 h. After cooling to rt, the resulting solid was collected by suction filtration, washed by 50% EtOH/EtOAc (2 × 1 L), and dried at 10−20 mmHg (60 °C, 4 h) to give product **7** (1.5 kg, 85%) as a pale solid, mp >300 °C. ^{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 °C; 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** (1.4 kg, 5.1 mol) and DMAP (30.0 g, 0.25 mol) were suspended in EtOAc (15 L) and stirred at rt. To the mixture was added slowly over 1 h $POCl_3$ (1.9 L, 20.8 mol), and the mixture was then heated to reflux for another 2 h to give a clear solution. After cooling to rt, the reaction solution was poured slowly into ice−water (20 L) and stirred for 2 h. The resulting solid was filtered, washed with water (2 × 2 L), and dried to give the crude product **1** (1.4 kg), which was suspended in DMF (4 L) and stirred at rt for 1 h. The solid was filtered, washed with EtOAc (3 × 1 L), and dried at 10−20 mmHg (50 °C, 4 h) to give product **1** (1.3 kg, 88%) as a faint brown solid, mp: 255−258 °C. ^{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

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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 °C; 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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Author Contributions

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Notes

The authors declare no competing financial interest.

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