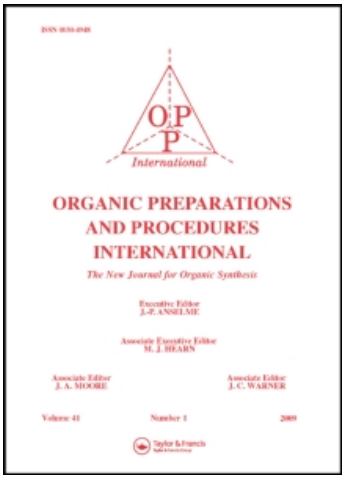

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An Improved Non-chromatographic Scale-up Synthesis of a New 1,6,7,8-Substituted-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid as a Potent Bacterial Topoisomerase Inhibitor

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An Improved Non-chromatographic Scale-up Synthesis of a New 1,6,7,8-Substituted-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid as a Potent Bacterial Topoisomerase Inhibitor

Xun Li,[1] Scott Youells,[1] Ronald K. Russell,[1] Armin Roessler,[2] Tobias Schmid,[2] Roger Faessler,[2] Michele A. Weidner-Wells,[1] Eugene B. Grant,[1] and Mark J. Macielag[1]

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7-[4-(2-Amino-1-chloroethylidene)piperidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**10**) is a potent bacterial topoisomerase inhibitor. *In vitro*, compound **10** is two-fold more potent than gemifloxacin when tested against ciprofloxacin-resistant *Streptococcus pneumoniae* clinical isolates (MIC_{90} = 1 μg/mL); it is also more potent than ciprofloxacin and gemifloxacin when tested against a collection of methicillin-resistant *Staphylococcus aureus* (MIC_{90} = 2 μg/mL) and coagulase-negative staphylococci isolates (MIC_{90} = 1 μg/mL).[1,2] In order to prepare 100 g of compound **10** to facilitate *in vivo* investigation, it was decided to attempt to improve some of the steps of the original discovery medicinal chemistry (Discovery) route, an eight-step convergent synthesis with merely 6% overall yield of **10**,[1,2] and address the scale up issues that were identified in the following steps: *first*, the high exothermicity of the use of sodium hydride (NaH) to generate triethyl 2-chloro-2-phosphonoacetate anion in the Horner-Wadsworth-Emmons reaction and its quenching (*Step 1*, *Schemes 1*), *second*, the reduction of ester **2** using DIBALH resulted in a 44% yield of alcohol **3** after chromatography (*Step 2*, *Schemes 1*), *third*, the product **4** of Mitsunobu reaction also required chromatographic purification (*Step 3*, *Schemes 1*), *fourth* the preparation of difluoroborate ester **7** required a large excess (11.9 equiv) of borontrifluoride etherate and extended reaction times (48–72 h), but gave only moderate to fair yields (50–78%) of **7** by precipitation of the crude product with diethyl ether

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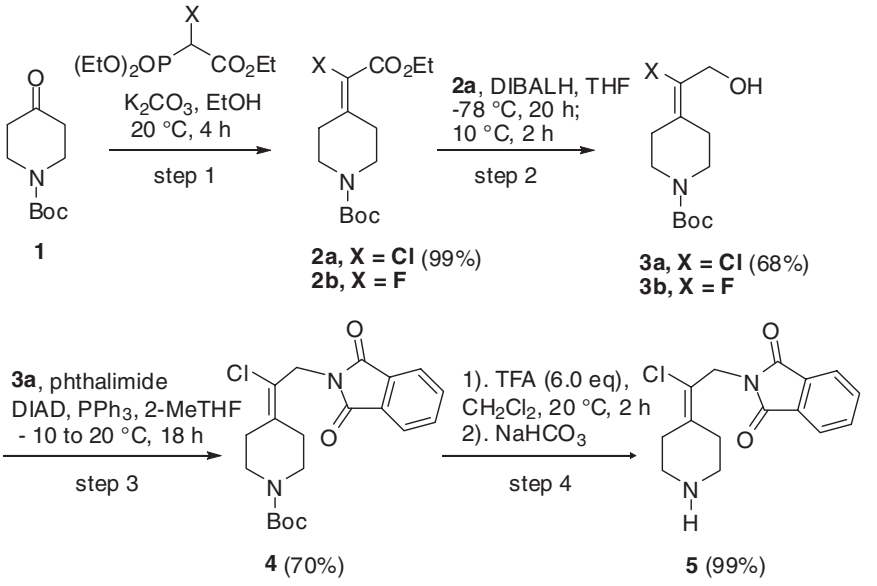
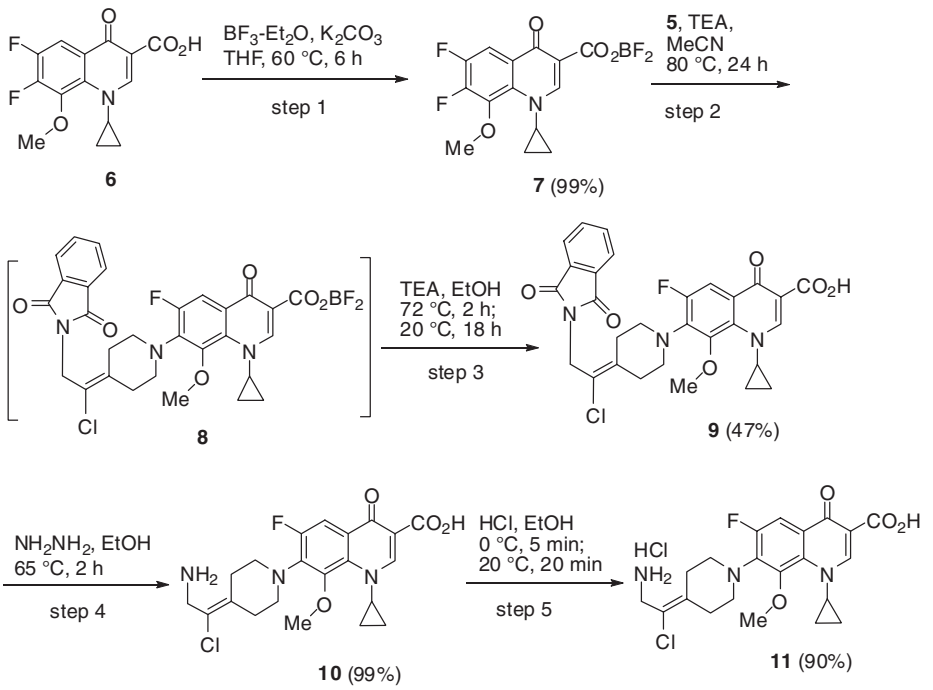


