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Development of an Efficient Synthesis of the Pyrrolquinolone PHA-529311

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Abstract:

An efficient synthesis of *N*-(4-chlorobenzyl)-2-(2-hydroxyethyl)-8-(morpholin-4-ylmethyl)-6-oxo-6H-pyrrol[3.2.1-*ij*]quinoline-5-carboxamide (5) was developed. The route was chosen due to its reasonable length (seven steps), solubility of intermediates, and capabilities of the pilot and production facilities. The critical transformations in this route were the selective iodination of an aniline, formation of the quinolone, and Sonogashira coupling/pyrrole formation. In addition, removal of residual palladium and copper from the penultimate and final products, which was of lower concern during the discovery phase of development, became a difficult process chemistry issue on scale-up.

Introduction

The herpesviruses comprise a large family of DNA viruses. They are also a source of the most common viral illnesses in humans, including the herpes simplex viruses (HSV), cytomegalovirus (CMV), varicella zoster virus (VZV), and Epstein−Barr virus (EBV). While the treatment of HSV infections with acyclovir and similar nucleoside analogues was one of the first success stories in antiviral chemotherapy, substantial unmet medical needs still remain. In particular, effective and safe treatments for CMV, VZV, and EBV infections remain elusive. The herpesvirus polymerase was chosen as the therapeutic target because polymerase is known to be an essential enzyme and is a proven antiviral target. In vitro assays were developed for CMV, HSV, VZV, and EBV viral polymerases, and for human alpha-, delta-, and gamma-polymerases. Previously, Pharmacia has reported naphthalenes **1**, quinolines **2**, oxazinoquinolines **3**, and thienopyridines **4** to possess broad-spectrum antiviral activity against the herpesviruses.[1] More recently, a novel class of compounds, the pyrroloquinolines **5**, which show improved activity against herpesvirus DNA polymerases has been described.[2] In vitro assays have demonstrated potent inhibition of HCMV, HSV-1, and VZV polymerases, with good selectivity from human α-, δ-, or γ-polymerases[2] (Scheme 1).

We were asked to develop a synthesis of compound **5** which could be used to prepare multikilogram quantities. After examination of several feasible synthetic routes, the route outlined in Scheme 2 was selected for scale-up based on the following criteria: reasonable length (seven steps), solubility of intermediates, and capabilities of the pilot and production plants. The critical transformations in this route were the selective iodination to provide aniline **9**, cyclization to the quinolone **11**, and Sonogashira coupling/pyrrole formation to provide **12**. Removal of residual palladium and copper from the penultimate and final products became a difficult process chemistry issue on scale-up.[3]

Results and Discussion

The preparation of nitrobenzene **7** was easily accomplished by amination of 4-nitrobenzyl bromide, **6**, using toluene as solvent and morpholine as the base as well as the nucleophile. Addition of 3 equiv of morpholine to a toluene solution of **6** results in complete reaction in less than 2 h. The product is isolated in 93% yield after workup by crystallization from toluene/Isopar C (available from Exxon). On 40-kg scale the reaction proceed as expected, but isolation required two crops to provide the expected yield. Reduction of **7** was carried out using THF as solvent and 5% Pt/C as catalyst. After reduction and clarification, the solvent was exchanged from THF to Isopar C to precipitate the product **8**, in 91% yield in the lab. On 40-kg scale the reduction proceeded rapidly and completely; however, the yield was improved to 94%.

Iodination of **8** using either *N*-iodosuccinimide or iodine resulted in none of the desired monoiodide product. We then tried using iodine monochloride as iodinating reagent. Initial attempts to iodinate **8** used iodine monochloride (ICl) in methylene chloride and acetic acid. These conditions resulted in only 56% yield of the desired iodoaniline **9** and large amounts of black tar. NMR examination of this tarry material

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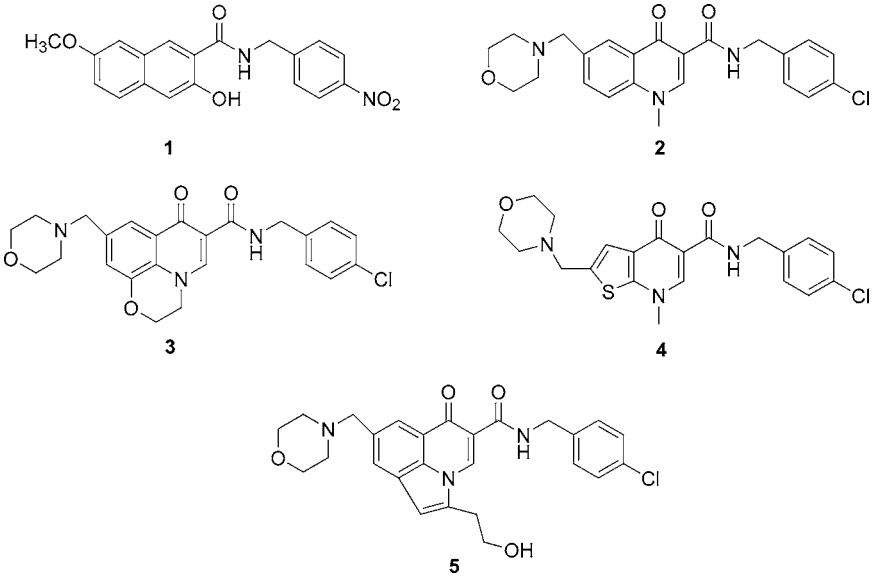
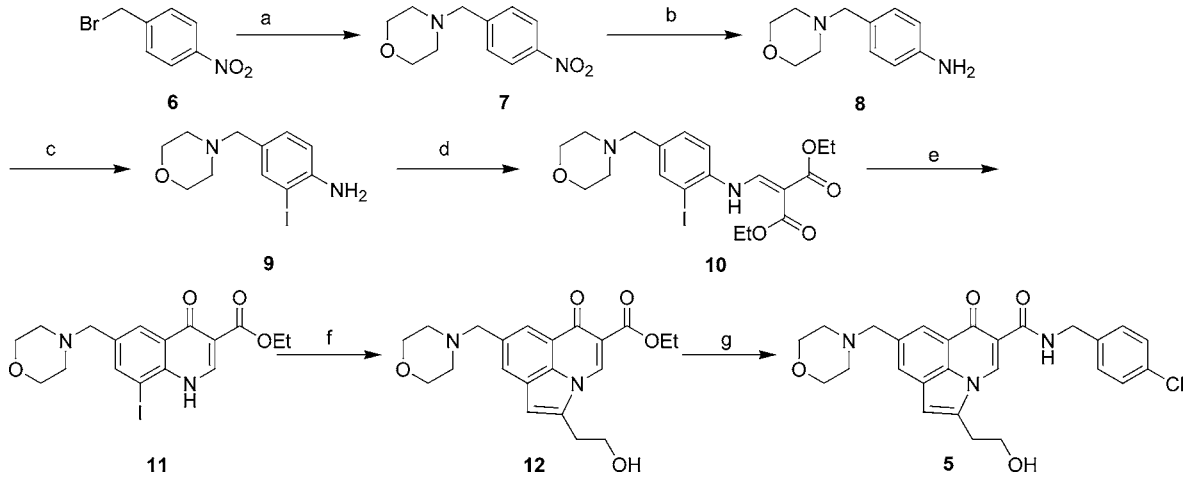
Scheme 1. **Reported polymerase inhibitors**



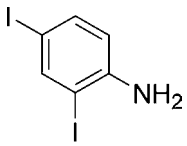
Scheme 2. **Synthetic scheme chosen for development**[a]



[a] Reagents and conditions: a) morpholine, toluene; b)H_2, 5%Pt/C, THF; c) ICl, HOAc, MeOH, CH_2Cl_2; d) DEEM, toluene; e) P_2O_5, MsOH; f) CuI, $Cl_2Pd(PPh_3)_2$, TEA, 3-butyn-1-ol , EtOH; g) 4-chlorobenzylamine, ethylene glycol.

showed it to be a single material, closely resembling the desired product. The aromatic ring appeared to be iodinated, but the morpholine ring is seen to be nonsymmetrical. Stirring this tar in methanol and aqueous sodium bisulfite leads to recovery of **9** along with some very polar products. The desired monoiodide prepared by this method required purification by column chromatography before it could be carried into the next step. We subsequently found that iodination with iodine monochloride in a mixture of methylene chloride/methanol/acetic acid gave good yields of the monoiodinated product and that running at low temperature (<0 °C) improves the selectivity and yield in the reaction.

The stoichiometry of acetic acid was found to be important in this reaction. With less than 2 equiv of acetic acid, the reaction stalled with more than 10% starting material remaining and gave a dirty mixture, while with 2 equiv or more, the reaction went well. The stoichiometry of the ICl was more difficult to optimize. Reactions conducted with 1.0, 1.1, 1.25, 1.5, and 2.0 equiv in the initial charge of ICl demonstrated that at least 1.25 equiv are required to drive the reaction to less than 3% starting material. Using more than 2.0 equiv led to some overreaction byproducts, but the yield was not significantly reduced. The major side product isolated from this reaction was the diiodide **13**, resulting from



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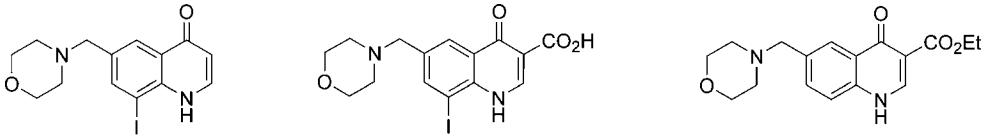
an apparent ipso attack of iodine and loss of the morpholinomethyl group. The optimized conditions of adding 1.25 equiv of ICl with 2.0 equiv of acetic acid at −15 °C and then warming to 10−15 °C gave the cleanest conversion.

Initially we purified the crude **9** by chromatography. Even at high loading (5:1, silica/**9**) we achieved significant upgrading, and the enamine **10** produced in the next step was very clean. Although we were able to get crystalline product from the enamine (step 4) reaction without the

Scheme 3. **Cyclization Impurities**



14 **15** **16**

chromatography, the color and impurity profile were greatly improved with chromatographed **9**, and therefore we elected to include this purification in the initial piloting.