Scheme 1

(*Step 1*, *Scheme 2*), and *fifth*, a long reaction time (total 72 h) for *Steps 2* and *3* (of *Scheme 2*) that gave only low to moderate yield of product **9**.[1,2] Herein, we report an improved non-chromatographic scale up process for acid **10** and its hydrochloride salt **11** in 22% and 19% overall yields, respectively.



Scheme 2

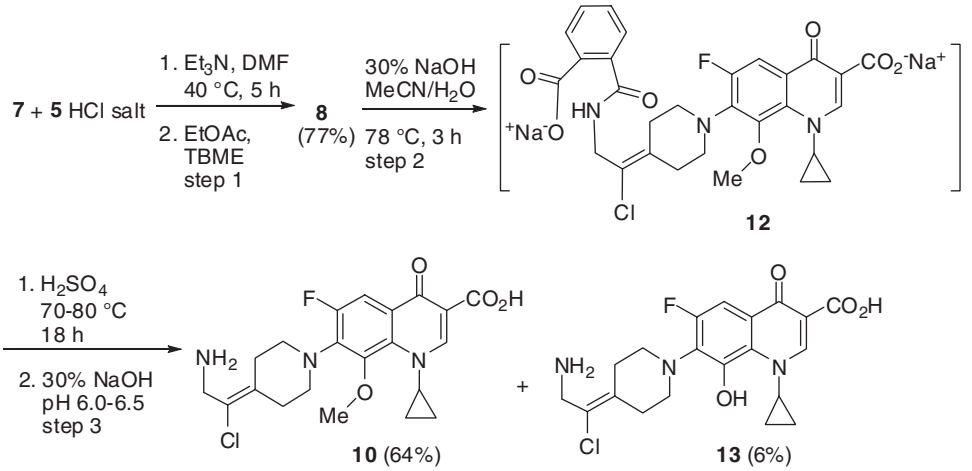
The two key building blocks, 2-[2-chloro-2-(piperidin-4-ylidene)ethyl]isoindoline-1,3-dione (**5**) and [1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-(oxo-κO)-3-quinolinecarboxylato-κO3]-difluoroboron (**7**), were coupled in *Step 6* to afford **8** via the displacement of the 7-fluoro group of compound **7** by the cyclic secondary amine of compound **5**. Compound **5** was prepared from commercially available *tert*-butyl 4-oxopiperidine-1-carboxylate (**1**) by a four-step synthetic sequence (*Scheme 1*). Although the Discovery procedure produced a high yield (95%) of chloroalkylidene ester **2a** by the Horner-Wadsworth-Emmons reaction of compound **1** (*Step 1*),[3–5] both the deprotonation of triethyl 2-chloro-2-phosphonoacetate using NaH in THF and the quench of the completed reaction were highly exothermic. The non-exothermic one-pot reaction process, originally developed for the synthesis of fluoroalkylidene carboxylate ester **2b** (the precursor of **3b**),[6] was also found useful for the preparation of **3a**. In practice, the treatment of triethyl 2-chloro-2-phosphonoacetate with K_2CO_3 in absolute EtOH and follow by addition of **1** at ambient temperature for 4 h afforded **2a** in quantitative yield *via* a non-exothermic reaction and without the need for chromatographic purification. Reduction of **2a** to the corresponding allylic alcohol **3a** using DIBALH in toluene led to a 44% yield of **3a** and required chromatographic purification (*Step 2*, *Scheme 1*). When toluene was replaced by THF as the solvent and the reaction was quenched with 40% Rochelle's solution,[7] **3a** was obtained in 62% yield without chromatography. The hydroxy group of **3a** was converted to the protected amine **4** using phthalimide under Mitsunobu reaction conditions,[8–10] and a 73% yield of pure **4** was obtained after recrystallization of the crude product from EtOAc/toluene (1/9). At this point, the Boc-protecting group of compound **4** was cleaved with trifluoroacetic acid (TFA) to afford the cyclic secondary amine **5** as a free base after aqueous alkaline workup.