Iodine monochloride is available as either a solid or 1 M solution in methylene chloride from a number of suppliers. For our initial piloting we used the methylene chloride solution from SAF. The iodination proceeded as expected, and the "chromatography" was actually a filtration through a plug of silica gel using (5:1 silica-to-crude product) followed by washing with ethyl acetate and Isopar C until all product was eluted. The product produced in this initial piloting was more than 90% pure by HPLC, and a small retention sample crystallized after standing at room temperature. The yield was 74% on 40-kg scale.

Formation of the enamine **10**, was a straightforward conversion from the aniline.

Heating the aniline and diethylethoxymethylene malonate (DEEMM) in refluxing toluene (112 °C) resulted in complete conversion in less than 6 h. Distillation of the toluene and addition of Isopar C led to crystallization of the desired **10** in 85% yield. On 50-kg scale the reaction proceeded as expected, but a lower than expected yield of 74% was recovered.

Two possible ring-closure procedures were examined for conversion of **10** to **11**. The first possibility explored was the thermal closure.[4] Heating a solution of **10** in diphenyl ether at 240−250 °C for 1−2 h produced the desired quinolone. The product could be crystallized by pouring the warm diphenyl ether solution into hexanes or Isopar C. We found that this thermal ring closure was concentration dependent and that at less than 6 mL/g low yields and poor product quality resulted. In addition, thermal stability data showed that the product degraded at the reaction temperature (∼240 °C for a neat sample), near those required for ring closure; no reaction was observed below 225 °C. The relatively high dilution, the very high temperature requirement, and the low margin for thermal stability caused us to abandon this method for use in the pilot plant. We therefore focused on the acid-promoted ring closure.

Although acid-promoted ring closures for tertiary anilines are fairly common, only a handful of reports of successful closures with secondary anilines have been reported.[5] We chose to explore the acid-promoted reaction using Eaton's reagent (a solution of P_4O_{10} in methane sulfonic acid). While this reagent has been reported to affect this type of cyclization on tertiary anilines,[5] its use was unknown on secondary anilines.[6] We explored the use of 4.0, 3.0, 2.2, 2.0, and 1.4 equiv of phosphorus pentoxide in methanesulfonic acid. For these experiments we used only the commercial Eaton's reagent[7] available from Aldrich at 7.7% w/w of P_4O_{10} in methanesulfonic acid. We found the highest yield with 4.0 equiv and observed no conversion with 1.4 equiv. The use of 4.0 equiv of phosphorus pentoxide gave a faster, cleaner reaction. Under these conditions there is only 2−3% of **9** formed in the reaction vs 6−7% using 2 equiv, and the reaction is more complete. With 4 equiv the yield is 70% on a 20-g lab scale vs 60% using 2 equiv. Pilot-scale operations were run with 15% (w/w) P_2O_5 in methanesulfonic acid to increase volume efficiency.

Workup of the reaction was simple but volume limited. The reaction is added to cold water, and the pH is adjusted to 6−7 with sodium hydroxide. The product is extracted into methylene chloride and is crystallized from methanol. We isolated and identified only three impurities from the reaction mixture (Scheme 3). Along with the desired **11**, we found the aniline **9**, the decarboxylated analogue **14**, and the carboxylic acid **15**. We prepared the authentic des-iodo material, **16**, but never observed formation of this material during the cyclization.

The cyclization was run on 30-kg scale in the pilot plant, and formation of the P_2O_5 in methanesulfonic proceeded smoothly, requiring only about 3 h of stirring to get a clear solution. Some problems were encountered in the extractions which required the addition of methanol. Overall, the process worked well, and the product was isolated in 62% yield on this scale.

The palladium-catalyzed coupling of **11** with terminal acetylenes was expected to provide the desired pyrrole[3.2.1-*ij*]quinolines.[8] This reaction was considered next. By generating **12** first, followed by **5**, metal removal could be effected at two stages, first with the more soluble ester **12**, and then finally with amide **5.** A variety of conditions were explored to develop a consistent and high-yielding reaction. Ethanol proved to be the best solvent for the Sonogashira coupling even though **11** has poor ethanol solubility. To obtain a stirrable slurry, 10 volumes of ethanol are needed, followed by warming to effect the dissolution of **11**.