Difluoroborate ester **7** was readily prepared form commercially available 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**6**) in quantitative yield, after the treatment of **6** with a slight excess of $BF_3{\cdot}Et_2O$ (1.35 equiv) and using K_2CO_3 (1.15 equiv) as an acid scavenger in refluxing THF for 6 h (*Step 1*, *Scheme 2*). The addition of an inorganic base (K_2CO_3) to this reaction was a key improvement to the Discovery route, since K_2CO_3 reacted efficiently with the by-product HF and formed insoluble KF salt, which precipitated out of the system, and drove the reaction to the completion.[11] The displacement of the 7-fluoro group of difluoroborate ester **7** with cyclic amine **5** led the borate ester intermediate **8**, which was not isolated and underwent alcoholysis *in situ* to the penultimate acid intermediate **9** in 47% yield (*Steps 2* and *3*, *Scheme 2*).[12] Attempts to improve the yield of **8** by replacement of Et_3N with *N*-methylpyrrolidine or by changing the solvent from MeCN to DMF were not fruitful and resulted in only a 35–48% yield of **8**. The moderate yields of *steps 2* and *3* could be attributed to the simultaneous occurrence of two competitive processes: the desired coupling of **5** and **7** to intermediate **8** and the cleavage of difluoroborate ester **7** (by HF generated in *Step 2*) back to starting acid **6** ($\sim$26%, $MH^+ = 296$), which in turn, formed an insoluble salt pair with amine **5** in MeCN.

The phthalimide protecting group of **9** was cleaved by treatment with eight equiv of hydrazine in refluxing methanol for 1 h to afford a mixture of the desired amine product **10** and the by-product, phthalhydrazide (*Step 4*, *Scheme 2*).[13,14] Use of 4.0 equiv of hydrazine resulted in incomplete conversion ($<$ 60% of **10**) after refluxing for 3 h while 6.0 equiv

of hydrazine gave 90% of **10** over the same time frame. When MeCN was added to the warm alcoholic mixture of **10** and phthalhydrazide, the by-product precipitated in nearly quantitative yield as a crystalline white solid that was easily removed by filtration. Concentration of the filtrate resulted in crude **10**, which was recrystallized from a mixture of MeOH and MeCN to provide pure crystalline free base **10** in a good yield (80%). Finally, compound **10** was converted to its hydrochloride salt, which was recrystallized from EtOH to afford pure crystalline HCl salt of **11** (99.9 HPLC area%) in excellent yield (90%) as a crystalline solid.

The use of inorganic base/acid as an alternative to hydrazine for cleavage of phthalimide **8** was also investigated.[15,16] The reaction of difluoroborate ester **7** with **5** hydrochloride salt[17] under modified reaction and work-up conditions resulted in quantitative yield of **8** as a solid of 77% chemical purity (HPLC area%) (*Step 1*, *Scheme 3*). After treatment with 30% aqueous NaOH, compound **8** was completely hydrolyzed to dicarboxylate sodium salt **12** *in situ*, which upon subsequent treatment with conc. H_2SO_4 resulting in 64% yield of **10** in fair chemical purity (93%, HPLC area%) along with demethylated **13** (6%) as a major by-product. As in the hydrazine cleavage conditions, this alternative route successfully afforded the desired final product **10** without chromatographic purification. In spite of the reasonable yield and purity of **10** obtained from these alternative conditions, the method would need to be further improved to meet the requirements of scale up production.



Scheme 3

In summary, an improved, reproducible, and non-chromatographic process has been developed for the large scale preparation of 7-[4-(2-amino-1-chloroethylidene)piperidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride salt (**11**) in 19% yield in nine steps with excellent chemical purity (>99.0 HPLC area%).