To achieve complete conversion of **11** to **12**, 1.5 equiv of 3-butyn-1-ol are required. This is due to competitive homocoupling of the alkyne to form diyne. The reaction consistently performed well using 2 equiv of triethylamine. It was found that a 10:1 ratio of $CuI:Cl_2Pd(PPh_3)_2$ is necessary to consume **11**. Initially the reaction was performed

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Table 1. **Metal removal from isolated 12**

		sample		product	
entry	treatment	Pd	Cu	Pd	Cu
1	EtOAc	397	14	241	13
2	ACN	89	328	18	27
3	solid TMT; EtOAc	115	170	71	71
4	NH_4O_2CH; acetone/MTBE	260	1	238	1
5	silica gel; acetone/MTBE	260	1	83	1
6	2-hydroxypyridine; EtOH/Hex	1551	96	1113	80
7	$Me_2NCH_2CH_2SH$; MTBE	1551	96	1608	10
8	IRC-748; MTBE	250	13	204	13
9	IRC-50; MTBE	250	13	143	13
10	alumina	1551	96	254	20
11	diphosphine; MTBE	151	50	27	10
12	diphosphine; MTBE	151	50	29	10

with 10 mol % CuI and 1 mol % $Cl_2Pd(Ph_3)_2$ in refluxing ethanol. Pyrrole formation was expedient under these reaction conditions with no evidence of the uncyclized material. Ultimately, it was determined that the optimal reaction conditions are the use of 1.5 equiv of 3-butyn-1-ol, 2 equiv of triethylamine, 5 mol % CuI and 0.5 mol % $Cl_2Pd(Ph_3)_2$, in 10 volumes of ethanol as solvent with removal of half of the ethanol by in-process atmospheric distillation. The reaction took 12−17 h under these conditions. The reaction was clean with no evidence of des-iodo **16** as a possible byproduct in the Sonogashira coupling. To ease the metal contamination issue, the Sonogashira coupling/pyrrole formation was attempted in the absence of copper with $Bn_4NCl/Pd(OAc)_2$ catalysis.[9] Even after heating for 4 days, there was no reaction.

To isolate the product, much of the ethanol was removed by distillation followed by addition of water and vacuum distillation to remove the remaining ethanol. Celite was added to the aqueous solution followed by acidification to pH 1 with HCl. If Celite was added after the HCl, the filtration was very slow. The resulting slurry was filtered with a water rinse. When **12** was isolated from the filtrate at this stage, it contained 242 ppm of Pd and 105 ppm of Cu. Therefore, studies were initiated to optimize metal reduction as shown in Table 1. The recrystallization solvent was examined, and as shown in entries 1 and 2 of Table 1, the use of acetonitrile offered a large benefit in terms of metal removal. Thus, subsequent isolations of **12** employed an ACN/MTBE solvent system. Stirring over solid trimercaptotriazine or Amberlite IRC resins, known metal chelators, was not useful (entries 3, 8−9). Ammonium formate or 2-hydroxypyridine were ineffective (entries 4, 6). While silica gel partially decreased the Pd levels, it was insufficient (entry 5). Dimethylaminoethanethiol allowed the removal of copper, but it had no effect on the palladium levels (entry 7). The use of an alumina plug was productive as were 1,2-diphenylphosphinoethane and 1,3-diphenylphosphinopropane (entries 10−12). Unfortunately, the diphosphines were ineffective when used with the crude reaction mixture.

Despite a great deal of effort, the consistent removal of palladium and copper remained elusive. Fortunately, the discovery that **12** is soluble in aqueous acid allowed a convenient method for metal removal. When the reaction is complete, the ethanol was removed by distillation followed by the addition of 6.3 volumes of water and 1.3 equiv of HCl. The resultant slurry was filtered through a filter aid. The pH needed to be less than 2, otherwise the protonated product was sequestered by the filter aid. The use of greater amounts of HCl caused an increase in the copper levels in the isolated **12**. The aqueous filtrate was treated with 80 wt % of Deloxan THP (available from Degussa AG) overnight followed by filtration and basification with Na_2CO_3. The pyrrole was then isolated by methylene chloride extractions and was crystallized from acetonitrile/*tert*-butyl methyl ether to give **12** containing 20 ppm Pd and 2 ppm Cu in 60−70% yield. This treatment consistently yields **12** with acceptable metal levels. Compound **12** is a canary-yellow-colored solid, but it turns purple upon exposure to light in the solid phase. Thus, **12** must be stored in the dark.

An alternate metal-removal method was also developed. Rather than treating the acidic filtrate with Deloxan THP, the pH was adjusted to 9 with aqueous K_2CO_3, and **12** was extracted into methylene chloride. The metals were removed by stirring the methylene chloride solution over 20 wt % *Si*-Thiol, a thiol end-capped silica gel (available from SiliCycle) for 12 h. In the pilot plant on 20-kg scale **12** was isolated by crystallization from acetonitrile/*tert*-butyl methyl ether in 84% yield with 38 ppm Pd and 42 ppm Cu. Further reduction in the metal levels was achieved by stirring a methylene chloride solution of **12** over 7 wt % *Si*-Thiol to give the desired product in 76% overall yield containing 17 ppm Pd and 1 ppm Cu.

In the final step ester, **12**, is converted to amide **5**. To achieve an efficient amidation, **12** was slurried in ethylene glycol with 3 equiv of 4-chlorobenzylamine. The slurry was heated at 130 °C to give a homogeneous solution, which was heated for 8 h. Upon completion of the reaction, the mixture was cooled to 105−110 °C and diluted with toluene. If toluene was not added, the reaction mixture solidified at temperatures below 100 °C. The resulting solution was slowly cooled to room temperature with added acetonitrile to aid in ethylene glycol removal. As long as product precipitation occurred at temperatures above 38 °C a filterable solid resulted. Since 4-chlorobenzylamine readily forms an insoluble carbonate salt, the excess amine must be removed. This was accomplished with pivaldehyde to form imine **17**. Although there are 2 equiv of 4-chlorobenzylamine remaining, it was found that only1 equiv needs to be converted to the imine. Crude **5** was isolated by filtration and washed with 2:1 toluene/acetonitrile.

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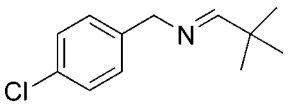

17

Purification of **5** was achieved by dissolving in hot 50% EtOH/THF followed by clarification. The filtrate was treated with hexanes to complete the product precipitation. After cooling, **5** was isolated by filtration. Removal of 2% **17** was effected by a simple re-slurry of **5** in 50% EtOH/THF to give the desired product in 67% yield from **12**. On pilot-plant scale the desired product was isolated in 74% isolated yield.

Conclusions

We were able to develop a scalable process for the preparation of **5** in seven steps and 15.5% overall yield from readily available commercial materials and demonstrate that process in the pilot plant. Key features of this process are the rugged ortho iodination of an aniline and reproducible, acid-catalyzed cyclization of **10** to provide high-quality, crystalline **11**. Sonogashira coupling/pyrrole formation then provides a high yield of crude **12**, which due to its solubility in aqueous acid facilitates removal of large quantities of metals. The fact that **12** is methylene chloride soluble allows the removal of the residual metals to an acceptable level. Both Deloxan THP in aqueous acid and Si−Thiol in methylene chloride effect the removal of palladium and copper from **12**.

Experimental Section

General Procedures. All reagents were commercially obtained and used as received unless otherwise noted. All nonaqueous reactions were performed in dry glassware under an atmosphere of dry nitrogen. Air- and moisture-sensitive liquids or solutions were transferred via syringe or polypropylene cannula. Organic solutions were concentrated by rotary evaporation at ~80 mmHg at less than 60 °C except where noted. Chromatographic purification of products was accomplished using forced flow chromatography on EM silica gel 60. Thin-layer chromatography was performed on Analtech Chromatography Products Uniplate silica gel GF 0.25 mm plates. Visualization of the developed chromatogram was performed by fluorescence quenching or phosphomolybdic acid (PMA) stain and/or 50% sulfuric acid char.

NMR spectra were measured on a Bruker AM-400 operated at 400 and 100 MHz, for ^{1}H and ^{13}C, respectively, with data reported as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), integration and coupling constant (J, Hz). ^{1}H−^{13}C Multiplicities are reported on the basis of DEPT data. Elemental analysis, Karl Fishers (KF), melt solvates, infrared spectra (IR), and thermogravimetric analyses (TGA) were obtained from Pharmacia and Upjohn Physical and Analytical Chemistry. HPLC analyses were carried out on an Agilent 1100 System. The following HPLC method was employed: stationary phase: 4.6 mm × 250 mm Zorbax RX-C8; flow rate = 0.7 mL/min; UV detection at 254 nm; mobile phase 50:50 CH_3CN/0.1 M NH_4OAc in H_2O; GC analyses were carried out with a Hewlett-Packard 5890a gas chromatograph. ICP analysis was used to determine residual palladium and copper levels.

4-(4-Nitrobenzyl)morpholine, (7). To a 2-L, three-neck, round-bottom flask, fitted with mechanical stirring, thermocouple, 250-mL addition funnel, and nitrogen inlet were charged 4-nitrobenzylbromide (100 g, 463 mmol) **(Caution. Strong irritant and lachrymator! Weigh in hood with door down and transport in stoppered flask!)** and 500 mL of toluene. A solution of morpholine (121 g, 1389 mmol) in 100 mL of toluene was added dropwise, keeping the temperature less than 50 °C. The solution was rinsed in with 50 mL of toluene. The resulting solution was stirred at less than 50 °C until the reaction was complete. TLC analysis; add 1 mL of reaction mixture to 1 mL of water, spot upper layer and elute with 1:1 ethyl acetate/heptane, visualize with UV. When complete, 500 mL of water was added, and the phases were separated. The organic phase was washed with 500 mL of saturated sodium bicarbonate. The organic phase was concentrated to less than 150 mL volume on the rotovap with a 60−70 °C bath. Isopar C (500 mL) was added to crystallize the product. The slurry was stirred at 20−25 °C for 30 min, filtered, and washed with 100 mL of Isopar C. The product was dried at 45 °C in a vacuum oven overnight. The yield was 96.0 g, 93%, of **8**: mp 80.3−82.1 °C. HPLC purity 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 9 Hz, 2 H), 7.43 (2, J = 8 Hz, 2 H), 3.62 (m, 4 H), 3.50 (s, 2 H), 2.37 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.9, 123.9, 67.3, 62.9, 54.0. Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61; found: C, 59.52; H, 6.34; N, 12.58.