Experimental Section

Starting materials, reagents, and solvents were obtained from commercial suppliers and were used without further purification. Melting points are uncorrected and were determined on a Thomas Hoover capillary melting point apparatus. ^{1}H-NMR spectra were recorded at 300 MHz on a Bruker Avance-300 instrument and or 400 MHz on a Bruker Avance-400 instrument. Mass spectra were obtained on an Agilent Series 180 LC/MS instrument (positive/negative modes). The purity/impurity ratios of compounds **1–5** were determined by *HPLC method A* with an Agilent Series 1100 system at UVmax = 210 and 254 nm, using a Phenomenex® Luna C_{18} (2) column (4.6 mm ID × 50 mm, 5.0 micron) at 35°C with flow rate of 1.0 mL/min and run time of 10.0 min. Solvents: A H_2O + 0.05% TFA, B CH_3CN; Gradient: B 30% /0.0 min, B 40%/1.0 min, B 90%/4.0 min, B 90%/8.0 min, B 30%/10.0 min. The purity/impurity ratios of compounds **6–14** were determined by *HPLC method B* with an Agilent Series 1100 system at UVmax = 210, 254, and 325 nm, using a Phenomenex® Luna C_{18} (2) column (4.6 mm ID × 50 mm, 5.0 micron) at 35°C with flow rate of 1.0 mL/min and run time of 10.0 min. Solvents: A H_2O + 0.05% TFA, B CH_3CN; Gradient: B 20%/0.0 min, B 20%/1.0 min, B 90%/5.0 min, B 45%/8.0 min, B 20%/10.0 min. All reactions were conducted in a 4-neck round bottom flask equipped with a thermocouple controller, a mechanical stirrer, a pressure-equalization dropping funnel, a nitrogen inlet/outlet adapter, and/or a condenser whenever it was needed.

tert-Butyl 4-(1-Chloro-2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (2a)

To a 5 L round bottom flask was added *tert*-butyl 4-oxopiperidine-1-carboxylate (**1**) (230.0 g, 1.73 mol) and EtOH (3.0 L). Triethyl 2-chloro-2-phosphonoacetate (275.0 mL, 1.27 mol) was added followed by K_2CO_3 (375.0 g, 1.73 mol) and the resulting mixture was stirred at 22°C for 4 h. The progress of the reaction was monitored by HPLC and LC-MS. Excess K_2CO_3 was removed by filtration and the filtrate was concentrated *in vacuo* to give a viscous oil, which was diluted with EtOAc (1.0 L), washed with a saturated Na_2CO_3 solution (1.0 L × 3), and dried over Na_2SO_4. The solvent was concentrated at 50°C under house vacuum (∼160 mmHg) to afford 371.0 g (99% yield; 99 HPLC area%) of **2a** as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): *d* 4.28 (q, 2 H, CH_2), 3.43–3.57 (m, 4 H, 2 CH_2), 2.84 (t, 2 H, 2 CH), 2.63 (t, 2 H, 2 CH), 1.48 (s, 9 H, 3 CH_3), 1.35 (t, 3 H, CH_3). ^{13}C-NMR ($CDCl_3$, 75.0MHz): δ 163.34, 154,67, 147.41, 117.81, 80.17, 61.59, 43.74 (2 C), 34.46, 31.97, 28.42 (3 C), 17.2. LC-MS: *m*/*z* 304 [MH^+], 326 [M+Na]$^+$, 629 [2M+Na]$^+$.

Anal. Calcd for ($C_{14}H_{22}ClNO_4$): C, 55.35; H, 7.30; Cl, 11.67; N, 4.61. Found: C, 55.31; H, 7.40; Cl, 11.33; N, 4.36.

tert-Butyl 4-(1-Chloro-2-hydroxyethylidene)piperidine-1-carboxylate (3a)

To a 12 L round bottom flask charged with compound **2a** (370.0 g, 1.29 mol) and THF (4.0 L) and cooled to −78°C, DIBALH (2.30 L, 2.90 mol; 1.5 M in toluene) was added dropwise over a 2 h period while the temperature was maintained below −63°C. After the addition, the reaction mixture was stirred at −75°C for 24 h, and then warmed to 10°C and stirred for 2 h; the progress of the reaction was monitored by HPLC, TLC, and LC-MS. Rochelle's solution (4.0 L, 400 g/1 L) was added dropwise over 3 h; the mixture

was warmed to 20°C and stirred for 24 h. After phase separation, the organic layer was concentrated *in vacuo* to yield 244.0 g of crude material as a viscous oil, which was diluted with EtOAc (1.0 L), washed with brine (1.0 L × 3), and dried over Na_2SO_4. The solvent was concentrated at 50°C under house vacuum (∼160 mmHg) to afford 186.0 g (62% yield; 98 HPLC area%) of compound **3a** as a yellowish solid, mp. 66–69°C. An additional 17.0 g (6% yield; 99 HPLC area%) of **3a** was extracted using EtOAc from the aqueous layer. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.61 (s, 1 H, OH), 4.34 (s, 2 H, CH_2), 3.39–3.51 (m, 4 H, 2 CH_2), 2.37–2.54 (m, 4 H, 2 CH_2), 1.48 (s, 9 H, 3 CH_3). ^{13}C-NMR ($CDCl_3$, 75.0 MHz): δ 154.69, 134.40, 127.25, 79.89, 62.30, 43.75 (2C), 30.87, 29.86, 28.42 (3 C). LC-MS: *m/z* 262 [MH^+], 284 [$M+Na]^+$.

Anal. Calcd for $C_{12}H_{20}ClNO_3$: C, 55.06; H, 7.70; Cl, 13.54; N, 5.35. Found: C, 55.04; H, 7.78; Cl, 13.14; N, 5.08.

4-[1-Chloro-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)ethylidene]piperidine-1-carboxylic Acid tert-Butyl Ester (4)

A 22-L round bottom flask was charged with 2-MeTHF (3.0 L), alcohol **3a** (295.2 g, 1.13 mol), phthalimide (231.9 g, 1.58 mol), and triphenylphosphine (411.0 g, 1.58 mol) and the mixture was stirred at 20°C. The reaction mixture was cooled to −10°C and diisopropyl azodicarboxylate (309.0 mL, 1.58 mol) was added dropwise at a such rate that the temperature remained below 10°C. After the addition, the mixture was stirred at 20°C for 18 h and the progress of the reaction was monitored by HPLC and LC-MS. The reaction mixture was quenched with deionized (D.I.) water (2 L) and then partitioned with EtOAc (3 L). After phase separation, the organic layer was washed with 4 N HCl solution (2 L), saturated $NaHCO_3$ solution (2 L), and brine (2 L), and dried over $MgSO_4$. The filtrate was concentrated at 60°C under house vacuum (∼ 120 mmHg) to afford a crude material, which was crystallized from EtOAc/toluene (1/9, vol/vol) to yield 321.7 g of compound **4** (73% yield, 98 HPLC area%) as a white solid, mp. 120–122°C. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.89 (dd, 2 H, 2 ArCH), 7.74 (dd, 2 H, 2 ArCH), 4.56 (s, 2 H, CH_2), 3.64–3.58 (m, 2 H, 2 CH), 3.50–3.41 (m, 2 H, 2 CH), 2.69–2.62 (m, 2 H, 2 CH), 2.55–2.45 (m, 2 H, 2 CH), 1.48 (s, 9 H, 3 CH_3). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 154.74, 136.41, 134.28 (2 C), 131.97 (2 C), 123.56 (2 C), 121.50, 79.74, 44.8 (2 C), 39.97, 30.98, 30.40, 28.45 (3 C). LC-MS: *m/z* 291 [$(MH\text{-}100)^+$], 391 [MH^+], 413 [$M+Na]^+$, 803 [$2M+Na]^+$.

Anal. Calcd for $C_{20}H_{23}ClN_2O_4$: C, 61.46; H, 5.93; Cl, 9.07; N, 7.17. Found: C, 61.13; H, 6.01; Cl, 8.87; N, 7.01.

2-[2-Chloro-2-(piperidin-4-ylidene)ethyl]isoindoline-1,3-dione (5)

To a 12 L round bottom flask was charged with compound **4** (368.0 g, 0.942 mol) and CH_2Cl_2 (3400 mL). The solution was stirred at 20°C under nitrogen. TFA (435.3 mL, 5.649 mol) was added over a 10 min period. The mixture was warmed to 38°C and stirred for 3 h; the progress of the reaction was monitored by HPLC and LC-MS. The solvent was removed at 40°C under house vacuum (∼120 mmHg) and the resulting TFA salt (579.6 g; 86 HPLC area%) was dissolved in CH_2Cl_2 (3.0 L). The organic solution was washed with 10% Na_2CO_3 solution (2.0 L × 2), brine (2.0 L), dried over $MgSO_4$, and then concentrated

at 50°C under house vacuum (~160 mmHg) to afford 289.9 g (105% isolated yield, 90.0 HPLC area%) of free base **5** as an off-white solid, mp. 101–104°C, after drying at 60°C under high vacuum (20 mmHg) for 20 h. ^{1}H- NMR ($CDCl_3$, 400 MHz): δ 7.88 (dd, 2 H, 2 ArCH), 7.75 (dd, 2 H, 2 ArCH), 4.62 (s, 2 H, CH_2), 3.04 (m, 2 H, 2 CH), 2.92 (m, 2 H, 2 CH), 2.66 (m, 2 H, 2 CH), 2.48 (m, 2 H, 2 CH), 1.91–2.19 (br s, 1 H, NH). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 167.72 (2 C), 136.40, 134.28 (2 C), 131,98 (2 C), 123.68 (2 C), 121.50, 45.6 (2 C), 39.92, 30.98, 30.46. LC-MS: *m/z* 291 [MH^+], 313 [M+Na]$^+$.

Anal. Calcd for $C_{15}H_{15}ClN_2O_2$: C, 61.97; H, 5.20; Cl, 12.19; N, 9.64. Found: C, 61.59; H, 5.05; Cl, 12.58; N, 9.47.