4-(4-Aminobenzyl)morpholine (8). To a 1-L autoclave were charged 5% Pt/C (3.3 g, 50% water wet) and **7** (125 g, 563 mmol). THF (600 mL) was added and the mixture purged with nitrogen (3×) and then hydrogen (3×). The resulting mixture was stirred under hydrogen pressure (50 psig) at high rpm (>300) at 60−70 °C until the uptake of hydrogen stopped (about 2 h). The resulting mixture was cooled to room temperature and filtered. The filter cake was washed with THF (2 × 200 mL), and the filtrate and rinses were charged to a 1-L, three-neck, round-bottom flask, fitted with mechanical stirring, thermocouple, and distillation head. The solution was vacuum distilled to a volume of 150 mL, and 600 mL of Isopar C was added. The mixture was concentrated to a volume of 200 mL and cooled to less than 20 °C. The resulting slurry was cooled to 0−5 °C and stirred for about 1 h. The slurry was filtered and washed with 100 mL of Isopar C. The product was dried in the vacuum oven at 50 °C and provided 99.4 g, 91% yield of **8**: mp 100.8−102.2 °C. HPLC purity 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 6 Hz, 2 H), 6.43 (d, J = 8 Hz, 2 H), 3.49 (m, 4 H), 3.19 (s, 2 H), 2.22 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 130.9, 115.6, 67.3, 63.4, 53.8; Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57; found: C, 68.94; H, 8.34; N, 14.58.

2-Iodo-4-(4-morpholinylmethyl)benzenamine (9). To a 2-L, three-neck, round-bottom flask fitted with mechanical stirring, thermocouple, 500-mL addition funnel, and nitrogen

inlet was charged **8** (40 g, 208 mmol) followed by methylene chloride (400 mL), methanol (80 mL), and acetic acid (24.9 g, 416 mmol). The resulting solution was cooled to −20 to −15 °C. A 1 M iodine monochloride solution in methylene chloride (370 g, 260 mL, 260 mmol) was added over about 30 min, keeping the temperature less than −15 °C. When the addition was completed, the cooling was removed and the reaction warmed to 10−15 °C. After 1 h, the reaction progress was monitored by GC: 1 mL of the reaction mixture was quenched into 1 mL of 10% aqueous sodium sulfite, and 1 mL of saturated bicarbonate was added; 5 drops of the lower phase was diluted with 1 mL of methylene chloride, and this was assayed by GC (injector 250 °C, initial oven temp 125 °C, initial time = 0, oven temp increased at 10 °C/min, final oven temp −275 °C, detector −275 °C, column 15 m DB-5SM). The reaction is complete when less than 5% starting material remained. When the reaction was complete, 250 mL of 10% aqueous sodium sulfite was added, followed by a solution of 70 g of 50% NaOH in 250 mL of water. The phases were separated, and the aqueous phase was washed with 100 mL of methylene chloride. The combined organic phases were washed with 100 mL of water and concentrated on the rotovap to a thick red oil.

The crude oil was dissolved in 200 mL of ethyl acetate, and 200 mL of Isopar C was added. The resulting mixture was filtered through 200 g of silica gel, and the cake was washed with 1500 mL of ethyl acetate. The organic phases were concentrated to a dark red oil at 60 °C on the rotovap. The oil was used as is in the next step; however, a purified sample did eventually crystallize: mp 55.3−62.1 °C. HPLC purity 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1 H), 7.25 (d, J = 8 Hz, 1 H), 6.82 (d, J = 8 Hz, 1 H), 3.85 (m, 4 H), 3.51 (s, 2 H), 2.58 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 139.9, 130.9, 129.3, 115.3, 84.3, 66.9, 62.5, 53.8.

Diethyl 2-({[2-Iodo-4-(morpholin-4-ylmethyl)phenyl]-amino}methylene)malonate (10). To a 1-L, three-neck, round-bottom flask, fitted with mechanical stirring, thermocouple, distillation head, and nitrogen inlet was charged **9** (50 g, 157 mmol) followed by diethylethoxymethylene malonate (37.4 g, 173 mmol) and toluene (115 mL). The resulting mixture was heated under nitrogen with a heating mantle with set point 120 °C. Toluene and ethanol (about 65 mL) were distilled during the heating period. When the pot temperature reached 120 °C, the distillation slowed. The reaction was assayed by TLC (elute with 1:1 ethyl acetate/heptane) and was judged complete (starting material less than 5%). The reaction mixture was cooled to 50 °C and vacuum distilled to about 100 mL volume. Isopar C (200 mL) was added and the mixture cooled to 20−25 °C, where the mixture crystallized over ∼30 min. The resulting slurry was stirred at 20−25 °C for 1 h, filtered, and washed with 75 mL of Isopar C. The product was dried in the vacuum oven at 50 °C overnight, providing 65 g of **10**. HPLC purity of sample was 92%. An analytically pure sample was prepared by recrystallization from toluene: mp 98−101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 13 Hz, 1 H), 7.89 (s, 1 H), 7.43 (d, J = 8 Hz, 1 H), 7.23 (d, J = 8 Hz, 1 H), 4.44 (q, J = 7 Hz, 2 H), 4.34 (q, J = 7 Hz, 2 H), 3.79 (m, 4 H), 3.51 (s, 2 H), 2.51 (m, 4 H), 1.46 (t, J = 7 Hz, 3 H), 1.40 (t, J = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 166.1, 151.6, 140.6, 140.2, 130.8, 116.4, 95.6, 89.3, 67.3, 62.3, 60.9, 60.6, 53.9, 14.8, 14.7; Anal. Calcd for $C_{19}H_{25}IN_2O_5$: C, 49.73; H, 5.16; N, 5.78; found: C, 49.62; H, 5.14; N, 5.68.

Ethyl 8-Iodo-6-(morpholin-4-ylmethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (11). *Preparation of Eaton's Reagent.* To a 250-mL, three-neck, round-bottom flask fitted with mechanical stirring thermocouple and nitrogen inlet, was charged phosphorus pentoxide dimer (23.3 g, 82 mmol). The stirring was started briefly to distribute the solids, and the stirrer was raised above the solids in the flask. Methanesulfonic acid (178 g, 120 mL, 1852 mmol) was added and the mixture warmed to 90 °C until all the phosphorus pentoxide dimer was dissolved. The resulting solution was cooled to less than 30 °C.

Cyclization Reaction. To a 500-mL, three-neck, round-bottom flask fitted with mechanical stirring, thermocouple, and nitrogen inlet, was charged **10** (20 g, 41 mmol) followed by Eaton's reagent. There was an exotherm to about 47 °C. The resulting dark-red solution was heated to 90 °C for at least 4 h. The reaction was checked by TLC (about 0.5 mL of reaction was quenched into 3−4 g of ice and the pH adjusted to 7−8 by addition of 50% NaOH, 2 mL of methylene chloride were added, and the lower layer was spotted and eluted with 5% methanol/95% methylene chloride). When completed, the reaction was cooled to less than 30 °C and poured into 200 g of ice. A solution of 50% NaOH (180 g, 2258 mmol) in 150 mL of water was slowly added until the pH was 5−6. Methylene chloride (200 mL) was added, and the addition of NaOH solution was resumed until the pH was 7−8, keeping the temperature less than 30 °C (use an ice bath if needed). The phases were separated, and the aqueous was washed with methylene chloride (1 × 100 mL). The combined organic phases were filtered through 5 g of silica gel, and the cake was washed with 300 mL of methylene chloride. The filtrates were concentrated on the rotovap to about 150-mL volume. Methanol (200 mL) was added and the solution concentrated to about 50-mL volume. Methanol (100 mL) was added and the mixture again concentrated to about 50-mL volume. The slurry was cooled to 0 °C, filtered, and washed with 50 mL of methanol. The product was dried in the vacuum oven at 50 °C overnight to provide 11.0 g (61% yield) of **11**: mp 195−203 °C. HPLC purity 96%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1 H), 7.99 (s, 1 H), 7.93 (s, 1 H), 4.06 (q, J = 7 Hz, 2 H), 3.40 (m, 4 H), 3.37 (s, 2 H), 2.21 (m, 4 H), 1.11 (t, J = 7 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.2, 164.7, 146.1, 143.5, 138.9, 136.4, 128.1, 126.5, 110.2, 66.5, 61.3, 60.2, 53.3, 14.6; Anal. Calcd for $C_{17}H_{19}IN_2O_4$: C, 46.17; H, 4.44; N, 6.35; found: C, 46.43; H, 4.37; N, 6.38.

Ethyl 2-(2−2-Hydroxyethyl)-8-(morpholin-4-ylmethyl)-6-oxo-6H-pyrrol[3.2.1-ij]quinoline-5-carboxylate (12). 11 (985 g; 2.23 mol), CuI (42.4 g; 0.22 mol; 0.1 equiv), and $Cl_2Pd(PPh_3)_2$ (15.7 g; 0.0226 mol; 0.01 equiv) were combined in a 22-L flask under nitrogen. Absolute ethanol (10