[1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-(oxo-κO)-3-quinoline-carboxylato-κO3]difluoroboron (7)

To a 12 L round bottom flask was charged with **6** (250.0 g, 0.847 mol), anhydrous THF (3.0 L) and K_2CO_3 (129.6 g, 0.938 mol, ~325 mesh). This suspension was stirred at 20°C under N_2 for 5 min and $BF_3{\cdot}Et_2O$ (123.4 mL, 0.938 mol) was added over a 5 min period; the mixture was heated to 66°C and refluxed for 6 h. The progress of the reaction was monitored by HPLC and LC-MS (when the reaction was incomplete, for example, 10% of starting acid **6** was determined to be present in the reaction mixture, a little more $BF_3{\cdot}Et_2O$ (20 mL, 0.158 mol) was added to the reaction, which drove the reaction to completion after refluxing an additional 2 h). The reaction mixture was cooled to 20°C and diluted with Et_2O (5.0 L) and stirred for 10 min (Et_2O was replaced by *t*-butyl methyl ether (TBME) when production was carried out on multi-kilogram scale). The solid was collected and washed with Et_2O (100 mL × 2) and then dried at 50°C under house vacuum (~160 mmHg) for 20 h to afford 398.0 g (137% yield; 98.4 HPLC area%) of crude **7**. This crude solid was suspended in MeCN (4.0 L) and stirred at 20°C for 20 min, the solid was filtered off and washed with MeCN (100 mL). The filtration cake was re-suspended and stirred in MeCN three additional times (2.0 L × 3, or until no more **6** could be detected by HPLC in the filtrate); the filtrates were combined and concentrated at 50°C under house vacuum (~160 mmHg). The resulting off-white crystalline solid was dried at 50°C under house vacuum (~160 mmHg) for 20 h to afford 282.6 g (97% yield; 99.6 HPLC area%) of pure **7**, mp. 226–228°C, lit.[11] mp. 226–228°C. HPLC (area%/retention time): **6**, <0.5%/4.64 min; and **7**, 99.5%/4.39 min. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.26–1.35 (m, 2 H, CH_2), 1.36–1.41 (m, 2 H, CH_2), 4.19 (s, 3 H, OCH_3), 4.54 (m, 1 H, CH), 8.28 (dd, 1 ArCH), 9.21 (s, 1 H, ArCH). ^{13}C-NMR (DMSO-d_6, 100.6 MHz): δ 170.21, 168.89, 159.29, 152.44, 150.38 (dd, $^1J_{CF} = 254.8$ Hz, $^2J_{CF} = 12.88$ Hz), 149.51 (dd, $^1J_{CF} = 257.13$ Hz, $^2J_{CF} = 15.29$ Hz), 141.78, 134.26, 119.20, 106.16, 63.72, 43.64, 8.71 (2 C). LC-MS: *m/z* 344 [MH^+], 709 [2M+Na]$^+$.

Anal. Calcd for $C_{14}H_{10}BF_4NO_4$: C, 49.02; H, 2.94; N, 4.08; B, 3.15; F, 22.15. Found: C, 49.18; H, 2.86; N, 3.91; B, 3.36; F, 22.03.

7-{4-[1-Chloro-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethylidene]piperidin-1-yl}-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (9)

A 22 L round bottom flask was charged with difluoroborate ester **7** (300.0 g, 0.874 mol), MeCN (8000 mL), and compound **5** (330.4 g, 1.136 mol). This suspension was stirred at 20°C under N_2 for 5 min, Et_3N (731.0 mL, 5.244 mol) was added over a 10 min period,

and the mixture was heated to 80°C and refluxed for 24 h; the progress of the reaction was monitored by HPLC and LC-MS. The formation of intermediate **8** was confirmed by LC-MS ($MH^+ = 614.2$) as well as HPLC spiked with an authentic sample of **8**. The reaction mixture was cooled to 60°C, EtOH (7000 mL) and Et_3N (731.0 mL, 5.244 mol) were added, and the mixture was heated to reflux at 72°C for 2 h, and then cooled to 20°C and stirred for 18 h. The yellow solid was collected, washed with hexane (200 mL × 2), and dried at 50°C under house vacuum (∼160 mmHg) for 20 h to afford 229.8 g (47% yield; 92 HPLC area%) of crude compound **9**, mp. 254–256°C, which was used in the next step without further purification. ^{1}H-NMR (CF_3CO_2D, 400 MHz): δ 10.81 (s, 1 H, OH), 8.76 (s, 1 H, ArCH), 7.49 (d, 1 H, 1 ArCH), 7.18 (dd, 2 H, 2 ArCH), 7.08 (dd, 2 H, 2 ArCH), 4.02 (s, 2 H, CH_2), 3.80–3.70 (m, 1 H, CH), 3.48–3.36 (m, 2 H, 2 CH), 3.31 (s, 3 H, OCH_3), 3.28–3.18 (m, 2 H, 2 CH), 2.58–2.46 (m, 2 H, 2 CH), 2.40–2.29 (m, 2 H, 2 CH), 0.79–0.66 (m, 2 H, CH_2), 0.53–0.39 (m, 2 H, CH_2). ^{13}C-NMR (CF_3CO_2D, 100.6 MHz): δ 172.41, 171.04 (2 C), 169.1, 156.61, 155.32 (d, $^1J_{CF} = 259.95$ Hz), 154.03, 152.99, 145.75, 136.36 (2 C), 134.68, 130.77 (2 C), 124.04 (2 C), 121.74, 109.34, 105.05, 65.04, 54.70, 54.29, 42,85 (2 C), 39.84, 28.91, 28.37, 8.82 (2 C). LC-MS: *m/z* 566 [MH^+], 588 [M+Na]$^+$, 1153 [2M+Na]$^+$.

Anal. Calcd for $C_{29}H_{25}ClFN_3O_6 \cdot 0.1\ CH_3CH_2OH$: C, 61.47; H, 4.52; Cl, 6.21; F, 3.33; N, 7.36. Found: C, 61.64; H, 4.79; Cl, 6.11; F, 3.27; N, 7.48.

7-[4-(2-Amino-1-chloroethylidene)piperidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (10)

A 12 L round bottom flask was charged with compound **9** (224.0 g, 0.396 mol) and MeOH (4.4 L). This suspension was stirred at 20°C under nitrogen and H_2NNH_2 (101.4 mL, 3.166 mol) was added over a 5 min period. The yellowish suspension was heated to 65°C and refluxed for 1 h, and the progress of the reaction was monitored by HPLC and LC-MS. The reaction was cooled to 60°C and MeCN (3.3 L) was added. The mixture was heated to reflux for 5 min (some phthalhydrazide precipitated during this period), and then was cooled to 24°C in a water bath. The off-white solid was collected and washed with MeCN (200 mL × 2) and dried at 50°C under house vacuum (∼160 mmHg) for 20 h to afford 69.6 g (108% yield; 98% of phthalhydrazide and ∼2% of **10**, HPLC area%) of phthalhydrazide as an off-white solid. The filtrate was concentrated at 60°C to afford 198.5 g (115% yield; 89 HPLC area%) of crude compound **10** as a yellowish solid.

A 12 L round bottom flask was charged with crude **10** (198.5 g) and MeOH (4.4 L). This suspension was heated to 65°C and refluxed for 20 h. MeCN (3.5 L) was added at 65°C and reflux was continued for 25 min; and then the solution was gradually cooled to 0°C and stirred for 30 min. The precipitated solid was collected, washed with MeCN (200 mL × 2), and dried at 50°C under high vacuum (∼4 mmHg) for 20 h to afford 138.0 g (80% yield; 99.4% of **10** and 0.35% of phthalhydrazide, HPLC area%) of free base **10** as a bright yellowish crystalline solid, mp. 186–188°C. An additional 66.3 g of yellow solid was obtained after concentration of the filtrate, which contained 58% of **10**, 22% of phthalhydrazide, along with 11% and 5% of two major uncharacterized impurities. ^{1}H-NMR of free base **10** (400 MHz, DMSO-d_6) δ 10.9 (s, 1 H, OH), 8.69 (s, 1 H, ArCH), 7.64 (d, 1 H, ArCH), 4.18 (m, 1 H, CH), 3.75 (s, 3 H, OCH_3), 3.48 (s, 2 H, NCH_2), 3.46–3.20

(m, 6 H, 2 CH_2 + NH_2), 2.64–2.52 (m, 2 H, CH_2), 2.51–2.48 (m, 2 H, CH_2), 1.18–1.08 (m, 2 H, CH_2), 1.07–0.96 (m, 2 H, CH_2). ^{13}C-NMR (CF_3CO_2D, 100.6 MHz): δ 175.33, 164.67, 155.72 (d, $^1J_{CF}$ = 259.86 Hz), 149.32, 144.85, 138.24, 132.91, 129.71, 128.86, 119.69 105.41, 61.71, 49.99, 49.35, 47.43, 42,95, 39.54, 30.37, 29.09, 7.56 (2 C). LC-MS: *m/z* 436 [MH^+], 893 [2M+Na]$^+$.

Anal. Calcd for $C_{21}H_{23}ClFN_3O_4 \cdot 0.1\ CH_3CN$: C, 57.87; H, 5.34; Cl, 8.06; F, 4.32; N, 9.87. Found: C, 57.92; H, 5.28; Cl, 7.77; F, 4.16; N, 10.13.