L) was added followed by triethylamine (630 mL; 4.52 mol; 2 equiv) and 3-butyn-1-ol (257 mL; 3.39 mol; 1.5 equiv). The mixture was fitted with a distillation head, and 5 L of ethanol was distilled. HPLC analysis of the pot residue revealed that the reaction was complete. Water (7 L) was added to the mixture, and the reaction was concentrated by vacuum distillation to remove the remaining ethanol. The solution was cooled to room temperature. Celite (450 g) was then added followed by the addition of 1 N HCl (3 L; 1.3 equiv) to yield a mixture of pH 1.2. The mixture was filtered through a Celite-coated, fritted glass funnel, and the filter cake was rinsed with 3 L of water. The filtrate was transferred to a 22-L flask and stirred overnight in the presence of Deloxan THP (726 g). The slurry was filtered on a fritted glass funnel with a 700-mL water rinse. The filtrate was transferred to a 20-L wash tank, and solid Na_2CO_3 (287 g; 2.71 mol; 1.2 equiv) was added portionwise (***Danger***: foaming!) to yield a solution of pH 9. The solution was extracted with methylene chloride (3 × 11 L). The organic layers were transferred portionwise to a 22-L flask and concentrated by vacuum distillation to a final volume of 6 L. Acetonitrile (1.3 L) and MTBE (7 L) were added, and the solution was concentrated to a final volume of 6 L by vacuum distillation. MTBE (7 L) was added, and the solution was concentrated to 6 L. MTBE (7 L) was again added, and the solution was concentrated to a final volume of 4 L. The resulting yellow slurry was cooled in an ice bath and then filtered onto a fritted glass funnel with a MTBE rinse. The resulting yellow solids were dried in a vacuum oven at 50 °C overnight to give 519 g of the light-sensitive **12** in 60% yield. ICP analysis showed 2 ppm Cu and 20 ppm Pd: mp 172 °C. HPLC purity >95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.84 (s, 1H), 7.72 (s, 1H), 6.68 (s, 1H), 4.33 (q, 2H, J = 7.1), 4.11 (t, 2H, J = 5.6), 3.68 (m, 4H), 3.58 (s, 2H), 3.55 (br s, 1H), 3.18 (t, 2H, J = 5.6), 2.43 (m, 4H), 1.38 (t, 3H, J = 7.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 163.1, 137.9, 137.4, 134.1, 132.5, 127.8, 125.0, 120.9, 120.7, 114.2, 108.3, 65.0, 61.4, 59.1, 51.6, 27.1, 12.4; IR (cm^{-1}) 3250 m, 2956 m, 1650 s, 1590 s, 1551 s, 1493 s, 1221 s; MS (70 eV) 384 (M^+); Elem. Anal. ($C_{21}H_{24}N_2O_5$) Calcd: C, 65.61; H, 6.29; N, 7.29; Found: C, 65.23; H, 6.39; N, 7.24; 20 ppm Pd; 2 ppm Cu.

***N*-(4-Chlorobenzyl)-2-(2-hydroxyethyl)-8-(morpholin-4-ylmethyl)-6-oxo-6H-pyrrol[3.2.1-*ij*]quinoline-5-carboxamide (5). 12** (800 g; 2.1 mol) was added to a 22-L, three-necked flask under nitrogen. Ethylene glycol (4.8 L) and 4-chlorobenzylamine (755 mL; 6.2 mol; 3 equiv) were added, and the suspension was heated at 132 °C for 8 h. HPLC analysis showed 98% conversion, so the reaction was cooled to 102 °C; toluene (2.4 L) was added followed by continued cooling to 75 °C. Acetonitrile (1.2 L) was added followed by the addition of pivaldehyde (215 mL; 2.1 mol; 1 equiv), precipitation occurred upon continued cooling to room temperature. The slurry was stirred at room temperature overnight and filtered on a fritted glass funnel. The poorly filtering cake was rinsed with ethanol (2 L) and acetonitrile (2 × 1 L), and the solids were dried in a vacuum oven at 55 °C for 2 days yielding 1318 g (132%) of the crude **5**. Crude **5** (660 g; 1.38 mol) was added to a 22-L, three-necked flask under nitrogen. Tetrahydrofuran (6 L) and ethanol (6 L) were added, and the slurry was heated to 65 °C to effect dissolution. The solution was transferred to a clean, 22-L flask through a heated in-line 0.6 μm filter using nitrogen pressure. The solution was reheated to 65 °C, and hexane (6 L) was added followed by cooling to room temperature and then to 5 °C. The slurry was filtered and rinsed with hexane; the solids were dried in a vacuum oven at 60 °C for 24 h to give 395 g of **5** (79% yield). ^{1}H NMR analysis shows the presence of 2−4% imine, **17**. High-quality material is obtained by adding tetrahydrofuran (7.3 L) and ethanol (7.3 L) to **5** (1475 g) in a 22-L flask. The resulting slurry was stirred for 3 h at room temperature followed by cooling to 5 °C. The slurry was filtered on a fritted glass funnel with a 2-L hexane rinse. The solids were dried in a vacuum oven at 60 °C overnight to give 1336 g (67% from **12**) of **5** as an off-white solid: mp 179.5 °C. HPLC purity >98%. ^{1}H NMR (400 MHz, DMSO) δ 10.14 (t, 1H, J = 6.1), 9.20 (s, 1H), 8.10 (s, 1H), 7.95 (s, 1H), 7.92 (s,1H), 7.38 (t, 4H, J = 9.0), 6.89 (s, 1H), 4.98 (t,1H, J = 4.8), 4.58 (d, 2H, J = 6.0), 3.77 (m, 2H), 3.67 (s, 2H), 3.56 (m, 4H), 3.16 (t, 2H, J = 6.1), 2.37 (m, 4H); ^{13}C NMR (100 MHz, DMSO) δ 178.5, 163.9, 141.7, 139.7, 138.5, 133.7, 131.5, 129.9, 130.0, 128.4, 127.8, 121.8, 121.5, 115.6, 109.9, 66.2, 62.4, 60.2, 53.1, 41.7, 28.5; IR (cm^{-1}) 3378 m, 3228 m, 1659 s, 1627 s, 1593 m, 1542 s, 1490 s; Elem. Anal. ($C_{26}H_{26}N_3O_4Cl$) Calcd: C, 65.06; H, 5.46; N, 8.75; Cl, 7.39; Found: C, 65.05; H, 5.41; N, 8.73; Cl, 7.43; LT 1 ppm Cu, LT 1 ppm Pd.

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