7-[4-(2-Amino-1-chloroethylidene)piperidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid Hydrochloride Salt (11)

A 12 L round bottom flask was charged with **10** (100.0 g, 0.229 mol) and EtOH (4.0 L) and the suspension was stirred under N_2 and cooled to 10°C. A solution of HCl in Et_2O (1.0 M, 252.4 mL) was added over a 25 min period while the reaction temperature was maintained between 8–10°C. After the addition, the mixture was stirred at 10°C for 5 min and warmed to 20°C and stirred for 20 min. Ethanol was removed *in vacuo* at 66°C to afford 134.6 g (98.4 HPLC area%) of the crude HCl salt **11** as a yellowish solid, which was suspended in EtOH (2.5 L) in a 5-L RBF, heated to 76°C and stirred for 5 min. EtOH (50 ml × 10) was added to the suspension in 5 min intervals until a clear solution was formed. The solution was cooled to 60°C and seeded with pure HCl salt **11** (>99.6 HPLC area%). The solution was gradually cooled to 0°C over a 1 h period and stirred at 0°C for 30 min. The solid was collected, washed with ice cold EtOH (100 mL × 2), and dried at 60°C under high vacuum (∼ 4 mmHg) for 60 h (weekend). There was obtained 88.9 g (82% yield; 99.9 HPLC area%) of pure HCl salt **11** as a slightly yellowish crystalline solid. Recrystallization of the mother liquor solid (19.4 g, 18% yield; 97.7 HPLC area%) in EtOH (388 mL) afforded an additional 8.6 g of HCl salt **11** (8% yield; 99.4 HPLC area%) also as a yellowish crystalline solid, mp. 178–180°C. ^{1}H-NMR of pure HCl salt **11** (400 MHz, CD_3CO_2D): δ 11.76–11.48 (br s, 3 H, OH + NH_2), 9.02 (s, 1 H, 2 ArCH), 7.88 (d, 1 H, 2 ArCH), 4.28 (m, 1 H, CH), 4.25 3.48 (s, 2 H, NCH_2), 3.86 (s, 3 H, OCH_3), 3.48–3.63 (m, 4 H, 2 CH_2), 2.46–2.78 (m, 4 H, 2 CH_2), 1.31 (m, 2 H, CH_2), 1.16 (m, 2 H, CH_2). LC-MS: *m/z* 436 [MH^+], 869 [2M-H]$^+$, 893 [2M+Na]$^+$.

Anal. Calcd for $C_{21}H_{23}N_3O_4ClF \cdot 1.0\ HCl \cdot 0.2\ CH_3CH_2OH \cdot 0.29\ H_2O$: C, 52.81; H, 5.34; N, 8.63; Cl, 14.57; F, 3.90; % H_2O, 1.06. Found: C, 52.78; H, 5.39; N, 8.34; Cl, 15.04; F, 3.75; % H_2O, 1.06.

Cleavage of Phthalimide Intermediate 8 Using Inorganic Base and Acid

A 1 L round bottom flask was charged with **5** HCl salt (19.1 g, 58.37 mmol), difluoroborate ester **7** (20.7 g, 60.34 mmol), DMF (72 mL), and Et_3N (17.9 mL, 128.47 mmol). The mixture was warmed to 35–40°C and stirred for 4–5 h (a yellowish solid precipitated after approximately 40 min). The suspension was cooled to 0–10°C, diluted with EtOAc (112 mL) and stirred for 2 h. The solid was collected, and washed with methyl *t*-butyl methyl ether (40 mL) to afford 35.8 g (77% of **8**, HPLC area%) of intermediate **8** as a yellowish solid.

Intermediate **8** was suspended in MeCN (48 mL) and deionized H_2O (100 mL), a solution of 30% NaOH (41.6 mL, 312 mmol) was added and this mixture was gradually heated to reflux at 78°C which resulted in the distillation of about 11.0 g of liquid containing

t-butyl methyl ether and Et_3N) and stirred for 3 h. The progress of the reaction was monitored by HPLC and LC-MS, both of which indicated that compound **8** was completely converted to **12** (LC-MS, $MH^+ = 584$, $M+Na^+ = 606$, $M+2Na^+ = 628$). The reaction mixture was cooled to 20°C and MeCN (54 mL) was added, followed by the addition of 50% aqueous solution of H_2SO_4 (16.6 mL) and then a 95–97% solution of H_2SO_4 (18.1 mL) (pH 1.5–2.0). The mixture was heated to 78°C again and stirred for 18 h. The progress of the reaction was monitored by HPLC and LC-MS, both of which indicated that amide **12** was almost completely hydrolyzed to amine **10**. The reaction mixture was cooled to 40°C, the mixture was diluted with deionized H_2O (128 mL) and titrated with 30% NaOH (21.7 mL) to pH 6.0–6.5. The resulting suspension was stirred at 20°C for 3 h, and the yellowish solid was collected and washed with deionized water (50 mL) to give 25.5 g (64% yield; 92.8 HPLC area% of **10** and 6.4% of 8-demethylated **13** ($MH^+ = 422$), HPLC area%) as a beige-yellowish solid, mp. 181–186°C.

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17. The hydrochloride salt of **5** was prepared by the treatment of compound **4** (10.0 g) with a solution of 19% HCl in ethanol (100 mL) at 20°C overnight. The resulting suspension was cooled to 0–5°C and the solid was collected. The filter cake was washed with cold ethanol (10 mL) and then dried in a vacuum oven at 60°C for 20 h to afford 7.3 g of **5**·HCl as an off-white solid.